Understanding the Gaps in Acute Coronary Syndrome Care in Australia

by

Derek P. Chew MBBS MPH

Thesis
Submitted to Flinders University
for the degree of

Doctor of Philosophy

School of Medicine
College of Medicine and Public Health

November 2017

TABLE OF CONTENTS

Summary

Acute coronary syndrome (ACS) is an area of cardiovascular medicine that is well served by an extensive and continuously evolving evidence base. Despite this, local clinical practice is often slow to adapt and effective delivery of the most modern care is not always assured. Furthermore, troponin assays with greater sensitivity have entered clinical practice, but evidence that clinical decision-making and care in ACS has effectively embraced this innovation is lacking.

To date, studies included within this thesis have observed a shortfall in the use of current evidence based therapies among patients at increased risk, despite a high level of knowledge and acceptance of the evidence, combined with a strong inverse relationship between the presence of clinical co-morbidities and the use of these therapies. Together with the observation of substantial variation in care across Australia and New Zealand, we have explored the clinical biases evident in clinician estimation of risk. In addition, there is a correlation between the work-force capacity and system-based approaches to the delivery of acute coronary syndrome care and the subsequent outcomes experienced by these patients. We have observed a reduction in mortality from myocardial infarction associated with the provision of a clinical network to rural centres in South Australia, as well as in improved efficiency and effectiveness of care with streamlined design of clinical services suggesting that improving clinical decision-making capacity combined with a more structured approach to care is associated with better outcomes.

This thesis is divided into 5 section.

The first section addresses the evidence that ACS care is heterogeneous across Australia within two registries temporally separated by a span of 5 years. Combined with these studies is an analysis exploring the incremental benefit of each component of current guideline recommendations in reducing 6-month mortality, and a modelling analysis that evaluates the potential gains from more complete application of the evidence base.

The second section explores the accuracy of physician estimated risk among patients with ACS when compared with objective risk stratification, in conjunction with the intuitive biases that influence the estimation of benefit from current therapies, combined with the observed deficits of care and associated inferior outcomes associated with risk underestimation. This section also includes the design of a cluster

randomised study exploring the impact of routine objective risk stratification on care and outcome currently ongoing in Australia.

The third section focuses on the emerging technology of high sensitivity troponin, an innovation that promises improved diagnosis, though the realization of this benefit has been uncertain to date. We have explored the clinical consequences of troponin elevation across a broad spectrum of emergency department presentations, and then studied the impact of high-sensitivity troponin reporting in the emergency department in one of the very few randomised clinical trials ever conducted in this area.

The fourth section addresses local health service design and its association with clinical outcomes in ACS. This section includes an assessment of quality activities in a nationally derived sample of hospitals, while another paper examines the impact of a state-wide program for improving ACS decision-making in rural areas of South Australia. The last paper in this section describes the impact of local disease based reconfiguration of a cardiology service and its impact on care, efficiency and outcome.

The fifth section describes the influences of policy/funding characteristics on clinical activity, specifically early invasive investigation of ACS contrasted against the provision of guideline recommended pharmacologies and cardiac rehabilitation. In addition, an editorial discussing the emergence of clinical care standards which seek to attenuate unwarranted variation or care is presented.

This thesis concludes with a putative framework for the rational adoption of the current evidence base and new technologies by leveraging decision algorithms to optimise the evaluation or risk and potential benefit.

A set of supporting documents providing further context and rationale for these investigations are also provided.

Publications included in this thesis

1. Chew DP, Amerena JV, Coverdale SG, et al. Invasive management and late clinical outcomes in contemporary Australian management of acute coronary syndromes: observations from the ACACIA registry. *Med J Aust*. 2008;188(12):691-697.

2. Chew DP, Amerena J, Coverdale S, Rankin J, Astley C, Brieger D. Current management of acute coronary syndromes in Australia: observations from the acute coronary syndromes prospective audit. *Intern Med J*. 2007;37(11):741-748. doi:10.1111/j.1445-5994.2007.01435.x.

3. Chew DP, French J, Briffa TG, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. *Med J Aust*. 2013;199(3):185-191. doi:10.5694/mja12.11854.

4. Chew DP, Anderson FA, Avezum A, et al. Six-month survival benefits associated with clinical guideline recommendations in acute coronary syndromes. *Heart*. 2010;96(15):1201-1206. doi:10.1136/hrt.2009.184853.

5. Chew DP, Huynh LT, Liew D, Astley C, Soman A, Brieger D. Potential survival gains in the treatment of myocardial infarction. *Heart*. 2009;95(22):1844-1850. doi:10.1136/hrt.2009.174276.

6. Chew DP, Junbo G, Parsonage W, et al. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. *Circ Cardiovasc Qual Outcomes*. 2013;6(3):299-308. doi:10.1161/CIRCOUTCOMES.111.000072.

7. Chew DP, Juergens C, French J, et al. An examination of clinical intuition in risk assessment among acute coronary syndromes patients: Observations from a prospective multi-center international observational registry. *Int J Cardiol*. 2014;171(2):209-216. doi:10.1016/j.ijcard.2013.12.010.

8. Chew DP, Astley CM, Luker H, et al. A cluster randomised trial of objective risk assessment versus standard care for acute coronary syndromes: Rationale and design of the Australian GRACE Risk score Intervention Study (AGRIS). *Am Heart J*. 2015;170(5):995–1004.e1. doi:10.1016/j.ahj.2015.07.032.

9. Chew DPB, Cullen L. The promise of high-sensitivity troponin testing. *Med J*

Aust. 2014;201(3):125-126. doi:10.5694/mja14.00858.

10. Chew DP, Briffa TG, Alhammad NJ, et al. High sensitivity-troponin elevation secondary to non-coronary diagnoses and death and recurrent myocardial infarction: An examination against criteria of causality. *European Heart Journal: Acute Cardiovascular Care*. December 2014. doi:10.1177/2048872614564083.

11. Chew DP, Zeitz C, Worthley M, et al. Randomised Comparison of High-Sensitivity Troponin Reporting in Undifferentiated Chest Pain Assessment. *Circ Cardiovasc Qual Outcomes*. 2016;9(5):542-553. doi:10.1161/CIRCOUTCOMES.115.002488.

12. Astley CM, MacDougall CJ, Davidson PM, Chew DP. Lost in Translation: Health Resource Variability in the Achievement of Optimal Performance and Clinical Outcome. *Circ Cardiovasc Qual Outcomes*. 2011;4(5):512-520. doi:10.1161/CIRCOUTCOMES.110.960229.

13. Tideman PA, Tirimacco R, Senior DP, et al. Impact of a regionalised clinical cardiac support network on mortality among rural patients with myocardial infarction. *Med J Aust*. 2014;200(3):157-160. doi:10.5694/mja13.10645.

14. Chew DP, Horsfall M, McGavigan AD, et al. Condition-specific Streaming versus an Acuity-based Model of Cardiovascular care: A Historically-controlled Quality Improvement Study Evaluating the Association with Early Clinical Events. *Heart, Lung and Circulation*. 2015;0(0). doi:10.1016/j.hlc.2015.05.023.

15. Chew DP, Macisaac AI, Lefkovits J, et al. Variation in coronary angiography rates in Australia: correlations with socio-demographic, health service and disease burden indices. *Med J Aust*. 2016;205(3):114-120.

16. Briffa TG, Hammett CJ, Cross DB, et al. Should fee-for-service be for all guideline-advocated acute coronary syndrome (ACS) care? Observations from the Snapshot ACS study. *Aust Health Rev*. 2015;39(4):379-379. doi:10.1071/AH14153.

17. Chew DP, Briffa TG. The clinical care standards in ACS: towards an integrated approach to evidence translation in ACS care. *Heart Lung Circ*. 2015;24(3):213-215. doi:10.1016/j.hlc.2014.12.159.

Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Specifically, each of these studies, I designed, in collaboration with co-investigators or individually, the methods and content of data collection. For all studies, I have planned and conducted the statistical analyses and written the first draft of the manuscript, except for chapter 12 (which formed part of Dr Carolyn Astley's DPH thesis, of which I was a supervisor). For each manuscript, I was either first author (i.e. chapters 1-11, 14,15,17) or senior author (i.e. chapters 12,13,16).

Signed.....

Date.....22nd November 2017.....

Acknowledgements

I dedicate this work to my wife and son, who have long endured my need to undertake research, analyse data and write manuscripts.

I am forever grateful to my many collaborators across Australia, who have provided me with knowledge, wisdom and a treasured sense of community.

I am honoured to be able to serve those patients with cardiovascular disease, who provide the inspiration and motivation for this work.

Introduction

In Australia, Acute Coronary Syndromes (ACS) account for over 10,000 deaths, more than 100,000 hospital admissions and approximately $1.8 billion dollars in direct health resources every year.[1] With this enormous burden of mortality, morbidity and costs, it is not surprising that this area of health is the focus of national and international clinical practice guidelines and nationally endorsed Clinical Care Standards.[2-6]

This thesis examines the evolving uptake of evidence based care for ACS in Australia through conduct and analysis of several registries. (Chapters 1-3) Yet, we continue to observe incomplete use of current evidence based therapies among patients at increased risk, despite a high level of knowledge and acceptance of the evidence, combined with a strong inverse relationship between the presence of clinical co-morbidities and the use of these therapies.[7] In order to articulate the value proposition for system change, we then model the potential lives saved from even modest improvement in the translation of the current evidence base. (Chapters 4-5)

We have sought insights into the drivers of this evidence practice gap, and have found potential mediators at the level of the physician estimation of risk. This thesis explores the accuracy of clinical risk assessment contrasted with well-established objective measures of risk within specific patients presenting with myocardial infarction across 4 countries. (Chapter 6) Within this work, we also examine the areas of collective clinical intuition associated with over-estimation, under-estimation and miss-interpretation of patient risk. (Chapter 7) We also describe the design and conduct of a cluster-randomised clinical trial examining the efficacy of routine objective assessment of patient risk in improving evidence based therapy provision. (Chapter 8)

Building on this experience, we explore the diagnostic utility of the emerging high sensitivity troponin T assay in its ability to more accurately identify the risk of recurrent myocardial infarction and death among patients with both recognised ACS and those with myocardial injury not known to be due to plaque rupture. (Chapter 9) This work highlights the need for clinical trials exploring the relative efficacy of proven coronary therapies among the large population of patients with myocardial injury not recognised to be experiencing myocardial infarction. (Chapter 10) In a prospective study we explore the ability of clinicians to effectively integrate novel diagnostic information to leverage more effective or efficient care. We report the design and outcomes of

routinely reporting high-sensitivity troponin testing in the emergency department in a multi-centre randomised clinical trial. (Chapter 11)

Beyond the clinician, there is a strong correlation between the work-force capacity and system-based approaches to the delivery of acute coronary syndrome care and the subsequent outcomes experienced by these patients. (Chapter 12) This thesis also interrogates the deficiencies in how the Australian health system delivers the acute care knowledge and expert decision-making, and examines how small and large-system redesign enable potential improvements in outcome. Specifically, we describe the reduction in mortality from myocardial infarction associated with the provision of a clinical network to rural centres in South Australia, combined with the reduction in acute events with the implementation of a streaming model of cardiovascular care. (Chapters 13-14) At a national policy level, we demonstrate the influence of funding models on the provision of invasive management contrasted with evidence based pharmacology in the management of ACS. (Chapter 15) These insights suggest the direct of health service reforms that may enable the more robust application of the current ACS guidelines and clinical care standards. (Chapters 16-17)

Recognising continued development of electronic systems in the clinical space, the conclusions of this thesis highlights the need for an integrated approach to effective translation of the ACS evidence base through real-time data collection and electronic decision-support to more effectively integrate new diagnostic and therapeutic innovation and distribute expertise in ACS care in order to improve clinical care and outcome.

References

1. Access Economics. The shifting burden of cardiovascular disease in Australia. *National Heart Foundation of Australia 2005*. 2005.

2. Chew DP, Scott IA, Cullen L, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ*. 2016;25(9):895-951. doi:10.1016/j.hlc.2016.06.789.

3. Chew DP, Scott IA, Cullen L, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *Med J Aust*. 2016;205(3):128-133. doi:10.5694/mja16.00368.

4. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2016;37(3):267-315. doi:10.1093/eurheartj/ehv320.

5. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal*. 2012;33(20):2569-2619. doi:10.1093/eurheartj/ehs215.

6. Australian Commission for Safety and Quality in Health Care. Acute Coronary Syndromes Clinical Care Standard. November 2014:1-20.

7. Huynh LT, Chew DPB, Sladek RM, Phillips PA, Brieger DB, Zeitz CJ. Unperceived treatment gaps in acute coronary syndromes. *International Journal of Clinical Practice*. 2009;63(10):1456-1464. doi:10.1111/j.1742-1241.2009.02182.x.

SECTION 1: DEFICIENCIES AND OPPORTUNITIES IN AUSTRALIAN ACUTE CORONARY SYNDROME CARE

1 CURRENT MANAGEMENT OF ACUTE CORONARY SYDROMES IN AUSTRALIA: OBSERVATIONS FROM THE ACUTE CORONARY SYNDROMES PROSPECTIVE AUDIT (ACACIA)

1.0 Title page: Current Management Of Acute Coronary Syndromes In Australia: Observations From The Acute Coronary Syndromes Prospective Audit (ACACIA)

Derek P. Chew [a], John Amerena [b], Steve Coverdale [c], Jamie Rankin [d], Carolyn Astley[a], David Brieger [e].

Author affiliations

[a]Flinders University/Flinders Medical Centre, South Australia, Australia

[b]Geelong Hospital, Victoria, Australia

[c]Nambour Hospital, Queensland, Australia

[d]Royal Perth Hospital, Western Australia, Australia

[e]Concord Hospital, New South Wales Australia

See appendix 1 for investigators

Running Title: ACS management in Australia.

Corresponding Author

Derek P. Chew MBBS MPH FRACP
Flinders Medical Centre
Flinders Drive, Bedford Park
South Australia, 5042
AUSTRALIA
Ph: +618 8404 2001
Fax: +618 8404 2150

1.1 Abstract

Background: Acute coronary syndromes (ACS) management is now well informed by guidelines extrapolated from clinical trials. However, the majority of these data have been acquired outside the local context. We sought to describe the current patterns of ACS care in Australia.

Methods: The ACACIA study is a prospective multi-centre registry of ST segment elevation myocardial infarction (STEMI), non-ST-segment elevation ACS high risk (NSTEACS-HR) and intermediate-risk (NSTEACS-IR) patients, involving 39 metropolitan, regional and rural sites. Data included hospital characteristics, geographic and demographic factors, risk stratification, in-hospital management including invasive services, and clinical outcomes.

Results: A cohort of 3402 patients was enrolled; the median age was 65.5 years. Female and non-metropolitan patients comprised 35.5% and 23.9% of the population, respectively. At enrolment, 756 (22.2%) were STEMI patients, 1948 (57.3%) were high-risk NSTEACS patients and 698 (20.5%) were intermediate-risk NSTEACS patients. Evidence-based therapies and invasive management use were highest among suspected STEMI patients compared with other strata (angiography: STEMI 89%, NSTEACS-HR 54%, NSTEACS-IR 34%, p<0.001) (percutaneous coronary intervention: STEMI 68.1%, NSTEACS-HR 22.2%, NSTEACS-IR 8.1%, p<0.001). In hospital mortality was low (STEMI 4.0%, NSTEACS-HR 1.8%, NSTEACS-IR 0.1%, p<0.001), as was recurrent MI (STEMI 2.4%, NSTEACS-HR: 2.8%, NSTEACS-IR 1.2%, p=0.052).

Conclusions: An “evidence-practice gap” in the management of ACS appears to exist, but this is not matched by an increased risk of in-hospital clinical events. Objective evaluation of local clinical care is a key initial step in developing quality improvement initiatives, and this study provides a basis for the improvement in ACS management in Australia.

1.2 Background

Within Australian, acute coronary syndromes (ACS) represent an enormous burden of care, in terms of morbidity, mortality and cost. Effective management of these patients is time-critical and resource intensive.[1] Fortunately, a substantial body of clinical research now informs almost every aspect of the care of these patients. Implementation of this evidence base should translate to improvements in patient outcomes and have been assimilated into clinical practice guidelines, both locally and internationally.[2, 3] While Australian patients and hospitals have contributed to many of these international clinical studies, it is uncertain how well these data have translated back to local clinical care for this heterogenous population.

International experience suggests that despite published guidelines, many patients with acute coronary syndromes remain 'under-treated' with limited access to invasive management and sub-optimal utilization of proven pharmacotherapies.[4-7] Local data documenting patient management are extremely limited. Factors likely to influence the under-utilization of therapies include under-recognition of patient risk and logistical limitations to the delivery of proven treatment strategies.[8] Such factors are infrequently addressed in the clinical studies that have formed the basis of our evidence base. Consequently, given the unique characteristics of Australia's demography and geography, the effective uptake and delivery of evidence-based care for Australian ACS patients warrants objective evaluation. Hence, a registry documenting the clinical presentation and management of ACS patients in Australia was conducted.

1.3 Methods

1.3.1 Patient Population

The Acute Coronary Syndrome Prospective Audit (ACACIA, protocol number PM_L_0051) was conducted between November 2005 and May 2006. This registry involved 39 hospitals across all states and territories of Australia. Enrolment at each site was consecutive, targeting 100 to 150 patients per site, and focused on patients admitted from the emergency department. Patients transferred into study centres were excluded if a substantial proportion of their initial management had been undertaken at a non-study centre (transfer>12 hours after initial presentation). Patients with acute coronary syndromes deemed secondary to other processes such as major trauma or surgery were excluded. Ethics committee approval was obtained from each site. Informed consent was obtained from all patients except for those patients who died before consent was sought and access to these medical records were granted by the local ethics committees.

1.3.2 Definition of ACS

Patients were included if they had presenting characteristics consistent with either ST segment elevation myocardial infarction (STEMI), or high or intermediate risk non-ST segment elevation acute coronary syndromes (NSTEACS HR and IR, respectively), as defined by the risk classification of the National Health Data Dictionary.[2, 9] Specifically, patients with presenting symptoms suggestive of angina or angina-equivalent were included as suspected STEMI if they had persistent ST elevation >1mm in 2 contiguous leads, or new/presumed new LBBB. Patients were included as NSTEACS-HR if ECG findings demonstrated ST depression >0.5mm, or T wave inversion ≥1.0 mm in > 2 contiguous leads, biomarker elevation (troponin or creatine kinase), haemodynamic compromise (cardiogenic shock, killip class >1 or mitral regurgitation or syncope), known left ventricular ejection fraction <40%, ventricular tachycardia, previous coronary revascularization, a history of diabetes or creatinine clearance <60ml/min. Patients were included as

NSTEACS-IR in the absence of high-risk characteristics, but one of the following was present: Q-waves or ST/T changes in 2 leads; age was >65 years; a history of prior coronary artery disease (previous event or coronary angiogram with a lesion>50%); known ejection fraction 40-50%; two or more coronary risk factors; prior aspirin use. Allocation to each risk stratum was centrally adjudicated using ECG and biomarker data.

1.3.3 Clinical variables

This registry focused on the demographic, clinical procedural and logistical factors involved in the management of ACS patients. These included presenting characteristics and clinical risk factors, time taken to access medical care, and the distance patients were transferred for ongoing care and invasive procedures. In-hospital management data focused on the use and timing of coronary angiography, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). In-patient use of antithrombotic therapies including intravenous glycoprotein IIb/IIIa inhibition, low molecular weight heparin, 3-hydroxy-methylglutaryl coenzyme A reductase inhibition (statin) therapy, Angiotensin converting enzyme (ACE)-inhibition/angiotensin receptor (AR)-antagonists, beta-blockers, and anti-platelet therapies both during hospitalisation and at the time of discharge were documented. Trained study nurses abstracted all data.

All cause mortality was recorded. Myocardial infarction (MI) required a rise in biomarkers, with a rise above the local threshold definition for troponin (I or T) and/or greater than twice the upper limit of normal for CK-MB (in the absence of CK-MB, CK was used). Recurrent MI was defined as a further >25% rise and/or >50% rise in the troponin (I or T) and CK-MB, respectively, 24 hours after admission. Following PCI and CABG, a level of CK-MB >3 times and >5 times-the upper limit of normal within 48 hours or new Q-waves was used, respectively. Stroke, cardiogenic shock, atrial and ventricular arrhythmias, bleeding events and acute renal failure relied on investigator-determined events through the use of protocol definitions. Where possible, objective evidence of

the event was also sought. Definitions for risk stratification, clinical management and outcomes were consistent with standard definitions as documented within the National Health Data Dictionary.[9]

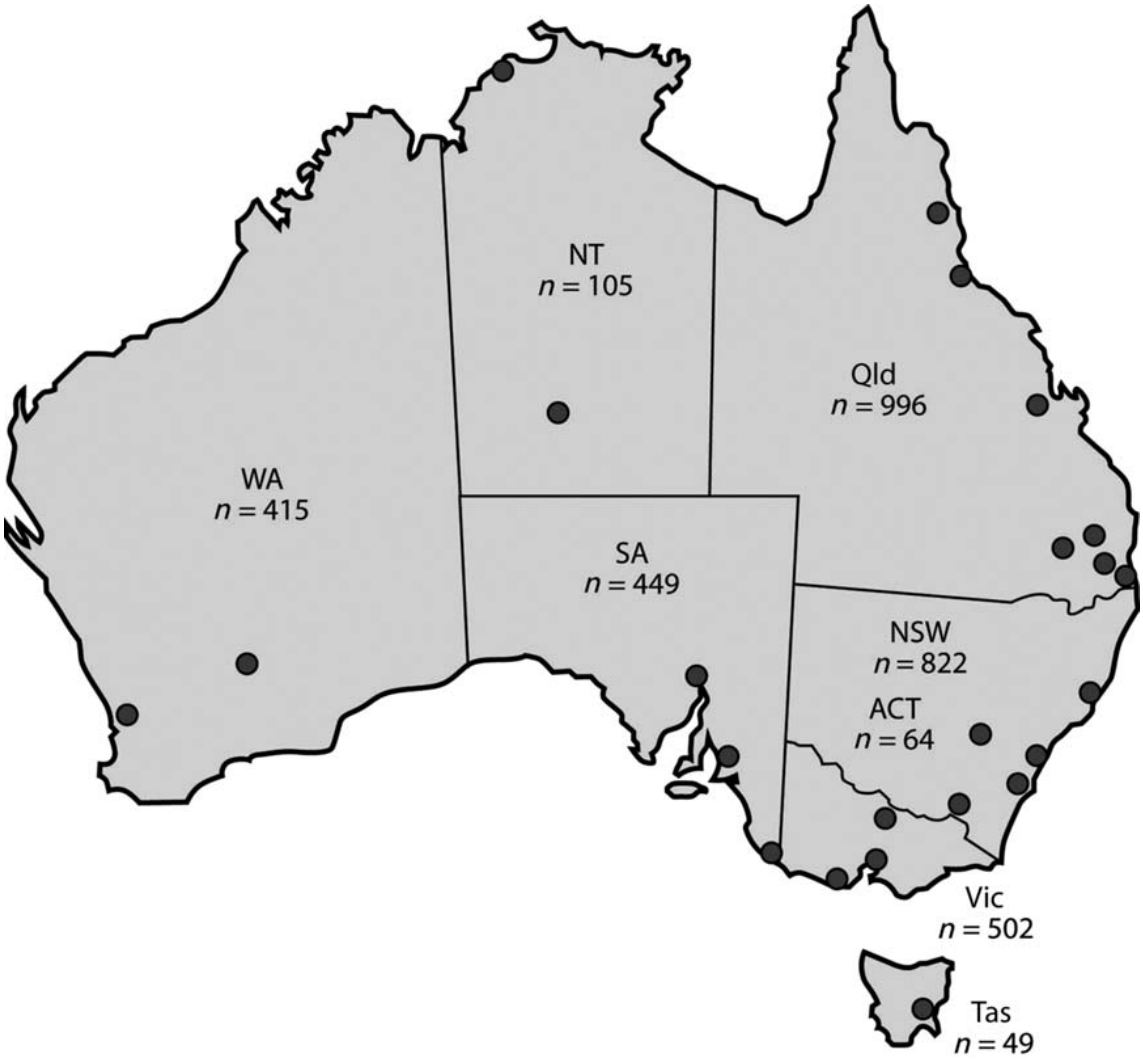
1.3.4 Statistical analysis

Demographic, clinical, procedural factors and outcomes are presented stratified by admission classification. Factors following a normal distribution are expressed as means (± standard deviation) and non-Gaussian factors are reported as medians (and inter-quartile ranges). Counts are presented as "n" (%). Comparisons between groups were performed using chi-square tests for binary factors and Kruskal-Wallis testing for continuous variables. Analyses are presented by admission stratum and by final discharge diagnosis. The use of therapies at discharge was assessed as the prescription of the 5 guideline-advocated secondary prevention therapies (aspirin, beta-blockers, ACE-inhibition or AR antagonists, statin therapy and clopidogrel) among those patients discharged alive, by discharge diagnosis. Prescription was considered compliant if the therapy was not prescribed, but a contraindication to the therapy was provided. Patients undergoing PCI or CABG without prior angiography due to known anatomy were excluded from the assessment of risk stratification testing rates (n=29). A probability of <0.05 is considered statistically significant. All analyses were performed using STATA 9.1 (College Station, TX).

1.4 Results

In total, 3402 patients were enrolled, drawn from all states and territories within Australia (Figure 1).

Figure 1: Locations of ACACIA Registry enrolment sites and numbers of patients enrolled in each State or Territory.



While the majority of patients were enrolled in metropolitan centres, regional and rural centres enrolled 700 (20.6%) and 114 (3.35%) patients, respectively. Of these sites: 10/39 (25.6%) had no on-site cath-lab; 3/39 (7.7%) offered only angiography; 8/39 (20.5%) provided angiography and PCI: while 18/39 (46.2%) of sites performed angiography, PCI and CABG within the institution. The median age was 65.5 years (i.q.r. 19.9 years) with 25.6% of patients > 75yrs, 35.5% of patients were female, and 26.1% and 63.8% of patients reported a history of diabetes and hypertension, respectively. An estimated glomerular

filtration rate less than 60ml/min/1.73m^2 was observed in 27.2% of patients. Prior known coronary heart disease was reported in 49.3 % of patients and 9.7% of patients were transferred for further investigation and management. As classified by the National Heart Foundation guidelines for the stratification of risk in ACS, 756 patients were categorised as suspected STEMI, 1,948 patients as suspected NSTEACS-HR, and 698 patients as NSTEACS-IR. The demographic and clinical characteristics of these patients are presented in table 1.

Table 1: Demographic and clinical characteristics

	STEMI (n=756)	***NSTEACS HR (n=1948)***	***NSTEACS IR (n=698)***
Age (yrs, mean ±SD)	62.0 (19.0)	68.4 (19.1)	61.2 (21.3)
Female Gender (n, %)	196 (25.9)	692 (35.5)	373 (47.8)
Diabetes (n, %)	135 (17.8)	752 (38.0)	0 (0)*
Hypertension (n, %)	375 (49.6)	1392 (71.4)	403 (57.7)
Dyslipidaemia (n, %)	339 (44.8)	1300 (66.8)	398 (57.0)
Current Smoking (n, %)	249 (32.9)	352 (18.1)	176 (25.2)
Family History of CAD (n, %)	286 (37.8)	647 (33.2)	284 (40.7)
Prior MI (n, %)	106 (14.0)	665 (34.2)	155 (22.2)
Prior PCI (n, %)	80 (10.6)	421 (21.6)	106 (15.2)
Prior CABG (n, %)	25 (3.3)	468 (24.2)	0(0)*
Prior Stroke (n, %)	23 (3.0)	162 (8.3)	41 (5.9)
Known PAD (n, %)	25 (3.3)	149 (7.6)	19 (2.7)
Prior Atrial fibrillation (n, %)	39 (5.2)	286 (14.7)	65 (9.3)

Creat. Cl.ml/min (median, 25th-75th percentile)	75.0 (61.3-89.1)	70.8 (53.5-87.5)	79.1 (65.9-93.1)
White cell count (mean, SD)	10.6 (4.5)	8.4 (3.5)	7.6 (3.0)
GRACE Score (median, 25th-75th pecrentile)	143 (123-168)	125 (101-154)	96 (81-117)

**NB: the presence of diabetes and prior CABG are criteria for classification as high-risk NSTEACS*

GRACE= Global Registry of Acute Coronary Events

1.4.1 Use of clinical guideline recommended therapies

Chronic aspirin use was reported in 45.6% of patients, and aspirin initiation within 24 hours of hospitalisation (or contra-indications stated) occurred in 47.3% of patients. Hence, aspirin use within 24 hours of hospitalisation was high (92.9%), although not complete. Chronic clopidogrel use was seen in 16.4% of patients, with a further 38.4% of patients having this agent initiated within the first 24 hours. Four percent of patients did not received aspirin or clopidogrel within the first 24 hours. Initial beta-blocker prescription was low at 54.4%, with these agents initiated within 24 hours in 22.6% of patients. Statin therapy within the first 24 hours was observed in 61.7%. However, the chronic use of these agents was reported in 45.9% of patients. An ACE-inhibitor or AR-antagonist was administered in 48.5%. Glycoprotein (GP) IIb/IIIa inhibition was administered in 66.4% of STEMI patients undergoing primary PCI. Among biomarker positive NSTEACS-HR patients undergoing invasive management 20.5% of patients received GP IIb/IIIa inhibition during the admission. Approximately half the NSTEACS-HR patients received low molecular weight heparin (51.8%), with lower rates among those presenting with STEMI and NSTEACS-IR (24.9% and 43.1%, respectively).

Rates of use of these therapies by discharge, assessed by discharge diagnosis and adjusted for stated contraindications, are displayed in table 2.

Table 2: Use of guideline-recommended secondary prevention therapies by discharge diagnosis adjusted for stated contraindication and survival to discharge

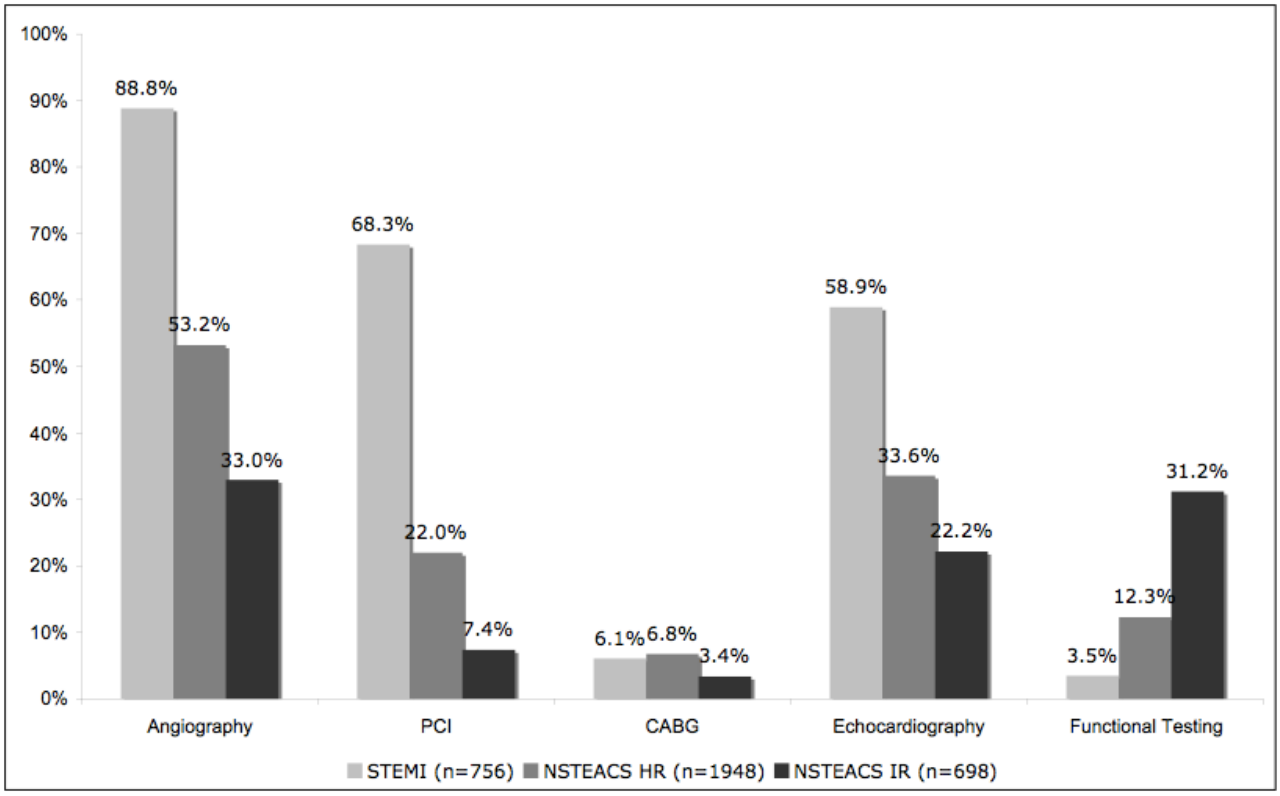
	STEMI (n= 686)	**NSTEMI (n=995)**	**Unstable Angina (n=814)**
Aspirin (n, %)	645 (94.0)	905 (91.0)	685 (84.2)
Clopidogrel (n, %)	567 (82.7)	645 (64.2)	406 (49.9)
Beta-blocker (n, %)	562 (81.9)	773 (74.3)	551 (67.7)
ACE-I/ARB (n, %)	569 (82.4)	722 (72.6)	525 (64.5)
Statin (n, %)	637 (92.9)	875 (87.9)	679 (83.4)

Prescription of aspirin and statin therapy remain high across all the discharge diagnoses with comparatively lower rates of beta-blockade, ACE-inhibition or AR- antagonism, and clopidogrel use. Of those patients surviving to discharge, only 58.2%, 35.0% and 23.5% of STEMI, non-ST elevation myocardial infarction and unstable angina patients were receiving all five guideline recommended secondary prevention therapies.

1.4.2 Investigations and invasive management

In the entire cohort, angiography was undertaken in 1,940 patients (57.0%), while revascularization by PCI and CABG were conducted in 996 patients (29.3%) and 202 patients (6.0%), respectively. The highest rates of invasive management were observed in patients presenting with suspected ST elevation MI (Figure 2).

Figure 2: Use of Investigations and revascularization by admission risk strata



Among patients with NSTEACS-HR, angiography was undertaken in 1037 (53.2%) patients, while PCI and CABG occurred in 22.0% and 6.8% of patients respectively. Of all the stenting procedures, 56.9% of patients received a drug eluting stent. Among patients admitted with high-risk and NSTEACS-IR, some form of risk stratification testing (angiography or functional testing) was undertaken in 62.3% and 59.0% of patients before hospital discharge, respectively.

1.4.3 Reperfusion for ST-segment elevation MI

Among the 756 patients presenting with suspected STEMI, 685 (90.6%) patients presented within 12 hours of symptom onset. Of these, 482 (70.4%) received some form of reperfusion therapy; a further 25 patients underwent reperfusion outside the 12 hour window. Of all the patients receiving reperfusion therapy, 311 patients (60.4%) received primary PCI, while the remainder received fibrinolysis. Rescue PCI for failed fibrinolysis was reported in 35 patients, representing 17.4% of patients receiving initial fibrinolysis.

1.4.3.1 Clinical outcomes

In-hospital outcomes by admission risk strata are displayed in table 3.

Table 3: In-hospital outcomes

	STEMI (n=755)	***NSTEACS HR (n=1948)***	***NSTEACS IR (n=697)***
In-hospital Death (n, %)	30 (4.0)	35 (1.8)	1 (0.1)
MI/recurrent MI (n, %)	18 (2.4)	54 (2.8)	8 (1.2)
Unplanned revascularization (n, %)	13 (1.7)	11 (0.6)	0
Bleeding (n, %)	48 (6.4)	65 (3.3)	10 (1.4)
Stroke (n, %)	5 (0.7)	8 (0.4)	0
Cardiogenic shock (n, %)	19 (2.5)	11 (0.6)	0
Acute Pulmonary Oedema (n, %)	43 (5.6)	47 (2.4)	0
Ventricular Arrhythmia (n, %)	124 (16.6)	77 (4.0)	6 (0.9)

New Onset AF (n, %)	44 (5.8)	59 (3.0)	11 (1.6)
Acute Renal Failure (n, %)	11 (2.0)	30 (1.5)	1 (0.1)

Overall, a low rate of in-hospital mortality (65/3386, 1.9%) was observed. When considered by discharge diagnosis, patients with STEMI and NSTEMI experienced similar rates of death (STEMI: 4.3% versus NSTEMI: 3.1%), recurrent MI (STEMI: 3.6% versus NSTEMI: 5.0%) and stroke (STEMI: 0.7% versus NSTEMI: 0.6%). However, new onset cardiogenic shock was more common among patient with STEMI (STEMI: 2.6% versus NSTEMI: 0.8%). When ventricular arrhythmias, new onset atrial fibrillation, urgent revascularization, pulmonary oedema, and acute renal failure were considered in conjunction with death, MI, stroke and bleeding, 65.6%, 79.2% and 93.8% of STEMI, NSTEMI and unstable angina patients, respectively experienced event free survival by the time of discharge.

1.5 Discussion

This study is unique in terms of providing insights into the contemporary management of ACS patients across Australia. By including patients from hospitals, spanning metropolitan, regional, and rural clinical environments, this registry offers the opportunity to explore the application of clinical guideline-recommended therapies and the use of early invasive management for patients across the spectrum of clinical risk, and within diverse clinical settings. Key observations include: a) quantification of the risk profile of patients with ACS in Australian hospitals; b) differential compliance with clinical guideline recommended pharmacotherapies with higher rates of aspirin and statin use, moderate use of clopidogrel, beta-blockers and ACE-inhibition/ARA, and low rates of glycoprotein IIb/IIIa inhibition; and c) suboptimal rates of reperfusion therapy for STEMI, and relatively low rates of early invasive management for high-risk NSTEACS patients.

In this registry, the median age was 65.5 years, with >25% over 75 years of age and one in 20 patients over the age of 85 years. Similarly, moderate renal

impairment (estimated creatinine clearance <60ml/min/1.73m^2) was present at baseline in over a quarter of patients, and 4.4% of patients had severe renal impairment. Almost half the patients reported a prior history of a coronary vascular event. Hence, patients with high-risk features represent a significant burden of clinical care in our local context. Yet, as a result of exclusion criteria exercised in clinical trials, the evidence-base from randomised clinical trial data regarding the optimal management of these patients remains limited, potentially accounting for the lower rates of guideline adherence observed in other similar observational studies with wide ranges of patient risk.[7, 10, 11]

This national "snap-shot" reports rates that are lower than single centre reports.[12] In general, adherence to guidelines remains highest among patients presenting with STEMI, with lesser degrees of adherence among the other groups. Nevertheless, among STEMI patients, the use of reperfusion therapy remains incomplete despite the robust clinical trial evidence supporting its use. The factors contributing to this observation require further clarification. While the use of aspirin is high, initiation of beta-blockade within the first 24 hours is surprisingly low and remains so even by discharge. Rates of glycoprotein IIb/IIIa inhibition are low, but higher when only those undergoing invasive management are considered. Further careful evaluation will be required to determine if these prescribing habits reflect concern regarding the data supporting these agents among ACS patients, or omissions of care. However, it is interesting to contrast glycoprotein IIb/IIIa inhibition use with the uptake of drug eluting stent (DES) implantation, given the more limited nature of the data supporting the effectiveness and cost effectiveness of DES among ACS patients. The nearly 80% clopidogrel use among STEMI patients reflects the high rate of revascularization in this population. In the absence of percutaneous coronary revascularization, prescription of clopidogrel was comparable to the other guideline advocated agents (~45%). In contrast, the use of statin therapy is high across risk groups, reflecting robust but still incomplete uptake of the extensive clinical trial data. These observations suggest substantial scope for locally based quality improvement initiatives, such as those which have been implemented with some success in some states as well as internationally.[13-16]

As with the use of pharmacotherapies, use of angiography and PCI were greatest among patients presenting with suspected STEMI, while only half of the NSTEACS-HR patients underwent invasive management. In contrast to the observations made within recent clinical trials, the rates of PCI and CABG were also low, consistent with other international registries.[17],[6, 18] Clearly, in contra-distinction to clinical trials, where sites are selected for their ability to complete clinical trial protocols, the rates observed in this registry likely reflect not only the decision making processes of the treating teams, but also patient preferences, and access to facilities required to conduct these procedures.[19] Hence, while the lower rates of invasive management are not entirely surprising, the determinants of access to procedures and the relationship between invasive therapy and outcome will be important observations from the 12 month follow-up of these patients.

Nevertheless, in hospital clinical events within this population are low even when these rates are considered by the final discharge diagnosis.[17, 20] These rates are lower than but consistent with events reported in international studies.[20, 21] Factors that may account for these low rates include the assessment of in-hospital events only,as opposed to 30-day events, and under-reporting of non-fatal events due to less vigilant assessment and recording in the clinical record. Specifically, this study required for the presence of objective documentation within the clinical record of all the outcomes reported here. Furthermore, the median GRACE risk scores of the populations would suggest that most patients were of intermediate risk for in hospital mortality. Nevertheless, declining early event rates among patients presenting with ACS have been reported by others internationally.[22] A more robust appraisal of the effectiveness of clinical care provided for ACS in Australia will be offered with the 6 and 12-month follow-up of these patients.

1.6 Conclusion

For clinical guideline-advocated therapies among patients presenting with suspected ACS, an “evidence-practice gap” does appear to exist in Australia, although patient preference and access to facilities able to perform procedures

may influence these observations. The relatively low rates of proven therapies use does not appear to be matched by an increased in-hospital clinical event rate, though late clinical events may present a different picture. Nevertheless, objective evaluation of local clinical practice patterns is a key initial step in developing quality improvement initiatives, and this study provides a basis for ongoing efforts to improve ACS management in Australia.

1.7 Appendix 1

Study Organization

Steering committee: Derek P. Chew: Flinders University/Flinders Medical Centre. **John Amerena**: Geelong Hospital. **David Brieger**: Concord Hospital. **Steve Coverdale**: Nambour Hospital. **Jamie Rankin**: Royal Perth Hospital.

Data management and analysis: Cardiovascular Outcomes Research (COR): Carolyn Astley, Danni Molloy, Sue Mattchoss, Luan Huynh

Sponsor: sanofi-aventis australia pty ltd

Investigators

Dr Tan Ren, Canberra Hospital, ACT; A/Prof David Brieger, Concord Hospital, NSW; A/Prof MA Fitzpatrick, Nepean Hospital, NSW; Prof Peter Fletcher, John Hunter Hospital, NSW; Dr David Rees, St George Hospital, NSW; Dr Craig Juergens, Liverpool Hospital, NSW; Dr Jonathon Waites, Coffs Harbour Hospital, NSW; Dr Greg Nelson, Royal North Shore Hospital, NSW; Dr Michael Sinclair, Dubbo Base Hospital, NSW; Dr John Amarena, Geelong Cardiology Practice, VIC; Prof Yean Lim, Western Hospital, VIC; Dr Mark Horrigan, Austin Health, VIC; Dr Leeanne Grigg, Royal Melbourne Hospital, VIC; Dr David Eccleston, The Northern Hospital Clinical Trials Unit, VIC; Dr Greg Szto, Peninsula Private Hospital, VIC; A/Prof Gishel New, Box Hill Hospital, VIC; Dr Christopher Medley, Wodonga Regional Health Service, VIC; Dr Steven Coverdale, Nambour General Hospital, QLD; Prof Laurie Howes, Gold Coast Hospital, QLD; Dr David Cross, Wesley Hospital, QLD; Dr Paul Garrahy, Princess Alexandra Hospital, QLD; Dr Darren Walters, The Prince Charles Hospital, QLD; Dr Spencer Toombes, Toowoomba Health Services, QLD; Dr Prasad Challa, Cairns Base Hospital, QLD; Dr Kumar Gunawardane, The Townsville Hospital, QLD; Dr William Parsonage, Royal Brisbane Hospital, QLD; Dr Raj Shetty, Rockhampton Hospital; A/Prof Derek Chew, Flinders Medical Centre, SA; Prof Stephen Worthley, Royal Adelaide Hospital, SA; Prof John Horowitz, The Queen Elizabeth Hospital, SA; Dr Samuel Varughese, Mt Gambier Hospital, SA; Dr Christopher Zeitz, Port Augusta Hospital, SA; Dr Margaret Arstall, Lyell McEwin Hospital, SA; Dr Jamie Rankin, Royal Perth Hospital, WA; Dr Barry McKeown, Fremantle Hospital, WA; Dr Johan Janssen, Kalgoorlie Regional Hospital, WA; A/Prof Joseph Hung, Sir Charles Gairdner Hospital, WA; Dr Philip Roberts-Thomson, Royal Hobart Hospital, TAS; Dr Marcus Iton, Darwin Private Hospital, NT; Dr Alex Brown, Menzies School of Health Research, NT.

1.8 References

1. (AIHW) AIoHaW. Heart, stroke and vascular diseases - Australian facts 2004. In: Foundation AaNH, ed. Cardiovascular Disease Series No 22: AIHW Cat. No. CVD 27.; 2004.

2. Guidelines for the management of acute coronary syndromes 2006. Med J Aust 2006;184(8 Suppl):S9-29.

3. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110(9):e82-292.

4. Sonel AF, Good CB, Mulgund J, et al. Racial variations in treatment and outcomes of black and white patients with high-risk non-ST-elevation acute coronary syndromes: insights from CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?). Circulation 2005;111(10):1225-32.

5. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. J Am Coll Cardiol 2005;45(6):832-7.

6. Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Jama 2004;292(17):2096-104.

7. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet 2002;359(9304):373-7.

8. Roe MT, Peterson ED, Newby LK, et al. The influence of risk status on guideline adherence for patients with non-ST-segment elevation acute coronary syndromes. Am Heart J 2006;151(6):1205-13.

9. Chew DP, Allan RM, Aroney CN, Sheerin NJ. National data elements for the clinical management of acute coronary syndromes. Med J Aust 2005;182(9 Suppl):S1-14.

10. Alexander KP, Roe MT, Chen AY, et al. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol 2005;46(8):1479-87.

11. Collinson J, Bakhai A, Flather MD, Fox KA. The management and investigation of elderly patients with acute coronary syndromes without ST elevation: an evidence-

based approach? Results of the Prospective Registry of Acute Ischaemic Syndromes in the United Kingdom (PRAIS-UK).[see comment]. Age & Ageing 2005;34(1):61-6.

12. Tang E, Wong CK, Wilkins G, et al. Use of evidence-based management for acute coronary syndrome. N Z Med J 2005;118(1223):U1678.

13. Scott IA, Eyeson-Annan ML, Huxley SL, West MJ. Optimising care of acute myocardial infarction: results of a regional quality improvement project. J Qual Clin Pract 2000;20(1):12-9.

14. Eagle KA, Gallogly M, Mehta RH, et al. Taking the national guideline for care of acute myocardial infarction to the bedside: developing the guideline applied in practice (GAP) initiative in Southeast Michigan. Jt Comm J Qual Improv 2002;28(1):5-19.

15. Scott IA, Coory MD, Harper CM. The effects of quality improvement interventions on inhospital mortality after acute myocardial infarction. Med J Aust 2001;175(9):465-70.

16. Department of Human Services V. Safer Systems Saving Lives. wwwhealthgovvicau/sssl 2006.

17. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomised trial. Jama 2004;292(1):45-54.

18. Carruthers KF, Dabbous OH, Flather MD, et al. Contemporary management of acute coronary syndromes: does the practice match the evidence? The global registry of acute coronary events (GRACE). Heart 2005;91(3):290-8.

19. Kandzari DE, Roe MT, Chen AY, et al. Influence of clinical trial enrollment on the quality of care and outcomes for patients with non-ST-segment elevation acute coronary syndromes. Am Heart J 2005;149(3):474-81.

20. Mehta RH, Roe MT, Chen AY, et al. Recent trends in the care of patients with non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE initiative. Arch Intern Med 2006;166(18):2027-34.

21. Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes. Variations in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2002;23(15):1177-89.

22. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. J Am Coll Cardiol 2000;36(7):2056-63.

2 INVASIVE MANAGEMENT PROVISION AND LATE CLINICAL OUTCOMES WITHIN CONTEMPORARY AUSTRALIAN ACUTE CORONARY SYNDROME MANAGEMENT: OBSERVATIONS FROM THE ACACIA REGISTRY

2.0 Title Page : Invasive Management Provision and Late Clinical Outcomes within Contemporary Australian Acute Coronary Syndrome Management: Observations from the ACACIA registry

Derek P. Chew [a], John Amerena[b], Steve Coverdale[c], Jamie Rankin [d], Carolyn Astley[a], Ashish Soman[e], David Brieger[f]

Author affiliations

[a]Flinders University/Flinders Medical Centre, [b]Geelong Hospital, [c]Nambour Hospital, [d]Royal Perth Hospital, [e]Sanofi-Aventis Australia, [f]Concord Hospital.

See appendix 1 for investigators

Running Title: ACS management in Australia.

Key Words: Acute coronary syndromes, Invasive Management, Quality of care

Corresponding Author

Derek P. Chew MBBS MPH FRACP

Flinders Medical Centre

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

2.1 Abstract

Objective: To describe the impact of invasive management on 12 month survival among suspected acute coronary syndrome (ACS) patients in Australia.

Design: Prospective nationwide multi-centre registry

Patients: Patients presenting to metropolitan and non-metropolitan hospitals with ST segment elevation MI (STEMI), and high/intermediate risk non-ST-segment elevation ACS (NSTEACS).

Interventions: Data abstraction included hospital characteristics, geographic and demographic factors, clinical risk stratification, and in-hospital management.

Main Outcome Measures: Mortality, MI or recurrent MI, revascularization and stroke at 12 months.

Results: Among 3402 patients originally enrolled, vital status was available in 3393 (99.7%) of patients. Patients from non-metropolitan areas constituted 810 (23.9%) of patients. Invasive management was more commonly undertaken among STEMI patients (STEMI: 89.7% vs. non-STEMI: 70.8% vs. Unstable angina: 44% vs. Stable angina: 35.8%, $p<0.001$). Factors most associated with receipt of invasive services include admission with suspected STEMI or high-risk NSTEACS, male gender and an onsite cardiac surgical service. Overall mortality by 12 months among STEMI, non-STEMI, unstable angina and stable angina patients was 8.0%, 10.5%, 3.3%, and 3.7% ($p<0.001$), respectively. After adjusting for a propensity model predicting early invasive management and other known confounders, early invasive management was associated with a 12-month mortality hazard ratio of 0.53 (95% 0.34-0.84, $p=0.007$).

Conclusions: A substantial burden of late morbidity and mortality persists among acute coronary syndrome patients within contemporary Australian clinical practice. An under-utilization of the invasive management strategy may be associated with an excess in 12-month mortality, suggesting the need for more complete application invasive management among these patients.

2.2 Introduction

Clinical trial evidence supports routine invasive management of acute coronary syndromes (ACS), with coronary angiography and subsequent revascularization when deemed clinically appropriate. These data demonstrate benefits in mortality with primary percutaneous coronary intervention (PCI) for ST elevation MI, and reductions in composite ischemic events among patients receiving successful medical reperfusion, failed medical reperfusion, and those presenting with high-risk ACS without initial ST-segment elevation.[1-3]

However, the provision of routine early angiography and revascularization in ACS management remains challenging. Such an approach requires access to cardiac catheterisation laboratories, the availability of trained staff, and adequately designed clinical networks to cope with the burden of ACS in the community. In Australia, this is made more complex by the issue of distances, requiring greater resource commitments. Local demonstration of the clinical effectiveness of the early invasive strategy for ACS management would assist the justifying broader support for this resource intensive strategy. Therefore, within a prospective national registry of ACS patients, we sought to document the 12-month case fatality rates for various ACS presentations, and explore the relationship between an invasive strategy and late mortality.

2.3 Methods

2.3.1 Patient Population

We conducted the Acute Coronary Syndrome Prospective Audit (ACACIA, protocol number PM_L_0051) between November 2005 and July 2007, involving 39 hospitals across all states and territories of Australia. These sites were selected to be representative of rural (25%) and metropolitan centres (75%), interventional (83%) and non-interventional (17%) centres and 52% of sites reported on-site cardiac surgical services. Each site sought consecutive enrolment of between 100 and 150 patients admitted from the local emergency service for suspected ACS (median: 99, range:75). ACS presentations considered secondary to major trauma or surgery were excluded. Patients transferred into study centres were excluded if a substantial proportion of their initial management was undertaken at a non-study centre (transfer>12 hours after initial presentation). Ethics committee approval was provided at each site. Informed consent was obtained from all patients except for those patients who died before

consent was sought and access to these medical records were granted by the local ethics committees.

2.3.2 Definition of ACS

Patients presenting with suspected ST elevation myocardial infarction (STEMI), high and intermediate risk non ST segment ACS (NSTEACS) as defined by the National Health Data Dictionary risk classification were eligible for enrolment, details of which have been described elsewhere.[4-6] Allocation to each risk stratum was centrally adjudicated to ensure consistency of enrolment criteria. The primary discharge diagnosis was site investigator determined, but confirmed by a central query process. Allocation to "non-cardiac chest pain" was made when ACS was excluded but no specific alternative diagnosis was made, while allocation to "other" diagnoses was undertaken when an alternative diagnosis was provided. Analyses in this study reflect the discharge diagnosis.

2.3.3 Clinical Factors and Invasive Management

Data pertaining to demographic, clinical, procedural, temporal and logistical parameters involved in the management of ACS patients were obtained. These variables focused on hospital characteristics, clinical risk factors, the time to various aspects of medical care, and the distance travelled for patients transferred for invasive procedures. The use of various medications including anti-thrombotics, statin therapy, angiotensin converting enzyme (ACE)-inhibition/ angiotensin receptor (AR)-antagonists, and beta-blockers in-hospital, at discharge, at 6 months and 12 months were also assessed.

Early invasive management was defined as patients undergoing angiography at any time within the acute hospital stay, regardless of transfer between acute care hospitals. Patients discharged home or to chronic care facilities and subsequently receiving outpatient angiography were not considered to have received an early invasive management strategy. The use and timing of PCI, and coronary artery bypass grafting (CABG) were also recorded. All data was abstracted by trained clinical trial co-ordinators.

Standard definitions consistent with the National Health Data Dictionary were used for in hospital events.[5] Specifically, MI required a rise in biomarkers, greater than the local threshold definition for troponin and/or more than twice the upper limit of normal for CK-MB (in the absence of CK-MB, CK was used). Recurrent MI required a further >25% rise in troponin or >50% rise in CK-MB, > 24 hours after admission. Following PCI and

CABG, a level of CK-MB >3 times and >5 times-the upper limit of normal within 48 hours of the procedure or new Q-waves was required, respectively. Stroke was investigator-determined with cerebral imaging reports sought where possible.

All-cause mortality was sought during the index hospitalisation, at 6 months, and 12 months. Among patients reported as lost to follow-up by the investigating site, a query to the Australian Institute of Health and Welfare National Death Register was undertaken to confirm vital status and cause of death. Late non-fatal recurrent acute coronary events, stroke and coronary revascularization relied on documentation by hospital discharge summaries and diagnosis-related group (DRG) coding reports.

2.3.4 Statistical analysis

Demographic, clinical, procedural factors and late outcomes are presented stratified by discharge diagnosis, focusing on patients with a "coronary" diagnosis (STEMI, non-STEMI, unstable angina and stable angina). Normally distributed variables are expressed as means (± standard deviation) and non-Gaussian factors are reported as medians (and inter-quartile ranges). Counts are presented as "n" (%). Chi-square tests were used for comparisons of binary outcomes between groups. Kaplan-Meier survival curves stratified by discharge diagnosis are plotted and compared by log-rank test. Assessment of late compliance was confined to patients without stated contra-indications who survived to 12-month . To evaluate the impact of invasive management on 12-month mortality, a propensity analysis was conducted.[7] A non-parsimonious logistic regression model describing the propensity for inpatient invasive management was developed including patient characteristics, past history and co-morbidities as well as the physician and hospital characteristics of each patient's initial presentation. Interactions between these variables were also explored. Patients undergoing PCI or CABG without prior angiography due to known anatomy were excluded (n=29). This model demonstrated a high predictive capacity with a C-index of 0.853 (Hosmer-Lemeshow goodness-of-fit test p=0.487) Among ACS patients surviving to hospital discharge, the association between inpatient angiography and 12-month mortality was then assessed through Cox proportional hazards modelling adjusting for key clinical covariates (GRACE risk score, age, killip class, renal function, diabetes, prior MI, prior cardiac failure, prior CABG, statin therapy, ACE-inhibition, stratified by admission diagnosis), and the propensity score as a continuous variable, with and without the inclusion of inpatient revascularization. The proportional hazards assumption was assessed for each covariate. The effect of GRACE score varied with time and was

therefore was entered in to the model as a time-varying covariate. A probability of <0.05 is considered statistically significant. All analyses were performed using STATA 9.1 (College Station, TX).

2.4 Results

Among the 3402 patients enrolled, 12-month vital status was confirmed in 3393 (99.7%) patients. Of the 9 patients without follow-up, consent was withdrawn in 5 patients and no follow-up was available in 4 patients. Seven hundred and fifty-five (22.3%) were admitted with suspected STEMI, while 1942 (57.2%) and 696 (20.4%) were considered high-risk NSTEACS patients and intermediate-risk patients respectively. Almost a quarter (810, 23.9%) of patients were enrolled from non-metropolitan centres and 119 (3.5%) of patients were indigenous. The median age was 65.5 (55.3-75.1) years, while 1202 (35.4%) and 886 (26.1%) were women and diabetic, respectively. An estimated creatinine clearance of <60ml/min/1.73m^2 was observed in 923 (27.3%) of the patients. A history of coronary artery disease was reported in 1673 (49.3 %) patients, while prior CABG and PCI was recorded in 492 (14.5%) and 606 (17.9%) patients, respectively. By discharge, 716 (21.1%), 1025 (30.2%), 812 (23.9%) and 137 (4.0%) patients were diagnosed with STEMI, non-STEMI, unstable angina and stable angina, respectively, while 528 (15.6%) and 175 (5.2%) patients were discharged under the diagnosis of non-cardiac chest pain and “other” diagnoses. (Table 1) The transition from the initial working diagnosis to final diagnosis is presented in figure 1.

Figure 1: Transition of patients from admission (working) diagnosis to final diagnosis

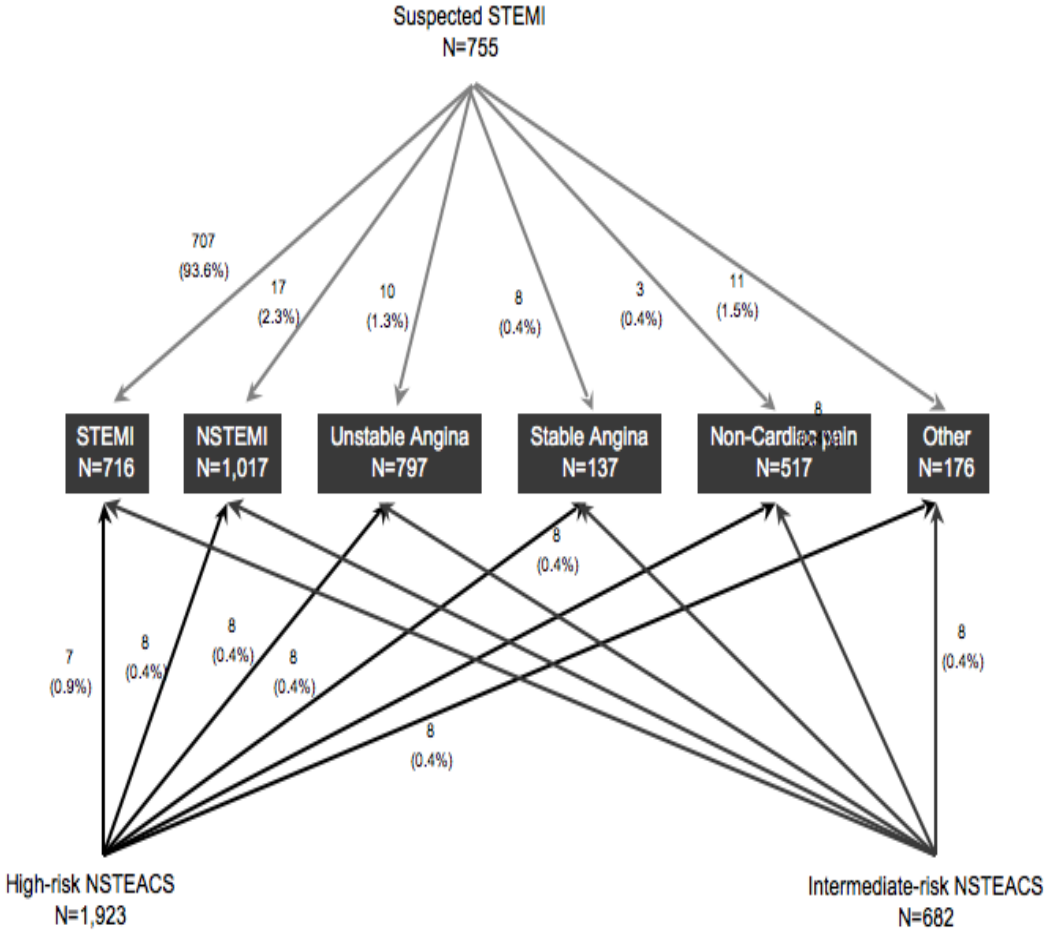


Table 1: Patient characteristics by discharge diagnosis

	STEMI (n=716)	***NSTEMI (n=1,025)***	***Unstable Angina (n=812)***	***Stable Angina (n=137)***	***Non Cardiac Chest Pain (n=528)***	***Other (n=175)***
Age (yrs, mean ±SD)	62.1 (19.9)	68.43(20.2)	68.1 (18.1)	65.1 (18.7)	60.0 (22.0)	69.1 (18.8)
Female Gender (n, %)	181 (25.3)	333 (32.5)	289 (35.6)	65 (47.5)	251 (47.5)	83 (47.4)
Diabetes (n, %)	134 (18.7)	289 (28.2)	260 (32.0)	40 (29.2)	110 (20.3)	53 (30.3)
Hypertension (n, %)	358 (50.0)	673 (65.7)	600 (73.9)	103 (75.2)	313 (59.3)	118 (67.4)
Dyslipidaemia (n, %)	326 (45.5)	595 (58.5)	627 (77.2)	90 (65.7)	299 (56.6)	95 (54.3)
Current Smoking (n, %)	237 (33.1)	234 (22.8)	130 (16.0)	31 (22.6)	109 (20.6)	32 (18.3)
Family History of CAD (n, %)	233 (32.5)	331 (32.3)	237 (29.2)	39 (28.5)	151 (28.6)	43 (24.6)
Prior MI (n, %)	97 (13.6)	288 (28.1)	343 (42.2)	43 (31.4)	102 (19.3)	51 (29.1)

Prior PCI (n, %)	75 (10.5)	144 (14.1)	259 (31.9)	31 (22.6)	74 (14.0)	23 (13.1)
Prior CABG (n, %)	22 (3.1)	160 (15.6)	220 (24.9)	22 (16.1)	55 (10.4)	31 (17.7)
Prior Stroke (n, %)	23 (3.3)	75 (3.3)	70 (8.6)	16 (11.7)	24 (4.6)	19 (10.9)
Known PAD (n, %)	24 (3.4)	83 (8.1)	55 (6.8)	6 (4.4)	16 (3.0)	10 (5.7)
Prior Atrial fibrillation (n, %)	35 (10.4)	125 (12.2)	144 (14.0)	12 (8.8)	55 (10.4)	46 (26.3)
Creat. Cl.ml/min (median, 25th-75th percentile)	74.5 (60.3-89.0)	70.8 (53.4-88.2)	74.7 (57.5-87.6)	72.9 (57.2-89.6)	78.8 (65.4-94.3)	68.4 (50.7-84.9)
White cell count (mean, SD)	10.8 (4.6)	8.7 (3.8)	7.7 (3.0)	7.7 (2.8)	7.6 (3.0)	9.4 (3.9)
GRACE Score (median, 25th-75th percentile)	144 (123-168)	135 (106-165)	112 (92-134)	107 (90-131)	95.5 (78-119)	131 (101-160)

STEMI= ST segment elevation MI, NSTEMI= Non ST segment elevation MI

2.4.1 Use of invasive management and other therapies

Invasive management including subsequent coronary revascularization during the index hospitalisation was more common among patients discharged with STEMI compared to other patients. The use of guideline-recommended therapies was also more frequent among these patients. (Table 2) Revascularization after the index admission was observed in 322 (9.5%) patients, at a median time of 63 (i.q.r. 26-137) days. Over 12-months, a loss of compliance was evident with all of the therapies, except for inhibitors of the renin-angiotensin system. This decline was most prominent with clopidogrel. (Figure 2)

2.4.2 Determinants of In-hospital Invasive Management

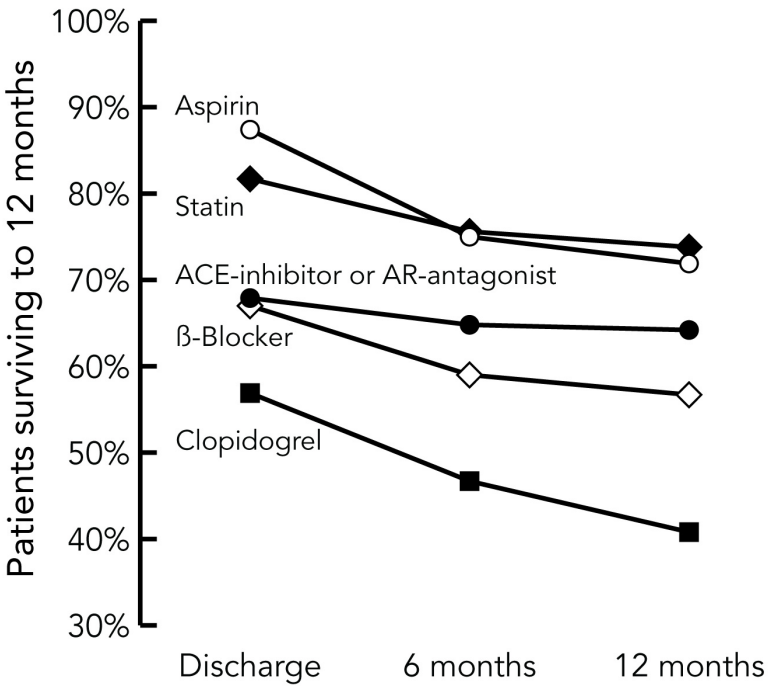
The clinical and demographic factors most strongly associated with receiving invasive management during the index hospitalisation were an onsite cardiac surgical service, presentation with suspected STEMI. Clinical factors associated with conservative management included diabetes, reduced renal function, prior MI, prior CABG, prior heart failure and a known history of congestive cardiac failure. For each decade above the median age, patients were 38.7% less likely to receive invasive management within the index hospitalisation. Patients enrolled at a non-metropolitan centres were less likely to receive invasive management (Table 3)

Table 2: Administration of clinical guideline medications, angiography and revascularisation among patients discharged with a "coronary diagnosis"

	STEMI (n=716)	*NSTEMI (n=1,025)*	*Unstable Angina (n=812)*	*Stable Angina (n=137)*	*P value*
Aspirin (n, %)	648 (90.5)	906 (88.4)	683 (84.1)	111 (81.0)	<0.001
Clopidogrel (n, %)	571 (79.8)	644 (62.8)	408 (50.3)	62 (45.3)	<0.001
Beta-blockers(n, %)	563 (78.6)	741 (72.3)	549 (67.6)	86 (62.8)	<0.001
ACE-inhibition or AR-antagonist (n, %)	571 (79.8)	722 (70.4)	523 (64.4)	93 (67.8)	<0.001
Statin (n, %)	639 (89.3)	876 (85.5)	676 (83.3)	103 (75.2)	<0.001
Angiogram (n, %)	642 (89.7)	726 (70.8)	36 (44.8)	49 (35.8)	<0.001
PCI (n, %)	509 (71.1)	349 (34.1)	116 (14.3)	12 (8.8)	<0.001
***Stent (n, %)**	484 (95.1)	340 (97.4)	114 (98.3)	12 (100.0)	0.163
CABG (n, %)	45 (6.3)	101 (9.9)	54 (6.7)	2 (1.5)	<0.001

* Received at least one stent among patients undergoing PCI during the index hospitalisationSTEMI= ST segment elevation MI, NSTEMI= Non ST segment elevation MI

Figure 2: Change in compliance with guideline advocated medications among survivors to 12 months



2.4.3 Long-term outcomes

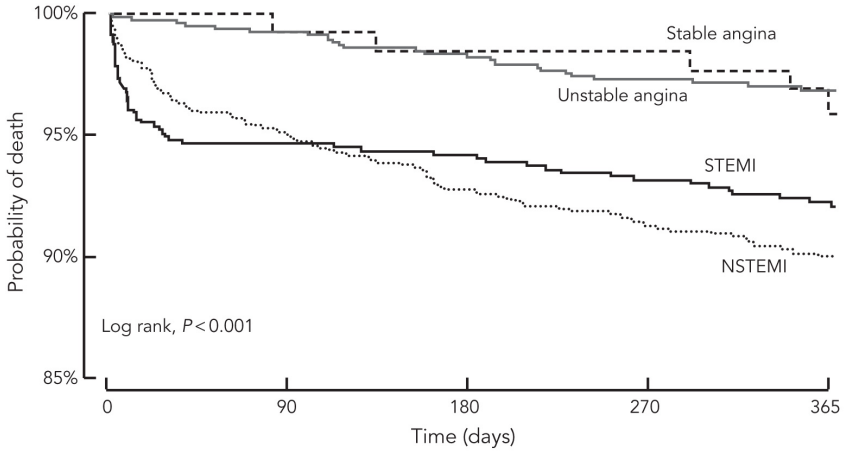
Twelve-month survival by discharge diagnosis is presented in figure 3. Mortality rates among patients with MI were similar, regardless of ST segment changes at the time of presentation. (STEMI 57/716 (8.0%) vs. non-STEMI 108/1025 (10.5%) vs. unstable angina: 27/812 (3.3%) vs. stable angina: 5/137 (3.7%) p<0.001). (STEMI vs. non-STEMI: p=0.071) Recurrent MI, and late coronary revascularization were more common in the high-risk cohort. Among patients discharged with “non-cardiac chest pain” and other diagnoses, mortality by 12 months was observed in 12 (2.3%) and 9 (5.2%) of patients.

2.4.4 Invasive management and 12-month mortality

Patients receiving invasive management during the index hospitalisation experienced a lower rate of late mortality compared with patients treated conservatively (invasive: 3.7% vs. conservative: 10.1%, p<0.001). This relationship persisted even when the

analysis was restricted to patients discharged alive with a “coronary diagnosis” (STEMI, non-STEMI, unstable angina and stable angina). (Hazard ratio 0.25, 95% C.I. 0.17-0.36, p<0.001) However, invasive management was correlated with lower risk and more prescription of guideline therapies. (table 5) After adjustment for the propensity score and other important confounders, invasive management was associated with a hazard ratio for 12-month mortality of 0.53 (95% 0.34-0.84, p=0.007). (Figure 4) This benefit was driven by revascularization. When the performance of either PCI or CABG during the index hospitalisation was adjusted for, angiography alone was no longer significantly associated with survival (HR; 0.84, 95% C.I 0.53-1.32, p=0.477) while the hazard ratio for revascularization was 0.30 (95% C.I 0.16-0.56, p<0.001).

Figure 3: Kaplan-Meier survival among patients discharged with a coronary diagnosis



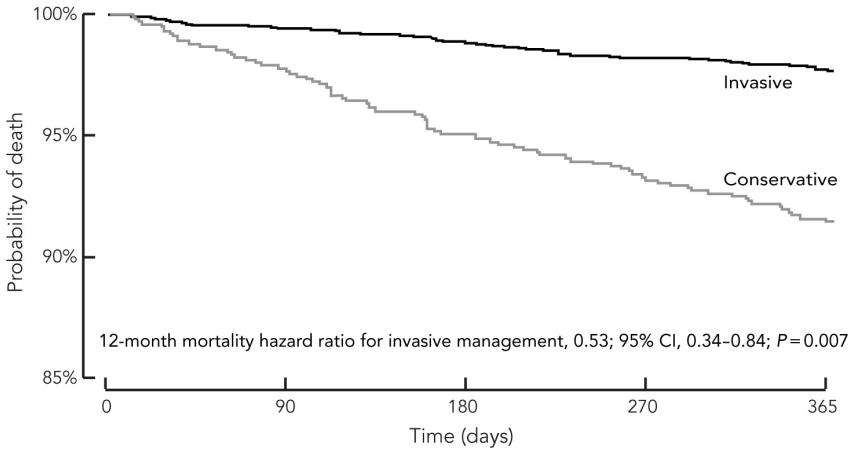
	Patients surviving				
Time (days)	0	90	180	270	365
STEMI	716	678	675	666	571
NSTEMI	1026	975	951	930	748
Unstable angina	811	804	794	785	654
Stable angina	137	136	135	135	105

Table 3: Likelihood for receiving invasive management during acute hospital admission period

	Odds ratio	*95% C.I.*	*P value*
eGFR<30ml/min/1.73m^2	0.35	0.21-0.60	<0.001
Prior CCF	0.39	0.28-0.56	<0.001
Non-metropolitan hospital	0.47	0.35-0.62	0.044
Prior CABG	0.48	0.36-0.62	<0.001
History of Diabetes	0.60	0.49-0.75	<0.001
History of COAD	0.69	0.50-0.94	0.022
History of CAD	0.71	0.55-0.94	0.019
History of Atrial fibrillation	0.75	0.56-1.0	0.049
Prior MI	0.77	0.61-0.98	0.034
GRACE Score >200 vs.<100	0.94	0.44-2.04	0.881
Age in years	0.97	0.96-0.98	<0.001
Male gender	1.47	1.22-1.79	<0.001
GRACE Score 101-150 vs. <100	1.77	1.35-2.33	<0.001
GRACE Score 151-200 vs.<100	1.96	1.28-2.99	0.002
Onsite Cardiac Surgical Service	4.13	2.29-7.45	<0.001
Admission with High-risk NSTEACS	5.10	2.84-9.13	<0.001
Admission with suspected STEMI	6.31	3.01-13.30	<0.001

C-Index: 0.853

Figure 4: Kaplan Meier survival by in-hospital invasive management among survivors to hospital discharge



	Patients surviving				
Time (days)	0	90	180	270	365
Invasive	1760	1747	1735	1716	1437
Conservative	867	846	820	800	641

Table 4: Clinical outcomes from enrolment to 12 months among patients discharged with a "coronary diagnosis"

	STEMI (n=716)	***NSTEMI (n=1,025)***	***Unstable Angina (n=812)***	***Stable Angina (n=137)***	***p-value***
Death (n,%)	57 (8.0)	108 (10.5)	27 (3.3)	5 (3.7)	<0.001
Re/myocardial Infarction (n, %)	59 (8.2)	127 (12.4)	28 (3.5)	3 (2.2)	<0.001
Stroke (n, %)	5 (0.7)	6 (0.6)	3 (0.4)	1 (0.7)	0.835
Revascularization* (n, %)	112 (15.6)	133 (13.0)	72 (8.9)	11 (8.0)	<0.001

* Revascularization (PCI or CABG) conducted after index hospitalization. STEMI= ST segment elevation MI, NSTEMI= Non ST segment elevation MI

Table 5: Baseline risk, medication prescription and persistence at 6 months between invasive and conservative groups among patients with a coronary diagnosis

	Conservative (n=882)	*Invasive (n=1785)*	*p-value*
GRACE Score (median, iqr)	134 (105-167)	126 (103-151)	0.0001
Medications at discharge			
Aspirin (n, %)	730 (82.8)	1677 (94.0)	<0.001
Clopidogrel (n, %)	405 (45.9)	1315 (73.7)	<0.001
Beta-blockers (n, %)	565 (64.1)	1358 (76.1)	<0.001
ACE-inhibit. or AR-antag. (n, %)	547 (62.0)	1356 (76.0)	<0.001
Statin (n, %)	657 (74.5)	1618 (90.6)	<0.001
Medication persistence 6 mths*	(n=818)	(n=1741)	
Aspirin (n, %)	579 (70.9)	1490 (85.6)	<0.001
Clopidogrel (n, %)	322 (39.4)	1062 (61.0)	<0.001
Beta-blockers (n, %)	489 (59.8)	1177 (67.6)	<0.001
ACE-inhibit. or AR-antag. (n, %)	500 (61.1)	1280 (73.5)	<0.001
Statin (n, %)	573 (70.1)	1503 (86.3)	<0.001

* Rates reported among survivors to 6 months

2.5 Discussion

This study represents the largest registry of ACS ever to be exclusively conducted throughout Australia. This study not only provides a unique perspective on the clinical characteristics, management and late clinical outcomes of Australian patients, but it also provides the opportunity to explore the clinical and geographic factors associated with the provision of care, in particular invasive management. Within this registry we observed: a) a late mortality rate among patients presenting with myocardial infarction of ~9 % regardless of ST segment status at the time of presentation; b) a persistent burden of recurrent MI and late revascularization; c) an incomplete provision of evidence-based therapies; and d) a relative mortality advantage associated with the provision of invasive management among ACS patients.

Within the era of evidence-based medicine, early mortality rates among ACS patients have declined.[8] However, in-hospital mortality rates are a poor reflection of the late mortality experienced by these patients. Within this broad cohort drawn from all states and territories, 1 in 11 patients discharged with the diagnosis of myocardial infarction had died by 12 months. We observed little difference in late mortality rate among patients presenting with or without ST segment elevation, as seen with other international registries.[9] In addition, these patients continued to experience a substantial burden of non-fatal recurrent ischemic events, in particular a high rate of late revascularization. Whether these clinical events represent recurrent ischemia in the context of an initial conservative strategy or planned delayed invasive management is uncertain.

Despite the substantial clinical trial evidence supporting early invasive management for high-risk ACS patients, application of these data within the local context appears incomplete. In contrast with patients discharged with the diagnosis of STEMI where 90% of patients had an assessment of their coronary vasculature, only 71% and 45% of patients discharged with non-STEMI and unstable angina, respectively, underwent assessment of their coronary vasculature before discharge. As seen in other studies, factors such as age, gender, and renal function influence this clinical decision.[10, 11] Furthermore, as expected given the national distribution of health services, we observed an influence of onsite clinical services, and rural versus metropolitan hospital location on the provision of invasive management.

Consistent with trial evidence, but of greater magnitude, was the relationship between undergoing early invasive management and mortality, even after adjustment for other

factors known to influence late outcome. These data reinforce the importance of invasive services delivery to all patients presenting with high-risk ACS. Furthermore, objective assessment of the proportion of patients undergoing invasive management represents a valuable measure for assessing quality of care and the effectiveness of regional health care systems.

However, the discordance between clinical trials and registries with regard to the mortality-benefit with invasive management requires careful consideration.[12] The "correlation" between the provision of other guideline therapies and invasive management among lower risk patients is an important observation.[13] On average, patients undergoing invasive management in this study received a better "total package" of care. While the "propensity" model for angiography demonstrated high discriminatory capacity (c-index-0.85), a benefit persisted even after adjusting for this factor and other known predictors of late mortality such as receipt of other guideline therapies. These analyses should not be interpreted as diminishing the importance of such therapies. Clearly, the most obvious possible explanation is the presence of unmeasured, but clinically appreciated, factors that influence the decision not to undertake early angiography, and these factors are very powerful in their effect on late mortality. Furthermore, these unmeasured factors need to be very prevalent, and more common among patients presenting with non-STEMI and unstable angina than STEMI patients. An alternative explanation is also plausible and likely to be working in concert with the incomplete adjustment mentioned above. Analyses of registry data have documented the "lower-risk" and "better-treated" nature of patients randomised in clinical trials.[14, 15] In this context, any therapy is likely to demonstrate a more modest relative benefit. When extending treatment strategies to higher-risk populations beyond those studied in clinical trials, a greater impact may be expected, hence widening the observed treatment effect. Therefore, while adjustment for physician selection is likely to be incomplete, even after propensity adjustment, a proportion of the late mortality observed in this registry is likely to be preventable by more complete application of the early invasive approach to ACS management in Australia.

2.6 Conclusions

A substantial burden of late morbidity and mortality persists among ACS patients managed in contemporary Australian clinical practice. The under-utilization of the invasive management strategy appears to be associated with an excess in mortality at 12-months. These data call for more complete application invasive management

among these patients, offering a performance measure for the objective assessment of the quality of acute coronary syndrome care.

2.7 References

1. Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomised clinical trials. *J Am Coll Cardiol.* Oct 3 2006;48(7):1319-1325.

2. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet.* Feb 18 2006;367(9510):579-588.

3. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomised trials. *J Am Coll Cardiol.* Jan 30 2007;49(4):422-430.

4. Guidelines for the management of acute coronary syndromes 2006. *Med J Aust.* Apr 17 2006;184(8 Suppl):S9-29.

5. Chew DP, Allan RM, Aroney CN, et al. National data elements for the clinical management of acute coronary syndromes. *Med J Aust.* May 2 2005;182(9 Suppl):S1-14.

6. Chew DP, Amerena J, Coverdale S, et al. Current management of acute coronary syndromes in Australia: observations from the acute coronary syndromes prospective audit. *Intern Med J.* Jul 23 2007.

7. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomised control group. *Stat Med.* Oct 15 1998;17(19):2265-2281.

8. Fox KA, Steg PG, Eagle KA, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *Jama.* May 2 2007;297(17):1892-1900.

9. Montalescot G, Dallongeville J, Van Belle E, et al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J.* Jun 2007;28(12):1409-1417.

10. Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Jama.* Nov 3 2004;292(17):2096-2104.

11. Roe MT, Peterson ED, Newby LK, et al. The influence of risk status on guideline adherence for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J.* Jun 2006;151(6):1205-1213.

12. Yan AT, Yan RT, Tan M, et al. In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. *Am J Cardiol.* Oct 1 2005;96(7):913-916.

13. Scott IA, Derhy PH, O'Kane D, et al. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. *Med J Aust.* Aug 6 2007;187(3):153-159.

14. Steg PG, Lopez-Sendon J, Lopez de Sa E, et al. External validity of clinical trials in acute myocardial infarction. *Arch Intern Med.* Jan 8 2007;167(1):68-73.

15. Kandzari DE, Roe MT, Chen AY, et al. Influence of clinical trial enrollment on the quality of care and outcomes for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J.* Mar 2005;149(3):474-481.

2.8 Appendix 1

Study Organization

Steering committee: Derek P. Chew: Flinders University/Flinders Medical Centre. **John Amerena**: Geelong Hospital. **David Brieger**: Concord Hospital. **Steve Coverdale**: Nambour Hospital. **Jamie Rankin**: Royal Perth Hospital.

Data management and analysis: Cardiovascular Outcomes Research (COR): Carolyn Astley, Danni Molloy, Sue Mattchoss, Luan Huynh

Sponsor: sanofi-aventis australia pty ltd

Investigators

Dr Tan Ren, Canberra Hospital, ACT; A/Prof David Brieger, Concord Hospital, NSW; A/Prof MA Fitzpatrick, Nepean Hospital, NSW; Prof Peter Fletcher, John Hunter Hospital, NSW; Dr David Rees, St George Hospital, NSW; Dr Craig Juergens, Liverpool Hospital, NSW; Dr Jonathon Waites, Coffs Harbour Hospital, NSW; Dr Greg Nelson, Royal North Shore Hospital, NSW; Dr Michael Sinclair, Dubbo Base Hospital, NSW; Dr John Amarena, Geelong Cardiology Practice, VIC; Prof Yean Lim, Western Hospital, VIC; Dr Mark Horrigan, Austin Health, VIC; Dr Leeanne Grigg, Royal Melbourne Hospital, VIC; Dr David Eccleston, The Northern Hospital Clinical Trials Unit, VIC; Dr Greg Szto, Peninsula Private Hospital, VIC; A/Prof Gishel New, Box Hill Hospital, VIC; Dr Christopher Medley, Wodonga Regional Health Service, VIC; Dr Steven Coverdale, Nambour General Hospital, QLD; Prof Laurie Howes, Gold Coast Hospital, QLD; Dr David Cross, Wesley Hospital, QLD; Dr Paul Garrahy, Princess Alexandra Hospital, QLD; Dr Darren Walters, The Prince Charles Hospital, QLD; Dr Spencer Toombes, Toowoomba Health Services, QLD; Dr Prasad Challa, Cairns Base Hospital, QLD; Dr Kumar Gunawardane, The Townsville Hospital, QLD; Dr William Parsonage, Royal Brisbane Hospital, QLD; Dr Raj Shetty, Rockhampton Hospital; Prof Derek Chew, Flinders Medical Centre, SA; Prof Stephen Worthley, Royal Adelaide Hospital, SA; Prof John Horowitz, The Queen Elizabeth Hospital, SA; Dr Samuel Varughese, Mt Gambier Hospital, SA; Dr Christopher Zeitz, Port Augusta Hospital, SA; Dr Margaret Arstall, Lyell McEwin Hospital, SA; Dr Jamie Rankin, Royal Perth Hospital, WA; Dr Barry McKeown, Fremantle Hospital, WA; Dr Johan Janssen, Kalgoorlie Regional Hospital, WA; A/Prof Joseph Hung, Sir Charles Gairdner Hospital, WA; Dr Philip Roberts-Thomson, Royal Hobart Hospital, TAS; Dr Marcus Iton, Darwin Private Hospital, NT; Dr Alex Brown, Menzies School of Health Research, NT.

3 ACUTE CORONARY SYNDROME CARE ACROSS AUSTRALIA AND NEW ZEALAND: THE SNAPSHOT ACS STUDY

3.0 Title page : Acute Coronary Syndrome Care Across Australia And New Zealand: The SNAPSHOT ACS Study

Authors: The SNAPSHOT ACS investigators

Running Title: A Snapshot of ACS care in Australia and New Zealand

Key Words: Acute coronary syndromes, Quality of care, Clinical Guidelines, Health Services

Corresponding Author

Derek P. Chew MBBS MPH FRACP

Flinders Medical Centre

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

3.1 Abstract

Objective: Strengthening the application of guideline recommended therapy for suspected acute coronary syndrome (ACS) is a major health priority in Australia and New Zealand. SNAPSHOT ACS was designed to characterise and follow-up management according to published guidelines bi-nationally.

Design, setting and subjects: All persons hospitalised with suspected ACS between 14-27th May 2012 were enrolled. Participating sites were identified through public records and Health Networks. Descriptive and logistic regression analysis was performed.

Main Outcome Measures: Rates of guideline-advocated investigations, therapies, and in-hospital death, new/recurrent myocardial infarction (MI), stroke, cardiac arrest and worsening heart failure.

Results: 285/478 sites provided details on 4,398 patients whose mean age 67 (standard deviation (SD) 15) years, 40% women and median GRACE score of 119 (IQR: 96-144). Most presentations were to major city hospitals (73%). MI was diagnosed in 33%, unstable angina in 21%, unlikely ischaemic in 27%, and other 19%. Of 1436 with MI; 71% with MI received angiography, 42% angioplasty and 8% CABG. Invasive management was less likely with increasing patient risk. (GRACE score <100: 90.1% vs. 101-150: 81.3% vs. 151-200: 49.4% vs. >200: 36.1%, p<0.0001). In-hospital mortality was 4.5% and re-MI 5.0%. After adjustment for patient risk, significant variation in care and outcome was evident at hospital classification and jurisdictional levels.

Conclusion: This first comprehensive combined Australia and New Zealand audit of ACS care identifies variations in the application of the ACS evidence-base while documenting varying rates of in-hospital clinical outcomes. A focus on integrated clinical service delivery may provide greater evidence translation to improve ACS outcomes in Australia and New Zealand.

3.2 Introduction

Despite well-developed guidelines for the management of Acute Coronary Syndromes, local registries demonstrate incomplete implementation of evidence-based recommendations within Australia and New Zealand (ANZ). Variations in care appear to correlate with differences in clinical outcomes. [1] [2-6] [7-10] Geographic challenges, patient characteristics including cultural diversity, health workforce and health policy environment represent likely factors impacting on the optimal translation of this evidence-base into timely, effective and risk-appropriate ACS care. [11,12]

Earlier audits of ACS hospitalisation in New Zealand have been critical in defining treatment and resource gaps evident in local practice.[9,13] Within Australia, registries have included relatively few patients from regional and remote centres.[7]

An association between health service design and workforce provision, and clinical outcomes has been observed locally.[14] Hence, gaining a bi-national, multi-health service perspective of current ACS management represents an essential step in health services re-design. The SNAPSHOT ACS study sought to inform these efforts by documenting care and outcome among suspected ACS patients through a comprehensive audit encompassing all hospitals and jurisdictions.

3.3 Methods

3.3.1 Study Design and Organization

The SNAPSHOT ACS study was a prospective audit of care provided to consecutive patients admitted with suspected ACS within a 2-week period across ANZ. This study was designed by an bi-national academic network of clinicians and researchers and developed as a collaborative quality initiative between the Cardiac Society of Australia and New Zealand (CSANZ), the Heart Foundation of Australia (HFA), the Australian Commission for Safety and Quality in Health Care (ACSQHC), The George Institute for Global Health, and

Health networks or State governments of NSW, QLD, Victoria, SA, and WA. (Appendix 1). The national organizations provided endorsement, in-kind resources and seed funding for central study management. State governments and Networks provided study coordinators to engage facilities, educate staff and assist with gaining ethics committee approval and data collection. The George Institute built the online database and co-ordinated data-management. All hospitals receiving patients with suspected ACS, public or private, metropolitan or rural, were identified and approached about participation. Although sites were trained and supported with data entry, each hospital's participation was discretionary and resourced locally. Written study protocols were provided to all participating sites and State-based education forums held to standardise recruitment and data collection. Results were fed back to each site, benchmarked against the State/Territory and national aggregate at the end of the audit.

The study was designed and managed by a steering committee with key stake-holder representation. Approval for the "opt-out" consent was sought at all sites, except NZ where expedited review by the National Multicentre Ethics committee agreed that this was an audit of health service delivery and a consent waiver applied. In participating Australian centres, ethics approval for the opt-out consent was granted in all but (2) sites in Victoria where an "opt-in" consent process was implemented. In Australia, a consent waiver was applied to all in-hospital ACS deaths.

3.3.2 Patient eligibility and classification

Patients were eligible if they were admitted for a suspected or confirmed ACS between May 14th 00:00 hours and May 27th 24:00 hours, 2012. Consecutive first admissions within the audit window were included. Patients were tracked for the duration of the acute care episode including all transfers between hospitals. Registrants were classified by primary discharge diagnosis into the following groups: "STEMI/Left bundle branch block (LBBB)" required ST elevation or LBBB on an electrocardiogram (ECG) at any time during the admission, with elevation of cardiac biomarkers except where they had died prior to biomarkers being drawn; "NSTEMI" required evidence of biomarker

elevation with or without ECG changes consistent with ischaemia, “Unstable angina”, and “chest-pain likely ischaemic” were entered separately but were condensed for these analyses: “Chest pain unlikely ischaemic” was extracted from the medical record reflecting local clinician determination. Where the diagnosis remained uncertain in the absence of definitive ECG changes and/or biomarker elevation, but where the patient received in-hospital coronary revascularization (either PCI or CABG), the classification of “chest-pain likely ischaemic” was applied. Where a clear alternative primary diagnosis emerged, or when evidence of myonecrosis was considered secondary to another disease process (e.g. pulmonary embolus) patients were grouped as “other diagnoses.”

