Acute Ischaemic Stroke Assessment: Overcoming Barriers to Effective Therapies

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ABSTRACT

Thrombolytic therapy for acute ischaemic stroke became standard of care in Australian hospitals in the early 2000s. Despite over 20 years of experience with this treatment, the national median hospital arrival to thrombolytic administration time, known as “door-to-needle time” (DNT) has remained relatively static at 75 minutes since public records began over a decade ago. At the same time, stroke DNT in other comparable advanced health systems such as the United Kingdom and the United States have improved substantially to well under 60 minutes. The stroke team at Box Hill Hospital, a tertiary hospital in metropolitan Melbourne, has reported the fastest DNT in Australia since 2020. This was achieved through a series of quality improvement projects. The results and learnings from the quality improvement program at Box Hill Hospital over the last decade are presented here.

This thesis includes original contributions to knowledge on three aspects of the acute stroke assessment and treatment. First, in terms of DNT, my early work explored how fast treatment may not be possible for up to one third of acute stroke patients due to patient or system related factors. This work laid the groundwork for identifying areas for targeted improvements and contributed to the design and implementation of a successful province-wide DNT quality improvement projects in Alberta, Canada. Subsequently, the effect of various interventions on DNT in the Australian context were quantified. In addition to showing that directly transferring the patients from triage to the CT scanner was associated with a 32.6% reduction in DNT, the presence of the Acute Stroke Nurse (ASN) was shown to decrease the DNT by 6.9% - an observation previously not quantified. The use of body camera, the first continuous workflow observation study of a “code stroke” process in the literature, showed the longest time spent during a code stroke at our centre was the multimodal scan (13 minutes), and the decision-making time was only 3.7 minutes. “Administrative work”, although occurring after the “needle time”, comprised the longest time in a code stroke (21 minutes). Demonstrating the feasibility of this method to closely examine processes paves the way for other centres to use this novel method to examine and identify areas for improvements in the acute stroke treatment workflow.

Second, we were one of the first groups in the world to study the door-in-door-out (DIDO) time in acute stroke patients with emergent large vessel occlusion (ELVO) presenting to a primary stroke centre (PSC). We found the median DIDO time to be around 120 minutes in

a metropolitan PSC with the longest component being the “scan to retrieval request” time. We found retaining the in-bound ambulance crew for the out-bound journey to be robustly associated with shorter DIDO times and ultimately proving a DIDO of 60 minutes is an achievable target for Australian metropolitan PSCs. Further, DIDO times in regional PSCs were examined in a state-wide study and our work suggested in Victoria, for sites >250 km from a comprehensive stroke centre (CSC), air transport resulted in faster ECR transfer time compared to road transport. The mode and travel times of ELVO transfers from regional sites to CSCs have not been studied systematically before.

Third, the thesis finishes by exploring a solution to an increasingly common barrier to intravenous thrombolysis (IVT) in patients taking, or presumed to be taking, direct oral anti-coagulant (DOAC). The extent of this problem was examined and through a pilot proof of concept study, the utility and correlation between the results of a qualitative point of care urine assay (DOASENSE^{TM}) with conventional plasma DOAC level measurement was explored in both patients presenting with acute stroke as well as those newly started on a DOAC. DOASENSE^{TM} was shown to be reliable, and the results from DOASENSE^{TM} may be particularly helpful in increasing the number of patients eligible for stroke thrombolysis in regional hospitals where rapid assessment of the presence or absence of DOAC in a IVT eligible patient is not possible.

The published works documented how the stroke team at Eastern Health identified barriers to treatment and developed, implemented, and evaluated strategies to overcome these; some novel and some adapted to an Australian context, to improve local and regional treatment access, DTN, DIDO and PSC to CSC transfer times. This has resulted in our hospital achieving consistently the fastest DTN in Australia. The barrier identification and interventions employed are presented here. The findings from this body of work have informed policy statements, service delivery, and importantly, provide the scientific basis to the recently released 30/60/90 Australian National Stroke Targets for Acute Stroke Treatment.

DECLARATION

I certify that this thesis:

1. does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and

2. the research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and

3. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Signed.....

Date.....12th April 2024……

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LIST OF ABBREVIATIONS

AHA	American Heart Association
ASN	Acute Stroke Nurse
AF	Atrial fibrillation
AuSCr	Australian Stroke Clinical Registry
AV	Ambulance Victoria
BHH	Box Hill Hospital
CSC	Comprehensive Stroke Centre
CT	Computed Tomography
DIDO	Door-in-door-out time
DNT	Door-to-needle time
DOAC	Direct Oral Anticoagulants
ECR	Endovascular Clot retrieval
ED	Emergency Department
ELVO	Emergent large vessel occlusion
EMS	Emergency Medical Services
EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial trial
FWCI	Field-Weighted Citation Index
GWTG	Get With The Guidelines
INR	International Normalised Ratio
IQR	Interquartile Range
ISTR	International Stroke Thrombolysis Register
IVT	Intravenous Thrombolysis
MIT	Medical Imaging Technologist
MMC	Monash Medical Centre
MR CLEAN	Multicentre Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands
mRS	Modified Rankin Scale
MSU	Mobile Stroke Unit
NINDS	National Institute of Neurological Disorders and Stroke
NNT	Number-needed-to-treat
PSC	Primary Stroke Centre
RCT	Randomised Controlled Trials
RMH	Royal Melbourne Hospital
SITS	Safe Implementation of Thrombolysis in Stroke
SSA	Stroke Society of Australasia
TGA	Therapeutic Goods Authority
TT	Thrombin Time
VST	Victorian Stroke Telemedicine
VKA	Vitamin K Antagonist

CHAPTER 1: CONTEXTUAL STATEMENT

1.1 Introduction

Stroke is a relatively new medical subspecialty. The first issue of the journal *Stroke* was published by the American Heart Association (AHA) in 1970. The first ever CT scan of a patient's brain came one year after that.[1] The American Stroke Association, originated as the Stroke Division of the AHA, celebrated its 25th year only in 2023. The inaugural scientific meeting of the Stroke Society of Australasia in Perth was in 1990, and the establishment of the National Stroke Foundation in Australia would come six years later. In the early 21st century, stroke remains the leading cause of disability worldwide and second leading cause of death.[2] Cerebrovascular disease was the third cause of death in Australia after ischaemic heart disease and dementia in 2021.[3] The number of Australians living with the effects of a stroke is projected to double from 445,087 in 2020 to 819,000 in 2050.[4]

1.11 Stroke in ancient times to late 19th century

The oldest scientific evidence of a human having lived with prolonged period of hemiparesis without evidence of a skull injury was found in an adult female mummy dated to the 25th Dynasty of Egypt (c. 747-656 BC).[5] The term "apoplexy" was first seen in the works by Hippocrates (460 BC).[6] Stroke, as it is understood today, is likely one of the many apoplectic syndromes described by Hippocrates, including the modern day diagnosis of epilepsy and migraine.[7] Under the influence of Galen's writings (129 – 216 AD), for over 1500 years until the Renaissance, apoplexy was understood through the lens of the humoral and supernatural theories.[8] Wepfer (1620 – 1695) was the first to recognise bleeding in to the brain as a distinct cause of apoplexy. It was another 200 years until Virchow (1821 – 1902) introduced the terms *apoplexia sanguinea* (hemorrhagic apoplexy of the brain), and *apoplexia ischaemica* (ischaemic apoplexy).[6] In the western traditions, bloodletting was the most common treatment used for apoplexy since medieval times. By the 19th century, the rationale for bloodletting changed from restoring humoral balance to

reducing the pressure of the blood, with the practice no longer recommended in the 12th edition of Osler's *Principles and Practice of Medicine* in 1935.[8] The term apoplexy last appeared in the 4th Revision of the International List of Causes of Death in 1929 and "stroke" (cerebrovascular disease) was first listed in the International Classification of Disease-8 in 1965.[6]

1.12 Stroke in the modern era

The first half of the 20th century was marked by the invention of cerebral angiogram and detailed clinicopathological description on various cerebral infarctions syndromes.[9, 10] This understanding of pathophysiology was followed by studies involving the use of anti-coagulants, anti-platelets, carotid endarterectomy and other vascular surgical techniques in stroke. The basis to stroke reperfusion therapy gathered pace from the 1960s beginning with the measure of regional cerebral blood flow in humans, ultimately leading to the concept of the ischaemic penumbra.[11] Early experience with thrombolysis in stroke also started around this time with renewal interest in the 1980s following the successful use of thrombolytics in coronary thrombosis.[12, 13, 14]