3.3.3 Patient risk, in-hospital care and outcome

Using a common case record form with standardised completion note, data collection focused on presenting characteristics, including clinical variables enabling the calculation of the GRACE risk score, as well as the logistical details of patient presentation and transfers between hospitals.[15] Care provided across all institutions involved in the acute care was documented, focusing on published guidelines and in-hospital events. In addition, each participating hospital was asked to complete a single survey describing local resources including cardiac investigation and management capabilities and workforce characteristics).

In-hospital mortality was inclusive of any cause mortality. New or recurrent MI (re-MI) in-hospital was defined as recurrent chest pain lasting ≥30 minutes and ≥2 mm of ST elevation within 18 hours of presentation, the development of a new LBBB pattern or new Q waves or the following biomarker patterns; a CK rise to >2 x Upper Reference Limit (URL) and >50% above previous baseline value; or CK-MB >50% above prior level or troponin level >20% above previous baseline. MI following PCI was defined as a CK/CK-MB/ troponin rise to >3x URL if not previously elevated or >50% and >20% rise above previous value for CK-MB and troponin, respectively, if previously elevated. Following CABG, new

MI required a rise of CK or CK-MB >10x and 5x the URL, respectively, if not previously elevated and a >50% rise above previous value if elevated, or a 10-fold elevation in troponin levels. Major bleeding was defined as an event requiring a blood transfusion or a fall in haemoglobin of > 4g/dL. Stroke was defined as a new neurological event involving single vascular territory, confirmed with neurological imaging. Cardiac arrest was defined as the sudden loss of cardiac function with loss of consciousness and spontaneous breathing. Worsening heart failure was defined as deterioration in Killip classification of one or more grade at any time during hospitalization. In-hospital major adverse cardiac events (MACE) included the occurrence of any one of the abovementioned events. Clinical event reporting relied on local documentation using a standardised completion note. Formal adjudication of events was not possible, however, an audit of 2-5% of all case record forms for data accuracy and quality was performed during and in the weeks following enrolment by coordinators across all jurisdictions.

3.3.4 Statistical analysis

Patient demographics and characteristics, rates of inter-hospital transfer, investigations and invasive procedures, and the provision of guideline recommended therapies among patients surviving to hospital discharge; and rates of in-hospital events are described by using standard descriptive statistics stratified by diagnosis, Australian Institute of Health and Welfare (AIHW) hospital classification and health jurisdictions (Australian States or territories and NZ).[4,5] When implementing the hospital classification, the two tiers of medium regional classification were combined, as were the other smaller hospitals due to small sample sises. Private hospitals were considered as a separate group. These criteria were also applied to the New Zealand hospitals. When stratifying by jurisdictions, the Australian Capital Territory (ACT) was combined with NSW, while Tasmania and the Northern Territory were combined due to small samples. Dichotomous variables being reported as counts of the total (n) and percentages (%), and compared by chi-square tests, while continuous variables were compared using the Kruskal-Wallis test and reported as a median and inter-quartile range.

Propensity-score adjusted estimates of the influence of hospital characteristics and health jurisdictions on early invasive management, discharge on 4 or 5 guideline therapies, rehabilitation referral and MACE where generated through logistic regression modelling stratified by discharge diagnosis. Assessment of angiography and MACE used the whole cohort, while the evaluation of rehabilitation and medications was confined to those with a discharge diagnosis of ACS. Propensity scores using age, gender, Global Registry of Acute Coronary Events (GRACE) score, diagnostic group, heart failure at presentation, renal impairment, diabetes, hypertension nursing home residence, dementia or cognitive impairment, private insurance and a primary language other than English, were constructed for both the "likelihood" of living in each jurisdiction and presenting to each hospital classification. Each model included the hospital classifications and health jurisdictions as indicator variables as well as their respective propensity score, when reporting the jurisdiction or hospital estimates. Interaction terms of each jurisdiction and hospital classification were constructed explored for significance. No interactions were evident. Confidence intervals for the odds ratios from these models were produced using the floating absolute risk method.[16] Given the observational and hypothesis generating nature of these analyses, no adjustment of significance levels was undertaken.Analyses were undertaken using STATA 11.2 (College Station, TX) and a p-value of <0.05 was considered statistically significant.

3.4 Results

3.4.1 Participating Hospitals

Of 525 hospitals approached to participate, 478 gained ethics approval and 435 provided site survey data. Within the 2-week enrolment period, 4,398 patients with suspected or confirmed ACS were identified from 286 hospitals providing registrants Hospitals not providing registrants were in smaller centres and did not treat suspected ACS patients within the registry window. (Table 1) The majority of patients presented to Principal Referral Hospitals (65.8%) or hospitals in large major cities (7.7%), while 7.3% presented to private hospitals. All other patients presented to regional or rural/remote hospitals. As for cardiac services available at the first presenting hospital, 79.7% of the total cohort of

patients presented where fibrinolysis could be administered and 59.0% capable of providing primary PCI. Only 3.4% of patients presented to hospitals with no reperfusion therapy for STEMI. Some 25.9% of patients required transfer to at least one other hospital. The distribution of hospital types by jurisdictions was comparable except for Victoria where a selective hospital recruitment strategy operated. (Table 1) Key patient characteristics by the type of hospital service are presented in the appendix.

Table 1: Enrolling hospital characteristics by Health Jurisdiction

	Total	NZ	NSW/ACT	QLD	VIC	WA	SA	NT/TAS	
Total Patients	4,398	1,007	1,140	695	726	354	362	114	
Estimated Suspected ACS admission rate per 100,000/year	420	588	380	398	336	381	553	397	
No. Hospitals Participating	435	39	130	121	46	53	39	6	
No. Hospitals Enrolling	286	35	91	61	41	21	32	5	
Peer Grouping (n, %)									
Principal Referral Hospitals (n)	88 (30.8%)	9 (25.7%)	29 (31.9%)	17 (27.9%)	19 (46.3%)	5 (23.8%)	5 (15.6%)	4 (80.0%)	<0.001
Large Metropolitan Hospitals (n,)	19 (6.7%)	4 (11.4%)	7 (7.7%)	2 (3.3%)	2 (4.9%)	3 (14.3%)	1 (3.1%)	0 (0%)	
Large Regional Hospitals (n)	19 (6.6%)	3 (8.6%)	4 (4.4%)	2 (3.3%)	6 (14.6%)	3 (14.3%)	0 (0%)	1 (20.0%)	
Medium Size Hospitals (n)	56 (19.6%)	8 (22.9%)	20 (22.0%)	10 (16.4%)	7 (17.1%)	0 (0%)	11 (34.4%)	0 (0%)	

*Dedicated higher cardiac acuity area such as intensive care, coronary care, high-dependency unit or integrated cardiac unit.

3.4.2 Acute Coronary Syndrome Patients

The risk profile of registrants was high, reflected in the GRACE score of 119 (interquartile range: 96-144) across the entire population and the score of 138 (interquartile range: 114-161) among those with a discharge diagnosis of MI. Indigenous/Pacific Islander/Maori peoples constituted 5.7% (n=252) of the population, while people from Asian and other non-Caucasian ethnicity accounted for 3.8% (n=165) and 5.8% ((n=256) respectively, English was not the primary language spoken in 294 (6.7%) of the population. Patient characteristics by discharge diagnosis are presented in table 2. Among patients discharged with a defined alternative diagnosis, 37.9% had a troponin result, above the local URL.

Table 2: Patient Characteristics by Clinical Diagnosis at the time of discharge

	Total (n=4398)	STEMI (n=421)	NSTEMI (n=1,015)	Unstable Angina Ischaemic CP (n=929)	CP not Ischaemic (n=1,196)	Other Diagnosis Secondary Myonecrosis (n=837)	P value
Age (yrs, mean ±SD)	66.5 (14.6%)	65.6 (14.4%)	71.2 (13.2%)	68.1 (12.9%)	62.1 (14.9%)	65.8 (15.7%)	0.001
Female Gender (n, %)	1771 (40.3%)	119 (28.3%)	376 (37.0%)	343 (36.9%)	567 (47.4%)	366 (43.7%)	<0.001
Creatinine (median, 25th-75th percentile)	84 (70-104)	89 (73-106)	89 (74-113)	86 (71-106)	78 (66-93)	85 (68-110)	<0.001
Killip Class II-IV at presentation (n,%)	599 (13.6%)	81 (19.3%)	206 (20.3%)	78 (8.4%)	69 (5.8%)	165 (19.7%)	<0.001
Presentation with cardiac arrest (n,%)	78 (1.8%)	35 (8.3%)	12 (1.2%)	4 (0.4%)	3 (0.3%)	24 (2.9%)	<0.001
GRACE risk score (median, 25th-75th percentile)	118 (95-144)	140 (118 -165)	137 (114-159)	115 (96-136)	101 (80-122)	120 (94-147)	0.001
Diabetes (n, %)	1115 (25.4%)	83 (19.7%)	314 (31.0%)	289 (31.1%)	217 (18.0%)	212 (25.3%)	<0.001
Hypertension (n, %)	2785 (63.4%)	229 (54.5%)	699 (68.9%)	677 (72.9%)	672 (56.2%)	508 (60.7%)	<0.001
Dyslipidaemia (n, %)	2391 (54.4%)	192 (45.7%)	588 (57.9%)	618 (66.5%)	578 (48.3%)	415 (49.6%)	<0.001
Current Smoking (n, %)	800 (18.2%)	130 (31.0%)	175 (17.2%)	134 (14.4%)	218 (18.2%)	143 (17.1%)	<0.001

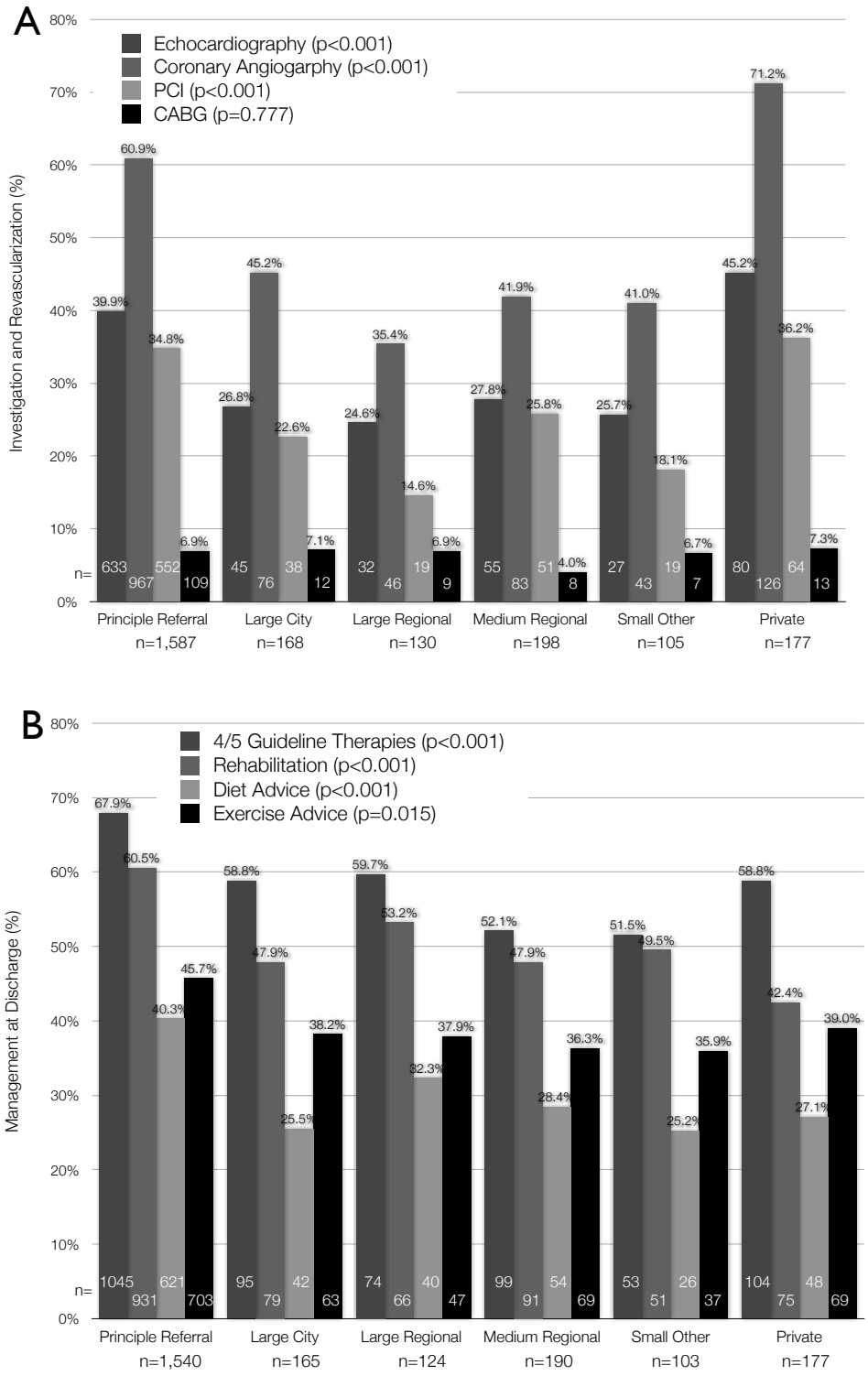
Prior MI (n, %)	1195 (27.2%)	75 (17.8%)	345 (34.0%)	335 (36.1%)	250 (20.9%)	190 (22.7%)	<0.001
Prior PCI (n, %)	892 (20.3%)	48 (11.4%)	184 (18.2%)	308 (33.2%)	199 (16.6%)	153 (18.3%)	<0.001
Prior CABG (n, %)	466 (10.6%)	21 (5.0%)	135 (13.3%)	133 (14.3%)	88 (7.4%)	89 (10.6%)	<0.001
Prior Atrial Fibrillation (n, %)	667 (15.2%)	31 (7.4%)	174 (17.2%)	126 (13.6%)	144 (12.0%)	192 (22.9%)	<0.001
Known PAD (n, %)	267 (6.1%)	22 (5.2%)	91 (9.0%)	67 (7.2%)	41 (3.4%)	46 (5.5%)	<0.001
Prior TIA/CVA (n,%)	454 (10.3%)	23 (5.5%)	144 (14.2%)	108 (11.6%)	93 (7.8%)	86 (10.3%)	<0.001
Major Bleeding Admission/Transfusion (n,%)	107 (2.4%)	10 (2.4%)	26 (2.6%)	20 (2.2%)	25 (2.1%)	26 (3.1%)	0.63
Active Cancer Limiting life expectancy (n,%)	106 (2.4%)	8 (1.9%)	27 (2.7%)	21 (2.3%)	26 (2.2%)	24 (2.9%)	0.76
Cognitive impairment/Dementia (n,%)	149 (3.4%)	11 (2.6%)	42 (4.1%)	27 (2.9%)	38 (3.2%)	31 (3.7%)	0.46
Nursing Home Resident	116 (2.6%)	13 (3.1%)	33 (3.3%)	28 (3.0%)	12 (1.0%)	30 (3.6%)	0.001

SD=standard deviation, CP=chest pain, STEMI/LBBB=ST-segment elevation myocardial infarction/Left bundle branch block, PAD= Peripheral artery disease, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery graft surgery, TIA=trans ischaemic attack, CVA=cerebrovascular accident,

3.4.3 Acute Coronary Syndrome Care

Among patients with a discharge diagnosis of STEMI/LBBB, 105 (25.0%) received fibrinolytic therapy, 163 (38.8%) received primary PCI, and 152 (36.2%) received no reperfusion therapy. Coronary angiography was provided to 1019 (71.0%) of patients with STEMI or NSTEMI, while PCI was undertaken in 610 (42.5%) of patients and a further 116 (8.1%) underwent CABG. However, reduced provision of invasive management with increasing risk was evident among these patients (GRACE score <100: 90.1% vs. 101-150: 81.3% vs. 151-200: 49.4% vs. >200: 36.1%, p<0.001). Figure 1 describes the provision of investigations and management stratified by first presenting hospital classification. Guideline-advocated investigation and therapies were provided in lower frequency in patients presenting to non-Principal Referral hospitals, regardless of patient transfers. Similar heterogeneity in the provision of care was observed when the results were stratified by jurisdictions. Variation in the timeliness of care was also evident across jurisdictions, most marked in the median time to angiography, and less striking variation in the overall lengths of stay. (Appendix Table 4)

Figure 1: Provision of A) investigations and revascularization, and B) therapies among patients with a diagnosis of ACS by Enrolling Hospital Classification (n refers to number of patients)



3.4.4 In-hospital outcomes

Figure 2 displays the in-hospital clinical outcome for registrants stratified by discharge diagnosis. In-hospital adverse outcomes remained highest among patients presenting with STEMI/LBBB. Importantly, in-hospital mortality and recurrent cardiac failure remains substantial among patients discharged with a diagnosis thought not to be ACS in origin. Figure 3 presents the clinical outcomes stratified by hospital classification in a) the entire cohort and b) those discharged with the diagnosis of ACS. Substantial heterogeneity in clinical events is evident over the peer group classifications.

Figure 2: In-hospital Clinical Events by Principle Diagnosis at the time of Discharge. (All comparisons of outcomes between diagnostic categories are significant [p<0.001])

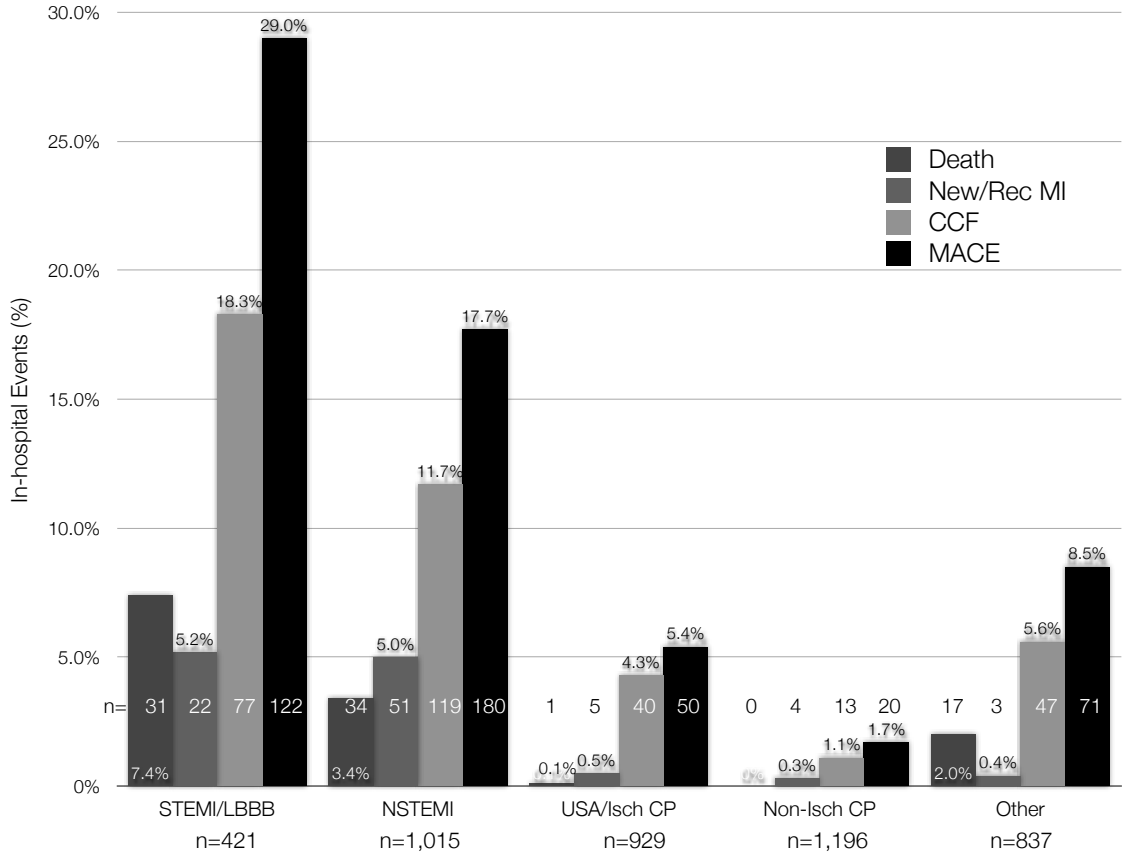
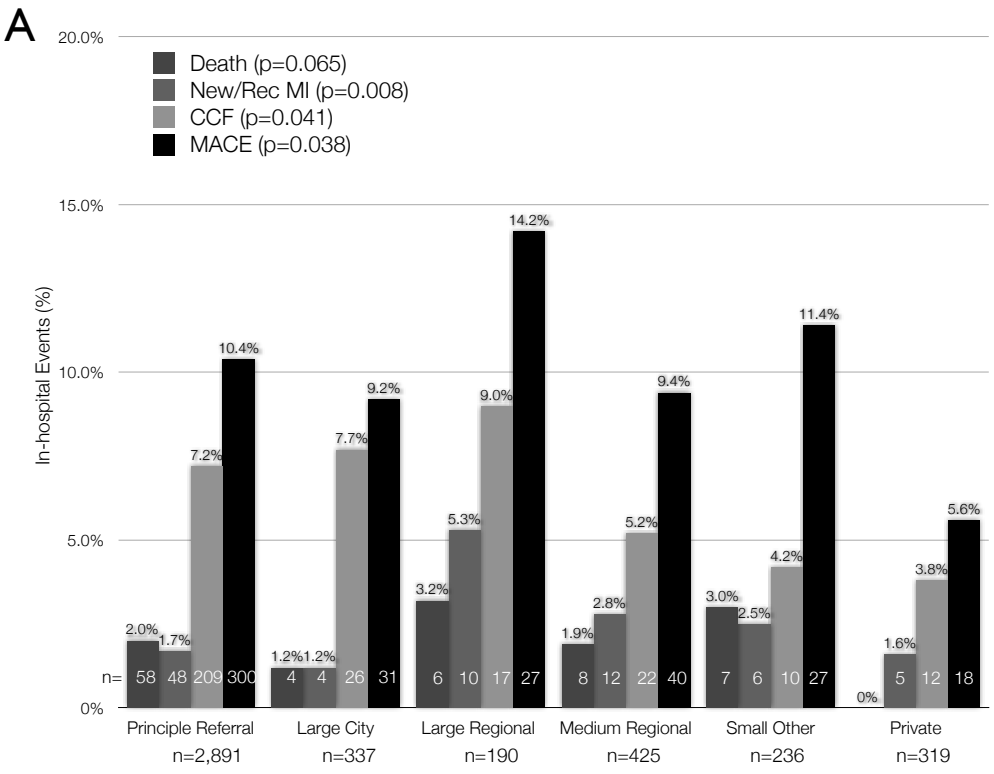
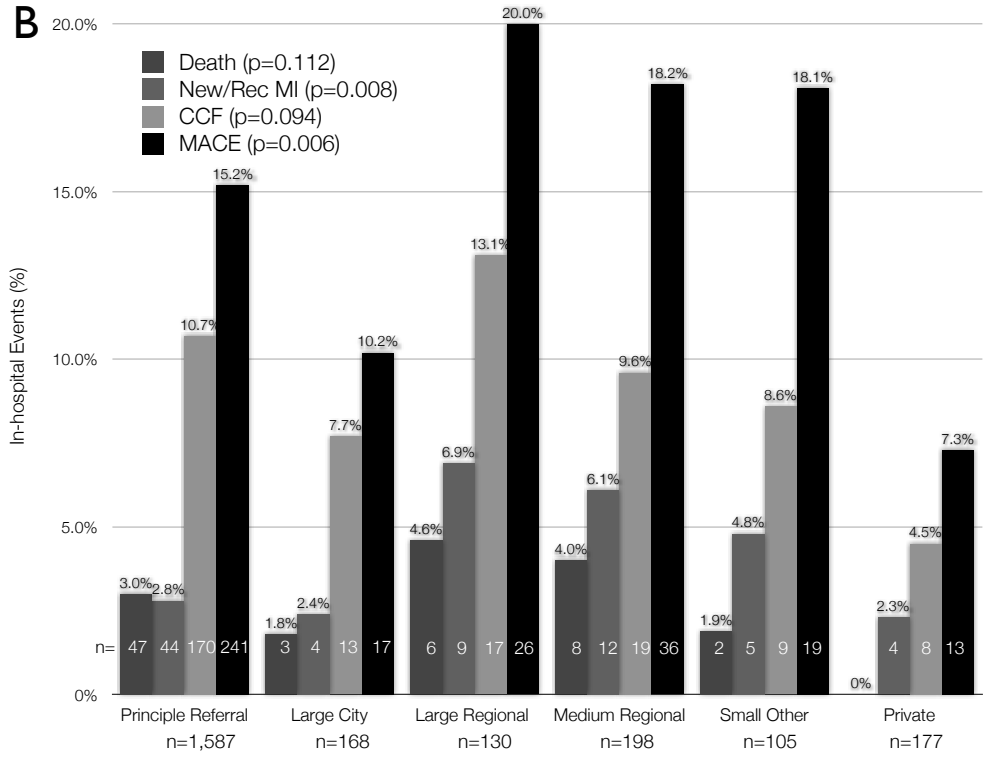


Figure 3: In-hospital Clinical Events among A) the entire cohort and B) with ACS Diagnosis by Enrolling Hospital Classification

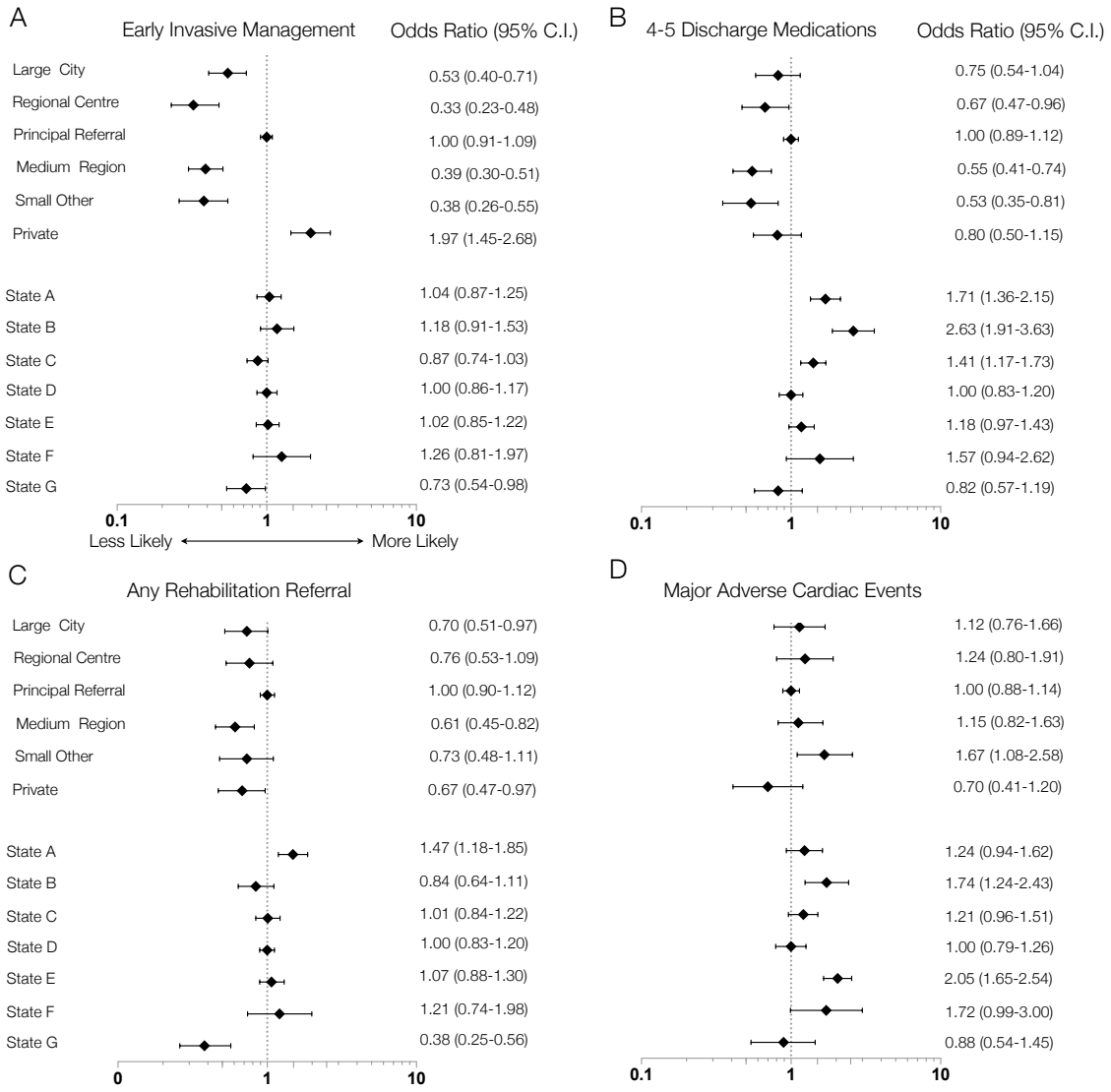




3.4.5 Adjusted Analyses

The propensity-adjusted odds ratios and confidence bounds describing the likelihood for undergoing inpatient angiography, receiving 4 or 5 guideline medications, referral to rehabilitation and experiencing in-hospital MACE is displayed in figure 4. Variation in provision guideline recommendations is evident, with a consistently lower likelihood of receiving therapies among patients originally presenting to non-principal referral centres. Patients in private hospitals were significantly more likely to undergo angiography, but not necessarily receive guideline medications or rehabilitation referral. A more striking difference in in-hospital clinical events was evident at the health jurisdiction level than between hospital types.

Figure 4: Adjusted odds ratios (& 95% C.I) for likelihood to undergo: A) Early Invasive Management, B) 4 or 5 Guideline recommended discharge medications, C) referral to cardiac rehabilitation and D) experience in-hospital MACE, by hospital classification and health Jurisdiction. (Foot-note: Confidence intervals have been produced using the floating absolute risk method, with "Principal Referral Hospitals" and "State D" used the referent categories)



3.5 Discussion

Optimizing outcomes following MI through standardization of care has emerged as a major near-term goal within the health agenda of Australia and New Zealand.[17] Evidence translation requires a more sophisticated understanding of

patient, clinical service and health policy level determinants of care provision. An integrated approach to health service design is paramount to meeting the needs of our culturally diverse and geographically dispersed communities. Through the most representative assessment of ACS health service resource, clinical care provision and outcome ever conducted across Australia and New Zealand, this study provides unique insights into the challenges facing the timely and effective provision of ACS care throughout Australasia. These include the complexity of patient comorbidities which bringing the logistic challenges of providing timely invasive management to many patients in remote, regional and outer metropolitan centres into sharper focus. [11,12] Variation in clinical decision-making, service availability and health policy may represent potential targets for improving the ACS evidence base translation and outcomes.

The efficient management of patients presenting with suspected ACS remains challenging. More sensitive markers of myonecrosis, such as high-sensitivity troponin assays, have not simplified this.[18] The substantial proportion of patients the suspicion of ACS, many with elevated troponin levels, who have a final diagnosis that is not ischaemic, or where ischaemia is considered secondary to another diagnosis, highlights these diagnostic confounders.[19,20] Our in-hospital data continue to demonstrate poor outcomes among such patients, as observed by others, though the current evidence informing their management is very limited.[21,22] Similarly, these data demonstrate the substantial burden of clinical complexity among ACS patients, with a relatively high prevalence of prior major bleeding events, cerebrovascular disease, cognitive impairment and concurrent malignancy.[23] This underscores the everyday challenges in applying the evidence among those with typical ACS presentations. In combination, these observations call for judicious and validated approaches to the development and implementation of clinical standards and performance measures to the evaluation of care that takes into account these diagnostic and therapeutic complexities.

This analysis highlights the potential sources of variation in care attributable to regional/geographic services and jurisdictional differences. Co-morbidities

among these patients are also common. Reduced application of evidence-based therapies among patients with increased co-morbidities remains evident in other studies.[24,25] Potentially, objective risk stratification in balancing benefit and risk may narrow the evidence-practice gap among such comorbidities.[26] The challenge of providing timely access to invasive management, not only in rural areas but also across the outer suburbs of our growing cities is highlighted by the fact that 27% of all ACS patients require transfer. Attempts to improve consistency and quality of care, such as the clinical guidelines and ACSQHC clinical standards will need to consider the significant issues of transfer and co-ordination of care particularly outside metropolitan areas if such initiatives are to be effective and cost-effective.

The broad hospital recruitment approach, consecutive enrolment, and high in-hospital event rates underscores the critical importance of representative patient inclusion when evaluating practice and outcome. [27] For the effective integration of the clinical guidelines, clinical standards and performance measures into everyday care, the real challenge is to develop mechanisms to enable such data to be acquired and fed-back on routine and sustainable basis.[28] The SNAPSHOT ACS study was the culmination of significant efforts to engage with national agencies including the ACSQHC, the AIHW, professional bodies (i.e. the HFA and CSANZ), while implementation critically depended on the State Clinical Networks within NSW, Victoria, QLD, WA and SA. However, the largest un-resourced effort required local hospital commitment to data collection and entry, an enormous effort that remains difficult to quantify but attests to the dedication of health care providers to the quality of ACS care and outcome. Future attempts to understand the lingering practice gaps will need to consider such resourcing issues carefully. Nevertheless, this study is unique in its ability to gain insights into the provision of care across multiple levels of decision-making (i.e. from bedside to service characteristics). Effectively delivering these insights to the key decision-makers at a clinical, a health service and health policy level to enable the design and implementation of fully integrated approaches to ACS care remains the “translational” promise of this initiative.

3.6 References

1 Authors/Task Force Members, Steg PG, James SK, Atar D*et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Euro Heart J* 2012. doi:10.1093/eurheartj/ehs215.

2 Anderson JL, Adams CD, Antman EM, *et al.* 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; **123**: e426–e579.

3 2011 Writing Group Members, Wright RS, Anderson JL, Adams CD*et al.* 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; **123**: 2022–2060.

4 Aroney C, Aylward P, Kelly A, at al. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. *Med J Aust* 2006; **184**: S1–30.

5 Chew DP, Aroney CN, Aylward PE, *et al.* 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. *Heart Lung Circ* 2011; **20**: 487–502.

6 Brieger D, Kelly A-M, Aroney C, *et al.* Acute coronary syndromes: consensus recommendations for translating knowledge into action. Med J Aust. 2009; **191**: 334–338.

7 Chew D, Amerena J, Coverdale S, *et al.* Invasive management and late clinical outcomes in contemporary Australian management of acute coronary syndromes: observations from the ACACIA registry. *Med J Aust* 2008; **188**: 691–697.

8 Aliprandi-Costa B, Ranasinghe I, Chow V, *et al.* Management and outcomes of patients with acute coronary syndromes in Australia and New Zealand, 2000-2007. *Med J Aust* 2011; **195**: 116–121.

9 Ellis C, Devlin G, Matsis P, *et al.* Acute Coronary Syndrome patients in New Zealand receive less invasive management when admitted to hospitals without invasive facilities. *N Z Med J* 2004; **117**: U954.

10 Ellis C, Gamble G, Hamer A, *et al.* Patients admitted with an acute coronary syndrome (ACS) in New Zealand in 2007: results of a second comprehensive nationwide audit and a comparison with the first audit from 2002. *N Z Med J* 2010; **123**: 25–43.

11 Ranasinghe I, Turnbull F, Tonkin A, et al. Comparative effectiveness of population interventions to improve access to reperfusion for ST-segment-elevation myocardial infarction in Australia. *Circ Cardiovasc Qual Outcome* 2012; **5**: 429–436.

12 Clark RA, Coffee N, Turner D, *et al.* Application of geographic modeling techniques to quantify spatial access to health services before and after an acute cardiac event: the Cardiac Accessibility and Remoteness Index for Australia (ARIA) project. *Circulation* 2012; **125**: 2006–2014.

13 Ellis C, Devlin G, Elliott J, *et al.* ACS patients in New Zealand experience significant delays to access cardiac investigations and revascularisation treatment especially when admitted to non-interventional centres: results of the second comprehensive national audit of ACS patients. *N Z Med J* 2010; **123**: 44–60.

14 Astley CM, Macdougall CJ, Davidson PM, Chew DP. Lost in translation: health resource variability in the achievement of optimal performance and clinical outcome. *Circ Cardiovasc Qual Outcome* 2011; **4**: 512–20.

15 Fox KAA, Dabbous OH, Goldberg RJ, *et al.* Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006; **333**: 1091.

16 Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991; **10**: 1025–35.

17 Smith MC. Towards national clinical care standards. *Med J Aust* 2012; **197**: 540.

18 Reichlin T, Hochholzer W, Bassetti S, *et al.* Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858-67

19 Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. *European Heart Journal* 2011; **32**: 404–11.

20 Gallagher S, Jones DA, Anand V, Mohiddin S. Diagnosis and management of patients with acute cardiac symptoms, troponin elevation and culprit-free angiograms. *Heart* 2012; **98**: 974–981.

21 Saunders JT, Nambi V, de Lemos JA, *et al.* Cardiac Troponin T Measured by a Highly Sensitive Assay Predicts Coronary Heart Disease, Heart

Failure, and Mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011; **123**: 1367–76.

22 Aldous SJ, Florkowski CM, Crozier IG, George P, Mackay R, Than M. High sensitivity troponin outperforms contemporary assays in predicting major adverse cardiac events up to two years in patients with chest pain. *Ann Clin Biochem* 2011; **48**: 249–255.

23 Steg PG, López-Sendón J, Lopez de Sa E, *et al.* External validity of clinical trials in acute myocardial infarction. *Arch Intern Med* 2007; **167**: 68–73.

24 Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. *Med J Aust* 2007; **187**: 153–159.

25 Joynt KE, Huynh L, Amerena JV, *et al.* Impact of acute and chronic risk factors on use of evidence-based treatments in patients in Australia with acute coronary syndromes., 2009.

26 Yan A, Yan R, Tan M, *et al.* Management Patterns in Relation to Risk Stratification Among Patients With Non-ST Elevation Acute Coronary Syndromes. *Arch Intern Med* 2007; **167**: 1009–1016.

27 Ferreira-Gonzalez I, Marsal JR, Mitjavila F, *et al.* Patient Registries of Acute Coronary Syndrome: Assessing or Biasing the Clinical Real World Data? *Circ Cardiovasc Qual Outcome* 2009; **2**: 540–547.

28 Chew D, Brieger D, Astley CM, Georgiou A. Measuring performance and outcomes of acute coronary syndromes management in Australia. *Med J Aust* 2012; **197**: 140–142.

4 SIX-MONTH SURVIVAL BENEFITS ASSOCIATED WITH CLINICAL GUIDELINE RECOMMENDATIONS IN ACUTE CORONARY SYNDROMES

4.0 Title Page: Six-month survival benefits associated with clinical guideline recommendations in acute coronary syndromes

D P Chew[1], F A Anderson[2], Á Avezum[3], K A Eagle[4], G FitzGerald[2], J M Gore[5], R Dedrick[2], D Brieger[6], for the GRACE Investigators

Author Affiliations

[1]Department of Cardiovascular Medicine, Flinders University, Adelaide, South Australia, Australia

[2]Center for Outcomes Research, University of Massachusetts Medical School, Boston, Massachusetts, USA

[3]Dante Pazzanese Institute of Cardiology, São Paulo, Brazil

[4]University of Michigan Health System, Ann Arbor, Michigan, USA

[5]Department of Cardiovascular Medicine, University of Massachusetts Medical School, Boston, Massachusetts, USA

[6]Department of Cardiovascular Medicine, Concord Hospital, Sydney, New South Wales, Australia

Corresponding Author

Derek P Chew,

Flinders Medical Centre,

Flinders Drive, Bedford Park, SA 5042,

Australia;

derek.chew@flinders.edu.au

Contributors Study concept and design: Chew Acquisition of data: Chew, Avezum, Eagle, Gore and Brieger Drafting of the manuscript: Chew and Brieger Critical revision of the manuscript for important intellectual content: Chew, Anderson, Avezum, Eagle, Gore, FitzGerald and Brieger Statistical analysis: FitzGerald and Dedrick Administrative, technical or material support: Anderson.

4.1 Abstract

Aims The authors sought to define which guideline-advocated therapies are associated with the greatest benefit with respect to 6-month survival in patients hospitalised with an acute coronary syndrome (ACS).

Methods and results The authors conducted a nested case–control study of ACS patients within the Global Registry of Acute Coronary Events cohort between April 1999 and December 2007. The cases were ACS patients who survived to discharge but died within 6 months. The controls were patients who survived to 6 months, matched for ACS diagnosis, age and the Global Registry of Acute Coronary Events risk score. Rates of use of evidence-based medications and coronary interventions (angiography, percutaneous coronary intervention and coronary artery bypass graft surgery) were compared. Logistic regression including matched variables was used, and the attributable mortality from incomplete application of each therapy was calculated. A total of 1716 cases and 3432 controls were identified. Coronary artery bypass graft surgery and percutaneous coronary intervention were associated with the greatest 6-month survival benefit (OR for death 0.60 (95% CI 0.39 to 0.90) and 0.57 (0.48 to 0.72), respectively). Statins and clopidogrel provided the greatest independent pharmacologic benefit (ORs for death 0.85 (0.73 to 0.99) and 0.84 (0.72 to 0.99)) with lesser effects seen with other pharmacotherapies.

Conclusions A diminishing benefit associated with each additional ACS therapy is evident. These data may provide a rational basis for selecting between therapeutic options when compliance or cost is an issue.

4.2 Introduction

Randomised clinical trials provide the evidence for modern clinical decision making. Consensus guidelines have become an important venue for translating trial data into routine care across a broad range of disease states, including acute coronary syndromes (ACSs).[1–5] However, resulting from the manner by which this evidence is acquired, the relative clinical value of each new guideline-advocated therapy, added to and independent of other therapies, is uncertain. Consequently, with novel evidence, clinical guideline recommendations are often additive but do not inform us of therapies that may be omitted. When considering coronary revascularisation for instance, because access to this therapy is difficult in many parts of the world, establishing the relative advantages of invasive management in the context of more complete application of medical management may be useful for guiding resource allocation. The lack of data informing the choice between therapeutic strategies (eg, optimal revascularisation vs β-blockade) is a consequence of trial design, as randomised trials are directed at balancing clinical heterogeneity and are only able to optimally answer one question per randomisation. To date, several observational analyses have explored the cumulative value of guideline application, but not the specific contribution of each therapy.[6 7] Furthermore, while clinical trials commonly advocate the application of all guideline-recommended therapies, such application is rarely complete. This is particularly relevant when considering recommendations based on clinical trials conducted in an era predating modern cardiologic practice, such as the relative value of β-blockade in the post-revascularisation era. Hence, consideration of guidelines does not always inform us of the correct choice between therapeutic recommendations when choices have to be made. Nor does it provide data on the relative incremental benefit of one therapy over the application of all others. This is more of an issue when recommendations suggest the continuation of multiple therapies for an indefinite duration, in which case compliance becomes problematic.

We sought to explore the incremental gain associated with each of the current guideline-advocated therapies assuming that all others have already been optimally applied. To evaluate the impact of guideline-advocated therapies on 6-month survival in patients with ACS, we conducted a nested case–control study drawn from the Global Registry of Acute Coronary Events (GRACE) cohort to evaluate the impact of guideline-advocated therapies and treatment strategies on 6-month survival in patients with ACS.

4.3 Methods

4.3.1 Study population

GRACE is designed to reflect an unselected population of patients with ACS, irrespective of geographic region. A total of 113 hospitals located in 14 countries in North and South America, Europe, Australia and New Zealand have contributed data to this study. Full details of the GRACE methods have been published elsewhere.[8–10]

Adult patients (>18 years old) admitted with a presumptive diagnosis of ACS at participating hospitals were potentially eligible for this study. Eligibility criteria were a clinical history of ACS accompanied by at least one of the following: electrocardiographic changes consistent with ACS, serial increases in biochemical markers of cardiac necrosis (creatine kinase-MB, creatine phosphokinase or troponin) and documented coronary artery disease. Patients with non-cardiovascular causes for the ACS clinical presentation, such as trauma or surgery, were excluded. The patients were followed-up at approximately 6 months by telephone, clinic visits or through calls to their primary care physician to ascertain the occurrence of several long-term outcomes. Where required, study investigators received approval from their local hospital ethics or institutional review board for the conduct of this study. Data were collected by trained study coordinators using standardised case report forms. Demographic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practises and a variety of hospital outcome data were collected. Standardised definitions of all patient-related variables, clinical diagnoses and hospital complications and outcomes were used.[8] All the cases were assigned to one of the following categories: ST segment elevation myocardial infarction (STEMI), non–ST segment elevation myocardial infarction (NSTEMI) or unstable angina. Data from the patients enrolled between April 1999 and December 2007 were used in this analysis.

4.3.2 Definition of cases and controls

A nested matched case–control design was used because a large cohort of patients was available in the GRACE registry, enabling more explicit control of known powerful confounders, and such an analysis would be less impacted by issues of loss to follow-up. *Cases* were defined as patients presenting with ACS who survived to hospital discharge but died from any cause within 6 months of follow-up. All-cause mortality was used, as it is less subject to interpretation, whereas the duration of 6 months was used to enhance the likelihood that these events were cardiovascular in nature.

Similarly, the patients presenting with an ACS who survived to 6 months were considered eligible controls. Standard definitions of ACS were used. The patients were with STEMI when they had new or presumed new ST segment elevation ≥1 mm seen in any location or new left bundle-branch block on the index or subsequent electrocardiogram with at least one positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of NSTEMI, at least one positive cardiac biochemical marker of necrosis without new ST segment elevation seen on the index or subsequent electrocardiogram had to be present. Unstable angina was diagnosed when the serum biochemical markers indicative of myocardial necrosis in each hospital's laboratory were within the reference range.

4.3.3 Matching

Where possible, the cases and the controls were matched in a 1:2 ratio (cases to controls) based on the following factors: clinical diagnosis at discharge (STEMI, NSTEMI and unstable angina), age strata (grouped by 5 years) and GRACE risk score (grouped by five points).11 The patients with scores <66 (845 patients (2%)) were excluded, as they were at very low risk, with only two deaths occurring in this group. Two controls were then found for each case.

4.3.4 Therapies and treatment strategies

We explored key guideline-recommended treatment strategies.3 4 Drug exposure was assessed by discharge prescriptions of aspirin, β-adrenoreceptor antagonists, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists, clopidogrel and statins. Long-term compliance at 6 months after discharge was not assessed. Glycoprotein IIb/IIIa inhibitors were aggregated at the class level and identified if used at any time during hospitalisation. The following invasive procedures during index hospitalisation were recorded: coronary arteriography, percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG). PCI occurring as reperfusion for ST elevation (primary PCI) or as revascularisation were modelled as a single variable. Procedures after the initial hospitalisation or during subsequent hospitalisations were not included (ie, the patients were considered not to have received angiography or revascularisation) because these procedures occurred outside the exposure period of this study and may have been triggered by recurrent events. Referral to cardiac rehabilitation was identified by documentation of referral as recorded by the local site, with actual attendance and completion of the programme not

confirmed.

4.3.5 Statistical analysis

All-cause mortality by 6 months was the dependent variable. Logistic regression including matched variables and all other potentially confounding variables (p>0.2) was undertaken. Independent variables included the recommended therapies (aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors, angiotensin-pathway blockers, β-adrenoreceptor antagonists, statins, arteriography, revascularisation and cardiac rehabilitation). These factors were considered independently and in conjunction with each other (revascularisation + statins + clopidogrel + rehabilitation + aspirin + β-adrenoreceptor antagonists + ACE inhibitor, etc). Other factors adjusted for in the model included the patient's country, diagnosis, cardiac arrest at presentation, Killip class and history of angina, myocardial infarction, heart failure, coronary artery disease, positive stress test, hypertension, dyslipidemia, LVEF, peripheral arterial disease, atrial fibrillation, transient ischaemic attack or stroke, diabetes, renal insufficiency, major surgery, venous thromboembolism, implantable defibrillators and major bleeding. A subanalysis confined to patients with STEMI was also conducted. In these models, the use of pharmacologic and catheter-based reperfusion was also assessed in conjunction with the other guideline recommendations.

Estimates from the logistic regression models and the rate of each therapeutic recommendation applied were used to estimate the adjusted attributable fraction (AF) of death preventable by the improved application of the clinical guidelines by calculating

$$\mathrm{AF} = \frac{\mathrm{Deaths}_{\mathrm{T}} - \mathrm{Deaths}_{\mathrm{NG}}}{\mathrm{Deaths}_{\mathrm{T}}}$$

where $\mathrm{Death}_{\mathrm{T}}$ is the total deaths predicted and $\mathrm{Deaths}_{\mathrm{NG}}$ is the deaths occurring among people not receiving the guideline-recommended therapy.12

Both the relative impact of each guideline (OR and 95% confidence interval (CI)) and the adjusted absolute contribution (AF, percentage and 95% CI) to 6-month survival were assessed for the entire population. The association between the number of guideline recommendations received (regardless of the specific guideline therapy given) and 6-month survival was assessed using logistic regression modelling and plotted in figure 1. In contrast, the predicted cumulative contribution of applying each of

the guideline recommendations sequentially (greatest to least) was calculated by adding the β-coefficients for each of the recommendations in order and plotted in figure 2. For these estimates, PCI and CABG were combined into a single variable of revascularisation because these treatments are most often mutually exclusive. Continuous variables are expressed as a mean (SD) or median and interquatile range for variables with non-Gaussian distributions. All discrete variables are expressed as counts and percentages of the study population (n). The analyses were conducted using the SAS V.9 (SAS Institute) and the Stata 9.2 (Stata Corporation). A probability of <0.05 was considered statistically significant.

Figure 1: ORs for 6-month mortality associated with number of evidence-based guideline recommendations used.

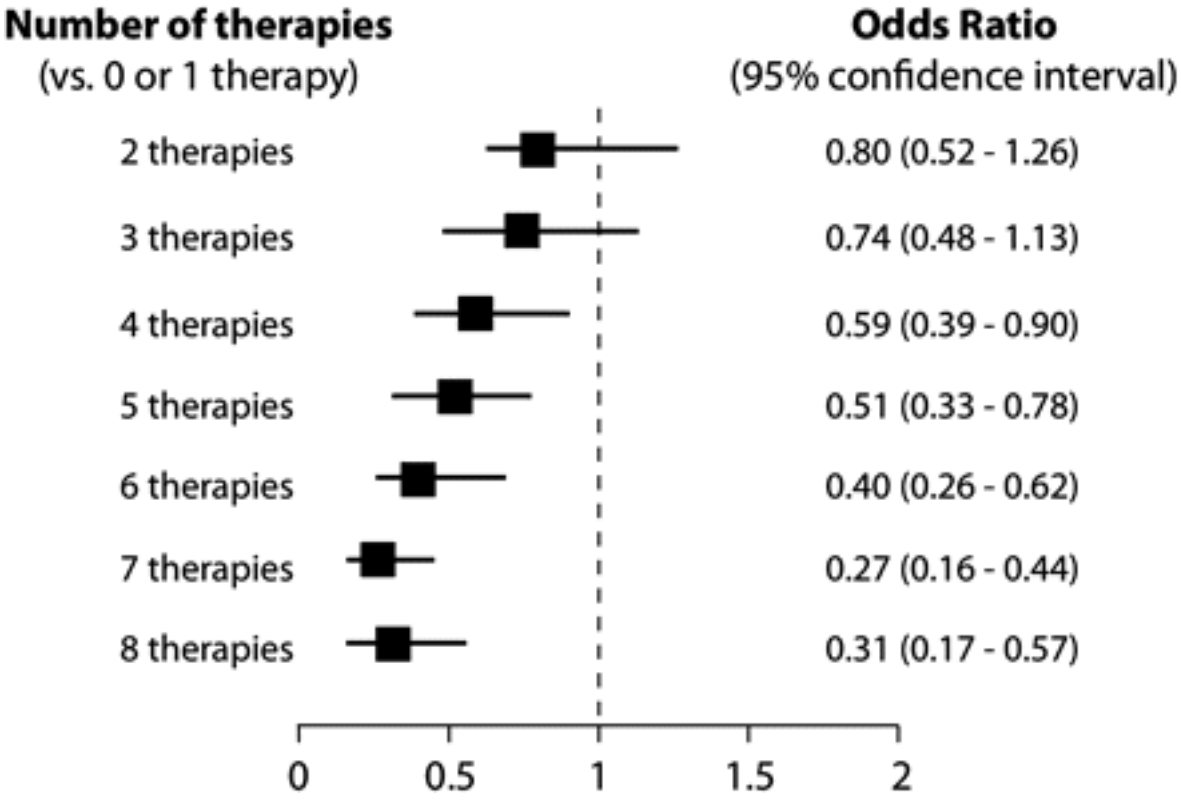
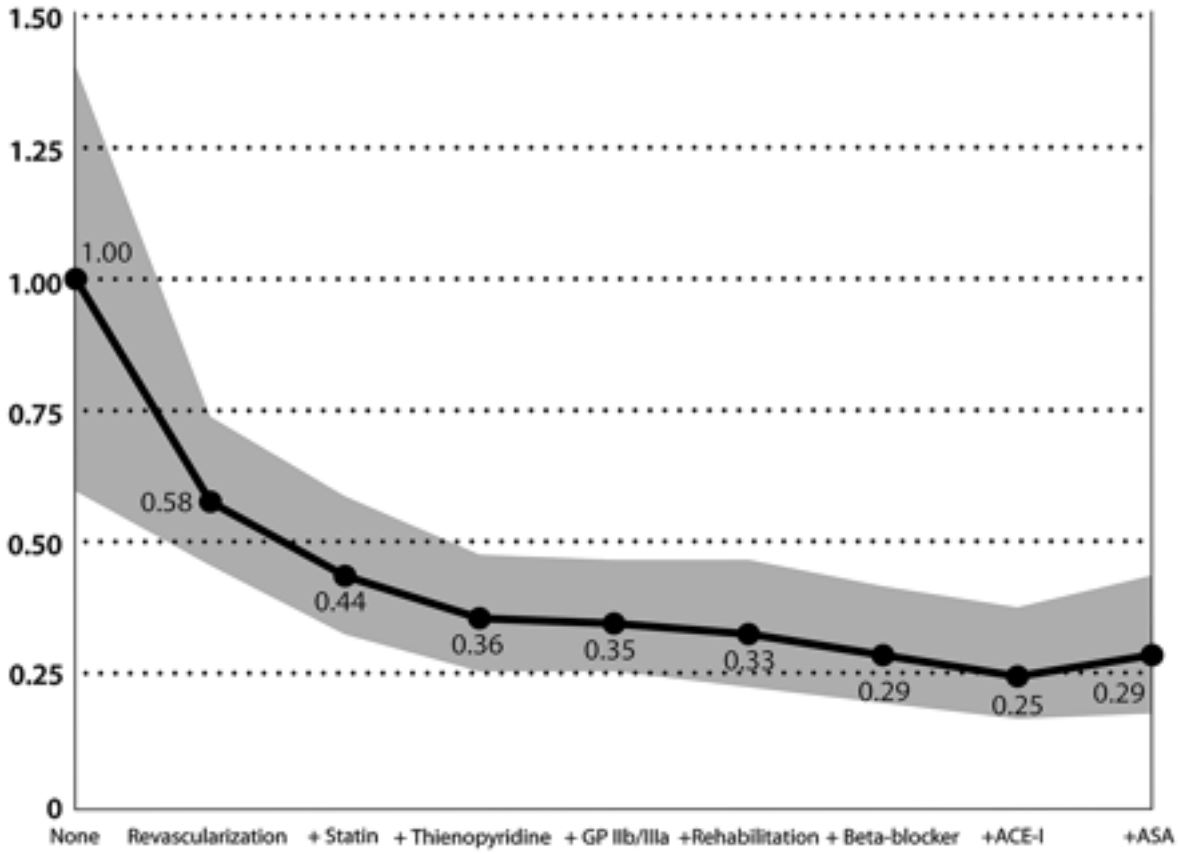


Figure 2: The mean effect of the sequential application of each guideline (greatest observed impact to least) and/or for 6-month mortality in patients with an ACS (PCI and CABG are considered revascularisation therapy). CIs are shown as the shaded area.



4.4 Results

Of the 41 320 patients with GRACE risk scores who survived to hospital discharge, 1852 patients died by 6 months, and of these, 1716 cases (93%) were identified as having appropriately matched controls (n=3432). The characteristics of the study population are described in table 1. The patients presenting with STEMI accounted for 37.2% of the overall population. Among several factors, patients dying within 6 months of hospital discharge were more likely to have a history of myocardial infarction and congestive heart failure and have hypertension, dyslipidemia and previous cerebrovascular disease.

Table 1: Baseline clinical and demographic characteristics

	Cases (n=1716)		Controls (n=3432)		p Value
	n	%	n	%	
Female	695	40.6	1401	41.0	0.83
Age, mean (SD)	75.4	(11.1)	75.3	(11.1)	0.76
Diagnosis					
ST segment elevation myocardial infarction	639	37.2	1278	37.2	0.65
Non–ST segment elevation myocardial infarction	744	43.4	1488	43.4	
Unstable angina	333	19.4	666	19.4	
GRACE risk score, mean (SD)	160.4	(33.5)	160.4	(33.6)	1.00
Medical history					
Angina	961	56.2	1817	53.2	0.04
Myocardial infarction	796	46.5	1145	33.5	<0.001
Congestive heart failure	518	30.4	585	17.1	<0.001
Angiogram diagnostic of coronary artery disease	629	37.6	962	28.5	<0.001
PCI	304	17.9	508	14.9	0.01
Coronary artery bypass graft	304	17.8	442	12.9	<0.001
Peripheral vascular revascularisation	11	1.3	18	1.0	0.55
Family history of coronary artery disease	176	21.2	405	22.8	0.36
Positive stress test	184	10.9	314	9.2	0.06
Hypertension	1231	72.1	2256	66.1	<0.001
Dyslipidemia	735	43.4	1434	42.2	0.42
Peripheral arterial disease	305	17.9	419	12.3	<0.001

Atrial fibrillation	290	17.1	428	12.6	<0.001
TIA/stroke	289	17.0	393	11.5	<0.001
Smoker	923	54.0	1625	47.6	<0.001
Former smoker	604	66.4	1017	63.6	
Current smoker	283	31.1	543	33.9	0.34
Status not recorded	23	2.5	40	2.5	
Diabetes	578	33.8	904	26.4	<0.001
Diet controlled	61	11.3	130	15.1	
Oral hypoglycemia	244	45.0	443	51.3	0.004
Insulin dependent	206	38.0	253	29.3	
No treatment used	18	3.3	23	2.7	
Not recorded	13	2.4	15	1.7	
Renal insufficiency	327	19.2	379	11.1	<0.001
No dialysis	226	83.4	273	88.4	0.09
Dialysis	45	16.6	36	11.7	
Major surgery/trauma	159	9.3	203	5.9	<0.001
Major bleeding	47	2.8	79	2.3	0.34
Implantable cardiac defibrillator	11	1.3	9	0.5	0.03
Venous thromboembolism	33	3.9	43	2.4	0.03
Presentation/in-hospital					
Cardiac arrest	33	1.9	80	2.3	0.37
Killip class					
I (no heart failure)	1122	65.4	2320	67.6	
II (rales)	428	24.9	752	21.9	0.09
III (pulmonary oedema)	149	8.7	318	9.3	
IV (cardiogenic shock)	17	1.0	42	1.2	

Left-ventricular ejection fraction	1148	67.3	2399	70.5	0.02
Country					<0.001
Argentina	99	5.8	263	7.7	
Australia/New Zealand	172	10.0	354	10.3	
Austria	15	0.9	43	1.3	
Belgium	80	4.7	219	6.4	
Brazil	132	7.7	214	6.2	
Canada	92	5.4	238	6.9	
France	100	5.8	279	8.1	
Germany	58	3.4	119	3.5	
Italy	22	1.3	100	2.9	
Poland	77	4.5	213	6.2	
Spain	62	3.6	206	6.0	
UK	142	8.3	241	7.0	
USA	665	38.8	943	27.5	

4.4.1 Use of guideline therapies

The reported use of individual guideline recommendations among the cases and the controls is presented in table 2. Overall, patients surviving to 6 months were more likely to receive a greater number of guideline therapies. The adjusted ORs for mortality by 6 months with increasing guideline use are shown in figure 1.

Table 2: Rates of individual evidence-based recommendations among cases and controls.

	Cases (n=1716)		Controls (n=3432)		p Value
	n	%	n	%	
Cardiac catheterisation	692	40.9	1772	51.9	<0.001
PCI	329	19.3	1111	32.5	<0.001
Coronary artery bypass graft surgery	49	2.9	150	4.4	0.01
ACE inhibitor	1148	67.4	2321	68.0	0.68
Aspirin	1563	91.2	3194	93.1	0.02
β-Blocker	1340	79.0	2775	81.3	0.05
Clopidogrel	661	39.0	1705	50.0	<0.001
Intravenous glycoprotein IIb/IIIa inhibitor	299	17.7	821	24.2	<0.001
Statin	951	55.7	2097	61.6	<0.001
Referral to cardiac rehabilitation	302	23.7	752	28.5	0.001

4.4.2 Guideline recommendations and 6-month survival

The independent and relative relationship between the use of each guideline and 6-month survival is given in table 3. After adjustment for clinical and regional factors, undergoing PCI or CABG was associated with the most substantial relative survival advantage. Pharmacotherapies most associated with an improved survival at 6 months were clopidogrel and statins. The absolute contribution to total mortality (attributable risk, associated with incomplete implementation of clinical guidelines, or the amount of mortality that may be prevented with complete application of a given therapy) is presented in table 4. Up to 31.9% and 9.7% of deaths by 6 months may be prevented

with more complete use of revascularisation and statin therapy, respectively.

Table 3: Relationship between evidence-based recommendations and 6-month survival in the overall population and among patients with STEMI

	OR	LCI	UCI	P value
Overall population				
Coronary artery bypass graft surgery	0.53	0.34	0.82	0.005
PCI	0.63	0.48	0.81	<0.001
Statin therapy	0.74	0.63	0.88	<0.001
Clopidogrel	0.80	0.67	0.95	0.01
Intravenous glycoprotein IIb/IIIa inhibitor	0.83	0.66	1.05	0.12
β-Blocker	0.86	0.71	1.05	0.15
Referral to cardiac rehabilitation	0.88	0.73	1.05	0.15
ACE inhibitor	0.91	0.77	1.07	0.25
Aspirin	0.97	0.73	1.29	0.83
Cardiac catheterisation	1.14	0.92	1.40	0.23
Patients with STEMI				
Coronary artery bypass graft	0.53	0.25	1.10	0.09
PCI	0.62	0.38	0.99	0.05
Intravenous glycoprotein IIb/IIIa inhibitor	0.63	0.43	0.92	0.02
Statin	0.67	0.49	0.90	0.01
Clopidogrel	0.78	0.57	1.08	0.14
β-Blocker	0.83	0.58	1.19	0.32
Referral to cardiac rehabilitation	0.84	0.62	1.14	0.26
ACE inhibitor	0.95	0.70	1.29	0.76
Aspirin	0.96	0.55	1.68	0.89
Fibrinolysis	0.96	0.70	1.30	0.77
Cardiac catheterisation	1.32	0.90	1.94	0.16

Table 4: Attributable Fraction of 6-month mortality associated with incomplete application of evidence-based recommendations

Guideline recommendation[*]	AF (%)	95% CI (%)
Revascularisation	31.9	19.4 to 42.4
Thienopyridine	10.9	2.3 to 9.8
Statin therapy	9.7	4.1 to 15.0
Rehabilitation referral	10.6	–2.4 to 21.5
ACE inhibitor	4.3	–0.1 to 9.4
Glycoprotein IIb/IIIa inhibition	1.9	–16.8 to 17.3
β-Blocker	0.1	–2.8 to 4.6

- [*] Effect of aspirin not estimatable.

4.4.3 Combined effects of guidelines: STEMI patients

In the smaller subset of patients with STEMI, the relationship between the guidelines was consistent with the analysis in the overall population. Apart from PCI, intravenous glycoprotein IIb/IIIa inhibition and statin therapy, many individual therapies did not reach statistical significance, contributed to by the smaller number of patients included. Fibrinolysis alone was not associated with reduced 6-month mortality after adjusting for other therapies (OR 0.96; 95% CI 0.70 to 1.30; p=0.77). When restricted to patients not receiving PCI (either as reperfusion or revascularisation), a significant benefit was observed (OR 0.74; 95% CI 0.56 to 0.99; p=0.04).

4.4.4 Combined effects of guidelines: all the patients

When modelled collectively, application of all guideline recommendations in the overall population was associated with a lower 6-month mortality (OR 0.29; 95% CI 0.19 to 0.44; p<0.001). In this analysis, little incremental gain in 6-month survival was observed with the application of more than six guideline recommendations, although there were wide confidence bounds around these estimates (figure 2).

4.5 Discussion

With the expanding evidence base provided by clinical trials, the number of therapies and treatment strategies advocated by expert clinical guidelines can only increase.[1–5] This increase places a burden on patients in terms of compliance and on health systems in terms of resource allocation. By weighing the relative and absolute value of each recommendation with respect to 6-month survival, in contrast with the other recommendations, this analysis may inform choice between therapies and strategies when such decisions need to be made. This analysis seeks to explore the relative mortality reduction associated with each guideline-recommended therapy after controlling for all others and describing the absolute proportion of lives that may be preserved with more complete application of each of the therapies. In this regard, coronary revascularisation appears to provide greater survival benefit than pharmacotherapy in relative terms. Among the pharmaceuticals, statin therapy and thienopyridines were associated with the greatest relative reductions in mortality. In absolute terms, more complete applications of revascularisation, statin therapy and clopidogrel have the greatest association with limiting the absolute numbers of lives lost by 6 months.

By the very nature of placebo-controlled clinical trial design, new evidence supporting novel treatment approaches provides evidence that is additive. Hence, these studies inform clinicians about the treatments that should be prescribed but rarely inform us of which therapies may be omitted. While the recent increase in non-inferiority studies provides some information regarding the choices between drugs, studies weighing the incremental value of well-established therapies in the modern era of ACS treatment are lacking.[13] For example, clinical evidence supporting the long-term use of β-blockade among patients with ACS predates the current era where a relatively high rate of coronary angiography and revascularisation is practised.[14] Hence, the incremental value of this guideline recommendation in the current context is unclear and is unlikely to be addressed in future randomised clinical trials.[15]

Consequently, within a nested case–control design, the impact of several therapeutic options can be weighted in the context of current clinical practise. With this analysis, estimates of the survival advantage with coronary revascularisation are greater than those observed in the clinical trials.[16–19] This may be because patients enrolled in randomised trials may not be representative of individuals presenting in clinical practise.[20] Our data are consistent with but extend beyond studies that support an

early invasive approach to the management of ACS, although unmeasured biases cannot be excluded. These observations suggest that invasive management resulting in revascularisation does provide a reduction in mortality, reinforcing the clinical trial data that have relied upon composite ischaemic end points and that have at times been inconsistent. The benefits associated with pharmacotherapeutic drugs such as statins and clopidogrel are also consistent with key clinical trials.21–24 In contrast, the relationship with fibrinolysis is more modest than that observed in clinical trials and may be accounted for by PCI occurring both as reperfusion and revascularisation being included in the model. When the analysis was restricted to the patients not receiving any form of PCI, a benefit comparable with effects seen in clinical trials is evident. The modest benefits observed with the use of aspirin were less striking than expected and are likely explained by the high rate of use and, therefore, a low capacity to detect a difference associated with this therapy. Of course, all of these relative effects will be influenced by the adoption of new therapies into current practise.

At a clinical level, being able to independently value these therapies may provide the rationale for choosing between treatments when a choice must be made, either for reasons of cost or compliance. Among pharmacotherapies, statins and clopidogrel seem to impart the greatest additional benefit in this analysis. These drugs should, therefore, be the focus of efforts to improve compliance. Conversely, these data are reassuring when considering stopping β-blockade among patients who are poorly compliant or face significant adverse effects. Consequently, such an analysis may further the interpretation of performance measures in ACS care, which currently tend to weigh these measures either equally or cumulatively.7 25 However, such analyses cannot displace clinical judgement when considering any individual patient. Rather, they reflect potential gains at a population or average patient level.

At a policy level, these data help inform quality improvement priorities. Coronary revascularisation is associated with the greatest survival benefit, in part related to its incomplete application. Hence, limitations in the conduct of revascularisation represent the largest missed opportunity for preventing deaths by 6 months among patients with an ACS.26 However, these data are in contrast to evidence suggesting a lack of mortality benefit associated with access to hospital with onsite invasive services.27 This difference likely reflects the focus on provision of rather than the opportunity for revascularisation between these two studies. These observations lend themselves to the development of institutional performance indicators that reflect the rate of coronary angiography and revascularisation provision and inform the design of healthcare

systems and referral patterns that support early access to invasive investigation and management.

4.5.1 Limitations

Several limitations should be considered. First, as with all observational studies, the possibility for unmeasured biases exists, thus leading to overestimation or underestimation of treatment effects. Specifically, there is the potential for selection of those controls with a greater likelihood for survival who are more likely to receive clinical guideline-recommended therapies and to be referred for cardiac rehabilitation. However, evidence suggests that biases towards lack of invasive management are coupled with underuse of guideline medications and interpreting the relative impact among therapies is less subject to this bias. Similarly, the case definition using all-cause mortality as opposed to cardiovascular mortality may bias towards a greater benefit seen with revascularisation but attenuate the observed impact of pharmacotherapies. Since angiography alone was not associated with any survival advantage, such biases would appear to be minimal, at least with respect to delivering invasive management, and it is the decision to undertake invasive management that is most likely coassociated with perceived survival.

Second, given that this analysis measures exposure to a guideline recommendation at a single time point (hospital discharge), bias towards revascularisation may exist. As ongoing adherence with pharmacotherapies is not measured, non-adherence may attenuate the benefit observed with drug therapies. Nevertheless, this is a persistent clinical problem compromising the effectiveness of all long-term therapeutic strategies. Adjustment for or exclusion of patients based on non-adherence would provide a false impression of true clinical effectiveness of these drugs. Third, the focus on patients that have survived to discharge may also provide a bias in favour of revascularisation because early mortality associated with revascularisation will not be included. However, inclusion of in-hospital deaths would confound the analysis because it is also unlikely that the pharmacotherapies (apart from fibrinolysis) are likely to impact these early events. Last, the ability to confidently estimate the benefits of therapies that are close to completely applied (or very rarely used) such as aspirin and β-blockade is limited in this approach because of a lack of power, resulting from either relatively small numbers of people not receiving these therapies.

4.6 Conclusions

Within the modern management of patients presenting with ACS, a broad array of therapies are available and are recommended in clinical guidelines. Among these options, coronary revascularisation seems to provide the most robust survival advantage, highlighting the importance of improved systems of care enabling greater access to invasive management in many parts of the world. Among pharmacotherapies, statins and clopidogrel are associated with the greatest benefit. These data may provide a rational basis for selecting between therapeutic options when compliance or cost is an issue.

4.7 Acknowledgments

The authors thank the physicians and nurses participating in the GRACE Study. Sophie Rushton-Smith, PhD, provided editorial support and was funded by sanofi-aventis. The GRACE Study is supported by an unrestricted educational grant from sanofi-aventis, Bridgewater, Massachusetts, USA, to the Center for Outcomes Research, University of Massachusetts Medical School. Sanofi-aventis had no involvement in the collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the paper for publication.

Competing interests DPC receives funding from sanofi-aventis Australia and MSD Australia. KAE receives funding from Biosite, Bristol Myers Squibb, Cardiac Sciences, Blue Cross Blue Shield of Michigan, Hewlett Foundation, Mardigian Fund, Pfizer, sanofi-aventis, Varbedian fund, National Heart, Lung and Blood NIH. FAA, ÁA, JMG, DB and RD receive funding from sanofi-aventis. Ethics approval The GRACE Study was conducted with the approval of each of the participating centres around the world. Provenance and peer review Not commissioned; externally peer reviewed.

4.8 References

1 Van de Werf F, Ardissino D, Betriu A, *et al*. Management of acute myocardial infarction in patients presenting with ST-segment elevation. the task force on the management of acute myocardial infarction of the European society of cardiology. *Eur Heart J* 2003;**24**:28–66.

2 Bertrand ME, Simoons ML, Fox KAA, *et al*. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002;**23**:1809–40.

3 Kushner FG, Hand M, Smith SC Jr, *et al*. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009;**120**:2271–306.

4 Anderson JL, Adams CD, Antman EM, *et al*. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American heart association task force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007;**116**:e148–304.

5 Aroney CN, Aylward P, Kelly AM, *et al*. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. *Med J Aust* 2006;**184**:S1–30.

6 Alexander KP, Roe MT, Chen AY, *et al*. Evolution in cardiovascular care for elderly patients with non–ST-segment elevation acute coronary syndromes: results from the CRUSADE National quality improvement initiative. *J Am Coll Cardiol* 2005;**46**:1479–87.

7 Mukherjee D, Fang J, Chetcuti S, *et al*. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes.

Circulation 2004;**109**:745–9.

8 Anonymous. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalised with acute coronary syndromes. *Am Heart J* 2001;**141**:190–9.

9 Eagle KA, Goodman SG, Avezum A, *et al*. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet* 2002;**359**:373–7.

10 Steg PG, Goldberg RJ, Gore JM, *et al*. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalised with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol* 2002;**90**:358–63.

11 Granger CB, Goldberg RJ, Dabbous O, *et al*. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;**163**:2345–53.

12 Benichou J. Methods of adjustment for estimating the attributable risk in case–control studies: a review. *Stat Med* 1991;**10**:1753–73.

13 Stone GW, McLaurin BT, Cox DA, *et al*. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;**355**:2203–16.

14 Anonymous. The beta-blocker heart attack trial. beta-Blocker Heart Attack Study Group. *JAMA* 1981;**246**:2073–4.

15 Chen ZM, Pan HC, Chen YP, *et al*. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**:1622–32.

16 Bavry AA, Kumbhani DJ, Rassi AN, *et al*. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomised clinical trials. *J Am Coll Cardiol* 2006;**48**:1319–25.

17 Cannon CP, Weintraub WS, Demopoulos LA, *et al*. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–87.

18 de Winter RJ, Windhausen F, Cornel JH, *et al*. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;**353**:1095–104.

19 Fox KA, Poole-Wilson PA, Henderson RA, *et al*. Interventional versus conservative treatment for patients with unstable angina or non–ST-elevation

myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomised Intervention Trial of unstable angina. *Lancet* 2002;**360**:743–51.

20 Steg PG, Lopez-Sendon J, Lopez de Sa E, *et al*. External validity of clinical trials in acute myocardial infarction. *Arch Intern Med* 2007;**167**:68–73.

21 Yusuf S, Zhao F, Mehta SR, *et al*. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.

22 Sabatine MS, Cannon CP, Gibson CM, *et al*. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 2005;**294**:1224–32.

23 Cannon CP, Steinberg BA, Murphy SA, *et al*. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol* 2006;**48**:438–45.

24 Hulten E, Jackson JL, Douglas K, *et al*. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomised controlled trials. *Arch Intern Med* 2006;**166**:1814–21.

25 Peterson ED, Roe MT, Lytle BL. The association between care and outcomes in patients with acute coronary syndrome: national results from CRUSADE (abstract). *J Am Coll Cardiol* 2004;**43**:406A.

26 Bhatt DL, Roe MT, Peterson ED, *et al*. Utilization of early invasive management strategies for high-risk patients with non–ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA* 2004;**292**:2096–104.

27 Van de Werf F, Gore JM, Avezum A, *et al*. Access to catheterisation facilities in patients admitted with acute coronary syndrome: multinational registry study. *BMJ* 2005;**330**:441.

5 POTENTIAL SURVIVAL GAINS IN THE TREATMENT OF MYOCARDIAL INFARCTION

5.0 Title Page: Potential Survival Gains in the Treatment of Myocardial Infarction

Derek P. Chew MBBS MPH FRACP FACC[a], Luan T. Huynh MSBS [a], Danny Liew MBBS PhD FRACP[b], Carolyn Astley RN[a], Ashish Soman MBBS[c], David Brieger MBBS PhD FRACP FACC[d]

Author affiliations

Derek P Chew: Flinders University/Flinders Medical Centre, Bedford Park, SA, 5042. Australia

Luan T. Huynh: Flinders University/Flinders Medical Centre, Bedford Park, SA, 5042. Australia

Carolyn Astley: Flinders University/Flinders Medical Centre, Bedford Park, SA, 5042. Australia

Danny Liew: St Vincent's Hospital, Fitzroy, VIC 3065, Australia

Ashish Soman: Sanofi Aventis Australia, Macquarie Park NSW 2113 Australia

David Brieger: Concord Hospital, Concord NSW 2139 Australia

Running Title: Missed opportunities in Australian ACS management.

Corresponding Author

Derek P. Chew MBBS MPH FRACP

Flinders University

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

5.1 Abstract

Objectives: Evaluate the potential impact of complete implementation of guideline recommendations in myocardial infarction care and contrast this with new innovations.

Design: Modelling of potential events-prevented from literature-based treatment effects and observed guideline recommendation utilization rates

Setting: Hospital-based care

Participants: Nationwide registry of 1630 myocardial infarction patients adjusted for age, gender and GRACE score extrapolated to population of 10,000 patients

Interventions: Literature-based efficacy estimates associated with guideline-recommended treatments and a putative therapy providing a 10% to 30% 12-month event reduction.

Main Outcome Measures: Mortality and recurrent MI or stroke by 30 days and 30 days to 12 months.

Results: Adjusted-mortality rates for optimally managed ST segment MI (STEMI) and non-ST segment MI (NSTEMI) patients to 30 days were 0.6% and 2.5%, respectively. Adjusted mortality from 30-days to 12 months was 1.8% among optimally managed patients. No reperfusion occurred in 30% of STEMI patients. Fewer than 4 guideline therapies were prescribed in 26% of patients at discharge. Compared with in-hospital care, better application of secondary prevention therapies provided the greater absolute gains (STEMI 23 lives/10,000 patients by 30 days, NSTEMI 43 lives/10,000 by 30 days, and secondary prevention 104 lives/10,000 by 12 months). A putative novel treatment reducing mortality by 30% among optimally managed patients would save a further 4 lives/10,000 by 12 months.

Conclusions: Potential gains from improved clinical effectiveness in MI care are likely to compare favourably with benefits achieved though innovations, and should inform priorities in research and implementation strategies for improving MI outcomes.

Abbreviations:

ACACIA= Acute Coronary Syndrome Prospective Audit

ACS: Acute coronary syndrome

MI = Myocardial Infarction

NSTEMI= Non ST segment Elevation Myocardial Infarction

PCI= Percutaneous Coronary Intervention

STEMI= ST segment Elevation Myocardial Infarction

5.2 Introduction

In recent decades, many advances have occurred in the management of myocardial infarction (MI). These include: emergent percutaneous coronary intervention (PCI) for reperfusion; potent anti-thrombotic agents; and HMG-CoA reductase inhibition. Collectively these therapies have led to a decline in MI mortality and morbidity, and are advocated in clinical guidelines.(1, 2) The drive for innovation continues in areas including device technologies, myocardial protection and stem cell technology.(3-5)

Yet, current studies frequently combine fatal and non-fatal outcomes or employ a non-inferiority design in recognition of a slowing in the reduction in MI mortality through innovation. In this context the incomplete application of evidence-based therapies within in-hospital care of ACS has also been documented and is associated with sub-optimal clinical outcomes in a number of studies.(6-8) Similarly, delays in hospital presentation and poor access among many patients are associated with increased adverse events and mortality.(9) Non-adherence with secondary prevention therapies is also associated with late mortality that could be prevented.(10)

Consequently, we explored the potential gains in lives-saved and events prevented through optimisation of each of these areas within the context of current Australian practice in the management of MI and contrasted these with the potential gains from putative novel treatments. Such an analysis may provide perspective for focusing efforts towards improving clinical outcomes.

5.3 Methods

5.3.1 Study Design and Patient Population

To evaluate the potential impact of more thorough application of proven evidence-based care, we developed a model that incorporated current utilisation rates in a nationwide audit of current acute coronary syndrome (ACS) management and treatment effects for various treatments established in large-scale randomised clinical trials or meta-analyses.

Details of the Acute Coronary Syndrome Prospective Audit (ACACIA, protocol number PM_L_0051) have been published elsewhere.(6, 7) Briefly, 100-150 consecutive if consenting patients with suspected ACS were enrolled from 39 hospitals across Australia between November 2005 and May 2006 (n=3,402) with 12-month follow-up in 99.7% of the cohort achieved by June 2007. Patients presenting with ACS secondary to other processes such as major trauma or surgery, were excluded. Ethics committee approval was provided at each site. Informed consent was obtained from all patients except those who died before consent was sought and permission for access to medical records for these patients was granted by the local ethics committees. Late events were centrally adjudicated. The present analysis is confined to patients with a final diagnosis of either ST-segment elevation (STEMI) (n=683) or non-STEMI (n=947), regardless of survival status, as determined by the enrolling site, and subsequently confirmed by central adjudication of electrocardiograms and biomarkers using standard accepted definitions.

5.3.2 Clinical Factors and Invasive Management

We collected variables focusing on time to presentation, times to treatment, therapies administered, and demographic and clinical factors known to be important for short and long-term risk stratification and risk adjustment.

Time to presentation among patients with STEMI was categorised as <3 hours, 3-6 hours and >6 hours. Reperfusion therapy for such patients was classified as no reperfusion, timely fibrinolysis (≤30 min from presentation), delayed fibrinolysis (>30 min from presentation), timely primary percutaneous coronary intervention (PCI) (≤90 min from presentation) and delayed primary PCI (>90 min from presentation). Timely early invasive management was defined as patients undergoing coronary angiography within 72 hours of presentation during the acute hospital stay, regardless of the need for transfer between acute care hospitals. Delayed intervention reflected angiography during the index hospitalisation but > 72 hours, while no early invasive management included those receiving no angiography or outpatient angiography. Patients undergoing revascularisation based on angiographic data predating the index admission were excluded. The use and adherence with anti-thrombotic therapy, HMG CoA reductase inhibition, angiotensin converting enzyme (ACE)-inhibitors/ angiotensin receptor (AR)-antagonists, and beta-blockers were evaluated at discharge. Patients with not prescribed therapies based on stated contraindications were exclued (e.g. beta-blockers and asthma, allergy to aspirin). Late loss of adherence was defined as the proportion of patients initially prescribed four or five guideline therapies who where alive and taking three or less therapies at 6-month follow-up.

5.3.3 Treatment Effects, 30-day and 12-month Event Rates and Costs

We estimated of treatment effects, where possible, from large-scale randomised clinical trials or meta-analyses as they provide robust and unbiased estimates of relative treatment effect size.(Table 2)

Since a contemporary completely untreated subgroup of MI patients is not available in the literature, we used the observed 30-day and 12-month mortality and MI and/or stroke rates for those patients receiving invasive management and four or more guideline recommended therapies adjusted for median age (65 yrs) , gender (male)

and median GRACE score (score 139) (C-statistic: 0.82) within the ACACIA registry as estimate for mortality and recurrent ischaemic events in an optimally managed population.

5.3.4 Effects of Omission of Proven Therapies

To estimate the effect of the omission of each therapy, treatment delay or loss of compliance on overall mortality, we used the inverse of the treatment effect of each (risk associated with omission [a]) multiplied by the proportion of patients not receiving that therapy (proportion of population at risk [b]). We then multiplied this figure by overall case-event rate for optimally-treated patients (the absolute risk [c]) and then by a population of 10,000 (absolute number of people [d]).(11)

For example:

(a) Aspirin provides a 24% reduction in mortality, so the excess mortality risk associated with omitting aspirin: 1/0.76=1.32;

(b) Assuming the observed rate of aspirin omission was 10% or 0.1;

(c) Using the observed 12-month case fatality rate for optimally managed patients of 5% or 0.05;

(d) Assuming 10,000 presentations with MI per year;

It follows that the absolute number of potential excess deaths resulting from omission of aspirin can be calculated as “(a x b +[1-b]-1) x c x d” or ([1.32 x 0.1]+[1-0.1]-1) x 0.05 x 10,000=16 deaths.

The following modifications to this basic analysis were made. Since STEMI and NSTEMI patients represent mutually exclusive groups and the impact of delay in presentation, mode of reperfusion and receipt of timely reperfusion on clinical events is confined to STEMI, we modelled these separately over 30 days, and then combined for

the assessment of secondary prevention therapies on events from 30 days to 12 months.

We modelled therapies cumulatively using the Mant-Hicks cumulative-relative-benefit approach.(12) To provide an estimate of the individual contribution of suboptimal delivery of care for each individual therapy, an average weighted effect for the number of patients in each group at risk (not receiving therapy) was also calculated. The average excesses in events due to delay, suboptimal adherence to guidelines in prescribed therapy and non-compliance were then summated, and presented as total excess deaths for STEMI, NSTEMI during the first 30 days and secondary prevention up to 12 months, as well as their components individual components.

Since a similar process applied to the prescription of therapies at discharge and non-adherence at 6 months would lead to an exceedingly large number of combinations without power to confidently estimate non-treatment rates (91 possible patterns of non-compliance= 8281 possibilities), we modelled discharge therapies in the sequence of aspirin, statin therapy, clopidogrel, angiotensin converting enzyme inhibition/angiotensin receptor antagonists and beta-blockers, with the proportion of “at-risk” patients representing those discharged alive on 4, 3, 2, 1 and no therapies. Lack of adherence was modelled as a single rate across the entire population, with its effects modelled as the “lack of use,” rather than an increased risk beyond the known magnitude of effect of agents as observed in some studies.(10) In addition, non-adherence was only not applied to aspirin and statin use, as these agents were rarely discontinued in the audit data. Putative novel therapy that was assumed to provide a further 10%, 20% and 30% relative risk reduction in 12-month clinical events where this benefit is confined to selected indications such as patients already optimally treated and contrasted this resultant effect with a 10-30% relative reduction in mortality resulting from a “system-wide” improvement in care delivery. Discrepancies between

the individual figures and totals reflect combined risks among patients and the effects of rounding.

5.3.5 Sensitivity Analysis

We undertook multi-way sensitivity analyses employing the analysis-of-extremes methodology, where the upper and lower confidence bounds for each variable was used when available (for treatment effect and case fatality rate), while using ±20% when confidence bounds were not available, with the lower bounds of treatment effects truncated at 1.0, to prevent the modelling of event-free advantage for omission of care.

5.4 Results

Among the 3402 patients enrolled in the ACACIA study, 1744 had a final diagnosis of MI, and a further 114 were excluded due to described contraindications, leaving1630 patients for this analysis. The median age was 65.3 years, while 28.6% were female, 24.3% were diabetic and 37.0% had a prior history of prior coronary artery disease. Overall, by 30 days and 12mths, 71/1630 (4.3%) and 155/1630 (9.5%) had died, respectively, while recurrent MI was observed in 104/1630 (6.4%) and 163/1630 (10.3%), respectively, at the same time points. Presentation delays, treatment delays and the utilisation of therapies during the acute in-hospital stay, as well as adjusted event rates up to 30 days and between 30 days and12-month among all patients, and those receiving optimal therapies are presented in Table 1.

Table 1: Characteristics, application of therapies and outcomes observed in the ACACIA population

	STEMI (n=683)	**NSTEMI (n=947)**	**All (n=1630)**
Age (years, median, IQR)	62.0 (19.2)	66.7 (20.4)	64.7 (20.2)
Male Gender (n, %)	513 (75.1)	651 (68.7)	1164 (71.4)
Diabetes (n, %)	130 (19.0)	266 (28.0)	396 (24.3)
Dyslipidaemia (n, %)	310 (45.4%)	550 (58.0)	860 (52.7)
Hypertension (n, %)	342 (50.1)	623 (65.7)	965 (59.2)
Current Smoker (n, %)	227 (33.2)	216 (22.8)	443 (27.2)
Prior MI (n, %)	92 (13.4)	258 (27.3)	350 (21.5)
Prior CABG (n, %)	21 (3.1)	150 (15.8)	171 (10.5)
Known CCF (n, %)	15 (2.1)	108 (10.5)	123 (7.1)
Creatinine Clearance (ml/min/1.73m^2, median, IQR)	73.3 (27.6)	69.0 (32.7)	71.6 (31.4)
Prior CVA (n, %)	23 (3.4)	70 (7.4)	93 (5.7)
Presentation Delay <3 hours (n, %)	486 (71.2)	508 (53.6)	994 (61.0)
Presentation Delay 3-6 hours (n, %)	84 (12.3)	163 (17.2)	247 (15.2)
Presentation Delay 6+ hours (n, %)	113 (16.5)	276 (29.1)	389 (23.9)

Primary PCI < 90 minutes (n, %)	105 (15.4)		
Primary PCI > 90 minutes (n, %)	187 (27.4)		
Fibrinolysis < 30 minutes (n, %)	137 (20.1)		
Fibrinolysis > 30 minutes (n, %)	42 (6.2)		
No fibrinolysis (n, %)	212 (31.4)		
GP IIb/IIIa inhibition used (n, %)	307 (44.9)	146 (15.4)	453 (27.8)
Angiography with 72 hours (n, %)	529 (77.4)	450 (47.5)	980 (60.1)
Angiography >72 hours (n, %)	83 (12.2)	229 (24.2)	311 (20.8)
No Angiography (n, %)	71 (10.3)	268 (28.3)	339 (19.1)
Aspirin at discharge (n, %)	633 (92.3)	868 (91.6)	1501 (92.1)
Statin at discharge (n, %)	608 (89.0)	808 (85.3)	1416 (86.9)
Clopidogrel at discharge (n, %)	534 (79.6)	605 (63.9)	1149 (70.5)
Beta-blocker at discharge (n, %)	538 (78.7)	672 (71.0)	1210 (74.2)
ACE-I/ARA at discharge (n, %)	540 (79.0)	661 (69.7)	1201 (73.6)
All patients			
[8]Adjusted 30-day death	1.8% (1.0 to 3.2%)	2.4% (1.4 to 3.8%)	
Adjusted 30-day re-MI/stroke	6.7% (3.5 to 12.8%)	6.8% (5.0 to 8.9%)	
Adjusted 30 days to12 months death			3.5% (2.5 to 4.7%)

Adjusted 30 days to12 months re-MI/stroke			3.9% (2.9 to 5.2%)
Optimal Management*			
Adjusted 30-day death	0.6% (0.2 to 2.0%)	2.5% (0.9 to 7.0%)	
Adjusted 30-day re-MI/stroke	5.8% (3.5 to 9.7%)	5.2% (2.6 to 10.0%)	
Adjusted 30 days to12 months death			1.8% (1.1 to 2.9%)
Adjusted 30 days to12 months re-MI/stroke			4.1% (3.2 to 5.3%)

MI= Myocardial Infarction, CABG=Coronary Artery Bypass Grafting, CCF= Congestive Cardiac Failure, CVA= Cerebrovascular Accident, PCI = Percutaneous Coronary Intervention, GP = Glycoprotein, ACE-I= Angiotensin Converting Enzyme inhibition, ARA= Angiotensin Receptor Antagonist.

ᵟRates adjusted for age (median), gender(male) and median GRACE score (139)

* For STEMI patients: Reperfusion, Early Invasive Management and GP IIb/IIIa Inhibition, For NSTEMI patients: Early Invasive Management and GP IIb/IIIa Inhibition, For Secondary Prevention: 4 or 5 guideline recommended therapies at discharge and adherent at 6 months.