Alongside the development of intensive care units and coronary care units in the 1950s, the importance of allied health input for stroke patients, and in particular, organised stroke rehabilitation units, also occurred in that decade.[15, 16, 17] Description of comprehensive stroke unit, focusing on both the acute and rehabilitation aspects of care, would come later in the 1970s. The role of stroke unit care in improving mortality and dependency post-stroke was increasingly recognised by 1993 and confirmed in systematic reviews a few years later.[18, 19]

By the late 1990s, stroke was no longer considered an "untreatable disease" (Figure 1). The results of the landmark National Institute of Neurological Disorders and Stroke (NINDS) study in 1995 established intravenous thrombolysis (IVT) as that standard of care for eligible patients with acute ischaemic stroke. Another quarter of a century would pass before the successive publications of five randomised controlled trials (RCT) in 2015, cemented the role of endovascular clot retrieval (ECR) over IVT alone in patients with emergent large vessel occlusion (ELVO) in the anterior circulation.[20]

It is in this context that clinician scientists across Australia have continued to push the boundaries of acute reperfusion therapies. Trials that showed the superiority of tenecteplase over alteplase in patients with ELVO, the safer tenecteplase dosing of 0.25mg/kg over 0.4mg/kg, and finally, the extension of the IVT window from 4.5 hours to 9 hours from stroke onset based on CT perfusion parameters, were all conducted and published within the last decade by research groups in Australia.[21, 22, 23]

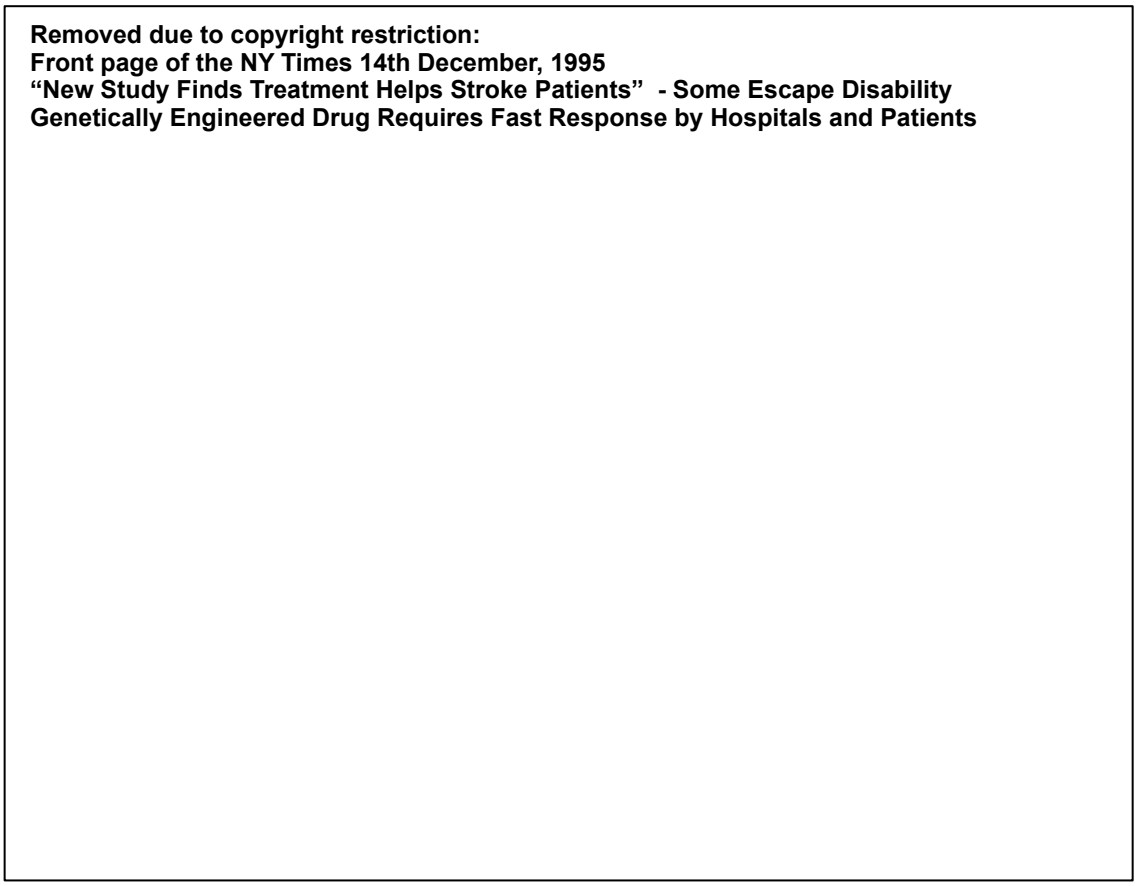


Figure 1: Front page of The New York Times the day after the NINDS study was published in the New England Journal of Medicine with quote from Dr James Grotta

1.2 The importance of fast treatment times

Pooled analysis of early IVT trials reported an adjusted odds ratio for a dichotomised favourable versus unfavourable outcome at 3 months after stroke of 2.81 (95% CI 1.75 – 4.50) compared to 1.55 (95% CI 1.12 – 2.15) in patients treated in 0-90 minutes and 91-180 minutes from symptom onset respectively.[24] Individual patient data meta-analysis

showed a number-needed-to-treat (NNT) to achieve a favourable outcome was 5, 9 and 19 for onset to treatment times of within 90 minutes, 91-180 minutes and 181-270 minutes.[25] Further, an updated analysis in 2016 confirms the benefit is the greatest with earlier IVT and the effect is independent of age or stroke severity.[26] Results from recent IVT and ECR trials have shown a subset of patients are “slow progressors” – the ischaemic penumbra remains viable and not infarcted more than 6 to 24 hours from stroke onset.[23, 27] This does not negate time is still brain. For the “fast progressors”, the benefit of stroke perfusion therapies remain extremely time sensitive, where the neuron loss per minute may be as high as >27 million per minute when compared to <35000 per minute in “slow progressors”.[28]

The NNT of acute stroke interventions are shown in Table 1.[29] Furthermore, recent analysis showed a DNT of less than 45 minutes may also be associated with lowest mortality and readmission rates with every 15 minutes increase in DNT up to 90 minutes of hospital arrival associated with higher all-cause mortality (adjusted HR 1.04, 95% CI 1.02 – 1.05).[30]

Treatment	Outcome at 3 months	NNT
IVT within 3 hours	Return to usual activities	10
IVT within 3 - 4.5 hours	Return to usual activities	19
ECR within 6 hours	Death/Dependence	5
Stroke Unit Care	Death/Dependence	28
Aspirin within 48 hours	Recurrent stroke/death	109

Table 1: Number needed to treat (NNT) of acute ischaemic stroke interventions

1.21 Door-to-needle time (DNT) in the United States

In real world practice from 2003 to 2007 in the United States, hospitals reported onset-to-door time was under one hour in 28.3% of stroke patients. While these patients were more likely to receive IVT compared to patients arriving later from onset, their door-to-needle time (DNT) was longer and only 18.3% had a DNT of less than 60 minutes.[31] Patients who arrived earlier actually waited longer to receive IVT. These findings are similar to those of other national registries around the same period.[32] The AHA launched the Get With The Guidelines (GWTG) *Target: Stroke* initiative in January 2010 with the primary goal for participating hospitals to provide IVT to at least 50% of their acute ischaemic stroke patients with a DNT of one hour or less by suggesting 10 key best practice strategies.[33] This target was achieved within 3 years but more importantly, lower in-hospital mortality and lower rates of haemorrhagic complications were also observed.[34]

Subsequent *Target: Stroke* campaigns and their goals are as follow:

Campaigns	**Goals**
Target: Stroke Phase II 2014-2018	DNT within 60 minutes in at least 75% of patients treated with tPA and within 45 minutes in at least 50% of patients
Target: Stroke Phase III 2019 - present	DNT within 60 minutes in at least 85% of patients treated with tPA Door-to-device times within 90 minutes for direct-arriving patients and within 60 minutes for transfer patients in 50% or more in those treated with ECR

The improvement in DNT translates to improved patient outcomes in those treated as shown in Table 2. [35, 36]

Clinical Outcomes Pre-Target: Stroke, Target: Stroke Phase I, and Target: Stroke Phase II

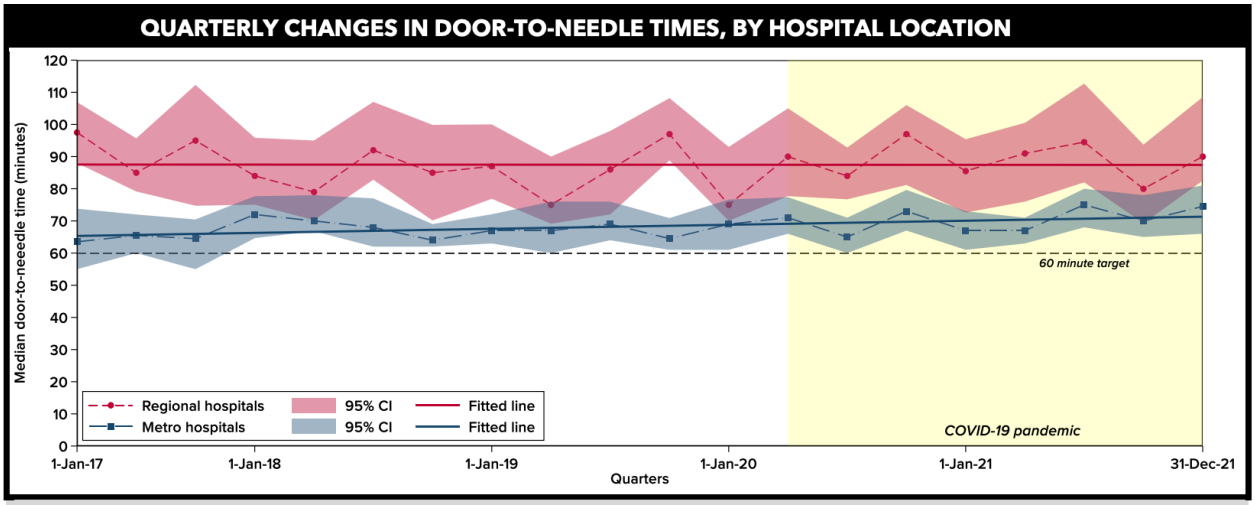
Outcome	Pre-Target: Stroke (n=24,365)	Post-Target: Stroke Phase I (n=44,257)	Post-Target: Stroke Phase II (74,447)	P value	Adjusted OR 95% CI (Phase I vs Pre Target: Stroke)	Adjusted OR 95% CI (Phase II vs Pre Target: Stroke)
In-Hospital Mortality	10.0%	8.2%	6.2%	<0.0001	0.85 (0.80-0.91)	0.72 (0.67-0.77)
Discharge Home	35.8%	41.5%	49.0%	<0.0001	1.21 (1.16-1.27)	1.35 (1.27-1.45)
Ambulatory Status Independent	41.5%	44.6%	52.7%	<0.0001	1.05 (0.99-1.22)	1.35 (1.27-1.45)
Symptomatic ICH within 36 Hours	5.7%	4.5%	3.6%	<0.0001	0.79 (0.72-0.86)	0.67 (0.61-0.73)

Table 2: Clinical outcomes associated with *Target: Stroke* Phase I and Phase II

1.22 Motivation for this thesis

Meretoja et al in Helsinki demonstrated a reduction of DNT from a median of 105 (IQR 65 – 120) to 20 (IQR 14-32) is possible over a 13 year period from 1998 to 2011 .[37] Other hospitals with highly motivated stroke champions, such as the Royal Melbourne Hospital (RMH) in the early 2010s, and Christchurch Hospital, New Zealand, in the late 2010s, have all reported dramatic reduction of DNT.[38, 39] However, apart from Helsinki, there is little evidence in the literature that these centres can or have maintained fast DNT over a sustained period of time. Further, these centres represent a tiny fraction of all the hospitals that provide IVT. Importantly, there has been no successful intervention to improve stroke reperfusion time on a national basis in Australia.

Australia lags the UK and USA in terms of proportion of patients with DNT of less than 60 minutes from hospital arrival, 29% compared to 68% in the USA, and 61% in the UK.[40] Figure 2 shows the stagnation of the Australian national median DNT since 2017, irrespective of the locality of the hospital, with regional hospitals having longer DNT compared to metro sites.[41]



Data derived from a sub-set of 46 hospitals that have consistently participated in the AuSCR between 2017 and 2021 and contributed ≥30 episodes each calendar year.
* Includes episodes of ischaemic stroke provided thrombolysis only.

Figure 2: Quarterly median DNT from 2017 to 2021 by hospital location

It is in this context that I undertook a suite of work to improve the stroke reperfusion metric, to shorten the onset to treatment times and maximise IVT treatment eligibility. This thesis presents reports of my efforts to do so within a large Australian tertiary hospital – Box Hill Hospital (BHH) in Melbourne.

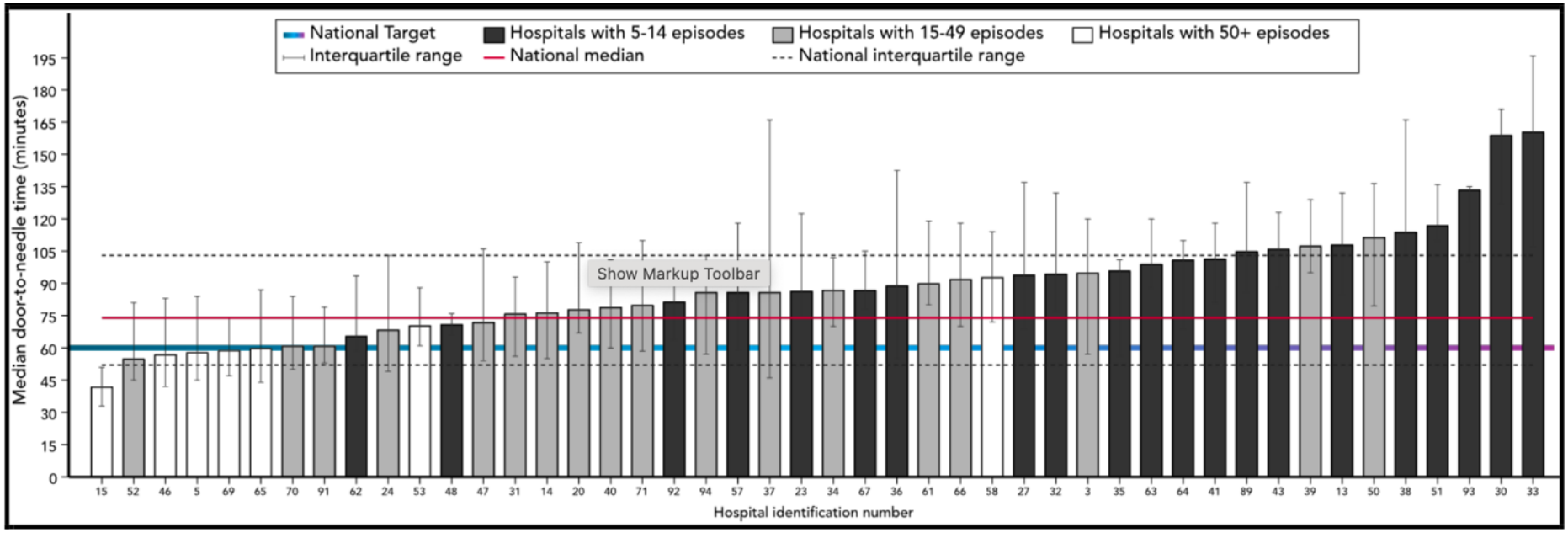
1.3 The Hyperacute Stroke Service at Eastern Health

BHH is part of Eastern Health, the largest metro health service by land size covering 2816km^2 from the inner eastern suburbs to the outer east, with a primary and secondary catchment population of about 1 million (Figure 3). The acute stroke services at Eastern Health are concentrated at BHH where the acute stroke unit is based, and thrombolysis is provided 24/7. Emergency Departments (ED) at Maroondah Hospital, and Angliss Hospital do not treat acute strokes, and patients presenting directly to those hospitals are transferred to BHH for assessment after triage by their EDs. BHH is the busiest Primary Stroke Centre (PSC) in Victoria by the number of stroke admissions, assessing approximately 1250 Code Stroke annually with about 700 admissions to the stroke unit.

Figure 3: Primary and secondary catchment area of Eastern Health. PJC = Peter James Centre; YRH = Yarra Ranges Health

1.3.1 Acute stroke quality improvement program at Eastern Health

I completed my second year of core neurology training at Eastern Health in 2012. After 18 months of further fellowship training with the Calgary Stroke Program in Canada, I returned to Eastern Health as a part-time consultant neurologist in 2015. My clinical and research interest was in improving the hyperacute stroke assessment and workflow processes. Together with the acute stroke nurses (ASNs), we devised a continuous hyperacute stroke quality improvement program. The core component was a weekly meeting involving the ASNs, stroke registrar and stroke fellow. During the meeting, we reviewed all the reperfusion cases in the past 7 days. Areas for improvements were identified with feedback promptly discussed with the staff members involved. These may include the nurse in ED or the medical imaging technologist who scanned the patient. A quarterly meeting was also set up, involving a group of internal and external stakeholders, including representatives from local area command of Ambulance Victoria (AV), nursing and medical leads of the Emergency Department and the chief CT medical imaging technologist. My leadership role was formalised in 2019 when I was appointed as the clinical lead for hyperacute stroke and stroke research at Eastern Health. Incremental improvement in DNT was achieved against a national trend of DNT stagnation. Figure 4 shows the leading position of BHH (Hospital ID 15, first on the left) compared to other centres nationally. Since 2020, BHH has had the fastest median DNT in Australia. (Table 3)



Excludes episodes where thrombolysis was provided prior to arrival or after 4.5 hours of arrival.
Number of episodes with door-to-needle times by hospital range from 5 to 101.
Excludes data from 7 hospitals with <5 episodes.