Table 2: Literature-based estimates of relative increase in events related to the non-receipt of various components of ACS care. Risk associated with omission calculated as the inverse of the clinical trial based estimate or relative benefit

	Relative Risk	*Upper Estimate*	*Lower Estimate*	*Reference*
Presentation				
No delay	1			(23)
Delay 3-6hrs	1.21	1.45	1	(23)
Delay 6>hrs	1.47	1.76	1.18	(23)
Reperfusion				
PPCI optimal	1			(23)
PPCI delay	1.24	1.49	1	(23)
Lysis optimal	1.1	1.32	1	(23)
Lysis delay	1.28	1.52	1.02	(23)
None	1.47	1.76	1.18	(23)
Invasive management				
Timely invasive	1			
Delayed Invasive	1.10	1.21	0.75	(21)
None	1.22	2.00	0.75	(24)
Pharmacotherapy				
GP IIb/IIIa inhibition	1.09	1.18	1	(25)
ASA	1.32	1.43	1.22	(26)
Statin	1.45	1.56	1.35	(27)
Clopidogrel	1.41	1.79	1.11	(28)
ACE-inhibition or ARB	1.19	1.37	1.03	(29)
Beta-blocker	1.30	1.45	1.18	(30)

Loss of adherence modelled as the “lack of benefit” except of for invasive management where omission was permitted to be associated with possible benefit.

Estimates of the effects of omission associated with evidence-based therapies based on the literature are presented in Table 2.

5.4.1 Impact of Early Management of STEMI

For patients presenting in a timely manner, receiving timely reperfusion and early invasive management with concomitant glycoprotein IIb/IIIa inhibition, the age, gender and GRACE risk score adjusted 30-day mortality and recurrent MI/stroke rates was very low, 0.6% (0.2 to 2.0%) and 2.5% (0.9 to 7.0%), respectively. However, these patients represented only 13.5% of the STEMI population. Imputing the relative benefits associated with timely presentation, early reperfusion, mode of reperfusion, subsequent early invasive management and glycoprotein IIb/IIIa inhibition, to the remaining population of STEMI patients yields a further 23 lives saved and 198 events prevented per 10,000 presentations. (Table 3) Components of this benefit are presented in table 3. Only 5% of the deaths (1/23) are attributable to receiving fibrinolysis rather than PCI as reperfusion therapy in a timely manner.

Table 3: Potential opportunities for lives saved and non-fatal events prevented and components of these benefits (with sensitivity analysis) through better application of therapies and possible novel innovations.

	Deaths per 10,000	*Range in Sensitivity analysis*	*Recurrent MI or Stroke per 10,000*	*Range in Sensitivity analysis*
Total events: STEMI	23	2 to 60	213	24 to 527
Delayed Presentation	6	1 to13	60	14 to127
Fibrinolysis rather than PPCI	1	0 to 5	12	0 to 45
Delayed PPCI	3	0 to 10	38	0 to 92
Delayed Fibrinolysis	1	0 to 3	11	1 to 26
No Reperfusion	7	3 to 17	83	25 to 161
Delayed Invasive Management	0	0 to1	2	0 to 4
No Invasive Management	1	0 to 7	5	0 to 27
Total Events: NSTEMI	43	0 to 177	55	0 to183
Delay Invasive Management	4	0 to 10	3	0 to8
No Inv Invasive management	16	0 to 87	11	0 to 67
No GP	21	0to 59	40	0 to 96

Total events: Secondary Prevention	104	27 to 266	191	61 to 605
Therapies				
Lack of Prescription	46	16 to 101	121	36 to 229
Non-adherence	58	11 to165	69	24 to 376
Putative Novel Therapy	Optimal*	All**	Optimal	All
10% Reduction	1	34	4	96
20% Reduction	3	67	9	192
30% Reduction	4	101	13	288

PPCI= Primary Percutaneous Coronary Intervention

* Optimal = For STEMI patients: Reperfusion, Early Invasive Management and GP IIb/IIIa Inhibition, For NSTEMI patients: Early Invasive Management and GP IIb/IIIa Inhibition, For Secondary Prevention: 4 or 5 guideline recommended therapies at discharge and adherent at 6 months.

** All = a benefit that applies to the entire population.

5.4.2 Impact of the Early Management of NSTEMI

Among optimally treated NSTEMI patients, receiving early invasive management and intravenous glycoprotein IIb/IIIa inhibition, the observed adjusted 30-day mortality and recurrent ischaemic event rates were 2.5% (0.9 to 7.0%) and 5.2% (2.6%to10.0%), respectively. Optimal management of these patients was observed in 12.4% of patients. Extending the benefit of these more complete and timely use of invasive management and glycoprotein IIb/IIIa inhibition to the entire population would be associated with a 43 lives saved and 55 recurrent events prevented among 10,000 presentations. Components of this benefit are presented in table 3.

5.4.3 Impact of Secondary Prevention Therapies

Among patients discharged alive, 76.3% of patients were prescribed 4 or more guideline recommended chronic pharmacotherapies, and by 6 months 22.4% of these patients were no longer adherent (taking 3 or less therapies). The observed adjusted mortality and recurrent ischemic rates were 1.8% (1.1 to 2.9%) and 4.1% (3.2 to 5.3%) from 30 days to 12 months, respectively. Ensuring more complete prescription and adherence to proven therapies to the entire population would be associated with a further 104 lives saved and 191 recurrent ischaemic events prevented per 10,000 presentations. (Table 3) Figure 2 describes the observed adjusted-mortality and the model-projected rates associated the increasing use of guideline recommended therapies.

5.4.4 Impact of Novel Therapeutic Approaches

Within this national audit, only 4.0% of all MI presented within three hours of symptom onset and received timely reperfusion with either PCI or fibrinolysis for STEMI, or received early invasive management with glycoprotein IIb/IIIa inhibition in the context of NSTEMI, and were then discharged on four or five therapies with maintained late

adherences to these therapies. The benefits associated with a novel therapeutic approach yielding a further 10%, 20% and 30% relative reduction in mortality and/or non-fatal ischaemic events among these optimally managed patients and all patients, regardless of the extent of concomitant therapy, by 12 months are presented in table 3.

5.5 Discussion

By drawing on data from randomised clinical trials and systematic reviews and combining these with contemporary Australian evidence regarding the application of such therapies, we have demonstrated that the potential gains that may be achieved with widespread application of current therapeutic approaches are much greater than those that may arise from future innovations in the management of MI. Among current recommendations, improving prescription of medications at discharge and ensuring late adherence are likely to provide the greatest reductions in subsequent mortality and non-fatal ischaemic events. A greater absolute number of fatal and non-fatal ischaemic events are likely to be prevented by more complete application of any treatments as opposed to the choice between these treatments. Lastly, consideration of the costs relevant to the provision of care and subsequent events, may provide context for the design, implementation and resourcing of strategies for improving the quality of care of ACS patients.

In extrapolating clinical research efficacy to an observed broader community, we draw upon two robust sources of data. First, randomised clinical trial data represent the best estimates of relative treatment efficacy, effectively eliminating clinical heterogeneity. However, the potential “absolute” impacts of such therapies in terms of lives saved or events prevented are governed by their uptake and the baseline risk of the population, both of which cannot be evaluated within the protocol-driven trial designs that often employ stringent inclusion and exclusion criteria. Second, clinical registries seeking to enrol consecutive patients and evaluate the application of care within a realistic clinical

context are apt at documenting utilisation and risk, but are inferior for evaluating efficacy, due to unmeasured biases. Consequently, a hybrid approach, incorporating both sources and encompassing the cost implications, has the possible strength of informing “value” choices that must be made before “investing” in the onward development and delivering of any treatment strategy.(11) In this regard, investment in research and strategies directed at the better application of guideline-advocated pharmacotherapies and ensuring adherence is likely to provide the greatest future reductions in mortality and non-fatal ischaemic events in clinical care. This observation is conservative, given the relatively short time frame (12 months) considered in this study.

Our analysis also suggests that there is more to be gained with the broader application of these therapies to those patients who are currently not receiving care, as opposed to the choice between therapies amongst those who are. The greatest potential gains appear to reside with extending reperfusion therapy to all patients, increasing access to angiography and more complete application of secondary prevention therapies. Such observations do not seek to ignore the many challenges and barriers in applying evidence-based care to many patients with increased clinical complexity and frailty. Instead, it argues for research focused on overcoming these challenges. However, these observations are in stark contrast to the current research and development focus on the choice between primary PCI and fibrinolysis in STEMI and the numerous “non-inferiority” studies evaluating various anti-thrombotic strategies among patients presenting with non-ST-segment elevation ACS.(13-16) Resources may be better directed towards evaluating the factors limiting the application of care to the broader and generally higher-risk clinical community, and confirming the absolute benefits among such patients.

These potential opportunities should also be contrasted with the possible gains provided by innovation such as new reperfusion approaches, refinements in technologies such as drug-eluting stents and emboli protection devices, and stem cells for myocardial repair. (3, 5, 17, 18) These approaches are very costly in both their development and implementation, despite their benefits often being restricted to relatively limited indications or small subgroups of patients. Similarly, the relatively restrictive inclusion and exclusion criteria employed in many modern trials limits their generalizability and therefore uptake by the broader community. Furthermore, it is noted that despite the evolution in ACS management, few therapies in more recent years have singularly reduced mortality by the magnitude of 10%. In addition, given the highly selected populations of patients included in these clinical trials, the generalizability of the small mortality benefits observed in the broader population remains in question. In contrast, system-wide improvements in care delivery, such as standardised discharge tools, have provided 12-month mortality benefits well in excess of this relative magnitude of a novel therapy.(19)

5.5.1 Limitations

Several limitations should be considered. First, inherent in any modelling undertaking, this analysis describes possible rather than actual gains, and is dependent on the assumptions made. Such characteristics are unavoidable in any forward-looking projection, and estimates have been either conservative or based on robust data. Second, the age, gender and GRACE score adjusted base rates for 30-day and 12-month mortality for patients treated optimally are drawn from a relatively small number of patients leading to greater uncertainty. However, these estimates may well underestimate the risk since registry evidence documents the bias towards the more complete use of treatments among lower-risk patients.(20) In addition, we have confined the benefits of invasive management to 30-day outcomes, potentially undervaluing the impact of invasive management on late events. This is conservative

as the confidence bounds are broadest for this intervention.(21) Nevertheless, assuming the benefit of invasive management persists to 12 months does not result in gains that exceed those seen with secondary prevention. Furthermore, while varying these rates does impact the absolute numbers of events attributable to various "omissions of care", the relative relationship between quality improvement and innovation remains unchanged. Third, it is assumed that the relative effects of therapies are applicable to those in whom it is not applied and that the effect of these therapies remains independent of each other. Several studies have demonstrated that patients not receiving therapies are more often those at increased risk, who potentially stand to gain a greater benefit in absolute terms.(20, 22) Furthermore, while there is likely to be diminishing return from the cumulative use of all the guideline therapies, this effect is accounted for the methods of the analysis. While true interaction between therapies is not accounted for here, subgroup analyses of clinical trials have rarely shown true interactions between therapies, other clinical risk factors and treatment effects. Hence, while this approach represents a relatively "conservative" perspective, more rigorous evaluation of the impact of therapies among under-served high-risk groups is greatly needed.

5.6 Conclusions

Within the context of current Australian management of ACS, quality improvement initiatives directed at the prescription and persistence of secondary prevention therapies are likely to have the greatest potential for the reduction of both mortality and recurrent events. Optimising access to any form of reperfusion and invasive investigation is also likely to provide greater mortality benefits than novel therapies and strategies that further refine these treatments or strategies.

5.7 Appendix

Study Organization

Steering committee: Derek P. Chew: Flinders University/Flinders Medical Centre. **John Amerena**: Geelong Hospital. **David Brieger**: Concord Hospital. **Steve Coverdale**: Nambour Hospital. **Jamie Rankin**: Royal Perth Hospital.

Data management and analysis: Cardiovascular Outcomes Research (COR): Carolyn Astley, Danni Molloy, Sue Mattchoss, Luan Huynh

Sponsor: sanofi-aventis australia pty ltd

Investigators

Dr Tan Ren, Canberra Hospital, ACT; A/Prof David Brieger, Concord Hospital, NSW; A/Prof MA Fitzpatrick, Nepean Hospital, NSW; Prof Peter Fletcher, John Hunter Hospital, NSW; Dr David Rees, St George Hospital, NSW; Dr Craig Juergens, Liverpool Hospital, NSW; Dr Jonathon Waites, Coffs Harbour Hospital, NSW; Dr Greg Nelson, Royal North Shore Hospital, NSW; Dr Michael Sinclair, Dubbo Base Hospital, NSW; Dr John Amarena, Geelong Cardiology Practice, VIC; Prof Yean Lim, Western Hospital, VIC; Dr Mark Horrigan, Austin Health, VIC; Dr Leeanne Grigg, Royal Melbourne Hospital, VIC; Dr David Eccleston, The Northern Hospital Clinical Trials Unit, VIC; Dr Greg Szto, Peninsula Private Hospital, VIC; A/Prof Gishel New, Box Hill Hospital, VIC; Dr Christopher Medley, Wodonga Regional Health Service, VIC; Dr Steven Coverdale, Nambour General Hospital, QLD; Prof Laurie Howes, Gold Coast Hospital, QLD; Dr David Cross, Wesley Hospital, QLD; Dr Paul Garrahy, Princess Alexandra Hospital, QLD; Dr Darren Walters, The Prince Charles Hospital, QLD; Dr Spencer Toombes, Toowoomba Health Services, QLD; Dr Prasad Challa, Cairns Base Hospital, QLD; Dr Kumar Gunawardane, The Townsville Hospital, QLD; Dr William Parsonage, Royal Brisbane Hospital, QLD; Dr Raj Shetty, Rockhampton Hospital; A/Prof Derek Chew, Flinders Medical Centre, SA; Prof Stephen Worthley, Royal Adelaide Hospital, SA; Prof John Horowitz, The Queen Elizabeth Hospital, SA; Dr Samuel Varughese, Mt Gambier Hospital, SA; Dr Christopher Zeitz, Port Augusta Hospital, SA; Dr Margaret Arstall, Lyell McEwin Hospital, SA; Dr Jamie Rankin, Royal Perth Hospital, WA; Dr Barry McKeown, Fremantle Hospital, WA; Dr Johan Janssen, Kalgoorlie Regional Hospital, WA; A/Prof Joseph Hung, Sir Charles Gairdner Hospital, WA; Dr Philip Roberts-Thomson, Royal Hobart Hospital, TAS; Dr Marcus Iton, Darwin Private Hospital, NT; Dr Alex Brown, Menzies School of Health Research, NT.

5.8 References

1. Aroney CN, Aylward P, Kelly AM, Chew DPB, Clune E. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. Medical Journal of Australia. [Review]. 2006 April;184(8):S1.

2. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. Circulation. 2008 January 1;117(2):296-329.

3. Gick M, Jander N, Bestehorn HP, Kienzle RP, Ferenc M, Werner K, et al. Randomised evaluation of the effects of filter-based distal protection on myocardial perfusion and infarct size after primary percutaneous catheter intervention in myocardial infarction with and without ST-segment elevation. Circulation. 2005 September 9;112(10):1462-9.

4. Armstrong PW, Granger CB, Adams PX, Hamm C, Holmes D, Jr, O'Neill WW, et al. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomised controlled trial. Jama. 2007 January 1;297(1):43-51.

5. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, et al. Bone marrow cells regenerate infarcted myocardium. Nature. 2001 April 4;410(6829):701-5.

6. Chew DP, Amerena J, Coverdale S, Rankin J, Astley C, Brieger D. Current management of acute coronary syndromes in Australia: observations from the acute coronary syndromes prospective audit. Intern Med J. 2007 November;37(11):741-8.

7. Chew DP, Amerena JV, Coverdale SG, Rankin JM, Astley CM, Soman A, et al. Invasive management and late clinical outcomes in contemporary Australian management of acute coronary syndromes: observations from the ACACIA registry. Med J Aust. 2008 June 6;188(12):691-7.

8. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J, et al. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet. 2002 February 2;359(9304):373-7.

9. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. Circulation. 2005 February 2;111(6):761-7.

10. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med. 2006 September 9;166(17):1842-7.

11. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007 June 6;356(23):2388-98.

12. Mant J, Hicks N. Detecting differences in quality of care: the sensitivity of measures of process and outcome in treating acute myocardial infarction. BMJ. 1995 September 9;311(7008):793-6.

13. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003 January 1;361(9351):13-20.

14. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. Lancet. 2006 February 2;367(9510):579-88.

15. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006 November 11;355(21):2203-16.

16. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomised trial. Jama. 2004 July 7;292(1):45-54.

17. Laarman GJ, Suttorp MJ, Dirksen MT, van Heerebeek L, Kiemeneij F, Slagboom T, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med. 2006 September 9;355(11):1105-13.

18. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet. 2006 February 2;367(9510):569-78.

19. Eagle KA, Montoye CK, Riba AL, DeFranco AC, Parrish R, Skorcz S, et al. Guideline-based standardised care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. J Am Coll Cardiol. 2005 October 10;46(7):1242-8.

20. Fox KA, Anderson FA, Jr, Dabbous OH, Steg PG, Lopez-Sendon J, Van de Werf F, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart. 2007 February;93(2):177-82.

21. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomised clinical trials. J Am Coll Cardiol. 2006 October 10;48(7):1319-25.

22. Alexander KP, Roe MT, Chen AY, Lytle BL, Pollack CV, Foody JM, et al. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol. 2005 October 10;46(8):1479-87.

23. Boersma E. Does time matter? A pooled analysis of randomised clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J. 2006 April;27(7):779-88.

24. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomised controlled trial. Jama. 2003 September 9;290(12):1593-9.

25. Boersma E, Harrington RA, Moliterno DJ, White H, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. Lancet. 2002;360(9329):342-3.

26. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 January 1;324(7329):71-86.

27. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomised controlled trials. JAMA. 1999;282(24):2340-6.

28. Sabatine MS, Hamdalla HN, Mehta SR, Fox KAA, Topol EJ, Steinhubl SR, et al. Efficacy and safety of clopidogrel pretreatment before percutaneous coronary intervention with and without glycoprotein IIb/IIIa inhibitor use. Am Heart J. 2008 May;155(5):910-7.

29. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. Am J Med. 2003 October 10;115(6):473-9.

30. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999 June 6;318(7200):1730-7.

SECTION 2: CLINICIAN ESTIMATION OF RISK AND APPROPRIATENESS OF CARE: CAN THEY BE INFLUENCED?

6 PERCEIVED RISK OF ISCHAEMIC AND BLEEDING EVENTS IN ACUTE CORONARY SYNDROMES

6.0 Title page: Perceived Risk of Ischaemic and Bleeding Events in Acute Coronary Syndromes

Derek P. Chew MBBS MPH [1], Ge Junbo MD [2], William Parsonage MBBS [3], Prafulla Kerkar DM, DNB(card.)[4], Vitaly A. Sulimov MD, PhD [5], Matthew Horsfall RN [6], Sue Mattchoss RN [1], For the PREDICT Study Investigators

[1] Department of Cardiology, Flinders University/Flinders Medical Centre, Adelaide, SA Australia

[2] Department of Cardiology, Zhongshan Hospital, Shanghai, China

[3] Department of Cardiology, Royal Brisbane & Women's Hospital, Brisbane QLD, Australia

[4] Department of Cardiology, King Edward VII Memorial Hospital, Mumbai, India

[5] Department of Cardiology, 1st Moscow Medical Academy, Moscow, Russia

[6] South Australian Health and Medical Research Institute, Adelaide, SA, Australia

Running Title: Physician Prediction of Recurrent ACS events

Key Words: Acute coronary syndromes, Risk Estimation, Risk scores, Quality of care

Corresponding Author

Derek P. Chew MBBS MPH FRACP

Flinders Medical Centre

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

6.1 Abstract

Background: Acute coronary syndrome (ACS) registries report incomplete guideline therapies use especially amongst the highest risk patients. Whether this treatment gap results from misperceptions of risk by physicians is uncertain.

Methods and Results: The PREDICT study was a prospective ACS registry in Australia, China, India and Russia, involving 58 hospitals between May 2009 and February 2011. In-hospital care, and events upto 6-months were assessed. At least 2 clinicians involved in the patient's care estimated the untreated risk, and change in risk with each therapy. Physician risk assessment and objective risk measures (e.g. GRACE score) for death and death/MI and bleeding events were compared using the c-statistic and integrated discrimination improvement (IDI). In total, 1542 patients and 4230 patient-specific physicians' estimates were obtained. Of responding clinicians, 81.9% were cardiovascular specialist (years of practice: mean 11.5 (SD: 7.7) years). The median physician perceived risk of 6-month death was 25% [i.q.r.: 14-35%]. The GRACE score was superior to physician estimation (c-statistic: GRACE score: 0.812 [95% C.I. 0.772-0.851] versus Physician: 0.652 [95% C.I. 0.596-0.708], p<0.0001). The GRACE score added to clinician intuition improved discrimination (IDI: 0.0632 [S.E. 0.012, p<0.0001). Invasive management correlated with physician's estimated risk, but not with GRACE risk. Among patients not at high-risk by physician estimation, increased risk by GRACE score was associated with higher mortality (3.7% versus 0.8%, p<0.001).

Conclusions: Objective risk assessment provides superior risk discrimination when compared with physician-estimated risk. Whether systematic use of objective risk stratification improves clinical outcomes should be studied in appropriately designed clinical trials.

Key Words: Acute coronary syndromes, Risk Estimation, Risk scores, Quality of care

6.2 Introduction

In terms of recurrent ischaemic and bleeding events, patients presenting with acute coronary syndromes (ACS) represent a diverse spectrum of clinical risk. The application of current therapies, including invasive management, based on risk is advocated by clinical guidelines.[1,2] [3,4]Hence, the translation of evidence-based clinical guidelines to optimal clinical outcomes is dependent on accurate risk assessment, the appropriate balancing of risk and benefit within the individual patient, combined with the availability of these proven technologies and therapies. Furthermore, this complex assessment often also needs to be performed in a time-critical manner.[5,6] Several national and international registries continue to document the incomplete application of clinical guideline recommended therapies in most parts of the developing and developed world, spurring several initiatives focused on improving the quality of ACS care.[6-8]

Interestingly, the largest evidence-practice gap appears to be among the patients at highest risk of recurrent ischaemic events.[9-11] However, these patients are also at the greatest risk of bleeding events and other adverse outcomes associated several therapies.[12,13] The factors contributing to this disconnect are not well documented but may include: the limited evidence in these high-risk groups often excluded from clinical trials; a perception that the risk of adverse events with therapy may exceed the benefits; a misperception of risk leading to an under appreciation of the benefit associated with therapies; and a possible sense of futility, where little benefit is expected among patients at the extremes of risk.

Consequently, we sought to explore how well clinicians: a) estimated the risk of mortality and bleeding events among ACS patients; b) weighed the benefits and risks of current ACS guideline recommended therapies in a patient specific context; and c) evaluate whether care provided correlated with perceived and calculated risk, within several culturally diverse societies.

6.3 Methods

6.3.1 Study design:

The Perceived Risk of ischaemic and bleeding events In acute Coronary syndrome patients (PREDICT) was a prospective multi-centre international registry including 4

countries (Australia, China, India and Russia) and involving 58 hospitals enrolling ACS patients between May 2009 and February 2011. Ethics committee approval was provided at each site and informed consent was obtained from all patients prior to enrollment in the study.

6.3.2 Patient population:

A structured enrolment process (e.g. first patient of the day or first 5 patients of the week etc.) was encouraged at each site but consecutive recruitment was not required. Patients were considered eligible for enrolment if they presented with suspected ST elevation myocardial infarction (STEMI) high risk (HR) and intermediate risk (IR) non-ST segment ACS (NSTEACS). Specifically, patients with symptoms suggestive of angina or angina-equivalent were included as suspected STEMI if they had persistent ST elevation >1mm in 2 contiguous leads, or new/presumed new LBBB. Patients were included as NSTEACS-HR if ECG findings demonstrated ST depression >0.5mm, or T wave inversion ≥1.0 mm in > 2 contiguous leads, biomarker elevation (troponin or creatine kinase MB fraction), haemodynamic compromise (cardiogenic shock, Killip class >1 or mitral regurgitation or syncope), known left ventricular ejection fraction <40%, ventricular arrhythmias, previous coronary revascularization, a history of diabetes or creatinine clearance <60ml/min/1.72m^2. Patients were included as NSTEACS-IR in the absence of high-risk characteristics, but one of the following was present: Q-waves or ST/T changes in 2 leads; age was >65 years; a history of prior coronary artery disease (previous event or coronary angiogram with a lesion>50%); known ejection fraction 40-50%; 2+ coronary risk factors; prior aspirin use. ACS admission deemed secondary to other causes such as major trauma or surgery were excluded. Allocation to each risk stratum was centrally adjudicated to ensure consistency of enrolment criteria. The primary discharge diagnosis was determined by the investigator, but confirmed by a central query process.

6.3.3 Clinical Factors and Hospital Management

Within the baseline hospitalization, clinical characteristics required for calculating the Global Registry of Acute Coronary Events (GRACE), Thrombolysis in Myocardial Infarction (TIMI) and PURSUIT risk scores for recurrent ischemic events and the ACUITY and CRUSADE scores for bleeding were obtained through the completion of a standard case-record form. [14,15] [16-19] The provision of clinical guideline recommendations including: reperfusion therapy (either by fibrinolysis or primary PCI);

early invasive management; prescription of aspirin, clopidogrel, HMG-CoA reductase inhibition, beta-blockers and ACE-Inhibitors or angiotensin receptor antagonists at discharge were also assessed at the time of discharge. Early invasive management was defined as angiography at any time within the acute hospital stay, regardless of transfer between acute care hospitals. Patients discharged with planned outpatient angiography where not considered as having received an early invasive management strategy. All baseline clinical and outcome data was abstracted by trained clinical trial co-ordinators or clinicians, and at study completion, independent country specific monitors audited data pertaining to clinical events and vital status.

6.3.4 Clinical events

All cause mortality, new or recurrent MI, stroke and clinical bleeding events were sought during the initial hospital admission, at 30 days, 3 months, and 6 months using standard definitions. Late events were obtained at the time of clinical review or by telephone. MI required a rise in biomarkers, greater than the local threshold definition for troponin and/or more than twice the upper limit of normal for CK-MB (in the absence of CK-MB, CK was used). Recurrent MI required a further >25% rise and/or >50% rise in the troponin and CK-MB, respectively, > 24 hours after admission. Following PCI and CABG, a level of CK-MB >3 times and >5 times-the upper limit of normal within 48 hours or new Q-waves was required consistent with the universal definition, respectively.[20] Stroke required a sudden onset of a new neurological deficit consistent with a single vascular territory supported by cerebral imaging reports where possible. Bleeding events were defined using the ACUITY criteria, specifically a fall in hemoglobin of >3g/dL, any blood transfusion, bleeding requiring a surgical/procedural intervention, or a vascular access site haematoma of >5cm in diameter.[21] TIMI and GUSTO bleeding criteria were also applied. [22] All events were independently adjudicated by a clinical events committee.

6.3.5 Physician assessment of risk

Using a standardised case-record from, translated into the local language where required, physicians directly involved in the care of each specific patient were asked to assess the patient's individual baseline "untreated" risk of death, new or recurrent myocardial infarction, stroke or bleeding at 30 days, 3 months and 6 months in absolute terms. E.g. "Among 100 patients like this patient, how many will have died by 6 month if they received no treatment?" For the same patient, they were asked to

estimate the risk of these ischaemic and bleeding events associated with the provision of early invasive management and guideline advocated pharmacotherapies. Other medical and non-medical barriers to care such as cost or patient refusal were also recorded. At least two physician assessments were obtained per patient, and these assessments were completed as close to admission as possible, before the provision of coronary angiography or other discharge medication. Self-reported physician characteristics including the year of primary medical degree, specialist cardiologist qualification and year this qualification was obtained was also recorded.

6.3.6 Statistical Analysis

Continuous variables are expressed as a mean ± standard deviation (SD) or median and inter-quartile ranges for variables with non-gaussian distributions. All discrete variables are expressed as counts (n) and percentages (%) of the study population (N). In univariate analysis, binary outcomes were compared by chi-square tests, while continuous variables were compared by Kruskal-Wallis testing and reported as a median and inter-quartile range. Baseline characteristics and outcomes are presented by country and for the entire study. The median (25^{th} and 75^{th} percentiles) for physician estimated untreated risk of death, GRACE risk score predicted mortality, and observed mortality by 6-months were calculated within increments of 10 of the GRACE risk score from <40 to ≥200, and plotted. The primary analysis assessed physician risk estimation of death by 6 months with no treatment with the GRACE risk-score predicted mortality by comparisons of the respective areas under the ROC curves (AUC).[23] An analysis, stratified by enrolling country using bootstrapped methods for inferring differences between the AUCs was also undertaken. This stratified analysis yielded similar results and the un-stratified results are presented. Similarly, to account for correlations of risk estimates between physicians for each patient, an analysis using the “average physician estimate” compared with the GRACE risk score is also presented. To quantify the additional value of adding the risk scores to physician discrimination of

risk, the integrated discrimination improvement (IDI) was also calculated.[24] These analyses were also undertaken for the endpoint of death or MI. Ancillary analyses of TIMI and PURSUIT assessed risk and actual risk was also undertaken. The Physician-estimated bleeding risk, ACUITY and CRUSADE risk scores for bleeding were correlated with all bleeding events, as well as those bleeding events adjudicated by the ACUITY, TIMI and GUSTO definitions using the same methodology.

The perceived relative mortality risk (reduction or increase) associated with each therapy was calculated for each doctor-patient interaction in the following manner: perceived relative risk= perceived risk $_{(treated)}$/perceived risk$_{(untreated)}$. A similar calculation was used to estimate the perceived relative increased risk of bleeding events. To explore the relationship between the care provided, and perceived or predicted risk, respectively, the physician perceived risk of mortality at 6 months was stratified into <10%, 10.1-20%, 20.1-30% and >30.1%, while the GRACE score was stratified into low, intermediate, high and very high at the cut-points of <100, 100-150, 151-200 and 201+. Use of therapies and invasive management were examined by chi-square test within each classification only. To examine the relationship between unrecognised risk and outcome, the GRACE risk score was dichotomised at 150 (high risk >150), while recognised high-risk was arbitrarily determined to be those patients identified as being in the top 25% of risk estimated by physicians. Comparisons of the clinical outcomes of 6-month death were then examined in 4 groups: 2 concordant (considered high or low by both GRACE score and Physician estimate) and 2 discordant (considered high by GRACE score but low by physician or high by physician but low by GRACE criteria). All analyses were undertaken using the STATA 11.2. For all analyses, a probability value of <0.05 were considered statistically significant.

6.4 Results

6.4.1 Patient population

In total, 1575 patients with myocardial infarction or high-risk ACS provided informed consent and were enrolled in the study of whom 1542 had all components required for analysis of the GRACE score. Of these 495, 416, 384 and 247 patients were enrolled from China, Australia, India and Russia, respectively. The majority of the participating hospitals were in metropolitan centres (47 of 58). Rural hospitals comprised a small proportion of participating hospitals (Australia [3/12], China [1/16], India [5/10], and Russia [2/20],). The median age of these patients was 60.3 years (SD ±12.0 years) and 350 (22.7%) were female. Hypertension, diabetes, hypercholesterolaemia and current smoking were reported in 882/1542 (57.2%), 408/1542 (26.5%), 603/1542 (39.1%) and 528/1542 (34.2%), respectively. Patients presenting with ST elevation MI constituted 836/1542 (54.2%) of the population. Demographic, clinical characteristics and outcome of the patients stratified by country of enrollment are presented in table 1 and 2. The overall median GRACE score was 105 (85-125) leading to a predicted risk of 6-month mortality of ~5% and death by 6 months was observed in 48/1542 (3.1%). Of the 4230 patient-specific physician estimates of risk and benefit provided, 47.4% were male, 81.9% identified themselves as having a country specific cardiovascular specialist qualification, with a mean of 11.5 (SD: 7.7) years of clinical practice. The median physician perceived risk of 6-month death was 25% [i.q.r.: 14-35%].

Table 1: Demographic and clinical characteristics by enrolling country.

	Australia (n=416)	China (n=495)	India (n=384)	Russia (n=247)	Total (n=1542)	P value
Age (yrs, mean ±SD)	60.9 (12.6)	60.7 (11.6)	57.4 (11.2)	58.6 (12.0)	60.3 (12.0)	<0.001
Female Gender (n, %)	92 (22.1)	114 (23.0)	92 (24.0)	52 (21.1)	350 (22.7)	0.864
STEMI (n, %)	122 (29.3)	359 (72.5)	208 (54.2)	147 (59.5)	836 (54.2)	<0.001
NSTEMI (n, %)	292 (70.2)	136 (27.4)	175 (45.6)	99 (40.1)	702 (45.5)	<0.001
Diabetes (n, %)	132 (31.7)	102 (20.6)	142 (37.0)	32 (13.0)	408 (26.5)	<0.001
Hypertension (n, %)	248 (59.6)	278 (56.2)	171 (44.5)	185 (74.9)	882 (57.2)	<0.001
Dyslipidaemia (n, %)	262 (63.0)	131 (26.5)	45 (11.8)	165 (66.8)	603 (39.1)	<0.001
Current Smoking (n, %)	130 (31.3)	212 (42.8)	80 (20.9)	106 (42.9)	528 (34.2)	<0.001
Family History of CAD (n, %)	169 (40.6)	61 (12.3)	34 (8.9)	109 (44.1)	373 (24.2)	<0.001
Prior CAD (n, %)	264 (36.5)	69 (13.9)	49 (12.8)	105 (42.5)	375 (24.3)	<0.001
Prior MI (n, %)	99 (23.8)	29 (5.9)	49 (12.8)	60 (24.3)	237 (15.4)	<0.001
Prior CABG (n, %)	63 (15.1)	0	1 (0.3)	5 (2.0)	69 (4.5)	<0.001
Prior Atrial Fibrillation (n, %)	14 (3.4)	8 (1.6)	1 (0.3)	21 (8.5)	44 (2.9)	<0.001
Prior Heart Failure (n, %)	18 (4.3)	7 (1.4)	3 (0.8)	41 (16.6)	69 (4.5)	<0.001
Known PAD (n, %)	7 (1.7)	13 (2.6)	1 (0.3)	13 (5.6)	34 (2.2)	<0.001
Prior CVA (n,%)	15 (3.6)	30 (6.1)	3 (0.8)	15 (6.1)	63 (4.1)	<0.001

Admission Systolic BP (mmHg [mean, SD])	142 (26)	128 (24)	127 (24)	131 (25)	132 (26)	<0.001
Admission Heart Rate (bpm [mean, SD])	78 (20)	76 (16)	82 (19)	76 (16)	78 (18)	<0.001
Height (cm [mean, SD])	170.3 (8.9)	168.1 (6.8)	164.9 (8.4)	172.6 (8.5)	168.6 (8.5)	<0.001
Weight (kg [mean, SD])	84.7 (18.6)	69.3 (10.7)	67.7 (10.9)	83.0 (14.6)	75.2 (15.9)	<0.001
Creat. Cl.ml/min (median, 25th-75th percentile)	65.4 (52.2-82.1)	69.3 (57.4-87.2)	62.0 (53.3-79.7)	61.2 (50.9-74-6)	65.3 (53.7-81.4)	<0.001
Dialysis dependent	2 (0.5)	4 (0.8)	2 (0.5)	0	8 (0.5)	0.552
Killip Class (median, 25th-75th percentile)	1 (1)	1 (1)	1(1-2)	1 (1-2	1 (1-2)	<0.001
White cell count (median, 25th-75th percentile)	8.7 (7.1-11.1)	8.7 (7.0-11.4)	10.6 (8.4-13.5)	9.2 (7.3-11.9)	9.2 (7.2-12.0)	<0.001
Presentation with cardiogenic shock (n,%)	2 (0.5)	15 (3.0)	21 (5.5)	10 (4.0)	48 (4.1)	<0.001
Presentation with cardiac arrest (n,%)	13 (3.1)	6 (1.2)	11 (2.9)	3 (1.2)	33 (2.1)	0.138
Frailty Score (1-7) (median, 25th-75th percentile)	2 (2-3)	3 (2-4)	2 (2-3)	3 (2-4)	3 (2-4)	<0.001
Physician Predicted 6 mth Death (%, median, 25th-75th percentile)	15 (8-25)	30 (20-40)	20 (13-30)	30 (19-43)	25 (14-35)	<0.001
GRACE risk score (median, 25th-75th percentile)	98 (79-122)	106 (88-129)	109 (88-125)	105 (86-127)	105 (85-125)	<0.001
TIMI risk score (STEMI) (median, 25th-75th percentile)	3 (1-4)	3 (2-5)	4 (2-5)	3 (1-5)	3 (2-5)	<0.001
TIMI risk score (NSTEACS) (median, 25th-75th percentile)	4 (3-5)	3 (3-4)	3 (3-4)	3(3-4)	3 (3-4)	<0.001
PURSUIT risk score (STEMI) (median, 25th-75th percentile)	21 (16-22)	21 (16-22)	21 (20-22)	21 (19-21	21 (19-22)	0.0022
ACUITY risk score (median, 25th-75th percentile)	10 (7-14)	12 (9-15)	12 (8-15)	12 (9-16)	11 (8-15)	<0.001
CRUSADE risk score (median, 25th-75th percentile)	26 (19-35)	25 (18-33)	32 (24-39)	30 (22-37	29 (19-36)	<0.001

Table 2: Clinical outcomes stratified by enrolling country.

	Australia (n=416)	China (n=495)	India (n=384)	Russia (n=247)	Total (n=1542)	P value
30-day Mortality (n, %)	7 (1.7)	4 (0.8)	20 (5.4)	5 (2.0)	37 (2.3)	<0.001
3-Month Mortality (n, %)	9 (2.2)	6 (1.2)	22 (5.7)	6 (2.4)	43 (2.7)	0.001
6-Month Mortality (n, %)	11 (2.6)	7 (1.4)	23 (6.0)	7 (2.8)	48 (3.1)	0.003
30-day MI (n, %)	9 (2.2)	19 (3.8)	4 (1.0)	27 (10.9)	59 (3.8)	<0.001
3-Month MI (n, %)	9 (2.2)	19 (3.8)	6 (1.6)	28 (11.3)	62 (4.0)	<0.001
6-Month MI (n, %)	12 (2.9)	19 (3.8)	7 (1.8)	28 (11.3)	66 (4.3)	<0.001
30-day CVA (n, %)	1 (0.24)	3 (0.6)	0 (0)	2 (0.8)	6 (0.4)	0.326
3-Month CVA (n, %)	1 (0.24)	3 (0.6)	0 (0)	2 (0.8)	6 (0.4)	0.326
6-Month CVA (n, %)	1 (0.24)	3 (0.6)	0 (0)	2 (0.8)	6 (0.4)	0.326
30-day Protocol Bleed (n, %)	33 (7.9)	15 (3.0)	2 (0.5)	9 (3.6)	59 (3.8)	<0.001
3-Month Protocol Bleed (n, %)	40 (9.6)	16 (3.2)	2 (0.5	9 (3.6)	67 (4.4)	<0.001
6-Month Protocol Bleed (n, %)	45 (10.8)	17 (3.4)	2 (0.5)	9 (3.6)	73 (4.7)	<0.001
6-Month Death or MI (n, %)	21 (5.1)	25 (5.1)	29 (7.6)	33 (13.4)	108 (6.9)	<0.001
6-Month MACE (n, %)	63 (15.1)	42 (8.5)	30 (7.8)	41. (16.6)	176 (11.4)	<0.001

6.4.2 Correlation between perceived risk and estimated risk

Physician perceived risk and GRACE risk score predicted risk of death by 6 months, along with the observed 6-month mortality rate, plotted by the GRACE risk score are presented in figure 1. The variation in physician estimated risk for all levels of the GRACE risk score was substantial. The rise in median physician perceived risk was modest except in the very highest patients by GRACE risk score. Hence, physicians commonly over-estimated the risk of 6-month mortality among those with a lower GRACE score risk, and under-estimated risk among those with a high GRACE score.

Figure 1: Physician-estimated mortality risk (median, 25th and 75th percentiles), and GRACE predicted mortality risk and observed mortality by 6 months plotted by incremental increases of 10 in GRACE risk score.

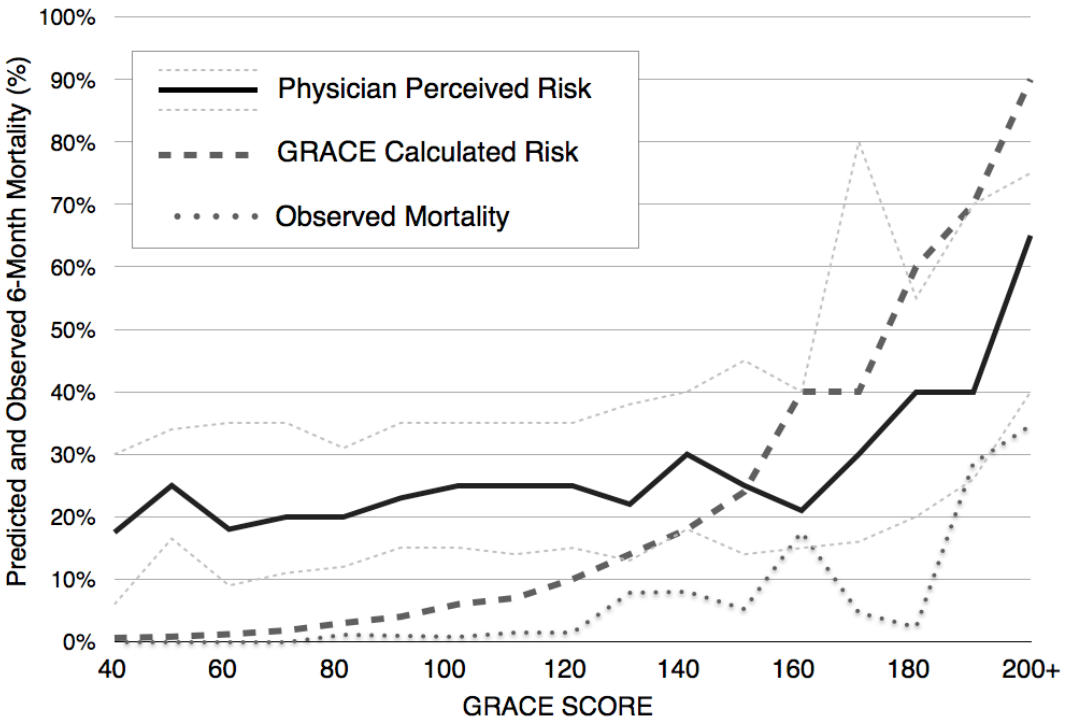
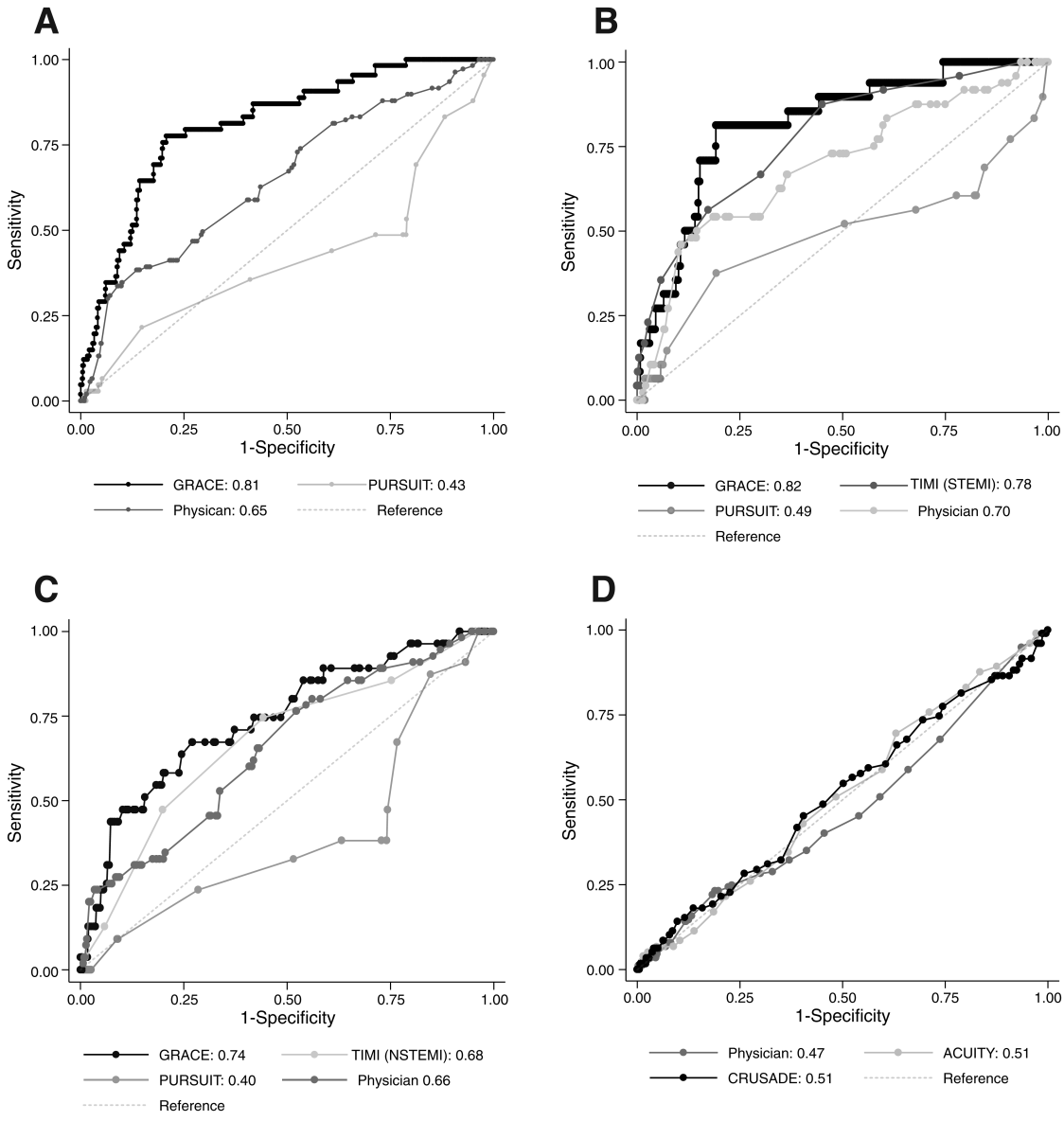


Figure 2 displays the discriminatory characteristics for physician-estimated risk, the GRACE risk score, the TIMI risk score and the PURSUIT risk score. The GRACE risk score demonstrated significantly superior discrimination to physician risk estimation with a c-statistic of 0.812 (95% C.I. 0.772-0.851) compared with 0.652 (95% C.I. 0.596-0.708), p<0.0001. Results were similar when stratified by enrolling country (Physician: 0.695 (0.629-0.740) vs. GRACE score: 0.818 (0.779-0.857), p<0.001). Using the average physician estimate for each patient observed modest improvement (average of physicians: 0.679 [95% C.I.: 0.629-0.740) vs. GRACE: 0.815 (95% C.I. 0.754-0.874), p=0.0016). Similarly, a moderate improvement in physician prediction was evident when assessing 30-day mortality (physician estimate: 0.713 [95% C.I.: 0.653-0.773) vs. GRACE: 0.793 (95% C.I. 0.744-0.842), p=0.0183).

Figure 2: Physician estimated risk and Clinical Risk Score performance for A) Death by 6 months in total population, B) Death by 6 months in STEMI population; C) Death by 6 months in NSTEACS population and b) Major bleeding by 6 months in total population.



Adding the GRACE score to physician estimation improved the discrimination with an IDI of 0.0632 (SE: 0.012, $p<0.001$). Calibration with actual outcomes was modest with both GRACE and physician estimated risk with Hosmer-Lemeshow statistic p values of 0.0149 and 0.220, respectively, with both approaches overestimating actual risk. Among STEMI patients, the TIMI risk score performed as well as the GRACE score, but this was not observed among NSTEMI patients. Within this study, the PURSUIT risk score demonstrated very poor predictive performance. Both the GRACE risk score and physician estimated risk performed less well for the endpoint of death or MI within six months. (Table 3)

When assessing bleeding risk, physician estimated, the CRUSADE and the ACUITY risk score demonstrated poor discriminatory capacity for bleeding events using all definitions. Predictive capacity of the ACUITY risk score was modestly improved when applied to bleeding events adjudicated by the TIMI major and minor definitions, but was less discriminatory when the TIMI minimal bleeding was included in the endpoint. A similar relationship was observed with the GUSTO definitions of bleeding. (Table 3)

Table 3: Risk discrimination by physician estimation and risks scores for ischaemic and bleeding events.

	C-statistic (95% C.I.)	*P-value*	*IDI (S.E)*	*P value*	*C-statistic*	*P-value*	*IDI (S.E)*	*P value*
Endpoint	**6 month Mortality**				**6 Month Death or MI**			
Physician determined	0.652 (0.596-0.708)				0.595 (0.560-0.631)			
GRACE risk score	0.812 (0.772-0.851)	<0.001	0.0632 (0.0122)	<0.001	0.629 (0.596-0.663)	0.102	0.0182 (0.0031)	<0.001
TIMI risk score (STEMI)	0.779 (0.713-0.845)	<0.001	0.0659 (0.0188)	<0.001	0.576 (0.527-0.625)	<0.001	0.0094 (0.0026)	<0.001
TIMI risk score (NSTEACS)	0.675 (0.601-0.748)	0.737	0.0077 (0.0042)	0.069	0.581 (0.522-0.640)	<0.001	0.0010 (0.0021)	0.654
PURSUIT risk score	0.426 (0.362-0.489)	<0.001	0.0059 (0.0015)	<0.001	0.484 (0.446-0.522)	<0.001	0.0020 (0.0006)	0.00157
Endpoint	**Any Bleeding Event**				**ACUITY Bleeding**			
Physician determined	0.471 (0.426-0.515)				0.508 (0.460-0.557)			
ACUITY risk score	0.511 (0.470-0.553)	0.172	0.0001 (0.0002)	0.505	0.497 (0.451-0.543)	0.743	0.000 (0)	0.930
CRUSADE risk score	0.513 (0.469-0.558)	0.173	0.0001 (0.0001)	0.684	0.542 (0.494-0.590)	0.344	0.0004 (0.0003)	0.226

Endpoint	TIMI Major/Minor Bleeding				Any TIMI Bleeding			
Physician determined	0.498 (0.308-0.550)				0.396 (0.325-0.466)			
ACUITY risk score	0.589 (0.487-0.691)	0.064	0.0014 (0.0003)	0.092	0.546(0.472-0.620)	0.003	0.0013 (0.0007)	0.052
CRUSADE risk score	0.458 (0.341-0.575)	0.726	0.0001 (0.0002)	0.353	0.436 (0.364-0.509)	0.403	0.0010 (0.0005)	0.063
Endpoint	**GUSTO Sev/Mod Bleeding**				**Any GUSTO Bleeding**			
Physician determined	0.466 (0.360-0.571)				0.477 (0.425-0.531)			
ACUITY risk score	0.503 (0.399-0.607)	0.653	0.0001 (0.002)	0.0585	0.507 (0.456-0.558)	0.425	0.0001(0.0002)	0.521
CRUSADE risk score	0.392 (0.293-0.491)	0.344	0.0020 (0.0009)	0.0267	0.505 (0.471-0.520)	0.447	0.000 (0)	0.785

P values represent comparisons of c-statistics between risk scores and physician estimation (analysis not stratified by country)

6.4.3 Physician estimated benefits with evidence-based therapies

By contrasting the physician estimated 6 months event rates associated with each of the guideline recommended therapies, an estimate of the perceived relative risk reduction or increase of each therapy was derived and are presented in table 4. While individual estimates varied greatly, these estimated benefits for aspirin, clopidogrel and statins were generally consistent with literature-based estimates of efficacy with these therapies with the exception of early invasive management, ACE-inhibition or angiotensin receptor blockers and beta-blockers where the perceived benefits where greater than observed in clinical trials.

Table 4: Perceived relative risk of guideline recommended therapies on specific outcomes by 6 months.

	Death	***New/recurrent MI***	***CVA***	***Bleeding***
Aspirin (mean, SD)	0.81 (0.40)	0.80 (0.54)	0.89 (0.68)	1.42 (1.25)
Clopidogrel (mean, SD)	0.76 (0.40)	0.76 (0.82)	0.85 (0.42)	1.47 (1.13)
Statin (mean, SD)	0.77 (0.44)	0.75 (0.53)	0.83 (0.57)	1.56 (1.48)
ACE-I/ARB (mean, SD)	0.76 (0.50)	0.75 (0.46)	0.83 (0.46)	N/A
Beta-blocker (mean, SD)	0.75 (0.41)	0.74 (0.65)	0.85 (0.48)	N/A
Invasive Management (mean, SD)	0.64 (0.43)	0.63 (0.70)	0.86 (0.58)	N/A

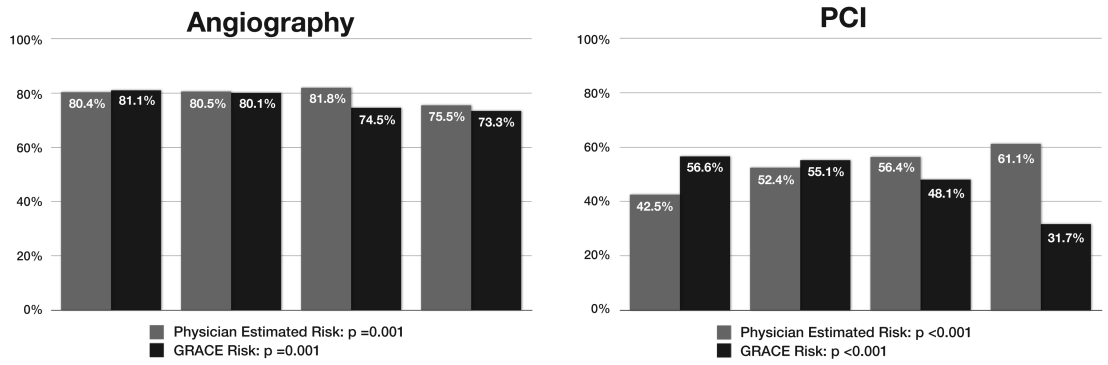
N/A: not asked.

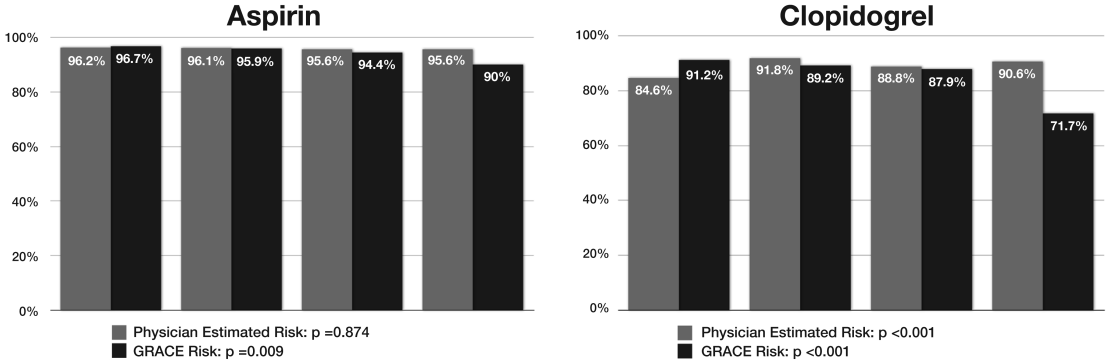
6.4.4 Relationship between perceived risk the use of guideline recommendations.

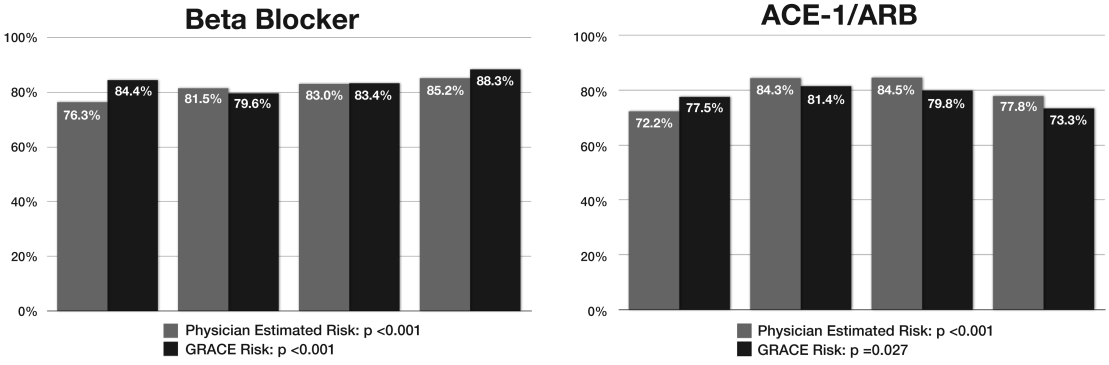
Figure 3 describes the rate of guideline recommended therapies stratified by physician perceived risk. While there was a high use of aspirin, clopidogrel and statins among all

the perceived risk groups, there appeared to be a greater use of PCI and to a lesser degree beta-blockers among patient perceived to be at greater risk. However, when stratified by GRACE risk score, this relationship is no longer seen, with reductions in PCI, clopidogrel, beta-blockers, and to a moderate degree, ACE-Inhibitors/angiotensin receptor antagonists amongst the highest risk patients.

Figure 3: Figure 4: Rates of a) Angiography and b) Percutaneous Coronary Intervention (PCI) and prescription at discharge of c) aspirin, d) clopidogrel, e) statins, f) beta-blockers, and g) angiotensin converting enzyme inhibition (ACE-I) or angiotensin receptor antagonists (ARB) stratified by GRACE risk score (Low<100, intermediate<100-150, High 150-200, Very High>200) and physician-predicted risk of death by 6 months (<10%, 10-20%, 20-30%, >30%). (See next page)

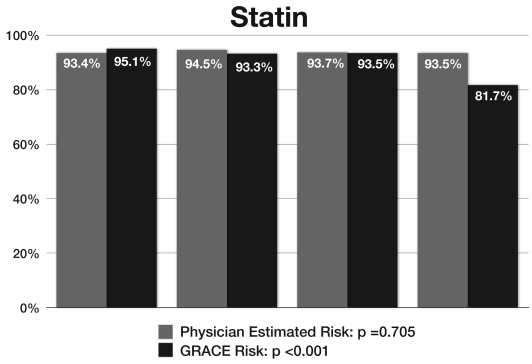






GRACE category	<100	100-150	150-200	>200
Physician category	<10%	10-20%	20-30%	>30%

GRACE category	<100	100-150	150-200	>200
Physician category	<10%	10-20%	20-30%	>30%

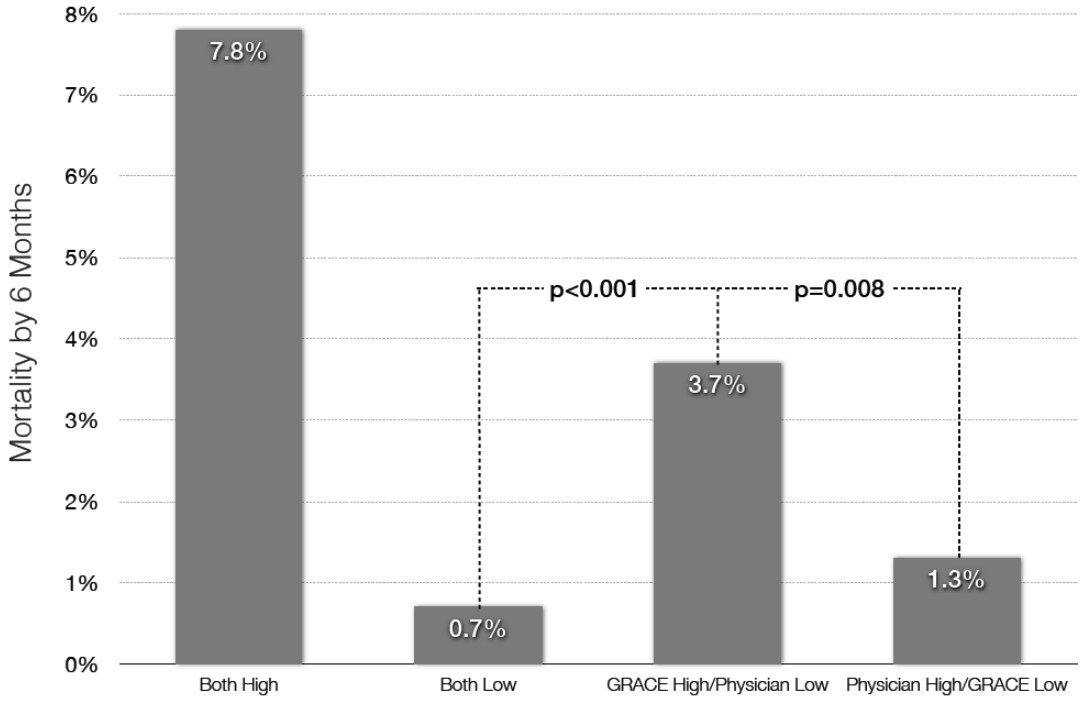


GRACE category	<100	100-150	150-200	>200
Physician category	<10%	10-20%	20-30%	>30%

6.4.5 Mortality by Concordant/Discordant risk estimation

Mortality rates among patients deemed to be at high-risk or not-high risk by both GRACE score and physician estimation (concordant estimation) were clearly at high and low, respectively. However 6-month mortality among patients not at high-risk by physician estimation but at high-risk by GRACE risk score was significantly higher than those perceived to be at high-risk by clinicians with a low GRACE risk (p=0.008), and those concordantly deemed to be at low risk by both scores (p<0.001). (Figure 4)

Figure 4: Death by 6-months stratified by concordant and discordant estimation of risk using physician estimation (dichotomised at the highest 25% of risk) and GRACE score (dichotomised at 150).



6.5 Discussion

By formally assessing physician estimated risk of clinical events without treatment and with various therapies, this study has provided several clinical insights that may have implications for how we translate our established ACS evidence base into more complete care and outcome. First, when directly questioned regarding the estimated risk of clinical events, clinicians generally over-estimated the risk of recurrent ischemic and bleeding events, but this estimation of risk was insensitive to risk as quantified by the GRACE risk score except in the very high risk. Second, risk estimation using the GRACE risk score, and the TIMI risk scores were superior to physician-estimated risk, while the PURSIUT risk score performed poorly. Third, bleeding estimation by clinicians and the ACUITY and CRUSADE risk scores remains poor though these results may be influenced by event recognition. Fourth, physicians appeared to "over-value" the relative impact of invasive management, beta-blockers and ACE-inhibitors/angiotensin receptor antagonists compared to literature-based estimates. Fifth, clinical perception of risk and "miss-classification of risk appears to influence PCI rates and may be associated with differences in clinical outcomes.

While not unexpected, prediction of mortality-risk based on objectively quantified clinical criteria provides superior risk estimation than clinical impression. While similar performance was observed among STEMI patients, the GRACE risk score derived from a large-scale registry appeared to perform better than those derived from randomised clinical trials for NSTEMI patients.[25] This may reflect the more selected populations included in trials compared with registries. Nevertheless, the discrimination of the GRACE risk score within populations drawn from emerging economies is reassuring of the relevance of this score in their clinical practice. However, while discrimination remains robust, the calibration of risk estimation within this study was poor. This likely reflects the non-consecutive nature of the enrollment design of this

study, and the consequent selection of lower risk patients for inclusion that differed between countries. In contrast, the clinical and ACUITY and CRUSADE score capacity to discriminate the risk of bleeding events by any of the accepted definitions was poor. Differences between counties may reflect variations in the local practices that therefore influence the detection of late bleeding events. However, these observations suggest a need to better evaluate factors associated with bleeding within prospective large-scale registries and enabling development of more discriminatory bleeding risk scores, as well as establishing robust systems for evaluating bleeding events, given the emergence of more potent long-tern anti-thrombotic therapies. [26-28]

The correlation between patient-specific physician estimates of treatment benefit combined and the greater provision of PCI is reassuring of an evidence-based approach to coronary revascularization as observed by others.[29] However, the lower rate of PCI among the GRACE-identified high-risk patients, combined with the increased mortality risk among physician deemed non-high-risk but GRACE estimated high risk raises the possibility that more widespread and systematic use of risk stratification may lead to improved outcomes among patients presenting across the spectrum of ACS.[29,30] This observational study was not designed to address such a question, but with the emergence of electronic medical records, the capacity to formally integrate risk prediction into the patient admission process while prompting the delivery of evidence-based recommendations raises the potential that integrated electronic systems may be able to improve outcomes. Formal appropriately designed and cluster-randomised studies of electronic risk stratification combined with guideline recommendations represent an opportunity to validate a system-based approach to improve ACS outcomes in the developing and developed world.

6.6 Conclusion

Risk prediction with the GRACE risk score provides superior risk discrimination when compared with physician estimated risk and other clinical-trial derived risks scores. Estimation of bleeding events clinically or with the ACUITY and CRUSADE risk scores are poor. Systematic uptake of objective risk stratification should be studied in appropriately designed clinical trials.

6.7 Acknowledgements: Authorship Contributions

Each author has directly contributed to conduct of this study. Specific contributions are a follows. Study Design: DC; Data Collection: SM, CA; Data Management and Analysis: DC, MH; Manuscript writing: DPC; Manuscript review: All

6.7.1 Funding sources: Role of the Sponsor

This study was sponsored by Sanofi-Aventis Asia-Pacific. However, the protocol was conceived and designed by DC, and the sponsor has not had direct access to the data. The sponsor has reviewed the manuscript but has not influenced its content

6.7.2 Disclosures

Author DC has advised the National Heart Foundation of Australia in the development of a clinical risk stratification tool aimed at improving clinical care in regional Australia. Author WP has received grant support from Abbott, Roche and Siemens with respect to biomarker research that pertains to risk stratification. All other authors have no other conflicts of interest to declare with respect to the content of this manuscript.

6.8 References

1. Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Hasdai D, Astin F, Astrom-Olsson K, Budaj A, Clemmensen P, Collet JP, Fox KA, Fuat A, Gustiene O, Hamm CW, Kala P, Lancellotti P, Maggioni AP, Merkely B, Neumann FJ, Piepoli MF, de Werf Van F, Verheugt F, Wallentin L. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *European Heart Journal*. 2012; Oct;33(20):2569-619

2. Authors/Task Force Members, Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, ESC Committee for Practice Guidelines, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Windecker S, Achenbach S, Badimon L, Bertrand M, Botker HE, Collet JP, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann FJ, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2011; 32:2999–3054.

3. 2011 Writing Group Members, Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, Ettinger SM, Fesmire FM, Ganiats TG, Jneid H, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP, Jacobs AK. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011; 123:2022–2060.

4. 2011 Writing Group Members, Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NAM, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM, Jacobs AK. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011; 123:104–123.

5. Nallamothu B, Fox K, Kennelly B, de Werf Van F, Gore J, Steg P, Granger C, Dabbous O, Kline-Rogers E, Eagle K, GRACE Investigators. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart*. 2007; 93:1552–1555.

6. Fox K, Cokkinos D, Deckers J, Keil U, Maggioni A, Steg G. The ENACT study: a pan-European survey of acute coronary syndromes. European Network for Acute Coronary Treatment. *Eur Heart J*. 2000; 21:1440–1449.

7. Fox K. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes The Global Registry of Acute Coronary Events (GRACE). *European Heart Journal*. 2003; 24:1414–1424.

8. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC, Pollack CV, Gibler WB, Ohman EM, CRUSADE Investigators. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement

Initiative. *JAMA*. 2004; 292:2096–2104.

9. Fox K, Anderson F, Dabbous O, Steg P, Lopez-Sendon J, de Werf Van F, Budaj A, Gurfinkel E, Goodman S, Brieger D. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart*. 2007; 93:177–182.

10. Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. *Med J Aust*. 2007; 187:153–159.

11. Roe M, Peterson E, Newby L, Chen A, Pollack C, Brindis R, Harrington R, Christenson R, Smith S, Califf R, Braunwald E, Gibler W, Ohman E. The influence of risk status on guideline adherence for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J*. 2006; 151:1205–1213.

12. Manoukian S, Feit F, Mehran R, Voeltz M, Ebrahimi R, Hamon M, Dangas G, Lincoff A, White H, Moses J, King S, Ohman E, Stone G. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *J Am Coll Cardiol*. 2007; 49:1362–1368.

13. Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, Manoukian SV, Nikolsky E, Lansky AJ, Kirtane A, White HD, Colombo A, Ware JH, Moses JW, Ohman EM. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. *European Heart Journal*. 2009; 30:1457–1466.

14. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf Van F, Avezum A, Goodman SG, Flather MD, Anderson FA, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006; 333:1091.

15. Boersma E, Pieper K, Steyerberg E, Wilcox R, Chang W, Lee K, Akkerhuis K, Harrington R, Deckers J, Armstrong P, Lincoff A, Califf R, Topol E, Simoons M. Predictors of outcome in patients with acute coronary syndromes without

persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation*. 2000; 101:2557–67.

16. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV, Peterson ED, Alexander KP. Baseline Risk of Major Bleeding in Non-ST-Segment-Elevation Myocardial Infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. *Circulation*. 2009; 119:1873–1882.

17. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000; 102:2031–2037.

18. Antman E, Cohen M, Bernink P, McCabe C, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000; 284:835–842.

19. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. 2010.

20. Third Universal Definition of Myocardial Infarction. 2012;:1–18.

21. Stone G, McLaurin B, Cox D, Bertrand M, Lincoff A, Moses J, White H, Pocock S, Ware J, Feit F, Colombo A, Aylward P, Cequier A, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen L, Rupprecht H-J, Hoekstra J, Mehran R, Ohman E, ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006; 355:2203–2216.

22. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey KW, Moliterno DJ, Lincoff AM, Armstrong PW, de Werf Van F, Califf RM, Harrington RA. A Comparison of the Clinical Impact of Bleeding Measured by Two Different Classifications Among Patients With Acute Coronary Syndromes. *J. Am. Coll. Cardiol.* 2006; 47:809–816.

23. Hanley J, McNeil B. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983; 148:839–843.

24. Pencina MJ, D Agostino RB, D Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. *Statist. Med.* 2007; 27:157–172.

25. de Araujo Goncalves P. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *European Heart Journal*. 2005; 26:865–872.

26. Mega JL, Braunwald E, Wiviott SD, Bassand J-P, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KAA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FWA, Gibson CM. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome. *N Engl J Med*. 2011;:111113050015006.

27. Wiviott S, Braunwald E, McCabe C, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F, Ardissino D, De Servi S, Murphy S, Riesmeyer J, Weerakkody G, Gibson C, Antman E. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; 357:2001–2015.

28. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2009; 361:1045–1057.

29. Yan AT, Yan RT, Huynh T, Casanova A, Raimondo FE, Fitchett DH, Langer A, Goodman SG, Canadian Acute Coronary Syndrome Registry 2 Investigators. Understanding physicians' risk stratification of acute coronary syndromes: insights from the Canadian ACS 2 Registry. *Archives of Internal Medicine*. 2009; 169:372–378.

30. Yan A, Yan R, Tan M, Fung A, Cohen E, Fitchett D, Langer A, Goodman S. Management Patterns in Relation to Risk Stratification Among Patients With Non-ST Elevation Acute Coronary Syndromes. *Arch Intern Med*. 2007; 167:1009–1016.

7 AN EXAMINATION OF CLINICAL INTUITION IN RISK ASSESSMENT AMONG ACUTE CORONARY SYNDROMES PATIENTS: OBSERVATIONS FROM A PROSPECTIVE MULTI-CENTRE INTERNATIONAL OBSERVATIONAL REGISTRY

7.0 Title page : An Examination of Clinical Intuition in Risk Assessment Among Acute Coronary Syndromes Patients: Observations from a Prospective multi-centre international observational registry

Derek P. Chew [*], Craig Juergens [†], John French [†], Will Parsonage [§], Matthew Horsfall [δ], David Brieger [Ψ], Stephen Quinn [*] For the PREDICT study Investigators

[*] Department of Cardiology, Flinders University/Flinders Medical Centre, Adelaide, SA Australia

† Department of Cardiology Liverpool Hospital, Liverpool, NSW, Australia

[§] Department of Cardiology, Royal Brisbane & Women's Hospital, Brisbane QLD, Australia

[δ] South Australian Health and Medical Research Institute Adelaide, SA, Australia

[Ψ] Department of Cardiology, Concord Hospital, Sydney NSW, Australia

Running Title: Clinical Intuition in ACS Risk Assessment

Word Count: Abstract: 250, Text: 3550 excluding abstract, Total: 6848, References: 20

Corresponding Author

Derek P. Chew MBBS MPH FRACP

Flinders Medical Centre

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

7.1 Abstract

Background: As there are limited data evaluating “clinical intuition” in risk prediction among acute coronary syndromes (ACS) patients. We evaluated the relationship between perceived and “scored” risk in ACS patients, and their association with care and outcome.

Methods and Results: Within a prospective multi-centre international ACS study from 58 hospitals in Australia, China, India and Russia enrolling patients between May 2009 and February 2011, at least 2 physicians involved in each patient’s care estimated the patient’s untreated risk, and the change in risk with invasive management. The association between clinical factors and physician perceived risk was assessed with multilevel mixed-effects regression models. Risk under-estimation was defined as when physician-predicted risk was lower than GRACE score calculated risk and was used to compare clinical care and 6-month mortality. In total, 1542 patients and 4230 patient-specific physicians’ estimates were obtained. By 6 months 48/1542 (3.1%) of patients had died compared with an estimated rate of 2.5% with full treatment. Advanced age, hypotension, tachycardia and ST changes on ECG were associated with increased perceived risk, while female gender was associated with lower perceived risk. Clinician risk underestimation was associated with less guideline therapy and higher 6-months mortality. (Not under-estimated: 10/967 (1.0%) vs. one physician underestimated: 25/429 (5.8%) vs. all physician’s underestimated: 13/146 (8.9%), Any underestimation vs. no underestimation adjusted OR: 6.0 [95% C.I.: 2.3-15.5, p<0.001]).

Conclusions: Clinical risk prediction using established risk characteristics is not consistently observed in clinical practice. Studies evaluating the implementation and outcomes associated with objective risk prediction are warranted.

Key words: Acute Coronary Syndromes, Risk Prediction

7.2 Introduction

Risk assessment is essential for effective allocation of therapeutic interventions when therapies are associated with the potential for both benefit and harm. “Clinical intuition” plays a large-role in risk assessment, but direct evidence of proficiency compared with established risk scores is limited.[1] The routine invasive strategy of coronary angiography and revascularisation in acute coronary syndromes (ACS) represents an archetypical example of this risk-based decision-making challenge. The observation that patients at highest risk undergo angiography less frequently than intermediate risk patients classified by the Thrombolysis in Myocardial Infarction (TIMI) and Global Registry for Acute Coronary Events (GRACE) risk scores within ACS registries, suggests the presence of biases in clinical decision-making.[2,3] Similar patterns are evident amongst specific high-risk subgroups including female gender, the elderly, those with renal impairment and diabetes.[4-6] These observations may suggest risk aversion among clinicians and/or patients, or may indicate other biases influencing the assessment of risk and benefit by physicians. Whether this represents a misperception of risk (i.e. under or over estimation of risk) or the influence of other clinical factors impacting the perceived risks and benefits of invasive management remains unclear.[7,8]

While intuitive assessment is inherently individualised, rational risk assessment based on clinical characteristics should be observable and potentially quantifiable. Furthermore, if clinical intuition is superior to score-based risk assessment, by refinement using by patient characteristics not included in risk scores, then such influences should also be observable. Therefore, we explored whether biases representing “under-weighing” or “over-weighing” of risks and perceived benefits were observable within a multi-national registry comparing physician-determined risk with GRACE-risk score estimated risk. Specifically, we sought to: 1) evaluate whether established clinical factors influenced physician risk perception in a magnitude that was similar to components of the GRACE risk score; 2) determine whether other clinical and functional factors imparted a observable impact on physician perception of risk and benefit; and 3) explore whether these physician intuition of risk and benefit correlate with provision of care and outcome.

7.3 Methods

7.3.1 Study Design and Population

The Perceived Risk of ischaemic and bleeding events In acute Coronary syndrome patients (PREDICT) was a prospective multi-centre international registry of ACS patients was conducted in Australia, China, India and Russia (58 hospitals) between May 2009 and February 2011. Details of the study have been published elsewhere.[9] Local ethics approval was obtained at each site with each patient providing informed consent prior to enrolment in the study. Eligible patients presented with either suspected ST elevation myocardial infarction (STEMI) or high and intermediate risk non-ST segment ACS (NSTEACS) using the National Heart Foundation risk stratification criteria.[10] Enrolment was centrally adjudicated to ensure consistency of enrolment criteria. Suspected ACS admissions deemed secondary to other causes such as major trauma or surgery were excluded. The primary discharge diagnosis was determined by the investigator, but confirmed by a central query process. Since the comparison was between clinical and risk-score based risk assessment within the same patient, consecutive enrolment was encouraged but not mandated, and was implemented based on local resource availability.

Clinical and demographic data enabling the calculation of the GRACE risk score were collected soon after admission.[11] A scaled frailty index assessing the need for additional supports in activities of daily living was also evaluated on each patient. Guideline recommendations including early invasive management and pharmacotherapies by discharge were documented. Trained clinical trial co-ordinators or clinicians abstracted all baseline clinical and outcome data by case-note review and telephone follow-up. All missing data for establishing eligibility, calculating the GRACE risk score, frailty assessment of clinical events were re-queried in the data-management process. At study completion, independent country specific monitors audited data pertaining to clinical events and vital status.

7.3.2 Physician assessment of ischaemic and bleeding risk

Physicians directly involved in each specific patient's care were asked to estimate the patient's individual baseline "untreated" absolute risk of death or bleeding events by 6 months. Physicians were also asked to estimate the effect of guideline recommended therapies by estimating the risk of the event for that patient treated with each individual guideline therapy alone. Assessments were completed as close to admission as possible, before the provision of coronary angiography (except in the case of primary

PCI) or other discharge medications. A standard physician questionnaire documented clinical experience duration described as years since graduation and whether they held a specialist qualification. At least two physician assessments were obtained per patient. While corroboration between physicians could not be prevented, such discussions were discouraged.

7.3.3 Clinical Events

All cause mortality and clinical bleeding events were sought during the initial hospital admission, through to 6 months using standard definitions. Bleeding events were defined using the ACUITY criteria, specifically a fall in hemoglobin of >3g/dL, any blood transfusion, bleeding requiring a surgical/procedural intervention, or a vascular access site haematoma of >5cm in diameter.[12] Independent adjudication of all events was undertaken.

7.3.4 Statistical Analysis

Continuous variables are expressed as a mean ± standard deviation (SD) or median and inter-quartile ranges for variables with non-normal distributions. Discrete variables are expressed as counts (n) and percentages (%). Six-month "untreated" mortality and bleeding risk estimates were taken directly from the physician questionnaire while the 6-month "treated" mortality and bleeding estimates for invasive management, and all therapies fully implemented, were derived as the product of the physician-estimated incidence rate ratios for each therapy (e.g. 6-month death $_{\text{(with therapy)}}$/ 6-month death $_{\text{(no therapy)}}$: for each of aspirin, clopidogrel, statin, ACE-Inhibitor/ARB, beta-blocker and early invasive management). Inter-rater variation in the estimation of untreated risk between physicians was compared with the kappa statistic.

Physician-predicted probabilities were converted to odds, log-transformed and these log-odds were regressed on GRACE risk factors (age, presenting heart rate (HR) and systolic blood pressure (SBP), baseline creatinine, biomarker elevation, ST segment change, presentation with cardiac arrest, hypertension, peripheral vascular disease and prior PCI) and clinical characteristics in the multilevel mixed-effects linear regression models to enable comparison with the odds ratios for 6-month death from the GRACE model.[11] However, physician-perception of risk only varied at the extremes of heart rate and systolic blood pressure, and these were modelled as HR < or ≥ 110 bpm, and SBP < or ≥ 100 mmHg. Frailty (frailty score < or≥ 4), gender, diabetes, weight <60kg, prior coronary artery bypass grafting, a history of atrial fibrillation, prior heart failure, cerebrovascular disease, or chronic lung disease and years of physician

experience (1-5years, 5-10 years, 10+ years) were also added to the model to assess the impact of additional clinical and physician factors on risk prediction. Exploring the association between clinical factors and perceived impact of early invasive management, physician estimates for mortality and bleeding with and without treatment were used to generate odds ratios, log-transformed and then modelled in multilevel mixed effects linear regression clustered on the same county site and patient characteristics. To allow for cultural and health system differences in risk determination and the multi-centre design, random intercepts for country, site and patient were entered into the multi-level models with age (in 10 year groups), gender, frailty and physician experience also included as random coefficients at the country level. Standardised normal probability plots assessing distribution residuals were found to be acceptable.

Direct comparison of physician-estimated with GRACE-calculated risk demonstrated inferior risk assessment with clinician intuition (C-Statistic: GRACE: 0.812 versus Physician: 0.652 $p<0.0001$).[9] Hence, under-estimation of a patient's risk was determined by subtracting the GRACE-calculated mortality rate from each physician-estimated mortality rate for each given patient with a negative value representing risk under-estimation. A patient level analysis of the care provided (angiography, PCI and CABG, and prescription/contraindication to recommended medications) and 6-momth mortality, grouping patients by those in whom "no physician underestimated" risk versus "at least 1 underestimated" risk and those where "all physicians underestimated" their risk was undertaken, using chi-square and Kruskal-Wallis testing for dichotomous and continuous variables, respectively. Mortality by 6 months and "any underestimation" of risk was also multi-level mixed effects logistic regression with GRACE score and frailty entered as fixed effects, and country and site as random effects. All analyses were undertaken using the STATA 11.2. A probability value of <0.05 was considered statistically significant.

7.4 Results

Of the 1575 patients enrolled, 32 had incomplete data preventing calculation of the GRACE risk score, or were lost to follow-up, leaving 1542 patients (Australia [n=416], China [n=495], India [n=384], and Russia [n=247],) and 4230 patient-specific physicians estimates. Among the 58 enrolling hospitals, 11 were non-metropolitan hospitals (Australia [3/12], China [1/16], India [5/10], and Russia [2/20],). Of the responding clinicians, 81.4% identified themselves as cardiovascular specialists, with

11.5 (SD: 7.7) years of clinical experience. The median time between admission and risk assessment was 1.2 days (i.q.r.: 0.3-5.1 days), and the median time between physician assessments for each patient was 19 minutes (i.q.r.: 0-58 minutes). The consistency of 6-month mortality estimation between clinicians for the same specific patient was poor (kappa statistic: 17.6% agreement, $p<0.001$) improving to modest (kappa statistic: 45.5% agreement, $p<0.001$) when considered as deciles of risk. (Figure 1) The median perceived 6-month mortality for the entire population of 25% (i.q.r: 14-35%) was much higher than the GRACE score predicted median mortality of 6% (i.q.r.: 3-10%). The fully treated 6-month mortality estimate for the population was 2.5% (i.q.r.: 0.7-7.6%) while the observed 6-month mortality was also 48/1542 (3.1%). The median estimated risk of bleeding within by 6 months was 5% (i.q.r: 1-10%) increasing to 12% (i.q.r: 4-25%) with full treatment, while the observed bleeding rate by 6 months using the ACUITY definition was 73/1542 (4.7%). Physicians with <5 years, 5-10 years and 10+ years of experience over estimated 6-month mortality risk by a median 19% (i.q.r: 5-32%), 13% (i.q.r: 1-29%) and 9% (i.q.r: -1-22%), respectively, ($p=0.0001$). Patient characteristics arbitrarily divided into tertiles of physician estimated-risk are described in Table 1. Patients in the clinician-estimated highest risk groups were less frequently female and present with ST segment elevation MI (STEMI) but were no more likely to be of older age. A modest relationship between the GRACE score and TIMI scores were observed.

Table 1: Clinical characteristics stratified by tertiles of average physician estimated risk

	Low (n=520)	Intermediate (n=531)	High (n=491)	Total	p-value
Predicted risk of 6mth death (%, i.q.r.)	8 (11)	23 (11)	44 (32)	22 (24)	<0.001
Age (years, median, i.q.r)	59.3 (16.5)	59.7 (16.7)	60.6 (17.2)	59.9 (17.2)	0.249
Female (n, %)	140 (26.9)	101 (19.0)	109 (22.2)	350 (22.7)	0.009
Country (n, %)					
Australia	222 (42.7)	127 (23.9)	67 (13.7)	416 (27.0)	<0.001
China	96 (18.5)	176 (33.2)	223 (45.4)	495 (32.1)	
India	148 (28.5)	155 (29.2)	81 (16.5)	384 (24.9)	
Russia	54 (10.4)	73 (13.8)	120 (24.4)	247 (16.0)	
STEMI (n, %)	198 (38.1)	298 (56.1)	342 (69.6)	836 (54.4)	<0.001
NSTEACS (n, %)	322 (61.9)	233 (43.9)	149 (30.4)	702 (45.6)	<0.001
Diabetes (n, %)	165 (31.7)	140 (26.4)	103 (21.0)	409 (26.5)	0.001
Hypertension (n, %)	308 (59.2)	300 (56.5)	274 (55.8)	882 (57.2)	0.053
Hyperlipidaemia (n, %)	228 (43.9)	190 (35.8)	185 (37.8)	603 (39.1)	0.021
Current Smoker (n, %)	143 (27.5)	178 (33.5)	207 (42.2)	528 (34.2)	<0.001
Heart Rate (bpm, mean± SD)	77 (22)	77 (22)	76 (21)	76 (22)	0.963
Systolic BP (mmHg, mean± SD)	134 (20)	130 (33)	130 (32)	130 (35)	<0.001
Killip Class (Median, i.q.r)	1 (1)	1 (1)	1 (1)	1 (1)	0.143
eGFR (mls/min/1.73m^2)	67.0(29.4)	63.0 (26.3)	65.5 (27.5)	65.4 (27.6)	0.053
Cardiac Arrest (n, %)	4 (0.8)	3 (0.6)	26 (5.3)	33 (2.1)	<0.001
Cardiogenic Shock (n, %)	6 (1.2)	11 (2.1)	31 (5.3)	48 (3.1)	<0.001
Prior MI (n, %)	82 (15.8)	84 (15.8)	71 (14.5)	237 (15.4)	0.795
Prior CCF (n, %)	19 (3.7)	26 (4.9)	24 (4.9)	69 (4.5)	0.539
Prior CABG (n, %)	39 (7.5)	17 (3.2)	13 (2.7)	69 (4.5)	<0.001
Known COPD (n, %)	16 (3.1)	29 (5.5)	26 (5.3)	71 (4.6)	0.125
Prior CVA (n, %)	19 (3.7)	24 (4.5)	20 (4.1)	63 (4.1)	0.778
GRACE Score (Median, i.q.r)	100 (43)	105 (40)	108 (43)	105 (41)	<0.001
TIMI Score (STEMI) (Median, i.q.r)	3 (3)	3 (3)	3 (3)	3 (3)	0.008
TIMI Score (NSTEMI) (Median, i.q.r)	3 (1)	3 (1)	3 (1)	3 (1)	0.585
Frailty Score	2 (1)	3 (2)	3 (2)	3 (2)	<0.001

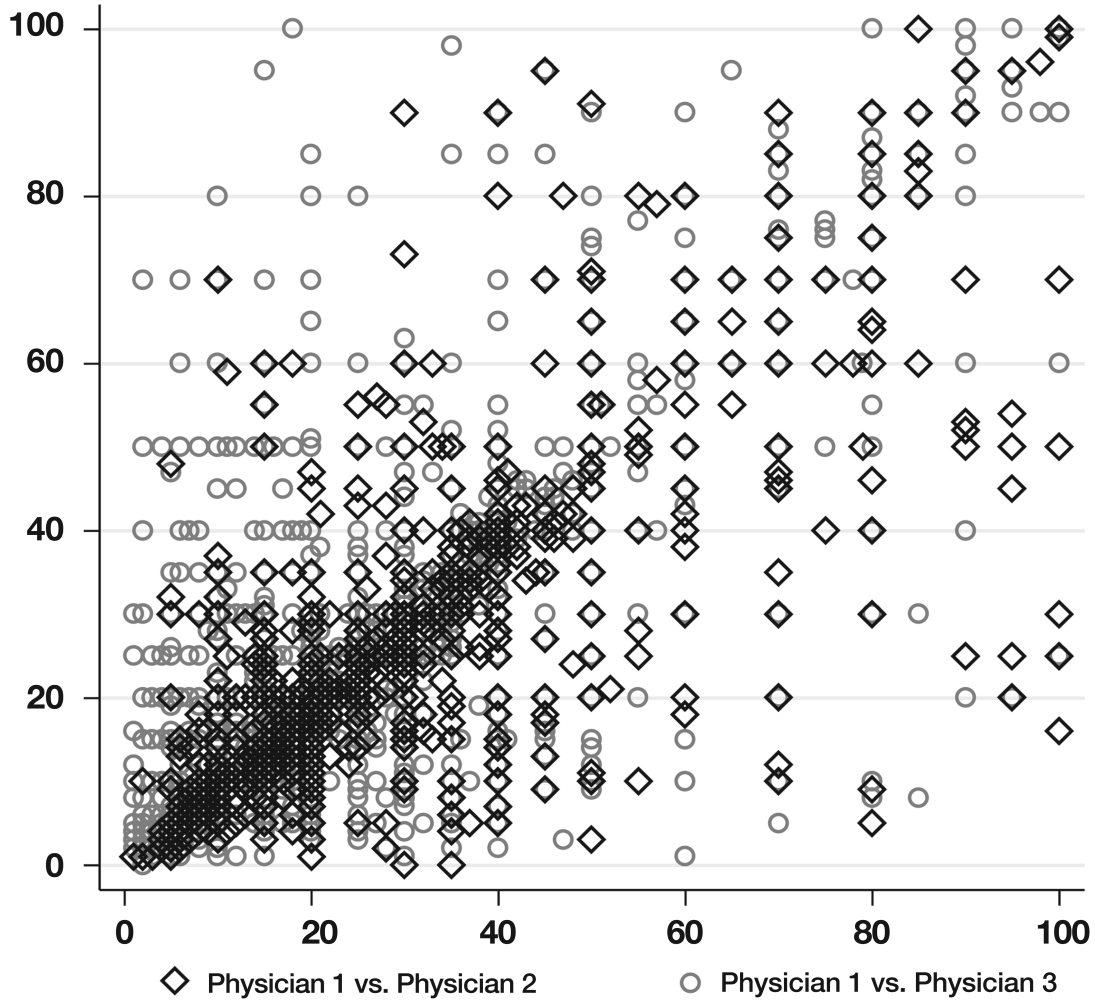
7.4.1 Physician perceived risk and GRACE risk score characteristics

Each component of the GRACE score was associated with an increase in physician-estimated risk except for admission creatinine and biomarker elevation. (Table 2) For HR, SBP and age, a significant association with perceive risk was not evident until the extremes of these parameters. Presentation with pulmonary congestion or cardiac arrest was associated with an increased perception of risk. Baseline creatinine, and prior heart failure were not associated with physician-perceived risk.