Figure 4: Door-to-needle time by Hospital from the Australian Stroke Clinical Registry report 2022

YEAR	NUMBER OF THROMBOLYSED CASES IN AUSCR	AUSCR MEDIAN DNT	BHH MEDIAN DNT	BHH AUSCR NATIONAL RANKING
2016	486	72	N/A	N/A
2017	N/A*	73	53	7th
2018	1939	71	53	6th
2019	1463	72	50	3rd
2020	1538	75	45	1st
2021	1320	77	46	1st
2022	1296	74	42	1st
2023**	-	-	40	-

Table 3: Australia's door-to-needle time from 2016 to 2021 from publicly available information. *No number reported. **Unpublished data

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1.3.2 Stroke fellowship program at Eastern Health

The stroke fellowship program at Eastern Health is a 12-month position for an advanced trainee to gain additional clinical and research experience in stroke medicine after completion of their two core years of advanced training. Since 2019, the position has been filled by a physician trainee prior to their entry to the neurology advanced training program, typically post graduate year 4. The main aim of the program was therefore slightly shifted to develop the trainee's research, presentation, and academic writing skills. All fellows had minimal experience in these domains prior to commencing their fellowship. There is one fellowship position per year. The fellow supports Code Stroke and does a clinic one third of the week, another third of the week is spent on their own research project, and the rest of the time they support activities in the stroke trials unit. The fellow is expected to work on projects that would result in at least one first authored paper and a presentation at a national conference. I have been the sole research supervisor for the fellow since 2019. This has allowed me to design and implement a program of projects to examine and improve the acute stroke assessment processes.

1.4 Structure of the thesis

There are two main parts to a PhD by "Prior Published Works", the contextual statement that presents the "story" of the research, and the selected manuscript already published prior to the commencement of the candidature. This thesis presents the process barriers to effective administration of stroke reperfusion therapy, how these barriers were systematically identified, and importantly the outcomes of the quality improvement effort led by me at Eastern Health.

The remainder of this chapter will continue as the contextual statement, describing the findings and significance of the published work in the context of the historic and contemporary literature. Chapters 2 to 4 consist of manuscripts organised under three themes. Chapter 2 includes the three papers that advanced the understanding of how DNT may be improved in the Australian context, and also the novel use of body camera in understanding code stroke workflow. Chapter 3 contains the collection of papers that

outline our findings in door-in-door-out (DIDO) workflow in ELVO transfers. We are one of the first groups internationally to study the components of this metric. The final paper in the chapter includes data to support how PSC may play an important role even in the era of ECR for ELVO, arguing against blanket PSC bypass for ELVO. The two papers in Chapter 4 address an important knowledge gap - the extent to which DOAC is a barrier to thrombolysis. This chapter also presents a practical solution, which has the potential to increase the number of patients able to receive IVT, particularly patients in regional areas. Chapter 5 is the concluding commentary highlighting the original contribution of this work to the literature and the future directions in overcoming barriers to effective therapies to acute ischaemic stroke.

Except for the first publication (Chapter 2.1), all the publications are a product of the quality improvement efforts conducted by members of the stroke team at BHH between 2015 and 2022. Contributions from different authors on each publication will be outlined in respective co-authorship statements preceding the papers along with impact factors and citation metrics. Nine papers are included in this thesis. Five papers were first authored by a stroke fellow, one by an advanced trainee in neurology, and one by a medical student. Besides the two papers for which I was first and primary author, I have instigated, designed, planned, extensively revised, and edited the original draft for the remaining seven papers as the last and most significant author.

1.5 Barriers to fast DNT

1.5.1 Proportion of patients in which fast DNT is possible

In February 2010 when *Target: Stroke* announced the goal of 50% of patients treated with a DNT of under 60minutes, it was unclear how many patients would be reasonably excluded due to delays that may be considered “unavoidable”. For example, blood pressure lowering below a systolic of 185mmHg, clarification of stroke onset time in the absence of a reliable collateral history in an aphasic patient, and other life supporting interventions such as seizure management or emergency intubation. The first manuscript in this thesis (Chapter 2.1) analysed the reasons for DNT delays in 102 consecutively

thrombolysed patients over a 12 month period from June 2012 at Foothills Medical Centre, a major academic stroke centre in Calgary, Alberta, Canada. Delays were categorised into two groups. Patient-related reasons (medical and thrombolysis eligibility), and hospital or systems reasons. Potential delays were documented in 58% of the patients. While many patients had one reason only, 11 had three or more reasons. Overall, up to 31% of patients experienced delays due to medical or eligibility-related reasons. Previous studies have identified various patient characteristics, and therefore, non-modifiable factors such as older age, female sex and lower stroke severity as associated with slower treatment times. In contrast, our study quantified a variety of patient-related reasons, such as treatment of hypertension, intubation and determination of eligibility, accounting for longest delays in DNT. Importantly, one of the key findings of this study was that patient delays were not predominantly caused by a small number of factors, rather, a wide range of factors contributed. Potential delays were identified in 59 out of 102 patients, 32 had one reason, 16 had two, 9 had three and 2 had more than three reasons noted.

We argued hospitals and systems reasons may be reduced or eliminated by quality improvement efforts, while delays may be inevitable in patients with “patient-related” reasons. In reality, at least some of the patient-related delays may also be reduced by focused quality improvement efforts. For example, emergent blood pressure lowering, and intubation, may benefit from specific streamlined protocols for hyperacute stroke patients rather than the usual ad-hoc approach by individual clinicians, especially when medical practitioners from the stroke team are often not directly involved in the emergency stabilisation of hyperacute stroke patients. These tasks are in the domain of the emergency physicians. It became obvious that engagement with various stakeholders involved in the acute stroke assessment and management process is vital to address all the factors that may delay treatment in any individual patient.

The categorisation of delay factors was adopted by my co-authors, Noreen Kamal and Eric E. Smith, to examine the GWTG-Stroke dataset, and similar results were confirmed in a cohort of more than 55,000 patients.[42] These results suggest a “whole of hospital” approach is needed for improving DNT. The learnings from the results of these papers, together with “team-based approach” and “prompt data feedback” as adopted from *Target: Stroke*, contributed to the methodology and success of the first, large scale provincial DNT improvement project involving mostly small, regional sites in Alberta, Canada. The provincial median DNT improved from 70 (IQR 51-93) to 39 (IQR 27-58) minutes. At the

same time, the percentage of patients discharged home, and median 90-day home time were also increased, 45.6% to 59.5%, and 43.3 (IQR 27 – 56) to 53.6 (IQR 37 to 65) days respectively, both (p,0.005).[43, 44] In contrast, results from similar initiatives, but using a different methodology in Australia around the same time have failed to improve DNT substantially in selected sites across three Australian states.[45, 46] The reasons for failure appear multifaceted and were outlined in detail by the authors.

1.5.2 DNT at Box Hill Hospital 2003 - 2019

BHH has the fastest median door-to-needle time in Australia over consecutive years since 2020. From a service provision perspective, there are many metropolitan PSCs in Australia with similar size and setups as BHH. Examining our acute stroke treatment metrics over multiple years provided insight about quality improvement initiatives that are effective in the Australian context. For example, preparation of alteplase as soon as a potential thrombolysis candidate presents, even before brain imaging, was never a possibility in Australia due to different reimbursement rules in different countries by pharmaceutical companies, but is utilised by centres in the United States to shorten door-to-needle time.[33] On the other hand, prehospital emergency medical services (EMS) in Australia are typically organised at a state level, compared to multiple different public and private service providers in the United States, which can make standardisation of prehospital protocols, such as pre-notification, difficult. The paper in Chapter 2.2 detailed the interventions employed by the stroke team in BHH since 2011, and the effect of the individual interventions.

Over a period of 17 years at BHH, 15 different strategies were used to improve DNT. Since most of the strategies were progressively implemented since 2011, the DNTs were analysed in terms of pre-intervention period (2003 – 2011) and intervention period (2011-2019). Overall, 1250 patients were thrombolysed. The number of patients treated within 60 minutes of hospital arrival was 22.5% before 2011, and gradually increased to 71% in 2019. Median DNT fluctuated between 70 to 93 minutes in the earlier years and decreased to 58 minutes and 51 minutes in 2015 and 2019 respectively.

Transferring the patient directly to the CT room without stopping at the ED was associated with the largest decrease in DNT in multivariate linear regression modelling with the estimated effect outlined in Table 4. This was followed by an organisational factor, which is a dummy variable used to account for all the unmeasured and unmeasurable factors and interventions. For example, the number of registrars, as well as the number of hours during which they are onsite have increased over the years, but analysis of the effect of these interventions in isolation was not possible.

This paper is the first to quantify the direct effect of the presence of the ASN on DNT. It is important to note this effect is independent from the "Direct to CT" and the organisational factor. The ASN role is shared by two nurses, covering business hours only (Monday to Friday, 0800 to 1700). The percentage of patients who went "Direct to CT" however improved across all hours of the day over the years, suggesting intervention during business hours when the stroke team presence is the strongest, does carry over to other times of the day and week.

VARIABLES	ESTIMATES (%)	95% CI (%)	P-VALUE
"DIRECT TO CT"	-32.6	-38.2, -26.9	<0.001
ORGANISATIONAL FACTOR	-21.9	-27.7, -16.1	<0.001
ACUTE STROKE NURSE	-6.9	-13.5, -0.3	0.005

Table 4: Modifiable factors associated with faster DNT and their estimates.

Recognising the importance of the ASN role in achieving faster DNT, the ASN working hours were extended from weekdays 0800 to 1600 hours. Beginning in 2020, there is now an ASN onsite at BHH from 0800 hours to 2000 hours, Monday to Friday, and 0800 hours to 1200 hours Saturday.

Despite being a single centre study, due to the relatively large number of patients included (n = 513 vs n = 737 during 2003-2011 and 2012-2019 respectively), we demonstrated that associated with these changes, a higher proportion of patients achieved functional independence at 3 months in the period with improved DNT and no differences in mortality.

In the paper we suggested the establishment of local hospital working groups, similar to our weekly review model at BHH, may be the key to improving DNT in Australian hospitals. The effect of some changes or interventions, including the weekly review and staffing changes, is impossible to quantified individually. The inclusion of “organisational factor” as a variable acknowledges the various changes at a whole of system level that made a positive impact on DNT. Although the improvement in DNT was quite small towards the end of the study period, the tightening of the IQR suggests less variability, and this also points towards a more consistent hyperacute stroke workflow overall, regardless of the characteristics of the patients being treated, which should be similar across multiple years.

Importantly, the findings from this paper suggest strengthening the role of ASNs may play a critical role in improving stroke reperfusion metrics more broadly in the Australian context. In a large metropolitan PSC, ASNs are likely the only member of the stroke team who had or could establish institutional knowledge and cultivate a fast DNT culture amongst different team members who “come and go”. In regional hospitals, it may be unrealistic to have a dedicated ASN role. However, in contrast, the ED nursing workforce is relatively smaller and the turnover of medical staff is much higher than metropolitan sites. For smaller regional sites, developing and embedding “stroke champions” within the ED nursing workforce may therefore be more feasible than having a dedicated ASN.

The results of this paper attracted interest from the *Angel’s Initiative*. *Angel’s Initiative* is a non-promotional health care project of Boehringer Ingelheim International GmbH to improve stroke care around the world. Two of the authors, together with the director of Emergency Medicine at BHH, were interviewed by the *Angel’s* team in 2022 with clips incorporated into their online educational video repertoire.

1.5.3 Continuous observation workflow time study of “Code Stroke”

The reasons for the small incremental reduction of DNT in recent years at BHH were not immediately apparent when the paper was submitted in early 2021. Increased community awareness of stroke as an emergency is reflected in the dramatic increase in the number of “Code Stroke” presentations from just under 500 per year in 2012 to 1298 in 2019. Separate analysis of data from the BHH’s departmental stroke database (not published), suggests the increased stroke treatment window is not solely responsible and in fact played only a small role in this. Indeed, while the extended time window has opened up more treatment opportunities, this only benefits a small number of patients, as is evident by the 8 years of recruitment of 225 patients from 28 centres of the trial by Ma et al.[23] The net effect of the extended time window is that Code Stroke is being activated for a lot more patients presenting to the hospital beyond 4.5hrs from stroke symptom onset yet they do not met the criteria for reperfusion therapy. Among these would be patients with already established ischaemic changes on the CT scan, or minor stroke in which the risk and benefit of current reperfusion therapy favours conservative treatment, and lastly stroke mimics. Could the large number of Codes per day be a factor in the lack of more substantial DNT improvement? How much resource is required in a Code Stroke?

The Code Stroke response varies from hospital to hospital, but in general it is a resource intensive exercise. Typically, the simultaneous notification to all relevant parties about an incoming Code – CT medical imaging technologist (MIT), medical and nursing staff in the emergency department, ASN, stroke research coordinator, junior medical staff of the stroke team (which typically includes the stroke registrar and the resident), can be quite disruptive to the normal workflow of all these individuals. There has been no published literature on using observational time and motion study in the Code Stroke setting until recently.[47] The simple method of involving someone, typically a volunteer medical student, to stand with a clipboard at Code Stroke has not worked in the past at our hospital. Professional scribes are common in the American hospitals and theoretically could collect the information required, but despite some local interest, there remains no such role in Australian EDs.[48]

The study was inspired by seeing security guards at our hospital start wearing body cameras in the late 2010s, albeit for a different purpose. A continuous observation

workflow time study involving a body camera worn by the stroke registrar or the ASN may provide insight as to the resource utilisation of Code Strokes. Specific precautions were taken to ensure the data obtained by the body camera could only be used for the purpose of the study and the video would be reviewed by members of the study team, but not stored after reviewed. Other ethical considerations such as opt-out consent from other staff members and timing of consent are outlined in the paper, included in Chapter 2.3 of this thesis.

Over a six-month study period from January 2020, video and audio recordings were available on 100 Codes, which translated to about 1 in 5 Codes being captured. We were fortunate that plastic gowns were not mandatory until towards the middle of 2020 during the COVID-19 pandemic, as the gown prohibited the use of a wearable device on top of it. This is the first study of its kind in a Code Stroke setting and a number of novel observations were made.

The median time of a Code Stroke was 54.2 minutes (IQR 39.1-74.1). The median time of different components of the team journey, from receiving the code notification to the team leaving the ED, were able to be broken down (Figure 5). 13 cases received thrombolysis and 6 were transferred for ECR, with the median DNT and DIDO time being 37.8 minutes (IQR 32.2 -45.2) and 48.1 minutes (IQR 34.0 – 51.1) respectively. Based on the data collected, a theoretical ideal DNT of 21 minutes was calculated. Decision making is surprisingly a small part of the overall workflow, with a median “CT completion to decision made” time of 3.7 (IQR 1.2 – 8.0) minutes. There are clearly some significant outliers as the range is 0 – 31.5 minutes, reflecting the very straight forward cases through to the cases which require complex decision making.

Administrative work is the largest component of a Code, regardless of whether a Code was stood down before or after the patient being scanned. This information, while not entirely surprising to the registrars involved in the day-to-day assessment of Code Stroke, is important to be quantified so the stroke team can be resourced adequately.

Based on the data from this study we were unable to identify factors which might explain the stagnation in DNT improvement in recent years. Instead, we were able to model an ideal DNT for our centre based on the existing workflow and resourcing. Having a realistic, achievable target is important. A visible, renewed focus on improving DNT, which

persisted despite the multiple challenges posed by the COVID-19 pandemic, may have contributed to the continued decrease in DNT at BHH since the completion of the study.

This paper was published early in 2023 in BMJ Neurology Open. This is the first paper in the literature to demonstrate that body camera is a feasible and acceptable way to obtain workflow data in the Code Stroke setting. A subsequent manuscript from Canada published in October 2023 by Koca et al is the only other time and motion study in the Code Stroke setting using slightly different study methodology.[47] Indeed, replacing the use of observer, as employed in Koca et al's study, with body camera, may help increase the uptake of workflow observation study by other stroke centres in examining and improving their assessment and treatment workflow.