Table 2: Odds ratios (& 95% C.I.) for the physician-perceived mortality risk associated with clinical characteristics included in the GRACE risks score obtained in multivariate modelling compared with published estimates obtained from the GRACE dataset.

GRACE Risk Factor Physician Observed	Odds Ratio	95% C.I.	P value	GRACE Risk Factor GRACE Calculated	Odds Ratio	P-value for difference
Age group	1.06	1.02-1.09	0.001	**Age group**	1.8	<0.001
Tachycardia	1.37	1.18-1.58	<0.001	**HR per 30bpm**	1.2	0.076
Hypotension	1.76	1.39-2.24	<0.001	**SBP per 20**	1.2	0.002
Creatinine group	0.995	0.98-1.02	0.643	**Creatinine per 88umol/L**	1.2	<0.001
Killip Class	1.17	1.10-1.24	<0.001	**Killip per Class**	1.5	<0.001
ST segment change	1.16	1.08-1.25	<0.001	**ST segment change**	1.6	<0.001
Biomarker Positive	1.005	1.00-1.01	0.033	**Biomarker Positive**	1.6	<0.001
Cardiac Arrest	3.205	2.57-4.00	<0.001	**Cardiac Arrest**	2.6	<0.001
HTN	0.93	0.88-0.99	0.024	**HTN**	1.2	<0.001
Prior CCF	1.12	0.94-1.33	0.191	**CCF**	1.5	0.001
Prior PVD	1.23	1.00-1.51	0.047	**PVD**	1.4	0.209
Prior PCI	0.95	0.84-1.07	0.371	**Prior PCI**	0.8	0.005

Figure 1: Correlation between first, second and third physician estimates of 6-month mortality for each patient



7.4.2 Multivariable adjusted estimates

Figure 2 displays the odds ratios for physician-estimated 6-month mortality associated with the GRACE score components, and other clinical factors potentially influencing physician risk prediction. The addition of clinical factors had little impact on the estimates associated with the GRACE score components. Among the additional clinical factors assessed, only prior coronary artery bypass grafting, female gender and frailty were associated with significant modification of risk assessment. Patients at increased frailty (score≥4) were perceived to be at greater risk while female gender was associated with a lower physician perceived risk.

7.4.3 Perceptions of mortality benefit from invasive management

Physicians perceived a significant benefit from early invasive management in reducing 6-month mortality (unadjusted OR: 0.49 (95% C.I. 0.47-0.51). In multivariable analysis,

the baseline perceived benefit from invasive management was an odds ratio of 0.73 (95% C.I.: 0.59-0.89). (Figure 3a) A higher perceived risk of death and presentation with hypotension were associated with a greater perceived benefit from invasive management. Increased age, female gender, cardiac arrest at presentation, renal impairment and prior or current evidence of heart failure were associated with a lower perceived benefit from invasive therapy. More experienced clinicians estimated less benefit from invasive management than less experienced clinicians.

7.4.4 Perceptions of bleeding risk from invasive management

Overall, clinicians estimated a 2.68 (95% C.I. 2.56-2.81) fold increased in the relative odds of bleeding associated with invasive management when compared with conservative management. (Figure 3b) In adjusted analysis, the baseline estimated perceived increase risk was 1.80 (95% C.I. 1.29-2.51). Clinical factors associated with a significant increase in the perception of bleeding risk included age >85yrs and pulmonary oedema at presentation. More experienced clinicians perceived a greater bleeding risk than less experienced clinicians. A perception higher absolute mortality risk was associated with a lower estimated risk of bleeding events with invasive management. Table 3 describes the rates of angiography and PCI stratified by the clinical characteristics associated with the significant differences in the perception of risk.

Table 3: Proportion of patients receiving coronary angiography and percutaneous coronary intervention (PCI) stratified by clinical characteristics associated with greater or less perceived benefit/risk with invasive management.

	Received angiography			Received PCI		
	Present (n,%)	Absent (n,%)	p-value	Present (n,%)	Absent(n,%)	p-value
Age >75yrs	126/200 (63.0)	1100/1342 (82.0)	<0.001	80/200 (40.0)	742/1342 (55.3)	<0.001
Female Gender	264/350 (75.4)	962/1192 (80.7)	0.032	152/350 (43.4)	670/1192 (56.2)	<0.001
Hypotension (SBP<100mmHg)	103/147 (70.1)	1123/1395 (80.5)	0.003	83/147 (56.5)	739/1395 (53.0)	0.420
Tachycardia (HR>100 bpm)	45/66 (68.2)	1181/1476 (80.0)	0.020	26/66 (68.2)	796/1476 (53.9)	0.021
Presentation with Cardiac Arrest	22/33 (66.7)	1204/1509 (79.8)	0.065	19/33 (57.8)	803/1509 (53.2)	0.619
ST segment changes on ECG	932/1154 (80.8)	294/388 (75.8)	0.035	644/1154 (55.8)	178/388 (45.9)	0.001
Prior CCF	27/69(39.1)	1199/1473 (81.4)	<0.001	11/69(15.9)	1199/1473 (55.1)	<0.001
Killip Class >2	243/323 (75.2)	983/1219 (80.6)	0.032	165/323 (51.1)	657/1219 (53.9)	0.360
Creatinine 0.8-1.6mg/dL	902/1123 (80.3)	273/331 (82.5)	<0.001	612/1123 (54.5)	179/331 (54.1)	0.001
Creatinine >1.6mg/dL	47/84 (56.0)	273/331 (82.5)		28/84 (33.3)	179/331 (54.1)	
BMI <20kg/m^2	66/81 (81.5)	1160/1461 (79.4)	0.651	36/81 (44.4)	786/1461 (53.8)	0.100
Diabetes	305/408 (74.8)	921/1134 (81.2)	0.006	173/408 (42.4)	649/1134 (57.2)	<0.001
Frailty Score >4	634/856 (74.1)	592/686 (86.3)	<0.001	427/856 (49.9)	395/686 (57.6)	0.003

7.4.5 Relationship between recognition of risk, treatments received and outcome

Underestimation of risk by at least one physician involved in their care was observed in 575 (37.3%) of the patients. While rates of angiography were similar, fewer patients in whom the risk was underestimated underwent PCI (None underestimated: 554/967 (57.3%) vs. one underestimated: 220/429 (49.0%) vs. all underestimated: 58/146 (39.7%) p<0.001). Underestimation of risk was associated with a lower rate of guideline advocated therapies and a higher rate of these treatments being deemed not indicated or contra-indicated. (Table 4) By 6-months, mortality rates were higher among patients in whom the risk was underestimated. (None underestimated: 10/967 (1.0%) vs. one underestimated: 25/429(5.8%) vs. all underestimated: 13/146 (8.9%). After adjusting for GRACE risk and frailty, any physician underestimation of risk was associated with a 6.0 fold increase in 6-month mortality (95% C.I.: 2.3-15.5, p<0.001).

Figure 2: Odds ratios (& 95% C.I.) for increased physician-perceived mortality risk associated with clinical characteristics included in the GRACE risks score and other clinical characteristics potentially associated with risk perception in multivariate modelling.

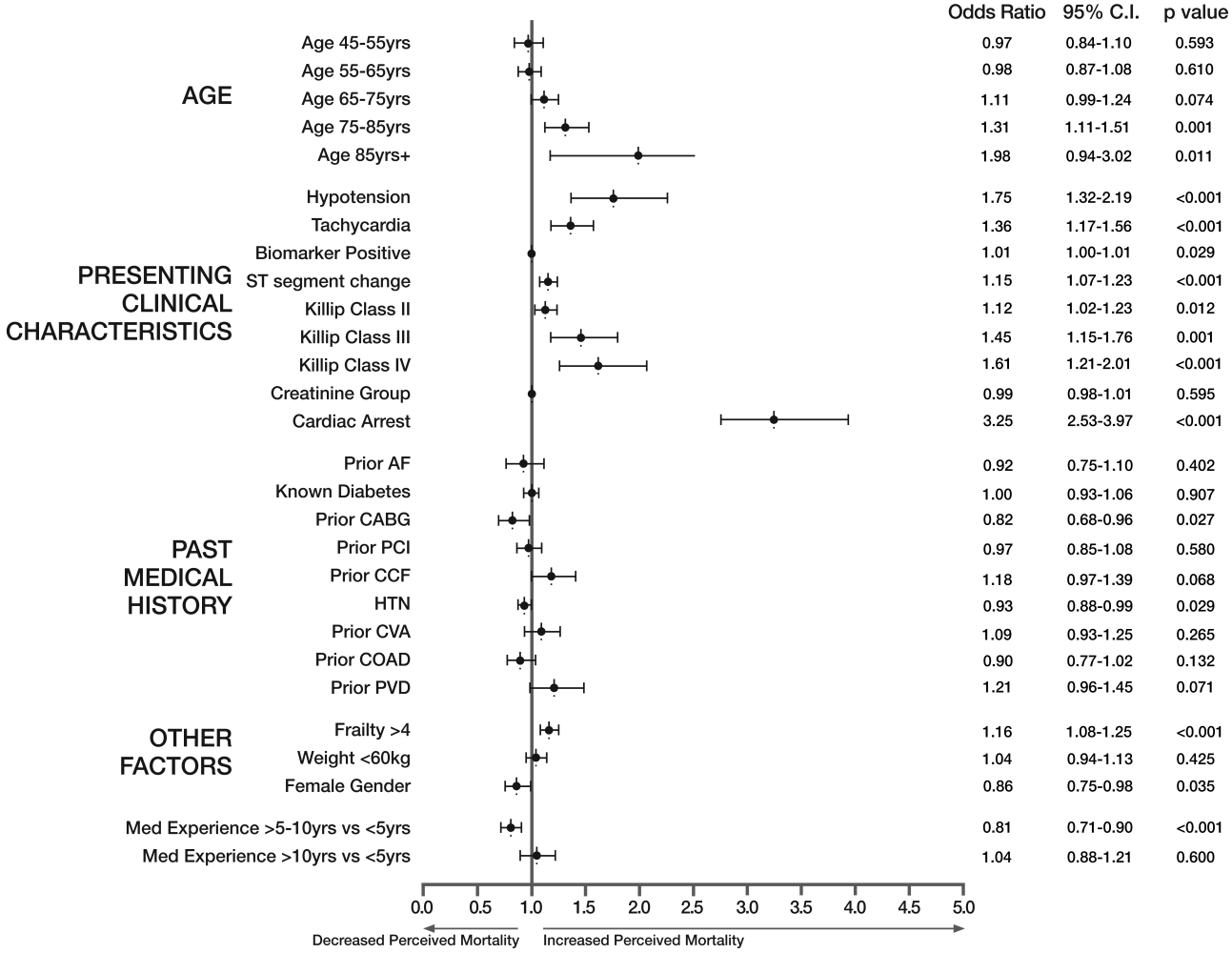
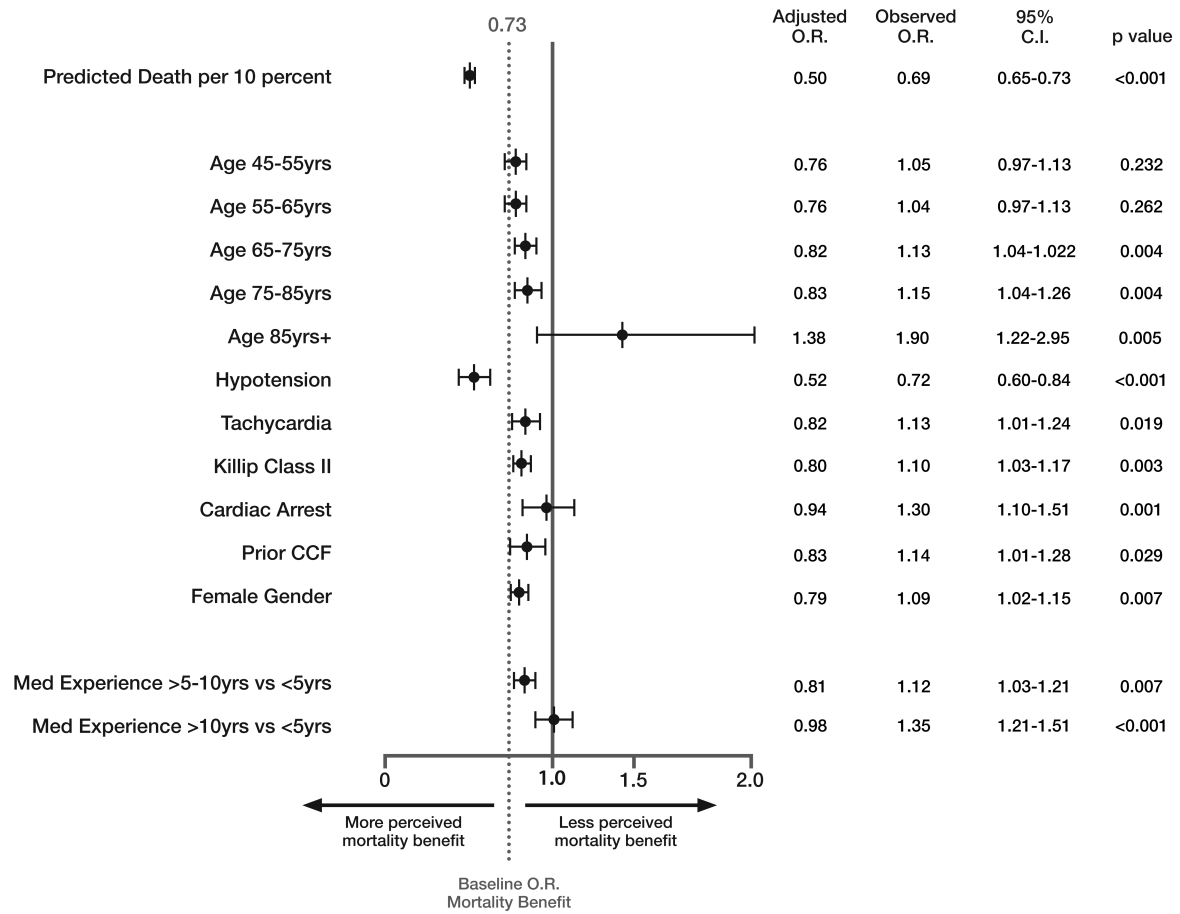


Figure 3: Odds ratios (& 95% C.I.) for clinical characteristics associated with greater or lesser physician-perceived: a) 6-month mortality benefit (baseline benefit OR 0.73 [95% C.I. 0.59-0.89]) and b) 6-month bleeding (baseline risk OR: 1.80 [95% C.I. 1.29-2.51]) associated with an early invasive management in multivariate modelling.

a)



b)

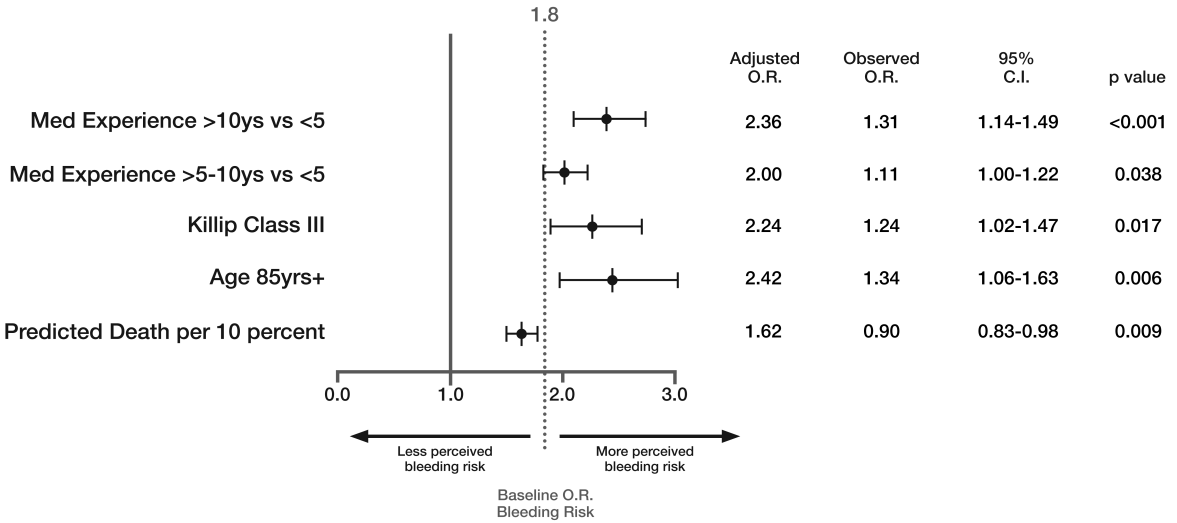

1.8
Adjusted O.R.
Observed O.R.
95% C.I.
p value
Med Experience >10ys vs <5
2.36
1.31
1.14-1.49
<0.001
Med Experience >5-10ys vs <5
2.00
1.11
1.00-1.22
0.038
Killip Class III
2.24
1.24
1.02-1.47
0.017
Age 85yrs+
2.42
1.34
1.06-1.63
0.006
Predicted Death per 10 percent
1.62
0.90
0.83-0.98
0.009
0.0
1.0
2.0
3.0
Less perceived bleeding risk
More perceived bleeding risk
Baseline O.R. Bleeding Risk

Table 4: Relationship between underestimation of risk and reported prescription, deemed non-indication and contraindication, and omission of clinical guideline recommended therapies.

(n=1542)		Not Underestimated n=967	One or two Underestimated n=429	All Underestimated n=146	P value
Aspirin	Prescribed (n, %)	940 (97.2)	394 (91.8)	134 (91.8)	<0.001
	Omitted (n, %)	1 (0.1)	15 (3.5)	2 (1.4)	
	Not indicated (n, %)	16 (1.7)	16 (3.7)	6 (4.1)	
	Contra-indicated (n, %)	10 (1.0)	4 (0.9)	4 (2.7)	
Clopidogrel	Prescribed (n, %)	907 (93.8)	331 (77.2)	116 (79.5)	<0.001
	Omitted (n, %)	0 (0)	18 (4.2)	7 (4.8)	
	Not indicated (n, %)	43 (4.5)	67 (15.6)	20 (13.7)	
	Contra-indicated (n, %)	0 (0)	18 (4.2)	7 (4.8)	
Statin	Prescribed (n, %)	924 (95.6)	379 (88.3)	133 (91.1)	<0.001
	Omitted (n, %)	2 (0.2)	28 (6.5)	5 (3.4)	
	Not indicated (n, %)	25 (2.6)	16 (3.7)	8 (5.5)	
	Contra-indicated (n, %)	16 (1.7)	6 (1.4)	0 (0)	
ACE-I or ARB	Prescribed (n, %)	805 (83.3)	307 (71.6)	103 (70.6)	<0.001
	Omitted (n, %)	2 (0.2)	23 (5.4)	3 (2.1)	
	Not indicated (n, %)	97 (10.0)	83 (16.4)	32 (21.9)	
	Contra-indicated (n, %)	63 (6.5)	17 (3.7)	8 (5.5)	
Beta-blockers	Prescribed (n, %)	817 (85.5)	330 (76.9)	108 (74.0)	<0.001
	Omitted (n, %)	0 (0)	15 (3.5)	4 (2.7)	
	Not indicated (n, %)	88 (9.1)	67 (15.6)	22 (15.1)	
	Contra-indicated (n, %)	62 (6.4)	17 (4.0)	12 (8.2)	

7.5 Discussion

Risk stratification is a critical component of effective and cost effective provision of evidence-based therapies. Several risk scores have been developed as tools to assist in risk stratification in ACS. However, these are not in widespread use and 'clinical intuition' has been relied upon historically. Yet much evidence indicates that intuition is inferior to risk scoring.[13-16] In this study of physician-perception of risk compared to risk scoring shows that clinical intuition is heterogeneous, poorly correlated between clinicians and often inaccurate with implications for clinical care and outcome. First, the influence on clinical intuition of clinical factors with a continuous or graded relationship to risk, was only evident at the extremes of these characteristics suggesting a tendency to detect only the very high-risk patients. Second, a systematic bias towards lower risk among women was evident. Third, a perception of less benefit from invasive management among the frail and elderly was observable. Fourth, a greater baseline physicians perceived risk was associated with more perceived benefit from invasive management and less bleeding risk, and this is associated with higher rates or more timely invasive management. Also, the underestimation of risk was associated with less guideline medications use, less invasive management and higher 6-month mortality. These observations suggest the routine incorporation of objective risk stratification into clinical practice may improve consistency of risk prediction and outcome through more accurate alignment of risk and care. This should be formally evaluated within appropriately designed clinical trials.

Risk assessment by clinical intuition often requires years of experience, as observable in this study. However effective learning requires environments that are sufficiently regular to reliably identify factors associated with risk, with a sufficiently prolonged exposure to provide the opportunity to correlate these factors with outcome. Considering the declining in-hospital mortality and morbidity event rates associated with ACS, with shortened lengths of stay, a limited capacity to evaluate late outcomes among many patients discharged from the acute care setting may now exist. Hence, the capacity to establish and refine clinical intuition-based risk prediction is challenging in current models of health care delivery.[17] Conversely, this experience of low in-hospital event rates may explain the ~90% perceived relative risk reduction attributed by clinicians to the complete provision of guideline recommendations by clinicians, an

observation that is remarkably consistent with the observed event rate in the patient cohort.

In assessing the association with individual clinical characteristics and the perception of risk, these observations suggest that clinician evaluate characteristics in a binary manner.[15,18] While age and haemodynamic status are known to relate to measured mortality in a continuous nature, but their influence on physician-estimated risk appears more dichotomous. Such observations suggest that misperceptions of risk may arise from the cumulative but subtle changes in risk characteristics that may be under-appreciated by clinical intuition. Furthermore, well established predictors of risk such as renal impairment, prior stroke and known heart failure were not independently associated with perceived risk suggesting that immediately available factors such as ECG changes and haemodynamics have a greater influence on intuitive risk assessments.[18] Female patients with ACS appear to be independently associated with a lower perceived mortality risk, less benefit from and, hence, less provision of invasive management. This observation confirms prior observations that female patients often receive fewer guideline therapies and experience poorer outcomes compared with their male counterparts, and demonstrates that risk misperception may explain some of this evidence practice gap.[5,19] These observations reinforce the need for programs that elevate awareness of the risk-profile of female patients presenting with ACS.

We found that underestimation of risk, while defined stringently, is prevalent and is associated with a higher 6-month mortality rate. Combined with the marked heterogeneity in risk prediction across physicians assessing the same patient may represent an opportunity to improve the translation of the ACS evidence-base into care and outcome through standardizing this process. Hence, coupling objective risk assessment with definitive evidence-based recommendations may be important in translating risk stratification to effective decisions and outcomes. This hypothesis should be formally tested in appropriately designed cluster randomised clinical trials, the feasibility of which is likely to improve with the increasing uptake of electronic health record systems.[20]

7.5.1 Limitations

Several issues should be considered when interpreting these results. First, these observations do not exclude that capacity for some clinicians to undertake accurate risk stratification outside this study. These results are a collective impression of the clinical factors that appear to influence the risk assessment among the patients by physicians

involved in this study. Generalization to other health care settings and clinicians should be undertaken with caution and ideally requires ongoing local validation. Second, we cannot conclude the clinicians involved in this study actually used these specific clinical factors in their risk stratification estimations of the specific patients. We can only observe patterns of perception of risk and associations with practice and outcome. Nevertheless, the clinical characteristics explored represent well-published and objectively validated factors associated with mortality, and their disregard in risk assessment would bias towards a null association, as observed with renal impairment. Third, this study sought risk assessment as close as possible to the bedside. Hence, examining risk prediction in a time-critical environment may have compromised the accuracy of the physician risk prediction. It should be highlighted that the design of study did not prohibit the use of ancillary and readily available risk prediction tools. Nevertheless, such environments represent the clinical realities of modern care and such arguments suggest the need to supportive tools for clinical decision making in these environments.

7.6 Conclusions

Clinical risk assessment among patients with ACS remains highly heterogeneous with variable associations between established clinical risk factors and physician predicted risk. Underestimation of risk is associated with lower use of guideline advocated therapies and increased late mortality. Clinical incorporation of risk stratification coupled with evidence-based decision support should be evaluated in appropriately designed clinical trials.

7.7 Acknowledgements

Authorship Contributions

Each author has directly contributed to conduct of this study. All authors have had access to the data and all drafts of the manuscript. Specific contributions are a follows. Study Design: DC; Data Collection: SM, CA; Data Management and Analysis: DC, MH; Manuscript writing: DPC; Manuscript review: All

Funding sources: Role of the Sponsor

This study was sponsored by Sanofi-Aventis Asia-Pacific. However, the protocol was conceived and designed by DC, and the sponsor has not had direct access to the data. Analysis and drafting of the manuscript has been conduced with full independence from the sponsor. The sponsor has reviewed the manuscript but has not provided any modification to its content.

Disclosures

Author DPC has advised the National Heart Foundation of Australia in the development of a clinical risk stratification tool aimed at improving clinical care in regional Australia. Author WP has received grant support from Abbott, Roche and Siemens with respect to biomarker research that pertains to risk stratification. All other authors have no other conflicts of interest to declare with respect to the content of this manuscript.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) DPC, CJ, JF, WP, MH, DB, SQ have direct support from Sanofi Aventis for the submitted work; (2) None have relationships with any other companies with the exception of those stated above that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) DPC, CJ, JF, WP, MH, DB, SQ have no non-financial interests that may be relevant to the submitted work.

7.8 References

1. Yan AT, Yan RT, Huynh T, Casanova A, Raimondo FE, Fitchett DH, Langer A, Goodman SG, Canadian Acute Coronary Syndrome Registry 2 Investigators. Understanding physicians' risk stratification of acute coronary syndromes: insights from the Canadian ACS 2 Registry. *Archives of Internal Medicine*. 2009; 169:372–378.

2. Fox K, Anderson F, Dabbous O, Steg P, Lopez-Sendon J, de Werf Van F, Budaj A, Gurfinkel E, Goodman S, Brieger D. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart*. 2007; 93:177–182.

3. Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. *Med J Aust*. 2007; 187:153–159.

4. Hung J, Brieger DB, Amerena JV, Coverdale SG, Rankin JM, Astley CM, Soman A, Chew DP. Treatment disparities and effect on late mortality in patients with diabetes presenting with acute myocardial infarction: observations from the ACACIA registry. *Med J Aust*. 2009; 191:539–543.

5. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, LaBresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L, for the Get With the Guidelines Steering Committee and Investigators. Sex Differences in Medical Care and Early Death After Acute Myocardial Infarction. *Circulation*. 2008; 118:2803–2810.

6. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC, Pollack CV, Gibler WB, Ohman EM, CRUSADE Investigators. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA*. 2004; 292:2096–2104.

7. Yan R, Yan A, Tan M, McGuire D, Leiter L, Fitchett D, Lauzon C, Lai K, Chow C, Langer A, Goodman S, Investig C. Underuse of evidence-based treatment partly explains the worse clinical outcome in diabetic patients with acute coronary syndromes. *Am Heart J*. 2006; 152:676–683.

8. Yan A, Yan R, Tan M, Fung A, Cohen E, Fitchett D, Langer A, Goodman S. Management Patterns in Relation to Risk Stratification Among Patients With Non-ST Elevation Acute Coronary Syndromes. *Arch Intern Med*. 2007; 167:1009–1016.

9. Chew DP, Junbo G, Parsonage W, Kerkar P, Sulimov VA, Horsfall M, Mattchoss S, for the Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndrome Patients (PREDICT) Study Investigators. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. *Circulation: Cardiovascular Quality and Outcomes*. 2013; 6:299–308.

10. Aroney C, Aylward P, Kelly A, Chew D, Clune E. National Heart Foundation of

Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. *Medical Journal of Australia*. 2006; 184:S1–.

11. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf Van F, Avezum A, Goodman SG, Flather MD, Anderson FA, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006; 333:1091.

12. Stone G, Ware J, Bertrand M, Lincoff A, Moses J, Ohman E, White H, Feit F, Colombo A, McLaurin B, Cox D, Manoukian S, Fahy M, Clayton T, Mehran R, Pocock S, ACUITY Investigators. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA*. 2007; 298:2497–2506.

13. Lee KL, Pryor DB, Harrell FE Jr, Califf RM. Predicting outcome in coronary disease statistical models versus expert clinicians. *The American journal of …*. 1986;

14. Kong DF, Lee KL, Harrell FE Jr, Boswick JM. Clinical experience and predicting survival in coronary disease. *Archives of internal …*. 1989;

15. Grove WM, Zald DH, Lebow BS, Snitz BE, Nelson C. Clinical versus mechanical prediction: a meta-analysis. *Psychol Assess*. 2000; 12:19–30.

16. Dawes RM. The robust beauty of improper linear models in decision making. *American Psychologist*. 1979; 34:571–582.

17. A Universal Model of Diagnostic Reasoning. 2009;:1–7.

18. Tversky A, Kahneman D. Judgment under Uncertainty: Heuristics and Biases. *Science*. 1974; 185:1124–1131.

19. Blomkalns A, Chen A, Hochman J, Peterson E, Trynosky K, Diercks D, Brogan G, Boden W, Roe M, Ohman E, Gibler W, Newby L, CRUSADE Investigators. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol*. 2005; 45:832–837.

20. Diamond GA, Kaul S. By desperate appliance relieved? On the clinical relevance of risk stratification to therapeutic decision-making. *Am. J. Cardiol.* 2012; 109:919–923.

7.9 Appendix: Study organization

Steering committee: Professor Derek Chew (Australia), Professor Ge Junbo (China), Professor Prafulla Kerkar (India), Dr William Parsonage (Australia), Professor Vitaly Sulimov (Russia). **Clinical Research Organization:** Flinders Cardiac Research: Sue Mattschoss, Matthew Horsfall, Helen Hughes.
Australia: Dr Julian Vaile, Flinders Medical Centre, Bedford Park SA; Dr Margaret Arstall, Lyell McEwin Hospital, Elizabethvale SA; Dr Prasad Challa, Cairns Base Hospital, Cairns QLD;Dr Nicholas Collins, John Hunter Hospital, New Lambton NSW; A/Prof Craig Juergens, Liverpool Hospital, Liverpool NSW: Dr Drew Fitzpatrick, Nepean Hospital, Kingswood NSW; Dr William Van Gaal, The Northern Hospital, Epping VIC: Dr William Parsonage, Royal Brisbane & Women's Hospital, Herston QLD; Dr Steven Coverdale , Nambour General Hospital, Nambour QLD; Dr David Cross, Wesley Hospital, Auchenflower QLD; Dr Jonathon Waites, Coffs Harbour Hospital, Coffs Harbour NSW; Dr Ananth Prasan, St George Hospital, Kogarah NSW; Dr Jamie Rankin , Royal Perth Hospital, Perth WA;
China Dr Junbo GE, The Affiliate Zhongshan Hospital of Fudan University, Shanghai; Dr Daifu ZHANG, Shanghai Dongfang Hospital, Shanghai; Dr Gen XU, The Second Affiliate Hospital of Zhejiang University, Hangzhou; Dr Xingwei ZHANG, The Second Hospital of Hangzhou City, Hangzhou; Dr Jiangui HE, The First Hospital of Sun Yat-Sen University, Guangzhou; Dr Chun WU, The Affiliate Hospital of Beijing University, Beijing; Dr Guangping Li, The Second Affiliate Hospital of Tianjing Medical University, Tianjing; Dr Guoxian Qi, The First Affiliate Hospital of Chinese Medical University, Shenyang; Dr Shumei Ma, The Second Affiliate Hospital of Chinese Medical University, Shenyang; Dr Zhanquan Li, Liaoning Province Hospital, Shenyang; Dr Weimin LI, The First Affiliate Hospital of Ha'erbin Medical University, Ha'erbin; Dr Zuyi Yuan, The First Affiliate Hospital of Xi'an Transportation University, Xi'an; Dr Jianhong Tao, Sichuan Province Hospital , Chengdu; Dr Xingbing Liu, The Affiliate Hospital of Sichuan University, Chengdu; Dr Lin Cai, The Third Hospital of Chengdu City, Chengdu; Dr Jianmei Li, The Second Hospital of Yunnan Province, Kunming;
India: Dr Prafulla Kerkar, KEM Hospital & G.S. Medical College, Parel, Mumbai – 12; Dr Nakul Sinha, Sanjay Gandhi Post Graduate Institute (SGPGI), Lucknow – 226014; Dr Sengottuvelu, Dr. G.S. Heart Clinic, T. Nagar, Chennai – 17; Dr G S Wander , Hero DMC heart institute Dayanand Medical College, Ludhiyana 141001; Dr Prashant Jagtap, Wockhardt Heart Hospital, Corporation Colony, Nagpur – 440010; Dr C.Raghu , Prime Hospital, Ameer Pet,HYDERABAD - AP – 500038; Dr Devang Desai, E-5 Swaminarayan Complex, Char Rasta, Surat – 395002; Dr Anupam Shah, Ashwini Sahakari Rugnalaya & Resarch Centre, Solapur – 413002; Dr Balbir Singh, Medanta – The Medicity, Gurgaon, Haryana – 122001; Dr Samir Dani, Lifecare Institute of Medical Science & Research, Narangpura, Ahmedabad – 380014;
Russia: Dr Vladimir Barbarich, City clinical hospital # 1, Novosibirsk; Dr Natalya Yarochno , City hospital # 34, Novosibirsk; Dr Dmitry Duplyakov, Regional cardiology dispensary, Samara; Dr Zhanna Kobalava, City clinical hospital # 64, Moscow; Dr Nina Novikova , Clinic of cardiology of the First Moscow Medical Academy named after IM Sechenov, Moscow; Dr Vagan Mkrtchyan, Hospital for wars veterans, Moscow; Dr Olga Shuyskaya , Central military clinical hospital of Federal Security Service, Moscow; Dr Zaur Shogenov , City clinical hospital # 81, Moscow; Dr Yuriy Titkov, Clinical hospital# 122, St-Petersburg; Dr Sergey Sayganov, Clinical hospital# 1, St-Petersburg; Dr Anna Cherkashina, Regional clinical hospital, Irkutsk; Dr Privalov Dmitry , City clinical hospital # 51, Moscow; Dr Andrey Sirov , Clinical Hospital Medical Unit of the Main Department of Internal Affairs, Moscow; Dr Igor Staroverov, A.L.Myasnikov Institute of Clinical Cardiology, Russian Cardiology Research Center, Moscow; Dr

Tatiana Yurchak, City clinical hospital # 7, Moscow; Dr Larisa Tokareva , Hospital of Ministry of Internal Affairs, Moscow; Dr Georgiy Gazaryan, The Moscow City Research Institute of Emergency Care. NV Sklifosovsky , Moscow; Dr Alexey Demiynenko, Central Military Clinical Hospital № 2 named after PV Mandryka Russian Ministry of Defense , Moscow; Dr Svetlana Boldueva, St-Petersburg Medical Academy named after II Mechnikov, St-Petersburg; Dr Vladimir Kuznetsov, Clinical Emergency Hospital № 15, Volgograd.

8 A CLUSTER RANDOMISED TRIAL OF OBJECTIVE RISK ASSESSMENT VERSUS STANDARD CARE FOR ACUTE CORONARY SYNDROMES: RATIONALE AND DESIGN OF THE AUSTRALIAN GRACE RISK SCORE INTERVENTION STUDY (AGRIS)

8.0 Title page : A Cluster Randomised Trial Of Objective Risk Assessment Versus Standard Care For Acute Coronary Syndromes: Rationale and Design of The Australian GRACE Risk score Intervention Study (AGRIS)

Derek P Chew MBBS MPH[1], Carolyn M. Astley RN DrPH[1,2], Heather Luker MPH[3], Bernadette Alprandi-Costa RN[3], Graham Hillis MBBS PhD[4], Clara K Chow MBBS PhD[5,6], Steve Quinn PhD[1], Andrew T Yan MD[7], Chris P. Gale PhD[8], Shaun Goodman MD[7], Keith AA Fox MBBS[9], David Brieger MBBS PhD[3]

Author Affiliations

[1] School of Medicine, Flinders University of South Australia, Adelaide, Australia

[2] South Australian Department of Health/Flinders University, Adelaide, Australia

[3] Concord Hospital, University of Sydney, Sydney, Australia

[4] School of Medicine, University of Western Australia, Perth, Australia

[5] The George Institute for Global Health, University of Sydney and Westmead Hospital, Sydney, Australia

[6] Division of Cardiology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Canada

[7] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK

[8] University of Edinburgh, Edinburgh, UK

Running Title: GRACE risk score Intervention Study

Key Words: Acute Coronary Syndromes, Risk Stratification, Quality of Care

Corresponding Author

Derek P Chew MBBS MPH

Flinders University

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

Email: derek.chew@flinders.edu.au

8.1 Abstract

Background: Assessing risk and weighing the potential benefits from evidence-based therapies are essential in the clinical decision making process of optimizing care and outcomes for patients presenting with acute coronary syndromes (ACS). Such practices are advocated in international clinical guidelines of ACS care. While the GRACE risk score (GRS) is a guideline advocated, well-validated risk stratification tool, its utility in improving care and outcomes remains unproven, and its application has been limited in routine clinical practice.

Objective: This study will assess the effectiveness using the GRS tool and treatment recommendations during patient assessment on improving the application of guideline-recommended therapies in ACS care.

Design: This study employs a prospective cluster (hospital-level) randomised open-label blinded endpoint (PROBE) design to evaluate objective measures of hospital performance, with clinical events adjudicated by a blinded event committee. This randomised study is nested within the established CONCORDANCE registry of ACS patients, with existing methods for data collection and monitoring of care and clinical outcomes. The hospital-level intervention is the integration of the GRS into routine ACS patient assessment process. The study will assess the use of early invasive management, prescription of guideline recommended pharmacology and referral to cardiac rehabilitation by hospital discharge; with the key composite clinical endpoint of cardiovascular death, new or recurrent myocardial infarction, in-hospital heart failure or cardiovascular readmission at 12 months. Health economic impacts of

risk stratification implementation will also be evaluated. The study will recruit 3000 patients from 30 hospitals.

Summary: The AGRIS trial will establish the effect of routine objective risk stratification using the GRACE risk score on ACS care and clinical outcomes.

8.2 Introduction

Clinical risk assessment is an important step in the effective translation of proven therapies into improved clinical practice and is routinely recommended in international guidelines of acute coronary syndrome (ACS) care.(1-3) However, it has been repeatedly demonstrated that clinical risk assessment based on physician perception is heterogeneous and potentially associated with sub-optimal provision of care when compared with objective risk assessment.(4-6) Risk stratification using risk scores build upon objective clinical characteristics are appealing as they provide a standardised assessment of risk, and may offer more consistent risk assessment in clinical environments where clinical experience with the ACS management is limited.

Several objective measures of risk have been developed. The Thrombolyis in Myocardial Infarction (TIMI) risks scores for both ST segment elevation myocardial infarction (MI) and non-ST segment elevation ACS were developed from clinical trial datasets and have some appeal given their relative ease of implementation. (7,8) The Global Registry for Acute Coronary Events (GRACE) risk score is a well established set of clinical risk stratification indices developed from a clinical registry of >100,000 patients enrolled from 247 hospitals in 30 countries and refined in a smaller subset of patients.(9-11) Using age, hemodynamics, ECG changes, cardiac marker elevation, renal function, and cardiac arrest on presentation, this objective assessment of risk has been validated in several international clinical datasets demonstrating a high level of discriminatory performance.(6,12) Comparisons of the TIMI and GRACE scores suggest greater risk discriminatory performance with the latter.(6,12) However, the impact of the routine adoption of such a risk score into ACS clinical

decision-making has not been studied within a prospective randomised controlled clinical trial.

The use of risk tools at the bedside is heterogenous, with uncertainty as to how it may influence clinical decision-making and a strong reliance on physician intuition-based risk assessment.(13) Limited utilization within clinical practice provides an opportunity to evaluate the impact of the routine application of objective risk stratification on clinical practice, potentially providing an evidence base for its recommendation in practice guidelines.

The following research hypothesis will be addressed: Objective risk stratification using the GRS Tool and treatment recommendations will improve the achievement of hospital-level performance measures, and secondarily, provide a cost-effective approach to improving ACS outcomes.

8.3 Methods

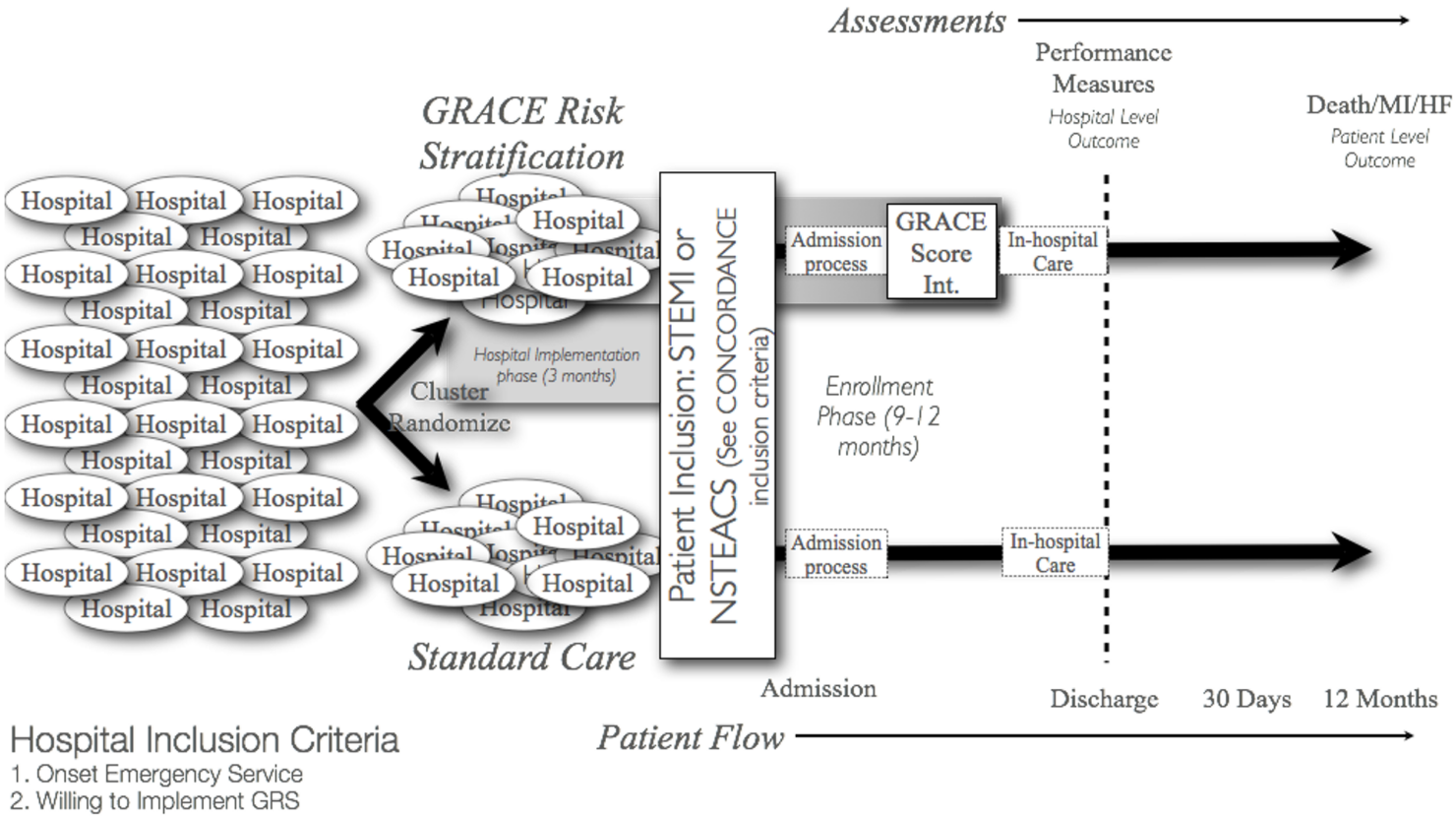
8.3.1 Objective

The AGRIS study (registered with Australian and New Zealand Clinical Trial Registry (http://www.anzctr.org.au/ ACTRN12614000550606) seeks to enhance evidence-based risk assessment and clinical decision-making, and as a consequence, reduce the mismatch between patient risk, ACS care and clinical outcomes.

8.3.2 Study Design

This study employs a prospective cluster (hospital-level) randomised open-label, blinded endpoint (PROBE) design to evaluate objective measures of hospital performance and clinical events in Australia. (Figure 1)

Figure 1: Cluster randomised design of GRACE risk score versus standard care study schematic.



Given that clinical care among patients within hospitals is correlated and the intervention is system-based, randomization and the implementation of the GRS tool and treatment recommendations at the level of the hospital will be required, since clinician contamination would occur if randomization occurred at the patient level. Since the intervention is directed at supporting decision-making, blinding of the intervention is not appropriate. To facilitate trial conduct and ensure consistent evaluation of study endpoints, the study employs a randomised-registry approach, and is nested within the already established CONCORDANCE registry of ACS patients, where existing mechanisms for clinical data collection using an “opt-out” consent process are currently ongoing.(14,15) The hospital and patient level eligibility criteria are presented in Table 1.

Table 1: Hospital and Patient Selection Criteria

Hospital Level Inclusion Criteria	Presence of onsite 24/7 emergency services
	Cardiology/medicine unit willing to implement the GRACE Risk tool and treatment recommendation plan into their care process
Hospital level Exclusion Criteria	Hospitals with an existing implemented risk stratification support system for the management of ACS patients
Patient Level Inclusion Criteria	Symptoms consistent with acute cardiac ischaemia for >10mins within 24 hours of presentation to hospital plus one of the following:
	ECG changes: • transient ST segment elevation of 0.5mm in 2 or more contiguous leads; • ST segment depression of 0.5mm in 2 or more contiguous leads; • New T wave inversion of 1 mm in 2 or more contiguous leads; • New Q waves [1/3 height of R wave or >0.04 seconds]; • New R wave > S wave in lead V1; or, • New left bundle branch block
	Elevated cardiac biomarkers: • Troponin T or I above the upper reference limit (URL); • CK-MB 2x URL; or, • If there is no CK-MB available, then total CK greater than the local URL
	Documented coronary artery disease: • History of MI or angina; • Congestive cardiac failure due to ischaemia; • Resuscitated sudden cardiac death; • Prior or new positive stress test with or without imaging; • Prior or new, cardiac catheterisation, percutaneous coronary artery intervention or coronary artery bypass graft surgery documenting coronary artery disease
	At least 2 of the following High Risk features: • Haemodynamic compromise (SBP<90 mmHg and HR >100 bpm) • Left ventricular systolic dysfunction (LVEF<0.40);

	• Presence of known diabetes • Documentation of chronic kidney disease (estimated GFR <60mls/min/m^2)
	ACS patients who meet the inclusion criteria but die before the opt-out consent process will be included using a waiver of the opt-out process where permitted by local ethics committee approval.
Patient Level Exclusion Criteria	Patients presenting to hospital with an ACS accompanied with, or precipitate by significant co-morbidity e.g. motor vehicle accident, trauma, severe gastrointestinal bleeding.
	Peri-operative or peri-procedural MI
	Patients already recruited into the study

8.3.3 Hospital Randomization and Subject Eligibility

Hospitals enrolling at least 10 ACS patients per month (i.e. allowing for a 12-month enrolment period) will be invited to participate. Hospitals agreeing to participate will be classified into 4 strata based on their sise and their previous performance within the CONCORDANCE registry. Within these 4 strata, hospitals will be randomised 1:1 to implement the GRS tool and treatment recommendations or to continue with standard care. A statistician who is independent of the CONCORDANCE registry will generate the randomisation schedule. Hospitals will be randomised once all ethics and research governance approvals have been received, and the hospital executive has signed the Cluster Guardian Randomisation Consent. Patients with objective evidence of an ACS event will be eligible for inclusion and those with a GRS calculated to be >118 will be considered at high-risk.(11) Hospital and patient eligibility and exclusion criteria are described in Table 1.

8.3.4 The intervention: The GRACE risk tool and treatment plan

The GRS requires assessment of basic clinical data including symptoms, clinical findings, past medical history, ECG, biomarkers and basic biochemistry to predict the 6 month mortality risk of each patient with suspected ACS. The GRS tool can be completed as a paper-based worksheet or electronically, and provides both a risk assessment and simple treatment recommendations that can be applied at the time of initial patient assessment. (Figure 2)

Simple dichotomous management recommendations with respect to use and timing of early angiography and possible revascularization as well as anti-thrombotic therapies, secondary prevention therapies and referral to cardiac

rehabilitation will be made. The worksheet will consist of the following (Figure 2):

1. Risk stratification calculator assessing ischaemic risk using the current version of the GRS and bleeding risk using the score derived from the Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines CRUSADE registry (16);
2. Nomograms for the quantification of patient-specific ischemic and bleeding risk, as well as individualised incremental reductions in recurrent events by applying literature-based estimates of treatment-effect associated with invasive management and secondary prevention therapies to the baseline risk (11,16,17);
3. Treatment recommendations based on risk;
4. Space for the admitting clinician to document the intended therapies and whether each of these therapies is “indicated”, “not-indicated” or “contra-indicated” will also be included on the worksheet.

Adherence to these treatment recommendations will not be considered mandatory, and all decisions regarding patient care will be at the clinician’s discretion. To maximise the uptake of the tool, sites will be permitted to locally adapt the layout and treatment recommendations contained in the GRS and treatment plan. Local changes will be approved by a chair(s) of the Steering Committee who will ensure that these recommendations include appropriate recommendations for the process measures included in the primary endpoint of the AGRIS study (i.e. coronary angiography, secondary prevention drugs and rehabilitation for high-risk patients) to maintain core

consistency across all intervention sites. Further details of the implementation process are included in the appendix.

Control: Hospitals randomised to the control arm will continue to deliver standard care and enroll ACS patients into the CONCORDANCE Registry using the existing opt-out consent process. Data, including all baseline measures and clinical assessments, therapies and timing of treatments, will be recorded in the CONCORDANCE Registry electronic case report form.

8.3.5 Implementation of the GRACE risk tool

The GRS tool and treatment recommendations will be embedded into routine clinical assessment and management procedures at each of the hospitals randomised to the active arm. A 3-month implementation period, aimed at educating all relevant clinical staff on the rationale and utilization of the GRS tool, will be followed by the active recruitment period (estimated 9-12 months).

The engagement of local leaders will be necessary to a) facilitate staff education regarding the relevance and utility of objective risk stratification and b) establish appropriate local processes to ensure integration of the GRS tool into routine clinical practice.

During the implementation period, an external trainer, independent of the CONCORDANCE registry, will work closely (3-4 visits over up to 3 months) with each hospital to facilitate the incorporation of the risk assessment worksheet into current work practices using a standardised set of training materials. A key feature of this process will be the identification of a local clinical champion at each site and assessment of the barriers and facilitators to implementing the GRS tool. Frequency of the visits will be determined by the local uptake of the

tool. Differentiation between the GRS tool and standard care will be critical to the scientific integrity of this study. As a consequence, every effort will be made to ensure the consistent uptake of the intervention at the hospitals randomised to the active arm.

Figure 2: Example of GRACE risks score estimation worksheet

Hospital Name

AGRIS Study Worksheet Page 1

URN: 012345678
SURNAME
First Name
DOB: 01/02/34

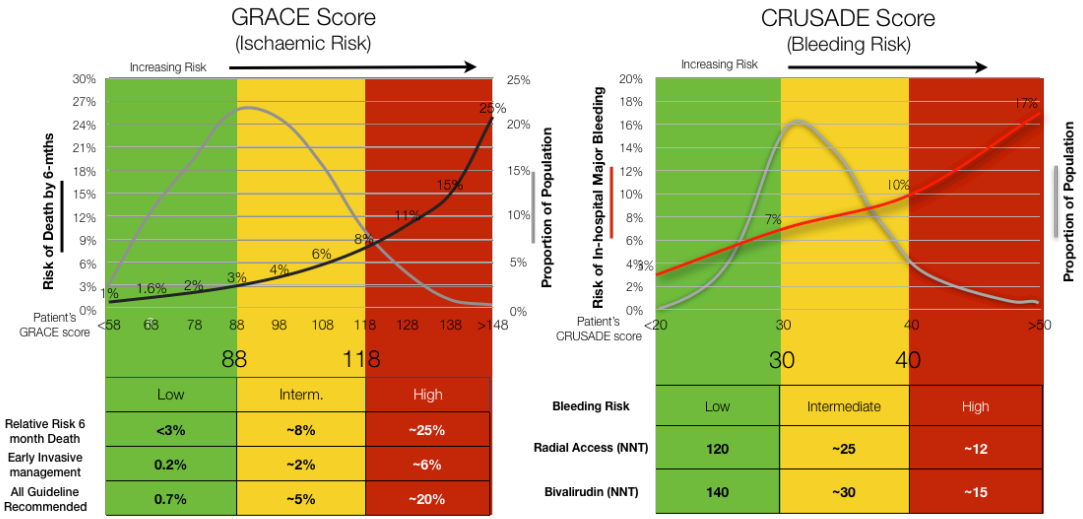
Step 1: Use the following table to calculate patient's GRACE Risk Score and CRUSADE Bleeding Risk Score

Age (years)	points	Patient
<40	0	
40-49	18	
50-59	36	
60-69	55	
70-79	73	
80+	91	
HR (bpm)	**points**	
<70	0	
70–89	7	
90–109	13	
110–149	23	
150–199	36	
>200	46	
SBP (mmHg)	**points**	
<80	63	
80–99	58	
100–119	47	
120–139	37	
140–159	26	
160–199	11	
>200	0	
Creatinine (umol/L)	**points**	
0–34	2	
35–70	5	
71–105	8	
106–140	11	
141–176	14	
177–353	23	
≥354	31	
Clinical	**points**	
Killip Class I	0	
Killip Class II	21	
Killip Class III	43	
Killip Class IV	64	
ST Deviation	30	
Troponin (+)	15	
Cardiac Arrest	43	
GRACE Score		

Base Hct%	points	Patient
<31	9	
31-33.9	7	
34-36.9	3	
37-39.9	2	
≥40	0	
eGFR (ml/min)	**points**	
≤15	39	
>15-30	35	
>30-60	28	
>60-90	17	
>90-120	7	
>120	0	
Heart Rate (bpm)	**points**	
≤70	0	
71-80	1	
81-90	3	
91-100	6	
101-110	8	
111-120	10	
>120	11	
SBP (mmHg)	**points**	
≤90	10	
91-100	8	
101-120	5	
121-180	1	
181-200	3	
>200	5	
Clinical	**points**	
Female	8	
CCF	7	
Vasc Dis.	7	
Diabetes	6	
CRUSADE		

Notes on using scores:
- Use heamodynamic characteristics at the time of presentation
- Killip Class I= Clear lung fields,
- Killip Class II= Crepitations in lower ones
- Killip Class III= Creps in the Upper Zones
- Killip Class IV: Pulmonary Oedema or Cardiogenic Shock
- ST deviation= ST elevation or Depression >1mm
- STEMI and NSTEMI in Bleeding score are mutually exclusive. Score STEMI if there is any ST elevation.

Step 2: Use the nomograms below to estimate the patient specific risk and estimated benefit from guideline recommended therapies



ARR: Absolute Risk Reduction in 6 month death associated with provision of therapy

The GRACE Score is: .....

The Risk Strata is: (circle one)
- Low (≤88)
- Intermediate (89-118)
- High (>118)

The CRUSADE Score is: .....

The Risk Strata is: (circle one)
- Low (≤30)
- Intermediare (31-40)
- High (>40)

Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2011;32:2999–3054.

Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091–1091.

Subherwal S, Bach RG, Chen AY, et al.. Baseline Risk of Major Bleeding in Non-ST-Segment-Elevation Myocardial Infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. Circulation. 2009;119:1873–1882.

Hospital Name
AGRIS Study Worksheet Page 2

Please File in Medical Record

URN: 012345678
SURNAME
First Name
DOB: 01/02/34

Step 3: Specific recommendations to consider based on scores

Step 4: Confirm intended therapies
Please tick (✓) intended utilisation for guideline recommendations below

LOW	INTERMEDIATE	HIGH	Commentry	Intended	Not Intended	Contra-indicated(Please state reason)
Aspirin	Aspirin	Aspirin	Unless contraindicated, allergy, high bleeding risk			
Ischaemia testing			Reserve for low risk			
	Clopidogrel or Ticagrelor with aspirin	Clopidogrel or Ticagrelor with aspirin	Initiate soon after establishing diagnosis			
	Prasugrel with aspirin	Prasugrel with aspirin	May consider in Primary PCI for STEMI, and NSTEACS for undergoing PCI			
	Low molecular weight heparin or UF heparin	Low molecular weight heparin or UF heparin	Consider in patients with biomarker elevation and/or dynamic ECG changes			
	Coronary Angiography	Coronary Angiography	If Intermediate risk (GRS≥89) and no contra-indication to coronary angiography, consider angiography within 96 hours (NICE guidance)			
		Coronary Angiography within 24 hours	If very high risk (GRS>140) and no contra-indication to coronary angiography, , consider angiography within 24hours of admission			
	Bivalirudin	Bivalirudin	For patients undergoing coronary angiography if at high risk of bleeding			
		Glycoprotein IIb/IIa inhibitors	Consider at the time of PCI, but balance against bleeding risk			
Assessment of left ventricular function	Assessment of left ventricular function	Assessment of left ventricular function	All patients unless recently performed			
ACE inhibition/ARB	ACE inhibition/ARB	ACE inhibition/ARB	Indicated in Hypertension, Diabetes, LV dysfunction			
B Blockers	B Blockers	B Blockers	Indicated in all MI, UA with LV dysfunction			
Statins	Statins	Statins	All patients unless not tolerated			
Cardiac rehabilitation	Cardiac rehabilitation	Cardiac rehabilitation	Give advice on follow-up, management of cardiovascular risk factors, management/information concerning their medications, life style changes			

Signature (Medical): .....

Role: Date:

Signature (Nursing): .....

Role: Date:

8.3.6 Outcome measures

The primary outcome measure of this study will be hospital performance measured by the composite endpoint of adherence to performance measures by the time of discharge among those patients discharged alive. Key secondary clinical endpoint will evaluate the composite endpoint of cardiovascular death, new or recurrent myocardial infarction, in-hospital heart failure or cardiovascular readmission at 12 months. A detailed description of the outcome measures is described in Table 2. Health economic impacts of risk stratification will also be evaluated.

Table 2: Study Outcomes

Outcome	Definition	
Measures of Performance in Hospital (Primary Composite Outcome)	1. Receipt of inpatient angiography during the index hospitalization where the patient's GRACE risk score is >130 2. Prescription of at least 4 of the 5 clinical guideline advocated therapies at discharge if there is no stated contraindicated (patients with a stated contraindication will be coded as compliant), a. Aspirin≥75mg/day; b. A HMG-CoA reductase inhibitor; c. A beta-blocker; d. A $P2Y_{12}$ inhibitor; e. An ACE-Inhibitor or ARB where is a history of hypertension, diabetes or known LV impairment) 3. Documentation of referral to cardiac rehabilitation services. Each of the criteria will be evaluated separately and aggregated to a possible score of 3 (i.e. 1 for inpatient angiography, 1 for at least 4 of the 5 secondary prevention pharmacotherapies, and 1 for referral to a secondary prevention program).	
Measures of Clinical Outcome (Secondary outcomes)	The composite endpoint of cardiovascular death, new or recurrent myocardial infarction, in-hospital heart failure or cardiovascular readmission by 12 months.	
	Cardiovascular death	Death due to myocardial infarction, sudden cardiac death, heart failure or cardiogenic shock, stroke, and other causes including pulmonary embolism, or aortic aneurysm rupture.
	New/Recurrent MI(28)	New MI: A rise and/or fall of biomarkers with at least one value above the 99th percentile of the URL with at least one of the following; • Symptoms of ischaemia • ECG changes indicative of new ischaemia, new ST-T changes or new LBBB • Development of pathological Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

		• Sudden unexpected cardiac death, involving cardiac arrest, and accompanied by presumably new ST elevation, or new LBBB. • Pathological findings of an acute myocardial infarction Re-MI: • In participants without MI at admission, a MI after enrolment but prior to angiography will be diagnosed when any elevation of troponin or CK-MB >ULN occurs (or CK >ULN in the absence of MB determination). • In participants with MI at presentation, in whom the elevated troponin or CK-MB (or CK) levels are documented to be falling or have returned to normal, diagnosis of a second MI requires: o New elevation of troponin or CK-MB >ULN (or CK >ULN in the absence of MB determination) if the troponin or CK-MB (or CK) level has returned to <ULN, or o Rise by >20% or 50% above the previous nadir level if the troponin or CK-MB (or CK) level, respectively, has not returned to <ULN. • In participants with MI at presentation, in whom the peak troponin or CK-MB (or CK) has not yet been reached, diagnosis of a second MI requires: o Recurrent chest pain ≥30 minutes, or o New ECG changes consistent with MI, and o The next troponin or CK-MB (or CK) level measured approximately 8-12 hours after the event be elevated by at least 50% above the previous level. MI following PCI: cTn values >5 x 99th percentile URL in patients with normal baseline values or a rise of cTn values >20% if the baseline values are elevated and are stable or falling and either: • Symptoms suggestive of myocardial ischemia; • New ischemic ECG changes or new LBBB; or • Angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or • Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.

		MI following CABG: elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (>99th percentile URL) and either: • New pathological Q waves or new LBBB, or • Angiographic documented new graft or new native coronary artery occlusion, or • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
	In-hospital heart failure	New or worsening heart failure will be defined as the change of 1 or more in the patients Killip Class, between the presentation Killip Class and the worst Killip class documented for the patient during their hospitalisation.
	Cardiovascular readmission	Subsequent hospital admission for unplanned coronary revascularization (non-elective PCI or CABG); cerebrovascular accidents with cerebral imaging; cardiac arrhythmias; Congestive cardiac failure without MI; or unstable angina
Health Economic Evaluation	• Assessment of Quality of Life (EQ-5D) instrument at 1 year.(29) • Resource use including the costs associated with implementation, and cost over 12 months, including: o Medicare data in consenting patients (Medical Benefits Schedule (MBS), o Medication use from Pharmaceutical Benefits Schedule (PBS); and, o In-patient admissions from the AN-Diagnosis Related Group (DRG) in participating hospitals.	

8.3.7 Ethical considerations

Approval will be sought from each participating center's Human Research Ethics Committee (HREC), Research Governance Officer, local head of department and hospital executive. Participation of medical practitioners, hospitals and patients in the study will be voluntary.

8.3.8 Individual patient consent

Patient enrolment to the study will employ an opt-out consent process conducted jointly for both AGRIS and CONCORDANCE components of the study. The opt-out consent process is an accepted standard in Australia for studies that represent a low or negligible risk of harm to the participants. The required conditions for approval of opt-out consent are described in the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research, and such an approach has been used in other studies in of ACS in Australia. (18) All patients will be informed of their right to withdraw from the study at any time without prejudice to their medical and/or nursing care at that time or in the future. A waiver of consent will be sought for patients who die before the informed consent process can be initiated, consistent with the National Statement. This will ensure the study is representative of all ACS patients, since it is important to include the sub-set of patients who die early during their admission to hospital.

A random subset of patients (n=1000) will be asked to provide written informed consent (opt-in) to allow for data linkage between the CONCORDANCE registry and Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Scheme

(MBS), as required by the Australian Commonwealth Department of Health. Patients will be informed as to how their data may be linked and shared and the type of data that will be collected. These data will contribute to the cost-effectiveness analysis.

8.3.9 Data-collection and follow-up procedures

Collection of baseline clinical and therapeutic management data will be conducted through the established and ongoing CONCORDANCE registry involving both tertiary and non-tertiary hospitals.(19) Consequently all baseline information processes of care and clinical outcomes will be collected through this registry. Prior to commencing site recruitment for this randomised study, local procedures for patient identification and inclusion to the registry will be reconfirmed and examined for temporal stability during the implementation phase of the intervention. All patients will be followed up for clinical events at 12 months from the date of hospital discharge. Follow up visits may be performed via telephone, patient letter, and if the patient is not contactable, contact will be made with their stated primary care physician to obtain vital status and any readmission information. If no participant data is available at the 12-month time point, the participant's name will be checked against the Australian National Death Index for mortality status to ascertain the vital status at 12 months. Late clinical evaluations (hospital discharge to final study contact) will be conducted by study coordinators and supplemented by all hospital records even if representation is to a hospital that differs from that of index hospitalization. Source documents will be sought to enable independent adjudication. Quality of life measures, using the 5-level EQ-5D instrument, will also be collected at 12 months.

8.3.10 Statistical Methods and sample sise determination

8.3.10.1 Determination of sample size and study power

In the existing CONCORDANCE data set (n=5396), 2320 (43%) are classified as high-risk (GRACE risk score >118). Among these patients, the mean use of guideline recommendations (use of coronary angiography, discharge on at least 4 of aspirin, statin, $P2Y_{12}$ inhibition, beta-blocker, ACE-inhibitor/ARB, and referral to any secondary prevention program) is 49.7%. Assigning each of the three above indices a score of one, (i.e. inpatient angiography=1, discharge on optimal medical therapy=1, rehabilitation referral=1) results in a proportion of optimally treated patients of 43%, with an intra-cluster correlation coefficient (ICC) of 0.16.

To observe an increase in the proportion to 64% assuming an ICC of 0.16 with >80% power and an alpha of 0.05 will require a sample size of 15 clusters per arm with >37 individuals per cluster per arm. Therefore, this study will enroll 40 high-risk patients per cluster or 600 patients per arm. However, it will be important to recruit all patients presenting with an ACS diagnosis regardless of risk as their management will also likely be influenced by the intervention and the benefits of some recommendations (like angiography) are not as well established in this group. The total samples size will therefore be inflated 2.5 fold (100 patients per site to 3000 patients). Outcomes in this whole cohort will be assessed as a secondary endpoint.

In statistical power calculation, we also examined data within the ACACIA registry, including many sites participating in the CONCORDANCE registry. In this study, 2704 patients were admitted with either ST-elevation myocardial infarction or high-risk ACS and by discharge, 64 (2.5%) had died and 419

(15.9%) were not deemed to have an ACS diagnosis. Of those surviving to hospital discharge, 1053 (47.4%) died, suffered a recurrent MI, or required a cardiovascular readmission within 12 months. To assess clustering of the composite clinical outcome measure by hospital, the ICC (estimated to be 0.031) was calculated from 3402 patients (39 centers throughout Australia).

By sampling 40 high-risk patients (GRACE risk score >118) from each of 15 hospitals in each group (30 hospitals in total), will achieve ~80% power to detect a relative difference in the composite endpoint of 25% (48.0% in the usual care group vs. 36% in the intervention group) using a two-sided Z test (un-pooled), with a significance level of 0.050, and with the ICC set at 0.031. However, since the participating hospital numbers are constrained by the number of hospitals in the CONCORDANCE network and this magnitude of difference in clinical events is considered unlikely, the clinical events will be considered as secondary exploratory endpoints.

8.3.10.2 Methods of statistical analyses

The primary analysis will compare the efficacy of risk stratification with the GRS tool intervention versus standard care in improving the primary performance measure endpoint in the population alive at the time of discharge and among patients with a GRACE risk score>118 for the primary clinical endpoint. To account for between-cluster variance, a generalised estimating equation (GEE) regression model with log link and binomial family will be used for this purpose. The initial analysis will simply compare composite outcome rates at 12 months between the two groups. Any variables in baseline analyses that differ between the two groups will then be included in the GEE model. The primary analysis will

be on an intention to treat basis. Multiple imputations may be used to replace missing values if the assumptions appear to have been met.

Differences between the groups in freedom from mortality, recurrent MI and cardiac readmission (i.e. the individual components of the composite outcome) will be assessed by Cox proportional hazards model survival analysis after evaluation of the proportional hazards assumption. The relationship between clinical guideline adherence (as measured by performance indicators) and late clinical events among individual patients will also be evaluated in survival analysis. Secondary outcomes including the interactions between the GRT use and hospital or clinical service characteristics, and ACS performance measures and late clinical outcomes will be examined using two-level random effects linear and logistic regression models respectively.

Within-trial cost-effectiveness from admission to 12 months will then be analysed allowing for bivariate uncertainty with bootstrapping of patient costs and effects to maintain covariance structure. Patient level measures of utility derived from the EQ-5D instrument will be integrated with survival curves to estimate quality adjusted life years in each trial arm. Within-trial incremental costs associated with the GRACE risk tool and treatment recommendation plan and with standard care will be estimated from patient data on MBS, PBS and hospital use. Local resources used in implementing the GRS will be included in the cost effectiveness analysis.

8.3.11 Study Organization

The study is being conducted by the Sydney Local Health District Concord Hospital and a Steering committee of senior cardiologists and trial

methodologists. The Steering Committee is responsible for all aspects of the study design and implementation. A clinical endpoint adjudication committee (CEAC), independent of all study investigators and the project and data management groups, will review all deaths (i.e. to adjudicate the cause of death) and new/recurrent myocardial infarction (spontaneous or peri-procedural events) and associated source documents according to the requirements of the protocol. The CEAC will employ two independent cardiologists to review each event in a blinded manner, with disagreements decided by a third reviewer blinded to the outcome of the prior reviews. A data safety monitoring board (DSMB) consisting of members who are external to the study, is responsible for safeguarding the interests of study participants, and will assess the safety and efficacy of study procedures. This committee will meet when 50% of the patients have been enrolled. Data management is being provided by the Centre for Outcomes Research (COR) at The University of Massachusetts Medical School, Worcester, MA, USA. Data management will be responsible for data programming, query tracking and resolution. Support for the implementation of the GRS tool and treatment recommendation plan will be coordinated by South Australian Health and Medical Research Institute (SAHMRI) in cooperation with members of the Steering Committee. The study is supported by an unrestricted grant from Astra Zeneca Australia.

8.4 Discussion

While risk stratification using risk scores in the management of ACS is advocated in clinical practice guidelines, the value of this activity in terms of the

improving care and patient outcomes has not been prospectively demonstrated.(1,20,21) Refining risk-based decision-making may reduce access inequities in rural, outer metropolitan health services due to limited expert care. Similary, informing “misperceptions” of risk that lead to under-treatment of high-risk patients in metropolitan hospitals are putative benefits of using objective risk scores.(22) Importantly, practices that efficiently optimise clinical decision-making may have significant relevance in countries where access to experienced health services is hampered by geographic distance such as Australia and Canada, or where the workforce capacity is challenged by the growing burden of care resulting from the urbanization of developing economies.(23) However, an evidence base is required if the routine use of objective risk stratification is to be a focus of efforts to translate guidelines into improved care.

Contemporary data indicate under-utilization of early invasive management and proven pharmacotherapies in ACS care.(24) Effective ACS management requires rapid and accurate risk assessment and the timely delivery of resource intensive therapies. Faced with increasing patient complexity, where relative risks and benefits are often more difficult to weigh, it is not surprising that current care is sub optimal.(25) Current evidence suggests that under-appreciation of risk is prevalent and is associated with reduced access to care and worse clinical outcomes.(4,5)

When compared with objective risk assessment, physician estimated risk appears to offer less discriminatory performance. A study of physician perception of risk compared with objective risk stratification provided by the

GRS among 1,542 ACS patients in Australia, China, India and Russia has reconfirmed this under-appreciation of risk and explored the potential consequences of this misperception.(6) Compared with the GRS, physicians generally over-estimated low risk patients and under-estimated high risk patients within actual clinical settings. Adding the GRS to physician estimation improved the discriminatory capacity significantly (Integrated Discrimination Index (S.E.): 0.063 (0.012), p<0.001). Furthermore, when care was correlated with physician perception of risk, percutaneous coronary intervention (PCI) rates were higher among those at higher perceived risk. In contrast, when care was correlated with objectively measured risk using the GRS, lower PCI rates among objectively high-risk patients was evident.(22) By 6-months, mortality rates were higher among patients in whom the risk was underestimated. (Not under-estimated: 10/967 (1.0%) vs. one physician underestimated: 25/429 (5.8%) vs. all physician's underestimated: 13/146 (8.9%). After adjusting for GRS and frailty, any physician underestimation of risk was associated with a 6.0 fold increase in 6-month mortality (95% C.I.: 2.3-15.5, p<0.001). Similar results have been observed in the Canadian setting.(13) Hence, miss-perception of risk, when compared with objective risk assessment appears may be associated with less care and worse clinical outcomes.

It is intuitive that improving physician application of risk stratification will improve outcomes through more risk appropriate care (e.g. more PCI among high-risk individuals and more prescription of, and adherence to, evidence-based therapies due to a greater appreciation of future ischaemic risk). However the hypothesis derived from these observational data requires prospective validation in a randomised controlled trial. It is anticipated that patients cared for

in hospitals randomised to risk stratification using the GRS tool will experience improved adherence to evidence-based care and clinical outcomes. However, there remains a risk that patients cared for in hospitals randomised to the risk stratification tool will have an increased incidence of procedure or drug-related complications without an improvement in outcomes.(26) Consistent with this, one study has shown that electronic decision support in the intensive care environment has been associated with an increase in morbidity and mortality.(27) Within this study, risk score-based treatment recommendations will not override clinical judgment, but equipoise regarding the study question remains.

8.4.1 Limitations

Three key factors will need to be considered in the conduct of the study. First, when implementing the GRS tool, ensuring persistence of the intervention within local practice will be paramount. Second, ensuring the intervention specifically targets the clinical process of risk assessment without leading to a reorganization of local systems of practice will be important in the interpretation of the study findings. Third, while clarifying patient risk and providing evidence-based recommendations, effective translation of the evidence base may depend on local infrastructure and cultures. Nevertheless, this pragmatic design is essential to understand the value of risk scores in contemporary practice. Exploration of the ancillary health service characteristics (e.g. local patient education practices) associated with successful uptake and delivery of risk-informed care will require additional investigations and sub-studies.

8.5 Conclusion

A unique interventional study providing contextual evidence-based decision-support support directly at the point of care may be a step forward in improving clinical outcomes by improving clinical guideline adherence and reducing inequities in health care provision in areas where access to clinical expertise is limited. However, the validity of this strategy should be tested within a robust randomised comparison. Understanding the impact of this approach will inform current efforts to minimise the heterogeneity in ACS care through the use of evidence-based decision support, not only in ACS care but also across the broader emerging health agenda.

8.6 Disclosures

This study was conceived by authors DC and DB, and all aspects of the study's design and conduct have been determined by the steering committee and project management team. All study analyses, the drafting and editing of this paper and its final contents are the work of the listed authors . The study is supported by an unrestricted grant from Astra Zeneca Australia.

8.7 Appendix: Implementation Process

After gaining executive support, our team will work with local clinical leaders (i.e. medical and nursing) to identify local barriers and appropriate evaluation strategies, to plan, engage, implement and develop feedback opportunities for implementation refinement. The process of implementation will include an assessment of the local culture including: the availability of leadership for engagement; the openness of clinicians for change; existing communication strategies and knowledge pathways; identification of system and process evaluation measures; and clinical support and referral networks within and between metropolitan, rural and regional hospital networks. An implementation plan that aligns with the hospital's existing service needs for effective and timely decision-making, communication, quality data collection, reporting and onward referral will be developed. A tailored pre-implementation program emphasising the potential benefit of the intervention to local workflows and broader organisational needs will be delivered in a flexible and locally appropriate manner prior to implementation at active sites. Descriptions of local barriers and solutions experienced during the site implementation will be recorded with a structured interview to inform future efforts in generalising the study findings. These include local workforce characteristics, leadership structure, and the integration of medical and nursing teams as well as local quality activities and resourcing.

The intervention has been designed to provide a relative advantage to the clinician's workflow, offering decision support regarding the appropriateness of key evidence-based therapies, while providing an objective foundation of patient-specific risk for communicating with patients and referral hospitals where transfer is required. The intervention is delivered via a simple and adaptable worksheet, supported by Class 1 recommendations within international guidelines. The core characteristic of objective risk stratification remains preserved within an adaptable tool and the opportunity to measure local performance as a consequence of worksheet use has been built in. The

implementation team will establish feedback and evaluation strategies to ensure maintenance of the intervention for the study duration and beyond. A period of three months has been allocated to implementing the intervention into local routine practice before patient recruitment commences, during which time uptake of the tool will be monitored.

8.8 References

1. Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). European Heart Journal. 2012 Aug 24.

2. Chew DP, Aroney CN, Aylward PE, Kelly A-M, White HD, Tideman PA, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart Lung Circ. 2011 Aug;20(8):487–502.

3. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011 May 9;123(18):e426–e579.

4. Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. Med J Aust. 2007 Aug 1;187(3):153–9.

5. Yan A, Yan R, Tan M, Fung A, Cohen E, Fitchett D, et al. Management Patterns in Relation to Risk Stratification Among Patients With Non-ST Elevation Acute Coronary Syndromes. Arch Intern Med. 2007 May 5;167(10):1009–16.

6. Chew DP, Junbo G, Parsonage W, Kerkar P, Sulimov VA, Horsfall M, et al. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. Circulation: Cardiovascular Quality and Outcomes. 2013 May 21;6(3):299–308.

7. Morrow D, Antman E, Charlesworth A, Cairns R, Murphy S, de Lemos J, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. 2000 Oct 1;102(17):2031–7.

8. Antman E, Cohen M, Bernink P, McCabe C, Horacek T, Papuchis G, et al. The

TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000 Aug 1;284(7):835–42.

9. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Archives of Internal Medicine. 2003 Oct 27;163(19):2345–53.

10. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, de Werf Van F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004 Jun 9;291(22):2727–33.

11. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf Van F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. BMJ; 2006 Nov 25;333(7578):1091–1.

12. de Araujo Goncalves P. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. European Heart Journal. 2005 Mar 21;26(9):865–72.

13. Yan AT, Yan RT, Tan M, Casanova A, Labinaz M, Sridhar K, et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. European Heart Journal. 2007 May 1;28(9):1072–8.

14. Lauer MS, D'Agostino RB. The randomised registry trial--the next disruptive technology in clinical research? N Engl J Med. 2013 Oct 24;369(17):1579–81.

15. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, et al. The design and rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). Heart Lung Circ. 2013 Jul;22(7):533–41.

16. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline Risk of Major Bleeding in Non-ST-Segment-Elevation Myocardial Infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. Circulation. 2009 Apr 13;119(14):1873–82.

17. Chew DP, Anderson FA, Avezum A, Eagle KA, Fitzgerald G, Gore JM, et al. Six-month survival benefits associated with clinical guideline recommendations in acute coronary syndromes. Heart (British Cardiac Society). 2010 Aug pp. 1201–6.

18. National Health and Medical Research Council. National statement on ethical conduct in human research. 2007.

19. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, et al. The design and rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). Heart Lung Circ. 2013 Jul;22(7):533–41.

20. Authors/Task Force Members, Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2011 Dec 1;32(23):2999–3054.

21. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 23;130(25):2354–94.

22. Chew DP, Juergens C, French J, Parsonage W, Horsfall M, Brieger D, et al. An examination of clinical intuition in risk assessment among acute coronary syndromes patients: Observations from a prospective multi-center international observational registry. Int J Cardiol. Elsevier; 2013 Dec 19.

23. Astley CM, Macdougall CJ, Davidson PM, Chew DP. Lost in translation: health resource variability in the achievement of optimal performance and clinical outcome. Circulation: Cardiovascular Quality and Outcomes. 2011 Sep 1;4(5):512–20.

24. Chew DP, French J, Briffa TG, Hammett CJ, Ellis CJ, Ranasinghe I, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. Med J Aust. 2013;199(3):185–91.

25. Joynt KE, Huynh L, Amerena JV, Brieger DB, Coverdale SG, Rankin JM, et al. Impact of acute and chronic risk factors on use of evidence-based treatments in patients in Australia with acute coronary syndromes. Heart (British Cardiac Society). 2009 Sep pp. 1442–8.

26. Coiera E, Westbrook J. Should clinical software be regulated? Med J Aust. 2006 Jun 1;184(12):600–1.

27. Han Y, Carcillo J, Venkataraman S, Clark R, Watson R, Nguyen T, et al. Unexpected increased mortality after implementation of a commercially sold computerised physician order entry system. Pediatrics. 2005 Dec 1;116(6):1506–12.

28. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. 2012. pp. 1581–98.

29. Kim J, Henderson RA, Pocock SJ, Clayton T, Sculpher MJ, Fox KAA, et al. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomised Intervention Trial of unstable Angina (RITA-3). J Am Coll Cardiol. 2005 Jan 18;45(2):221–8.

SECTION 3: CLINICAL ADOPTION OF NEW INFORMATION: A FOCUS ON HIGH-SENSITIVITY TROPONIN T

9 THE PROMISE OF HIGH-SENSITIVITY TROPONIN TESTING

9.0 Title page : The promise of high-sensitivity troponin testing

Derek P Chew MBBS MPH FRACP[1], & Louise Cullen MBBS, FACEM[2]

Author Affiliations

[1]School of Medicine, Flinders University of South Australia, Adelaide, Australia
[2]Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Brisbane QLD

Key Words: Troponin, Myocardial Infarction

Corresponding Author

Derek P Chew MBBS MPH FRACP

Flinders University

Flinders Drive, Bedford Park

South Australia, 5042, AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

9.1 Abstract

The development of troponin assays have revolutionised the care of these patients suspected and confirmed acute coronary syndromes. However, incremental improvements in analytic performance threaten to undo some of the gains offered by troponin testing. While increased sensitivity ensures that missed myocardial infarction far less likely, the compromise comes as a reduced specificity and consequently a lower positive predictive value for MI when faced with a positive test. Merely improving test performance without an adaptive response in clinical decision-making and test interpretation remains a key driver in increasing costs and inefficiencies. While troponin assays with higher analytical performance may well offer improved patient outcomes through lower rates of missed MI, they may also increase the investigative burden borne by patients with abnormal test results due to the many non-coronary causes of detectable troponin. Diagnostic innovations must be imbedded within more effective clinical practices and practice environments with a clear understanding of the utility of the innovation and equipped to appropriately harness the value of new diagnostic information. Such improvements in service design will need to embrace more robust protocols for risk quantification before troponin testing is requested, coupled with pathways for very early discharge and possible investigations within the ambulatory care settings. Similarly, a more sophisticated evidence base informing the investigation and management of patients with elevated troponin level not considered to be due to an acute coronary syndrome is urgently required. Only through further clinical and health service research combined with clinical practice reforms will we truly realise the promise of high-sensitivity troponin testing.

9.2 Editorial

The development of troponin T and I assays in the assessment and management of patients with chest pain have revolutionised the care of these patients suspected and confirmed acute coronary syndromes.[1] The availability of these assays have increased the identification of patients at increased risk of recurrent cardiac events, as well as improved the selection of patients who may benefit from early invasive management and revascularization and more potent anti-thrombotic therapy. Development of point-of-care testing instruments has extended the reach of these assays to inform the care of patients presenting in rural and remote areas of Australia.[2]

However, incremental improvements in analytic performance, with the emergence of assays that are now able to detect serum troponin in up to half the apparently normal population threatens to undo some of the initial gains offered by troponin testing.[3] While increased sensitivity ensures that the problem of missed myocardial infarction (MI) far less likely, the compromise comes as a reduced specificity and consequently a lower positive predictive value for MI when faced with a positive test.

This edition of the Journal presents two articles that highlight the issues. A large single centre observational study comparing emergency department (ED) flow and cardiac investigations before and after the implementation of a troponin I assay with improved analytical precision, although not truly a high-sensitive assay according to agreed standards, demonstrates moderate reductions in ED assessment times with no significant difference in the ED admission and discharge proportions.[4,5] Hence, it appears that the availability of a troponin assay with higher analytic precision offered the opportunity to arrive at a clinical decision to admit or discharge earlier, but did not change the overall proportions of those decisions. {Need Reference for MJA paper} Of note, there was a significant 8% increase in angiography rate without a commensurate increase in the rate of coronary revascularization, suggesting a greater rate of invasive investigation that did not lead to coronary lesion specific therapy. No difference in in-hospital mortality was observed and differences in late outcomes would be of great interest but are no currently available.

The second article contemplates the utility of extending troponin testing into primary care for the assessment of chest pain, underscoring the challenges of troponin result interpretation when faced with a single elevated value in a clinical setting were serial testing within hours is impractical due to the relatively slow turnaround time in results. {Reference the paper} Thus, for the assessment of chest pain in primary care, troponin testing may be of utility in reassuring the clinician in the context of an intermediate or low clinical suspicion for MI, critically, when sufficient time has passed since the resolution of symptoms to allow for evidence of myonecrosis (elevation of troponin values) to emerge if it was destined to do so. The pragmatic issue of receiving results in a timely manner to enable an appropriate clinical response remains problematic.

Both of these articles highlight the challenges in translating this diagnostic innovation into effective health care and improved outcomes. Merely improving test performance without an adaptive response in clinical decision-making and test interpretation is a possible driver for increased costs and inefficiencies.[6] While troponin assays with

higher analytical performance may well offer improved patient outcomes through lower rates of missed MI, they may also increase the investigative burden borne by patients with abnormal test results due to the many non-coronary causes of detectable troponin. Complicating this issue is the knowledge that troponin elevation deemed not to be due to unstable coronary plaque remains a marker of increased late mortality, though the current evidence based is unable to offer advice as to the appropriate investigation and management of this common situation.[7]

If we are to reap the returns of improved patient outcome, with more efficient clinical care though the widespread adoption of innovations in diagnostic testing such as high-sensitivity troponin assays and point-of-care devices, then this adoption will need to be mirrored by a similar evolution in clinical decision-making. Diagnostic innovations must be imbedded within more effective clinical practices and practice environments with a clear understanding of the utility of the innovation and equipped to appropriately harness the value of new diagnostic information.[8] Such improvements in service design will need to embrace more robust protocols for risk quantification before troponin testing is requested, coupled with pathways for very early discharge and possible investigations within the ambulatory care settings.[9-11] Similarly, a more sophisticated evidence base informing the investigation and management of patients with elevated troponin level deemed not due to an acute coronary syndrome is urgently required. Only through further clinical and health service research combined with clinical practice reforms focused on maximizing the “rule-out” decision of a negative result and risk information provided by a positive result will we truly realise the promise of high-sensitivity troponin testing.

9.3 References.

1. Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomised trial. JAMA. 2001 Nov 21;286(19):2405–12.

2. Tideman PA, Tirimacco R, Senior DP, et al. Impact of a regionalised clinical cardiac support network on mortality among rural patients with myocardial infarction. Med J Aust. 2014 Feb 17;200(3):157–60.

3. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009 Aug 27;361(9):858–67.

4. Apple FS. A New Season for Cardiac Troponin Assays: It's Time to Keep a Scorecard. Clin Chem. 2009 Jun 26;55(7):1303–6.

5. Wu AHB, Christenson RH. Analytical and assay issues for use of cardiac troponin testing for risk stratification in primary care. Clin Biochem. The Canadian Society of Clinical Chemists; 2013 Aug 1;46(12):969–78.

6. Diamond GA, Kaul S. How would the Reverend Bayes interpret high-sensitivity troponin? Circulation. 2010 Mar 16;121(10):1172–5.

7. Petrie CJ, Weir RAP, Anwar MS, et al. High sensitivity troponin T in acute medicine; more questions than answers? Qjm. 2014 Feb 20;107(3):193–200.

8. Nadia Bandstein MD, Rickard Ljung MP, Magnus Johansson MP, Martin J Holzmann MP. Accepted Manuscript. J Am Coll Cardiol. Elsevier Ltd; 2014 Mar 25;:1–31.

9. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. J Am Coll Cardiol. 2013 Oct 1;62(14):1242–9.

10. Than M, Cullen L, Reid CM, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. The Lancet. Elsevier; 2011 Mar 26;377(9771):1077–84.

11. Aldous SJ, Richards MA, Cullen L, et al. A New Improved Accelerated Diagnostic Protocol Safely Identifies Low-risk Patients With Chest Pain in the Emergency Department. Academic Emergency Medicine. 2012 May 17;19(5):510–6.

10 HIGH SENSITIVITY-TROPONIN ELEVATION SECONDARY TO NON-CORONARY DIAGNOSES AND DEATH AND RECURRENT MYOCARDIAL INFARCTION: AN EXAMINATION AGAINST CRITERIA OF CAUSALITY

10.0 Title page : High Sensitivity-Troponin Elevation Secondary to Non-Coronary Diagnoses and Death and Recurrent Myocardial Infarction: an examination against criteria of causality

Derek P Chew MBBS MPH FRACP FACC[1], Tom G Briffa BPhysEd, MPhysEd, PhD[2], Nasser J Alhammad MBBS[3], Matt Horsfall RN[4], Julia Zhou BPharm[1], Pey Wen Lou MBBS[3], Penelope Coates MBBS, FRACP, FRCPA[5], Ian Scott MBBS, MHA, MEd, FRACP[6], David Brieger MBBS, MMed (Clin Epi), PhD, FRACP[7], Stephen J Quinn B Math, MMath, PhD[1], John French MBBS, PhD[8]

Author Affiliations

[1]School of Medicine, Flinders University of South Australia, Adelaide, Australia

[2]School of Population Health, University of Western Australia, Perth, Australia

[3]Cardiology, Flinders Medical Centre, Southern Adelaide Local Health Network, Adelaide, Australia

[4]South Australian Health and Medical Research Institute, Adelaide, Australia

[5]SA Pathology, Adelaide, Australia

[6]School of Medicine, University of Queensland, Brisbane, Australia

[7]Concord Clinical School, University of Sydney, Sydney, Australia

[8]South Western Sydney Clinical School, University of New South Wales, Sydney, Australia

Key Words: Troponin, Myocardial Infarction, Mortality, Epidemiology

Corresponding Author

Derek P Chew MBBS MPH FRACP

Flinders University

Flinders Drive, Bedford Park

South Australia, 5042, AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

10.1 Abstract

Background: Myocardial injury provoked by illness unrelated to unstable coronary plaque is common, but uncertainty about a cause-effect relationship with future events challenges the appropriateness of initiating cardiac-specific therapies. We examined the causal relationship between troponin elevation in non-coronary diagnoses and late cardiac events using the Bradford-Hill criteria for causality.

Methods and Results: Patients presenting acutely to South Australian public hospitals receiving at least one troponin between September 2011 and September 2012 were included. Diagnoses were classified as coronary, non-coronary cardiac and non-cardiac using International Classification of Diseases-10AM codes. The relationship between maximally-observed troponin using a high-sensitivity troponin T assay and adjudicated cardiac and non-cardiac mortality, and subsequent MI were assessed using competing-risk flexible parametric survival models.

Troponin results were available for 38,161 patients of whom, 12,645 (33.6%), 3,237 (8.5%), and 22,079 (57.9%) patients were discharged with coronary, non-coronary cardiac and non-cardiac diagnoses, respectively. Troponin >14ng/L was observed in 43.6%, and 13.8% had prior coronary disease. Maximal troponin <100ng/L were more common among non-coronary diagnoses. The relationship with cardiac mortality was stronger among the non-coronary diagnosis group (Troponin 1000ng/L: Coronary HR: 5.1 [95% CI 4.0-6.6] vs. Non-Coronary HR: 16.3 [95% CI 12.6-22.4]). The temporal hazard for cardiac death was highest soon after presentation in both groups (TnT>50x URL: Coronary hazard: 2.8 deaths/1000 patient-days vs. Non-Coronary hazard: 11.7 deaths/1000 patient-days). Among non-coronary diagnoses, the hazard for recurrent MI was higher but did not vary with time.

Conclusions: Consistency with causal criteria between secondary myocardial injury and cardiac events suggest the need for trials exploring cardiac-specific interventions in this population, that are appropriately designed to address competing risks.