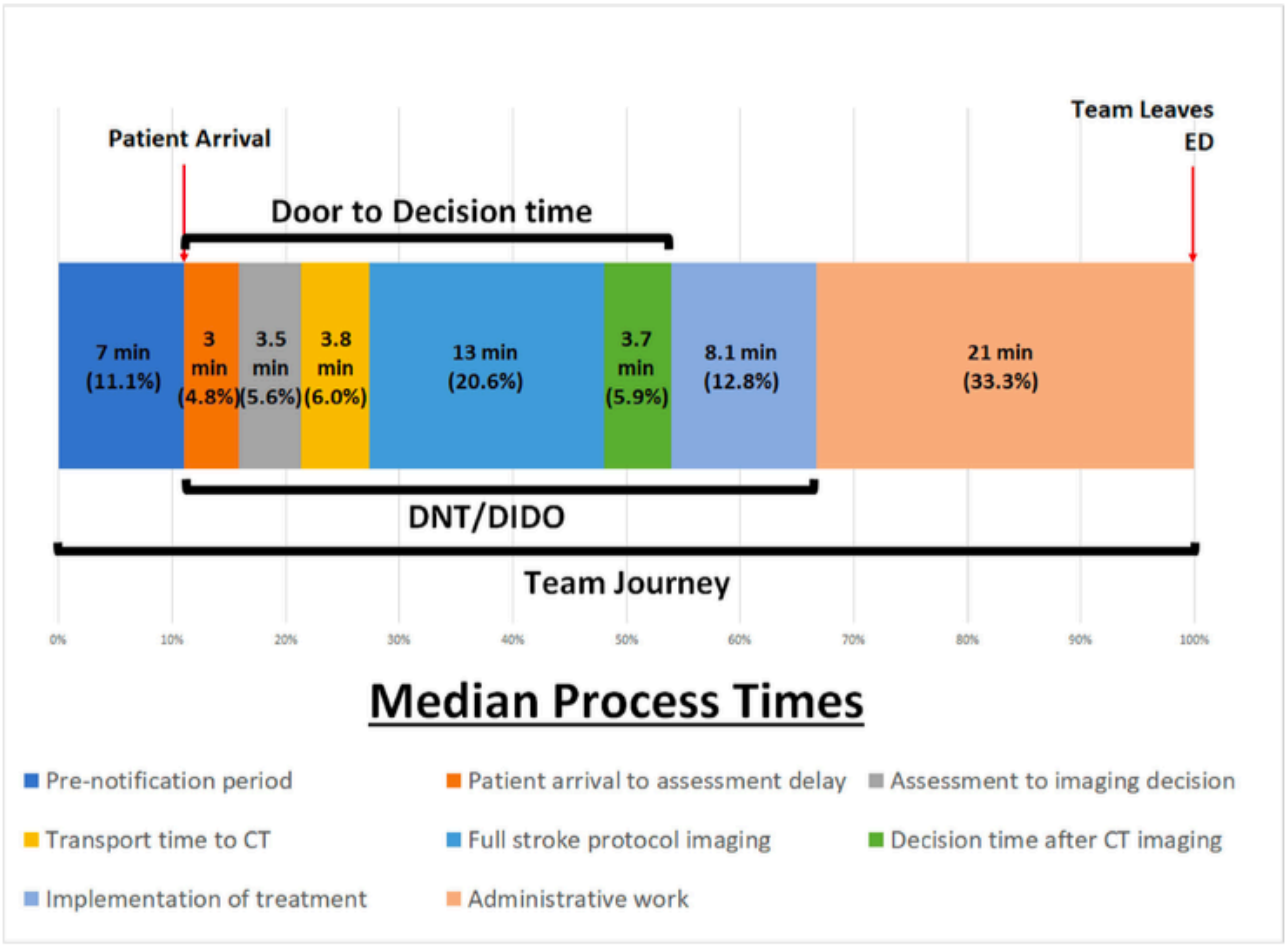

Figure 5: Median process times during a Code Stroke

1.6 Door-in-door-out (DIDO) time for emergent large vessel occlusion

Similar to IVT, the efficacy of ECR is time sensitive and earlier treatment clearly leads to better outcomes.[49] In contrast to the scepticism IVT faced in the late 1990s, the result of the ECR trials was embraced and disseminated by emergency physicians in journals and websites.[50] Buy-in from emergency physicians and nurses in acute reperfusion therapy is paramount as the hyperacute stroke workflow occurs almost exclusively within the emergency department and the usual members of the stroke team are typically not onsite 24 hours a day in the Australian setting.

The clinical translation of ECR trials presents an enormous challenge to all health services.[51] The number of patients who were transferred from PSC to CSC were relatively small in the ECR trials, and these transferred patients on average experienced a two hour delay in symptom onset-to-reperfusion time, compared to patients directly presented to CSC.(7) Most CSCs in Melbourne, except Monash Medical Centre, are located within a relatively small radius from the city centre. In combination with a generally younger demographic in the central city, most stroke patients therefore live closer to a PSC than a CSC. (Figure 6)

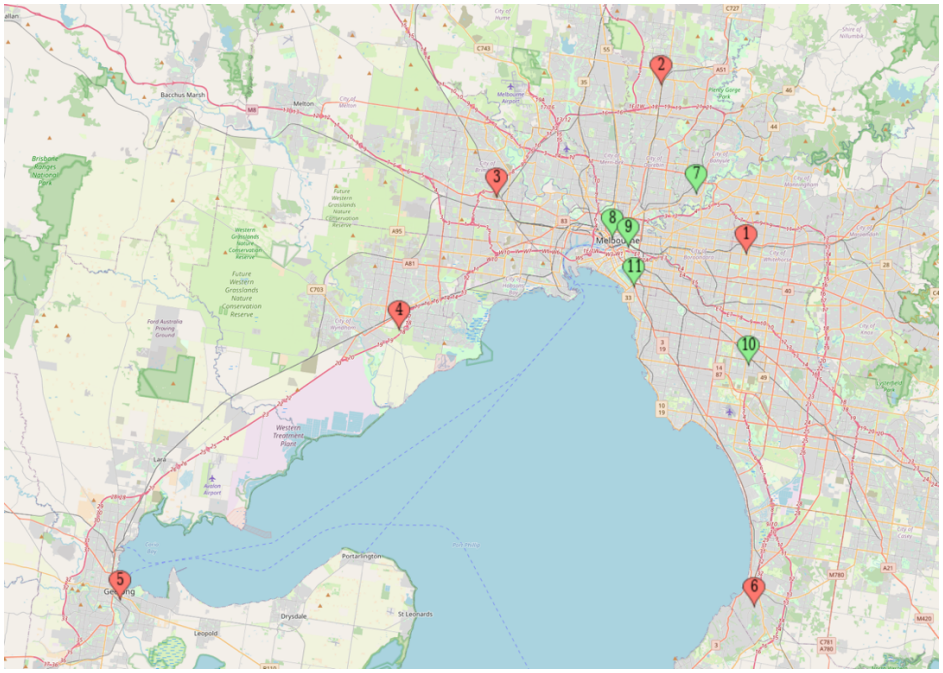

Figure 6: Map of metropolitan Melbourne with hospitals that provide IVT in 2023

Red dots: Primary Stroke Centre (PSC). 1. Box Hill Hospital, 2. Northern Hospital, 3. Sunshine Hospital, 4. Werribee Mercy Hospital, 5. University Hospital Geelong, 6. Frankston Hospital

Green dots: Comprehensive Stroke Centre (CSC). 7. Austin Hospital, 8. Royal Melbourne Hospital, 9. St Vincent's Hospital, 10. Monash Medical Centre, 11. The Alfred Hospital

Optimising the intrahospital processes and interhospital transfer workflow is therefore critical to maximise the powerful effect of ECR. None of the landmark ECR trials have explicitly reported DIDO times as a metric but have used metrics such as onset-to-groin and reperfusion times when compared between transferred or direct-admit patients. Onset-to-reperfusion encapsulates the whole patient journey from stroke onset to angiographic reperfusion but does not separate out the processes occurring along the care continuum. Other metric such as “picture to puncture” was proposed but did not gain much traction.[52] DIDO, at least in the metropolitan setting, is largely determined by the processes within the PSC. DIDO is also a standard metric in the cardiology literature in the treatment of acute myocardial infarction. What is the real-world metrics for ELVO transfer in metropolitan Melbourne in the ECR era? Targets exist for DNT, but what would be a reasonable DIDO time for ELVO patients first presented to a PSC?

1.6.1 DIDO at Box Hill, Northern and Sunshine Hospital; 2015 – 2016

There were five PSCs in metropolitan Melbourne in 2015; University Hospital Geelong, Western Hospital, Northern Hospital, BHH, and Frankston Hospital. The one extra PSC shown in Figure 6 is Werribee Mercy Hospital. The IVT service in Werribee started in 2018 and is supported by the Victorian Stroke Telemedicine (VST) Service. BHH and Western Hospital were the only PSCs involved in EXTEND-IA, a local Melbourne ECR trial. Of the 35 patients randomised to ECR in EXTEND-IA, only four were transferred patients, with others directly presenting to RMH. Although emergency patient transfers between hospitals are common, normal transfer procedures were not suitable for the time-critical hyperacute transfer of ELVO patients. For example, most inter-hospital transfers are typically accompanied by a copy of all the clinical documentation at the initial hospital, and different ambulance crews are used for the inbound and outbound journey. By convention, the transfer process is initiated at the referring hospital only after clinicians at the destination hospital have accepted the transfer. While proper clinical handover is important for patient safety, these existing procedures delay the ELVO transfer workflow. The manuscript in Chapter 3.1 examines the ELVO transfer workflow metrics in the three PSCs in metropolitan Melbourne. The hyperacute stroke imaging and assessment workflow was similar across all PSCs at the time. All PSCs provide 24/7 IVT and there were no formal or

informal ECR bypass protocols involving these PSCs at the time of the study. The main motivation for the study was to understand the DIDO times in all the PSCs in Melbourne in the months since ECR became standard of care (end of 2015). The result would then guide appropriate DIDO targets based on real world metrics and identify areas for improvement.

Over a 19-month period from January 2015, 86 patients were transferred for consideration of ECR from the three PSCs. 97% of the transferred patients met the trial inclusion criteria of MR CLEAN, the first of the five landmark ECR trials.[53]

The median DIDO was 106 minutes (IQR 86 – 143) for all three PSCs combined. The use of the same in-bound and out-bound ambulance crew, presentation during working hours (0800 to 1700) and individual PSC site were associated with shorter DIDO times in multivariate analysis. The individual median DIDO times of the three PSCs were not reported in the manuscript, but are included here in Table 5:

SITE	NUMBER OF PATIENTS	MEDIAN DIDO (IQR)
BOX HILL	39	103 minutes (75-116)
SUNSHINE	20	131.5 (91.5 – 171)
NORTHERN	8	135 (94 – 169.5)

Table 5: DIDO times of Box Hill, Western and Northern Hospitals between 2015-2016

We found the longest component of DIDO was “CT-to-Retrieval-Request”, which represents 59% of the DIDO time (Figure 7). We proposed two practical steps that could shorten this segment. The first was by keeping the in-bound ambulance crew at the PSC when there is a high clinical suspicion of ELVO. The same ambulance crew transfers the patient off the CT scanner, back to the stretcher and continues the out-bound journey. The second step, given most of the transferred patients met clinical trial criteria, was that the stroke team at PSC should not pause the patient flow while waiting for formal acceptance by the CSC. The latter strategy remains challenging at times for patients who are more

medically complex and do not fit neatly into trials' inclusion criteria but may nevertheless still likely benefit from ECR.

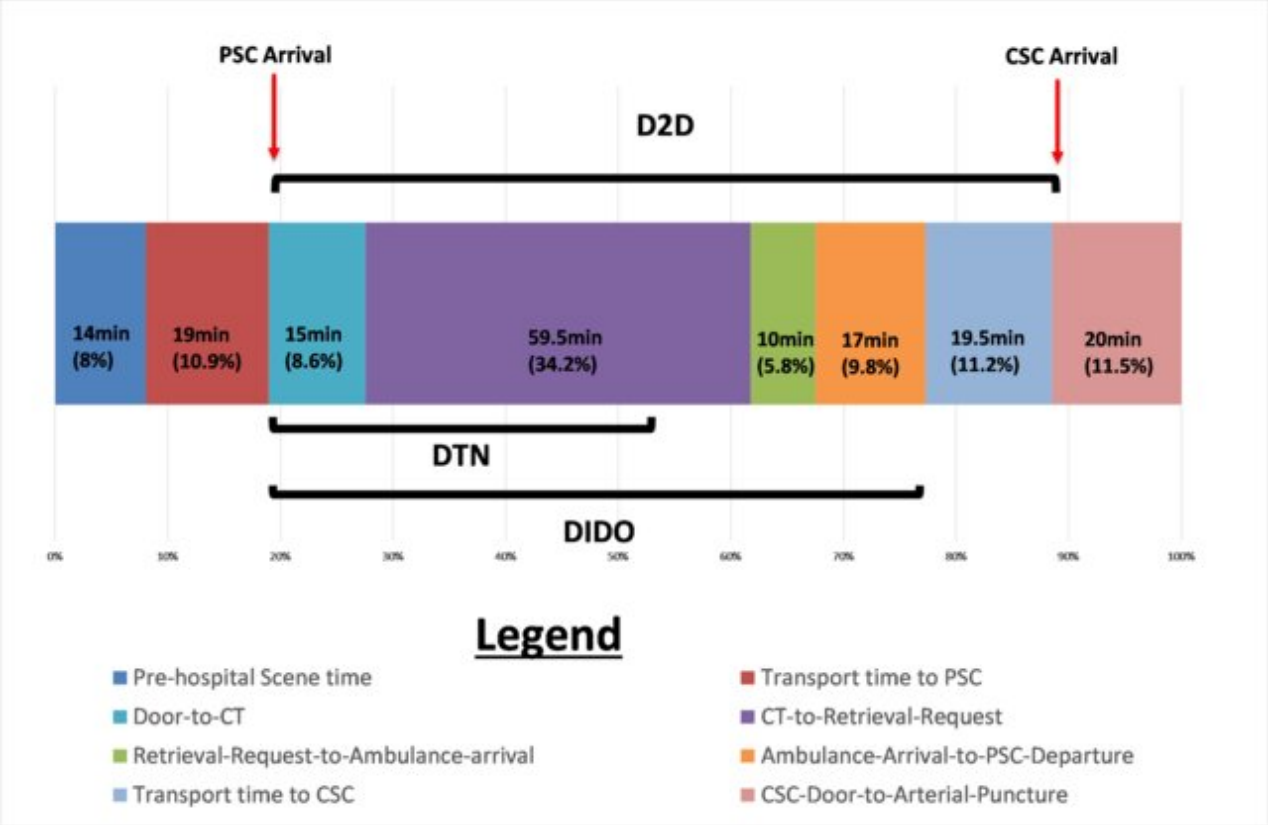

Figure 7: Deconstruction of the ECR treatment workflow at PSC. Median times are shown

This paper was submitted to *Stroke* in March 2017, accepted and published online in the same month. One group in Rhode Island, Providence, United States also independently used DIDO as a metric on ELVO transfer as part of a quality improvement program in a network of 14 PSCs.[54] Their paper was accepted in *JAMA Neurology* in February and published online in May 2017. While the setting and transfer protocols are quite different to our paper, the striking similarity is in the baseline DIDO times - their median PSC DIDO improved from 104.5 minutes (IQR 78-121) to 64 minutes (IQR 51-88).

Based on the top 15th percentile of our data, we proposed a DIDO of 75 minutes would be a reasonable initial target. This paper was the first paper to deconstruct the ELVO transfer process at PSC. Citations include policy documents by various professional bodies, including *Mechanical thrombectomy for acute ischaemic stroke: an implementation guide for the UK.*[55]

1.6.2 Setting a new DIDO target of 60 minutes

A median DIDO of just under 60 minutes during working hours was achieved at Box Hill in 2018. By this time, 133 patients had been transferred during a period of just over 3.5 years from January 2015 to October 2018. We analysed these cases in detail, outlining the interventions we made at a hospital system level and analysing delay factors as per classifications used previously. This manuscript is included in Chapter 3.2.

It is important to note changes in the organisation of the stroke services in Melbourne before discussing the results of the manuscript. The Victorian State Government, through Safer Care Victoria, was the first jurisdiction in Australia to release a state-wide protocol for ECR in February 2016.[56] At the same time, VST continued to expand hyperacute stroke coverage in regional Victoria with eventual complete coverage of all major regional public hospitals in the state by 2018. The increasing patient volume, together with new trial evidence to extend the treatment window from 6 hours to up to 24 hours for eligible patients, led to the update of the state-wide protocol in October 2018 to include Monash Medical Centre (MMC) as the second state-wide ECR centre effective from late 2017.[57] Austin Hospital has no formal state-wide ECR designation, but remains the third highest volume ECR centre in Melbourne. Austin performs ECR on direct presenters and accepts transfers from other sites, including St Vincent's when their interventional team is not on site, the Northern Hospital, as well as Box Hill when the angiography suites at RMH and MMC are occupied. Travel time by ambulance from BHH to RMH, and MMC and Austin are all similar despite RMH being 5km further, as there is no highway component in the journey from BHH to MMC. There is no state-wide coordination of ECR transfers and the CSC destinations for ELVO patients at PSC remain at the discretion of the PSC stroke team.

In addition, the Melbourne Mobile Stroke Unit (MSU) started operation from late 2017. In the supplemental material included in Chapter 3.2 it was stated the MSU has an intended operational radius of 20km centred on RMH and hence minimal overlap with BHH's catchment area. This was probably the case initially but, in reality, the MSU has attended patients as far away as 40km east from RMH, within the catchment of BHH/Eastern Health. The exact number of patients treated at individual CSCs, and their address at the time of their stroke, is not available in the public domain. The number of ECR transfers per

year from 2015 to 2018 and other baseline characteristics of the cohort was outlined in the Supplemental Table 1 of the paper. Up until the time of writing in early 2024, the number of ECR transfers per year from Box Hill has remained around 50 annually since 2015.