Translational Perspective: Troponin elevation precipitated by non-coronary events is common and demonstrates an association with late mortality that is analogous to spontaneous myocardial infarction resulting from unstable coronary plaque. These observations help inform the design of randomised clinical trials exploring the benefits and risk of therapies with established benefits in other cardiac conditions. Such studies will need to appropriately account for competing risks in this population of patients.

10.2 Introduction

Myocardial injury deemed secondary to non-coronary conditions, as opposed to acute coronary syndromes (ACS) due to unstable coronary plaque, is extremely common and remains a substantial clinical dilemma.(1-3) Mechanisms underlying secondary myocardial injury are often multifactorial and include supply-demand ischaemia (i.e. Type 2 Myocardial Infarction (MI)), direct myocardial toxicity and, potentially unrecognised plaque rupture (i.e. Type 1 MI).(1,2)

Clinically elucidating these mechanisms to inform rational treatment approaches remains challenging and applying the Third Universal Definition of MI criteria does not necessarily enhance clinical management decision-making.(4,5)

The development of troponin assays with greater sensitivity has markedly increased the recognition of myocardial injury seemingly unrelated to coronary plaque rupture.(6,7) While an increase in the risk of late mortality has been observed, it remains unclear whether this risk is completely attributable to the precipitating condition (i.e. troponin serving as a marker of severity for the non-cardiac condition) versus a cardiac risk related to the extent of myocardial injury.(8-10) Determining whether myocardial injury is on the causal pathway for subsequent cardiac events in patients with underlying non-coronary illnesses may provide a rationale for assessing cardiac specific therapies established for the management of spontaneous MI and other cardiac conditions.

Criteria used to explore causality elucidated by Bradford-Hill include: coherence of mechanistic understandings and epidemiological observations; biological plausibility for an exposure effect; the strength of association or biological gradient where an increased exposure is associated with an increased effect; specificity of the association between exposure and outcome; and consistency of association within differing clinical contexts; the temporal relationship between exposure and subsequent outcome; and analogy.(11,12) We examined the relationship between myocardial injury detected by a high-sensitivity troponin T (hs-TnT) assay deemed secondary to acute non-coronary illness and late cardiac outcomes through an adapted paradigm of causality, contrasting this with ACS presentations in a health service-wide study.

10.3 Methods

10.3.1 Study population

The study population comprised all patients presenting acutely to all publically funded hospitals in South Australia who received at least one troponin test between September 2011 and September 2012. Patients were followed for a minimum of 12 months, and

results of all pathology testing performed over this time, including all troponin, creatinine and haemoglobin, were linked with hospital International Classification of Diseases version 10 Australian Modified (ICD-10 AM) primary and secondary diagnosis codes. Contiguous admissions among transferred patients and subsequent readmissions to all public hospitals within the state were determined by linkage. The first admission within the 12-month sampling period, without a preceding admission in the prior 6-months, was considered the index admission, with all subsequent non-contiguous admissions to any hospital defined as a readmission. Deaths and their cause were identified through hospital records and state death registry. The Human Research Ethics Committee of the South Australian Department of Health provided approval to access to all datasets and this study complies with the Declaration of Helsinki.

10.3.2 Discharge diagnosis classification

Trained independent coding professionals, applying standardised audited protocols, used medical record clinical documentation and imaging and pathology data to classify primary and secondary diagnoses for each clinical presentations. These data are routinely used to examine incidence of disease presentations and procedures for public reporting nationally. Hospital presentations were subsequently categorised as either coronary, and potential coronary, (i.e. chest pain for cardiac exclusion) or non-coronary conditions based on their primary and secondary discharge ICD 10-AM coding (I20-25 and R074). All diagnostic codes for patients transferred between hospitals were interrogated to ensure potential coronary and non-coronary cardiac diagnosis patients were identified. All remaining patients were classified as non-coronary admissions and were further sub-classified by organ system using the primary ICD-10 AM code. Patient discharged with a primary or secondary non-coronary cardiac diagnosis (i.e. heart failure, rheumatic and valvular disease (I00-I09, I33-I39, I42-I43, I50), hypertensive disease (I00-I15), pericarditis and myocarditis (I30-I32, I40-I41), or cardiac arrhythmias (I44-I49), but without a coronary diagnosis were sub-classified as a non-coronary cardiac diagnosis.

Non-cardiac organ system diagnoses comprised the ICD 10-AM individual chapters A-G, I-K, L-N and the remainder grouped as a heterogeneous group of diagnoses. (Supplementary Table 1) Significant past medical conditions (e.g. diabetes, hypertension, liver disease) for each patient were determined by examining their hospitalizations for the preceding 10 years.

Table 1: Clinical Characteristics according to diagnosis at Index Hospitalisation.

	Coronary	Non-Coronary		Total	p-value
	(n=12,845)	**Cardiac (n=3,237)**	**Non Cardiac (n=22,079)**	**(n=38,161)**	
Age (years, median, i.q.r[a])	60.0 (47.6-73.7)	72.7 (57.9-83.2)	71.2 (54.1-82.6)	67.1 (51.4-80.7)	<0.001
Female (n, %)	5712 (44.5)	1551 (47.9)	11233 (50.9)	18496 (50.9)	<0.001
Troponin >14ng/L (n, %)	4819 (37.5)	1966 (60.7)	9825 (44.5)	16610 (43.5)	<0.001
Single Troponin result if TnT>14ng/L (n,%)	824 (17.1)	609 (31.0)	4566 (46.5)	5999 (36.1)	<0.001
Maximum In-hospital Troponin (ng/L, median, i.q.r[a])	7 (5-48)	21 (7-51)	12 (5-30)	11 (5-34)	<0.001
Universal Definition Rise and/or Fall* (n, %)	2943 (61.1)	699 (35.6)	2687 (27.4)	6329 (38.1)	<0.001
Diabetes (n, %)	1283 (10.0)	450 (13.9)	2914 (13.2)	4647 (12.2)	<0.001
Hypertension (n, %)	2326 (18.1)	944 (29.2)	4805 (21.8)	8075 (21.2)	<0.001
GFR[b] (mls/min/1.73m^{2,} median, i.q.r)	78 (60-113)	70 (49-99)	76 (53-109)	76 (55-109)	0.0001
Baseline Haemoglobin (g/dL, median, i.q.r[a].)	13.8 (12.7-14.9)	13.5 (12.0-14.7)	13.3 (11.8-14.5)	13.5 (12.1-14.7)	<0.001
Prior CAD	2167 (16.9)	479 (14.8)	2611 (11.8)	5257 (13.8)	p<0.0001
Prior MI[c] (n, %)	850 (6.6)	157 (4.9)	1000 (4.5)	2007 (5.3)	<0.001
Prior CCF[d] (n, %)	486 (3.8)	916 (28.3)	795 (3.6)	2197 (5.8)	<0.001
Prior CABG[e] (n, %)	148 (1.2)	45 (1.4)	204 (0.9)	397 (1.0)	0.016
Prior PCI[f] (n, %)	557 (4.3)	78 (2.4)	454 (2.1)	1089 (2.9)	<0.001
Known COPD[g] (n, %)	18 (0.1)	8 (0.3)	60 (0.3)	86 (0.2)	0.042
Prior CVA[h] (n, %)	7 (0.05)	0 (0)	20 (0.1)	27 (0.1)	0.138
Vascular Disease (n, %)	145 (1.1)	52 (1.6)	426 (1.9)	623 (1.6)	<0.001
Atrial Fibrillation (n, %)	825 (6.4)	1303 (40.3)	2108 (9.6)	4236 (11.1)	<0.001
Known Renal Disease (n, %)	782 (6.1)	377 (11.7)	2310 (10.5)	3469 (9.1)	<0.001
Dialysis Dependent (n, %)	47 (0.4)	32 (1.0)	215 (1.0)	294 (0.8)	<0.001
Chronic Liver Disease (n, %)	129 (1.0)	43 (1.3)	517 (2.3)	689 (1.8)	<0.001
Prior Cancer (n, %)	1087 (8.5)	370 (11.4)	3507 (15.9)	4964 (13.0)	<0.001
Dementia (n, %)	86 (0.7)	39 (1.2)	581 (2.6)	706 (1.9)	<0.001
12-Month Mortality (n, %)	732 (5.7)	431 (13.3)	3312 (15.0)	4475 (11.7)	<0.001
12-Month Cardiac Mortality (n, %)	404 (3.2)	209 (6.5)	716 (3.2)	1329 (3.5)	<0.001
12-Month Cardiac Mortality (n, %)	328 (2.6)	222 (6.9)	2596 (11.8)	3146 (8.2)	<0.001
12-Month Recurrent MI[a] (n, %)	478 (3.7)	132 (4.1)	515 (13.7)	1125 (3.0)	<0.001
Admitted (n, %)	6616 (51.5)	2013 (62.2)	11248 (50.9)	19874 (52.1)	<0.001
Aspirin (n, %)**	4036 (61.0)	1022 (50.8)	4349 (38.7)	9407 (47.3)	<0.001

Statin (n, %)**	4175 (63.1)	966 (48.0)	4894 (43.5)	10035 (50.5)	<0.001
Other Oral Anti-platelets (n, %)**	2155 (32.6)	276 (13.7)	1515 (13.5)	3946 (19.9)	<0.001
ACE-I/ARB (n, %)**	3345 (50.6)	1093 (54.3)	4740 (42.1)	9178 (46.2)	<0.001
Beta-blocker (n, %)**	2766 (41.8)	1153 (57.3)	3308 (29.4)	7227 (36.4)	<0.001
Angiogram (n, %)**	1771 (26.8)	86 (4.3)	47 (0.4)	1094 (9.6)	<0.001
Revascularization (n, %)**	999 (15.1)	1 (0.05)	10 (0.1)	1010 (5.1)	<0.001

[a]i.q.r.=interquartile range, [b]GFR=Glomerular Filtration Rate, [c]MI=Myocardial Infarction, [d]CCF=Congestive Cardiac Failure, [e]CABG=Coronary Artery Bypass Grafting, [f]PCI=Percutaneous coronary intervention, [g]COPD= Chronic Obstructive Pulmonary Disease, [h]CVA=Cerebrovascular Accident.

* Percentage of patients with a positive troponin (>14ng/L)

** Reported as a proportion of those patient admitted. Also, coronary diagnosis group includes patients admitted for the exclusion of ACS.

10.3.3 Troponin sampling and classification

The indication and timing for troponin testing was clinically determined. All troponin samples were analysed using a hs-TnT assay (Elecys Roche Diagnostics: no detectable troponin: 3 ng/L, threshold of detection: 5 ng/L; 99th percentile upper reference limit in a normal population (no acute disease): 14 ng/L). All troponin levels ≥ 5ng/L were available for this analysis. Any troponin result >14 ng/L within the index hospitalization was defined as being elevated. The maximal in-hospital troponin level was transformed using a restricted cubic spline with knots at 14 ng/L (1 x URL), 75 ng/L (5 x URL), 150 ng/L (10 x URL), 300 ng/L (20 x URL), and 750 ng/L (50 x URL) to explore the continuous relationship between the maximum observed troponin level and outcome. Informed by the dose response characteristics of observed in the spline transformation, maximally-observed in-hospital troponin levels were also divided into ordinal categories (<14ng/L, 14-74 ng/L, 75-149 ng/L, 150-749 ng/L, 750-1499 ng/L and ≥ 1500 ng/L) to enable temporal assessments. Troponin profiles for any given individual were considered to have “a rise and/or fall” (i.e. consistent with the Universal Definition of MI) if sequential values over the index hospitalization demonstrated a relative increase or decrease of >5ng/L if the initial level ≤14 ng/L, and >8ng/L relative change if the initial level was >14 ng/L.(3,13) (14) All assays were performed within a centralised laboratory with standardised testing and reporting protocols.

10.3.4 Outcomes

This analysis examined “all-cause”, cardiac and non-cardiac mortality. Based on classifications available from death certificates, deaths were classified as cardiac if the primary, or associated cause of death was recorded as an acute cardiac condition (i.e. acute MI, acute pulmonary oedema, cardiac arrhythmia and sudden cardiac death) or a chronic cardiac condition with no other antecedent non-cardiac cause of death (e.g. ischaemic heart disease or heart failure). Deaths coded as primarily due to cancer, sepsis, failure of a non-cardiac organ, dementia or sepsis without a cardiac antecedent were coded as non-cardiac. Two clinicians determined cause of death separately with disagreements adjudicated by a third (<2% of deaths), without knowledge of troponin. Recurrent MI was defined as a readmission with an ICD-10 AM code for MI (I21-25), validated by a documented concomitant rise and/or fall in troponin during that admission.

10.3.5 Statistical analysis

Analyses examined the relationship between troponin elevation and subsequent outcomes using the criteria of Bradford-Hill for causality where applicable.(11) Consistency was examined by assessing the relative hazard ratio associated with a troponin elevation (>14ng/L) and cardiac/non-cardiac mortality stratified primary organ system groups.

For subsequent analyses, patients were grouped as coronary, non-coronary cardiac and non-cardiac (i.e. the latter two termed non-coronary) to simplify the number of comparisons. Specificity of troponin elevation for all-cause, cardiac and non-cardiac and recurrent MI by 12-months was assessed as the proportion of these events observed among patients with and without initial troponin elevation within the aforementioned three diagnostic groups using a simple 2x2 contingency table with chi-square analysis. Strength of association (also biological gradient) between troponin and outcome was evaluated by examining the magnitude of troponin elevation as a continuous variable with spline-transformation and recurrent MI, and cardiac and non-cardiac mortality over the follow-up duration. The temporal relationships between troponin elevation, and outcomes were examined by assessing the troponin as categorised maximally-observed troponin level allowing these to interact with time as a time-varying co-variate.

Beyond the analysis of specificity, all other analyses employed cause-specific flexible parametric models with cardiac and non-cardiac mortality examined as competing risks.(15-17) Similarly, models for recurrent MI accounted for total mortality as a competing risk. For each model the distribution of knots was selected by optimizing the

Akaike and Bayes information criteria in methods described by Lambert and Royston.(16) To attenuate the confounding by observed differences in the baseline characteristics between groups, gender, age in years, baseline glomerular filtration rate, baseline haemoglobin level, history of coronary artery disease, prior heart failure, prior valvular heart disease, known liver disease, chronic obstructive airways disease, requiring permanent dialysis, a history of malignancy, and dementia were included as covariates in the regression models. The temporal rise and/or fall in troponin was examined in the model, but after inclusion maximal troponin level, the temporal pattern was no longer significant, and no interaction as observed, and this characteristic was excluded from the final model. These flexible parametric models were used to predict instantaneous hazards for cardiac and non-cardiac mortality and recurrent MI, and the hazard ratios examining the strength of association between maximally-observed troponin levels used the estimated hazard at a troponin level of 5ng/L as the base hazard. Only adjusted instantaneous hazards and hazard ratios are presented. All analyses were undertaken using STATA 13.1 (College Station TX, USA) and a p-value of 0.05 was considered statistically significant.

10.4 Results

10.4.1 Patient characteristics

During the 12-month sampling period 39,806 individual index presentations without prior admission in the preceding 6-months with at least one troponin assessment were identified. After exclusion of 1645 (4.1%) patients with missing diagnostic coding, age, creatinine or haemoglobin values or cause of death information, 38,161 patients were available for analysis. A coronary or non-coronary cardiac diagnosis was included in the primary or secondary diagnostic codes in 12,845 (33.7%) and 3,237 (8.5%), respectively, while the remaining patients 22,079 (57.9%) had non-cardiac organ system diagnoses. Prior CAD was more common among patients with a coronary diagnosis (2167/12845 [16.9%]) than those with non-coronary cardiac (479/3237 [14.8%]) or non-cardiac (2611/22,079 [11.8%]) diagnoses ($p<0.0001$). Table 1 describes the clinical characteristics of each of these diagnostic groups.

10.4.2 Association between Troponin elevation and Outcomes

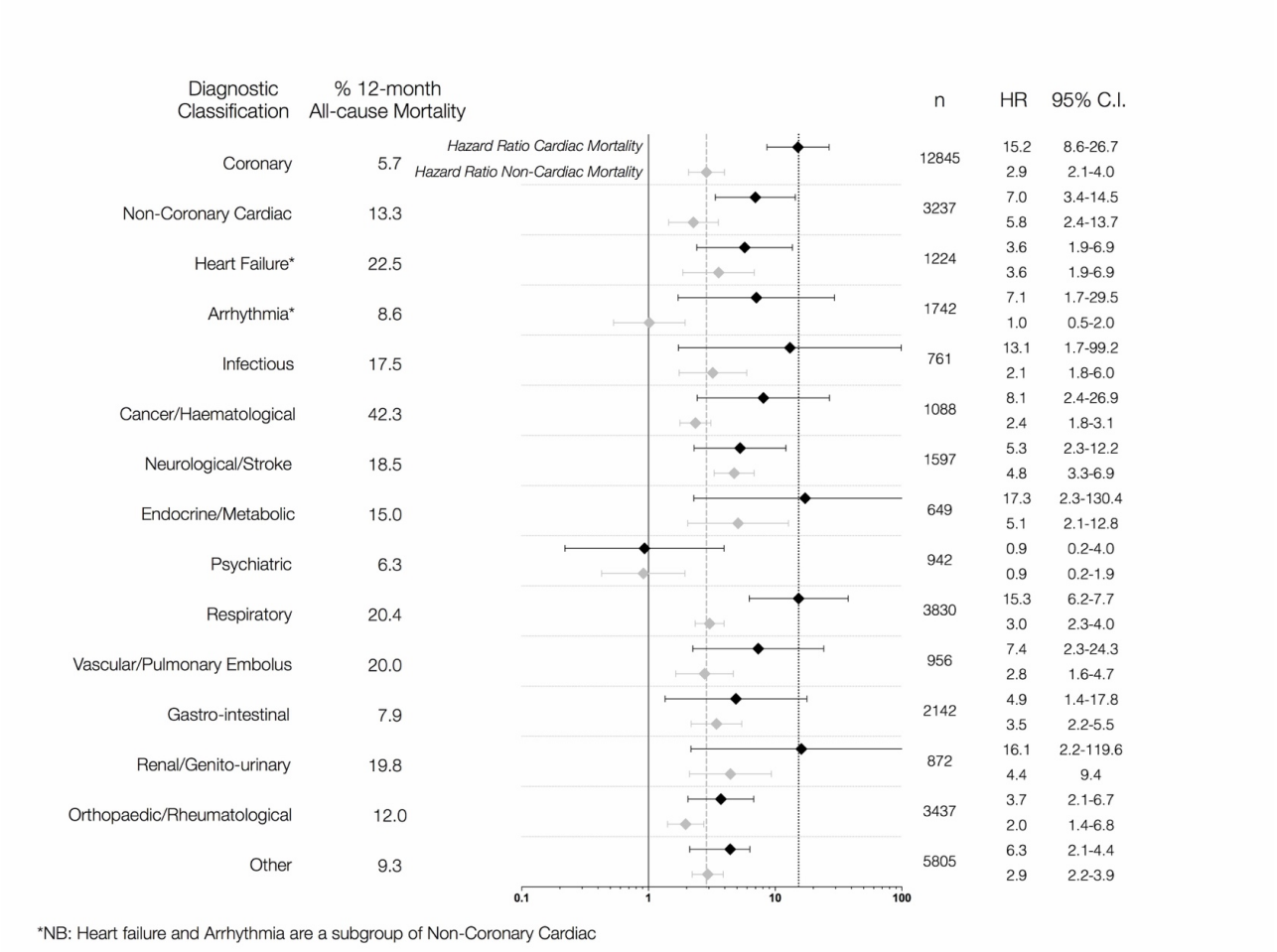
During the index hospitalization, an elevated troponin (>14 ng/L) was identified on at least one occasion in 16,616 patients (43.6%). Prior CAD was more common among patients with a coronary diagnosis (2167/12845 [16.9%]) than with non-coronary cardiac (479/3237 [14.8%]) or non-cardiac (2611/22,079 [11.8%]) diagnoses ($p<0.0001$). A “rise

and/or fall" in troponin was evident in 2943/4819 (61.1%), 699/1966 (35.6%) and 2689/9825 (27.4%) ($p<0.0001$) of patients within the coronary, non-coronary cardiac and non-cardiac groups, respectively. By 12 months, the mortality rates among the three groups were 732/12,845 (5.7%), 431/3237 (13.3%) and 3312/22,079 (15.0%), respectively. Among patients with an elevated troponin, a rise and/or fall pattern was associated with a slightly greater risk of cardiac death (rise/fall: 623/6329 [9.8%] versus no rise/fall: 630/10281 [6.2%], $p<0.001$) and new or recurrent MI (rise/fall: 472/6329 [7.5%] versus no rise/fall: 516/10281 [5.0%], $p<0.001$), and lower risk for non-cardiac death (rise/fall: 849/6329 [13.4%] versus no rise/fall: 1714/10281 [16.7%], $p<0.001$), although the overall rates of non-cardiac death remained higher.

10.4.3 Consistency of relationship between elevated troponin and mortality

Figure 1 depicts the cause-specific hazard ratios for cardiac and non-cardiac mortality associated with an elevated troponin across the 15 ICD-10 organ-specific groups. Hazard ratios associated with troponin elevation were generally higher for cardiac death compared with non-cardiac death, though the degree of risk varied across diagnostic groups. The relative hazard for non-cardiac death associated with any troponin elevation was more consistent across the diagnostic groups than for cardiac death with the exception of psychiatric disorders where troponin elevation was not associated an excess hazard ratio for cardiac or non cardiac death.

Figure 1: Cause-specific hazard ratios for mortality with elevated troponin (>14ng/L) by primary diagnosis grouped by organ system.



*NB: Heart failure and Arrhythmia are a subgroup of Non-Coronary Cardiac

10.4.4 Specificity for death and new or recurrent MI

Among those patients who died by 12 months, an elevated troponin level was evident in 3816/4475 (85.3%) of patients. This proportion was higher among coronary or non-coronary cardiac diagnoses, compared with non-cardiac presentations. An elevated troponin level was observed during the index hospitalization in 988/1224 (80.7%) of patients experiencing a subsequent new or recurrent MI, with similar specificity across the three groups. (Table 2) Within each diagnostic group, the specificity of troponin elevation for late events was moderate, ranging from 41% for non-cardiac death in the non-coronary cardiac population, to 66% for all-cause mortality within the coronary population. (Table 2)

Table 2: Proportion of patients experiencing mortality or recurrent MI[a] within 12 months stratified by troponin level above upper reference limit (>14ng/L) within the index hospitalization. Specificity: Proportion of events among patients without Troponin elevation. Mediation: Proportion of relative increased odds ratio for an event mediated by elevated troponin.

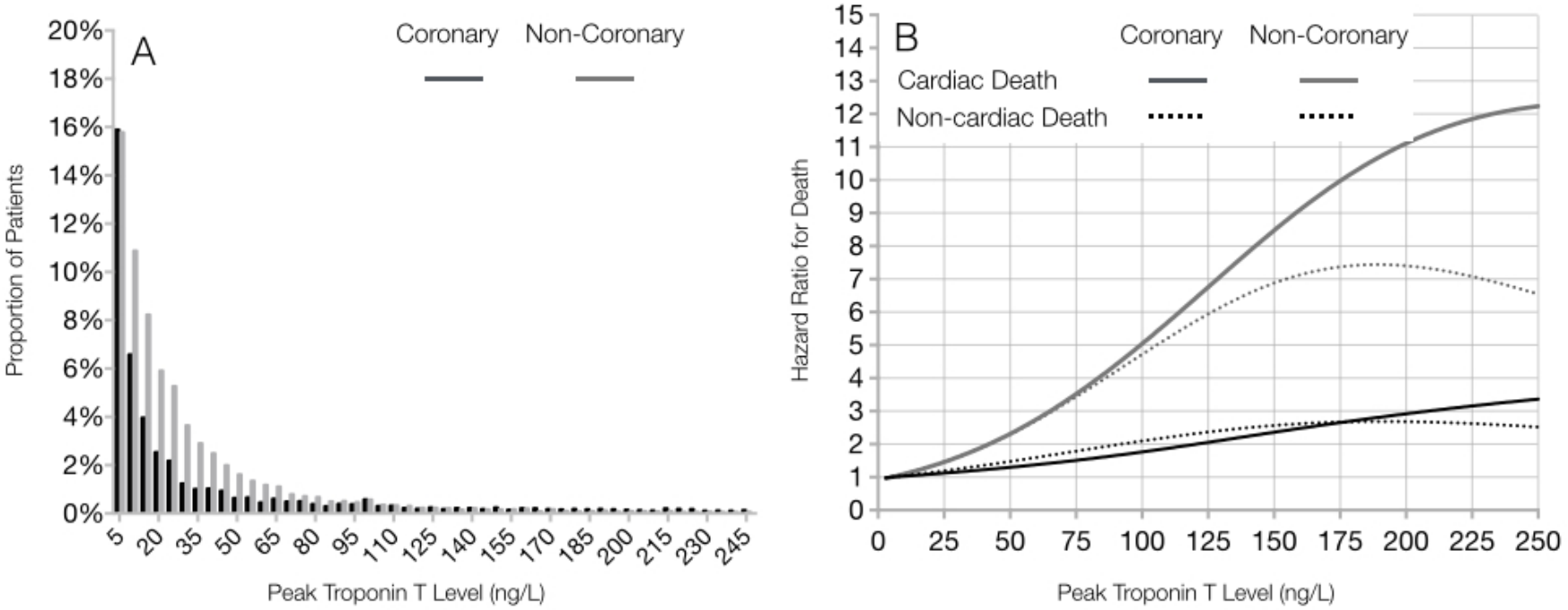
	Proportion of Events in Troponin Positive patients			Specificity
Admission Classification	Troponin ≤14ng/L (n/N, [%])	Troponin >14ng/L (n/N, [%])	% Event in Troponin (+) pts.	% Event Free in Troponin ≤14ng/L (n/N, [%])
		Coronary Diagnoses		
All Death	63/8026 (0.8)	669/4819 (13.9)	91	7964/12115 (66)
Cardiac Death	13/8026 (0.2)	391/8026 (8.1)	97	8031/12441 (64)
Non-cardiac Death	50/8026 (0.6)	278/8026 (5.8)	85	7976/12517 (64)
12-month Recurrent MI[a]	83/8026 (0.6)	367/8026 (5.8)	82	7943/12395 (64)
		Non-coronary Cardiac Diagnoses		
All Death	33/1271 (2.6)	398/1966 (20.2)	93	1238/2806 (44)
Cardiac Death	8/1271 (0.8)	201/1966 (10.2)	96	1263/3028 (42)
Non-cardiac Death	25/1271 (2.0)	197/1966 (10.2)	89	1246/3015 (41)
12-month Recurrent MI[a]	24/1271 (1.9)	132/1966 (6.7)	85	1247/3081 (41)
		Non-Cardiac Diagnoses		
All Death	563/12254 (4.6)	2749/9825 (28.0)	83	11691/18676 (62)
Cardiac Death	55/12254 (0.5)	661/9825 (6.7)	93	12199/21363 (57)
Non-cardiac Death	508/12254 (4.1)	2088/9825 (6.7)	80	11746/18483 (60)
12-month Recurrent MI[a]	129/12254 (1.1)	489/9825 (5.0)	79	12125/21461 (57)

[a]MI=Myocardial Infarction, [b]OR= Odds Ratio, [c]CI=Confidence Interval

10.4.5 Biological gradient and outcome

Patients with secondary myocardial injury more frequently exhibited maximally-observed troponin levels <100ng/L. (Figure 2) Focusing on maximally-observed elevations of troponin <250ng/L demonstrates a steeper rise in the estimated risk of both cardiac and non-cardiac death, than observed among patients with a coronary diagnosis. (Figure 2)

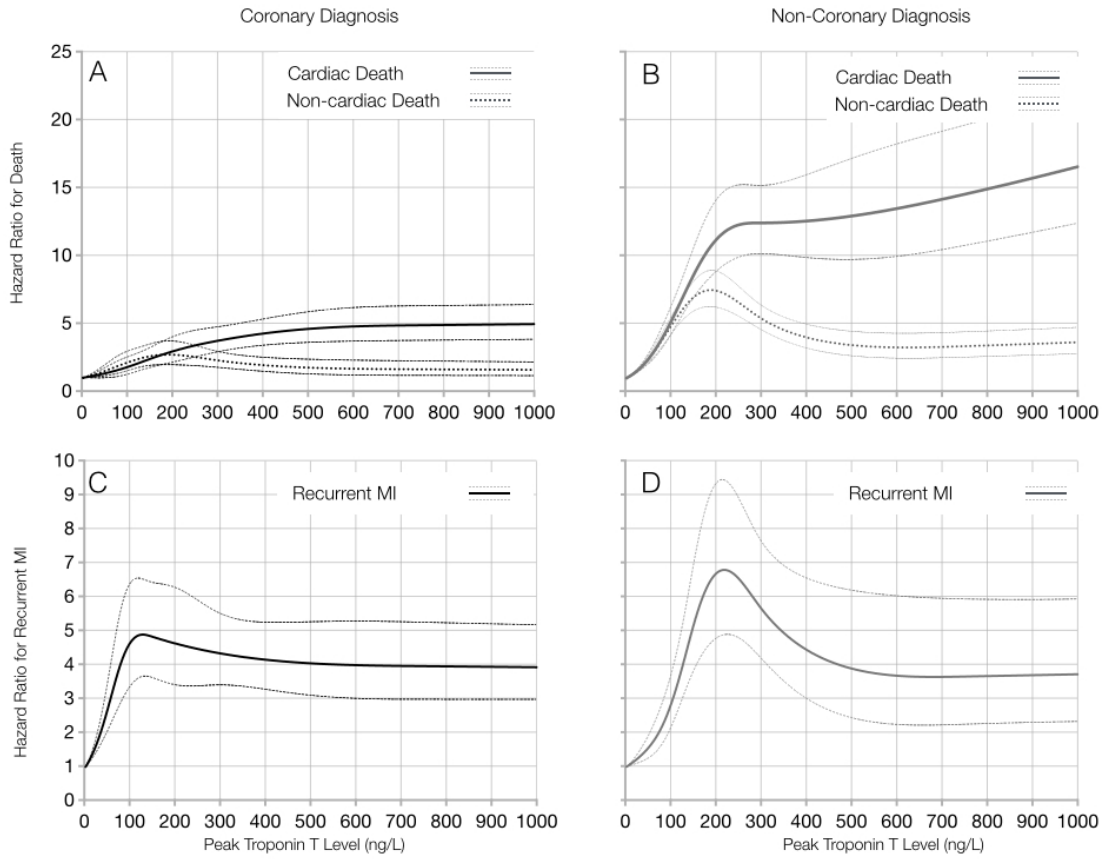
Figure 2: The frequency distribution (A) and relative hazard (B) between cubic spline transformed maximal observed in-hospital troponin levels less than 250ng/L and cardiac mortality (solid line with confidence intervals) and non-cardiac (dotted line with confidence intervals) among patients with coronary (black) and non-coronary diagnoses (grey).



However, with elevations beyond 100ng/L, the risk of cardiac death exceeded that of non-cardiac death for non-coronary presentations. The risk of non-cardiac deaths appears to plateau at troponin levels of 150-200ng/L then declines. This relationship is more marked with non-coronary diagnoses. Overall among patients with a non-coronary or non-cardiac diagnostic classification, the relative hazard was substantially higher than those with a coronary diagnosis for the same level of troponin elevation (Troponin level 1000ng/L: Coronary Hazard Ratio: 5.1 [95% CI 4.0-6.6] vs. Non-Coronary Hazard Ratio: 16.8 [95% CI 12.6-22.4]). (Figure 3)

The estimated hazard ratio for new or recurrent MI also rises in association with increasing maximal-observed troponin levels, though a modest decline in risk is observed at very high troponin peaks among patients with a coronary discharge diagnosis. Similarly, the risk for new or recurrent MI rises more steeply with increasing troponin levels among patients with non-coronary discharge diagnosis, reaching a higher hazard ratio, with a more prominent decline in the risk with further increases in troponin maximally observed levels. (Figure 3)

Figure 3: Relationship between cubic spline transformed maximal observed in-hospital troponin levels and cardiac mortality (solid line with confidence intervals) and non-cardiac (dotted line with confidence intervals) (A-B), and recurrent myocardial infarction (C-D) among patients with coronary (A-C) and non-coronary diagnoses (B-D).

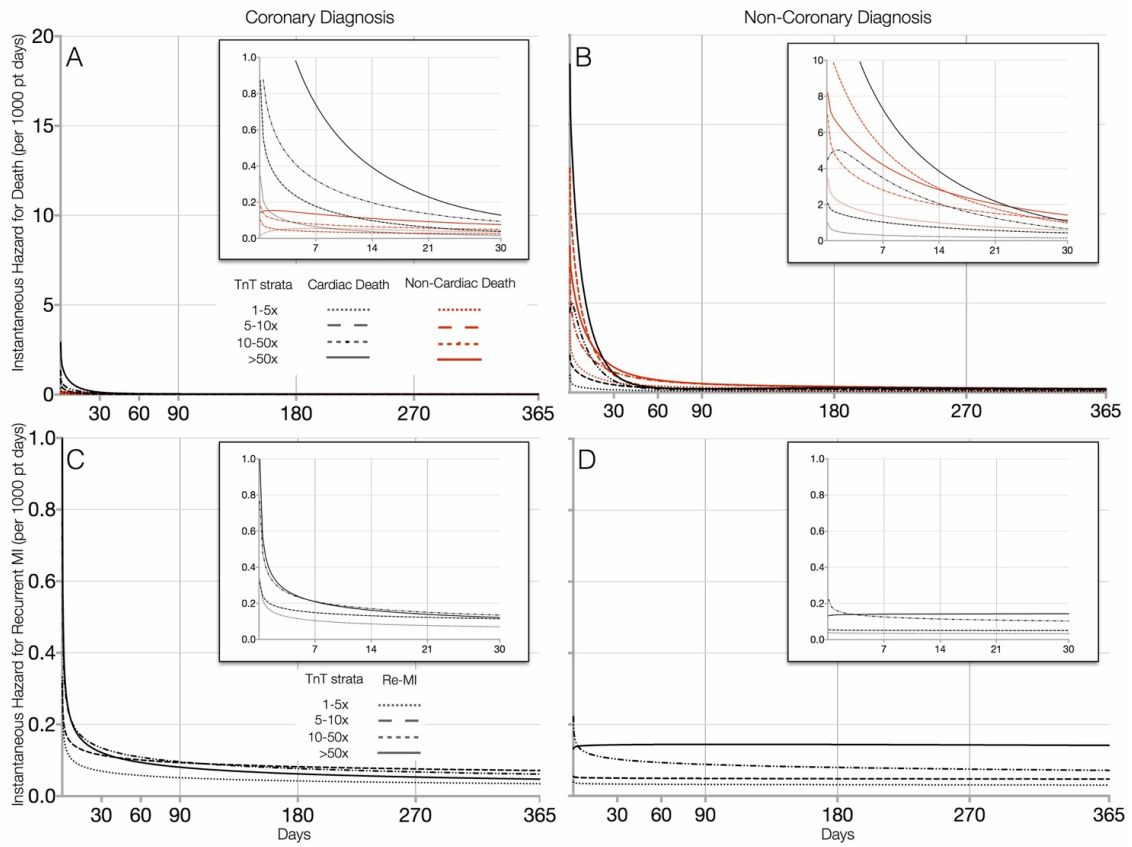


10.4.6 Temporal relationship between troponin and outcome

Figure 3 explores the temporal relationship between the degree of troponin elevation and the occurrence of death and new or recurrent MI. Among patients with both coronary and non-coronary diagnoses, the instantaneous hazard for mortality is highest in the days following admission and declines rapidly in the subsequent weeks. This pattern is similar for cardiac and non-cardiac death, and the degree of hazard is proportional to the magnitude of initial myocardial injury. Overall, the estimated hazard observed among patients with a non-coronary diagnosis is higher (At day 1, TnT>50x URL: 11.7 deaths/1000 patient-days) than those with a non-coronary diagnosis (At day 1, TnT>50x URL: 2.8 deaths/1000 patient-days), with the estimated cumulative incidence for total mortality at 30 days with these levels of troponin elevation of 20.5% and 2.9%, respectively.

The temporal relationship for new or recurrent MI was highest in the first 30 days following the index hospitalization, declining to a constant hazard throughout the remaining 12-month period among coronary diagnosis patients. (Figure 4) In contrast, the hazard for new or recurrent MI among patients with a non-coronary hospitalization was constant over and proportional to the degree of troponin elevation over the follow-up period except for a small early excess hazard among those troponin elevations between 10-50 times the upper reference limit.

Figure 4: Temporal relationship between maximal-observed troponin level and instantaneous hazard (events per 1000 patient days) for cardiac (black) and non-cardiac (red) mortality (A-B) and recurrent myocardial infarction (C-D) by increasing levels of maximal-observed in-hospital troponin among patients with coronary (A-C) and non-coronary diagnosis (B-D). Hazard within the first 30-days enlarged in the inset (NB: different scale in mortality insets).



10.5 Discussion

Myocardial injury precipitated by non-coronary conditions is more commonly observed with the availability of high-sensitivity troponin assays. (18-20) In a diversified population receiving troponin testing as part of physician determined care, myocardial injury detected using a hs-TnT assay was found to be more common and associated with greater estimated risk among patients admitted for non-coronary compared with coronary diagnoses. By examining the implications of troponin elevation for late events using an adaption of the Bradford-Hill causality criteria, our findings would appear to satisfy many of these characteristics including: a risk pattern that is strikingly analogous to Type 1 MI; moderate specificity of troponin elevation for 12-month mortality and recurrent MI; a generally consistent hazard across a range of clinical diagnoses; a clear

biological gradient between maximally observed troponin levels and cardiac mortality (but not with non-cardiac mortality), but a plateauing relationship with recurrent MI; and a temporal profile of an early excess in the hazard of death, but not recurrent MI. The criteria of plausibility and coherence are met through the extensive evidence linking myocardial injury and left ventricular impairment in spontaneous and peri-procedural with subsequent events.(21-23) The remaining criterion of "experimentation" will require the conduct of randomised trials of current and emerging therapies aimed at limiting the extent or impact of myocardial injury among this substantial patient population who have been actively excluded from clinical trials for whom the cardiovascular evidence base remains limited.

The Third Universal Definition of MI has sought to facilitate diagnosis and management by defining Type 2 MI as supply-demand ischaemia with corroborative evidence beyond biomarker changes such as ischaemic changes on ECG or myocardial imaging, or coronary lesions on coronary angiography.(3) Such corroborative evidence is often inconclusive, non-specific, and at times difficult to pursue clinically with invasive or CT angiography when faced with patients experiencing significant co-morbidities. Even within the selective context of ACS trials, patients without documented obstructive coronary stenosis on coronary angiography are enrolled and poorer clinical outcomes have been observed.(24) Such studies have had limited powered to assess the impact of specific therapies or interventions. This analysis demonstrates that, regardless of The Universal Definition, myocardial injury detected in the context of non-coronary conditions confers a greater biological gradient for mortality and particularly cardiac mortality, than seen with coronary conditions, combined with a similar temporal risk profile. Furthermore, higher maximally observed troponin levels confer a greater hazard ratio for cardiac death as opposed to non-cardiac death, with these curves appearing to diverge at maximal observed troponin levels of approximately 100-150ng/L, suggesting a greater opportunity for providing benefits with cardiac specific therapies based on the maximally observed troponin level.

The risk for new or recurrent MI in non-coronary conditions rises to a maximally observed troponin around ~250 ng/L but then declines with increasing levels. This pattern has previously been documented within Type I MI populations.(25) This decline in subsequent MI risk associated with supra-elevated troponin levels may reflect a lower likelihood for recurrent MI in the presence of large areas of initially infarcted myocardium, combined with the competing risk of mortality associated with extensive myocardial injury. However, in contrast to the temporal profile of recurrent MI seen with Type 1 MI, the instantaneous hazard for recurrent MI in non-coronary diagnoses is constant over

the duration of follow-up. This contrast is consistent with the differences in our current understanding of the underlying pathology (i.e. coronary plaque instability in Type 1 MI versus supply-demand imbalance in Type 2 MI). Therefore, significant clinical equipoise regarding the likely benefits of a strategy based on treating fixed coronary lesions to prevent future cardiac events remains.

These findings appear to suggest that secondary myocardial injury lies along the "causal pathway" to late events, though commentary on more proximate or distal factors along this pathway cannot be made. The extent that risk is "modifiable" and whether currently available cardiac therapies, specifically those targeting left ventricular dysfunction, late arrhythmias, and plaque stability, such as coronary angiography and possible revascularization, and anti-thrombotic pharmacotherapies, confer benefit are issues that carry significant implications for optimal clinical management in a very large proportion of patients. To date, trials of these therapeutic approaches have largely excluded such patients due to competing risks of non-cardiac events. Yet, cardiac events among these patients are substantial. Defining the magnitude of benefit and risk with cardiac-specific therapies, as well as the appropriate patient population can only be determined in large-scale randomised controlled trials designed to account for competing risks.

10.5.1 Limitations

Several limitations should be considered. It is recognised that the indication and timing of troponin sampling was at clinical discretion, and it remains possible that the measured maximal troponin levels did not capture actual peak levels. Such random miss-classification may have confounded the assessment of the pattern of troponin elevation and estimates of the hazard. However, failure to detect subsequent troponin elevation among those with initial normal troponins would introduce a bias leading to conservative estimates of risk. Similarly, miscoding of discharge diagnostic classification, specifically the failure to clinically appreciate coronary plaque instability (Type 1 MI) as an underlying cause for the troponin elevation may also have occurred, attesting to the challenges of diagnosing and coding MI in the context of other concurrent illness. Also, the precise timing of procedures is not available to examine peri-procedural MI. As a consequence, both true Type 1/4/5 MI due to new plaque rupture/coronary occlusion or Type 2 MI due to supply demand ischaemia may have occurred but remained un-diagnosed by the clinical teams despite the documented rise in troponin. Recognizing this challenge further underscore the difficulties on implementing current definitions of MI in the context of non-cardiac conditions, particularly in the absence of coronary imaging, and the

potential opportunities for reducing mortality by extending cardiac therapies to this large population of patients.

10.6 Conclusion

A health-service wide analysis examining troponin elevation among patients with clinical conditions not considered due to ACS portends a causal relationship to cardiac mortality. These observations suggest the need for trials exploring cardiac specific interventions in this population that are appropriately designed to address competing risks.

10.7 Acknowledgments

We would like to thank Ms Elodie Janvier for her editorial assistance in preparing this manuscript.

DPC and MH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures: All authors have no conflicts of interest to declare pertaining to the current submitted work. External funding support was not provided for this analysis.

10.8 References

1. French JK, White HD. Clinical implications of the new definition of myocardial infarction. 2004;**90**:99–106.

2. White HD. Pathobiology of Troponin Elevations. *J Am Coll Cardiol*. Elsevier Inc; 2011;**57**:2406–2408.

3. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction, Authors/Task Force Members Chairpersons, Biomarker Subcommittee, Katus HA, Apple FS, Lindahl B, Morrow DA, ECG Subcommittee, Clemmensen PM, Johanson P, Hod H, Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Intervention Subcommittee, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012. p. 1581–1598.

4. Januzzi JL, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *European Heart Journal*. 2012;**33**:2265–2271.

5. Kelley WE, Januzzi JL, Christenson RH. Increases of Cardiac Troponin in Conditions other than Acute Coronary Syndrome and Heart Failure. *Clinical Chemistry*. 2009;**55**:2098–2112.

6. Baron JM, Lewandrowski EL, Januzzi JL, Bajwa EK, Thompson BT, Lewandrowski KB. Measurement of High-Sensitivity Troponin T in Noncardiac Medical Intensive Care Unit Patients: Correlation to Mortality and Length of Stay. *American Journal of Clinical Pathology*. 2014;**141**:488–493.

7. Hillis GS, Welsh P, Chalmers J, Perkovic V. The Relative and Combined Ability of High-Sensitivity Cardiac Troponin T and N-Terminal Pro-B-Type Natriuretic Peptide to Predict Cardiovascular Events and Death …. *Diabetes*. 2014.

8. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E. A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease. *N Engl J Med*. 2009;**361**:2538–2547.

9. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;**304**:2503–2512.

10. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, Wild P, Genth-Zotz

S, Warnholtz A, Giannitsis E, Möckel M, Bickel C, Peetz D, Lackner K, Baldus S, Münzel T, Blankenberg S. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA*. 2011;**306**:2684–2693.

11. The Environment and Disease: Association or Causation? Royal Society of Medicine Press; 1965;**58**:295–300.

12. Howick J, Glasziou P, Aronson JK. Evidence-based mechanistic reasoning. *JRSM*. 2010;**103**:433–441.

13. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, Katus HA, Giannitsis E. Absolute and Relative Kinetic Changes of High-Sensitivity Cardiac Troponin T in Acute Coronary Syndrome and in Patients with Increased Troponin in the Absence of Acute Coronary Syndrome. *Clin Chem*. 2011;**58**:209–218.

14. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S, Mueller C. Utility of Absolute and Relative Changes in Cardiac Troponin Concentrations in the Early Diagnosis of Acute Myocardial Infarction. *Circulation*. 2011;**124**:136–145.

15. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med*. 2002;**21**:2175–2197.

16. Hinchliffe SR, Lambert PC. Flexible parametric modelling of cause-specific hazards to estimate cumulative incidence functions. *BMC Med Res Methodol*; 2013;**13**:1–1.

17. Nelson CP, Lambert PC, Squire IB, Jones DR. Flexible parametric models for relative survival, with application in coronary heart disease. *Stat Med*. 2007;**26**:5486–5498.

18. Mantzouris T, Gauer R, Mackler L. Clinical Inquiry: Elevated troponin but no CVD: what's the prognosis? *J Fam Pract*. 2013;**62**:585–598.

19. Iversen K, Køber L, Gøtze JP, Dalsgaard M, Nielsen H, Boesgaard S, Bay M, Kirk V, Nielsen OW. Troponin T is a strong marker of mortality in hospitalised patients. *Int J Cardiol*; 2013;**168**:818–824.

20. MD PH, PhD MSM, PhD TKM, MD NS, PhD KEJAM. Usefulness of Troponin T to Predict Short-Term and Long-Term Mortality in Patients After Hip Fracture. *Am J Cardiol*.; 2014;**114**:193–197.

21. Leonardi S, Thomas L, Neely ML, Tricoci P, Lopes RD, White HD, Armstrong PW, Giugliano RP, Antman EM, Califf RM, Newby LK, Mahaffey KW. Comparison of the Prognosis of Spontaneous and Percutaneous Coronary

Intervention–Related Myocardial Infarction. *J Am Coll Cardiol*; 2012;**60**:2296–2304.

22. Tricoci P, Leonardi S, White J, White HD, Armstrong PW, Montalescot G, Giugliano RP, Gibson CM, de Werf Van F, Califf RM, Harrington RA, Braunwald E, Mahaffey KW, Newby LK. Cardiac troponin after percutaneous coronary intervention and 1-year mortality in non-ST-segment elevation acute coronary syndrome using systematic evaluation of biomarker trends. *J Am Coll Cardiol*. 2013;**62**:242–251.

23. Bonaca M, Scirica B, Sabatine M, Dalby A, Spinar J, Murphy SA, Jarolim P, Braunwald E, Morrow DA. Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I. *J Am Coll Cardiol*. 2010;**55**:2118–2124.

24. Planer D, Mehran R, Ohman EM, White HD, Newman JD, Xu K, Stone GW. Prognosis of Patients With Non–ST-Segment–Elevation Myocardial Infarction and Nonobstructive Coronary Artery Disease: Propensity-Matched Analysis From the Acute Catheterization and Urgent Intervention Triage Strategy Trial. *Circ Cardiovasc Interv*. 2014;7(3):285-293

25. Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. *J Am Coll Cardiol*. 2001;**38**:979–986.

11 A RANDOMISED COMPARISON OF HIGH-SENSITIVITY TROPONIN REPORTING IN UNDIFFERENTIATED CHEST PAIN ASSESSMENT

11.0 Title page : A Randomised comparison of High-Sensitivity Troponin Reporting in Undifferentiated Chest Pain Assessment

Derek P. Chew MBBS MPH[1,2], Christopher Zeitz MBBS PhD[3,4], Matthew Worthley MBBS PhD[3,4], Hugh Grantham MBBS[1], John Beltrame BMBS PhD[3,5], Margaret Arstall MBBS PhD[6], Penelope Coates MBBS[7], Carolyn Astley DrPH[1,8], Stephen Quinn PhD[1], Julie Ratcliffe PhD[1], Matthew Horsfall RN[9], Philip G Aylward BMBCh PhD[1,2].

[1]Flinders University, Adelaide, South Australia, Australia

[2]Flinders Medical Centre, Adelaide, South Australia, Australia

[3]University of Adelaide, Adelaide, South Australia, Australia

[4]The Royal Adelaide Hospital, Adelaide, South Australia, Australia

[5]The Queen Elizabeth Hospital, Adelaide South Australia, Australia

[6]The Lyell McEwen Hospital, Adelaide, South Australia, Australia

[7]SA Pathology, SA Health Adelaide, South Australia, Australia

[8]Heart Foundation, South Australian, Australia

[9]SA Health, Adelaide, Australia

Short Title: Impact of HS troponin reporting on Practice and Outcomes

Subject terms: Diagnostic Testing; Health Services; Mortality/Survival

Corresponding Author

Derek P. Chew MBBS MPH FRACP

Flinders Medical Centre

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

Email: derek.chew@flinders.edu.au

11.1 Abstract

Background: High-sensitivity troponin (hs-Tn) assays promise greater discrimination of evolving myocardial infarction but the impact of un-guided implementation on the effectiveness of care is uncertain.

Methods and Results: We evaluated the impact of hs-TnT reporting on care and outcome among chest pain patients presenting to 5 emergency departments within a multi-centre randomised trial. Patients were allocated to hs-TnT reporting (hs-report) or standard reporting (std-report) (Roche Elecys). The primary endpoint was death and new or recurrent ACS by 12 months.

A total of 1937 patients without ST-segment elevation were enrolled between July 2011 and March 2013. The median age was 61 (interquartile range: 48-74) years; 46.3% were female. During the index hospitalization, 1466 patients (75.7%) had maximal troponin <30ng/L within 24 hours. Randomization to hs-report format did not alter the admission rate (hs-report: 57.7% vs. std-report: 58.0%, p=0.069). There was no difference in angiography (hs-report: 11.9% vs. std-report: 10.9%, p=0.479). The hs-reporting did not reduce 12-month death or new/recurrent ACS in the overall population (hs-report: 9.7% vs. std-report: 7.2% [HR: 0.83 (0.57-1.22), p=0.362]). However, among those with troponin levels <30ng/L, a modest reduction in the primary endpoint was observed (hs-report: 2.6 % vs. std-report: 4.4%, [HR: 0.58, 95% C.I. 0.34-0.1.00, p=0.050).

Conclusion: High-sensitivity troponin reporting alone is associated with only modest changes in practice. Clinical effectiveness in the adoption of high-sensitivity troponin may require close coupling with protocols that guide interpretation and care.

Trial Registration: (http://www.ANZCTR.org.au/ACTRN12611000879965)

Key Words: troponin T; acute coronary syndrome; diagnosis; emergency department; clinical trial

11.2 Background

While the clinical guideline-recommended management of patients presenting with high-risk features suggestive of acute coronary syndromes (ACS) is relatively well-defined, the management of patients with low and intermediate risk chest pain is more heterogeneous.[1-3] Nevertheless these patients represent, by far, the greatest proportion presenting to emergency services for evaluation of suspected ACS.[4] The efficient identification of the few patients who are in the early stages of an ACS, among the many patients presenting with non-cardiac chest pain remains a key clinical challenge.

Troponin testing has revolutionised the care of suspected ACS patients, by improving the diagnostic sensitivity, and identifying those patients who derive a greater absolute benefit from potent anti-platelet agents, early angiography and revascularization.[5-7] Consequently, troponin results have substantial clinical and resource implications for the patient and the health care system.

More recently, troponin assays with increased diagnostic precision have been developed. These assays are able to determine serum troponin levels at the 99th percentile of a reference population with <10% coefficient of variation.[8-10] Several investigators have demonstrated increased sensitivity and high negative predictive value, but reduced specificity and lower positive predictive value with these assays.[11,12] Clinical interpretation of low levels of troponin elevation requires careful consideration of ACS likelihood.[13] Potentially, improvement in discriminatory capacity with high sensitivity troponin may lead to fewer missed myocardial infarction (MI), and enable rapid discharge of patients without evolving ACS, but the concern that these benefits may be offset by the possible risks associated with the over-investigation of patients

with elevated troponin results not related to ACS remains. To explore whether there is greater risk discrimination with impact on cardiac investigations, management and outcome, we conducted a randomised study examining the effects of unguided troponin reporting down to levels achievable with a high-sensitivity troponin T assay on in-hospital clinical care and death or recurrent ACS admission by 12 months among a broad population of patients presenting with undifferentiated chest pain.

11.3 Methods

11.3.1 Study Design and Patient Population

This study was a prospective multi-center trial comparing serum troponin levels reported at either levels consistent with a standard troponin T assay or at levels achievable with a high-sensitivity assay, randomised in a 1:1 ratio at the patient level. [14] Patients were screened and enrolled in the emergency departments (ED) at 5 metropolitan hospitals in Adelaide, and followed for a duration of 12 months after randomization. Each of these hospitals provided emergency services 24 hours per day and all but one had dedicated chest pain assessment units. The study was approved by each hospital's human research ethics committee and all participants provided written informed consent. (Australian New Zealand Clinical Trials Registry [http://www.anzctr.org.au/] registration number ACTRN12611000879965.)

Patients presenting to the ED with clinical features of chest pain or suspected ACS (chest pain or overwhelming shortness of breath (>10 min at rest < 24 hours from the time of presentation) in whom the treating physician deemed a measurement of the serum troponin was required were eligible. Patients were excluded if they were less than 18 years of age; had evidence of ST-segment elevation on presenting electrocardiograph (ECG); required permanent dialysis; had suspected ACS secondary to other causes (severe anaemia, sepsis etc,); were unable to complete a clinical history questionnaire due to language or co-morbidity; or were unable or unwilling to

provide written informed consent. Patients were prospectively sub-classified by the National Heart Foundation ACS Guidelines risk classification using clinical characteristics such as haemodynamic compromise, ECG changes, biomarker elevation, presence of prior coronary disease and diabetes (supplementary Table 1) with this information made available to the treating physician.[15]

Randomization was blocked by hospital and Heart Foundation clinical risk strata, evaluated using a standardised questionnaire completed by trial staff. Clinical components of the Global Registry of Acute Cardiac Events (GRACE) risk score, and Thrombolysis In Myocardial Infarction (TIMI) risk were also documented but not used in randomization.[16,17]

11.3.2 Randomisation Allocation and Intervention

Patients undergoing troponin testing were identified soon after presentation, before samples were sent for pathology testing in order to limit delays of usual patient assessment. Within the hours of 9am-5pm, dedicated study nurses stationed within the ED ensured that the initial ECG did not demonstrate ST segment elevation and then approached each patient. Outside these times, patients were not included. Following written informed consent, the clinical risk strata was determined and patients were randomised to troponin testing reported to either standard troponin T levels (std-report; actual level 30ng/L (i.e. levels below 29 ng/L reported as "<29") and above [<29 ng/L: normal, 30-100 ng/L: borderline abnormal, and >100 ng/L: myocardial injury]) or high-sensitivity format (hs-report: actual level >3ng/L [normal: <=14 ng/L, >14 ng/L: myocardial injury]) using sequentially numbered sealed envelopes. Pre-prepared blood request forms within each sealed envelope were then used to inform the state-wide pathology service of the randomised allocation and the required reporting format. All patients underwent troponin testing at ED presentation, 3 hours and 6 hours after presentation unless discharged prior to these times at clinical discretion. Troponin

testing outside protocol-defined time-points was permitted at the treating clinicians discretion, but reporting of the result was restricted to the allocated format for the index admission. Physicians receiving reports in the std-report format were not permitted to request results in the hs-report. No recommendations regarding repeat testing and specific care were provided in the report and all subsequent care was determined by the treating clinicians. Only standardised advice regarding interpretation of the tests (sensitivity of the test and upper limited of the reference range) was provided by the pathology service. Standard reporting was maintained for all patients not enrolled for the entire duration of the study and subsequent admissions for study participants. To minimise the risk of contamination and crossover between study arms associated with the use of seperate conventional and high-sensitivity assays, all troponin tests were performed using the Elecsys Troponin T high sensitive (TnT-hs)-cobas (Roche Diagnostics) and only the reporting was changed for the study patients.

11.3.3 Measures of Care and Clinical Outcomes

Measures of Care: Clinical care was measured by the frequency of functional testing, echocardiography and invasive angiography and revascularization by 12 months, and the use of guideline recommended therapies. In addition, patients were assessed for ED length of stay, total length of stay, and readmission for cardiovascular causes. Late outcomes were captured through a state-wide universal hospital administrative system that includes all readmissions, and is linked to the death registry, enabling evaluation of late survival. The details of readmissions were then sourced from the treating hospitals. Patients were also contacted at 30-days, 6-months and 12-months, to assess for vital status, re-hospitalizations and quality of life (EQ-5D).

Clinical Outcomes: The primary outcome was the cumulative composite endpoint of all-cause mortality and new or recurrent ACS (beyond the first 24 hours of enrolment) up to 12 months. New or recurrent ACS was defined: as MI with a rise and/or fall in

cardiac biomarkers, or a new myocardial defect on cardiac imaging, and consistent with the Universal Definition[18] (using troponin levels >30 ng/dL) ; or unstable angina defined as chest pain/discomfort with a crescendo pattern or occurring at rest, associated with: dynamic ECG changes consistent with ischaemia; or functional testing consistent with ischaemia; and/or demonstrated coronary stenosis>70% by visual estimation. All index presentations and outcomes were independently adjudicated by cardiologists without involvement in the care of patient. Through this process, MI diagnosed within the first 24 hours of presentation were considered as an 'index event' and were not included in the primary outcome. Secondary outcomes included: cardiovascular mortality; individual components of the primary endpoint; cerebrovascular accidents (CVA) with cerebral imaging; atrial or ventricular arrhythmias; congestive cardiac failure without MI; representation for chest pain; and significant bleeding using the Bleeding Academic Research Consortium (BARC) definitions (Definition 2-5).[19]

A Clinical Event Committee (CEC), chaired by an experienced cardiologist and managed by an independent member of the data-management group, provided blinded evaluation of all components of the primary endpoint including index (within 24 hours of initial presentation) and subsequent MI. A Data and Safety Monitoring Board assessed the study safety through the evaluation of all in-hospital and post-discharge (≤7days) clinical events including representations to hospital.

11.3.4 Statistical Analysis

Since randomisation occurred prior to troponin testing, the primary analysis population included all randomised patients regardless of the initial troponin level and all analyses were conducted as "intention-to-treat". Subsequent analyses were also confined to patients with maximal peak troponin levels within 24 hours of <30 ng/L where differences in the reporting format existed between the two study arms. Baseline

clinical characteristics were presented for all patients and by troponin report type. Continuous variables are expressed as medians with interquartile ranges, while categorical and count variables are presented as frequency (percentage). Patient baseline characteristics, inpatient investigation, therapies, and outcomes between the randomised groups were compared using chi-square or Fisher's exact tests for categorical variables and using Kruskal-Wallis tests for continuous variables.

The rates of death and new/recurrent ACS at 12-months as well as the composite primary endpoint at 30-days was examined in the entire population, and stratified by maximal in-hospital troponin (<5ng/L [below level of detection {LoD}], 5-14ng/L {LoD to hs-TnT upper reference limit (URL_{hsTnT}), 15-29ng/L [URL_{hsTnT} to standard report reference limit (URL_{std})], 30-100ng/L (URL_{std} to older MI thresholds) and >100ng/L) as well as by clinical risk strata. The primary analysis compared the time to first occurrence of the primary endpoint between the high-sensitivity and standard troponin format study arms using univariable Cox model with hospital random effects (shared frailty model) to account for correlated readings within hospitals. Twelve-month freedom from mortality, recurrent MI and cardiac readmission was also assessed using the same methods. Time to event curves were plotted for the entire population and among those with a peak troponin <30 ng/L within the first 24 hours using a cumulative incidence function.

To explore the whether the troponin reporting format may influence decisions to admit or discharge patients from the ED when the Heart Foundation risk strata were also considered, a logistic regression model with ED discharge as the dependent variable, and report type, risk strata and interaction terms for each risk strata by hs-report type as independent variables was used. Similarly, the influence of the level of peak troponin within the first 24 hours and the randomised reporting format on the provision of cardiac investigations, coronary revascularisation, and recommended

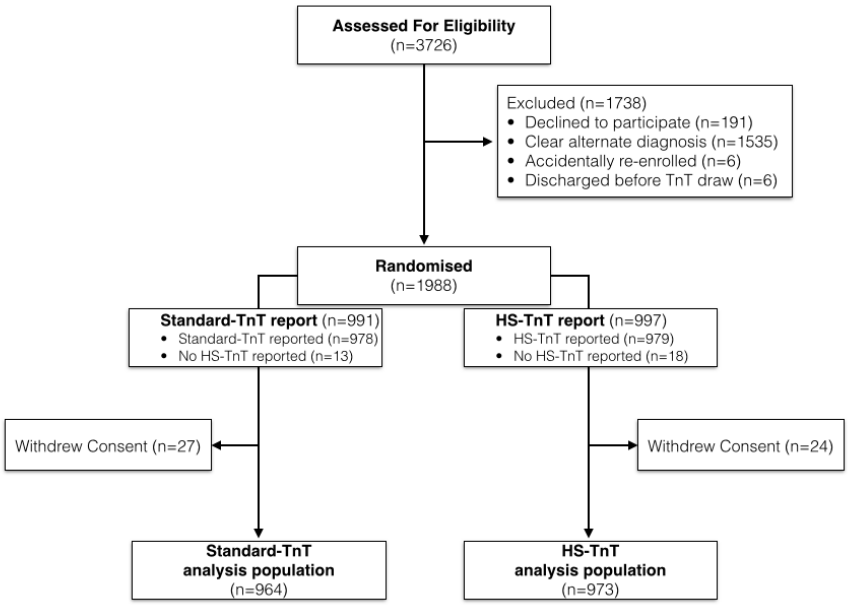
pharmacologies were explored within logistic models. Within these models, the investigation or therapy was modeled as the dependent variable, with the troponin strata, the reporting format, and an interaction term for each troponin strata by hs-report type modeled as independent variables.

Sample Size estimation: Assuming the correct management of these patients translates to reduction in death or ACS admissions, from 8.6% to 5.1%, a sample size of 828 patients per arm (power of 80% at an alpha of 0.05) was required for the primary analysis. The planned sample size was 2000 patients. A probability of <0.05 is considered statistically significant. All analyses were performed using Stata 13.1 (College Station, TX).

11.4 Results

In total, 1988 patients (53% of the screened population) were randomised in the study between July 2011 and March, 2013. Among these patients 51 patients withdrew consent during the follow-up period, leaving 1937 patients for analysis (973 receiving a high sensitivity report and 964 patients receiving the standard report). Reflecting the pragmatic nature of the study, 31 patients had haemolyzed blood samples without repeat troponin testing requested, and these patients have been retained in the intention-to-treat analysis. A summary of patient flow and exclusions is provided in Figure 1.

Figure 1: Consort diagram describing patient flow



Risk

stratification criteria observed that 1421 (73.4%) were either intermediate or high risk, while 1466 patients (75.7%) had a peak troponin level less than 30 ng/L, and 230 patients (11.9%) within the first 24 hours. The median time from symptom onset to ED presentation and presentation to consent was 2.2 hours (range 0.7-5.6), and 30 min (range 16-51), respectively. Baseline clinical characteristics are presented in Table 1.

Table 1: Baseline clinical characteristics by troponin report type

Characteristic	Total (n=1937)	High Sensitivity Troponin Report (n=973)	Standard Troponin Report (n=964)	P-value
Age (years, median, i.q.r)	61.3 (48.6-73.9)	61.6 (48.7-73.8)	60.7 (48.3-74.3)	0.804
Female Gender	46.3%	47.3%	45.3%	0.391
Presentation with Chest pain or Shortness of Breath	89.1%	88.8%	89.3%	0.684
Time to Presentation (hours, median, i.q.r)	2.2 (0.7-5.5)	2.1 (0.6-5.2)	2.5 (0.8-5.8)	0.237
Time from Presentation to Consent (min, median, i.q.r)	30 (16-51)	30 (16-50)	30 (17-53)	0.657
Heart Rate (mmHg, median, i.q.r)	76 (66-88)	76 (66-88)	76 (66-88)	0.899
Systolic Blood Pressure (mmHg, median, i.q.r)	140 (124-155)	139 (123-154)	140 (125-156)	0.240
ST Deviation on ECG	13.3%	12.6%	14.0%	0.376
Baseline Creatinine (mmol/L median, i.q.r)	75 (64-89)	75 (64-89)	74 (63-89)	0.269
Heart Foundation Classification				0.509
High Risk	653 (33.7)	35.0%	32.5%	
Intermediate Risk	768 (39.7)	39.1%	40.3%	
Low or No Risk	516 (26.6)	27.3%	26.0%	
GRACE score (median, i.q.r.)	78 (56-108)	79 (56-110)	78 (57-107)	0.489
TIMI risk score (median, i.q.r.)	2 (1-3)	2 (1-3)	2 (1-3)	0.446
Current Smoker	18.4%	18.3%	18.6%	0.574
Known Hypertension (n,%)	51.8%	51.2%	52.4%	0.596
Known Hyperlipidaemia (n, %)	52.4%	52.3%	53.%)	0.974
Diabetes Mellitus (n, %)	18.6%	19.2%	18.0%	0.471
Family History of IHD (n, %)	54.1%	53.4%	54.8%	0.325
Prior Myocardial Infarction (n, %)	17.3%	16.7%	18.0%	0.438
Prior Coronary Intervention (n, %)	15.2%	16.3%	14.1%	0.171
Prior CABG (n, %)	8.3%	8.2%	8.3%	0.951
Prior Cerebrovascular disease (n, %)	7.9%	7.7%	8.1%	0.760
Prior Chronic Lung disease (n, %)	9.9%	10.0%	9.8%	0.902
Peripheral Vascular disease (n, %)	7.3%	6.9%	7.7%	0.515
Known Malignancy (n, %)	10.3%	10.1%	10.5%	0.769
Impaired activities of daily living (n, %)	3.4%	3.1%	3.8%	0.425

Morbid obesity (n, %)	11.0%	10.6%	11.3%	0.611
Maximal Troponin Strata (n=1906)				0.400
Undetectable	31.0%	32.5%	29.6%	
5-14 ng/L	33.8%	32.0%	35.7%	
15-29 ng/L	12.1%	12.8%	11.4%	
30-100 ng/L	18.9%	18.4%	18.9%	
>100 ng/L	4.4%	4.3%	4.5%	

Categorical variables compared by chi-square test. Continuous variables compared by Kruskal-Wallis test.

IHD: Ischaemic Heart Disease, CABG: Coronary Artery Bypass Grafting, HF: Australian Heart Foundation. GRACE: Global registry of Acute Cardiac Events, TIMI: thrombolysis in myocardial infarction, i.q.r: interquartile range, TnT: Troponin T, ECG: Electrocardiogram

11.4.1 In-hospital care and discharge diagnosis

There was no difference in the overall proportion of patients discharged home directly from the ED with high-sensitivity reporting (hs-report report: 406/971 (41.8%) vs. std-report: 389 (40.1%) p=0.514). However, among patients classified as low or no risk by Heart Foundation Criteria, a higher rate of discharge from the ED was observed in the hs-report group (hs-report: 168/253 (66.4%) vs. std-report: 148/263 (56.3%) p=0.010), though discharge rates were non-significantly lower in the moderate risk and no different in the high risk groups, respectively, with the hs-report (moderate risk: hs-report: 131/380 (34.5%) vs. std-report: 155/262 (40.2%) p=0.068, high-risk: hs-report: 108/340 (31.8%) vs. std-report: 86/313 (27.5%) p=0.488; Interaction p value=0.029). There was no difference in subsequent inpatient cardiac investigations and management. Specifically, there was a non-significant increase coronary angiography among patients randomised to the hs-report, with a non-significant increase in revascularization was evident by 12 months. Antiplatelet therapy and statin therapy were prescribed in the same frequency in both treatment groups. The overall use of cardiac investigations and management stratified by troponin reporting is presented in the Table 2.

Table 2: Investigations and management by troponin report type during index presentation

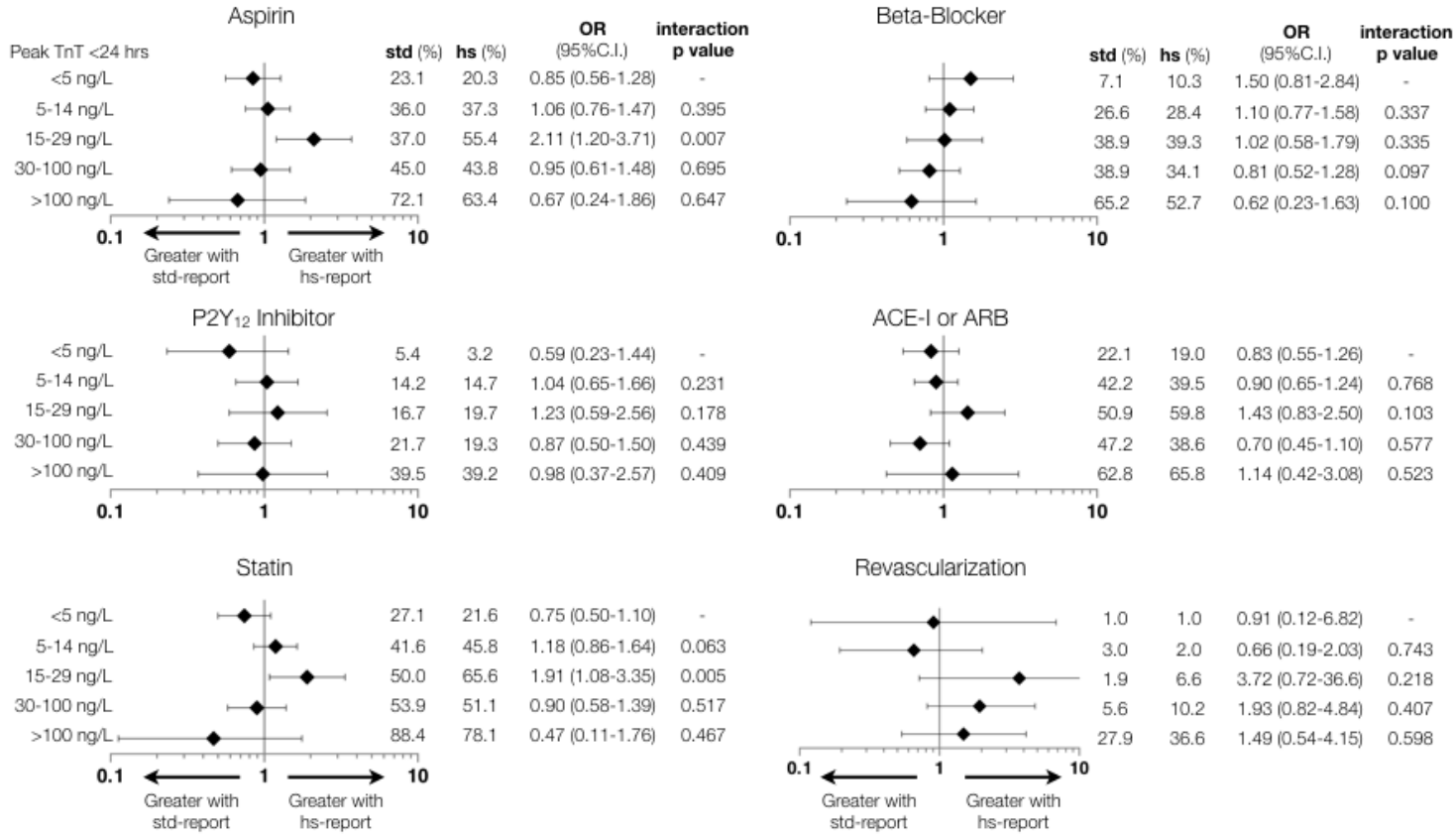
Characteristic	Total (n=1937)	High Sensitivity Troponin Report (n=973)	Conventional Troponin Report (n=964)	P-value
ED Disposition				
Admitted	57.8%	57.7%	58.0%	0.067*
Discharged	41.1%	41.8%	40.4%	
Left at own risk	1.0%	0.5%	1.6%	
Discharge (TnT<30ng/L)	46.0%	49.1%	46.4%	0.045
Echocardiography	18.5%	18.8%	18.2%	0.711
Functional study	22.6%	22.2%	23.0%	0.663
Angiogram by 12 mths	11.4 %	11.9%	10.9%	0.479
Revascularization by 12mths	5.4%	5.2%	3.8%	0.138
Medications at discharge				
Aspirin	35.8%	36.1%	35.5%	0.771
Other Antiplatelet agent	14.0%	13.7%	14.2%	0.723
Statin	42.6%	42.7%	42.6%	0.994
ACE-I or ARB	37.8%	36.5%	39.1%	0.234
Beta-blocker	26.3%	26.1%	26.5%	0.862
ED LOS (hrs, i.q.r)	5.4 (3.7-7.5)	5.4 (3.7-7.6)	5.4 (3.6-7.3)	0.330
Hospital LOS (days, i.q.r)	0.9 (0.2-2.0)	0.9 (0.2-2.0)	0.9 (0.2-2.0)	0.958
Final Index admission diagnosis				0.084
Undiagnosed chest pain	38.0%	37.0%	39.0%	
Stable Angina	2.2%	2.7%	1.7%	
Unstable Angina	4.8%	3.8%	5.8%	
Myocardial infarction	4.1%	4.2%	3.3%	
Hearth Failure	1.8%	2.0%	1.7%	
Arrhythmia	7.4%	8.8%	6.0%	
Pericardial disease	1.2%	1.1%	1.4%	
Other Non-Cardiac	40.5%	40.4%	40.6%	
Coronary Diagnosis	11.1%	10.7%	11.4%	0.612
Non-coronary cardiac diagnosis	10.5%	11.9%	9.0%	0.037
Patients with TnT<30ng/L within 24 hours	Total (n=1466)	High Sensitivity Troponin Report (n=738)	Conventional Troponin Report (n=728)	P-value
Discharged	46.0%	49.1%	46.4%	0.045

Echocardiography	14.7%	15.6%	13.7%	0.318
Functional study	22.7%	21.4%	24.0%	0.230
Angiogram by 12 mths	7.1%	7.6%	7.6%	0.458
Revascularization by 12mths	2.2%	2.3%	2.1%	0.750
Medications at discharge				
Aspirin	32.2%	33.1%	31.2%	0.430
Other Antiplatelet agent	110.9%	10.7%	11.1%	0.512
Statin	38.1%	38.9%	37.2%	0.512
ACE-I or ARB	35.0%	34.3%	35.7%	0.565
Beta-blocker	21.8%	22.6%	20.9%	0.417

Categorical variables compared by chi-square test, or Fisher's exact test (*).
Continuous variables compared by Kruskal-Wallis test.
ED: Emergency Department, LOS: Length of Stay. Coronary diagnosis=Myocardial Infarction, Unstable angina or Stable angina. Non-Coronary Cardiac Diagnosis= Heart Failure, Arrhythmia or Pericardial Disease. TnT: Troponin T, ECG: Electrocardiogram, ACE-I: Angiotensin Converting Enzyme – Inhibitor, ARB: Angiotensin Receptor Blocker.

However, among patients with a peak troponin within 24 hours of 14-29 ng/L, there was a significant interaction between the use of the hs-report and the prescription of aspirin (hs-report: 55.4% vs std-report 34.0%, p=0.006, interaction p value=0.007) and statins (hs-report: 65.6% vs std-report 5.0%, p=0.017, interaction p value= 0.005) at discharge. (**Figure 2).**

Figure 2: Interaction between troponin reporting type, peak troponin level within 24 hours and the use of ACS guideline advocated therapies.



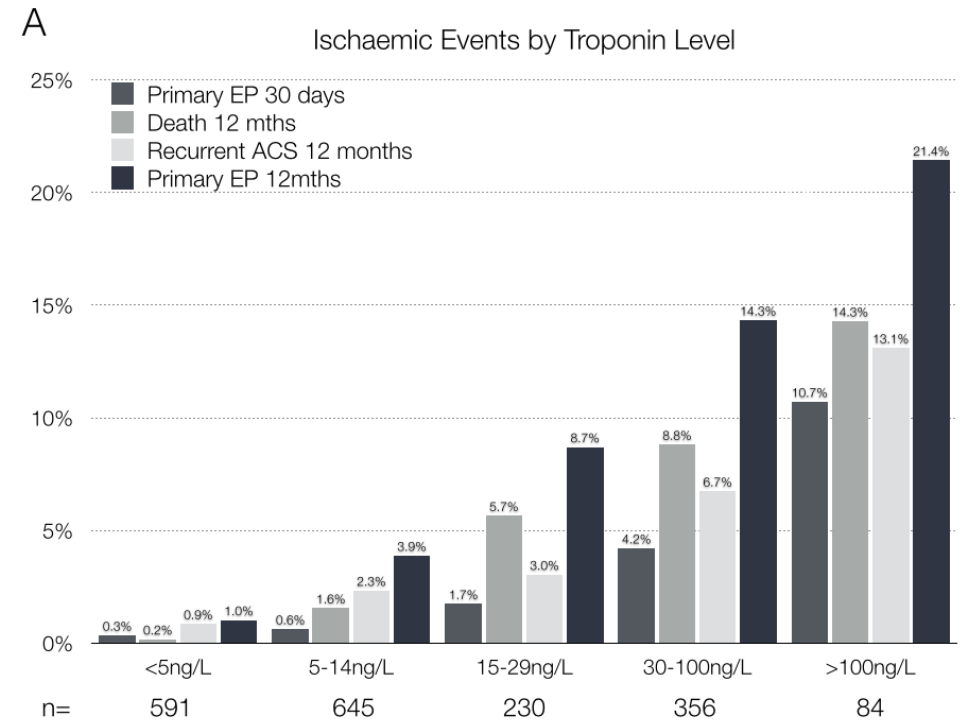
A non significant increase in revascularisation was observed in this group, and there was no significant interaction between the reporting format, the troponin level and the prescription of the other pharmacotherapies.

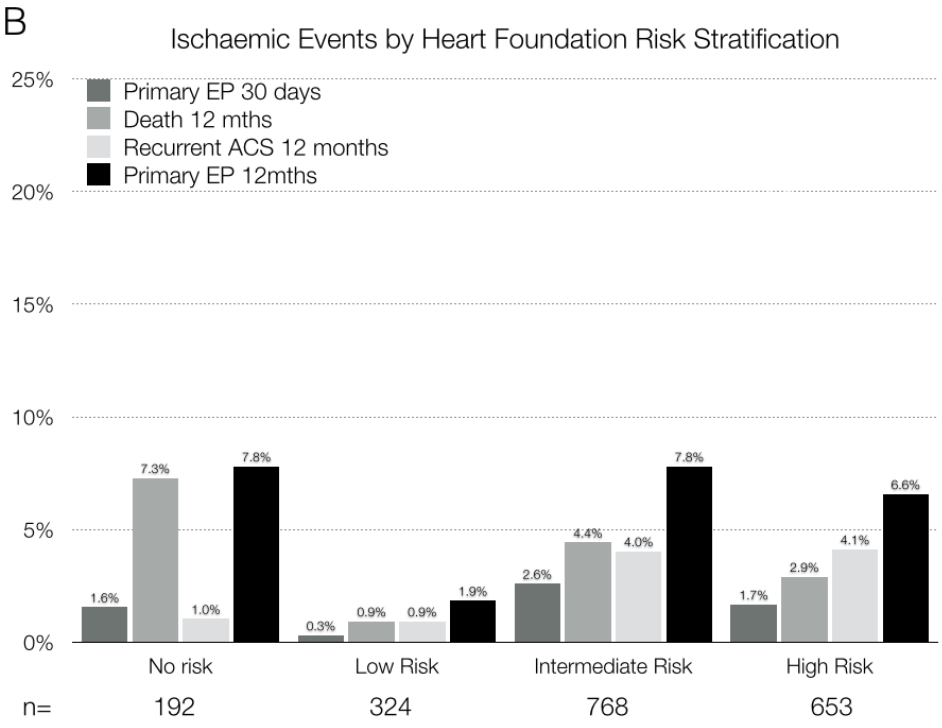
The Clinical Event Committee determined final diagnosis is shown in table 2. There was no increase in the proportion of patients with the diagnosis of MI within the first 24 hours of admission. There was a significant increase in the proportion of patients discharged with a non-coronary cardiac diagnosis. The proportion of patients discharged with a non-cardiac diagnosis was similar between the two groups.

11.4.2 Troponin level and clinical events

There was a strong association between the maximal in-hospital troponin level within 24 hours and the risk of subsequent clinical events (Figure 3).

Figure 3: Clinical Outcomes stratified by: a) maximal troponin level during index presentation, and; b) National Heart Foundation Risk Classification.





For patients with a troponin level below the reportable limit (<5 ng/L), there were no deaths and 2 ACS events (1 MI and 1 unstable angina) observed within the first 30 days of follow-up. By 12 months there was 1 death and 5 ACS events (3 MIs and 2 unstable angina) observed in this group. Nevertheless, there remained a substantial number of hospital re-presentations in this group, largely driven by re-presentations with chest pain. With modest elevations in either the initial troponin or the maximal observed troponin level there was an increased rate of 30-day and 12-month mortality, new or recurrent myocardial infarction, and admissions for heart failure. This increased risk was observed among patients with levels of between 5-14ng/L, considered within the normal range, with a clear linear trend of increased risk associated with elevations beyond this level. In contrast, stratification by the risk criteria demonstrated poor discrimination for 30-day and 12-month events.

11.4.3 Clinical events by troponin reporting

Overall there were no differences in the primary endpoint at 12-months for patients randomised to the high-sensitivity troponin report compared with the standard troponin report (hs-report: 57/973 (9.7%) vs. std-report: 69/964 (7.2%) [HR: 0.83 (0.57-1.22), p=0.362]) (Table 3).

Table 3: Event rates and hazard ratios at 30-day and 12-month, by troponin report type among all randomised patients

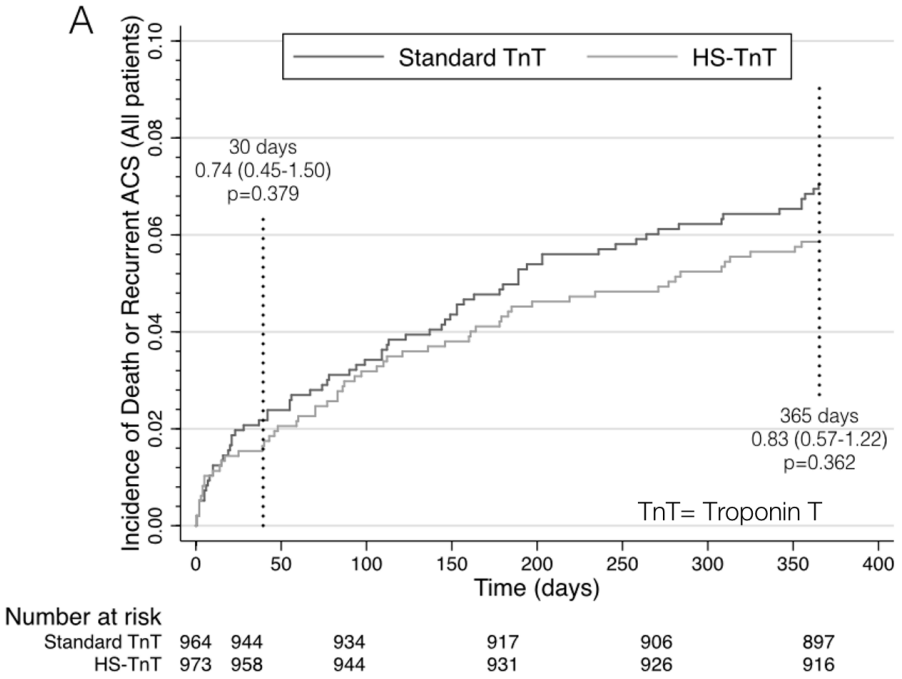
Characteristic	High Sensitivity Troponin Report (n=973)	Standard Troponin Report (n=964)	Hazard Ratio (95% C.I.)	P-value
Clinical outcomes at 30 days				
Primary Endpoint	1.54 (0.09-2.54)	2.07 (1.34-3.20)	0.74 (0.45-1.50)	0.379
Death	0.62 (0.03-0.14)	0.83 (0.04-1.65)	0.74 (0.26-2.11)	0.580
Myocardial Infarction	0.82 (0.41-1.64)	0.93 (0.49-1.79)	0.88 (0.61-1.27)	0.500
Unstable Angina	0.31 (0.01-1.0)	0.41 (0.02-1.10)	0.74 (0.15-3.69)	0.716
CVA	0.51 (0.21-1.23)	0.52 (0.02-1.24)	0.99 (0.52-1.90)	0.980
Major bleeding	2.26 (1.49-3.41)	1.24 (0.71-2.18)	1.82 (0.78-4.3)	0.166
Re-presentation for Chest Pain	4.53 (3.38-6.03)	3.53 (2.53-4.90)	1.29 (0.83-2.01)	0.263
Readmission for Heart Failure	1.03 (0.55-1.90)	0.41 (0.16-1.10)	2.48 (0.72-7.92)	0.124
Readmission for Arrhythmia	1.34(0.78-2.29)	0.52 (0.22-1.24)	2.59 (0.92-7.26)	0.071
Any CV event	9.66 (7.96-11.69)	7.16 (5.70-8.98)	1.37 (1.00 -1.89)	0.047

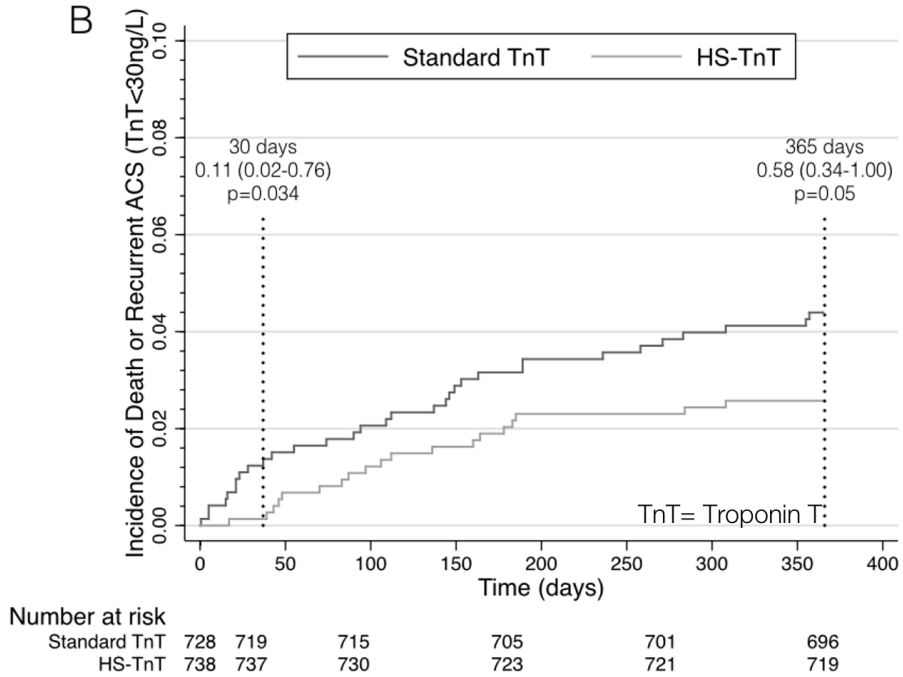
Clinical outcomes at 12 months				
Primary Endpoint	5.86 (4.55-7.35)	7.05 (5.60-8.86)	0.83 (0.57-1.22)	0.362
Death	3.08 (2.17-4.38)	4.15 (3.06-5.61)	0.74 (0.50-1.10)	0.135
Myocardial Infarction	2.06 (1.43-3.17))	2.18 (1.43-3.23)	0.94 (0.64-1.40)	0.768
Unstable Angina	1.23 (0.70-2.16)	1.14 (0.63-2.05)	1.08 (0.62-1.87)	0.781
CVA	1.08 (0.54-2.16)	1.45 (0.86-2.44)	0.78 (0.44-1.36)	0.380
Major bleeding	4.01 (2.94-5.45)	2.49 (1.68-3.69)	1.56 (0.84-2.88)	0.166
Representation for Chest Pain	13.46 (11.47-15.77)	13.28 (11.29-15.59)	0.98 (0.78-1.25)	0.908
Readmission for Heart Failure	3.70 (2.68-5.09)	2.90 (2.01-4.18)	1.23 (0.75-2.00)	0.414
Readmission for Arrhythmia	4.73 (3.56-6.26)	4.88 (3.69-6.44)	0.97 (0.65-1.46)	0.902
Any CV event	24.67 (22.08-27.50)	24.07 (21.49-26.89)	1.04 (0.87-1.25)	0.639

Kaplan-Meier failure rates (expressed as percentage and 95% C.I.) Comparisons using univariate random effects Cox model (shared frailty: enrolling hospital) for hazard ratio, 95% confidence bounds and p value.

However, the composite death and repeat cardiovascular admissions (i.e. representations for chest pain, recurrent MI, CVA, major bleeding, heart failure or cardiac arrhythmia) were increased at 30 days in the overall population (hs-report: 94/973 (9.7%) vs. std-report: 69/964 (7.2%) [HR: 1.37 (1.00-1.89), p=0.047]) and when confined to patients with troponin levels <30ng/L. This was driven by an increase in early non-coronary representations, and was no longer significant at 12 months. Among patients with a maximal level below 30ng/L, randomization to the high-sensitivity report was associated with a reduction in the primary endpoint at 30 days (hs-report: 1/738 (0.1%) vs. std-report: 9/728 (1.2%), HR: 0.11 [95% C.I. 0.02-0.76], p=0.034), and by 12 months (hs-report: 19/738 (2.6%) vs. std-report: 32/728 (4.4%), HR: 0.58 [95% C.I.0.34-0.10], p=0.05). (Table 4) A modest reduction in the risk of death (hs-report: 7/738 (1.0%) vs. std-report: 17/728 (2.3%), HR: 0.44 [95% C.I.0.17-0.97], p=0.044) remained evident at 12 months, and all of these deaths were adjudicated to be of cardiac cause. Figure 4 shows the Kaplan Meier event curves for the overall population and patients with troponin level <30ng/L within 24 hours.

Figure 4: Kaplan-Meier failure function for: a) overall population and b) patients with troponin level <30ng/L within 24 hours stratified by type of troponin reporting. (ACS: Acute Coronary Syndrome, TnT: Troponin T)





11.5 Discussion

This study is among the first to evaluate the impact of unguided troponin T reporting to levels capable with a high-sensitivity troponin T assay, on clinical care and outcome within a randomised clinical trial embedded within routine emergency department (ED) care. Within this heterogenous study cohort, a substantial number of clinical events are evident by 12 months. Furthermore, clear gradient of increased risk for new or recurrent ACS events and mortality are observed at 30 days and 12 months with increased levels of peak troponin observed within the first 24 hours, even among patients with detectable levels considered within the normal range for the assay studied. However, we observed only modest impact on clinical practice considering the greater degree of information offered by the high sensitivity troponin result, with only minor reduction in the rate of discharge from hospital, and a non-significant increases in hospital admissions and revascularization overall. An increased use of aspirin and statins was seen among patients with a peak troponin within 24 hours of 14-29 ng/L. Nevertheless, a modest reduction in death and recurrent ACS was observed within 30 days and by 12 months, with a reduction in mortality also observed at 12 months. Further realising the promise of greater risk discrimination by informing the better selection of patients for cardiac investigations and treatments through hs-troponin testing may require a commensurate adaptive change of clinical decision-making. Adoption of hs-TnT reporting should be clinically integrated with robust protocols validated in appropriately designed randomised clinical trials.

The proportion of patients within this cohort with an initial troponin level of <15ng/L within 24 hours was 64%, and is comparable to other large-scale population based samples.[4] However, we observed a higher absolute risk of all-cause death and/or recurrent ACS at both 30 days and 12 months than reported in these other studies potentially reflecting differing clinical thresholds for troponin testing in the ED.[4] The gradient of increasing risk of cardiac events that is evident even at levels within the

described reference limits is also consistent with several population-based studies suggesting the potential opportunities for proven cardiac investigation and therapies to improve outcomes if extended to this very large patient population.[20]

Despite the increased interest, reporting of the troponin T level without integration with clinical protocols had a relatively little impact on admission and cardiac investigations, with modest differences in discharge rates among patients at low and intermediate risk based on other clinical criteria. Non-significantly higher rates of coronary angiography and coronary revascularization were seen and an increase in the use of aspirin and statins was observed among the patients with modest peak troponin levels documented within 24 hours. These data are in contrast to a previously reported observational study examining the impact of implementing a troponin I assay with greater sensitivity performance.[21] Potential factors contributing to the discordant results in that observational study include: a greater difference in the information being provided to the clinician resulting from a much greater difference in assay performance between the two troponin I tests assessed; the post–hoc exclusion of patients with an alternate non-cardiac diagnosis; and the impact of secular changes in clinical practice that is difficult to control for when conducting a before and after comparisons of health care innovations.

Given the limited impact on care, the modest reduction in recurrent cardiac events and mortality should be interpreted with caution, especially considering the multiple comparisons and the lack of difference seen for the primary outcome analysis. Nevertheless, subtle differences in practice, particularly among patients with other non-coronary cardiac conditions may account for differences in outcomes observed. The overall higher re-presentation rate for patients receiving hs-TnT testing requires further explanation, and is potentially related to identification of modest elevations in troponin during the index presentation leading to an increase in non-coronary cardiac diagnoses

and subsequent care in addition to the modest differences in pharmacology observed. Knowledge of these diagnoses may influence patient behaviour and outcome after initial presentation highlighting the need for studies of diagnostic testing to evaluate late outcomes beyond the initial diagnostic process. Nevertheless, effective implementation of hs-TnT testing is also likely to require strategies that incorporate better management of patients with non-ischaemic causes of myocardial injury.

The routine use of hs-TnT assays incorporated into protocols of care is currently advocated in ACS guidelines, particularly for identifying patients suitable to early discharge.[3] This study highlights the inertia of clinical decision-making in response to the adoption of new diagnostic and therapeutic innovations. Availability of troponin results with greater diagnostic precision alone did not substantially improve the effectiveness or efficiency of care, particularly among patients with low or no detectable troponin T. The very modest change in practice may reflect many factors including a lack of clinical appreciation of the increased risk for future events associated with low level elevations in troponin, or the lack of mature decision-making and established investigative/management pathways for the care of patients with and without evidence of low grade myocardial injury. Of significance is that hs-TnT assays are yet to be approved by the FDA for routine use in the United States, while HealthPACT (Australian Health Technology Assessment Agency) and the Canadian Agency for Drug and Technologies in Heath currently recommend against routine use as recently as in 2011 and 2013, respectively.[22,23] Recent publications from the National Institute for Health and Care Excellence (NICE) in the UK reinforce these recommendations calling for more research evaluating the true clinical and health service impacts of this diagnostic innovation and the design of clinical protocols to effectively optimise their use.[24] Several non-comparative observational series and small scale randomised feasibility studies have been performed.[25-28] This study suggests the routine use of hs-TnT reporting may be associated with reduced mortality and recurrent ACS. However,

for widespread use of hs-TnT testing in routine practice to be advocated, the incremental gains in clinical effectiveness of new hs-troponin based protocols should be demonstrated within appropriately designed randomised clinical trials, as called for in international guidelines.[3]

11.6 Conclusion

High-sensitivity troponin provides useful risk information, but routine reporting without integration within protocols is associated with only modest changes in practice. Nevertheless, beyond the diagnostic process, routine use may improve late outcomes. Adoption of high-sensitivity troponin testing is likely to require coupling with management protocols that guide interpretation and care if the benefits of greater diagnostic discrimination are to be harnessed. Such protocols should be validated in comparative clinical trials.

11.7 Acknowledgements and disclosures

Author Responsibility

All Authors were involved with the study design and implementation. DPC and MH were responsible for the data collection and analysis. The initial draft of the manuscript was written by DPC and reviewed by each of the authors. DPC had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis. The authors have no conflicts to declare.

Sources of Funding

This study was supported by the National Health & Medical Research Council of Australia (Grant number APP1024008) and the South Australian Department of Health.

Acknowledgement

The authors would like to thank Marleesa Ly for her editorial support.

11.8 References

1. Chew DP, Aroney CN, Aylward PE, Kelly A-M, White HD, Tideman PA, Waddell J, Azadi L, Wilson AJ, Ruta L-AM. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart Lung Circ. 2011;20:487–502.

2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2354–2394.

3. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GYH, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European Heart Journal. 2016;37:267–315.

4. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Cardiol. 2014;63:2569–2578.

5. Heeschen C, Hamm C, Goldmann B, Deu A, Langenbrink L, White H. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. Lancet. 1999;354:1757–1762.

6. Morrow DA, Cannon CP, Rifai N, Frey MJ, Vicari R, Lakkis N, Robertson DH, Hille DA, DeLucca PT, DiBattiste PM, Demopoulos LA, Weintraub WS, Braunwald E, TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomised trial. JAMA. 2001;286:2405–2412.

7. Newby L, Ohman E, Christenson R, Moliterno D, Harrington R, White H, Armstrong P, de Werf Van F, Pfisterer M, Hasselblad V, Califf R, Topol E. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin t-positive status: the paragon-B troponin T substudy. 2001;103:2891–2896.

8. Apple FS, Collinson PO, for the IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays. Clin Chem. 2011;58:54–61.

9. Apple F, Wu A. Myocardial infarction redefined: role of cardiac troponin testing. Clin Chem. 2001;47:377–379.

10. Apple FS. A New Season for Cardiac Troponin Assays: It's Time to Keep a Scorecard. Clin Chem. 2009;55:1303–1306.

11. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009;361:858–867.

12. Januzzi JL, Bamberg F, Lee H, Truong QA, Nichols JH, Karakas M, Mohammed AA, Schlett CL, Nagurney JT, Hoffmann U, Koenig W. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. Circulation. 2010;121:1227–1234.

13. Diamond GA, Kaul S. How would the Reverend Bayes interpret high-sensitivity troponin? Circulation. 2010;121:1172–1175.

14. Astley CM, Beltrame JF, Zeitz C, Worthley M, Coates P, Murray A, Arstall M, Grantham H, Dunn R, Quinn S, Aylward PE, Chew DP. Study design of embracing high-sensitivity troponin effectively: the value of more information: a

randomised comparison. Contemporary Clinical Trials. 2014;39:183–190.

15. Aroney C, Aylward P, Kelly A, Chew D, Clune E. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. Medical Journal of Australia. 2006;184:S1–S35.

16. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf Van F, Avezum A, Goodman SG, Flather MD, Anderson FA, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091–1091.

17. Antman E, Cohen M, Bernink P, McCabe C, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000;284:835–842.

18. Thygesen K, Jaffe AS, Simoons ML, White HD, Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction, Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, Biomarker Subcommittee, Katus HA, Apple FS, Lindahl B, Morrow DA, ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Imaging Subcommittee, Underwood R, Bonow JJ, Pinto F, Gibbons RJ, Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Morais J, Aguiar C, AlMahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, et al. Third universal

definition of myocardial infarction. J Am Coll Cardiol. 2012 Oct 16;60(16):1581-98.

19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardised bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.

20. Chew DP, Briffa TG, Alhammad NJ, Horsfall M, Zhou J, Lou PW, Coates P, Scott I, Brieger D, Quinn SJ, French J. High sensitivity-troponin elevation secondary to non-coronary diagnoses and death and recurrent myocardial infarction: An examination against criteria of causality. Eur Heart J Acute Cardiovasc Care. 2015;4(5):419-28

21. Mills NL, Churchhouse AMD, Lee KK, Anand A, Gamble D, Shah ASV, Paterson E, MacLeod M, Graham C, Walker S, Denvir MA, Fox KAA, Newby DE. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. JAMA. 2011, 305(12):1210-6.

22. Forel D. Technology Brief: High sensitivity troponin assays for the diagnosis of myocardial infarction (version 1.0). Brisbane, Queensland: Health Policy Advisory Committee on Technology Australia and New Zealand; August 2012. WP042 (V1.0), pages1-13

23. Recommendations for the Use of Troponin Assays for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department. Canadian Agency for Drugs and Technologies in Health. March 2013. Volume 2 Issue 1B: 1-10. ISSN: 1927-0127

24. Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays): NICE Diagnostic Guidance (DG15). UK Diagnostic Advisory Committee NICE. 2014:1–53. ISBN: 978-1-4731-0776-2

25. Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, Aldous S, Meller B, Tate JR, Reichlin T, Hammett CJ, Zellweger C, Ungerer JPJ,

Rubini Gimenez M, Troughton R, Murray K, Brown AFT, Mueller M, George P, Mosimann T, Flaws DF, Reiter M, Lamanna A, Haaf P, Pemberton CJ, Richards AM, Chu K, Reid CM, Peacock WF, Jaffe AS, Florkowski C, Deely JM, Than M. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol*. 2013;62:1242–1249.

26. Than M, Aldous S, Lord SJ, Goodacre S, Frampton CMA, Troughton R, George P, Florkowski CM, Ardagh M, Smyth D, Jardine DL, Peacock WF, Young J, Hamilton G, Deely JM, Cullen L, Richards AM. A 2-Hour Diagnostic Protocol for Possible Cardiac Chest Pain in the Emergency Department. *JAMA Intern Med*. 2014;174:51-8.

27. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, Moehring B, Ziller R, Hoeller R, Rubini Gimenez M, Haaf P, Potocki M, Wildi K, Balmelli C, Freese M, Stelzig C, Freidank H, Osswald S, Mueller C. One-Hour Rule-out and Rule-in of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T. *Archives of Internal Medicine*. 2012;172:1211–1218.

28. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, Lewis PS, Smith A, Mackway-Jones K. The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. Heart. 2014 Sep 15;100(18):1462-8

SECTION 4: WHAT ROLE DOES THE DESIGN OF HEALTH SERVICES CONTRIBUTE TO CLINICAL OUTCOMES IN ACS CARE

12 LOST IN TRANSLATION: HEALTH RESOURCE VARIABILITY IN THE ACHIEVEMENT OF OPTIMAL PERFORMANCE AND CLINICAL OUTCOME

12.0 Title page: Lost In Translation: Health Resource Variability In The Achievement Of Optimal Performance And Clinical Outcome.

Authors

1. Ms Carolyn Astley RN, BN(Hons), DrPH candidate, Flinders Medical Centre/ Flinders University, South Australia, Australia

2. Associate Professor Colin MacDougall BA(Hons), MA, PhD, Discipline of Public Health and Southgate Institute for Health, Society and Equity, Flinders University, South Australia, Australia

3. Professor Patricia Davidson, RN, BA, MEd. PhD, Centre for Cardiovascular Chronic care, University of Technology, Sydney, New South Wales, Australia

4. Professor Derek Chew MBBS, MPH, Flinders Medical Centre/ Flinders University, South Australia, Australia

Subject heads: acute coronary syndromes, epidemiology, information technology, health policy and outcomes research.

Correspondence:
Department Cardiology,
Flinders Medical Centre,
Level 6, FPH
1 Flinders Dve.,
Bedford Park, Adelaide,
SA 5042, AUSTRALIA
Ph. +61 8 8204 5667.
Fax. +61 8 8204 5000

12.1 Abstract

Background: An evidence-practice gap in acute coronary syndromes (ACS) is commonly recognised. System, provider and patient factors can influence guideline adherence. Through using guideline facilitators in the clinical setting the uptake of evidence-based recommendations may be increased. We hypothesised that facilitators of guideline recommendations (systems, tools and workforce) in acute cardiac care, were associated with increased guideline adherence and decreased adverse outcome.

Methods and results: A cross-sectional evaluation of guideline facilitators was conducted in Australian hospitals. The population was derived from the Acute Coronary Syndrome Prospective Audit (ACACIA) and assessed performance, death and recurrent myocardial infarction (death/re-MI) at 30-days and 12-months.

Thirty five hospitals and 2,392 patients participated. Significant associations with decreased death/re-MI were observed with: *hospital strategies* to facilitate primary percutaneous coronary intervention for ST-elevation MI patients, (38/428 [8.9%] vs. 30/154 [19.5%], p <0.001) and after adjustment, (OR 0.47 [95% CI; 0.24-0.90-], p < 0.023), *electronic discharge checklists* (none; 233/1,956 [11.9%], integrated; 43/251[17.1%], p=0.069, electronic; 6/124[4.8%], p < 0.001) and after adjustment, (integrated vs. none; OR 1.66 [95% CI; 0.98-2.80], p=0.057 and electronic vs. none: OR 0.49 [95% CI; 0.35-0.68], p < 0.001) and *intensive cardiac care(ICCU) staff* to patient ratios, (neither: 200 /1,257 (15.9%), CCU: 135/1,051 (12.8%), ICCU: 8/84 (9.5%), p= 0.049 and after adjustment, (CCU vs. neither, OR 0.74; [95% CI, 0.47-1.14], p = 0.172 and ICCU vs. neither, OR 0.55; [95% CI, 0.38-0.81], p= 0.003).

Conclusion: Facilitating uptake of evidence in clinical practice may need to consider quality improvement systems, tools and workforce to achieve optimal ACS outcomes.

252 words

Key words: acute cardiac care, acute coronary syndromes, guideline adherence, knowledge translation, quality improvement

12.2 Introduction

Implementation of evidence-based guidelines can improve clinical outcomes in acute coronary syndrome (ACS) care yet adherence with recommendations is often sub-optimal. [1-3] Professional organizations in the United States have developed systems and tools to increase the uptake of guideline-based care and have shown variable increases in optimal outcomes.[4,5] This variability may be explained by local health service characteristics including geographical location, resources and workforce capacity. [1, 2, 6, 7] In Australia, with a population of approximately 22 million, concentrated in coastal cities, health disparities exist for individuals living in rural and remote locations despite a universal health insurance system.[8,9,10]

Understanding health service characteristics that may facilitate evidence translation is an important issue to consider in the clinical practice environment and may be associated with outcomes. Six specific hospital strategies *(Table 1)* have been shown to facilitate primary percutaneous coronary intervention (PPCI) and increased rates of survival of patients with ST-segment elevation myocardial infarction (STEMI).[4,11] Quality improvement (QI) tools including ACS early invasive management algorithms, clinical pathways or discharge checklists and resources, including clinical advocates and financial resources, have been observed to be associated with increased guideline adherence.[6,12] Studies have reported that workforce is an important factor influencing adverse events and mortality. Nurse to patient ratios, hospitalization on a weekend versus a weekday and access to invasive services have been shown to influence outcomes. [7, 13,14] The purpose of this research was to identify factors facilitating guideline adherence in the management of ACS. We hypothesised that guideline facilitators such as quality improvement systems, tools, resources and workforce may be associated with increased guideline adherence, (as measured by

performance indicators for ACS care) and clinical outcomes within the acute cardiac care environment.

12.3 Methods

12.3.1 Study Population and Data collection

We used a cross-sectional objective design to evaluate hospital guideline facilitating factors and corresponding performance and clinical outcome. The study cohort comprised ACS patients derived from the Acute CoronAry syndrome ProspeCtIve Audit (ACACIA) details of which have been described previously.[1] Briefly, the study population comprised 3,402 consenting patients from 39 Australian hospitals representing all states and territories, prospectively and consecutively enrolled between December 2005 and June 2006, with 12 month follow-up in 99.7% of patients.[1] Hospitals were selected based upon the volume of ACS patients and were representative of all states and territories in Australia and of metropolitan (76%), regional (21%) and rural (3%) hospital type. Participant hospitals were a combination of interventional (83%) or non-interventional (17%) centers and 52% had cardiac surgical facilities.[1] Patients were included who were experiencing suspected STEMI or high risk non-ST-segment-elevation ACS as defined by national definitions held by the Australian Institute of Health and Welfare.[15] Patients were excluded if they presented with ACS assessed as secondary to other processes. Ethics committee approval was obtained from each hospital and informed consent from all patients except for those who died before consent was obtained. For these patients, access to medical records was granted by local ethics committees. In the ACACIA registry six and twelve month outcomes were obtained via phone call to the patient. Upon reporting of presentation to another hospital, a discharge summary or International Coding of Disease (ICD) report was requested from that facility. Having failed to contact the patient by the end of the study through a relative, general practitioner or hospital-based administrative systems,

death was ascertained by submission to the Australian Institute of Health and Welfare's National Death Register to confirm vital status and cause of death. Data on non-fatal outcomes were centrally adjudicated by trained physicians in an objective process using discharge summaries and ICD reports. The final diagnosis at discharge of either; STEMI, non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina, as determined by the enrolling site, was confirmed by central adjudication of electrocardiograms and biomarkers using accepted definitions.[16] This analysis was confined to patients with a final diagnosis of ACS (n= 2559), regardless of survival status. Specifically events occurring among patients dying within the index hospitalization were included in the cumulative 30-day and 12-month outcomes.

We invited all hospitals that had previously participated in the ACACIA registry, to participate in an evaluation of guideline facilitating factors. The head of department determined the required ethical and clinical governance approval. Subsequent to appropriate approval, a nominated liaison person, either the head nurse or doctor of the unit, provided information regarding the guideline facilitators that existed in their specific cardiac unit for the period of enrollment in the ACACIA registry. During the ACACIA registry, hospital sites were not given any feedback on performance and outcome audit data until the end of the study, thus limiting influence on guideline facilitators during the course of the enrolment period. A uniform method of data collection was applied using site visits or phone calls, conducted by an expert cardiovascular nurse using a standardised protocol *(Table 1).* While questions were directed to the site liaison person regarding the presence of guideline facilitators, the specific purpose of either the site visit or phone call was to collect a paper copy of the QI tool, which was then graded according to pre-determined definitions of guideline facilitators in an objectively assessable process *(Table 2).*

Guideline facilitators are defined in *Table 2* and were derived from the literature and template documents of the Door to Balloon Alliance for Quality, the Can Rapid risk

stratification of UnStable Angina patients Suppress aDverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) and Guidelines Applied in Practice (GAP) QI tool templates and the European Society of Cardiology's Working Group for Acute Cardiac Care.[6,12,17,18] Concordance between site information and definition criteria was achieved by cross-checking the site protocol information with the content criteria taken from the literature, a role performed by the same researcher who conducted the site evaluations. A site algorithm, pathway or checklist had to meet the definition of the tool according to the literature and tool templates and have all variables present in the content.

In the assessment of QI tools, in addition to content evaluation, each tool was classified by how it was deployed within the workflow and coded as 'reference', (information available but not part of the workflow), 'integrated into the workflow', (information available at the point of care) or electronic. To determine levels of workforce, a combination score (nursing full time equivalent, head of department and number of doctors on ward round) was calculated from the information obtained from the site evaluation and compared against the ESC Workforce recommendations in order to code each site as an intensive cardiac care unit (ICCU), cardiac care unit (CCU) or neither.[18]

Table 1. Standardised questions for evaluation of QI systems, tools, resources and workforce

Evaluation questions for quality improvement systems, tools and resources
• Can you explain your process for treating STEMIs?
• Did you have a protocol in place for in-hospital management for nursing and medical care?
• What was the discharge process to ensure patients received appropriate therapies?
• What resources (aliquot of money or personnel role) did you have for QI activities? Was someone designated to be a clinical cardiology advocate who reviews, disseminates and propose new QI initiatives?
Evaluation questions for workforces characteristics
• How many beds in the unit, what was the nursing full time equivalent for this number of beds?
• What was the % of nurses with postgraduate cardiac training?
• Does the unit have a cardiologist as head of department?
• What was the number of consultants/ registrars/resident medical officers on weekday ward round?
• What type of roster did the consultants work?
• How many and what level of doctor was available if a patient went into cardiogenic shock at 2pm and 2am on a weekday?
• What was the number of consultants/ registrars/resident medical officers on weekend ward round?
• How many and what level of doctor was available if a patient went into cardiogenic shock at 2pm and 2am on a weekend?

Table 2. Definitions of guideline facilitating factors*

Guideline facilitating factor	Definition	Evaluation content
Hospital strategies for reducing door to balloon time [4]	• Emergency medicine physician activates the cardiac catheterization laboratory(CCL) • A single call to a central page operator activates the CCL • Emergency department(ED) activate CCL while patient is en route to hospital • Expectation that CCL staff arrive within 20-30 minutes of page • Attending cardiologist always on site • Staff in ED and CCL use real-time data feedback.	• Recorded as present or absent
Risk stratification tool [16]	assists with risk-based decision making at admission according to ACS guidelines.	• Symptoms, ECG, biomarkers co-morbid risk, classifies as high, intermediate or low risk NSTEACS. • Provides recommended management pathway based upon the acquired information.
Early invasive management algorithm [6]	recommends urgent angiography within 24-48 hours for high risk NSTEACS patients.	• Criteria: elevated biomarkers, ST deviation, recurrent ischemia ± heart failure, haemodynamic instability, positive noninvasive stress test, PCI within the past 6 months, prior CABG, left ventricular dysfunction, sustained VT

		• Admission: aspirin, heparin, glycoprotein IIb/IIIa receptor blockers, clopidogrel • Discharge: aspirin, clopidogrel or combination, beta blocker, lipid lowering agents, ACE/ARB inhibition.
Clinical pathway [12]	identifies in-hospital therapeutic, educational and rehabilitation milestones divided by time periods (1st 24 hours, next 24 hrs and discharge).	• Diagnostic tests, reperfusion and interventional procedures, pharmacological therapies, • Counseling, education, physical activity.
Discharge checklist [6]	a reminder tool for prescription of guideline therapies at discharge, which requires verification by a medical officer.	• Recommends aspirin, clopidogrel, beta blocker, ACE/ARB inhibition and lipid lowering agents • Dietary targets, where to seek advice for smoking cessation and exercise and physician appointment.
Clinical cardiology co-advocate [6]	a clinician leader who reviews, disseminates and proposes new quality improvement initiatives.	• Recorded as present or absent
Financial resource [6]	a staff position or quantum of money for QI initiatives.	• Recorded as present or absent
Workforce capacity: recommendations of the Taskforce of the European Society of Cardiology Working	<u>Intensive care unit (ICCU)</u> Nurses: 2.8 nurses/bed Physicians: < than 6 beds: 1:3, > than 6 beds: 1:4.	• Classified based on self-reported staffing levels • All taskforce criteria need to be met • Physician capacity determined by medical officer attendance at

group on acute cardiac care.[18]	Intermediate cardiac care unit (CCU) Nurses: 1.8 nurses/bed Physicians: < than 12 beds: 1:6, > than 12 beds: 1:8.	weekday and weekend decision-making ward rounds.

*PCI: percutaneous coronary intervention, CABG: coronary artery bypass surgery, VT: ventricular tachycardia, ACE/ARB inhibition: angiotensin converting enzyme inhibitor/angiotensin receptor blocker

12.3.2 Outcome

The primary outcome for this study was the combined clinical events of death and recurrent myocardial infarction (death/re-MI). Death was defined as death from any cause at any time during the study period. Recurrent MI was defined as a further > 25% rise and/or > 50% rise in the Troponin (I or T) and CK-MB respectively, 24 hrs after admission. Following PCI and coronary artery bypass graft (CABG) surgery, a level of CKMB > 3 times and > 5 times the upper limit of normal within 48 hours or new Q-waves were used respectively.[1] These outcomes were assessed at 30-days and 12-months.

The secondary outcome for this study was guideline adherence as measured by the performance indicators of door-to-balloon time, invasive management and prescription of discharge guideline therapies. Door to balloon time (DTBT) was defined as time from hospital presentation to first balloon inflation in a PPCI procedure.[4] Invasive management was defined as cardiac catheterization within 48 hours of hospital presentation.[1] Guideline medications were defined as the number prescribed at the time of discharge, unless a stated contraindication, including antiplatelet (aspirin, thienopyridine), angiotensin converting enzyme (ACE) inhibition/angiotensin receptor (AR) - antagonists, beta blockers and statin therapies among patients discharged alive.[1]

12.3.3 Statistical analysis

The prevalence of guideline facilitators are described as counts (%). The proportion of patients with a DTBT of ≤ 90 minutes, receiving early invasive management and 4 or more guideline therapies by the presence or absence of each guideline facilitator were compared by chi-square test. For assessment of patient outcome variability across sites, we measured 6-month mortality from the ACACIA registry compared with the

predicted site specific median Global Registry of Acute Coronary Events (GRACE) risk score for death/re-MI at 6-months.[19] GRACE score variables included age, heart rate, systolic blood pressure, serum creatinine, heart failure Killip Class, cardiac arrest at admission, ST-Segment deviation, elevated cardiac enzymes at both admission and discharge as well as past history of MI and in-hospital PCI or CABG.[19]

To account for baseline patient risk, the availability of hospital services and the multi-center nature of the patient sample, adjusted analyses including the GRACE risk score, the presence of onsite angiography, interventional cardiology and cardiac surgical services were undertaken using logistic regression clustered by hospital, therefore using standard error estimates that allow for intra-hospital correlation.[19] The interaction between workforce characteristics and the presence of quality improvement tools were also assessed in these models. The workforce analysis was restricted to metropolitan hospitals with all coronary revascularisation services, staffing levels for intensive cardiac care unit (ICCU) criteria *(Table 2),* with adjustment for staffing levels by patient risk profile.

Using the known baseline rate of early invasive management of 70%, a median level of guideline facilitator use of 3.9 out of 5, a prevalence of QI tools of approximately 50% and a total sample size of 2,392, this study had a 90% power to detect a difference of at least 6% in the rate of early invasive management use and at least a 0.15 change in mean number of guideline therapies and 80% power to detect a 5% or more difference in 12-month death/re-MI among patients treated in hospitals with or without guideline facilitators. A multivariable logistic regression statistical model was used. All analyses were conducted with STATA 10.1 (College station, TX) and a probability level of <0.05 was considered to be statistically significant.

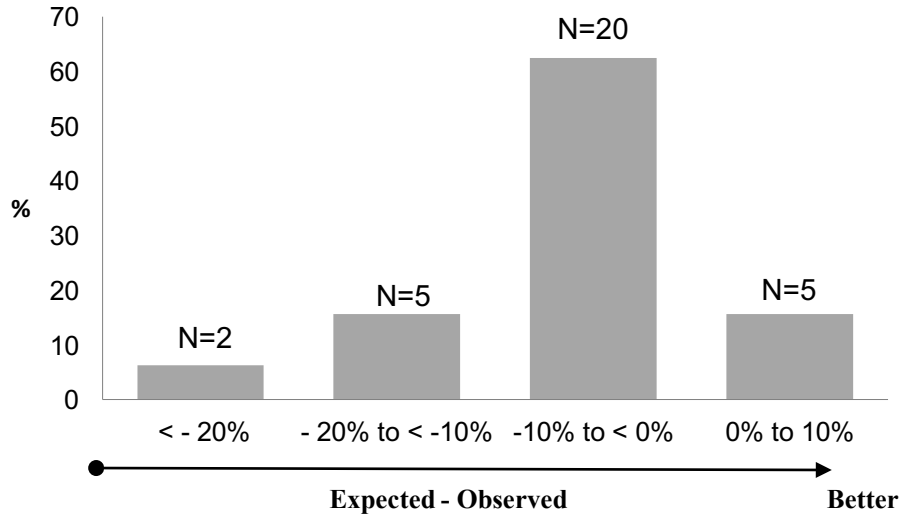
12.4 Results

Of the 39 Australian hospitals that participated in the ACACIA registry and were invited to participate in this study, 35 (90%) accepted. There were 26 (74%) metropolitan hospitals and 9 (26%) rural/regional hospitals and details of hospital characteristics are presented in *Table 3.* Of the four hospitals that did not participate, two declined due to lack of staff members who could determine what tools and resources were available during the study time period, two did not reply to follow-up phone calls and all four were of regional hospital type. Of the 2,559 ACACIA patients with a final discharge diagnosis of STEMI, NSTEMI or Unstable Angina, 2,392 patients were included in this analysis from participating sites.

12.4.1 Patient outcome variability

For each participating hospital we measured the median expected rate of 6-month death/re-MI by GRACE score minus the observed rate of 6-month death/re-MI from the ACACIA registry *(Figure 1).* Thus a negative range represents actual observed event rates that are higher than the expected rate, based upon patient risk characteristics. This assessment observed substantial variability, with the majority of hospital sites displaying higher observed event rates than expected *(Figure 1*).

Figure 1. Proportion of hospitals with expected minus observed rates of 6-month death and recurrent myocardial infarction by GRACE score.



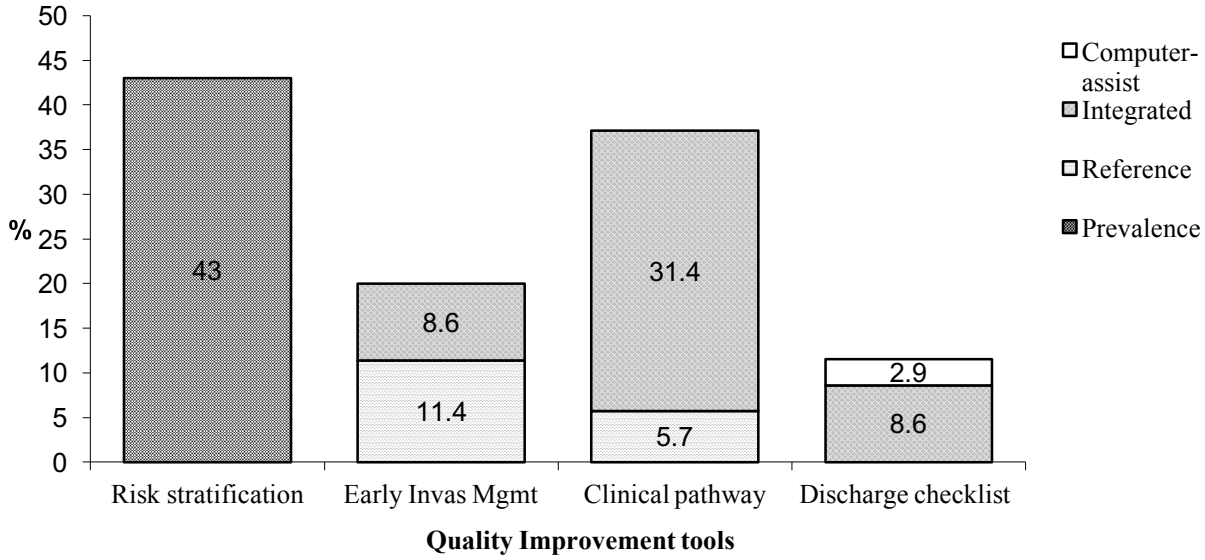
12.4.2 Quality improvement systems

Only 20 (57.1%) hospitals had at least 1 of the 6 assessed hospital strategies to facilitate PPCI for STEMI patients and 3 was the maximum at a single hospital. The presence of strategies were associated with a lower but non-significant door to balloon time, (median minutes, interquartile range: present, 100.5 (82.9, 143.0) vs. not present, 121 (87.9, 168.9), p= 0.071). Among patients treated in a hospital with any strategies, there was a significantly decreased rate of death/re-MI at 30-days (38/428 (8.9%) vs. 30/154 (19.5%), p < 0.001) and 12-months (55/428 (12.8%) vs 34/154 (22.1%), p = 0.006), which persisted at 30 days after adjusting for patient risk and the presence of invasive facilities within the presenting hospital, (30-days: odds ratio (OR) 0.47 [95% confidence interval (CI); 0.24-0.90], p = 0.023 and 12-months: OR 0.59 [95% CI;0.34-1.05], p = 0.076).

12.4.3 Quality improvement tools

The prevalence of QI tools and the way they were deployed in the workflow are described in *Figure 2*. Only 19 (54%) hospitals had at least 1 of the 4 assessed QI tools and 3 was the maximum at a single hospital.

Figure 2. Prevalence and deployment of quality improvement tools.



The presence of a *risk stratification tool (Table 2)* was associated with significantly lower rates of angiography, (tool 780/1,175 (66.4%) vs. no tool 885/1,217 (72.7%), p = 0.001) but not prescription of discharge guideline therapies (4 or more guideline therapies; tool 815/1,175 (69.4%) vs. no tool 852/1,217(70.0%), p= 0.172). Among patients treated in a hospital with a risk stratification tool, there were significantly higher rates of 12-month death/re-MI but after adjustment this was no longer significant (tool vs. no tool: OR 1.33; [95% CI, 0.89-2.00], p = 0.155) (*Table 4)*.

The presence of an *early invasive management algorithm (EIMA) (Table 2)* was significantly associated with lower rates of angiography, (tool 421/633 (66.5%) vs. no tool 1,244/1,759 (70.7%), p = 0.048) but not prescription of discharge guideline

therapies, (4 or more guideline therapies; tool 452/633 (71.4%) vs. no tool 1215/1,759 (69.0%) p= 0.718). Among patients treated in a hospital with an EIMA, there was no association with 30-day and 12-month death/re-MI *(Table 4*) nor in the way tools were deployed in the workflow *(Table 5).*

The presence of a *clinical pathway (Table 2)* observed no association with rates of angiography, (tool 701/989 (70.9%) vs. no tool 964/1,403 (68.7%), p= 0.256) or with prescription of discharge guideline therapies, (4 or more guideline therapies; tool 667/989 (67.4%) vs. no tool 1000/1403 (71.2%), p= 0.110). Among patients who were treated in a hospital with a clinical pathway there was no association with 30-day or 12-month death/re-MI *(Table 4),* nor in the way tools were deployed in the workflow (*Table 5).*

The presence of a *discharge checklist (Table 2)* was not associated with prescription rates of discharge guideline therapies, (4 or more guideline therapies; tool 262/375 (69.9%) vs. no tool 1403/1956 (71.7%), p= 0.631). However at one site, which had an electronic discharge checklist, we observed a non-statistically significant increased rate of prescription of discharge guideline therapies (4 or more guideline therapies; electronic 91/124 (73.4%) vs. non-electronic 1647/2372(69.4%), p=0.351). Among patients that were treated in a hospital with a discharge checklist and discharged alive, there was no association with 30-day or 12-month death/re-MI *(Table 4).* However in the same hospital with an electronic discharge checklist, deployment of such a tool showed a significantly lower rate of 12-month death/re-MI *(Table 5)*,which persisted after adjustment at 30-days, (integrated vs. none; OR 1.46 [95% CI; 0.95-2.23], p=0.078 and electronic vs. none; OR 0.57 [95% CI; 0.40-0.79], p 0.001) and 12-months, (integrated vs. none; OR 1.66 [95% CI; 0.98-2.80], p=0.057 and electronic vs. none; OR 0.49 [95% CI; 0.35-0.68], p < 0.001).

Table 3. Cardiac services in metropolitan and regional/rural hospitals*

Hospital services	Metropolitan (n = 26)	Regional/rural (n= 9)	Total (N= 35)
†Cathlab only	1	2	3
Angioplasty services	5	1	6
Cardio-thoracic surgery	15	3	18
†ACS presentations/year	700 (550-1000)	334 (186-560)	600 (400-800)
Staff cardiologist/physicians	10 (8-14)	3.5 (1-8)	8 (6-13)
Angiography laboratories	2 (1-2)	5 (0-1)	2 (1-2)
Angiograms per year``	1600 (900-2200)	0 (0-1200)	1250 (140-2000)
Interventional cardiologists	5 (4-6)	0 (0-2)	4
Interventions /year	531 (444-794)	0 (0-300)	437 (0-600)
Surgeons	2 (0-3)	0 (0-5)	1(0-3)
†CCU beds	10 (8-14)	7 (5-8)	8.5 (6-12)

*Values are expressed as median, interquartile range (i.q.r.).

†Cathlab indicates cardiac catheterisation laboratory; ACS, acute coronary syndrome; CCU, cardiac care unit

Table 4. Quality improvement tools and 30-day and 12-month death/re-MI*[*]

QI tools		Tool	No Tool	P value
Risk stratification				
	30 day death/re-MI	115/1,175 (9.8)	94/1217 (7.7)	0.074
	12-mth death/re-MI	193/1,175 (16.4)	150/1,217 (12.3)	0.004
Early invas. mgmt alg.				
	30 day death/re-MI	47/633 (7.4)	162/1,759 (9.2)	0.173
	12-mth death/re-MI	87/633 (13.7)	256/1,759 (14.5)	0.618
Clinical pathway				
	30 day death/re-MI	90/989 (9.1)	119/1,403 (8.5)	0.598
	12-mth death/re-MI	144/989 (14.6)	199/1,403 (14.2)	0.796
Discharge checklist				
	30 day death/re-MI	26/375(6.9)	123/1,956 (6.3)	0.640
	12-mth death/re-MI	49/375(13.1)	233/1,956 (11.9)	0.530

[*]Death/re-MI, indicates combined endpoint of death and recurrent myocardial infarction.

Unadjusted values are expressed as n/N (%)

Table 5. Deployment of quality improvement tools and 30-day and 12-month death/re-MI[*]

Quality improvement tool	None n/N (%)	Reference n/N (%)	P value, reference versus none	Integrated n/N (%)	P value, integrated versus none	Electronic n/N (%)	P value, electronic versus none
Early invas mgmt.alg.							
30-day death/re-MI	162/1,759 (9.2)	24/373 (6.4)	0.019	23/260 (8.8)	0.880	-	
12-mth death/re-MI	256/1,759 (14.5)	50/373 (13.4)	0.741	37/260 (14.2)	0.952	-	
Clinical pathway							
30-day death/re-MI	119/1,403 (8.5)	15/137 (10.9)	0.354	75/852 (8.8)	0.956	-	
12-mth death/re-MI	199/1,403 (14.2)	19/137 (13.9)	0.899	125/852 (14.7)	0.874	-	
Discharge checklist							
30-day death/re-MI	123/1,956 (6.3)	-		22/251 (8.8)	0.037	4/124 (3.2)	< 0.001
12-mth death/re-MI	233/1,956 (11.9)	-		43/251 (17.1)	0.069	6/124 (4.8)	< 0.001

[*]Death/re-MI indicates combined endpoint of death and recurrent myocardial infarction.

Unadjusted values are expressed as n/N (%).

Table 6. Quality improvement resources and 30-day and 12-month death/re-MI[*]

QI resource	Present	Not present	P value	Adjusted OR[†] (95% CI)	P value
Clinical advocate					
30-day death/re-MI	60/727(8.2)	149/1,665(8.9)	0.579	0.86 (0.54-1.36)	0.524
12-mth death/re-MI	96/727(13.2)	247/1,665(14.8)	0.295	0.80 (0.48-1.33)	0.400
Financial resource					
30-day death/re-MI	70/751(9.3)	139/1,641 (8.5)	0.494	0.99 (0.65-1.50)	0.979
12-mth death/re-MI	104/751(13.8)	239/1,641(14.6)	0.643	0.83 (0.54-1.28)	0.417

[*]Death/re-MI indicates combined endpoint of death and recurrent myocardial infarction.

Unadjusted values are expressed as n/N (%).

[†]Adjusted values are expressed as odds ratio (OR) and 95% confidence intervals (CI). Adjustment covariates include admission GRACE risk score and the presence of invasive services in the presenting hospital.

12.4.4 Quality improvement resources

Eleven (31.4%) hospitals had a QI resource, either as a *clinical advocate (Table 2)* [9 (26.0%)] or a *financial resource (Table 2)* [9 (26.0%)] and 7 (20.0%) hospitals had both. The presence of a *clinical advocate* was not associated with rates of angiography, (present 503/727 (69.2%) vs. not present 1,162/1,665 (69.8%), p= 0.769) or prescription of discharge guideline therapies, (4 or more guideline therapies; present 487/727(67.0%) vs. not present 1180/1665(70.9%), p= 0.115). Among patients treated in a hospital with a clinical advocate there was no association with 30-day and 12-month death/re-MI *(Table 6).*

The presence of a *financial resource* was not associated with rates of angiography, (present 515/751 (68.6%) vs. not present 1,150/1,641 (70.1%), p= 0.458) but was significantly associated with lower of discharge guideline therapies, (4 guideline therapies; present 516/751 (68.7%) vs. not present 1151/1641 (70.1%) p= 0.042). Among patients treated in a hospital with a financial resource there was a non-significant, decreased rate of 12-month death/re-MI *(Table 6).*

12.4.5 Workforce capacity

Among hospitals that qualified to be either an *intensive cardiac care unit* (*ICCU*) or *intermediate cardiac care unit (CCU) (Table 2)* there was no association with rates of angiography, (neither: 807 /1,133 (71.2%), CCU: 802/1,175 (68.3%), ICCU: 56/84 (66.7%), p= 0.251), or prescription of discharge guideline therapies, (4 or more guideline therapies; neither: 771/1,133 (68.0%), CCU: 837/1,175 (71.2%), ICCU:59/84 (70.2%), p= 0.733) either on weekdays or weekends.

Among patients who were treated in hospitals that qualified to be either an ICCU or CCU there was a significant association with decreased rates of 30-day death/re-MI on a weekend, (neither: 132 /1,257 (10.5%), CCU: 75/1,051 (7.1%), ICCU:

2/84 (2.4%)%, p= 0.002), which persisted after adjustment, (CCU vs. neither, OR 0.71; [95% CI, 0.41-1.23], p= 0.230 and ICCU vs. neither, OR 0.13; [95% CI, 0.05-0.38], p < 0.001). Analysis for patients on weekdays showed a similar relationship *(Table 7).* There were also decreased rates of 12-month death/re-MI for patients on a weekend, (neither: 200 /1,257 (15.9%), CCU: 135/1,051 (12.8%), ICCU: 8/84 (9.5%), p= 0.049), which persisted after adjustment, (CCU vs. neither, OR 0.74; [95% CI, 0.47-1.14], p = 0.172 and ICCU vs. neither, OR 0.55; [95% CI, 0.38-0.81], p= 0.003). Analysis for patients on weekdays showed a similar relationship *(Table 7).*

Among patients treated in a hospital that qualified to be an ICCU, there were also significantly decreased rates of adjusted 30-day and 12-month death/re-MI, when the unit had an early invasive management algorithm (p, < 0.001) or an electronic discharge checklist (p, < 0.001).

We also assessed whether having more guideline facilitators (n= 8) per site were associated with a greater decrease in rates of death/re-MI. As expected, amongst a heterogeneous set of guideline facilitators, there was a non-linear association between number of cumulative facilitators per site and average 6-month death/re-MI.

Table 7. Workforce capacity on weekdays and 30-day and 12-month death/re-MI[*]

Death/re-MI	Neither	CCU	ICCU	P value	CCU adjusted OR[†] (95% CI)	P value	ICCU adjusted OR[†] (95% CI)	P value
30-day								
Weekday	112/1,133(9.9)	95/1,175(8.1)	2/84(2.4)	0.034	0.7 (0.45-1.24)	0.264	0.13 (0.05-0.38)	< 0.001
12-month								
Weekday	169/1,133(14.9)	166/1,175(14.1)	8/84(9.5)	0.380	0.8 (0.51-1.31)	0.414	0.58 (0.38-0.88)	0.011

[*]Death/re-MI indicates combined endpoint of death and recurrent myocardial infarction.

Unadjusted values are expressed as n/N (%).

[†]Adjusted values are expressed as odds ratio (OR) and 95% confidence intervals (CI). Adjustment covariates include admission GRACE risk score and the presence of invasive services in the presenting hospital.

12.5 Discussion

In an audit of Australian hospitals from the ACACIA registry we found considerable variation and greater rates of observed versus expected death and recurrent MI in the majority of hospitals. There were significant associations with decreased rates of 30-day and 12-month death/re-MI when patients were cared for in a unit that had; a) specific hospital strategies to facilitate PPCI, b) an electronic discharge checklist, c) ICCU levels of medical and nursing staff and d) both ICCU levels of staffing and the deployment of a QI tool. Quality improvement tools and resources were not prevalent and when they were, generally not significantly associated with performance or clinical outcome. These observations have implications for the design of health systems that are more able to translate the ACS evidence-base into clinical practice and outcome.

12.5.1 Quality Improvement systems

Bradley and colleagues[4] identified 6 specific hospital strategies and measured the degree to which they decreased DTBT. Of the 6, a cardiac catheterization laboratory team that arrives within 20-30 minutes of being paged produced the greatest decrease (19.3 minutes, p= 0.002).[4] In our study, this strategy was the most prevalent 19 (54.2%) as well as 20 (57%) hospitals with at least one strategy and only 3 (8.6%) with a maximum of 3 strategies. Importantly however we observed a 54% and 42% decrease in relative risk in 30-day and 12-month death/re-MI respectively. Though we lacked statistical power to see small differences, this highlights the importance of validating QI interventions by measuring both performance indicators and clinical outcomes and sharing the successful results. Quality improvement collaboratives such as the Door-to-Balloon Alliance have formed a network to share tools, resources and data reporting.[17]

12.5.2 Quality improvement tools and resources

Prior studies such as GAP and CRUSADE observed increased rates of performance indicators with QI tool use and resources when a standardised QI intervention was implemented and supported by resourced local project leaders who monitored and encouraged QI tool use.[6, 12] Our research expanded this work by studying what already existed in the clinical setting in the absence of a structured QI program and found a non-standardised collection of systems and tools and included measurement of clinical as well as performance indicator outcomes.

In our study QI tools were heterogeneous in content and application and observed no association with clinical outcome with the exception of an electronic discharge checklist. In fact, given the increased rates of death and recurrent MI observed at 12 months associated with some un-validated risk stratification tool deployment *(Table 4),* an increase in risk associated with tools cannot be excluded in this relatively small sample size. Such observations argue for the prospective and ongoing validation of QI tools across the spectrum of hospital performance characteristics to ensure a positive impact on poor performing hospitals without a concurrent negative impact on well-performing hospitals.

We also observed a non-significant association with decreased rates of 30-day and 12-month death/re-MI in the presence of a financial resource. Hospitals face significant challenges in implementing quality initiatives, developing sustainable processes and identifying an operational framework for successful implementation.[20] Quality improvement resources such as personnel, clinical advocates and funding allocations are needed to assist with these challenges; however their value needs to be validated.

12.5.3 Workforce capacity

Whilst prior literature shows that there are decreased rates of mortality and adverse events when nurse to patient ratios are high, [7,13] we included medical staff in the

evaluation of workforce capacity. Furthermore Kostis and colleagues [14] found higher mortality rates in patients with MI admitted on the weekend, suggesting more appropriate staffing and access to invasive services are needed. Our study results observed that clinical outcome is associated with ICCU levels of nursing and medical workforce, however in resource-constrained health systems the problems of an affordable but expert workforce with adequate staff to patient ratios makes it difficult to ensure patients presenting to health services across all environments, receive optimal care. Our study also observed a clinical association when a unit had both ICCU level workforce capacity and a QI tool deployed, which has implications for the development of quality improvement initiatives.

12.5.4 Clinical decision support systems

The observation that an electronic decision support tool deployed at discharge was associated with decreased rates of adverse outcome highlights the potential role of electronic systems in increasing expert capacity at the point of care. A systematic review by Kawamoto and colleagues[21] found that the key to a successful and sustainable clinical decision support system (CDSS) is that it must minimise the effort required by clinicians to receive and act on system recommendations. The four key features of CDSS critical for improving clinical practice are that it is automatically part of clinical workflow, available at the time and location of the decision-making, provides an individual recommendation and is electronic.[21] Our study found clinical association with the use of an electronic discharge checklist with the knowledge that this tool was integrated into the workflow consistent with Kawamoto's four successful CDSS features (Thomson D, unpublished data, 2009).[21]

12.5.5 Next steps

Building on the existing literature, these observations suggest that the optimal translation of ACS evidence may depend on health service capacity including guideline

facilitators such as QI systems and tools, workforce and expertise. This is supported by the observed association between decreased rates of adverse outcomes and quality improvement tools in the presence of greater workforce capability. Further, despite the importance of workforce on health, this has had scant attention in cardiology settings. Decision support systems offering guideline recommendations in the workflow, measuring performance and outcome and delivering feedback are not commonly available in the clinical environment. Increasing the capability for rapid, risk-based decision making at the point of care could be achieved with an ACS electronic clinical decision support tool and may have relevance in the developing world and in societies that are geographically challenged.[22]

Although such tools have the potential to bring best practice care to the clinician irrespective of their practice location and level of expertise or workforce capacity, it is necessary to conduct objective validation, including cost effectiveness. Large-scale attempts to validate the comparative effectiveness of such interventions have several benefits; first it may help address discrepancies in care identified in registries by providing guideline recommendations at the point of care. Second, it can provide a prospective real-time platform which automatically feeds data into collaborative registries. Third, it could increase equity of outcome by supporting the potential for more patients to receive best practice care. Fourth, it could provide a potentially cost-effective infrastructure as an alternative to the costly problem of providing an expert and adequately staffed workforce across the full diversity of health services.[22]

12.5.6 Limitations

There are several limitations to our study. These findings are hypothesis generating due to the observational nature of the study design and thus limit the ability to infer direct causality between guideline facilitators and outcome. The evaluation data were reported by a single respondent at the hospital who recalled retrospective data and reported policies and practices which were not independently confirmed, with the

exception of QI tools. These issues can be further explored in an upcoming prospective, randomised study. Our study may have been underpowered; however we included approximately 30% of metropolitan, adult, acute hospitals in Australia. While this study does exclude a large benefit from an eclectic collection of tools, associations were seen with the more standardised definitions of workforce and hospital strategies for facilitation of PPCI; hence standardised systems, tools and deployment may provide meaningful value. With a population the size of Australia's and approximately 80,000 ACS hospital admissions per year, [23] a large-scale study would require a national ACS registry effort to ensure a high level of hospital participation, with a significant financial, collaborative and government commitment. [22] In spite of these limitations, this study's strength is that it has undertaken a systematic evaluation of factors enabling guideline adherence and has observed associations with decreased adverse patient outcomes. Elucidating these factors is critical in developing rigorous evidence-based quality improvement initiatives.

12.6 Conclusion

We studied the role of guideline facilitators (QI systems, tools, resources and workforce) in translating evidence into practice and found clinical associations with strategies to facilitate PPCI, an electronic discharge checklist and ICCU levels of workforce. To deliver equitable and optimal care to patients, innovative quality improvement solutions which are proven, sustainable and cost effective are required.

12.7 Disclosures and Acknowledgements

Sources of Funding

This study was supported by a 2009 Faculty of Health Sciences Grant, Flinders University, S.A., Australia, and the 2009 Royal College of Nursing Australia (RCNA) Florence Nightingale Scholarship for doctoral or post-doctoral research.

The ACACIA study was sponsored by Sanofi-Aventis who had no influence on collection of care and outcome data in the main study or any part in this ancillary study.

Disclosures

The first author is a candidate for the Doctorate of Public Health (DrPH), Flinders University, S.A., Australia.

Acknowledgments

Professor Paddy Phillips, Chief Medical Officer, South Australian Department of Health Adelaide, Australia, who assisted in the review of this paper.

12.8 References

[1] Chew DP, Amerena JV, Coverdale SG, Rankin JM, Astley CM, Soman A and Brieger D on behalf of the ACACIA Investigators. Invasive management and late clinical outcomes in contemporary Australian management of acute coronary syndromes: observations from the ACACIA registry. Med J Aust. 2008; 188:691-7.

[2] Fox KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J for the GRACE Investigators. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet 2002; 359:373-77

[3] Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson MC, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock FW, Smith Jr. SC, Pollack Jr. CV, Gibler BW, Ohman ME, for the CRUSADE investigators. Utilisation of Early Invasive Management Strategies for High-Risk Patients With Non-ST-Segment Elevation Acute Coronary Syndromes: results form the CRUSADE Quality improvement Initiative. JAMA. 2004; 292; 2096-2104

[4] Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA, Roumanis SA, Curtis JP, Nallamothu BK, Magid DJ, McNamara RL, Parkosewich J, Loeb JM and Krumholz HM. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med. 2006; 355:2308-20.

[5] Peterson ED, Roe MT, Rumsfeld RE, Shaw RE, Brindis RG, Fonarow GC, Cannon CP. A Call to ACTION (Acute Coronary Treatment and Intervention Outcomes Network); A National Effort to Promote Timely Clinical Feedback and Support

Continuous Quality Improvement for Acute Myocardial Infarction. Circ Cardiovasc Qual Outcomes. 2009; 2; 491-499.

[6] Glickman SW, Boulding W, Staelin R, Mulgund J, Roe MT, Lytle BL, Rumsfeld JS, Gibler BW, Ohman ME, Schulman KA and Peterson ED. A framework for quality improvement: an analysis of factors responsible for improvement at hospitals participating in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. Am Heart J. 2007; 154:1206-20.

[7] Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staff levels and the quality of care in hospitals. N Engl J Med. 2002; 346:1715-22.

[8] Korda RJ, Butler JRG, Clements MS, Kunitz SJ. Differential impacts of health care in Australia: trend analysis of socioeconomic inequalities in avoidable mortality. International Journal of Epidemiology 2007; 36:157-165.

[9] Smith KB, Humphreys JS, Wilson MGA. Addressing the health disadvantage of rural populations: how does epidemiological evidence inform rural health policies and research? Aust. J. Rural Health. 2008; 16: 56-66.

[10] Commonwealth of Australia 2010, Australia to 2050: future challenges. Available: http://www.treasury.gov.au/igr/igr2010/report. (Accessed:11 Nov.2010)

[11] McNamara RL, Wang Y, Herrin, J, Curtis J, P, Bradley E. H, Magid D. J, Peterson E. D, Blaney M, Frederick P. D, Krumholz H. M. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006; 47:2180-6

[12] Mehta RH, Montoye CK, Faul J, Nagle DJ, Kure J, Raj E, Fattal P, Sharrif S, Amlani M, Changezi HU, Skorcz S, Bailey N, Bourque T, LaTarte M, Mclean D, Savoy S, Werner P, Baker PL, DeFranco A and Eagle KA on behalf of the American College of Cardiology Guidelines applied in Practice Steering Committee. Enhancing quality of care for acute myocardial infarction: shifting the focus of improvement from key indicators to process of care and tool use: the American College of Cardiology Acute Myocardial Infarction Guidelines Applied in Practice Project in Michigan: Flint and Saginaw Expansion. J Am Coll Cardiol. 2004; 43:2166-73.

[13] Kane RL, Shamliyan TA, Mueller C, Duval S, Wilt TJ. The association of registered nurse staffing levels and patient outcomes: systematic review and meta-analysis. Medical Care. 2007;45:1195-204.

[14] Kostis WJ, Dermissie K, Marcella SW, Shao Y-H, Wilson AC, Moreya AE for the Myocardial Infarction Data Acquisition System (MIDAS 10) Study Group. Weekend versus Weekday Admission and Mortality from Myocardial Infarction. N Engl J Med. 2007;356:1099-109.

[15] Chew DP, Allan RM, Aroney CN, Sheerin NJ. National data elements for the clinical management of acute coronary syndromes. Med J Aust. 2005; 182:S1-14.

[16] Aroney CN, Aylward PE, Kelly A, Chew DP, Clune E. Guidelines for the management of acute coronary syndromes 2006. Med J Aust. 2006; 184:S9-29.

[17] Bradley EH, Nallamothu BK, Stern AF, Cherlin EJ, Wang Y, Byrd JR, Linnander EL, Nazem AG, Brush JE, Krumholz HM. The Door-to-Balloon Alliance for Quality:

Who Joins National Collaborative efforts and Why? Joint Comm J Qual and Pt Safety. 2009; 35:93-99

[18] Hasin Y, Danchin N, Filippatos GS, Heras M, Janssens U, Leor J, Nahir M, Parkhomenko A, Thygesen K, Tubaro M, Wallentin LC and Zakke I on behalf of the Working Group on Acute Cardiac Care of the European Society of Cardiology. Recommendations for the structure, organization, and operation of intensive cardiac care units. Eur Heart J. 2005; 26:1676-82.

[19] Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg GP, Gore JM, Budaj A, Avezum A, Flather MD and Fox KAA for the GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month post discharge death in an international registry. JAMA. 2004; 291:2727-33.

[20] Glickman SW, Baggett KA, Krubert CG, Peterson ED, Schulman KA. Promoting quality: the health-care organization from a management perspective. Int J Qual Health Care. 2007; 19:341-8

[21] Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ. 2005; 330(7494):765.

[22] Astley CM, Tonkin AM, Mahar LJ, Davidson PM, Boyden AN, Huang N, Brieger DB, Pradhan M, George MV, Mattschoss SF, Chew DP. Clinical effectiveness in everyday practice: improving outcomes for all patients through a national ACS data collaborative. IMJ. 2011;41,206-210;[Epub ahead of print].

[23] Access Economics 2009. The economic costs of heart attack and chest pain (acute coronary syndromes). Available: http://www.accesseconomics.com.au/publicationreports/. (Accessed:October 2009).

13 IMPACT OF A REGIONALISED CLINICAL CARDIAC SUPPORT NETWORK ON MORTALITY AMONG RURAL PATIENTS WITH MYOCARDIAL INFARCTION

13.0 Title page : Impact Of A Regionalised Clinical Cardiac Support Network On Mortality Among Rural Patients With Myocardial Infarction

Phillip Tideman [1,2], Rosy Tirimacco [1,2], David Senior [3], John Setchell [4], Luan Huynh [1], Rosanna Tavella[5], Philip E Aylward [1], Derek P. Chew [1]

Author affiliations

[1] Flinders University/Southern Adelaide Local Health Network

[2] Integrated Cardiovascular Clinical Network (ICCNet), Country Health South Australia Local Health Network

[3] Rural Doctors Workforce Agency, South Australia

[4] Royal Flying Doctor Service Central Operations

[5]Statewide Cardiology Clinical Network, SA Health

Running Title: Impact of a Cardiac Network in South Australia.

Key Words: Acute Myocardial Infarction, Regionalized Cardiovascular care, Remote care

Corresponding Author

Derek P Chew MBBS MPH
Flinders University
Flinders Drive, Bedford Park
South Australia, 5042
AUSTRALIA
Ph: +618 8404 2001
Fax: +618 8404 2150

13.1 Abstract

Objective: Due to remote geography, many myocardial infarction (MI) patients continue to experience increased mortality. We evaluated the impact of a regionalised cardiac clinical support network on 30-day mortality among MI patients in an Australian rural setting.

Design, Setting and Subjects: An integrated cardiac support network incorporating standardised risk stratification, point-of-care troponin testing and cardiologist-supported decision-making was progressively implemented in non-metropolitan areas of South Australia from 2001-08. Evaluation of rural and metropolitan MI patient outcomes using hospital administrative data and state-wide death records from 1st July 2001 to 30th June 2010 was undertaken.

Main Outcome: Risk-adjusted 30-day Mortality.

Findings: 29 623 independent contiguous episodes of MI were identified. The mean predicted 30-day mortality was lower among rural patients compared with metropolitan patients, while actual mortality rates were higher. (30-day mortality: Rural: 705/5630 (12.52%) vs. 2140/23993 (8.92%), adjusted odds ratio (OR): 1.46, [95% C.I 1.33-1.60], p<0.0001). After adjustment for temporal improvement in MI outcome, availability of immediate cardiac support was associated with a 22% relative odds reduction in 30-day mortality (OR: 0.78, [95% C.I 0.65-0.93], p=0.007). A strong association between network support and transfer of patients to metropolitan hospitals was observed, with lower mortality observed among transferred patients.

Interpretation: Cardiologist-supported remote risk stratification, management and facilitated access to tertiary hospital-based early invasive management are associated with an improvement in 30-day mortality for patients presenting with MI. These interventions closed the gap in mortality between rural and metropolitan patients in South Australia.

13.2 Introduction

Modern evidence-based acute myocardial infarction (MI) care incorporates a rich array of therapeutic strategies with demonstrable reductions in mortality.(1,2) However, their optimal implementation is dependent on timely access to expert clinical assessment, risk stratification, and resource-intensive coronary reperfusion or revascularization. (3-5) Consequently, due to geography many MI patients continue to experience disparities in clinical care and outcome.(6)

To optimise acute coronary syndromes (ACS) management, many regions have begun developing cardiac clinical networks aimed at supporting capacity in primary care through the provision of expert risk stratification at the point of initial patient presentation, combined with efficient systems for transferring patients, to centralised, skilled and resource intensive management such as coronary revascularization in a time critical manner.(7-9) These networks require careful design, co-ordination, and engagement with primary care practitioners, combined with ongoing clinical commitment and resources, but may provide benefits that exceed the gains achievable by many new innovations in therapy.(10) Hence, we sought to evaluate the impact of such a cardiac clinical network on 30-day mortality among acute MI patients presenting in a rural setting.

13.3 Methods

13.3.1 Study Population

South Australia is a state of approximately 1.64 million people spanning just under 1,000,000 km^2. Adelaide has 7 metropolitan hospitals, while the 66 rural cities and towns have local hospital facilities serving their population of over 600,000 people. In rural areas, the 4 largest cities have populations of 15,000-24,000 with access to 3 consultant general physicians. The next 20 larger towns have < 15,000 peopple (with most < 5,000 residents) and are served by small rural hospitals and occasional visiting cardiologists. For this study, all hospitals outside the 7 metropolitan hospitals were classified as rural hospitals. Invasive services are only available within the metropolitan hospitals.

13.3.2 The Integrated Cardiovascular Clinical Network

Through 2001 to 2008, the Integrated Cardiovascular Clinical Network (ICCNet), designed to support general medical practitioners and nurses in the rural areas, was

implemented rural South Australia. The ICCNet "clinical network" integrated three key design features (Table 1): i) standardised risk stratification and evidence-based treatment protocols (3,4); ii) "point-of-care" testing for whole-blood Troponin T levels with central quality control; and iii) a designated on-call consultant cardiologist with redundancy to ensure response within 10 minutes with facsimile-based ECG interpretation, and facilitation of transfer to metropolitan hospitals by Royal Flying Doctor Service with Emergency Medical Retrieval Team support if deemed necessary. Rural participants of the network also received regular education. (Table 1)

Table 1: Essential Components of the ICCNet Service

Cardiopulmonary resuscitation/Advanced Life Support capable clinician
Cardiac monitor/defibrillator on site
Clinical History by Medical or Nursing clinician
Onsite ECG and remote interpretation capability,
Biochemical markers available at point of care,
Acute medications guided by agreed protocols,
Timely access to coronary angiography, PCI, CABG, cardiac rehabilitation service co-ordinated though metropolitan hospital services,
Regular comprehensive clinical follow-up, combined with clinical and technical quality assurance.

By 2008, this service was available to all 66 rural hospitals.

13.3.3 MI Admissions, Transfers, and Mortality

Using administrative data patients with a final diagnosis of MI between 1st July 2001 and 30th June 2010 were identified for analysis. Within this dataset, patient age, gender, principal diagnosis, significant co-morbidities including diabetes, hypertension, significant renal and hepatic dysfunction, prior stroke, left ventricular failure, dementia and components of the Charlson index, as well as in-hospital procedural data (angiography), length of stay, transfers and final patient disposition were available for analysis.(11) The principal diagnosis of MI, and sub-classifications of MI were identified using using the ICD-10 AM classification (I21.0-5). Routine identification of discharge status and destination and transfer- related admissions permitted linkage of records for the same patient receiving acute care in several hospitals and avoiding double-counting of contiguous admissions. Patients were classified as "rural" or "metropolitan"

based on the hospital of their first presentation. The total length of stay was calculated as the time from admission to the first hospital to the time of discharge from acute care, regardless of final hospital location. Linkage of these data to the state death registry enabled the capture of 30-days mortality. Since cause of death was not reliably available, all cause mortality was used to avoid any systemic biases in the coding of causality. The ICCNet project was approved through the Flinders Medical Centre Human Research Ethics committee, and access to this data in was granted by the office of the Chief Executive, SA Health.

13.3.4 Statistical Analysis

To evaluate the relationship between availability of the ICCNet service and mortality, 30-day death rates among MI patients presenting to rural hospitals before and after the clinical network implementation were compared. These comparisons were contrasted with mortality rates among primary MI presentations in metropolitan hospitals. A full description of the statistical approach is provided in the appendix. (Appendix 1)

13.4 Results

13.4.1 Population Characteristics

From July 2001 to June 2010, 34 172 admissions with a diagnosis of acute MI were identified. Of these 4549 patients were transferred from rural centres to metropolitan hospitals resulting in 29 623 independent episodes of contiguous acute care. Overall, 5630 patients presented initially to a rural hospital. The mean predicted in-hospital mortality rate was slightly lower among rural patients (rural 7.3% vs. metropolitan 7.6%, $p<0.001$). The risk profiles of the populations by rural and metropolitan category and before and after joining the clinical network are displayed in Appendix 2. There was a small decline in predicted risk over time.

13.4.2 Mortality Rates

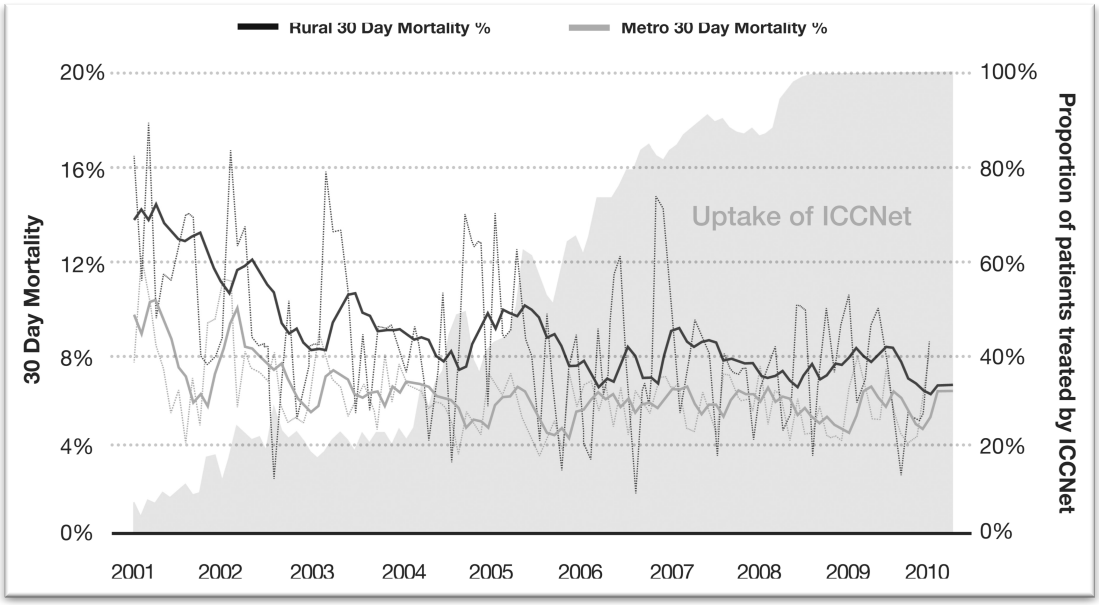
Thirty-day mortality rates were higher among patients presenting to rural areas compared with metropolitan hospitals. (30-day mortality: Rural: 705/5630 (12.52%) vs. Metropolitan: 2140/23993 (8.92%), $OR_{risk\text{-}adj}$: 1.81, [95% C.I 1.46-2.23], $p<0.001$) In both metropolitan and rural patients, mortality rates declined over the decade (per year $OR_{risk\text{-}adj}$: 0.97 [95% C.I 0.95-0.99], $p<0.001$). However, these declines were greater in rural areas (interaction between year and rural location: $p=0.04$). In 2001, the adjusted

odds ratio for patients presenting to rural areas was 1.69 [95% C.I 1.40-2.04], p<0.001, but by 2010, this was no longer significant ($OR_{risk-adj}$: 0.92 [95% C.I 0.75-1.13], p=0.44). (Appendix 3)

Compared with patients presenting to rural hospitals before the availability of the network, mortality was lower among hospitals integrated into the clinical network. (30-day mortality: Rural, Before-ICCNet: 337/2419 (13.93%) vs. After-ICCNet: 368/3211 (11.46%) vs. Metropolitan: 2140/23,993 (8.92%), p<0.0001). After adjusting for baseline co-morbidities and MI characteristics, presentation to an ICCNet hospital was associated with a 22% relative odds reduction in the risk of 30-day mortality ($OR_{risk-adj}$: 0.78, [95% C.I 0.65-0.93], p=0.007) compared with other rural centres, though these patients remained at increased risk of 30-day mortality compared with patients presenting to metropolitan hospitals (ICCNet hospital vs. Metro: $OR_{risk-adj}$: 1.57, [95% C.I 1.38-1.79], p<0.0001).

By strata of predicted risk, the observed mortality rates among rural patients were greater than those presenting to metropolitan centres across the spectrum of risk although most of the excess mortality was observed in the intermediate risk groups (5-20% predicted risk). (Figure 1) Reductions in rural mortality rates amongst these intermediate risk patients accounted for the majority of the mortality reductions over time.

Figure 1: Thirty-day mortality among rural patients with and without availability of the ICCNet contrasted with metropolitan areas, stratified by predicted mortality risk among patients treated between 2001 and 2010.



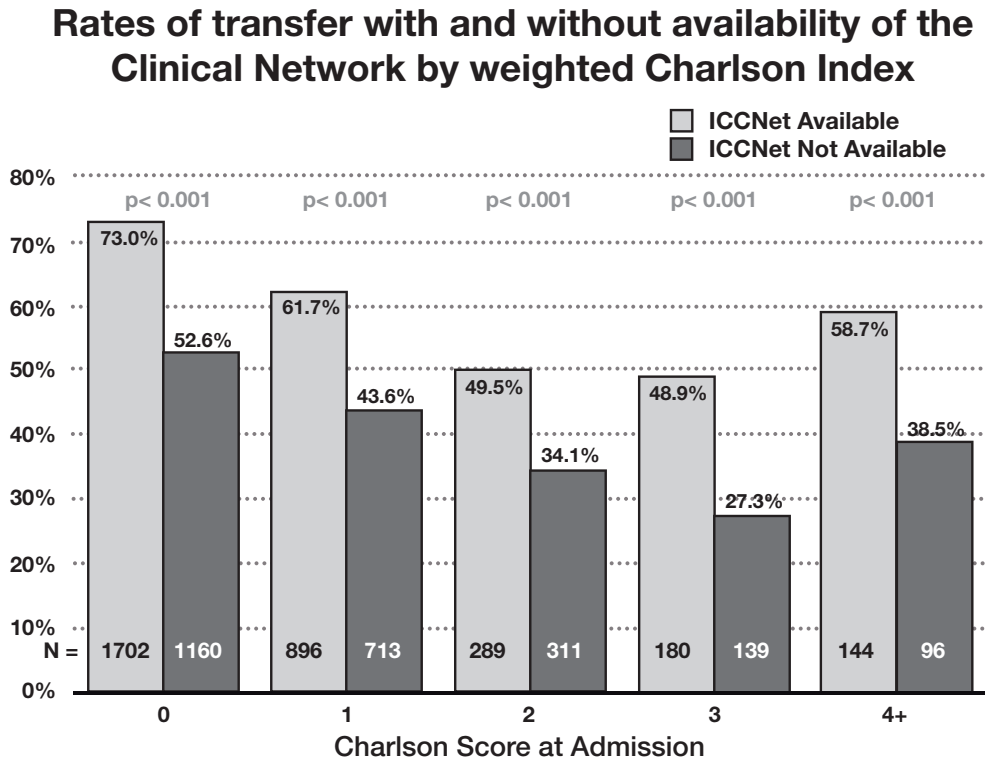
13.4.3 Transfers and Angiography

There was a strong association between clinical network implementation and the rate of transfer of rural patients to metropolitan hospitals. (Transfer frequency: Before ICCNet: 1102/2419 (54.6%) vs. After ICCNet: 2100/3211 (65.4%), p<0.001) Increased transfers were not associated with an increase in the total median length of stay for each admission compared with metropolitan presentations, but a lower total length of stay compared with before-ICCNet admissions. (Metropolitan: 4.78 (i.q.r. 3.10-7.78) days vs. After ICCNet: 4.63 (i.q.r. 2.03-7.92) days vs. Before ICCNet: 5.08 (i.q.r. 2.69-7.93) days, p=0.0001.

Increased transfer rates were paralleled by increased rates of invasive management. Nevertheless, the proportion of patients receiving angiography was lower for patients presenting to rural hospitals compared with metropolitan hospitals during the entire analysis period. (Angiography: Rural: 1551/5630 (27.55%) vs. 11019/23993 (45.93%) p<0.001) This difference diminished over the decade. (Appendix 4) After adjusting for comorbidities and year of presentation treatment at clinical network available hospital was associated with a higher relative rate of angiography ($RR_{risk\text{-}adj}$: 1.30 [95% C.I 1.08-1.55], p=0.004). Mortality among rural patients treated at clinical network available hospitals was also lower compared with before the network was implemented, after

accounting for angiography ($OR_{risk-adj}$: 0.82, [95% C.I. 0.67-0.97], p=0.012). Mortality rates among rural patients receiving angiography were comparable to patients presenting to metropolitan hospitals (Metro 457/11019 (4.2%) vs. 46/1551 (3.0%), $OR_{risk-adj}$: 0.73 (0.52-1.02, p=0.062).

Figure 2: Rates of transfer among rural patients presenting with myocardial infarction between 2001 and 2010 with and without availability of the ICCNet stratified by weighted Charlson Index.



13.4.4 Co-morbid Risk

Increasing comorbidities, as measured by the Charlson index, were associated with a lower likelihood of transfer among rural patients with an odds ratio for transfer of 0.73 (95% C.I. 0.70-0.77, p<0.001) for each additional point of the Charlson Index. Presentation to a hospital where ICCNet was available was associated with a 2.2-fold increase (OR for transfer: 2.23, 95% C.I. 1.99-2.49, p<0.001) in the likelihood of transfer to a metropolitan hospital across all degrees of comorbid risk with an associated reduction in mortality among those with increased mortality. (Figure 4)

13.5 Discussion

The challenges in the delivery of the modern MI evidence-based care to remote regions serviced almost exclusively by primary care physicians without ready access to immediate expert clinical advice and technologies for invasive management remain. Consequently, disparity in MI mortality rates among rural patients remains.(12-14) This temporal analysis demonstrates a reduction in acute mortality associated with a networked approach to MI care that facilitated early cardiac specialist opinion, refined risk stratification through “point-of-care testing” of whole-blood troponin, enabling the early application of evidence-based therapies, and co-ordinated transfer of high-risk patients to tertiary referral centres for early invasive management and revascularization as needed. In demonstrating a population wide reduction in acute mortality, this analysis demonstrates the effectiveness of a management paradigm that supported clinical decision-making in primary care and improved the availability of cardiovascular technologies among rural patients. Such observations may have relevance for other regions where an expansive geography compromises the delivery of evidence-based therapies, and may also have resonance in the developing world where limitations in cardiac specialist capacity will require more streamlined approaches to the management of cardiac emergencies.

Substantial debate has focused on regional reperfusion services for ST-segment elevation MI, arguing for timely co-ordinated transfer of patients to high volume centres for primary percutaneous coronary intervention (PCI) or facilitated PCI. (7,15-17) Such debates are of limited relevance in populations where distances to PCI centres exceeds 250km, and for the larger proportion of MI patients who present without ST-elevation. Remote support for risk stratification in primary care, within the context of substantial geographic distances and limited local facilities may well provide greater mortality reductions than many emerging therapeutic innovations currently undergoing intense research, and achieve this with lower costs. (18)

Key to a networked program is an integrated intervention.(8) While remote approaches have demonstrated efficacy in the management of chronic heart conditions, merging decision-making with technology-dependent care remains challenging.(19) Timely clinical expertise was combined with enhanced local risk assessment, standardised clinical protocols, and central commitment to the urgent transfer of higher risk patients in this intervention. This integrated approach more closely replicates care in metropolitan centres and led not only to a reduction in mortality, but also to a decrease

in the overall length of stay for rural patients, suggesting efficiency gains combined with outcome benefits. These data help quantify the benefits associated with such an intervention and inform health policy “value” choices for these rural settings.(20)

However, the interpretation of this study should consider the non-randomised nature of the intervention. While we cannot exclude a temporal improvement in MI outcomes among rural patients, as seen among the metropolitan population, these benefits were temporally associated with an increase in invasive management and alternative explanations for the improvement in rural MI outcomes would also need to account for the disproportionately greater benefit among rural patients than seen among patients from metropolitan areas.

This study has potential application for other geographically challenged regions of Australia, and may also present an approach for developing countries where economic and geographic challenges mean that a greater proportion of acute care falls to primary care services with less access to specialist service. A critical health policy consideration in such environments is how to effectively increase risk stratification and decision-making capacity locally, and provide timely access to expensive technologies and therapies efficiently. These issues are even more pressing in the developing world, where limitations of clinical specialist expertise are substantial even within more urban centres, and the density of high-end cardiac experts and technologies is lower than observed in the developed world.(8,9) By documenting improved outcomes and reduced disparities in the rural areas of a wealthy, developed country, an integrated cardiac clinical network approach may represent a relevant health-service design consideration in the developing world which needs to meet the looming burden of acute cardiovascular disease foreshadowed by their increasingly urbanizing population.

13.6 Conclusions

A clinical network remote specialist-supported risk stratification and decision-making in primary care, standardised management protocols including early thrombolysis and increased access to early invasive management is associated with an improvement in hospital mortality for acute MI presentations and was able to reduce the gap in mortality between rural and metropolitan patients.

13.7 Acknowledgements

The authors would like to sincerely thank all South Australian rural doctors and nurses who have embraced this model of care, cardiologists who have supported the network, Country Health South Australia who provided operational funding, AHMAC for initial funding to set up the network and all iCCnet scientific and administrative staff.

13.8 References

1. Ford E, Ajani U, Croft J, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007 Jun 1;356(23):2388–2398.

2. Fox KAA, Steg PG, Eagle KA, et al. Decline in Rates of Death and Heart Failure in Acute Coronary Syndromes, 1999-2006. JAMA. 2007 May 2;297(17):1892–1900.

3. Aroney C, Aylward P, Kelly A et al. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. Medical Journal of Australia. 2006 Apr 1;184(8):S1–35.

4. Chew DP, Aroney CN, Aylward PE, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart Lung Circ. 2011 Aug;20(8):487–502.

5. White HD, Chew DP. Acute myocardial infarction. The Lancet. 2008 Aug;372(9638):570–584.

6. Fox K, Goodman S, Anderson F, et al. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). Eur Heart J. 2003 Aug 1;24(15):1414–1424.

7. Henry T, Sharkey S, Burke M, et al. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. Circulation. 2007 Aug 1;116(7):721–728.

8. Ting H, Krumholz H, Bradley E, et al. Implementation and Integration of Prehospital ECGs Into Systems of Care for Acute Coronary Syndrome. A Scientific Statement From the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008 Aug 1;118(10):1066–1079.

9. Le May M, So D, Dionne R, et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2008;358(3):231–240.

10. Chew DP, Huynh LT, Liew D, et al. Potential survival gains in the treatment of myocardial infarction. Heart. 2009 Nov;95(22):1844–1850.

11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development

and validation. J Chronic Dis. 1987;40(5):373–383.

12. Baldwin L-M, MacLehose RF, Hart LG, et al. Quality of care for acute myocardial infarction in rural and urban US hospitals. J Rural Health. 2004;20(2):99–108.

13. Joynt KE, Harris Y, Orav EJ, Jha AK. Quality of care and patient outcomes in critical access rural hospitals. JAMA. 2011 Jul 6;306(1):45–52.

14. Ross JS, Normand S-LT, Wang Y, et al. Hospital remoteness and thirty-day mortality from three serious conditions. Health Aff (Millwood). 2008 Oct;27(6):1707–1717.

15. Henry T, Unger B, Sharkey S, et al. Design of a standardised system for transfer of patients with ST-elevation myocardial infarction for percutaneous coronary intervention. Am Heart J. 2005 Sep 1;150(3):373–384.

16. Nallamothu B, Krumholz H, Ko D, et al. Development of systems of care for ST-elevation myocardial infarction patients: gaps, barriers, and implications. Circulation. 2007 Jul 1;116(2):e68–e72.

17. Sorensen JT, Terkelsen CJ, Nørgaard BL, et al. Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. European Heart Journal. 2011 Feb 14;32(4):430–436.

18. Ranasinghe I, Turnbull F, Tonkin A, et al. Comparative effectiveness of population interventions to improve access to reperfusion for ST-segment-elevation myocardial infarction in Australia. Circulation: Cardiovascular Quality and Outcomes. 2012 Jul 1;5(4):429–436.

19. Clark RA, Inglis SC, McAlister FA, et al. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. BMJ. 2007 May 5;334(7600):942.

20. Bakal JA, Kaul P, Welsh RC, et al. Determining the cost economic “tipping point” for the addition of a regional percutaneous coronary intervention facility. Can J Cardiol. 2011 Sep;27(5):567–572.

13.9 Appendix 1

To adjust for differences in baseline clinical risk we examined clinical factors associated with in-hospital mortality within 60% of the patients presenting to metropolitan hospitals (training set) and then the performance of the model in the remaining 40% of metropolitan patients (validation set). The final logistic regression model included: type of MI; age (in 5 year groups); prior heart failure; cardiogenic shock; arrhythmia on presentation; cerebrovascular disease; renal failure; known ischaemic heart disease; dementia; and the weighted Charlson index.(12) The discrimination of the model was assessed using the area under the receiver-operating characteristic reported as the C-statistic. The calibration of the final model was assessed using Hosmer-Lemeshow goodness-of-fit test in 10 groups where a low χ^2-statistic, and therefore a non-significant p-value indicates concordance between observed and model predicted event rates. The final model described the risk in-hospital and 30-day mortality with a C-statistic of 0.866 and 0.829, with the goodness-of-fit test of p=0.116 and p=0.286, respectively. Within the rural population, this model's c-statistic was 0.853 and 0.818 for in-hospital and 30-day mortality respectively. This model was then used to estimate the predicted mortality rate within the metropolitan and rural populations. This predicted risk was then stratified as ≤5%, 5.1-10% 10.1-15%, 15.1-20% and >20%. This model was also used to adjust comparisons between clinical network available rural presentations, clinical network not available rural presentations and metropolitan presentations.

Rates of 30-day mortality by network classification are plotted by year and compared by chi-square tests in univariate comparison. The uptake of the integrated clinical network by rural hospitals is plotted as a proportion of total rural hospitals over time. Rates of angiography for rural stratified by adoption of the clinical network and metropolitan patients over time were also plotted. Given that clinical co-morbidities are known to influence referral for angiography, the weighed Charlson Index was used to assess the association between patient comorbidity, transfer inpatient angiography and mortality, with scores of 5 or more aggregated due to small patient numbers. Rates of transfer among rural patients, angiography, and 30-day mortality were then compared across these strata for patients presenting to rural hospitals before and after the availability of the clinical network in rural centres. To assess the relationship between predicted patients risk and actual mortality between rural and metropolitan patients over time, 30-day mortality among rural and metropolitan patients were plotted, stratified by predicted patient risk. Kaplan Meier survival by ICCNet and Non-ICCnet

rural presentation and Metropolitan presentations were plotted. Factors following a normal distribution are expressed as means (± standard deviation) and non-Gaussian factors are reported as medians (and inter-quartile ranges). Counts and proportions are presented as “n” (%). A probability of <0.05 is considered statistically significant. All analyses were performed using STATA 11.0 (College Station, TX).

13.10 Appendix 2: Demographic and Clinical Characteristics by Metropolitan and Rural Presentation

Characteristic	Metro N=23993	Rural N=5630	p-value	Before ICCNet N=2419	After ICCNet N=3211	p-value
Age (yrs ±SD)	69.26 (14.51)	70.01 (14.18)	0.002	69.59 (14.13)	70.32 (14.21)	0.065
Female Gender (n, %)	8439 (35.17)	1979 (35.15)	0.975	1144 (36.63)	835 (34.52)	0.388
Diabetes (n, %)	4513 (18.80)	1125 (19.98)	0.044	544 (22.49)	581 (18.09)	<0.001
Hypertension (n, %)	11274 (49.91)	2118 (37.62)	<0.001	785 (32.5)	1333 (41.51)	<0.001
Anterior Myocardial Infarction (n, %)	3885 (16.19)	1023 (18.17)	<0.001	529 (21.87)	494 (15.38)	<0.001
Prior Heart Failure (n, %)	4766 (19.86)	1051 (18.67)	0.042	483 (19.97)	568 (17.69)	0.030
Prior CVA (n, %)	641 (2.67)	136 (2.42)	0.279	61 (2.52)	75 (2.34)	0.653
Prior or Known Malignancy (n, %)	372 (1.55)	120 (2.13)	<0.001	53 (2.19)	67 (2.09)	0.788
Prior Ischaemic Heart Disease (n, %)	13535 (56.41)	2312 (41.07)	<0.001	818 (33.82)	1494 (46.53)	<0.001
Known Valvular Heart Disease	1812 (7.55)	251 (4.46)	<0.001	71 (2.94)	180 (5.61)	<0.001
Chronic Airways disease (n, %)	1443 (5.97)	352 (6.25)	0.427	169 (6.99)	183 (5.70)	0.048
Peripheral Vascular Disease (n, %)	973 (4.06)	161 (2.85)	<0.001	71 (2.94)	90 (2.80)	0.768
Known Renal Disease (n, %)	2431 (10.13)	407 (7.23)	<0.001	160 (6.61)	247 (7.69)	0.122
Known Liver Disease (n, %)	122 (0.51)	27 (0.48)	0.783	14 (0.58)	13 (0.40)	0.350
Dementia (n, %)	658 (2.74)	96 (1.71)	<0.001	47 (1.94)	49 (1.53)	0.232
Neurological Condition (n, %)	461 (1.92)	103 (1.83)	0.650	55 (2.27)	48 (1.49)	0.031
Cardiogenic Shock (n, %)	681 (2.84)	118 (2.10)	0.002	48 (1.98)	70 (2.18)	0.612

14 CONDITION-SPECIFIC STREAMING VERSUS AN ACUITY-BASED MODEL OF CARDIOVASCULAR CARE: A HISTORICALLY-CONTROLLED QUALITY IMPROVEMENT STUDY EVALUATING THE ASSOCIATION WITH EARLY CLINICAL EVENTS

14.0 Title page: Condition-specific streaming versus an Acuity-based model of cardiovascular care: A historically-controlled quality improvement study evaluating the association with early clinical events

Derek P Chew MPH [1,2,3,] Matthew Horsfall RN [2,3,] , Andrew D McGavigan MD [1,2] , Philip Tideman MBBS [1,2,] Julian C. Vaile MD [1,2,] Catherine O'Shea [2,] Belinda Moyes MHP BHA [4,] Carmine De Pasquale PhD [1,2]

Author Affiliations

[1]School of Medicine, Flinders University of South Australia, Adelaide, Australia

[2]Department of Cardiovascular Medicine, Southern Adelaide Local Health Network, Adelaide, Australia

[3]Health Systems Research, South Australian Health and Medical Research Institute, Adelaide, Australia

[4]Flinders Medical Centre, Southern Adelaide Local Health Network, Adelaide, Australia

Running Head: The Impact of Streaming in Cardiac Care

Corresponding Author

Derek P Chew MBBS MPH

Flinders University

Flinders Drive, Bedford Park

South Australia, 5042

AUSTRALIA

Ph: +618 8404 2001

Fax: +618 8404 2150

Email: derek.chew@flinders.edu.au

14.1 Abstract

Background: Ensuring optimal evidence translation is challenging when health-service design has not kept pace with developments in care. Differences in patient outcomes were evident when specific cardiac conditions were discordant with the subspecialty of the cardiologists managing their care. We prospectively explored the clinical and health service implications of a “condition-based” redesign in cardiac care delivery, rather than acuity-based, within a tertiary hospital.

Methods: Prospective evaluation of a disease-specific streaming model of care compared to propensity-matched historical controls, among cardiac patients admitted to a tertiary hospital cardiology unit was undertaken. The outcome measures of 30-day death, and readmission for myocardial infarction, cardiac arrhythmia, and heart failure were explored.

Results: In total, 2018 patients admitted subsequent to the implementation of the streaming model were compared with 1830 patients admitted prior. The median age was 68.9 years, and 39.5% were female. There was no significant difference in the overall proportion of patients admitted with an acute coronary syndrome, arrthythmia or heart failure, nor their Charlson index before and after streaming. Subsequent to the implementation, there was a reduction in the use of angiography (pre: 35.4% vs. post: 31.2%, p=0.007) and echocardiography (pre: 59.4% vs. post: 55.6%, p=0.007). A reduction in length of length of stay was observed in the entire cohort (Pre: 2.7 (range: 1.2-5.0) days vs. post: 2.3 (range1.0-4.5) days, p=0.0003). By 30 days, the propensity-adjusted hazard ratio for major adverse cardiac events and death or any cardiovascular admission was 0.76 (95% C.I. 0.59-0.97, p=0.026).

Conclusion: Cardiac service redesign that streams cardiac patients by presenting diagnosis into teams designed to treat that condition may provide capacity and productivity gains for health services striving to improve outcome and efficiency.

Key Words:
Cardiac Care, Health service design, healthcare quality improvement

14.2 Introduction

While modern cardiac care has borne witness to a rich and rapidly expanding evidence-base, translation of this into clinical practice remains a challenge. The optimal use of new diagnostic modalities is often duplicative during early implementation.[1,2] Similarly, the uptake of new therapies is often slow, lagging significantly behind the availability of clinical trials and their assimilation into well-respected practice guidelines.[3-5] It has long been recognised that diagnostic and therapeutic innovations must be coupled with an adaptive re-design in health care decision-making and delivery in order to fully realise the promise of improved clinical outcomes and efficiencies.[6,7] Ensuring clinical practices remain current in a consistently effective manner remains difficult for many sectors of the health system, especially where practices and services have evolved organically without specific design considerations.[8,9]

Increasing generalist capacity has not demonstrated benefits in outcome.[10] Rather, health services have increasingly become reliant on subspecialty expertise to optimise clinical decision-making when adopting health innovations, which is often accessed based on perceived acuity rather than actual risk.[11,12] Such subspecialty approaches are not always scalable i.e. increasing expert clinical decisions requires a proportionate increase in the presence of expert decision-makers. This is especially the case when considering the needs of hospital networks distributed over several geographic locations, especially rural sites.[13] Hence, this may lead to missed opportunities in providing ideal care and sub-optimal outcomes among those unable to access this expertise. Consequently, the organisation of services into a form that is

more conducive to the effective uptake of the emerging evidence-base, i.e. subspecialty decision-making, remains a translational imperative. In examining relevance of this question, we retrospectively explored the impact of subspecialty cardiology care on tertiary hospital cardiology inpatients and found evidence of variation in clinical outcomes. We observed that within our own service, patients treated with cardiac conditions such as acute coronary syndromes (ACS) and cardiac arrhythmias experienced inferior outcomes when cared for by cardiologists with subspecialty credentials that were discordant with that condition. For example, patients with acute coronary syndromes treated by non-interventional cardiologists experienced a 31% relative increase in late mortality, largely among patients with lower risk clinical characteristics. Therefore, in response to this finding, we have prospectively examined whether clinical outcomes can be improved through the implementation of a "condition-based" redesign in cardiac care delivery within a tertiary referral hospital.

14.3 Methods

14.3.1 Study Design

In response to observed heterogeneity when examining clinical care and outcome stratified by cardiology subspecialty group (i.e. interventional cardiologist, heart failure subspecialist, electrophysiologist) the health service structure was changed to a disease presentation-based streaming design in December 2013. We planned and implemented a re-design of the cardiology service to provide a condition-specific model of care and evaluated this with a historically-controlled patient level analysis. Patients coming under care were not directly informed of the changes in our model during this period since the activity was considered a quality improvement initiative. The Southern Adelaide Clinical Human Research Ethics Committee provided approval for access to health service and outcome data. While patient level data were used to electronically link index admissions with procedures and readmissions, patients were not directly

contacted for the purposes of this study and no patients level identifying details were used in analysis.

14.3.2 The Clinical Service

The Flinders Medical Centre is a tertiary referral hospital serving the southern communities of Adelaide, South Australia with a catchment population of approximately 300,000 metropolitan and 200,000 rural individuals. Each year, the cardiac service admits ~3000-4000 patients, the vast majority being direct emergency admissions via emergency department (ED) or transfers from rural hospitals. Onsite cardiac capabilities include percutaneous coronary intervention, coronary artery bypass grafting, pacing, simple and complex mapping and electrophysiology ablative procedures, advanced echocardiography as well as a pulmonary hypertension and heart failure service. It is staffed by 17 consultant cardiologists (12.5 FTE), with 4 onsite advance trainees in cardiology, and junior medical staff on 3 monthly rotations. Consultant subspecialty classification was self-deemed, but local credentialing requirements ensure that cardiologists have undergone post-fellowship training, and maintain professional development and procedural volumes consistent with nationally accepted standards where available.

14.3.3 The Quality Improvement Intervention

14.3.3.1 Pre-Streaming Acuity-based Cardiac Service Structure:

The inpatient care was provided on 2 wards allocated by patient acuity: a coronary care and a general cardiology ward, each with an advance trainee registrar, a resident and 2 interns, as well as a daily consultant ward round. Registrars rotated between these wards, and the angiography and echo services on a 3 monthly basis. Consultants rotated on ward service for a week at a time, with allocation to each ward made irrespective of subspecialty group, with an even distribution between the

coronary care and general cardiology ward service. Non-elective presentations were admitted to either the coronary care unit or the general cardiac ward based on clinically determined patient acuity and the perceived need for monitoring. In general, patients with a troponin elevation >100ng/L, those requiring CPAP for acute pulmonary oedema, or patients with ventricular arrhythmias or other evidence of haemodynamic compromise were preferentially admitted to the coronary care ward. Patients presenting chest pain, without objective evidence of ischemia were admitted to a separate chest pain assessment unit (CPAU), and managed by the clinical team responsible for the coronary care unit.

14.3.3.2 Post-Streaming Disease-based Cardiac Service Structure:

Following the implementation of the presentation/disease-specific streaming model, patients were admitted to three cardiac units (acute coronary syndrome, arrhythmia and heart failure [including structural heart disease]) based on the principal diagnostic classification determined on their initial medical assessment in the ED or peripheral hospital. Registrar and junior medical staff clinical and training responsibilities were aligned to serve the disease specific streams and to optimise continuity in decision-making Registrar rotation was maintained at 3 monthly cycles, training in investigative modalities was implemented in a longitudinal structure (i.e. the registrar responsible for the ACS service would attend the catheter laboratory following their inpatient ward round and contribute to the investigation and decision-making on the patients under their inpatient care). The consultants rotated though the three services on a weekly basis. No net increases in resources were incurred. Clinicians with subspecialty expertise within each of the three cardiac conditions were identified as leaders to provide informal guidance on unit practices, but no new protocols or specific treatment pathways were implemented.

Admission unit classification was determined at a registrar level, except for overnight admission (10pm to 8am) where more junior medical officers are on-site, though re-

allocation based on diagnosis was undertaken on the morning handover meeting at the discretion of the treating teams. Patients with chest pain, without objective evidence of ischemia, but with known coronary disease or high risk features were admitted to the ACS service, while patients without these characteristics were discharged to return for early exercise stress testing (within 48-72 hours). Patients were triaged between the geographic coronary care and general cardiology ward locations based on clinical acuity and the need for monitoring as described above.

14.3.4 Evaluation of the Intervention

The hypothesis underlying the intervention was that a re-design of cardiac services along condition-specific streams would align clinical decision-making and risk assessment with more coordinated and timely access to key cardiac interventions and therapies, in turn leading to more risk appropriate treatment, shorter length of stay, and potentially improvement in outcomes. Given the “whole of department” level structural reorganization of the cardiac services studied under this intervention, with the prior organizational structure no longer in existence, exposure to the intervention was considered to be complete following the date of change. While this redesign offers the putative advantage of more rapid learning among junior medical teams leading to an increase in their capacity to initiate key cardiac investigations and management, the level at which the decision was made is challenging to study. Therefore, the evaluation of the intervention examined the clinical outcomes of all patients admitted within the cardiology units before and after the implementation of the streaming model as an overall measure of effectiveness. The primary outcome for the study were the composite clinical events of death or readmission for new or recurrent myocardial infarction, heart failure or cardiac arrhythmia within 30 days. Secondary outcomes included use and timing of cardiac procedures and length of stay as overall measures of the efficiency of decision-making and care provided under the new model.

14.3.4.1 Admitting Unit Classification:

Using hospital unit coding, patients admitted between December 2012-August 2013 and December 2013-August 2014, were classified as being treated under either the "pre-streaming" or "post-streaming" models of care, respectively. Patients admitted under a general medical unit at any time during their hospital admission were considered as general medical patients. Where patients were transferred between cardiac units, admissions were classified according to a hierarchy of heart failure, arrhythmia then ACS, reflecting the general flow of transfers given that heart failure represents a key final end-state of most cardiac conditions requiring more complex co-ordination of care (i.e. patients admitted to ACS then transferred to arrhythmia, then heart failure were counted as heart failure admissions).

14.3.4.2 Patient Diagnosis and Procedural Information:

The patient's principal admission diagnosis, recorded by trained administrative coders using standardised approaches to admission classification, was used to classify patients into specific cardiac diagnostic groups. Specifically, ICD-10-AM codes I21, I50 and I44-45, recorded as either the primary diagnosis, or up to 10 secondary diagnoses were used to allocate patients into the diagnostic groups of acute coronary syndrome, heart failure or arrhythmia, respectively. Patients with overlapping cardiac codes were allocated in the same hierarchy as described in the unit classification. Baseline demographic and clinical information relied on secondary diagnostic and procedural codes, as well as records from prior admissions retrospectively assessed for 5 years. Direct information in baseline creatinine, haemoglobin and troponin levels were also available through linkage with pathology systems. The proportion of patients receiving cardiac investigations and therapies such as echocardiography, coronary angiography, coronary revascularisation and pacing/implantable cardiac defibrillators, as well as the timing these procedure was determined by linking patient admission records with the

hospital electronic clinical reporting systems, with validation against the ICD-10-AM procedure coding.

14.3.4.3 Patient Outcomes:

Using these administrative data sources, total length of stay, all-cause mortality and major adverse cardiac events (MACE) within 30 days of discharge from index hospitalisation was determined. MACE was defined as death or readmission for new or recurrent myocardial infarction, heart failure or cardiac arrhythmia within 30 days. In addition, a second composite endpoint defined as death or all cardiovascular readmissions (i.e. readmission with any cardiac ICD-10-AM code as primary or secondary diagnosis) within 30 days was examined. Mortality data was confirmed by both hospital and state record systems. Readmission classification relied on the primary and secondary ICD-10-AM diagnoses, as well as supportive evidence from linked pathology and radiology systems and assessment of the discharge summary documentation.

14.3.5 Statistical Methods

Patients admitted to the cardiology unit before and after the period of streaming were compared. For each comparison, analyses included the entire cohort of cardiology patients and then subsequent analyses focus on patients within the specific diagnostic classifications of ACS, arrhythmia and heart failure. The use of cardiac investigations and therapies, reflecting the medical decision-making, was evaluated by examining the differences in the rates of the key cardiac investigation and treatments (i.e. echocardiography, coronary angiography, coronary revascularisation and cardiac pacing procedures) before and after streaming. The association between the streaming model of care and the efficiency of care was examined by assessing median time to these procedures and the total length of stay. Evaluation of the association between streaming and outcome examined all-cause mortality, MACE and death or recurrent

cardiovascular admissions by 30 days. Each of these comparisons relied on univariate comparisons with the exception of the outcome analyses where adjusted cox proportional hazards models were employed. To adjust for baseline differences in patient characteristics, a propensity score for the likelihood of being admitted before or after implementation of the streaming model was developed. Specification of the model was assessed using the link test and the final model included the principal cardiac diagnosis, age, gender, Charlson index, baseline creatinine level, haemoglobin level, troponin level, as well as atrial fibrillation, concurrent stroke, pulmonary disease and psychiatric diagnoses. Patients included in the propensity-adjusted models included only those within the range of common support propensity score (median bias after matching in cohorts (1.6%)), and the final models included the propensity score as a continuous variable, and consistency with the proportional hazards assumption was confirmed. A significance level of 0.05 was used, and all analyses were conducted using STATA 13.1 (College Station, TX).

14.4 Results

14.4.1 Intervention implementation

The service redesign was planned over a period of 12-months. Implementation of the new model of care required rearrangement of junior medical staff and consultant rosters, as well as a change in the organisation of nursing care. Specific workflow aspects considered in the implementation included: the timely access to decision-making managed by the senior registrar; the function of the model after-hours; and interactions with the emergency department and general medical units. Key factors in the acceptance of the new model were anticipated benefits to nursing efficiency, clinical team dynamics, training of junior medical staff, and co-ordination of clinical research activities. Support for the model was negotiated amongst the consultant

cardiologist and nursing teams as a trial for 12 months. Hospital executive support was gained once support from all stake-holders was in place, enabling changes to the admitting unit classifications. A date for the change in unit structure was set (0800hrs, December 4th, 2013) and all current inpatients and subsequent admissions were streamed to the condition specific units from that time forward. Once initiated, no subsequent modification of the model was undertaken.

During the implementation period, no change to the total staffing or overall cardiac service bed allocations was made. No additional funding for implementation was required. The frequency of ward rounds for each unit were maintained at one per day, with up to three concurrent rounds occurring across the cardiology service each morning. To maintain concordance between condition specific care needs and the treating team, reallocation between the units occurred at the morning handover meeting or following consultant assessment following the morning ward round. Since allocations to units overnight tended to rely on medical staff with less experience, reinforcement of clinical characteristics used to determine unit allocation required some modest reinforcement early in the implementation. Within the study period, 264 (13.3%) patients were transferred to at least one other unit within the cardiology service and 7 (0.4%) patients had a component of their care provided by all three cardiac units at some time during their in hospital stay. Patients admitted to one of the cardiac units but transferred to another non-cardiac inpatient unit were excluded from this analysis.

14.4.2 Patient Characteristics

A total of 3851 patients were discharged from the cardiology service within the study period, but the unit allocation could not be administratively determined in 3 patients, leaving 3848 patients included in the analysis. Of these patients, 1830 were prior to and 2018 were admitted subsequent to the implementation of the streaming model reflecting the natural growth of cardiac admissions. The median age of the population

was 68.9 (i.q.r. 57.2-79.3) years, while 1534/3848 (39.5%) were female. Key clinical characteristics stratified pre and post-streaming are presented in Table 1. There was no significant difference in the proportion of patients admitted with a final diagnosis of ACS, arrhythmia and heart failure before and after the implementation of streaming. After streaming was implemented, patients admitted to the cardiology units were more likely to have a history of prior myocardial infarction, heart failure, diabetes and hypertension but no more likely to have a history and atrial fibrillation, or malignancy.

Table 1: Baseline Characteristics stratified by admission before and after the implementation of the streaming model of care

Characteristic	Pre-streaming (n=1830)	Post-streaming (n=2018)	Total (n=3848)	P-value
Age (years, median, i.q.r)	68.7 (56.8-78.8)	69.2 (57.9-79.8)	68.9 (57.2-79.3)	0.170
Female Gender (n, %)	728 (39.8)	806 (39.9)	1534 (39.9)	0.920
Primary diagnostic group				
ACS (n, %)	950 (51.9)	1059 (52.5)	2009 (52.2)	0.071
Heart Failure (n, %)	188 (10.3)	235 (11.7)	423 (11.0)	
Arrhythmia (n, %)	347 (19.0)	323 (16.1)	670 (17.4)	
Other Diagnosis (n, %)	345 (18.9)	401 (19.9)	746 (19.4)	
ACS Type				
STEMI (n, %)	133 (7.3)	133 (6.6)	266 (6.9)	0.001
NSTEMI (n, %)	252 (13.8)	237 (11.7)	489 (12.7)	
Unstable Angina (n, %)	192 (10.5)	176 (8.7)	368 (9.6)	
Chest pain for Investigation (n, %)	366 (20.0)	509 (25.2)	875 (22.7)	
Initial eGFR (median, i.q.r)	74 (53-96)	72 (51-92)	73 (52-94)	0.029
Initial Haemoglobin (median, i.q.r)	133 (120-146)	133 (121-145)	133 (120-145)	0.859
Initial Troponin (median, i.q.r)	<29 (29-98)	<29 (29-77)	<29 (29-88)	0.463

Initial Troponin (mean, SD)	321 (1307)	324 (1701)	323 (1521)	
Initial Albumin (median, i.q.r)	37 (34-34)	37 (34-39)	37 (34-39)	0.132
Diabetes (n, %)	372 (20.3)	463 (22.9)	835 (21.7)	0.049
Hypertension (n, %)	693 (37.9)	833 (41.3)	1526 (39.7)	0.031
Prior Heart Failure (n, %)	319 (17.4)	414 (20.5	733 (19.1)	0.015
Prior Myocardial Infarction (n,%)	277 (15.1)	381 (18.9)	658 (17.1)	0.002
Known Atrial Fibrillation (n,%)	350 (19.3)	401 (19.9)	751 (19.5)	0.560
Prior Cancer (n, %)	348 (19.0)	386 (19.3)	734 (19.1)	0.930
Prior CVA (n, %)	1 (0.05)	2 (0.1)	3 (0.08)	0.622
Charlson Index 1 (n, %)	482 (26.3)	547 (27.1)	1029 (26.7)	0.660
Charlson Index 2 or more (n, %)	251 (13.7)	290 (14.4)	541 (14.1)	

ACS: Acute Coronary Syndrome, STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; eGFR: estimated Glomerular Filtration Rate.

14.4.3 Use of Investigation and therapies

Overall, there was a lower rate of echocardiography (post-streaming: 1121/2018 (55.6%) vs. pre-streaming: 1087/1830 (59.4%), p=0.016), with this reduction observed similarly among those with a final diagnosis of ACS, heart failure or arrhythmia, but not among those with a final diagnosis outside these groups. Use of angiography following the implementation was also lower (post-streaming: 630/2018 (31.2%) vs. pre-streaming: 647/1830 (35.4%), p=0.007), but no difference in those patients discharged

with myocardial infarction or unstable angina was observed, or those with an elevation in troponin T (Table 2). Consequently, the largest reductions were observed among those admitted for the ruling out of ACS, with a commensurate reduction in the provision of percutaneous coronary revascularisation or coronary artery bypass grafting in among these patients. Furthermore, a modest reduction in the time from admission to provision of angiography was also observed in the overall population (post-streaming: 17.9 (3.4-37.0) hours vs. pre-streaming: 19.8 (9.8-41.6), p=0.001), and among ACS patients (post-streaming: 16.2 (2.9-28.4) hours vs. pre-streaming: 18.1 (6.9-33.5), p=0.014). There was no observed difference in the rate of pacemaker or ICD use in hospital.

Table 2: Utilisation of cardiac procedures before and after the implementation of the streaming model of care

Characteristic	Pre-streaming (n=1830)	Post-streaming (n=2018)	Total (n=3848)	P-value
Echocardiography (n,%)	1087 (59.4)	1121 (55.6)	2208 (57.4)	0.016
Angiography (n,%)	647 (35.4)	630 (31.2)	1277 (33.2)	0.007
Angiography by Acute Coronary Syndrome type				
STEMI (n=266) (n, %)	123 (92.5)	125 (94.0)	248 (93.2)	0.625
NSTEMI (n=389) (n, %)	204 (80.5)	187 (79.9)	391 (80.0)	0.572
Chest Pain/UA (n=1243) (n, %)	183 (32.8)	174 (25.4)	347 (28.7)	0.004
PCI (n,%)	273 (14.9)	272 (13.5)	545 (14.2)	0.201
CABG (n,%)	86 (4.5)	60 (3.0)	146 (5.7)	0.017
PPM (n, %)	78 (4.3)	89 (4.4)	167 (4.3)	0.822
AICD (n, %)	19 (1.0)	23 (1.1)	42 (1.1)	0.762

ACS: Acute Coronary Syndrome, STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UA=Unstable angina. PCI= Percutaneous coronary intervention, CABG= Coronary Artery Bypass Grafting, PPM= Permanent Pacemaker, AICD= Automatic Implantable Cardiac Defibrillator

Among MI patients, there was a modestly greater initiation of statin therapy in hospital (post-streaming 241/370 (65.2%) vs. 222/385 (57.7%), p=0.035), and by discharge the proportion of patients receiving all 5 guideline advocated medications (i.e. aspirin, $P2Y_{12}$ inhibition, statin, ACE-I or angiotensin receptor antagonist (ARA) and beta-blockade) was also slightly higher (post-streaming 161/370 (43.5%) vs. 134/385

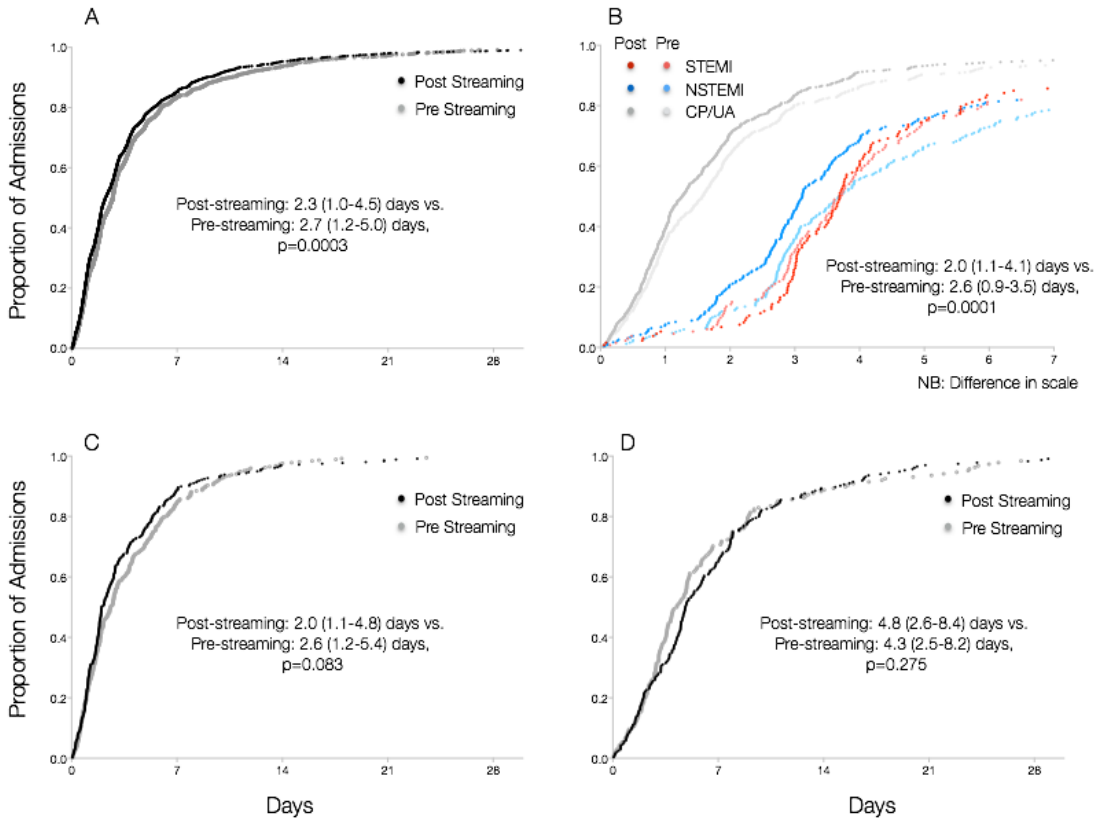
(34.8%), p=0.014). In those patients discharged from the heart failure service, there was no significant increase in patients being discharged on beta-blockers (post-streaming 176/235 (74.9%) vs. 129/188 (68.6%), p=0.153), or ACE-I/ARA (post-streaming 128/235 (54.5%) vs. 87/188 (46.3%), p=0.097). However, there was a small shift towards greater ACE-I use (post-streaming 85/235 (36.2%) vs. 49/188 (26.1%), p=0.026). Among patients with atrial fibrillation, there was a significant increase in the use of either warfarin or the newer oral anticoagulants following the implementation of streaming (post-streaming 146/2226 (64.4%) vs. 113/253 (44.7%), p<0.001).

14.4.4 Time to care and length of stay

A small increase in the time to echocardiography was observed (post-streaming: 20.1 (12.1-40.0) hours vs. pre-streaming: 18.2 (10.2-40.0), p=0.050). A modest reduction in the time to angiography was also observed in the overall population (post-streaming: 17.9 (3.4-37.0) hours vs. pre-streaming: 19.8 (9.8-41.6), p=0.001), and among ACS patients (post-streaming: 16.2 (2.9-28.4) hours vs. pre-streaming: 18.1 (6.9-33.5), p=0.014). However, for patients requiring inpatient CABG, significant reduction in the median delay to surgery was observed (post-streaming: 4.9 (3.2-8.0) days vs. pre-streaming: 6.4 (4.8-8.4) days, p=0.045).

An overall reduction in length of length of stay was observed in the entire cohort (median (i.q.r.) post-streaming: 2.3 (1.0-4.5) days vs. pre-streaming: 2.7 (1.2-5.0) days, p=0.0003) (Figure 1). This benefit was significant among patients within the ACS stream, and within this cohort, a consistent benefit was evident among all subgroups although the largest benefit was achieved in the non-ST segment elevation cohort. A similar reduction in length of stay was observed in the arrhythmia stream, while an increase in length of stay was evident in the heart failure cohort though neither of these differences achieved statistically significance.

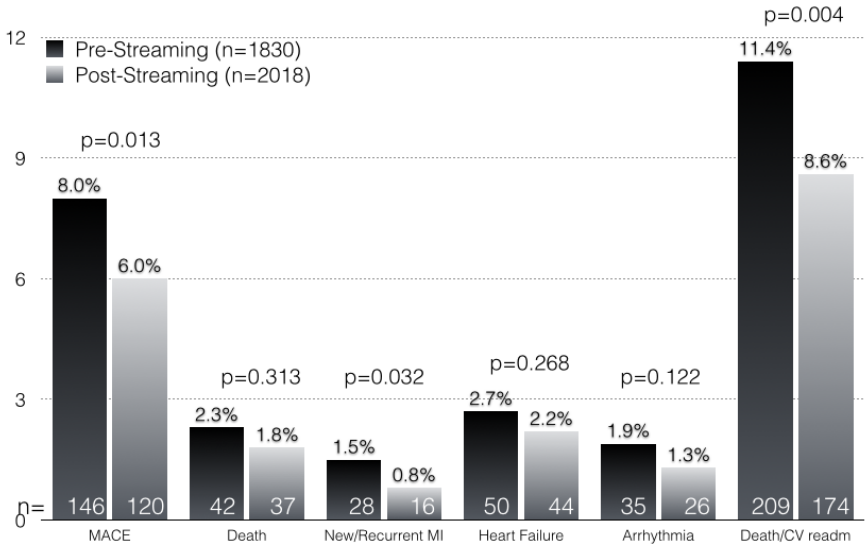
Figure 1: Length of Stay before and after the implementation of the streaming model of care in the (a) overall group, (b) ACS patients by diagnosis, (c) arrhythmia patients, and (d) patients with heart failure. ACS: Acute Coronary Syndrome, STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; CP/UA: Chest pain/Unstable Angina



14.4.5 Outcomes by 30 days

The characteristics of the propensity matched-cohort and unadjusted rates of death, MACE and any death/cardiovascular readmission by 30-days are presented in Tables 3 and Figure 2, respectively. Overall, there was a consistent relative reduction of each of these endpoints, which was of marginal significance for MACE and death or any cardiovascular readmission persisting within the propensity-adjusted analysis.

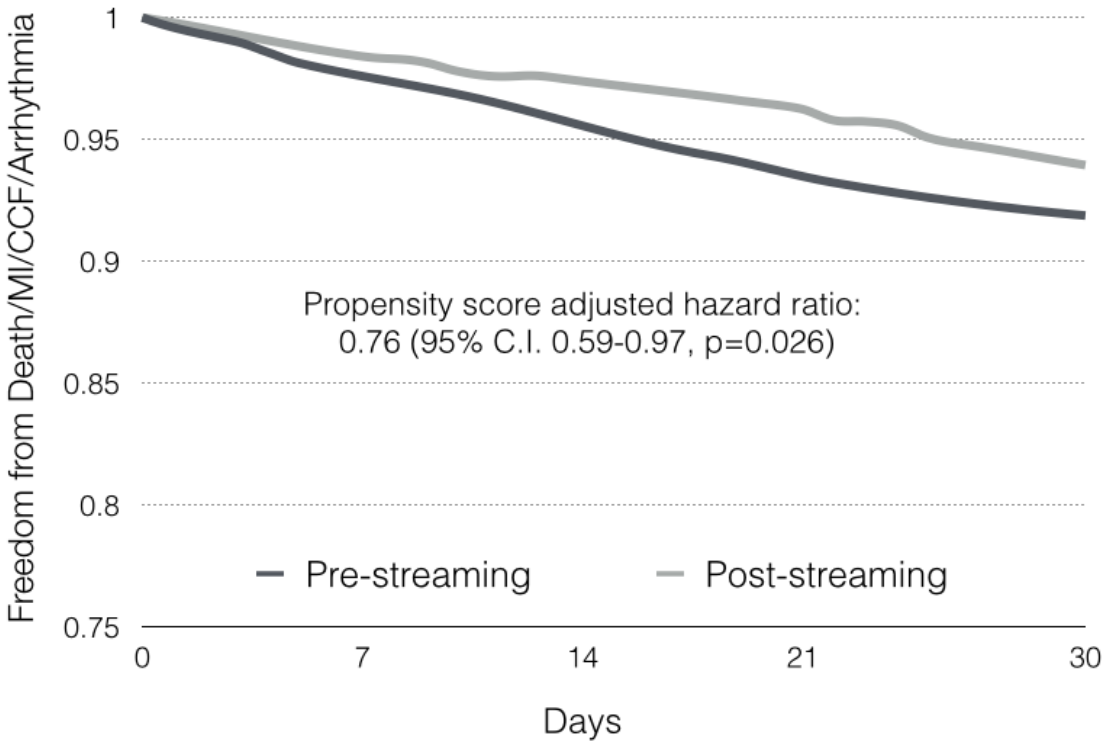
Figure 2: Unadjusted 30-day outcomes in the overall population. MI = Myocardial Infarction, CV = Cardiovascular



By 30 days, the propensity-adjusted hazard ratio for MACE and death or any cardiovascular admission was 0.76 (95% C.I. 0.59-0.97, p=0.026) and 0.76 (95% C.I. 0.61-0.93, p=0.008), respectively (Figure 3). Examining the association within each cardiac stream would suggest a stronger relationship between the implementation of a streaming model and reductions in death or any cardiovascular admission was more evident among patients with principal ACS (propensity-adjusted HR: 0.68, 95% C.I.

0.49-0.93, p=0.018) or arrhythmia (propensity-adjusted HR: 0.56, 95% C.I. 0.34-0.90, p=0.016) diagnoses, than with heart failure diagnoses (propensity-adjusted HR: 0.93, 95% C.I. 0.61-1.41, p=0.721) though the interaction between diagnosis and the observed benefit from streaming was not statistically significant.

Figure 3: Freedom from death, new-recurrent MI, heart failure readmission and stroke by 30 days, adjusted for propensity score.



14.5 Discussion

With increasing pressures to improve efficiency and productivity in modern acute care, continual health service redesign with approaches to ensure expert decision-making coupled with timely implementation of diagnostic and therapeutic interventions is needed. In acute cardiovascular care, there has been a robust history of streaming patients by acuity to ensure the timely provision of life-saving or complex therapies. The development of coronary care units for the urgent provision of fibrinolysis and cardiac defibrillation, as well as advanced heart failure services for the management of

cardiac transplantation are successful examples of this approach. [6,14,15] Similarly, chest pain assessment units emerged to enable more structured risk stratification, separating these patients from the heterogeneity of patient risk observed within ED presentations.[16] The innovation of “whole of service cardiac streaming” has sought to examine the impact of streaming all patients admitted to a cardiology unit into principal diagnostic streams irrespective of acuity with the aim of improving consistency of decision-making and efficiency in care. This analysis suggests that such service redesign, shifting from an acuity focus to a disease-specific focus may offer superior risk-appropriate care, with greater efficiency in service delivery combined with improvement in patient outcome.

Effective and cost-effective implementation of the rich cardiovascular evidence base is dependent on appropriate diagnostic and risk assessment, combined with timely access to diagnostic and therapeutic management strategies and their proficient delivery.[17,18] Given the often time critical and invasive nature of modern cardiovascular care, shortfalls in either of these aspects may result in inappropriate care, resulting in both overtreatment and under-treatment with an increased risk of suboptimal outcome as well as inefficiencies.[19,20] Ensuring that the highest level of clinical expertise is present at the start of this process is an obvious solution for optimising risk stratification and negotiating timely access to care. However, such investment is often not feasible, particularly as the complexity of care continues to expand and medical expertise continues to fragment and diversify. At the same time, a mature evidence-base should enable a greater proportion of the clinical workforce to make ever more complex decisions. The aim of the streaming model was to align the diagnostic classification of patients with the subspecialty expertise of the health care professionals treating them, in order to support the integrity of risk assessment, access and quality of care paradigm across the whole spectrum of cardiology admissions.

This analysis observed a modest decrease in the use of coronary angiography and revascularisation, driven by a reduction in the use of angiography in low-risk patients, but no difference in the already high rate of use in those with STEMI and NSTEMI. Similarly, there was no difference in the use of pacing procedures among those patients presenting with arrhythmia or heart failure diagnoses. These observations may suggest that the use of invasive procedures was more aligned with patient risk and consistent with evidence-based recommendations. In contrast, there was a reduction in length of stay for both ACS and arrhythmia diagnoses but no reduction among heart failure potentially reflecting the different factors determining length of stay in the therapeutically more complex heart failure patient. A more detail redesign of heart failure services integrating inpatient care with more sophisticated transition of care services may be required to realise effectiveness and efficiency gains.

With the improved efficiency, the observed reduction in subsequent composite events is reassuring. This would suggest that the streaming model was associated with improvements in aspects of care that are not well measured by assessing procedural rates and timing. Such aspects include completeness of pharmacotherapies and patient counseling and education. Streaming by diagnosis potentially enables more consistent provision of these aspects of care for a greater proportion of patients, suggesting that a key factor driving the benefits of the streaming model is the ability to enhance the effectiveness of nursing and junior medical staff roles. Furthermore, providing a continuous experience of patients with similar clinical conditions may enable more rapid acquisition of clinical experience, irrespective of subspecialisation, by allowing less experienced clinicians the opportunity to observe the correlation between negative prognostic patient characteristics and sub-optimal outcome. Hence, an additional benefit of the streaming model is it offers a more robust training environment. [21] Similarly, when considering the continual availability of innovations and new technologies in cardiovascular care, a more constant clinical team may

facilitate the more rapid and effective adoption of these innovations with commensurate adaptive evolution in other aspects care, thought this is yet to be demonstrated.

Several limitations should be considered. Given the difficulties in reorganizing clinician workflow and the inability to blind the allocation to streams, assessing the impact of a streaming model of care within a randomised clinical trial was considered to be insurmountably challenging. Therefore, we cannot exclude the possibility that these differences are driven by secular trends (i.e. the continued improvement of cardiac outcomes) leading to a reduction in the risk characteristics within the post-streaming cohort, although these differences persist within propensity-adjusted analysis. In addition, this analysis only presents 30-day mortality and readmission rates. The true value of this heath service redesign will need to be defined by longer-term follow-up and analyses.

14.6 Conclusions

Streaming of cardiology care by presenting disease rather than acuity is associated with reduced length of stay and superior short-term outcomes. Cardiac service redesign that extends the this model to presenting diagnosis may provide capacity and productivity gains for many health services striving to improve outcome and the efficiency of cardiac care.

14.7 Acknowledgement

The authors would like to thank Marleesa Ly for her editorial support in preparing this manuscript.

No external financial support.

Attribution

DPC, CDP, AMcG & JCV designed planned and implemented the intervention. MH & BM provided access to the data. DPC performed the analysis and drafted the initial manuscript. All authors have had access to the data and have provided input into the final manuscript.

Conflicts of Interest

None of the authors have any conflicts of interest with respect to the content of this manuscript.

14.8 References

1 Califf RM. Evaluation of diagnostic imaging technologies and therapeutics devices: Better information for better decisions. Am Heart J 2006;152:50–8. doi:10.1016/j.ahj.2005.10.001

2 Fonsec R, Negishi K, Otahal P, et al. Temporal Changes in Appropriateness of Cardiac Imaging. J Am Coll Cardiol 2015;65:763–73. doi:10.1016/j.jacc.2014.11.057

3 Fox KAA, Steg PG, Eagle KA, et al. Decline in Rates of Death and Heart Failure in Acute Coronary Syndromes, 1999-2006. JAMA 2007;297:1892–900. doi:10.1001/jama.297.17.1892

4 Chew DP, Huynh LT, Liew D, et al. Potential survival gains in the treatment of myocardial infarction. Heart 2009;95:1844–50. doi:10.1136/hrt.2009.174276

5 Al-Khatib SM, Hellkamp A, Curtis J, et al. Non-evidence-based ICD implantations in the United States. JAMA 2011;305:43–9. doi:10.1001/jama.2010.1915

6 Jollis JG, Roettig ML, Aluko AO, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. JAMA 2007;298:2371–80. doi:10.1001/jama.298.20.joc70124

7 Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. Stroke Unit Trialists' Collaboration. BMJ 1997;314:1151–9.

8 Joynt KE. Quality of Care and Patient Outcomes in Critical Access Rural Hospitals. JAMA 2011;306:45. doi:10.1001/jama.2011.902

9 Chew DP, French J, Briffa TG, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. Med J Aust 2013;199:185–91. doi:10.5694/mja12.11854

10 Goodrich K, Krumholz HM, Conway PH, et al. Hospitalist utilization and hospital performance on 6 publicly reported patient outcomes. J Hosp Med 2012;7:482–8. doi:10.1002/jhm.1943

11 Rothberg MB, Belforti R, Fitzgerald J, et al. Four years' experience with a

hospitalist-led medical emergency team: An interrupted time series. J Hosp Med 2011;7:98–103. doi:10.1002/jhm.953

12 Ayanian JZ, Hauptman PJ, Guadagnoli E, et al. Knowledge and practices of generalist and specialist physicians regarding drug therapy for acute myocardial infarction. New England Journal of Medicine 1994;331:1136–42. doi:10.1056/NEJM199410273311707

13 Dorsch M, Lawrance R, Sapsford R, et al. An evaluation of the relationship between specialist training in cardiology and implementation of evidence-based care of patients following acute myocardial infarction. Int J Cardiol 2004;96:335–40.

14 Katz JN, Shah BR, Volz EM, et al. Evolution of the coronary care unit: Clinical characteristics and temporal trends in healthcare delivery and outcomes*. Critical Care Medicine 2010;38:375–81. doi:10.1097/CCM.0b013e3181cb0a63

15 Takeda A, Taylor SJ, Taylor RS, et al. Clinical service organisation for heart failure. … Database Syst Rev Published Online First: 2012. doi:10.1002/14651858

16 Aroney CN, Dunlevie HL, Bett JHN. Use of an accelerated chest pain assessment protocol in patients at intermediate risk of adverse cardiac events. Med J Aust 2003;178:370–4.

17 Fonarow G, Adams K, Abraham W, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005;293:572–80.

18 Kamineni R, Alpert J. Acute coronary syndromes: initial evaluation and risk stratification. Prog Cardiovasc Dis 2004;46:379–92.

19 Chew DP, Junbo G, Parsonage W, et al. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. Circulation: Cardiovascular Quality and Outcomes 2013;6:299–308. doi:10.1161/CIRCOUTCOMES.111.000072

20 Scott I, Derhy P, O'Kane D, et al. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. Med J Aust 2007;187:153–9.

21 Mueller SK, Lipsitz S, Hicks LS. Impact of hospital teaching intensity on quality of care and patient outcomes. Med Care 2013;51:567–74. doi:10.1097/MLR.0b013e3182902151

SECTION 5 INSIGHTS INTO THE FACTORS THAT MAY DRIVE POLICY INTERVENTIONS AIMED AT IMPROVING ACS CARE

15 VARIATION IN CORONARY ANGIOGRAPHY RATES IN AUSTRALIA: CORRELATIONS WITH SOCIO-DEMOGRAPHIC, HEALTH SERVICE AND DISEASE BURDEN INDICES

15.0 Title page : Variation in Coronary Angiography across Australia: exploring the correlations with sociodemographic-health service and disease burden indices.

Derek P Chew[1,2], Andrew MacIssac[3], Jeff Lefkovits[3], Richard Harper[4], Luke Slawomirski[5], Matthew Horsfall[6,7], Heather Buchan[5], Chris Ellis[8], David Brieger[9], Tom Briffa[10]

Author Affiliations

[1] School of Medicine, Flinders University of South Australia, Adelaide, Australia

[2] Department of Cardiovascular Medicine, Southern Adelaide Local Health Network, Adelaide, Australia

[3] School of Medicine, St Vincent's Hospital, University of Melbourne, Melbourne Australia

[4] Monash Heart and Monash Cardiovascular Research Centre, Monash University and Monash Health.

[5] Australian Commission for Quality and Safety in Health Care, Sydney, Australia

[6] SA Health, Adelaide, Australia

[7] Health Systems Research, South Australian Health and Medical Research Institute, Adelaide, Australia

[8] Department of Cardiology, Greenlane CVS Services, Auckland City Hospital, Auckland, New Zealand

[9] Department of Cardiology, Concord Hospital, University of Sydney, Sydney, NSW.

[10] School of Population Health, University of Western Australia, Perth, Australia

Authors' declaration:
All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Running Title: Variation in Angiography in Australia

Key Words: Variation in Care, Health service, Coronary Angiography,

Myocardial Infarction

15.1 Abstract

Background: Variation in the provision of coronary angiography is associated with health care inefficiency and inequity. We explored geographic, socioeconomic, health service and disease indicators associated with variation in angiography across Australia.

Methods: Australian Census and National Health Survey data were used to determine socioeconomic, health workforce and service indicators. Hospital separations and coronary deaths were identified from the National Hospital Morbidity and Mortality databases 2011. Using all 61 Medicare Locals that are responsible for primary care, age-sex standardised rates of acute coronary syndrome (ACS) incidence, coronary angiography, revascularisation and mortality were tested for correlation, and adjusted using Bayesian regression.

Results: The variation in ACS rates was 3.7-fold and 2.3-fold for mortality, whereas angiography rates varied 5.3-fold. ACS and death rates within Medicare Locals were correlated (partial correlation co-efficient (CC): 0.52 ($p<0.0001$). There was modest correlation between ACS and angiography rates (CC: 0.31, $p=0.018$). Revascularisation as the proportion of angiography and the total angiogram rate was inversely correlated (CC: -0.71, ($p<0.0001$). Socioeconomic disadvantage and remoteness correlated with disease burden, ACS incidence and mortality, but not angiography. In the adjusted analysis, admissions to private hospitals demonstrated the strongest association with local angiography rates (71 angiograms (95% C.I. 47-93) per 100,000 for every 1000 admissions).

Conclusion: Variation in coronary angiography, not related to clinical need, occurs across Australia. A greater focus on clinical care standards and better distribution of health services will be required if these variations are to be attenuated.

15.2 Introduction

Coronary angiography for the management of coronary artery disease (CAD) is informed by an extensive evidence-base.[1-5] Variation in coronary angiography has been observed selectively in Australia.[6,7] This may be explained by heterogeneity in clinical need (i.e. variations in disease incidence or prevalence). However, variation unexplained by differences in disease burden highlights equity in health service access, differential over and under use of healthcare resources. These represent potential targets for policy interventions aimed at improving population health and a high quality health system.

Health care in Australia faces a combination of challenges. Geographic distribution of the population, and substantial cultural diversity, gives rise to complexity in providing access to clinical expertise and procedures such as angiography. Clinical audits of ACS practice document variation in components of guideline advocated care, in particular invasive management.[8-12] Australia's demography may contribute to heterogeneity in the access to health services, differential clinical needs and variation in care. Understanding the relative contribution of these factors has potential implications for both national policy, and local efforts to redesign health services. This analysis seeks to: a) explore the socioeconomic, geographic, and chronic disease associations with ACS incidence and mortality rates; and b) examine whether rates of coronary angiography correlate with indicators of disease burden, health access and clinical activity across the entire Australian population.

15.3 Methods

15.3.1 Data Sources

This analysis spans the entire Australian population of ~23.5 million people. Between 2010 and 2015, federal government support for primary care services was organised into 61 geographic locations, known as Medicare Locals.

15.3.2 Socioeconomic and health workforce data

Social, economic and health services characteristics of the Medicare Locals were sourced through a publicly available website which assimilates and publishes age and sex standardised rates including the estimated proportion of privately insured residents, and the proportion of indigenous residents all drawn from the 2011 Australian Census (conducted by the Australian Bureau of Statistics [ABS]).[13] In addition, the Socio-Economic Indexes for Areas (SEIFA) a relative measure of social and economic disadvantage (normalised to 1000, higher numbers imply more advantaged areas), are available. Medical workforce data were drawn from the Australian Health Practitioners Registration Authority's yearly survey that records primary locations of practice and specialisation of all registered medical practitioners. Furthermore, modelled rates of chronic cardiovascular conditions (prior myocardial infarction (MI) and angina, heart failure, stroke and rheumatic heart disease) utilising the estimates derived from the Australian Health Survey 2011-2013 (conducted by the ABS) were also available for all but 3 Medical Locals.

As an indicator of local clinical practice within each region, the "likelihood that a suspected ACS patient receives coronary angiography compared with the national average", was estimated from the SNAPSHOT ACS clinical audit published elsewhere.[9,10] (See supplement)

15.3.3 Rates of ACS, Angiography, Revascularisation and Mortality

The National Hospital Morbidity Dataset (NHMD) was used to identify ACS separations by ICD-10AM principal diagnosis codes of I20 and I21 and catheter procedures. Data on procedures undertaken as ambulatory care cases (e.g. outpatient angiography) were obtained from the Medicare Benefits Schedule, which is held by Medicare Australia. The combined total for angiography is presented throughout. All cardiac-specific admissions were used. Three of the seven state/territory jurisdictions did not report data for private hospital admissions, consequently, private hospital and total admissions were not available for three Medicare Locals. Deaths due to CAD were determined from the National Mortality Database (NMD). The AIHW's work program is conducted with oversight by its Ethics Committee and in accordance with the AIHW Act, the Privacy Act and any terms and conditions set by data providers, as is any release of data from the AIHW datasets. Separate Ethics Committee approval is not required for analysis of the AIHW's datasets that does not involve data linkage, such as the analysis that was undertaken for this study. The description of the data extraction process is provided in the supplementary information.

15.3.4 Statistical analysis

Standardised age and sex specific rates were calculated by dividing the number of ACS separations, inpatient and outpatient angiography, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) procedures and CAD deaths occurring in individuals aged 35 years and over (grouped in 5-year age intervals up to 85 years and over) and sex group by the corresponding population for that age and sex group and expressed per 100,000 individuals of the population. The 30 June 2001 Australian population was used as the standard population.

Socioeconomic, health service information, procedure and ACS incidence and mortality rates were stratified by geographic location of the Medicare Local, defined by the Australian Institute of Health and Welfare (AIHW), and compared using a Kruskal-

Wallis test. Univariate correlations between potential explanatory factors and rates for angiography, ACS and mortality were performed using partial correlations reporting the adjusted correlation co-efficient (CC) and p-value (i.e. strength of correlation: strong: >0.70, moderate: 0.50-0.69, weak: 0.3-0.49) . Separate correlation plots of ACS vs CAD mortality rates, and angiography vs ACS rates were generated with fitted linear predictions superimposed. To assess the potential overuse of angiography, the ratio of coronary revascularisation to coronary angiograms was calculated for each Medicare Local, and plotted as a function of the rate of coronary angiograms using the fractional polynomial estimate.

Given the small numbers of Medicare locals, and the availability of prior data to evaluate these relationships, a Bayesian linear regression approach was used (See Supplement). All analyses were undertaken using Stata 14.0 (College Station, TX) and a probability value of <0.05 was considered statistically significant.

15.4 Results

15.4.1 Characteristics of the Medicare Locals

Among the 61 Medicare Locals with socioeconomic data, 27 were categorised as metropolitan, 24 as regional and 10 rural based on AIHW criteria. Regional and rural locations were significantly more disadvantaged with higher proportions of the population on long-term unemployment support, greater reported delays in seeking medical consultation due to costs and lower proportions of private health insurance. Similarly, prevalence of smoking, obesity and chronic cardiovascular disease was higher in regional and rural areas than in metropolitan areas. There was no difference in the rate of total hospital admissions by geographic location, but a significantly lower rate of private hospital admissions in non-metropolitan locations, where few exist. (Table 1)

Table 1: Socioeconomic and health service characteristics and Age and sex standardised rates death, diagnosis, and coronary procedures by Medicare Locals stratified by Metropolitan, Regional and Rural Locations (*rates per 100,000 individuals unless otherwise specified)

	Total (n=61)	Metro (n=27)	Regional (n=24)	Rural (n=10)	P value
SEIFA (Score, mean, SD)	992 (42)	1022 (39)	976 (21)	955 (33)	0.001
Indigenous (%, mean, SD)	3.9 (5.5)	1.1 (0.7)	3.1 (2.1)	13.2 (8.1)	0.001
Long-term Unemployment (%, mean, SD)	3.5 (1.4)	2.6 (1.1)	4.1 (1.0)	4.6 (1.5)	0.001
Private Insurance (%, mean, SD)	44.3 (9.9)	51.7 (9.3)	40.8 (4.3)	33.0 (5.2)	0.001
Diabetes (%, mean, SD)	5.3 (1.0)	5.7 (1.1)	4.8 (0.7)	5.5 (0.9)	0.004
Hypertension (%, mean, SD)	10.2 (0.6)	10.2 (0.6)	10.3 (0.6)	10.1 (0.5)	0.994
****Smokers (%, mean, SD)**	19.1 (3.6)	16.2 (2.9)	21.4 (1.8)	22.8 (1.5)	0.001
****Obesity (%, mean, SD)**	28.3 (4.2)	25.5 (4.4)	30.6 (1.9)	31.4 (2.1)	0.001
Hypercholesterolaemia (%, mean, SD)	33.1 (1.7)	32.9 (1.4)	33.6 (1.8)	32.1 (2.2)	0.186
** **Chronic CV condition (rate, mean, SD)**	88 (14)	81 (11)	91 (9)	102 (21)	0.0002
Premature IHD deaths, (rate, mean, SD)	28.4 (10.2)	22.9 (5.1)	27.6 (3.4)	45.3 (13.3)	0.0001

Delay in Medical Consultation (%, mean, SD)	14.6 (3.6)	13.2 (3.8)	15.3 (2.9)	16.8 (3.1)	0.0065
Primary Care Physicians (rate mean, SD)	110.8 (17.4)	113.9 (22.1)	109.1 (10.8)	106.3 (15.8)	0.776
****Specialist Physician (rate, mean, SD)**	22.9 (21.6)	34.2 (26.7)	13.4 (6.5)	10.8 (6.4)	0.0017
Primary care health check (rate, mean, SD)	4266 (1181)	4336 (1034)	4548 (1239)	3401 (1111)	0.0321
Public Cardiac admissions (rate, mean, SD)	1684 (451)	1366 (274)	1826 (316)	2201 (479)	0.0001
§Private Cardiac admissions (rate, mean, SD)	752 (264)	861 (202)	717 (283)	527 (227)	0.021
ED presentations (rate, mean, SD)	30881 (11358)	24939 (11358)	32400 (9837)	43277 (17082)	0.0001
ACS angiography Likelihood, (mean, SD)	40.6 (16.7)	49.2 (17.2)	30.9 (8.9)	41.4 (18.2)	0.0006
Myocardial Infarction (mean, SD)	250 (63)	225 (48)	250 (46)	316 (90)	0.0034
Acute Coronary Syndrome (mean, SD)	419 (108)	375 (93)	423 (84)	532 (120)	0.0005
Coronary Angiography (mean, SD)	849 (236)	803 (167)	895 (300)	863 (218)	0.742
PCI (mean, SD)	212 (47)	222 (38)	215 (58)	178 (23)	0.0094
CABG (mean, SD)	70 (15)	64 (13)	74 (15)	75 (18)	0.0398
Revascularisation (mean, SD)	278 (49)	284 (41)	283 (61)	250 (25)	0.0890
#Premature IHD deaths	28.4 (10.2)	22.9 (5.1)	27.6 (3.4)	45.3 (13.3)	0.0001
#Premature CVA deaths	9.2 (2.4)	8.2 (1.6)	9.4 (1.7)	11.5 (3.7)	0.0001

Total Mortality (mean, SD)	88 (14)	81 (11)	91 (9)	102 (21)	0.0002
Population (mean, SD)	296666 (165595)	414767 (144115)	232023 (110353)	132939 (94442)	<0.0001

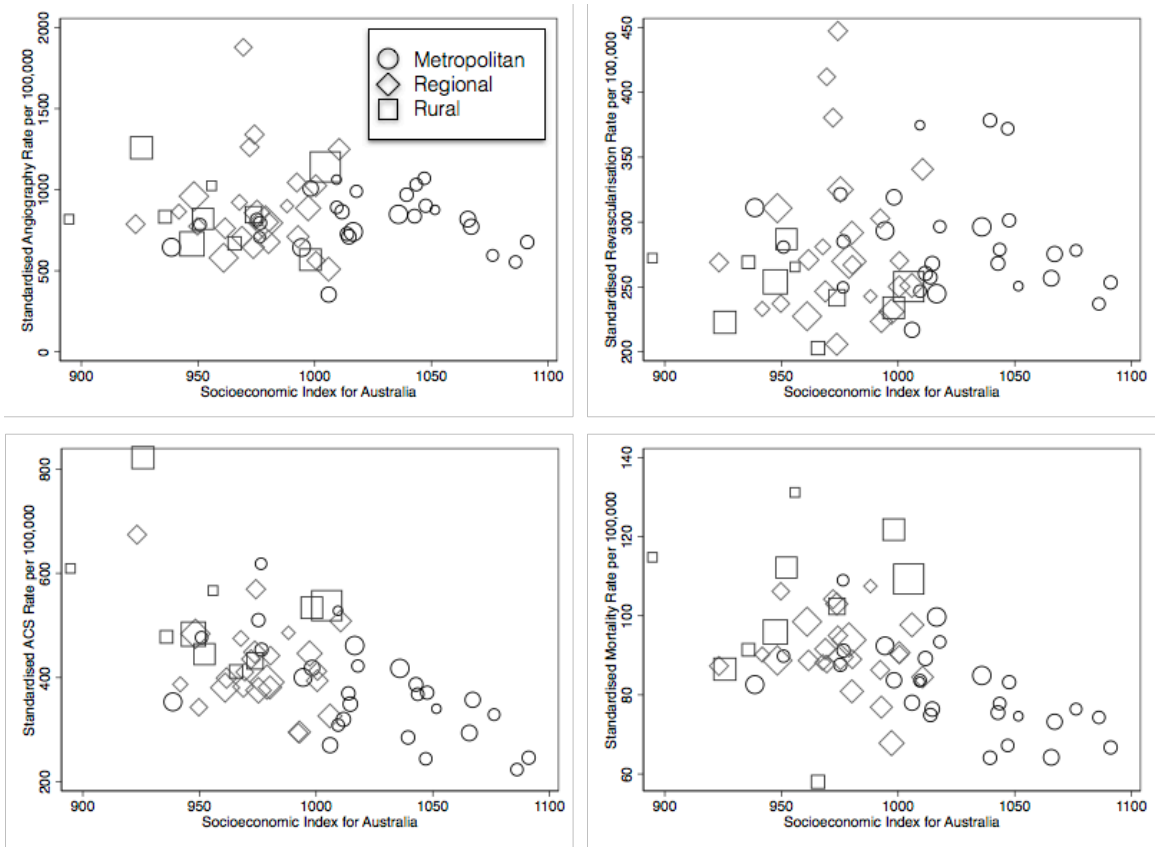
**Estimates from modelled data: not available for 3 Medicare Locals (all rural)

§ Data not released for 3 Locals (1 each for metropolitan, regional and rural)

Annualised rates per 100,000 individuals for 2008-2011

ACS rates were higher outside the metropolitan areas, but this was not reflected in a significantly higher rate of coronary angiography rates. PCI rates were significantly lower in non-metropolitan areas. In contrast rates of CABG were higher for patients from these locations. Overall there was no significant difference in combined coronary revascularisation rates when assessed by geographic location. Premature death from CAD and total mortality were higher in regional and rural areas. Between the lowest and highest rates observed by Medicare Locals, there was a 3.7-fold, 5.3-fold, 2.2-fold and 2.3-fold difference in the rates of ACS, angiography, revascularisation and CAD mortality, respectively. Figure 1 demonstrates the variation in ACS, angiography, revascularisation, and mortality rates in each Medicare Local by SEIFA index.

Figure 1: Variation in Angiography, Revascularisation and ACS and Mortality Rates plotted by Socioeconomic Index of Australia of the Medicare Local. (Shape of symbol reflects location [Metropolitan {circle}, Regional {diamond}, Rural {square} and size represents relative population)



15.4.2 Socioeconomic, Chronic health and Health Service Correlates with ACS and Mortality

Examining the rates of ACS within each Medicare Local demonstrates significant correlations with the rates of all-cause mortality, with partial correlation coefficient of 0.52 ($p<0.001$). There were strong correlations between socioeconomic measures and ACS incidence and mortality. (Table 2) Similarly, rates of smoking, obesity and chronic cardiovascular conditions all correlated with mortality with the former 2 correlated with ACS admissions as well. A strong negative correlation between the proportion of insured people in the Medicare Local and the ACS and all-cause mortality rates was also observed. Conversely, there was a negative correlation between medical workforce primary location and both ACS and mortality incidence, as well as a positive correlation between delaying consultation and these outcomes. An increased likelihood of receiving angiography in admitted patients with suspected ACS appeared to be associated with lower mortality rates. (Table 2)

Table 2: Correlation between indicators of socioeconomic status, health status, health workforce, access and clinical practice, and coronary angiography rates, ACS rates and mortality among Medicare Locals (% indicates correlation between percentage of population and angiography, ACS admission and mortality rates)

	Coronary Angiography rate Correlation coefficient (p-value)	ACS admission rates Correlation coefficient (p-value)	Total Mortality Rate Correlation coefficient (p-value)
Socioeconomic Indicators			
SEIFA	-0.11 (0.42)	-0.62 (<0.0001)	-0.54 (<0.0001)
Indigenous %	-0.08 (0.53)	0.53 (0.002)	0.30 (0.019)
Long-term Unemployment %	-0.07 (0.62)	0.60 (<0.0001)	0.46 (0.002)
Private insurance %	-0.15 (0.24)	-0.65 (<0.0001)	-0.62 (<0.0001)
Chronic Health Status Indicators			
Diabetes %	-0.22 (0.10)	-0.05 (0.72)	0.001 (0.94)
Hypertension %	-0.27 (0.03)	-0.17 (0.20)	0.16 (0.22)
Smoking %	0.25 (0.05)	0.61 (<0.0001)	0.62 (<0.0001)
Obesity %	0.15 (0.26)	0.51 (<0.0001)	0.65 (<0.0001)

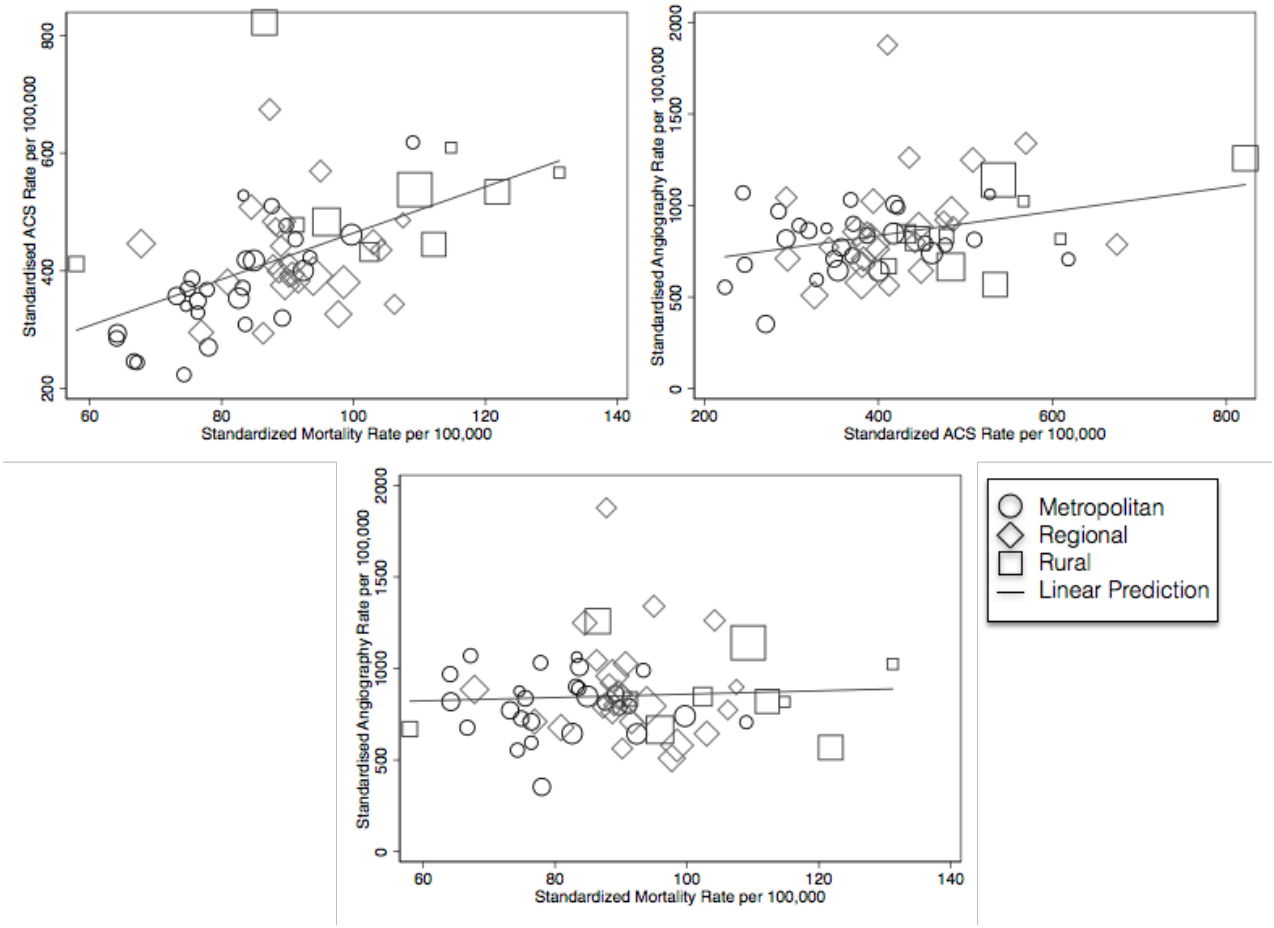
Hypercholesterolaemia %	0.16 (0.23)	-0.39 (0.002)	-0.08 (0.54)
Chronic CV condition %	-0.21 (0.12)	0.05 (0.70)	0.38 (0.0032)
Premature IHD deaths	0.13 (0.32)	0.59 (<0.0001)	0.58 (<0.0001)
	Access and Health Workforce Indicators		
Delay Medical Consult due to cost %	0.05 (0.69)	0.61 (<0.0001)	0.45 (0.0002)
Primary Care Physicians	-0.07 (0.59)	-0.26 (0.04)	-0.39 (0.002)
Specialist Physicians	0.12 (0.37)	-0.41 (0.002)	-0.47 (0.0002)
	Health Service Provision Indicators		
Primary Care 45yrs Health Check	0.28 (0.03)	0.02 (0.88)	-0.12 (0.35)
Public Cardiac Admissions	0.30 (0.02)	0.65 (<0.0001)	0.49 (0.0001)
Private Cardiac Admissions	0.44 (0.006)	-0.13 (0.32)	-0.42 (0.0001)
ED presentations	0.14 (0.28)	0.47 (0.001)	0.35 (0.005)
Likelihood of angiogram in suspected ACS%	0.06 (0.69)	-0.01 (0.96)	-0.40 (0.0017)

An adjusted analysis for mortality rate was performed to explore the potential relationship with the indicators of SEIFA, regional location, local cardiovascular health status (chronic cardiovascular conditions), ACS rates, workforce capacity (access to specialist physician care) and health service provision (cardiac admission rates to public and private hospitals). A rural location was associated with increased mortality (19 deaths (95% C.I. 10-27) per 100,000). Interestingly, the clinical likelihood to undergo coronary angiography in the context of ACS appeared to be associated with a modest reduction in mortality rates (3 fewer deaths (95% C.I. 1-5) per 100,000 for every 10% increased likelihood for angiography in suspected ACS admissions). After considering these two factors, socioeconomic index, disease burden, health service indictors, and angiography rates, were not significantly associated with the Medicare Local CAD mortality rate.

15.4.3 Socioeconomic, Chronic Health Status and Health Service Correlates with Angiography Rates

There was no correlation between measures of social disadvantage or health service availability and coronary angiography rates. (Table 2) A positive correlation between all cardiac admissions and angiography rates was evident, especially when confined to private hospital cardiac admissions rates. This correlation was no-longer evident when restricted to public hospital admissions. The likelihood for angiography among acute patients did not correlate with the overall rate of angiography in the Medicare Locals. There was a low correlation between the rates of angiography and the ACS (CC: 0.31, p=0.018), but no correlation with premature ischaemic heart disease deaths (CC: 0.13, p=0.315) or total CAD mortality (CC: 0.06, p=0.671). (Figure 2)

Figure 2: Correlation between ACS and Mortality, angiography and ACS, and angiography and mortality rates. (Shape of symbol reflects location [Metropolitan {circle}, Regional {diamond}, Rural {square} and size represents relative population)

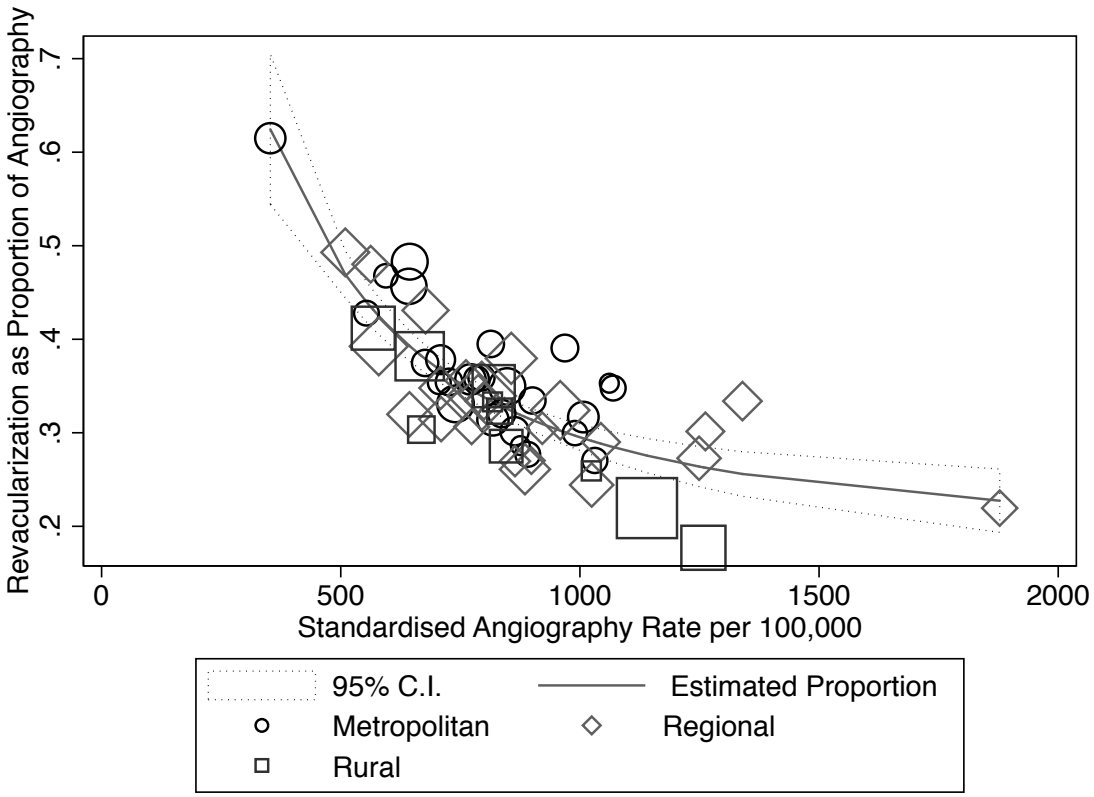


Within the adjusted model, private hospital cardiac admissions had a large influence on the angiography rate (71 angiograms (95% C.I. 47-93) per 100,000 individuals, for every 1,000 admissions). A more modest relationship between public hospital admission rates (44 angiograms (95% C.I. 25-63) per 100,000 individuals, for every 1,000 admission) and the angiography rate was evident. Socioeconomic indicators, regional location, and background ACS or chronic disease rates burden were not significantly associated with angiography rates.

15.4.4 Progression from Angiography to Revascularisation

Correlation between angiography and PCI, CABG surgery and any revascularisation was evident with correlation coefficient of 0.54 ($p<0.0001$), 0.44 ($p<0.0001$) and 0.65 ($p<0.0001$), respectively. Revascularisation rates as a proportion of angiography rates varied greatly, from a minimum of 17%, to a maximum of 61%. Overall, there was a striking negative correlation between with rate of angiography and the proportion of angiography proceeding to any form of coronary revascularisation (CC: -0.71 ($p<0.001$). (Figure 3) This was consistent with the individual modes of revascularisation (PCI CC: -0.62 ($p<0.001$) and CABG CC: -0.62 ($p<0.001$). There was no correlation between PCI rates and MI and ACS incidence, -0.11 ($p=0.402$) and -0.12 ($p=0.345$), respectively. However, correlation between rates of CABG provision, and MI and ACS rates were evident (MI CC: 0.53 ($p<0.0001$), ACS CC: 0.45 ($p=0.0003$).

Figure 3: Proportion, with fractional polynomial estimate (& 95% C.I.), of revascularisation and rate of angiography in each Medicare Local, (Shape of symbol reflects location [Metropolitan {circle}, Regional {diamond}, Rural {square} and size represents relative population



15.5 Discussion

We have observed that: 1) increasing socioeconomic disadvantage, rurality and chronic disease burden correlate with both rates of ACS and total mortality; 2) the medical workforce and admissions to private hospitals are negatively correlated with ACS incidence and mortality rates; 3) there is a negative association between coronary angiography rates and the burden of chronic cardiovascular disease and a modest positive association with ACS rates, but an association between angiography rates and local rates of cardiac admissions to private hospitals is evident; 4) there is a correlation between the rates of angiography and coronary revascularisation, but a negative correlation between the local angiography rates and the proportion of these procedures proceeding to revascularisation. These findings suggest that health reforms aimed at the appropriate use of diagnostic coronary angiography may be required to improve consistency and equity of access, and consequently, more efficient delivery of outcomes for the Australian community.

As expected, a correlation between the incidence of ACS, and CAD mortality is evident in the Australian population. Similarly, the excess in ACS rates among regional and rural locations is reconfirmed, as is the relationship between indicators of socioeconomic deprivation and chronic cardiac disease burden, and disease incidence and outcomes. However, the distribution of acute care services is negatively correlated with the incidence of disease in the population. This geographic mismatch has also been described elsewhere such as the United States, and highlights the influence of factors such as funding and workforce proficiency in delivering the services to non-metropolitan communities.[14-16]

A robust evidence-base supports the use of coronary angiography with subsequent revascularisation where deemed appropriate among troponin positive ACS patients.[17] However, among patients with stable CAD, the superiority of angiography and

revascularisation over a medical management is less robust.[5,18] This clinical evidence-base provides stark contrast for several observations. Firstly, the indicator most associated with variation in angiography appeared to be the cardiac admission rates to private hospitals, but an inverse correlation with ACS rates implies that these procedures are mainly being undertaken for indications other than ACS. Secondly, while angiography rates correlate with revascularisation, neither angiography nor PCI rates, (in contrast to CABG) correlate with ACS rates. Thirdly, angiography rates are negatively correlated with progression to revascularisation. These observations are inconsistent with the evidence-base for invasive management for non-ACS indications, with private institutions accounting for a higher proportion of the variation. CT coronary angiography for the investigation of non-acute CAD may attenuate the use of invasive angiography for this indication, but caution should be exercised since ample evidence demonstrates the greater drive for further investigations is precipitated by all forms of cardiac testing.[18,19]

These comparisons suggest potential policy targets for improving clinically appropriate use of coronary angiography. At the higher end of the patient risk spectrum, the Australian Commission for Safety and Quality in Health Care have developed clinical care standards for the management of ACS.[20] These standards may actually, appropriately increase the use of angiography for patients with myocardial infarction. Funding hospitals based on ACS performance measures may also be a factor that influences practice and outcome. Such reforms may assist in developing local clinical networks using telemedicine models that extend clinical expert decision-making into rural areas enable the more the appropriate selection of patients ACS for angiography. Conversely, while there is no current guidance for stable CAD in Australian, criteria for the appropriateness of angiography and revascularisation have been developed in the United States.[21] Importantly, United States Medicare and Medicaid reimbursement of invasive procedures is now linked to these appropriateness criteria. It is suggested that funding linked to the appropriateness of care or

the achievement of clinical care standards should be a focus of debate in any health care reform in Australia.

15.5.1 Limitations

Given the ecological study design, pockets of excellence in care and outcome likely exist but are obscured data aggregation. Furthermore, given the small number of Medicare Locals, a linear relationship between variables is assumed, and curvilinear relationships cannot be rule-out. The small sample of the SNAPSHOT ACS study should be acknowledged, with caution exercised when interpreting the association with mortality rates. While this relationship should be confirmed in larger studies, this finding is consistent with international large-scale data.[22] Similarly, we cannot fully exclude the possible under (misclassification) or over (double-counting secondary to inter-hospital transfers) reporting of ACS admissions or procedures, though systematic under-reporting is considered unlikely given the funding implications of these coding practices. Detailed interrogation of the system would require documentation of patient level characteristics and care, combined with an evaluation of the health service infrastructure extending beyond the availability of catheter laboratories, to other modalities of cardiac investigation such as CT coronary angiography and functional imaging. Such information is not currently available in Australia.

15.6 Conclusion

Significant variation in the provision of coronary angiography, not related to clinical need, is evident across Australia. A greater focus on clinical care standards and better distribution of health services will be required if these variations are to be attenuated.

15.7 Acknowledgement

The authors would like to thank the Australian Institute of Health and Welfare (AIHW) for providing data for this analysis.

Attribution

The authors planned and implemented the analysis. The first drafted the initial manuscript. All authors have had access to the data and have provided input into the final manuscript.

Disclosures

None.

15.8 References

1. Chew DP, Aroney CN, Aylward PE, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart Lung Circ. 2011 Aug;20(8):487–502.

2. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012 Oct;33(20):2569-2619.

3. Roffi M, Patrono C, Collet JP, et al 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016 Jan 14;37(3):267-315.

4. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007 Apr 12;356(15):1503–1516.

5. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease. N Engl J Med. 2015 Apr 2;372(14):1291-300.

6. Korda RJ, Clements MS, Kelman CW. Universal health care no guarantee of equity: Comparison of socioeconomic inequalities in the receipt of coronary procedures in patients with acute myocardial infarction and angina. BMC Public Health. 2009;9(1):460-472.

7. Australian Commission on Safety and Quality in Health Care and Australian Institute of Health and Welfare. Exploring Healthcare Variation in Australia: Analyses Resulting from an OECD Study. 2014 May pp. 1–96.

8. Chew DP, Amerena JV, Coverdale SG, et al. Invasive management and late clinical

outcomes in contemporary Australian management of acute coronary syndromes: observations from the ACACIA registry. Med J Aust. 2008 Jun 16;188(12):691–697.

9. Chew DP, French J, Briffa TG, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. Med J Aust. 2013;199(3):185–191.

10. Ellis C, Gamble G, Devlin G, et al. The management of acute coronary syndrome patients across New Zealand in 2012: results of a third comprehensive nationwide audit and observations of current interventional care. N Z Med J. 2013;126(1387):36–68.

11. Aliprandi-Costa B, Ranasinghe I, Turnbull F, et al. The design and rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). Heart Lung Circ. 2013 Jul;22(7):533–541.

12. Scott I, Derhy P, O'Kane D, et al. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. Med J Aust. 2007 Aug 1;187(3):153–159.

13. Public Health Information Development Unit (PHIDU). Social Health Atlas of Australia: Medicare Local (online). At: http://www.adelaide.edu.au/phidu/maps-data/data/ (accessed 7 April 2015). [Internet]. Available from: www.adelaide.edu.au/phidu/maps-data/data/

14. Horwitz JR, Nichols A, Nallamothu BK, et al. Expansion of Invasive Cardiac Services in the United States. Circulation. 2013 Aug 19;128(8):803–810.

15. Joynt KE. Rightsizing invasive cardiac services in the United States. Circulation. 2013 Aug 20;128(8):780–2.

16. Joynt KE. Quality of Care and Patient Outcomes in Critical Access Rural Hospitals. JAMA. 2011 Jul 6;306(1):45.

17. Hoenig MR, Aroney CN, Scott IA.. Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era .Cochrane Database Syst Rev 2014 Jan 1:1–62.

18. Foy AJ, Liu G, Davidson WR Jr, Sciamanna C, Leslie DL. Comparative Effectiveness of Diagnostic Testing Strategies in Emergency Department Patients With Chest Pain. JAMA Intern Med. 2015 Jan 26.

19. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. JAMA. 2011 Nov 16;306(19):2128–2136.

20. Chew DP, Briffa TG. The clinical care standards in ACS: towards an integrated approach to evidence translation in ACS care. Heart Lung Circ. 2015 Mar;24(3):213–215.

21. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate Use Criteria for Coronary Revascularization Focused Update. J Am Coll Cardiol. 2012 Feb 28;59(9):857–881.

22. Hansen KW, Sørensen R, Madsen M, , et al. Effectiveness of an early versus a conservative invasive treatment strategy in acute coronary syndromes: a nationwide cohort study. Ann Intern Med.; 2015 Nov 17;163(10):737–746.

16 SHOULD FEE-FOR-SERVICE BE FOR ALL GUIDELINE-ADVOCATED ACUTE CORONARY SYNDROME CARE? OBSERVATIONS FROM THE SNAPSHOT ACS STUDY

16.0 Title Page: Should Fee-for-Service be for all Guideline-Advocated Acute Coronary Syndrome Care? Observations from the SNAPSHOT ACS study.

Thomas G. Briffa[1] Christopher J. Hammett[2], David B. Cross[3],Andrew I. Macisaac[4], James M. Rankin[5], Neville Board[6], Bridie Carr[7], Karice K. Hyun[8], John French[9], David B. Brieger[10], Derek P. Chew[11].

[1]University of Western Australia, Crawley, WA 6009, Australia.

[2]Royal Brisbane and Women's Hospital, Brisbane, Qld 4029, Australia.

[3]Heart Care Partners, Auchenflower, Qld 4066, Australia.

[4]St Vincent's Hospital Melbourne, Fitzroy, Vic. 3065, Australia.

[5]Royal Perth Hospital, Perth, WA 6000, Australia.

[6]eHealth & Medication Safety, Sydney, NSW 2000, Australia.

[7]Agency for Clinical Innovation (ACI), Sydney, NSW 2057, Australia.

[8]The George Institute for Global Health, Camperdown, NSW 2050, Australia.

[9]Liverpool Hospital, Liverpool, NSW 2170, Australia.

[10]Concord Hospital, Concord, NSW 2139, Australia.

[11]Flinders University and Flinders Medical Centre, Bedford Park, 5042, SA, Australia.

Running Title: Fee-for-service and provision of ACS Care in Australia

Key Words: Acute coronary syndromes, Quality of care, Clinical Guidelines, Health Service

Corresponding Author

Tom Briffa

School of Population Health

University of Western Australia

WA

AUSTRALIA

Email: Tom.Briffa@uwa.edu.au

16.1 Abstract

Objective: Most clinicians treating uninsured patients within public hospitals are salaried on a sessional basis. Whereas, treating privately insured patients in both public and private hospitals, clinicians and their institutions are commonly directly reimbursed for selected services. We sought to explore the association of health insurance status on the provision of acute coronary syndrome (ACS) care in Australia.

Design, setting and subjects: Consecutive adults hospitalised with suspected ACS from 14-27th May 2012 enrolled in the Snapshot study of Australian and New Zealand patients. Descriptive and logistic regression analysis was performed.

Main Outcome Measures: In-hospital rates of guideline-advocated investigations and therapies.

Results: 247 hospitals (23 private) enrolled 3,391 patients with suspected ACS. A third of patients declared private insurance coverage of which 304/1088 (27.9) presented to private facilities. Compared with public patients, privately insured patients were more likely to undergo inpatient echocardiography, received early angiography and in those with a discharge diagnosis of ACS a higher rate of revascularisation (P<0.001); each of which attract potential fee-for-service. In contrast, privately insured ACS patients were less likely to be discharged on 4 or 5 guideline therapies and be referred to a secondary prevention program, neither of which directly attract a fee. Typically, as GRACE risk score rose so did the level of ACS care, however propensity adjusted analyses showed lower in-hospital adverse events among the insured group, (OR: 0.68 [95% C.I.: 0.52-0.88], p=0.004).

Conclusion: Fee-for-service reimbursement may explain differences in provision of selected guideline-advocated components of ACS care between privately insured and public patients.

16.2 Introduction

In Australia, the private health insurance system represents an “opt-in” method for increasing health consumer access, choice of physician and hospitals when requiring acute hospital services. The proportion of patients maintaining private insurance coverage varies between demographic groups, regions and states as well as over time, but is estimated by the Australian Institute of Health and Welfare (AIHW) to be 45.7% in 2012.[1]

Physician and institutional reimbursement within the private health insurance system is “service-based” where payment is provided for the care delivered, independent of the diagnosis. Whereas, the Australian public hospital system has moved to an “activity-based funding” model, where the activity is defined by both the diagnosis and the service provided, and physicians are salaried, with the State health systems receiving the payment.[2] Selectively, visiting medical officers are renumerated for providing cardiac procedures to uninsured patients in public facilities. Newer hospital funding models offer service providers premium payments (e.g. in Western Australia) where selected guideline-advocated care for a specific diagnosis, e.g. acute coronary syndrome (ACS), can be demonstrated and ideally under quality improvement initiatives.[3]

However, within the context of ACS management, not all components of guideline-advocated care are reimbursed in the private health system. Specifically, investigative services such as stress testing, echocardiography, coronary angiography, as well as therapeutic interventions such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) attract a specific fee to the treating physician or surgeon and institution. Other evidence-based and guideline recommended therapies, such as prescription of antiplatelet therapies, secondary prevention therapies and cardiac rehabilitation referrals are not independently funded and yet are considered to be standard care.[4]

We explored the association between a patient's declared private insurance coverage and the provision of evidence-based care and in-hospital major adverse cardiovascular events (MACE). Specifically, we examined whether the funding of specific ACS guideline recommended therapies and management approaches influenced their provision. Also, we analysed the interaction between private coverage, patient risk, measured by the GRACE risk score, and the care delivered within the Australian cohort of the bi-national snapshot of ACS care.

16.3 Methods

16.3.1 Study Design and implementation

The SNAPSHOT ACS study was a prospective consecutive registry of a cohort of suspected ACS patients presenting to both public and private hospitals across Australia and New Zealand for the last 2-weeks in May 2012. While the details have been published elsewhere,[4, 5] a summary of the study conduct, hospital recruitment and clinical and in-hospital adverse events are described here.

The registry was conducted as a collaboration between the Cardiac Society of Australia and New Zealand (CSANZ) and the Heart Foundation of Australia (HFA), with direct support from the Australian Commission for Safety and Quality in Health Care (ACSQHC), The George Institute for Global Health, Health networks or State governments of NSW, QLD, Victoria, SA, and WA. The study was implemented and managed by a centralised organising committee.

This study sought to include a representative sample of suspected ACS patients. Therefore, both public and private hospitals, in rural and metropolitan areas accepting ACS patients were approached for participation. To facilitate consecutive enrolment, an opt-out consent process was employed in all hospitals except for two sites in Victoria where an opt-in

consent process was required. Consent waiver applied to all in-hospital deaths within Australia.

Of the 525 hospitals approached, 478 agreed to participate and fulfilled ethics requirements and within the two-week period 286 hospitals (39 in New Zealand) enrolled patients. This analysis is confined to the 247 Australian hospitals. New Zealand patients were excluded because their system is different, and is characterised almost exclusively by 'public' management for an ACS. Consecutive patients presenting and admitted overnight with suspected ACS were registered and classified by their primary discharge diagnosis including: ST-segment elevation myocardial infarction (STEMI) or Left Bundle Branch Block (LBBB); non-ST segment elevation myocardial infarction (NSTEMI); unstable angina; chest pain "likely to be ischaemic"; chest pain "unlikely to be ischaemic"; and other diagnosis or secondary myocardial infarction (MI). Since ACS without biomarker elevation is a clinical diagnosis, unstable angina and chest pain likely to be ischaemic have been combined for this analysis.

16.3.2 Patient risk, in-hospital care and adverse events

Employing a standardised approach, each patient's presenting characteristics, clinical risk using the GRACE risk score, receipt of current guideline recommended therapies as well as transfers between acute hospitals were evaluated for the duration of the contiguous acute hospital admission. Provision of an early invasive management was defined as receiving coronary angiography at anytime during the acute hospital stay regardless of transfer, while the prescription of guideline medications was assessed at discharge. The provision of 4 or more of the 5 guideline recommended pharmacotherapies (i.e. aspirin, HMG-CoA reductase inhibition, a $P2Y_{12}$ inhibitor, beta-blocker and an angiotensin converting enzyme inhibitor or angiotensin receptor antagonist) was arbitrarily deemed as being "guideline compliant." Patients were also assessed prior to discharge for referral to secondary prevention service

(e.g. cardiac rehabilitation). Compliance with prescription medications and attendance to secondary prevention services was not assessed.

The in-hospital events of all-cause mortality, new or recurrent MI, stroke, cardiac arrest, worsening heart failure and major bleeding relied on clinician reporting at each hospital using standard definitions and a common completion note as previously described.[4] The occurrence of any one of these events during the acute hospital stay was included for the evaluation of composite endpoint of in-hospital MACE. Formal centralised adjudication of these events was not possible though monitoring of between 2-5% of clinical report forms for data accuracy and quality was undertaken during and within months after the enrolment window.

16.3.3 Patient insurance status

Recording of the insurance status of each patient, regardless of presentation to a public or private hospital, relied on the convention of self-reporting. During the course of the data collection, attempts to verify patient insurance status (either presence or absence) or extent of coverage with the insurer were not undertaken, although it is recognised that verification is commonly undertaken when patients are admitted or transferred to a private facility. Consequently, miss-classification due to under-reporting of insurance or misunderstanding regarding the presence of limitations to a patient's insurance coverage is possible. Hospitals were classified as private or public based on the AIHW hospital classification.[6] Patients with stated private insurance but treated within the public hospital system were classified as privately insured patients for this analysis.

16.3.4 Statistical analysis

Patient demographics and clinical characteristics including clinical risk of subsequent events was evaluated by the GRACE risk score were stratified by whether the patient declared insurance coverage. The rates of inter-hospital transfer, echocardiography, functional testing

and coronary angiography and revascularisation (PCI and CABG) as well as the provision of guideline recommended therapies among patients surviving to hospital discharge and in-hospital events by insurance coverage are presented as univariate analyses. Analyses exploring the investigation of patients with suspected ACS were conducted on the whole population and separately in the 2451 (73%) who were not transferred to another hospital for their ACS care. Evaluation of ACS treatments was restricted to those with a discharge diagnosis of ACS (STEMI or LBBB, NSTEMI, unstable angina, chest pain "likely to be ischaemic") where these therapies are potentially deemed more "appropriate." Dichotomous variables were reported as counts of the total (n) and percentages (%), and compared by chi-square tests, while continuous variables were compared using the Kruskal-Wallis test and reported as a median and inter-quartile range. To explore the relationship between patient risk and the likelihood of receiving early invasive management, the probability of inpatient angiography was plotted against an increasing GRACE risk score for patients with and without private insurance using a Lowess smoothing function. Formal interaction between patient risk, declared private insurance and the likelihood of receiving early invasive management was assessed by the interaction term patients insurance status*risk in logistic regression model with inpatient angiography as the dependent variable. The same methodology was used to evaluate the relationships between patient risk, insurance status, and the receipt of echocardiography, provision of revascularisation guideline medication, referral for secondary prevention and in-hospital MACE. The receipt of these process measures of care and adverse events were also evaluated using logistic regression to adjust for the propensity for being privately insured, modelled as a continuous variable, as well as the discharge diagnosis, age, GRACE risk score, smoking status, a history of cerebrovascular disease, and prior cancer; all factors known to influence the provision of care. The propensity score included age, GRACE score in four groups (i.e. <100, 100-150, 151-200, 201+), heart failure at presentation (i.e. Killip class >1), the interaction between

diabetes and dyslipidaemia, baseline creatinine, current smoking, prior MI, prior coronary revascularisation, known lung disease, prior bleeding event, known peripheral vascular disease, prior cerebrovascular accident or transient ischaemic attack and a history of active cancer, dementia and enrolling jurisdiction. (C-statistic: 0.69, goodness of fit test: p=0.749) These models were clustered based on enrolling hospital to account for correlation in treatments and events among patients enrolled at the same hospital. Analysis of margins was used to estimate adjusted differences in care and adverse event. Given the exploratory nature of these analyses, no adjustment for multiple testing was undertaken. All analyses were undertaken using STATA MP 11.2 (College Station TX USA) and a probability value of less than 0.05 was considered statistically significant.

16.4 Results

16.4.1 Participating Patients and Hospitals

During the two-week enrolment period a total of 3,391 patients were included, of whom 1088 (32.1%) declared private insurance coverage. Among the 247 Australian hospitals participating in the study, only 23 (9.3%) were private facilities. Hence, the large majority of privately insured patients presented to and were enrolled at public hospitals and only 304 (27.9%) were enrolled within the private hospital sector. Presenting clinical and demographic characteristics stratified by known private insurance status are presented in Table 1. The proportion of patients with and without private insurance discharged with the various diagnostic classifications was very similar. Patients with private insurance were less likely to present with heart failure, have diabetes, prior MI or be current smokers. Insured patients were unlikely to be indigenous and have English as a second language. However, patients with insurance were slightly older which contributed to a modestly greater median GRACE risk score.

Table 1: Patient characteristics at presentation by health insurance status

Characteristics, *n(%) unless specified*	Total *n=3391*	No Private Insurance *n=2303*	Private Insurance *n=1,088*	P value
Age (years, mean ±SD)	66.5 (14.6)	65.1 (15.1)	68.3 (13.7)	0.001
Female Gender	1349 (39.8)	907 (39.4)	442 (40.6)	0.490
Discharge diagnosis				
STEMI/LBBB	322 (9.5)	223 (9.7)	99 (9.1)	0.100
NSTEMI	755 (22.3)	510 (22.2)	245 (22.5)	
Unstable angina/ischaemic chest pain	756 (22.3)	502 (22.8)	254 (23.4)	
Chest pain: unlikely ischaemic	903 (26.6)	596 (25.6)	307 (28.2)	
Other Diagnoses/secondary myonecrosis	655(19.3)	472 (20.5)	183 (16.8)	
Diabetes	881 (26.0)	662 (28.8)	219 (20.1)	<0.001
Hypertension	2,164 (63.8)	1471 (63.9)	693 (63.7)	0.920
Dyslipidaemia	1,851 (54.6)	1245 (54.1)	606 (55.7)	0.371

Current cigarette smoker	647 (19.1)	531 (23.1)	116 (10.7)	<0.001
Prior MI	903 (26.6)	665 (28.9)	238 (21.9)	<0.001
Prior CABG	363 (10.7)	236 (10.3)	127 (11.7)	0.218
Prior TIA/CVA	327 (10.3)	238 (10.3)	89 (8.2)	0.047
Killip Class II-IV at presentation	440 (13.0)	340 (14.6)	100 (9.2)	<0.001
Presentation with cardiac arrest	59 (1.7)	44 (1.9)	15 (1.4)	0.269
GRACE risk score (median, 25^{th}-75^{th} percentile)	118 (95-142)	117 (93-143)	120 (100-143)	0.013
Creatinine at admission µmol/L (median, 25^{th}-75^{th} percentile)	84 (69-104)	84 (69-105)	83 (68-100)	0.036
Dementia or cognitive impairment	115 (3.4)	79 (3.4)	36 (3.3)	0.855
Nursing home resident	92 (2.7)	60 (2.6)	32 (2.9)	0.574
Indigenous Australian	120 (3.5)	114 (5.0)	6 (0.6)	<0.001
English as a second language	235 (6.9)	191 (8.3)	44 (4.0)	<0.001

SD=standard deviation, CP=chest pain, STEMI/LBBB=ST-segment elevation myocardial infarction/Left bundle branch block, PAD= Peripheral artery disease, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery graft surgery, TIA=trans ischaemic attack, CVA=cerebrovascular accident,

16.4.2 In hospital Investigations and care

Compared with patients without private insurance, privately insured patients were more likely to undergo inpatient echocardiography though this was not evident when confined to those patients with a discharge diagnosis of ACS. (Table 2) Similarly, privately insured patients were more likely to have received early angiography, with this association seen across all discharge diagnostic groups. This translated to a higher rate of revascularisation except among those discharged with an alternative, non-ACS diagnosis. (Table 3) Patients with private insurance were more likely to be transferred to receive these services (Private: 404/1088 (37.1%) vs. Public: 536/2303 (23.3%), p<0.001). Separately, an unadjusted analysis was done of 2451 (73%) patients who received all their ACS care in the hospital they presented to, differences in fee-for-service guideline-advocated care by health insurance status persisted.

In contrast, patients with a discharge diagnosis of ACS and private insurance were less likely to be discharged on 4 or 5 guideline therapies, and were less likely to have documented referral to a secondary prevention program (Figure 1).

Propensity adjusted analyses for the likelihood of receiving evidence-based investigations and therapies in patients with definite ACS demonstrate a significant increase in the use of echocardiography (OR: 1.55 [95% C.I.: 1.23-1.95], p<0.001), inpatient angiography (OR: 1.72 [95% C.I.: 1.32-2.22], p<0.001), and revascularisation (OR: 1.52 [95% C.I.: 1.16-1.98], p=0.002). However, this was not associated with an increase in the prescription of 4 or 5 guideline recommended therapies (OR: 0.89 [95% C.I.: 0.75-1.06], p=0.202), or referral to a secondary prevention program (OR: 0.98 [95% C.I.: 0.79-1.21], p=0.846).

Figure 1. Univariate analysis of the provision of evidence based management among patients with a discharge diagnosis of acute coronary syndrome.

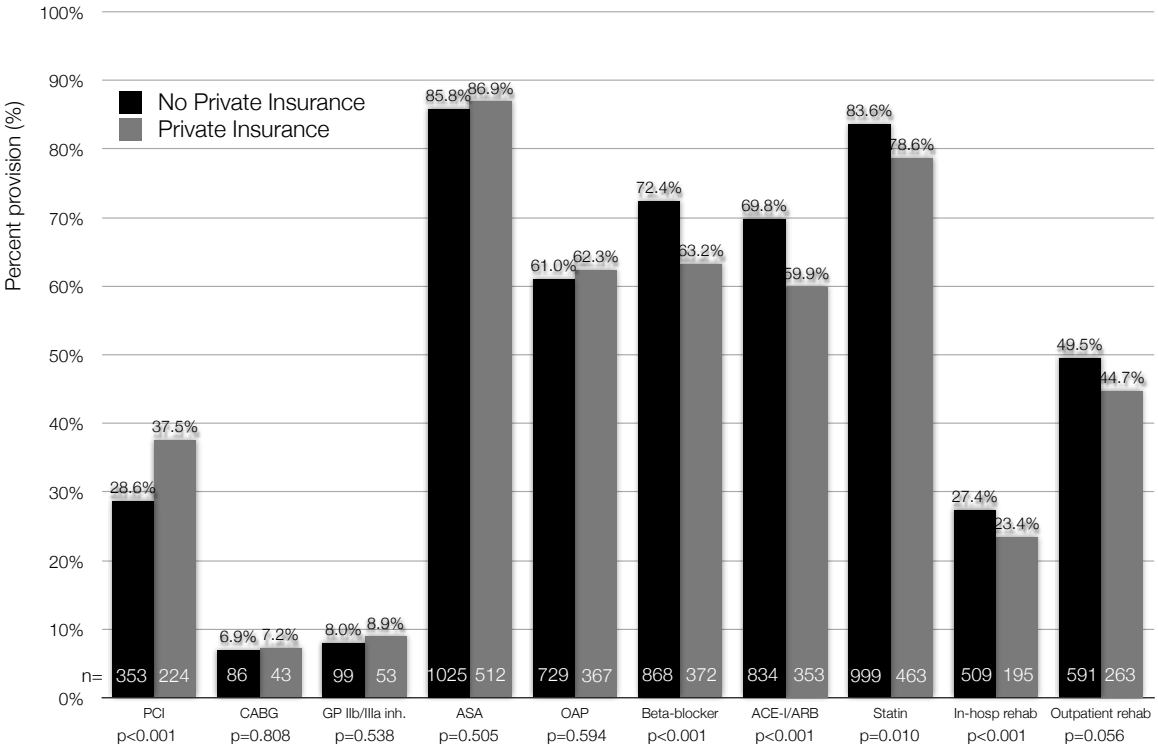


Table 2: Investigations by health insurance status among all patients admitted with suspected acute coronary syndrome.

	Total *n=3391*	**No Private Insurance** *n=2303*	**Private Insurance** *n=1088*	**P value**
Investigations, n (%)				
Exercise Test	299 (8.8)	214 (9.3)	85 (7.8)	0.156
Echocardiogram	1006 (29.7)	635 (27.6)	371 (34.1)	<0.001
Stress Echocardiogram	92 (2.7)	46 (2.0)	46 (4.2)	<0.001
Stress Nuclear Study	148 (4.4)	102 (4.4)	46 (4.2)	0.789
CT Coronary Angiogram	125 (3.7)	73 (3.2)	52 (4.8)	0.020
Coronary Angiogram	1301 (57.6)	813 (53.8)	488 (65.6)	<0.001

CT=Computed Tomography

16.4.3 Relationship to patient risk

Figures 2 and 3 displays the relationship between increasing GRACE risk score and the provision of the evidence-based components of ACS care. For all components, privately insured patients are more likely to receive investigations and therapies among the very low risk patient subsets. With increasing risk, only invasive management and revascularisation remained more likely to be provided among privately insured patients. There was not statistical interaction between patient risk and the use of these components of care.

Figure 2: Provision of echocardiography, inpatient angiography and revascularisation with increasing GRACE risk score stratified by private insurance status.

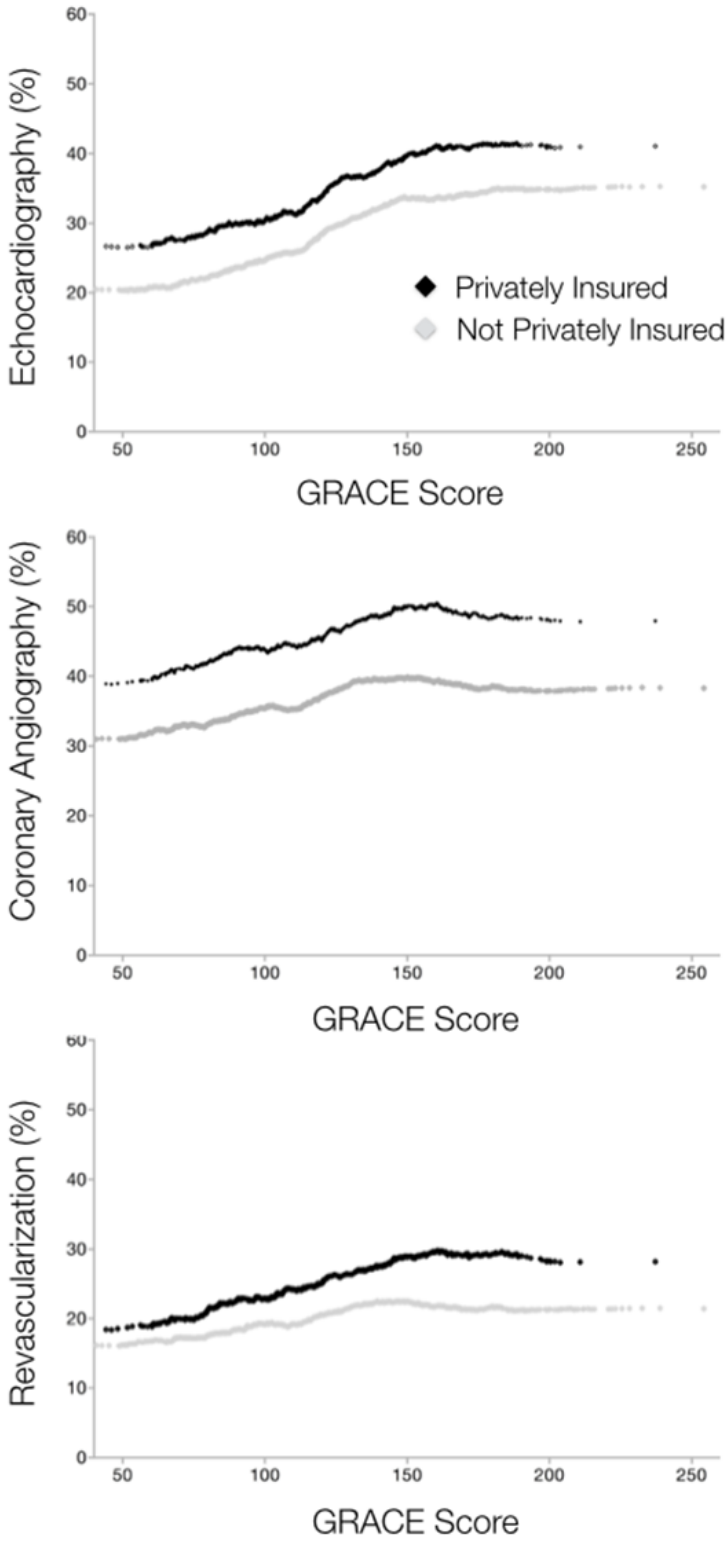


Figure 3. Provision of 4 or 5 guideline therapies, referral for secondary prevention and in-hospital major adverse cardiovascular event (MACE) with increasing GRACE risk score stratified by private insurance status.

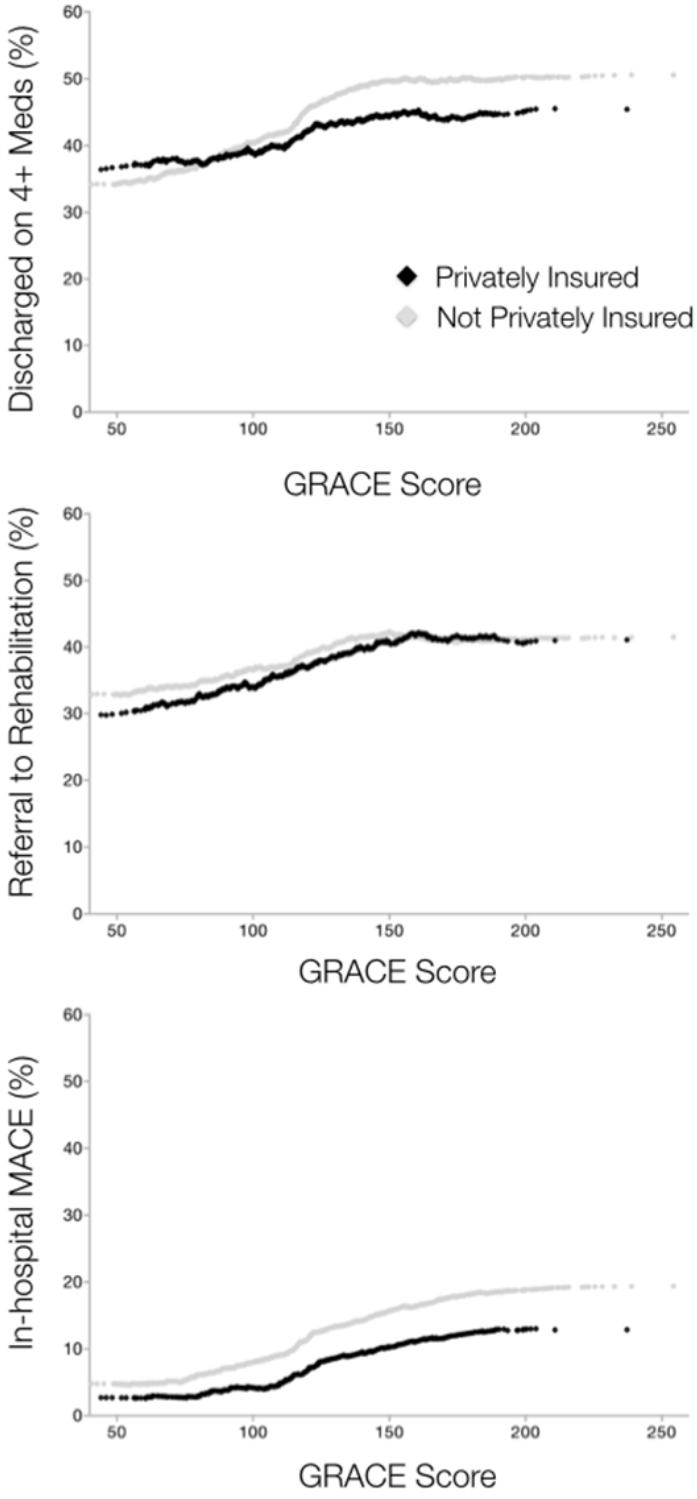


Table 3: Estimated proportion of patients receiving inpatient angiography and revascularisation adjusted for baseline risk and propensity for having private insurance.

	Inpatient angiography (%)			Revascularisation (%)		
Discharge diagnosis	Public	Private	P value	Public	Private	P value
STEMI/LBBB	75.4	83.5	0.19	67.2	75.0	0.929
NSTEMI	64.5	75.1	0.001	43.3	52.8	0.001
UA /ischemic chest pain	34.0	45.8	<0.001	17.2	23.4	<0.001
Non cardiac chest pain	12.7	19.6	0.047	0.2	0.4	0.23
Other	17.6	26.2	0.023	0.4	0.7	0.28

STEMI=ST elevation myocardial infarction; NSTEMI=non-STEMI; LBBB=left bundle branch block; UA=unstable angina;

16.4.4 In Hospital Adverse Events

When simply evaluating in-hospital events, privately insured patients experienced a lower rate of in-hospital death and worsening heart failure but not new or recurrent MI, or bleeding events. This was evident in the whole population and when the analysis was confined to the patients discharged with ACS. The incidence of in-hospital cardiac arrest was also numerically lower among patients with private insurance. In-hospital MACE was significantly lower among the insured patients, with this largely driven by differences among patients discharged with ACS, and in particular the incidence of in-hospital heart failure. (Table 4) This difference in MACE persisted after adjustment for the propensity score and baseline differences (OR: 0.68 [95% C.I.: 0.52-0.88], p=0.004). The plot of the likelihood of in-hospital MACE by GRACE risk score (Figure 3) demonstrates the greatest difference occurring among patients at the highest predicted risk. An estimated difference in in-hospital events at a GRACE risk score of 140 was 3.4%, while the difference at 220 was 6.2%.

Table 4: In-hospital outcomes within the cohort and patients with a final discharge diagnosis of acute coronary syndrome (ACS), by health insurance status

Patient group, *n (%)*	Total	No Private Insurance	Private Insurance	P value
Entire cohort	3391	2303	1088	
Death	63 (1.9)	51 (2.2)	12 (1.1)	0.025
Myocardial infarction	63 (1.9)	42 (1.8)	21 (1.9)	0.830
Worsening heart failure	667 (19.7)	495 (22.5)	172 (15.8)	<0.001
Cardiac arrest	65 (1.9)	51 (2.2)	14 (1.3)	0.066
Major bleeding	34 (1.0)	26 (1.2)	8 (0.8)	0.306
MACE	345 (10.2)	265 (11.5)	80 (7.4)	<0.001
Final diagnosis of ACS	1833	1235	598	
Death	49 (2.7)	40 (3.2)	9 (1.5)	0.031
Myocardial infarction	58 (3.2)	38 (3.1)	20 (3.3)	0.759
Worsening heart failure	405 (22.1)	313 (25.3)	92 (15.4)	<0.001
Cardiac arrest	50 (2.7)	39 (3.2)	11 (1.8)	0.104
Major bleeding	28 (1.6)	21 (1.7)	7 (1.2)	0.404
MACE	272 (14.8)	212 (17.2)	60 (10.0)	<0.001

MACE: Major Adverse Cardiac Event

16.5 Discussion

With its mix of public and privately insured patients, the Australian health care system represents a relatively unique opportunity to explore the potential relationship of direct fee-for-service on the provision of care and potentially clinical course. In the provision

of ACS evidence-based therapies, the entirety of care provided to patients without private insurance is within the public hospital system where the majority of physicians are salaried, and remuneration is not linked to the extent or quality of care provided. In contrast, among patients declaring private insurance, only a proportion of guideline-advocated therapies, specifically echocardiography, angiography and coronary revascularisation, are directly fee-for-service, while other components such as the prescription of medication and referral to secondary prevention, attract no specific fee. This analysis finds a consistent relationship between the remunerated components of ACS care and their provision that is evident across the entire spectrum of patient risk. Alternatively, receipt of these advocated elements of ACS care as a privately insured patient are easier to obtain, being done earlier and more likely to be done, than if a patient has to 'wait' within the public system. However, it's possible that such observations raise the question of whether the re-alignment of funding for all components of evidence-based care represents a rational policy approach to a nationally integrated strategy of improving outcome among ACS patients in Australia.

As part of the Health Reform and in conjunction with clinical groups and the States and Territories, the Australian Commission for Safety and Quality in Health Care (ACSHC) has recently developed an Australian Clinical Care Standard for the management of ACS and indicators to support local uptake of the Standard.[7]

Importantly, the guideline-advocated therapies assessed in this study underpin the new national Clinical Care Standard that will be proposed for ratification by the Council of Australian Governments Standing Council on Health at its final meeting in 2014. In combination with clinical registries that evaluate current care, these clinician- led initiatives have emerged as a more co-ordinated health policy approach aimed at driving evidence into practice. Furthermore, several of the Australian State government health departments have established cardiac networks, aimed at fostering clinical

engagement, to advise on the provision of local cardiac services. In combination, these efforts substantially enhanced the ability to design new approaches that enhance access, equity and quality of care among ACS patients.

Concurrently, federal funding of the public hospital system moved to an activity-based funding model in 2011, in which hospitals are funded based on the type and number of services they provide.[1] Observations such as this, raise the question of whether funding should not only include activity but also the quality of that care as measured by adherence to guideline advocated therapies.[2] The concept of premium payment for guideline-advocated ACS care is one option.[3]

Paying for performance in the provision of health care remains a vexed issue around the world.[3] Within Australia, the procedure based Medicare item number system has evolved into a "*de-facto* pay for performance" systems. The observation that increased transfer of patients and provision of these treatments is associated with fewer in-hospital MACE, particularly among the higher risk patients, suggests that direct fee-for-service for provision of the full complement of guideline-advocated therapies within ACS care should be debated. These data would suggest that specific payments for all components of ACS care would improve access to care, as evidenced by the increased rate of transfer among the currently insured patients, as well as increased provision of all evidence-base therapies. Furthermore, the observation that the relationship between patient risk and provision of therapies is only modest for privately insured patients suggests that such an approach to funding may overcome some of the risk-averse decision-making that occurs in the delivery of the ACS evidence base.[8]

However, while such an approach may be attractive within a system where access to expertise and technologies is not seamless, problems such as the intensive cardiac investigation and management of patients without ACS, or those at very extremes of risk where therapies are less likely to provide a benefit will need to be very carefully

considered. The development of appropriate use criteria and objectively measured risk stratification represent potential opportunities to both optimise and individualise care within a complex therapeutic environment.[9, 10] Linking premium payments to these guideline-advocated components of ACS care will require more sophisticated system-wide approaches to clinical documentation and data reporting. Furthermore, the implementation of such a system would require robust methods for documenting appropriateness and the health economic impact of such recommendations will need to be carefully evaluated and prospectively tested. Nevertheless, such approaches have already been adopted in the United States where health care funding of cardiovascular care has come under increased scrutiny in recent times.[9]

16.5.1 Limitations

Interpreting the findings of this study should be done with caution, as the potential for under-reporting of health insurance status in the most unwell exists. However, such misclassification would lead to a more conservative estimate in treatment received than is currently reported. It could also be that, because private patients have a higher GRACE score and a better comorbidity profile, they are more suited for invasive investigation and revascularisation. This study is observational in nature, it can only infer that the differences in fee-for-service structure accounted for all of the treatment differences observed. However, the difference in guideline-advocated components of ACS care are apparent, and the similarity between public and privately insured patients with respect to the suboptimal prescription of medications is indicative that many clinicians practice in both public and private systems. It is not possible to rule-out system access (e.g. angiography) and patient-level factors (e.g. return to work) to clinical services which may mitigate the differences in the components of ACS care seen here. This study has insufficient power to address the question of clinical risk and in-hospital adverse clinical events.

16.6 Conclusion

Within the Australian health care system, in which certain components of the ACS evidence base attract an incremental fee-for-service, a clear difference in the provision of these proven therapies is evident. Within the design of future health policies, consideration should be given to the remuneration for proven therapies in preference to those not supported by a robust evidence base, together with the development of a mature system for ensuring clinical appropriateness, quality improvement and enabling patient individualisation.

16.7 References

1. Australian Institute of Health and Welfare (AIHW) 2012. *Australia's health 2012.* Australia's health no. 13. Cat. no. AUS 156. Canberra: AIHW.

2. National Health and Hospitals Reform Commission. (2009). *A healthier future for all Australians: Final Report*, Canberra: Commonwealth of Australia.

3. Duckett, S. Designing incentives for good-quality hospital care. *Med J Aust* 2012; 196 (11): 678-679.

4. Chew DP, French J, Briffa TG, *et al.* Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. *Med J Aust* 2013; 199 (3): 185-191.

5. Ellis C, Gamble G, Devlin G, *et al.* The management of acute coronary syndrome patients across New Zealand in 2012: results of a third comprehensive nationwide audit and observations of current interventional care. *N Z Med J*. 2013; 126: 36-68.

6. Australian Institute of Health and Welfare (AIHW) 2014. Australian hospital statistics 2012-13. Health services series no. 54. Cat. no. HSE 145. Canberra: AIHW.

7. Australian Commission for Safety and Quality in Health Care (ACSQHC) 2013. *Clinical Care Standards*. Sydney. [Accessed 18 July 2014 at www.safetyandquality.gov.au/our-work/clinical-care-standards]

8. Chew DP, Junbo G, Parsonage W, *et al*. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. *Circ Cardiovasc Qual Outcomes* 2013; 6: 299-308

9. Patel MR; Dehmer GJ, Hirshfeld JW, Smith PK, Spertus J. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate Use Criteria for Coronary Revascularization Focused Update. *J Am Coll Cardiol* 2012;59(9):857-881.

10. Fox KA, Fitzgerald G, Puymirat E, *et al*. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014;4(2):e004425.

16.8 Appendix 1: Study Organization

Acknowledgements

Steering Committee

David Brieger (NSW), Co-chair, John French (NSW) Co-chair, Derek Chew (SA) Co-chair, Chris Ellis (NZ), Co-Chair, Gerry Devlin (NZ), Co-Chair, Chris Hammett (QLD), Bernadette Aliprandi-Costa (NSW), Isuru Ranasinghe (NSW), Bridie Carr (NSW), Julie Redfern (NSW), Fiona Turnbull (NSW), Carolyn Astley (SA), Tom Briffa (WA), Jamie Rankin (WA), Stephen Bloomer (WA), John Elliott (NZ), Jeff Lefkovits (Vic).

Project managers- State-based Cardiac Clinical networks

New Zealand- Greg Gamble, NSW/ACT- Bernadette Aliprandi-Costa , Bridie Carr, Karen Lintern, Queensland- Tegwen Howell, Cindy Hall, Susanne Spencer, Dayna Williamson, Victoria- Hella Parker, Julie Plunkett, Wendy Wallace-Mitchell, South Australia, TAS, NT- Rosanna Tavella, Carolyn Astley, Western Australia- Samantha Thompson

Data Management and analysis- The George Institute for Global Health and the South Australian Health and Medical Research Institute (SAHMRI):

Professor Fiona Turnbull, Dr Isuru Ranasinghe, Dr Julie Redfern, Karice Hyun, Matthew Horsfall, Helen Hughes

The SNAPSHOT ACS study was supported in part by: The Cardiac Society of Australia and New Zealand; The Heart Foundation of Australia, The Agency for Clinical Innovation (NSW), the Victorian Cardiac Clinical Network, the Queensland Cardiac Clinical Network, the Western Australian Cardiac Clinical Network and the South Australian Cardiac Clinical Network. The study was endorsed by the Australian Commission for Quality and Safety in Health Care.

17 THE CLINICAL CARE STANDARDS IN ACS: TOWARDS AN INTEGRATED APPROACH TO EVIDENCE TRANSLATION IN ACS CARE

17.0 Title page The Clinical Care Standards in ACS: towards an integrated approach to evidence translation in ACS care

Derek P. Chew MBBS MPH FRACP FACC FESC FCSANZ[1]

Tom G. Briffa [2] B PhysEd, MPhysEd, PhD

Author Affiliations

[1] School of Medicine, Flinders University of South Australia, Adelaide, Australia

[2] School of Population Health, University of Western Australia, Australia

Running Title: Clinical Care Standards in ACS care

Key Words: Acute Coronary Syndromes, Clinical Care Standards, Clinical Guidelines

Corresponding Author

Derek P Chew MBBS MPH
Flinders University
Flinders Drive, Bedford Park
South Australia, 5042
AUSTRALIA
Ph: +618 8404 2001
Fax: +618 8404 2150

17.1 Editorial

The evidence-base informing the management of acute coronary syndromes (ACS) is substantial and now encapsulated in numerous local and international clinical practice guidelines. These guidelines have sought to assimilate this evidence into carefully crafted and robustly debated practice recommendations representing the foundation of modern ACS care. [1-5] Yet, registries of Australian and New Zealand clinical practice continue to demonstrate evidence of incomplete clinical care and sub-optimal clinical outcomes among many patients presenting with ACS. [6-10] Disappointingly, sequential registries spanning nearly a decade of clinical experience continue to show significant challenges in the provision of reperfusion for ST segment elevation MI, variation in rates of angiography in non-ST elevation ACS, incomplete utilization of secondary prevention therapies and low rates of referral to cardiac rehabilitation. This inertia in the evolution of clinical practice suggests that elements beyond physician "knowledge of the evidence" are at play in compromising the optimal adherence to guideline recommended care. Such factors may include:

- challenges in accessing the essential cardiac expertise required to optimise decisions regarding the use modern ACS therapies;
- the city-centric geographic concentration of cardiac diagnostic and therapeutic technologies that are now critical to effective ACS care;
- current health information systems which have evolved to effectively report health resource utilization, but not the quality and outcomes associated this the care;
- as well as health policy settings that reward hospital and clinician activity but not outcome.

Until now, the impressive gains made in reducing ACS morbidity and mortality are the rewards of years of research and innovation; yet variation in care is apparent. Looking

forward, the next challenge is to ensure that these “hard-won gains” are experienced by all ACS patients across the diverse geographic and social landscape of Australia and New Zealand. The Clinical Care Standards in ACS, produced by the Australian Commission for Quality and Safety In Health Care represent an important step forward in aligning clinical, health service and health policy efforts in improving ACS care.

Deficiencies in physician knowledge alone do not account for the incomplete care observed in local ACS registries. Direct survey evaluation of physician knowledge and acceptance of the local ACS guidelines has shown that the uptake of this information among those providing care is high. [11] Concomitantly, both local and international studies that have evaluated physician assessment of patient risk has shown substantial variation in the accuracy of this activity, at least when contrasted against objectively derived risk scores.[12-15] Such risk assessment is at the core of patient-centric care since it is the critical first-step to shared decision-making. It should inform the discussion with patients about choices between invasive and conservative treatment strategies, especially for rural centres where the pursuit of an invasive management strategy often introduces the burden of long distance transfer. Similarly, communication of individualised patient-specific risks of future events may represent a significant opportunity for encouraging adherence with secondary prevention therapies and cardiac rehabilitation efforts that are known to improve outcome.[16] Consequently, while awaiting robust randomised trial evidence, incorporating objective risk assessment into ACS is strongly advocated in patient guidelines.[2, 4]

Beyond the individual clinician, the importance of the ‘system of care’ within which the clinician practices is widely recognised. Numerous quality improvement studies demonstrate the superior effectiveness of well-designed systems for delivering timely reperfusion and locally initiatives focusing on bettering adherence to evidence-based therapies [17-20] Furthermore, an area that has received relatively little attention until

recently is that of undifferentiated chest pain management in Emergency Departments. While the frequency of missed myocardial infarction remains relatively low, the life-threating consequences of missed diagnosis and the sheer volume of such presentations to our emergency departments, 700,000 per annum, necessitates timely and effective care. Refining risk estimation in a timely manner coupled with risk-appropriate subsequent investigation is needed. While emerging innovations such as highly sensitive troponin assays and CT coronary angiography are rapidly entering the routine clinical practice, effective decision tools to aid in patient selection are also required to optimise the risk-benefit profile when implementing these innovations in order to realise the promise of improved outcome.[21-25]

The ACS clinical standards, released in late 2014, represent a potential core pillar in local and national efforts to improve ACS care. The Clinical Care Standards can be differentiated from clinical practice guidelines in several ways. First, as opposed to the practice guidelines that are often expansive, highly technical and directed at informing clinicians, the clinical care standards are a minimalistic distillation of the core aspects of ACS care written from the patient's perspective. Second, as a consequence of the first, they represent a "prioritization" of the key elements of optimised care. For example, the emphasis is on the receipt of timely ECG assessment and reperfusion therapy for ST segment elevation MI, rather than considering choices between the different methods of reperfusion. Third, the prioritization focuses on the elements of care that may contribute to the greatest variation in care provision and outcome. Specifically, the standards address the issues of risk stratification informed care for patients presenting with undifferentiated chest pain, as well as an assessment of risk informing the choice for pursuing invasive as opposed to conservative management for patients with documented ACS. Last, through an extensive consultation process, these clinical care standards are now accepted by Federal and various State governments. Consequently, efforts to incorporate methods to measure clinical performance based

on these standards have commenced, and in time will be incorporated into the suite of indicators used to assess the proficiency and effectiveness of all hospitals in caring for the ACS patient.

Whether this “trinity” of clinical practice guidelines, clinical care standards and clinical performance indicators deliver improvements in care and outcomes for Australian and by possible extension in New Zealand ACS patients is yet to be demonstrated. However, their acceptance at a clinical, health service, State government and Australian Health Ministers Advisor Council (AHMAC) level signals a transformation in the receipt of ACS care. For the first time there is now consistency and nationally defined targets for optimal care ACS in Australia. Widespread assent to this trinity may help focus the State and Federal Health departments on health policy, funding and system requirements needed to enable equity of care. In addition it may serve to facilitate co-ordinated efforts between clinicians and health service providers in redesigning acute care systems optimally engineered to provide consistent and timely care. Most importantly, they should remind us, the clinicians, of what is not only effective in ACS care, but also what is most valued by our patients.

17.2 The Standards

- *Standard 1:* A patient presenting with acute chest pain or other symptoms suggestive of an acute coronary syndrome receives care guided by a documented chest pain assessment pathway.
- *Standard 2:* A patient with acute chest pain or other symptoms suggestive of an acute coronary syndrome receives a 12-lead electrocardiogram (ECG) and the results are analysed by a clinician experienced in interpreting an ECG within 10 minutes of the first emergency clinical contact.
- *Standard 3:* A patient with an acute ST-segment-elevation myocardial infarction (STEMI), for whom emergency reperfusion is clinically appropriate, is offered timely percutaneous coronary intervention (PCI) or fibrinolysis in accordance with the time frames recommended in the current National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes.
- In general, primary PCI is recommended if the time from first medical contact to balloon inflation is anticipated to be less than 90 minutes, otherwise the patient is offered fibrinolysis.
- *Standard 4:* A patient with a non-ST-segment-elevation acute coronary syndrome (NSTEACS) is managed based on a documented, evidence-based assessment of their risk of an adverse event.
- *Standard 5:* The role of coronary angiography, with a view to timely and appropriate coronary revascularisation, is discussed with a patient with a non-ST-segment-elevation acute coronary syndrome (NSTEACS) who is assessed to be at intermediate or high risk of an adverse cardiac event.
- *Standard 6:* Before a patient with an acute coronary syndrome leaves the hospital, they are involved in the development of an individualised care plan.

This plan identifies the lifestyle modifications and medicines needed to manage their risk factors, addresses their psychosocial needs and includes a referral to an appropriate cardiac rehabilitation or another secondary prevention program.

- This plan is provided to the patient and their general practitioner or ongoing clinical provider within 48 hours of discharge.

17.3 References

[1] Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). European Heart Journal 2012.

[2] Authors/Task Force Members, Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal 2011;32:2999–3054.

[3] Aroney C, Aylward P, Kelly A, Chew D, Clune E. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. Medical Journal of Australia 2006;184:S1–.

[4] Chew DP, Aroney CN, Aylward PE, Kelly A-M, White HD, Tideman PA, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart Lung Circ 2011;20:487–502.

[5] Amsterdam EA, Holmes DR Jr. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. Journal of the … 2014.

[6] Chew DP, Amerena JV, Coverdale SG, Rankin JM, Astley CM, Soman A, et al. Invasive management and late clinical outcomes in contemporary Australian management of acute coronary syndromes: observations from the ACACIA registry. Med J Aust 2008;188:691–7.

[7] Aliprandi-Costa B, Ranasinghe I, Chow V, Kapila S, Juergens C, Devlin G, et al. Management and outcomes of patients with acute coronary syndromes in Australia and New Zealand, 2000-2007. Med J Aust 2011;195:116–21.

[8] Chew DP, French J, Briffa TG, Hammett CJ, Ellis CJ, Ranasinghe I, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. Med J Aust 2013;199:185–91.

[9] Ellis C, Devlin G, Elliott J, Matsis P, Williams M, Gamble G, et al. ACS patients in New Zealand experience significant delays to access cardiac investigations

and revascularisation treatment especially when admitted to non-interventional centres: results of the second comprehensive national audit of ACS patients. N Z Med J 2010;123:44–60.

[10] Ellis C, Devlin G, Matsis P, Elliott J, Williams M, Gamble G, et al. Acute Coronary Syndrome patients in New Zealand receive less invasive management when admitted to hospitals without invasive facilities. N Z Med J 2004;117:U954.

[11] Huynh LT, Chew DPB, Sladek RM, Phillips PA, Brieger DB, Zeitz CJ. Unperceived treatment gaps in acute coronary syndromes. International Journal of Clinical Practice 2009;63:1456–64.

[12] Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. Med J Aust 2007;187:153–9.

[13] Scott I, Harper C. Guideline-discordant care in acute myocardial infarction: predictors and outcomes. Med J Aust 2002;177:26–31.

[14] Yan A, Yan R, Tan M, Fung A, Cohen E, Fitchett D, et al. Management Patterns in Relation to Risk Stratification Among Patients With Non-ST Elevation Acute Coronary Syndromes. Arch Intern Med 2007;167:1009–16.

[15] Chew DP, Junbo G, Parsonage W, Kerkar P, Sulimov VA, Horsfall M, et al. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. Circulation: Cardiovascular Quality and Outcomes 2013;6:299–308.

[16] Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458–73.

[17] Henry T, Sharkey S, Burke M, Chavez I, Graham K, Henry C, et al. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. Circulation 2007;116:721–8.

[18] Bradley E, Herrin J, Wang Y, Barton B, Webster T, Mattera J, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med 2006;355:2308–20.

[19] Astley CM, Macdougall CJ, Davidson PM, Chew DP. Lost in translation: health resource variability in the achievement of optimal performance and clinical outcome. Circulation: Cardiovascular Quality and Outcomes 2011;4:512–20.

[20] Hutchison AW, Malaiapan Y, Cameron JD, Meredith IT. Pre-hospital 12 lead ECG to triage ST elevation myocardial infarction and long term improvements in door to balloon times: The first 1000 patients from the MonAMI project. Heart Lung Circ 2013;22:910–6.

[21] Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67.

[22] Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, et al. Utility of Absolute and Relative Changes in Cardiac Troponin Concentrations in the Early Diagnosis of Acute Myocardial Infarction. Circulation 2011;124:136–45.

[23] Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. J Am Coll Cardiol 2013;62:1242–9.

[24] Than M, Cullen L, Reid CM, Lim SH, Aldous S, Ardagh MW, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. The Lancet 2011;377:1077–84.

[25] Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med 2012;367:299–308.

18 Concluding Commentary

18.0 Introduction

Co-ordinated policy, health service and clinical level adaptions and reforms are required if we are to effectively and efficiently leverage the opportunities to improve outcome offered to us by discovery science. In this thesis I have described the following:

- Sporadic clinical audits of Australian management of acute coronary syndrome care throughout the last decade (2002-2015) have demonstrated the slow uptake of evidence-based therapies despite the emergence of increasing robust multi-centre randomised clinical trial data supporting these therapeutic innovations. Sub-optimal application of proven therapies and interventions represent significant missed opportunities for reducing near-term recurrent events and mortality.
- Deficiencies observed when relying on clinician intuition in the estimation of patient specific risk, and therefore anticipated value provided by current and emerging evidence based therapies. Refining these risk estimations through decision-support may enhance this evidence translation.
- Adaption of clinical decision-making and health service delivery in response to diagnostic and therapeutic innovations is slow, often organic, rather than deliberate and considered. Clinical and health service reforms should be designed and tested before widespread implementation to ensure effectiveness and efficiency.
- Redesign of the health system continues to occur. We have highlighted service re-configurations that have been built on the design principle of improving the clinical decision as early as possible within the process of patient assessment while at the same time ensuring consistency in the provision of care. These clinical environments may be better placed to translate the innovations emerging from discovery science.

- Health systems function respond to the incentives that arise from health policy and finding environment. Therefore, health policy remains an unharnessed lever for improving the delivery of ACS care in within our community.

To date, we have not developed a co-ordinated approach that embraces change in Australia at all levels of the health system. Moving forward, a greater investment in understanding the solutions to translational barriers will be required. Aspects of a co-ordinated and vertically integrated approach to ACS evidence translation include:

- an alignment of national health policy that funds quality rather than activity;
- the development of standards and performance measures aimed at the core components of quality care to enhance health service redesign;
- health service implementation models that are conducive to the optimal care delivery;
- implementation of the electronic infrastructure supporting the consistency of clinical decision-making in time-critical and geographically challenged environment.
- development of the data-infrastructure to enable the routine collection of performance and outcome data informing all levels of the health system;

Yet, at the core of such reforms must be the patient's and community's preferences. Navigating the increasing complexity of the evidence base, guided by the health preferences and values of the individual remains the principal challenge in the effective translation of evidence to outcome. Finding value for ACS innovations at a patient-level defines the success of the continually evolving evidence base.

This chapter will summarise the experience with monitoring ACS care in Australia, describe the observed barriers that appear to limit translation of the evidence base, provide conceptual goals for overcoming these barriers and, describe some of the ongoing research designed to overcome these barriers, and finally propose an integrated model for closing the loop between evidence and practice through the real-time assimilation of clinical data with guideline recommendations.

18.1 How well is evidence being translated in Australian ACS care?

"If you can't measure it, you can't improve it." - Peter Drucker

Over the last 15 years, studies of Australian ACS practice and outcome have been challenging to implement and have used various funding models and sampling strategies. In large part, they have been the results of efforts by academic and clinical cardiologists from progressive institutions with an interest in evaluation of local practice and late clinical outcomes. These studies have either been: part of a local contribution to international studies with structured, but not a consecutive sampling method (e.g. the Australian and New Zealand cohort of the GRACE Study and the CONCORDANCE registry); local collaborative efforts to involve interested hospital for a specific quanta of patients, (e.g. the ACACIA registry): or an attempt to obtain an "as unbiased sample as possible" though the inclusion of all hospitals for a very short period of time (e.g. SNAPSHOT ACS). All of these registries have been funded by industry sponsorship, with the exception of SNAPSHOT ACS where funding was provided by collaborating health jurisdictions and non-governmental organisations. Currently, there is no national program for the evaluation of ACS care and outcome in Australia.

These registries were designed to assess the status of current practice, evaluating the extent of application of the current ACS evidence base, and demonstrating some evidence of variation between centres. The data have been vital in highlighting the "incompleteness" of care. Within the ACACIA registry (2005-2006), reperfusion for ST-segment elevation patients was provided in only 66.9% of potentially eligible patients (n=755), and timely therapy was administered in only 23% of the population.[1] Within this analysis, reperfusion was associated with a hazard ratio [HR] of 0.44 (95% CI, 0.25–0.78; P < 0.01) for mortality by 12 months, and timely reperfusion was associated with a 78% relative reduction in the hazards for mortality compared with no reperfusion (p=0.02). Disappointingly, the rate of no-reperfusion in the most recent data, derived from SNAPSHOT ACS (2012) from 420 patients demonstrates little improvement in this figure. [2,3]

Overall, the use of inpatient angiography and subsequent revascularization has increased slowly over the decade. This appears to have risen from approximately 50% in the GRACE registry (1999-2007), to 71% in ACACIA (2005-2005) and 82% in CONCORDANCE (2009-2015), although the most recent data from SNAPSHOT ACS (2012) observes a rate of 65% reflecting the inclusion of a more representative sample

of hospitals. Consequently, appropriate direct comparisons between samples is challenging because of variations in the classification of eligible patients and the greater influence of patient co-morbidities in the decision to provide care. In this context, the data point from SNAPSHOT ACS highlights the importance of the representativeness of the sampling framework in drawing conclusion, as well as the possible variation in care resulting from geographic factors.

In contrast, within these studies, the prescription of 4 or more clinical guideline advocated medications among patients with myocardial infarction has initially risen from 40% in the GRACE registry, to 71-72% in each the subsequent registries including SNAPSHOT ACS. While the initial rise is almost certainly explained by the emergence of new evidence, in particular, the $P2Y_{12}$ inhibitors, the plateau in the data acquired after 2005 suggest other factors are limiting the extension of this component of the evidence base. The fact that there is no decline in the estimate within SNAPSHOT ACS implies that geographic and hospital systems are not drivers of variation in the application of this recommendation. Hence, patient specific factors are the most likely determinants of the application of this aspect of the overall ACS evidence base.

Unfortunately, the data are not sufficiently consistent to be able to meaningfully evaluate the referral and uptake of cardiac rehabilitation services. This area suffers from a paucity of clear data due to variations in service definition as to what exactly constitutes a cardiac rehabilitation service (e.g. inpatient, outpatient or telemedicine) combined with the challenges in evaluating various aspects the rehabilitation process (i.e. referral versus attendance versus completion). Clearly, for the purposes of evaluating system performance, measuring referral is desirable, while for efficacy, recording completion may be of greater importance. Gaining clarity over these issues is critical for future efforts to consistently evaluate the uptake and efficacy of cardiac rehabilitation services in future efforts to reform practice and funding/policy.

It is important to acknowledge that while these recommended therapies and interventions are supported by robust evidence, it remains uncertain as to whether their universal application would lead to substantial reductions in future events. It is recognised that the benefits promised by more complete application of guideline recommendations may be mitigated by interactions with competing risks arising from co-morbidities at the patient level. Despite this acknowledgement, efforts to develop effective systems to enhance and optimise clinical decision-making and care delivery

should remain a goal for a self-improving health care system focused on the more effective delivery of an established evidence base.

18.2 Headwinds in the provision of evidence based therapies: Beyond the measurement of practice

Arguably the more valuable information provided by these registries are the insights into the potential barriers for improving the uptake in ACS care. Additional studies and analyses conducted in parallel to these audits have explored clinical, health service and health system factors that either facilitate or limit the provision of the established evidence-base.

18.2.1 Challenges at the physician-patient interface

The rational decision-making steps of physician application of the ACS evidence base for a given patient include: knowledge and acceptance of the evidence; assessment of the risk of current and recurrent ischaemic events; the weighting of potential competing risks in order to estimate overall risk and benefit; and the elucidation of the patient's preferences. Despite the extensive and robust nature of the clinical research that supports many ACS clinical guideline recommendations, the "clinical decision' remains plagued by a high-level of uncertainty. Examples include: uncertainty with how to integrate non-cardiac competing risks; uncertainty in new diagnostic information: and, the accuracy of patient-specific risks and benefits predictions provided by clinical intuition or risk scoring.

Reassuringly, knowledge of the evidence-base, and agreement with the recommendations do not appear to be a key driver of this variation. First, when Australian physicians are directly surveyed, their knowledge and agreement with the evidence are high. Furthermore, reported system barriers or limitations to the use of therapies due to patient complexity is noted to be an issue in a relatively small proportion of patients. Interestingly, when self-reported rates of guideline application were compared with audited rates, there was poor correlation and an over estimation between the perceived used and actual use of therapies.[4]

Competing risks, specifically patient co-morbidities and age, have a significant influence on both the risk of death and recurrent events, and the likelihood of developing complications from therapies. Analyses from these data highlight this clinical practice with markers of ischaemic risk being associated with an increase in the use of guideline advocated therapies, while increasing co-morbidities and age are

associated with decreasing use of therapies.[5] Hence, reflecting the real dissonance that often occurs in clinical decision-making, there is a tension between the cardiac risks and competing risk when deciding to provide each of the guideline recommendations. Unsurprisingly, this data is strongest with the use of invasive management, but is still evident with pharmacotherapies.[5] What remains uncertain is whether clinicians are sufficiently skilled to accurately estimate the relative impact of both cardiac risk and competing risks in order to make appropriate choices in the acute setting.

Hence, being able to weigh risk accurately becomes critically relevant in making appropriate and rational clinical decisions. When physician estimation of risk is directly assessed, performance against objective risk scores appear to be inferior with respect to the prediction of mortality and recurrent myocardial infarction.[6-8] Direct comparison of physician perception of risk compared with either the GRACE risk score or the TIMI risk score demonstrates reduced discriminatory capacity and an improvement in the net reclassification index when the GRACE score is used in addition to physician estimation.[9] Interestingly, within this cohort, the prediction of bleeding risk is poor, both clinically and through the use of risk scores. Formal examination of how clinicians weight the risk and benefit of therapies in response to specific characteristics would suggest that clinicians may underestimate subtle signals such as reduced renal function or tachycardia/hypotension and only register these factors as determinants of risk when observed at the extremes of these parameters (e.g. heart rate >110 bpm and systolic blood pressure <90mmHg).[10] Similarly, frailty imparts only a modest increase in the perception of risk while female gender is associated with a lower perceived risk despite an observed greater predicted risk and worse actual outcome.

The clinical response to risk perception is appropriate, with an increase in the clinical prediction of risk associated with an increase in the use of PCI and some pharmacotherapies.[10] However, when practice is correlated with measured parameters of risk, an inverse relationship is evident, with higher risk patients receiving less therapies. Overall, the under-appreciation of risk appears to be associated with lower rates of use of guideline recommended therapies, a higher perception that pharmacotherapies are not indicated or contraindicated, and a higher mortality rate by 6 months after adjustment for the GRACE risk score.

Of course, physician intuition as to the relative benefit associated with each of the components of guideline advocated care is relevant to clinical decision-making. Since

most clinical trials are designed to evaluate a new therapy in the context of optimal current care, it is difficult to determine the value of older therapies and recommendations in the context of the newer innovation. Evaluation of patients surviving to hospital discharge and comparing those alive versus those who have died by 6 months provides an estimate of the sequential and incremental benefit of each component of guideline recommended care.[11] Such an analysis suggests the greatest benefit arises from revascularization, and there is a diminishing return from sequential addition of specific therapies. Among the pharmacotherapies, the greatest benefit is associated with HMG-CoA reductase inhibitors and $P2Y_{12}$ inhibition, with a diminishing effect from ACE-inhibition /angiotensin receptor antagonists and beta-blockers. Interestingly, this relative benefit is consistent with the perceived relative benefit when clinicians are directly assessed.[9]

Nevertheless, efforts to improve the provision of reperfusion therapy for STEMI, early invasive management for patients with myocardial infarction, combined with the prescription of currently advocated pharmacotherapies are likely to provide greater near term gains in ACS event free survival than emerging diagnostic innovations such as copeptin in patients with chest pain, novel anthithombotic therapies such as vorapaxar or cangrelor, stem cells for LV recovery or potentially the routine use of PCSK inhibition in the post ACS environment.[12] Whether any of these innovations are sufficiently “disruptive” to make any of the existing therapies redundant has not been been determined.

A key remaining question is whether the routine integration of risk stratification using an established risk stratification tool such as the GRACE risk score leads to a better selection of patients and consequently better value in associated with given recommendations has not been robustly determined. While such a practice is strongly advocated in International and local guidelines, an evidence base supporting this recommendation is limited to observational data. Prospective validation that objective risk assessment drives more optimal care would be valuable before such practices are incorporated into measures of health service performance. Current trials exploring this question using hospital level cluster randomised designs have been initiated and are currently ongoing.[13]

18.2.2 How well does clinical decision making and health service design adapt to diagnostic and therapeutic innovation.

The integration of diagnostic and therapeutic innovation into the clinical decision-making remains challenging. This is highlighted by the developments in high-sensitivity troponin assays. Assessment of cardiac injury is now common practice across a broad spectrum of clinical presentations and yet the relationship between modest levels of myonecrosis and mortality or recurrent MI has not been clear. What is clear is that the technology offers the opportunity to "reset" the risk assessment thresholds potentially allowing for greater differentiation of individuals at risk from those at almost no risk of near-term cardiac events. Nevertheless, uncertainty around the interpretation and implementation has resulted in cautious recommendations regarding the use of high-sensitivity troponin testing in the clinical setting. Of even greater uncertainly is the clinical differentiation of types of MI (i.e. spontaneous plaque rupture [Type 1] versus supply demand ischaemia [Type2]) and myonecrosis arising from direct myocardial injury.

We have demonstrated the clear curvilinear relationship between modest troponin elevations and mortality and recurrent MI, contrasting the impact of cardiac injury among those thought to be due to ACS versus those secondary to other conditions (type II MI).[14] Importantly, in the setting of other presentations, the association between troponin elevations and subsequent events conforms to many of the causal principles first described by Austin Bradford-Hill, and the strength of this relationship appears to be greater than evident in type 1 MI.

However, extending the diagnostic information to the clinical environment without specific protocols does not lead to greater clinical discrimination. In our randomised comparison of high-sensitivity troponin reporting versus standard reporting, we observed no reduction or increase in admission, no difference in the use of diagnostic testing and no reduction in length of stay. By 12 months, there was no difference in the rates of recurrent MI or mortality combined. These findings would suggest that, just like therapeutic innovations, realizing the promise of advances in diagnostic testing will require a commensurate adaptive change in clinical decision-making, or a reprogramming of how we clinically evaluate risk and benefit in light of the greater level of information that advances in biomarker, imaging and genetic testing offer.

18.2.3 System factors limiting or facilitating evidence translation

Health service design represents an important target for facilitating the application of the evidence base. System-based interventions are associated with more-timely reperfusion among patients with STEMI and this appears to be associated with improvements in mortality. In other areas of ACS care, there is a distinct paucity of strategies aimed at improving the adherence in guidelines and a lack of evidence showing that the implementation of such approaches is associated with improvements in outcome.

One area where a system intervention aimed at supporting clinical capacity in rural areas has been shown to improve care and outcome is the implementation of a clinical support network within rural South Australia. We have shown an increase in the access to invasive management and improvement in 30-day mortality can be achieved with the delivery of risk stratification tools coupled with cardiologist-led decision-support at the point of care for patients presenting to rural centres with acute myocardial infarction.[15] Potentially, the benefits observed in the rural setting is more easily observed given the mortality rates in rural South Australia were nearly twice the rate of Metropolitan Adelaide at the beginning of the intervention.

Nevertheless, strategies to improve the consistency of clinical decision-making for patients with cardiovascular presentations is achievable even in metropolitan clinical services. In response to observations that patients with ACS and arrhythmias experiences superior outcomes when their care was directed by consultant cardiologists with subspecialty training congruent with their disease (i.e. Interventional cardiologists for ACS patients and electrophysiologists for arrhythmias), we redesigned the cardiology service at Flinders Medical Centre and prospectively evaluated the impact on clinical outcomes.[16] The design principle of this reform was to streaming patients by diagnostic categorisation in order to concentrate clinical decision-making, allowing more rapidly development of experience among training junior staff and nurses. Further, this sought to ensure that those providing investigative testing were also directly involved in the overall decision-making to improve the efficiency of care. This reform was associated with more risk-aligned use of investigations with a lower rate of echocardiography and angiography in lower risk patients, and an increase in the use of ACE-inhibition/angiotensin receptor antagonists in patients with ACS, and an increase in the use of oral anticoagulation among patients presenting with atrial fibrillation. Streaming patients by key diagnostic category was associated with a

reduction in length of stay across all diagnostic categories of chest pain through to unstable angina, NSTEMI and STEMI. Most importantly, a reduction in the rate of the composite endpoint of death, recurrent myocardial infarction, representation with arrhythmia and heart failure was observed when compared with historical controls by 30 days. Hence, benefits in terms of both outcome and efficiency can be gained with the redesign of modern cardiology services when such reform is aimed at improving the clinical decision-making capacity.

18.2.4 Policy is not designed to deliver quality

While seemingly distant to the provision of ACS care, current policy and funding approaches to components of cardiac care have a clear influence of the actual provision of care. Importantly, within the Australian health care system, certain investigations and procedures, specifically echocardiography, angiography and coronary revascularisation attract a fee when conducted in the private sector, but not in the public sector. In contrast, the prescription of guideline medications and referral to cardiac rehabilitation attract no such fee in either public or private health settings. Within the SNAPSHOT ACS dataset we have observed a correlation between a patient's private insurance status and the likelihood for coronary angiography and PCI.[17] Specifically, we have observed a higher rate of use of invasive management among the lower risk cohort of patients than evident among patients funded publically. Such a differential provision of care was not evident for the use of pharmacotherapies and referral to rehabilitation were assessed, regardless of the risk profile of the patient. These observations suggest the potential policies that provide incentives enhancing the provision of proven therapies may also improve outcome.

Observations at a national population level only serve to reinforce this observation. Using data aggregated at the primary care level from all Medicare Locals across Australia, we have demonstrated the variation in the provision of angiography, with a mismatch between the burden of cardiovascular disease and angiography rates. This analysis highlights a poor correlation between ACS rates and angiography, but a strong correlation between admissions to private hospitals and angiography rates. Most concerning was the strong inverse correlation between the local angiography rate and the local rate of revascularization. These data clearly demonstrate substantial unwarranted variation and suggest health service and policy interventions to improve the consistency of care will be required.

18.3 Conceptual characteristics of a system designed for evidence translation in ACS care

The likely factors providing headwinds for the effective and efficient adoption of new technologies and therapeutic innovations include: a) system characteristics that are not conducive to evidence-based decision making and the delivery of proven therapies; b) inadequacies in physician estimation of risk and benefit associated with current and emerging therapies; c) patient competing risks in terms of co-morbidities and socioeconomic factors that present challenges in applying the evidence; and lastly d) limited engagement of the patient's perspective in the relative priorities and relevance of components of modern ACS care. Research and implementation in each of these factors is ongoing. Such activities include the continued development of clinical guidelines and standards for ACS care. From these emerge the measures of ACS performance. Such measures improve the transparency of the care being provided and the outcomes achieved, enabling policy and health service decision-makers to implement strategies aimed at providing effective change. Improving clinician decision-making capacity, specifically the ability to improve diagnosis, quantify risk and assist in making the appropriate choices when offering therapies that are commonly invasive, at high social and economic cost will need to be integrated with these health service reforms. It should be noted, with diminishing overall event rates, and an increased burden of competing risks, the relative risks and benefits of such therapeutic choices become even more challenging to weigh. Of course, informing the very core of these decisions is the individual patients preference. Effective strategies to inform and engage patients in a meaningful manner, that is relevant to their specific life context will be essential if we are to improve those outcomes valued by our patients. Ensuring patient-centric care provision may also improve the efficiency of care.

Closing the loop in ACS translation will require the convergence of an information-gathering paradigm that meets all of these needs in a consistent and ongoing manner. While we remain far from a national system for the monitoring and improving ACS care in an evidence-based but patient centric manner, it is expected that with the maturation of electronic health systems, the capacity to develop an information system that is designed to improve the translation the evidence-base remains on the horizon.

18.3.1 The design of policy focused on outcomes and quality, not activity

In Australia, the funding of health care is complex, and is governed by a complicated set of agreements between the federal government and state governments with

respect to the distribution of federally collected taxation. In simplistic terms, the state governments are responsible for the acute public hospital sector where a large proportion of ACS is managed. This responsibility extends to hospitals in rural and regional centres, which remain the site of first medical contact for a considerable proportion of ACS presentations. The federal government is responsible for the funding of ambulatory care and provides a substantial contribution to the provision of acute services through subsidization of the private health system. Consumers, primarily through their private insurance contributions, constitute the remaining source of funding to acute coronary syndrome care.

However, this relationship is confounded by the introduction of the “activity based funding model” used by the federal government which allocates a proportion of the federal taxation funds to state governments for the provision of public hospital services based on the amount of activity being undertaken. The rationale behind this approach lies in the expectation that this mechanism will drive efficiency across the health care system. By setting a nationally standardised Net Efficient Price for the provision of specific services, with adjustments to account for some variation in patient acuity, remote location and indigenous status, it is expected that hospitals will either work to improve their efficiency for specific conditions and procedures, or make informed choices about the discontinuation of these services when they are unable to meet nationally benchmarked levels of efficiency. It is apparent that such a policy transparently aims to link the activities of clinical diagnosis and the specifics of care with funding. As such, this system critically depends on the quantitative infrastructure available at the local level. Specifically, for the system of activity based funding to drive the change at the care implementation level there needs to be accurate coding of diagnosis (with effective strategies to detect and prevent “gaming” through intentional miss-coding), combined with effective local infrastructure with the skills and capacity to evaluate the cost, and appropriateness of care. Currently, such infrastructure is often diminutive and immature and frequently disconnected from the clinical decision-makers responsible for the design of health services and the provision of care. Locally, this attempt for a direct and transparent mechanism for purchasing services is further disrupted by policies at a state government level where funds allocated under the activity based funding model are quarantined at the state treasury level and distributed to public hospital services under alternate, non-activity based or disease based formulae.

It is important to recognise that each of these avenues of funding is directed at activity rather than quality. Specifically, in the acute public hospital funding models are based on diagnosis related group classifications and procedural codes. Hence, these measures the frequency of a given activity, and consequently provide funding that is usually commensurate with the provision of service. At no stage of the resourcing of health services is the evaluation of quality or appropriateness, or superior outcomes factored into the funding algorithm.

If health policy is to effectively drive improved efficiency and more rapid integration of the emerging evidence into practice, its reach will need to directly influence the decision-makers that provide the health care and at the same time, innovations in policy will need to be informed more directly by the practices and performance of the health system as close to real time as possible.

18.3.2 Health Service design focused on delivery

Within the Australian context, the design of acute hospital services and transition of care services is the domain of the State Governments and State-based health services. Such services are placed to meet the geographic need of the community, but at the same time, must be structured with sufficient clinical critical mass to ensure the maintenance of clinical expertise in diagnosis and therapeutic proficiency. While hospital services are increasing being "designed," the development of acute hospital services have emerged largely as a "self-organising" systems with the development of strengths and proficiencies based on the perceived community needs, interacting with the interest of local clinicians. Considerations for service distribution has led to some restrictions and encouragement by state governments for the provision of specific skills and services, in particular the use of low-volume, high-cost, highly innovative technologies such as cardiac transplantation, cardiac surgical services, percutaneous structural heart disease procedures and some electrophysiology ablative procedures. The extent to which the clinical governance practices of ongoing audit, not only of procedural success but late outcome, credentialing and reaccreditation, as well as continuing practice improvement are exercised within the common clinical presentations (i.e. heart failure, atrial fibrillation chest pain and acute coronary syndromes) is likely to be much more varied across the Australian acute care environment.

Furthermore, ensuring cost-effectiveness of the health service adaptions in response to the emerging cardiac innovations is critical to ensuring sustainable evolution of the

care of acute coronary syndromes. An example of potential inefficiencies is in the assessment suspect ACS and the availability of troponin assays with greater sensitivity. Integrating these tests in the emergency department assessment of suspected ACS must include the rapid exclusion of patients in whom ACS is no longer a diagnostic consideration, combined with effective decision-making protocols for the consideration of other significant diagnostic possibilities among patients with an elevated troponin, some of which are immediately life-threatening. While such protocols are emerging, the effectiveness and cost effectiveness of these pathways requires careful evaluation in randomised trials in order to support their widespread adoption.[18,19]

However, while governance over service design within hospitals has developed, the design of services between the community and the hospital, between hospitals with differing levels of infrastructure and clinical capacity are only now becoming more structured and designed for improved proficiency. Critical in the design of these clinical networks is the development of system level decision-making with agreed protocols supported by the required logistical and clinical infrastructure to consistently execute high-level care across the entire clinical community. Specific examples of successful network integration include the trials of field triage for ST elevation MI where patients with a clear indication of reperfusion therapy based on the initial ECG, are transferred to hospitals able to provide primary PCI, bypassing smaller hospitals where such facilities are not available.[20] While such a system has demonstrated clear benefits with respect to reducing door to balloon time and mortality for patients presenting with ST-segment elevation MI, the consequences for the much larger proportion of patients who present directly to these smaller hospitals or those patients with myocardial infarction without ST segment elevation has not been well studied. Of even greater significance for long-term care, few innovations directed at shared decision making ensuring the effective transition of care back to the patient and primary care physicians have been implemented, though strategies the facilitate adherence through mobile technologies are emerging.[21]

18.3.3 Clinician decision-making based on more than intuition

As discussed earlier, we have also shown that within the process of clinical risk assessment, a critical step estimating the benefits and harms of various guideline recommendation, that clinical practice is imprecise. This results in over estimation of risk in the low risk patients leading to over-treatment, and underestimation of risk in the high-risk patients leading to under-treatment. We have demonstrated that such

imprecision appears to account for some deficiencies in care among high risk ACS patients, and is associated with an increased in mortality by 6-months.[9,10] Intervention studies exploring the utility of tools to improve risk stratification are currently underway. Our work, conducted in parallel with the major Australian registries has documented the impacts of the mismatch between where ACS patients present, and the guideline advocated therapies they receive. Apparent in these analyses is the particular dependency on access to clinician expertise. Specifically, when hospitals were assessed by the availability of core clinical expertise and infrastructural criteria, there was greater late survival observed among patients initially presenting to hospitals with superior competencies related to clinical expertise. This was not seen when outcomes were assessed against the presence of specific infrastructural characteristics. In general, the implementation of programmed decision-making was through protocols and pathways was modest, and not associated with superior outcomes, except in the area of STEMI activation aimed at reducing door to balloon time.[22] These observations resonate with the observations of improved outcome with the implementation of a rural clinical network.[15]

In addition, the impact of financial incentives for driving quality of care has been extensively discussed and explored internationally. Efforts to explore these options within the Australian Health Care system are only now just emerging. We have demonstrated the strong influence of procedural specific remuneration on practice within Australian ACS care. Specifically, since the provision of angiography and coronary revascularization attract a specific fee under Medicare and within private insurance reimbursement, while the prescription of guideline recommended pharmacotherapies do not, we were able to explore the influence of private insurance on the entire package of care among public and privately insured ACS patients.[17] Such observations highlight the need for focused reforms that alter the incentives influencing practice change.

18.3.4 Putting patient preferences at the centre of the system

The clinical evidence assimilated in clinical guidelines has by and large been acquired through the rigorous conduct of randomised clinical trials. These trials must focus on therapeutic efficacy of therapies, and as a result, are actively designed to mitigate patient complexity. At a clinical level, when enrolling patients into these studies, a substantial degree of patient selection compromises the generalizability of the evidence to the broader population managed in clinical practice. The limited nature of

the evidence base in addressing ACS patient with complex clinical conditions and competing medical and social priorities continues to be seen.[5,8]

For much of the generation of the evidence base and the development of guidelines, the ACS patient is a "silent partner." Yet, their "voice" in the translation of the evidence base is now recognised to be critical in achieving optimal outcomes. The vast majority of the ACS evidence base has been directed at reducing immediate and future mortality and recurrent MI. However, among patients with extensive comorbidities or advanced age, or where access to invasive management is associated with substantial social and geographic displacement, the benefits of evidence base therapies may be outweighed by poorly estimated or unmeasured harms. This is more relevant when care transitions into the chronic phase of self-care, where adherence depends on a patient's acceptance of the "value proposition" associated with secondary prevention therapies when weighed against the costs of financial imposition, modifications to lifestyle and self-image, as well as the side-effects of therapies. Understanding patient's priorities and expectations in a systematic manner is essential to the effective provision of health care, and provides the most important context for assessment of health service performance.

18.4 A vision for the future: Integrating real-time data, patient-specific risk and guideline recommendations.

By their very nature, clinical practice guidelines represent an assimilation of the "world's best evidence" regarding the assessment and management specific clinical conditions. As a consequence, their development often ignores the nuances of the local health system, in particular issues such as access and geographic distances, the societies cultural preferences, or the patient-specific priorities of the local community within which they seek to apply. This substantially hampers their relevance and applicability. Here lies the source of the Evidence-Practice Gap.

Optimal clinical decision-making, when applying the acute coronary syndrome (ACS) evidence base remains the fundamental process required for the effective and efficient translation of evidence to outcome. Yet, it is recognised that these decisions are not made in isolation, but are biased by the system within which we practice. They are influenced, not only by the complexity and diversity patient's clinical conditions and preferences, but also the access to clinical expertise, infrastructure and the funding/remuneration for these services. At the very heart of evidence-based translational decision-making is the "desire to realise value": value to the patient's

health outcomes and quality of life; value to the clinician in terms of perceived standards of care and remuneration; and, value to the health system with efficient and effective provision of health services. However, in order to facilitate rational decision-making, such "value propositions" must be informed by accurate and representative information regarding patient specific outcomes, patient preferences and system resources, and the financial drivers that motivate practice. Only through an integrated approach to health service reform that considers these factors will we have a health system that is designed to effectively and efficiently translate clinical guidelines into optimal ACS outcomes for the Australian community. A systematic approach should include:

1. Building the digital environment for the routine assessment of patient preference, clinical practice, patient outcome and system performance.
2. Providing the patient, clinician and health service with the relevant tools for integrating this knowledge of evolving ACS practice to facilitate informed patient centric clinical decision making, and health service/policy redesign.
3. Developing a clinical environment that is able to research and evaluate the relevance of emerging ACS innovations in improving Australian specific ACS outcomes.
4. Establish the capacity for a continuous and sustainable ACS guideline development platform.

A vision for the development of a "closed loop-real time capability" for translating evidence to clinical outcomes in the Australian environment is required. Clinical guidelines and therapeutic treatment effects are global but the absolute benefits in terms of improved outcomes is of local relevance. Consequently, there is a real need to closely integrate the continually evolving evidence-base with the constantly changing profile of patients presenting with ACS in order to facilitate patient-centric decision-making. By presenting patient relevant expected outcomes associated with various treatments and management strategies, this approach seeks to better inform the patient-doctor interaction, enabling patient choice.

18.4.1 Delivering real-time clinical outcomes expected treatment effects to the patient-doctor decision: Components of a System of Data that informs care.

Ongoing real-time data: There is a need to develop "sentinel sites" for the monitoring of current clinical care and outcomes within ACS. Selection of such sites will need to ensure representativeness of the target patient population, not just from the

perspective of geographic and cultural diversity, but also the inclusion of patients very early in the disease pathway (e.g. at the time of relatively undifferentiated clinical presentation) in order to capture the full diversity of patient care and outcome. As such, the establishment of sentinel sites will be designed to provide the broadest generalizability of the treatment effects.

A core clinical dataset: The determinants of outcome among patients with ACS are now well established. The key clinical determinants of recurrent mortality and recurrent clinical events, such as biomarker elevation, extent of ECG abnormalities, and haemodynamic compromise represent key factors which, when accurately assessed, demonstrate robust predictive performance for short term (i.e. 6-month) mortality and recurrent ischaemic events. Additional factors contributing to increase risk potentially not modifiable by current ACS therapies include age and frailty. Similarly, with an increasing burden of chronic disease within the community, the impact of competing risks is an increasingly important consideration necessary for optimizing decision making and outcomes in ACS care.

Capacity for data-linkage to ensure complete evaluation of patient outcome: The ability to ensure follow-up of all consenting patients through to12 month is an important aspect of the data infrastructure. Complete follow-up will ensure that the experience of those at highest risk of recurrent events, in whom care is most often sub-optimal, and where outcomes are worse, are captured. This is the patient subset that is frequently excluded from our clinical trial and therefore their care is frequently not informed by the current evidence base. Among these patients, care is most heterogeneous indicating that greater decision-making guidance may be of value, since the stakes are highest.

A real time analytic capability allowing for the development and continual updating of risk prediction models that account for competing risks: The central aim of these analyses is to provide accurate predicted outcomes for patients with ACS, while allowing a degree of patient individualization through the development of flexible models that include the characteristic that contribute to patient complexity.

Integration of current evidence and current expected outcomes at the point of the clinical decision-making: A mobile platform or web-based application for assimilating expected relative effect sizes associated with specific evidence based guideline recommendations with patient specific event rates in order to derive expected absolute benefits and risk that are relevant to the patients is critical. Decision-making at the bedside is complex for clinicians and being able to engage the patient in a discussion of appropriate and individualised care is often hampered by a lack of patient-specific

estimates of benefits and harms. Furthermore, it is the absolute benefits and harms associated with treatment or no-treatment that is relevant to patients. Simply stated, doctors lack the real time knowledge of patient specific risks and therefore are unable to accurately calculate the absolute benefits and harms necessary to inform patients and their families about the real choices they face. Estimating the confidence bounds or credible limits around these estimates is even more challenging and almost never presented for patient consideration since calculating these is time consuming and difficult without the use of electronic aides. In addition, the vast majority of the evidence-base assimilated in to ACS guideline recommendations focuses on efficacy and the statistical significance of this treatment effect, rather than effect size. This is a necessary consequence of the design of clinical trials with selective inclusion and exclusion criteria. The absolute effect size is dependent on the baseline risk of the population included in the trial and not necessarily representative of the patient for whom treatment is being considered, and therefore, reporting the relative effect size and "expecting" the clinician to do the calculations for estimating the patient specific absolute risk and benefit is common practice when writing guideline recommendations. Hence, it is not surprising that current attempts to facilitate the implementation of guidelines employ protocols that must take a "one-size fits all" approach, relying on very little and relatively unsophisticated risk stratification to inform what are often very expensive therapies such as transfer of patients from country areas to metropolitan centres for early invasive management. Writers of clinical guidelines recommendations and protocols have little choice but to recommend all therapies that are statistically significant as long as they have been evaluated in appropriate contemporary practice and have a net-favourable risk profile. A bedside application leveraging specific patient characteristics combined with the relative treatment effects vetted by national and international guidelines offers the clinician and the patient a more personalised "expected value" (and the credible limits) of each therapy and combination of therapies being offered in order to facilitate patient involvement in their clinical decision-making and care.

Continuous literature review and updating guidelines: Understanding the local deficiencies in care and outcome should allow for ongoing priority setting with regards to the evaluation of the literature. Current priorities established by knowledge of current practice and the potential benefits in filling these practice-gaps would inform the implementation of ongoing searches of the maturing literature seeking studies that inform specific the practice gap, or at least highlight unexplored areas for the attention of researchers and funders. As this evidence-base becomes more robust,

recommendations based on this evidence can be assimilated into guidelines in an electronic manner. As practice and outcomes evolve in response to these recommendations, new priorities for potential improvements in outcomes can be set.

18.4.2 Considerations when implementing a "Closed-loop system"

Privacy and data-integrity: **Representativeness:** An important consideration when analyzing observational data is the representativeness of the data being submitted. To ensure that the data is an unbiased sample of the population, sentinel reporting sites would need to commit to a continuous audit process that employed either a consecutive sampling (small sites with few patients) or random sampling (large sites with many patients) regimen. Data-monitoring processes and regular reconciliation with administrative data would be required. To facilitate this process, recruitment of health services with established or soon to be established electronic health records would be favourable.

Gaming: As a consequence of funding linked to clinical performance and outcomes, the possibility for clinician level and hospital level "gaming" in the reporting of local risk characteristics and practice is possible. Mitigating these risks by benchmarking various patient and practice level indicators against national level data, combined with routine physical data monitoring activities will need to be undertaken by the centralised data-management organization.

Privacy: Privacy of patient level records will need to remain a core principle of the data-management process. Maintaining privacy will need to be balanced against the desire to ensure the accuracy of data-linkage required for the follow-up of late events. At a practical level, these data will need to be collected under an ethical framework of "opt-out" consent where a patient is informed of their right to not have their data collected and are able to opt-out the late data collection process. Not explicitly opting out implies consent. Various models of data-linkage ensuring patient identifying data are not transmitted centrally to the data-management organization have been implemented. These include data linkage performed at the level of the health service or the State department of health (i.e. in health jurisdictions that have existing capacity for data-linkage) or data-linkage of encrypted data undertaken by a third independent party (e.g. the data-linkage unit of AIHW).

Data housing and Stakeholder Engagement: Assimilation of administrative, clinical reporting systems, pathology and pharmacy combined with patient risk and preference

information will need to be assimilated at the level of the health service, and sent in an encrypted format to a central data custodian, with the capacity to undertake data-linkage procedures to capture late follow-up of clinical events. While the capacity to undertake data-linkage of health records varies across the Australian jurisdictions, this ability continues to mature and the capacity to provide routine late follow-up data for ACS patients in a consistent manner will continue to improve. Similarly, organizations with the appropriate governance structures and analytic expertise combined with the content expertise in the area of cardiac care continue to strengthen. These organizations include: the Australian Cardiac Outcomes Registries (ACOR) [DPC serves on the steering committee], an independent entity established by the Cardiac Society of Australia and New Zealand for the purpose of housing and managing Australian data pertaining to cardiac care and outcomes; the Centre for Research Excellence in Cardiac Outcome based as the Monash Department of Epidemiology and Public Health [DPC is a chief investigator]; and the Australian Institute of Health and Welfare [DPC serves on the Cardiovascular Disease Expert Advisory Group]. Other key stakeholders with a keen interest in such data include: the Commission for Safety and Quality in Healthcare who developed the ACS clinical standards which are aimed at reducing unwarranted variation in ACS care; the National Health Performance Authority which manages public reporting of hospital performance; as well as the Independent Hospital Pricing Authority which determines the net efficient price for hospital services and may be an important vehicle for starting to price quality rather than just service provision within the system. In addition, substantial interest from state governments is also anticipated since they are responsible for a significant proportion of hospital funding. Similar interest is anticipated from private health insurers who are also motivated to seek greater efficiency and effectiveness from the health system. Other potential stakeholders include industry sponsors, though their participation is likely to require access to sensitive data and careful consideration for the governance structures would be required.

18.4.3 Stakeholders and Funding partnerships:

The costs of the development of a web-based or mobile application are relatively small in comparison to the costs of providing ACS care in Australia. Even a modest gain of a 1% reduction in costs or a 0.1% improvement in late clinical events would overwhelmingly support the development of such clinical tools. The infrastructure and associated costs of the acquiring the clinical data are also relatively small if the system of data-collection is integrated with the process of clinical documentation. Key costs in

the system is likely to be the centralised data-management and analysis organization required for data integrity. Nevertheless, this organization represents a highly scale-able infrastructure and the costs (~$1M/year) are still modest when considering the overall costs of ACS care in Australia. A contribution to these costs from the various stakeholders across the country would mean that the specific funding burden for any single stakeholder is unlikely to be overly onerous.

18.4.4 Potential Multi-level Benefits for ACS care

18.4.4.1 Patient-Doctor Level Benefits

More personalised risk stratification and estimates of value (i.e.net benefits and harms): Translating clinical trial evidence to recommendations for an individual patient remains challenging for clinicians, let alone patients. Being able to accurately communicate a patient's personal absolute risks and benefits, will facilitate patient engagement in the acute care decision-making, while presenting the counterfactual scenarios (recurrent event rates and mortality with and without secondary prevention treatments) will quantify the value proposition of lifestyle modification and adherence to long-term pharmacotherapies.

More complete assessment of risk: During the clinical assessment, the assessment of patient factor that drive appropriate risk based decision-making is often incomplete, as a consequence of a lack of the physician knowledge about the drivers of risk, or omission that result from complex and time pressured clinical environments. A digital inventory that facilitates more complete assessment would ensure that risk-based decision-making is optimised.

Less reliance on clinician specific experience: Incorporation of the objectively assessable measures of cardiac and non-cardiac risk will enable less experienced clinicians to not only fully evaluate the clinical and individual factors associated with increased risk, but also provide these clinicians with more precise quantitative estimates of the combined risk excess. (i.e. more accurate estimates of the actual expected absolute event rate given the various risk factors)

18.4.4.2 Health Service benefits

Current data on practice and performance that has patient specific context: Currently, the capacity to conduct clinical audit and provide real-time feedback to clinical practice has been limited largely due to the resource intensive nature of "double data entry," i.e. the need for additional time and effort required to enter data into electronic clinical

systems on top of the usual requirements for clinical documentation. The required clinical information collected as a byproduct of the doctor-patient risk stratification process has substantial utility in providing context for evaluating patient preferences, and clinician adherence with guideline recommendations and clinical care standards. Specifically, while current administrative data, cardiac procedural reporting systems and pharmacy dispensing systems are able to provide some information regarding practice, patient-specific clinical information critical for interpreting the quality of practice is often lacking. A tool designed to be implemented at the bedside offers the opportunity for the audit of practice and the evaluation of clinical outcomes, providing insights into the clinical decision.

Contemporaneous data that allows planning of service provision: Time delays in the acquisition of practice information and limited capacity for local evaluation of the effective of care represents important barriers to the ongoing adaptive design of health services. Better knowledge regarding the changing risk profile of local ACS patients, and in particular the impact of current and emerging therapies and technologies on this risk will inform ongoing service redesign to take advantage of these innovations. Similarly, better understanding or the under-served patient subgroups defined not only by clinical characteristics, but also temporal and health service characteristics (e.g. presentations after hours, or to less resourced hospitals within a local health network) presents an opportunity for the evolution of health services to meet the changing demands.

18.4.4.3 Whole of system benefits

Continual alignment of evolving guideline, clinical care standards and appropriateness criteria: At a national level, the enhanced capacity to evaluate care and outcome will allow continual evaluation of clinical guideline recommendations and clinical care standards for acute coronary syndromes. The ability to “close the loop” on evaluating the uptake and effectiveness of guideline recommendations and standards within Australian practice will ensure that current guidelines are focused on the areas of the greatest incremental gain when seeking to continually evolve practice and improve outcome. As proven practices become established as common-place, ongoing iterations of guidelines and standards should shift toward new areas of evidence and those areas where evidence is poorly implemented leading to inferior outcomes. As such, the process of guideline and standard development will become a dynamic and ongoing interaction between current practice and emerging evidence. Electronic implementation of guidelines and standards will shorten the delay in delivering up to

date recommendations to clinicians and patients, while digital infrastructure reporting the changes in practice and outcome allow more rapid evaluation of effectiveness and consequently cost-effectiveness of such recommendations.

Unlocking the influence of policy through more informed health care funding: Greater transparency regarding the provision and effectiveness of current and emerging therapies offers government greater opportunities to appropriately fund effective interventions. These opportunities are not just confined to specific therapeutic interventions but also to services and models of care such as rural out-reach services, telemedicine and the various models are cardiac rehabilitation and secondary prevention. A greater capacity to explore and evaluate the heterogeneity of service provision tightly linked to the evaluation of both clinical outcomes and potentially patient reported outcomes will allow government and payers to more directly fund effective and appropriate care, while disinvesting in inappropriate or out-date models of care. As such, payers will have far greater capacity to drive clinical change leading to more rapid adaptations that optimise both outcomes and efficiency at the same time.

Conduct of pragmatic clinical trials: Growth in the evidence-base also represents an important determinant of how practice changes and outcomes improve. Quantum gains in therapeutic innovation are not expected in the near-term, and areas lacking an evidence-base remain amongst high-risk patients (the elderly, those with renal impairment and those with a significant burden of other chronic disease), as well as within condition that have traditionally been excluded from ACS trials (e.g. type 2 MI, and stress cardiomyopathy). This data platform will facilitate the conduct of pragmatic clinical trial with direct relevance to the local community, with substantially lower resource costs than required for the conduct of industry-sponsored clinical trials. Through a “randomised-registry” approach, inserting randomization within routine clinical practice given a patient’s willingness to consent, this capability will allow for the design and conduct of clinical trials that inform the investment and dis-investment therapies. Similarly the conduct of cluster-randomised trials exploring of models of care among patient groups commonly excluded from clinical trials such as rural patients and those presenting after hours will enhance service design.

18.5 Conclusion

The decades long decline in the incidence of coronary heart disease (CHD) admissions, and consequently, the decline in CHD mortality observed worldwide and in

Australia is well recognized. This success is attributable in part, to both improvements in primary prevention and in the therapeutic innovations that now constitute modern ACS care. Over recent years, these improvements appear to be slowing, and observations from within the studies included in this thesis would suggest that reforms in how we deliver care may be as important, or potentially more important than seeking the next innovation. A system-wide approach to effective translation should establish the clinical and health service environment that embraces patient centric clinical care, enable continuous evaluation of practice and outcome, and provide an ongoing evaluation emerging clinical and health service priorities that will lead to improvements in patient outcomes. In doing so, establish the clinical governance, data and information framework, and inform the health policy settings that will enable the ongoing development and rapid translation of the ACS guidelines into practice and outcome for the Australian community. At multiple levels of health care delivery in Australia, the system is now primed to reform the manner in which it provides the ACS evidence based guidelines. The key gap in knowledge is defining the core local clinical, health service and health policy intervention that are effective and efficient at delivering the evidence base to the Australian community in a consistent and sustainable manner.

18.6 References

1. Huynh LT, Rankin JM, Tideman P, Brieger DB, Erickson M, Markwick AJ, et al. Reperfusion therapy in the acute management of ST-segment-elevation myocardial infarction in Australia: findings from the ACACIA registry. Med J Aust. 2010 Nov 1;193(9):496–501.

2. Chew DP, French J, Briffa TG, Hammett CJ, Ellis CJ, Ranasinghe I, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. Med J Aust. 2013;199(3):185–91.

3. Farshid A, Brieger D, Hyun K, Hammett C, Ellis C, Rankin J, et al. Characteristics and Clinical Course of STEMI Patients who Received no Reperfusion in the Australia and New Zealand SNAPSHOT ACS Registry. Heart Lung Circ. Elsevier; 2016 Feb;25(2):132–9.

4. Huynh LT, Chew DPB, Sladek RM, Phillips PA, Brieger DB, Zeitz CJ. Unperceived treatment gaps in acute coronary syndromes. International Journal of Clinical Practice. 2009 Oct;63(10):1456–64.

5. Joynt KE, Huynh L, Amerena JV, Brieger DB, Coverdale SG, Rankin JM, et al. Impact of acute and chronic risk factors on use of evidence-based treatments in patients in Australia with acute coronary syndromes. Vol. 95, Heart (British Cardiac Society). 2009 Sep pp. 1442–8.

6. Yan A, Yan R, Tan M, Fung A, Cohen E, Fitchett D, et al. Management Patterns in Relation to Risk Stratification Among Patients With Non-ST Elevation Acute Coronary Syndromes. Arch Intern Med. 2007 May 5;167(10):1009–16.

7. Yan R, Yan A, Tan M, McGuire D, Leiter L, Fitchett D, et al. Underuse of evidence-based treatment partly explains the worse clinical outcome in diabetic patients with acute coronary syndromes. Am Heart J. 2006;152(4):676–83.

8. Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. Med J Aust. 2007 Aug 1;187(3):153–9.

9. Chew DP, Junbo G, Parsonage W, Kerkar P, Sulimov VA, Horsfall M, et al. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. 2013 May 21;6(3):299–308.

10. Chew DP, Juergens C, French J, Parsonage W, Horsfall M, Brieger D, et al. An examination of clinical intuition in risk assessment among acute coronary syndromes patients: Observations from a prospective multi-center international observational registry. Int J Cardiol. Elsevier Ireland Ltd; 2014 Feb 1;171(2):209–16.

11. Chew DP, Anderson FA, Avezum A, Eagle KA, Fitzgerald G, Gore JM, et al. Six-month survival benefits associated with clinical guideline recommendations in acute coronary syndromes. Vol. 96, Heart (British Cardiac Society). 2010 Aug pp. 1201–6.

12. Chew DP, Huynh LT, Liew D, Astley C, Soman A, Brieger D. Potential survival gains in the treatment of myocardial infarction. Heart. 2009 Nov;95(22):1844–50.

13. Chew DP, Astley CM, Luker H, Alprandi-Costa B, Hillis G, Chow CK, et al. A cluster randomised trial of objective risk assessment versus standard care for acute coronary syndromes: Rationale and design of the Australian GRACE Risk score Intervention Study (AGRIS). Am Heart J. Elsevier; 2015 Nov;170(5):995–1004.e1.

14. Chew DP, Briffa TG, Alhammad NJ, Horsfall M, Zhou J, Lou PW, et al. High sensitivity-troponin elevation secondary to non-coronary diagnoses and death and recurrent myocardial infarction: An examination against criteria of causality. European Heart Journal: Acute Cardiovascular Care. 2014 Dec 11.

15. Tideman PA, Tirimacco R, Senior DP, Setchell JJ, Huynh LT, Tavella R, et al. Impact of a regionalised clinical cardiac support network on mortality among rural patients with myocardial infarction. Med J Aust. 2014 Feb 17;200(3):157–60.

16. Chew DP, Horsfall M, McGavigan AD, Tideman P, Vaile JC, O'Shea C, et al. Condition-specific Streaming versus an Acuity-based Model of Cardiovascular care: A Historically-controlled Quality Improvement Study Evaluating the Association with Early Clinical Events. Heart, Lung and Circulation. Elsevier; 2015;0(0).

17. Briffa TG, Hammett CJ, Cross DB, Macisaac AI, Rankin JM, Board N, et al. Should fee-for-service be for all guideline-advocated acute coronary syndrome (ACS) care? Observations from the Snapshot ACS study. Aust Health Rev. CSIRO PUBLISHING; 2015 Apr 27;39(4):379–86.

18. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, et al. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T. Annals of Emergency Medicine. 2016 Jan 8.

19. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009 Aug 27;361(9):858–67.

20. Carstensen S, Nelson GCI, Hansen PS, Macken L, Irons S, Flynn M, et al. Field triage to primary angioplasty combined with emergency department bypass reduces treatment delays and is associated with improved outcome. European Heart Journal. 2007 May 4;28(19):2313–9.

21. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomised Clinical Trial. JAMA. American Medical Association; 2015 Sep;314(12):1255–63.

22. Astley CM, Macdougall CJ, Davidson PM, Chew DP. Lost in translation: health resource variability in the achievement of optimal performance and clinical outcome. 2011 Sep 1;4(5):512–20.

19 Appendix: List of supporting articles

i. White, HD, **Chew, DP**. Acute Myocardial Infarction: Seminar. Lancet 2008; 372: 570–84

Summary article describing the status of myocardial infarction care. The article began the dialogue focusing on the need for systems to effectively deliver the currently proven evidence base.

ii. **Chew DP**. The last mile: improving patient outcomes within modern cardiovascular medicine. Heart Lung Circ. 2008;17 Suppl 4:S10-3. Epub 2008 Nov 8.

Viewpoint article discussing the need to increase focus on enhanced systems of care delivery in Australia.

iii. Brieger D, Kelly AM, Aroney C, Tideman P, Freedman SB, **Chew D**, Ilton M, Carroll G, Jacobs And I, Huang NP; on behalf of the National Heart Foundation ACS Implementation and Advocacy Working Group. Acute coronary syndromes: consensus recommendations for translating knowledge into action. Med J Aust. 2009 Sep 21;191(6):334-338. PubMed PMID: 19769557.

Position statement by the Heart Foundation with regards to the systems of care required for the effective provision of ACS care in Australia.

iv. Huynh LT, **Chew DP**, Sladek RM, Phillips PA, Brieger DB, Zeitz CJ. Unperceived treatment gaps in acute coronary syndromes. Int J Clin Pract. 2009 Oct;63(10):1456-64. PubMed PMID: 19769702.

Key work from a prior PhD student (Dr Luan Huynh) documenting the disconnect between physician perception of practice and actual care provided. This forms the rationale for routine electronic systems for documenting ACS care.

v. Brieger DB, Aroney CN, **Chew DP**, Kelly AM, Walters DL, Toohey CL, Boyden AN. Acute coronary syndromes: consensus recommendations for translating knowledge into action. Med J Aust. 2010 Jun 21;192(12):700-1.

Position statement on behalf of the ACS Implementation working group of the Heart Foundation advocating for clinical registries in ACS care in Australia

vi. Huynh LT, Rankin JM, Tideman P, Brieger DB, Erickson M, Markwick AJ, Astley C, Kelaher DJ, **Chew DP**. Reperfusion therapy in the acute management of ST-segment-elevation myocardial infarction in Australia: findings from the ACACIA registry. Med J Aust. 2010 Nov 1;193(9):496-501.

Observations from the ACACIA registry demonstrating the incomplete provision of reperfusion therapy and the associated increase in mortality in Australia.

vii. Astley CM, Beltrame JF, Zeitz C, Worthley M, Coates P, Murray A, Arstall M, Grantham H, Dunn R, Quinn S, Aylward PE, **Chew DP**. Study design of embracing high-sensitivity troponin effectively: The value of more information: A randomised comparison. Contemp Clin Trials. 2014 Sep 4;39(2):183-190. doi: 10.1016/j.cct.2014.08.012.

Design paper describing the NHMRC funded trial reported in chapter 11

viii. Kaambwa B, Ratcliffe J, Horsfall M, Astley C, Karnon J, Coates P, Arstall M, Zeitz C, Worthley M, Beltrame J, **Chew DP**. Cost effectiveness of high-sensitivity troponin compared to conventional troponin among patients presenting with undifferentiated chest pain: A trial based analysis. Int J Cardiol. 2017 Mar 2. pii: S0167-5273(17)31292-5. doi: 10.1016/j.ijcard.2017.02.141. PMID:28325612

Cost effectiveness paper describing the lack of cost effectiveness with routine unguided implementation of high-sensitivity troponin

ix. **Derek P. Chew**, MPH, FRACP, FACC, FCSANZa, Constantine N. Aroney, MD, FRACPb, Philip E. Aylward, FRACP, FCANZ, FRCP, FACCa, Anne-Maree Kelly, MClinEd, FACEM, FCCPe, Harvey D. White, FRACP, FACC, FESC, FAHA, FHKCC (Hon), FCSANZc, Philip A. Tideman, FRACPd, Jill Waddell, MPHf, Leva Azadi, MPHf, Alison J. Wilson, MBAf,∗ and Leah-Anne M. Ruta, PhDf2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS) 2006. Heart Lung Circ. 2011 Aug;20(8):487-502.

x. **Chew DP**, Brieger D, Astley CM, Georgiou A. Measuring performance and outcomes of acute coronary syndrome management in Australia. Med J Aust. 2012 Aug 6;197(3):140-2.

Advocacy document calling for an ACS registry in Australia

xi. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, **Chew DP**, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2015 Aug 29. pii: ehv320.

Current European Society of Cardiology Guidelines for non-ST segment ACS care. I served on the panel.

xii. Pathik B, De Pasquale CG, McGavigan AD, Sinhal A, Vaile J, Tideman PA, Jones D, Bridgman C, Selvanayagam JB, Heddle W, **Chew DP**. Sub-specialization in cardiology care and outcome: should clinical services be redesigned, again? Intern Med J. 2015 Sep 19. doi: 10.1111/imj.12909. [PMID: 26387874

Key observations describing the deficits care and outcome associated with non-aligned subspecialist care. Background observations providing rationale for chapter 14.

xiii. **Chew DP**, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, Woodruffe S, Kerr A, Branagan M, Aylward PE; NHFA/CSANZ ACS Guideline 2016 Executive Working Group:. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016.Heart Lung Circ. 2016 Sep;25(9):895-951. doi: 10.1016/j.hlc.2016.06.789. Epub 2016 Jun 16.

Current Heart Foundation and Cardiac Society of Australia and New Zealand

Guidelines for ACS Care. I chaired the writing committee.