Overall, the regression model showed a 14% year on year decrease in DIDO time, with the effect most dramatic during working hours from 0800-1700 as shown in Figure 1 of the manuscript and reformatted here in Figure 8.

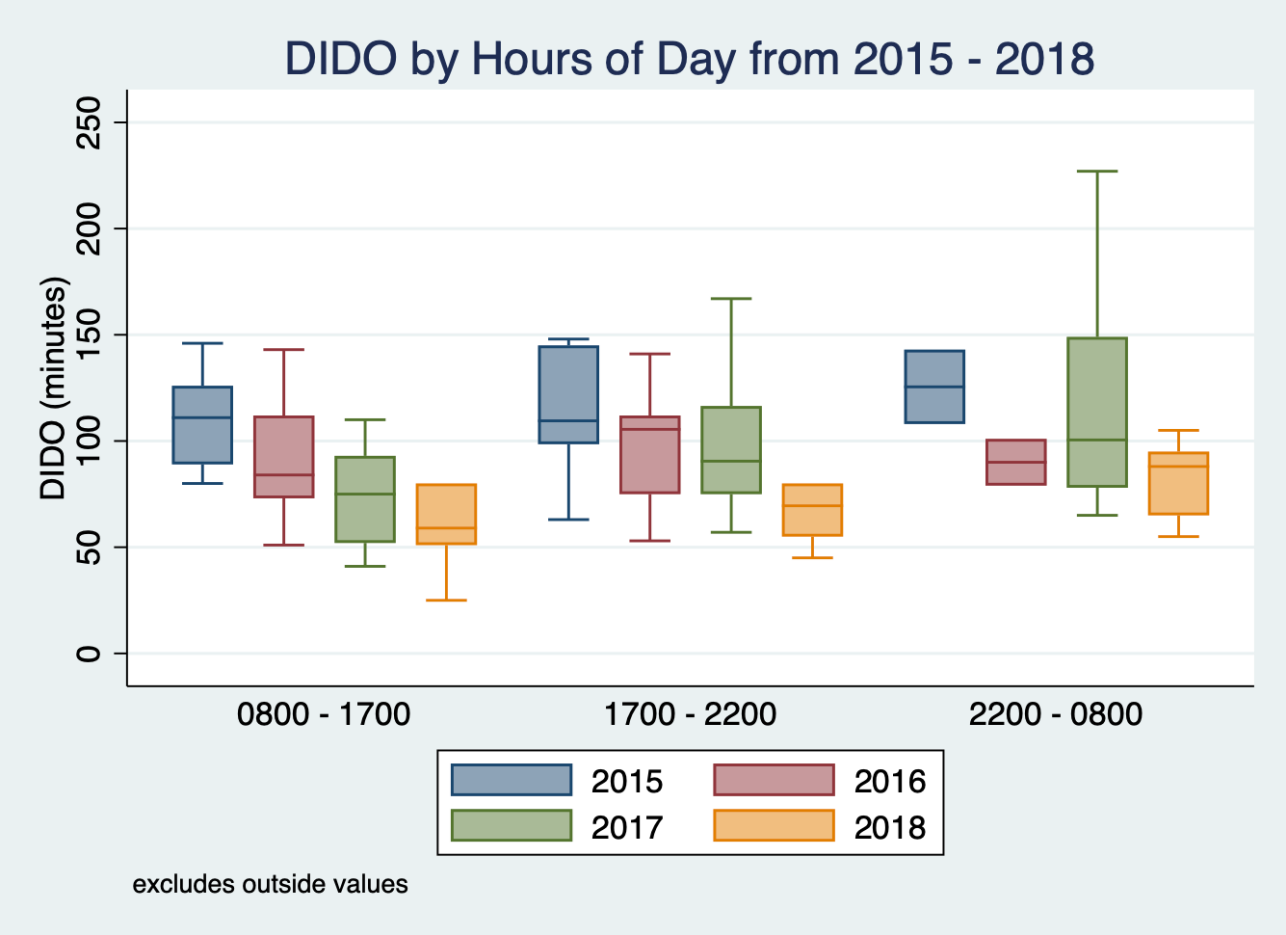

Figure 8: DIDO times by year and different hours of the day

Faster DIDO time was associated with the neurologist being onsite, and the responsible neurologist being a stroke neurologist rather than a neurologist with another subspeciality interest. These factors are probably a proxy for fast and definitive decision making (i.e. to transfer and not to transfer to CSC) by the PSC stroke team with the neurologist being the key decision maker for transfer. At times the neurologist might have helped the transfer

process by directly being involved in the liaison with the relevant CSC personnel (i.e direct discussion between the PSC neurologist with the CSC interventionalist, rather than the PSC registrar making all phone calls, although this variable was not captured in the study).

DNT time remained the same at 53 minutes from 2015 to 2018. The difference between the 75th and 25th quartiles decreased from 32 to 10 minutes over the four year period, indicating more patients are treated around the median. An increasing number of patients were transferred for primary ECR (i.e. without IVT), reflecting both the extended ECR treatment window, and also the increasing number of patients with contra-indications to IVT such as patients thought to be pre-medicated with an anti-coagulant and who were assumed to be anticoagulated. The delay identified confirmed a variety of factors across the patient care pathway, cementing the notion that improving the stroke assessment process requires a multifaceted approach.

Importantly, enrolment in clinical trials was not associated with longer DIDO time, but rather shorter times. Potential reasons including patients enrolled in acute stroke treatment trials typically had less co-morbidity, were discussed in the manuscript but one that was omitted was “deferred consent”. Most patients enrolled in acute reperfusion trials were enrolled under the “emergency treatment” provision in Victoria. Every opportunity to obtain consent was explored, but if that failed, the patient was randomised first, administered the assigned treatment, and the formal consent process was deferred until the patient either regained competency or when the next of kin became available after treatment was administered.[58] This is in accordance to Part 5 of the Medical Treatment Planning Decisions Act 2016 (Vic).[59] Not all jurisdictions have similar provision, with New South Wales a prime example. The optimal way to obtain consent in acute stroke trials remains an active area of research.[60] More data, in particular consumer engagement, is needed to support changes in other states as well as abroad.[61, 62, 63]

This paper sets a new international benchmark in DIDO times for ELVO transfer, in the same way as Meretoja et al’s DNT paper for IVT.[37] Similar analysis at University Hospital Geelong, a large PSC 60 km from Melbourne, reports a mean time of 120.5 minutes from 2016 - 2018, suggesting significant room for service optimisation at other sites locally.[64]

DIDO times are incorporated as a variable in the “Emergency Department minimum dataset” of AuSCr and reported for the first time in AuSCr’s 2022 annual report. The 2022 national median DIDO time was 124 (IQR 80.5 – 184.5) minutes for 251 episodes of

transfers. This likely represents only a very small fraction of ECR transfers nationally given the voluntary nature of AuSCr, and the relatively small number of episodes submitted in this first year of reporting. Data from this study suggested a median DIDO of 60 minutes is realistic in a metropolitan PSC setting. A DIDO target of 60 minutes was used in the Australian Stroke Coalition 30/60/90 National Stroke Targets Action Plan.[65] Citations by international bodies include US's *Specifications Manual for Joint Commission National Quality Measures.*[66].

1.6.3 DIDO times in the state of Victoria 2017 - 2018

Victoria is the first state in Australia to have a state-wide acute stroke telemedicine program servicing regional hospitals (VST). Having studied, improved, and published our experience in improving DIDO at BHH, we sought to understand DIDO across the whole state, including all sites forming the VST network and all major PSCs in metropolitan Melbourne. This included University Hospital Geelong, which operationally, despite the regional location, is the same as any other tertiary hospital in metro Melbourne. The aim is to understand the status quo of DIDO at a state level after the initial scoping study involving selected metro sites (Chapter 3.1), gather more up-to-date data for benchmarking and increase the awareness of DIDO among various stakeholders. This Victorian state-wide DIDO study is presented in Chapter 3.3. VST has included coverage to hospitals in Tasmania since the completion of the study data collection period and Tasmanian sites were not included in this paper. Data from 2017 to 2018 were included from multiple data sources: the VST database, PSC and CSC hospital databases and Ambulance Victoria records.

269 metro transfers were included and Table 6 shows the DIDO times from individual metro centres, excluding two sites with less than 10 transfers. The median metro DIDO was 107 min (IQR 84 – 145) for metro sites, unchanged from 2015-2016 (Chapter 3.2). All metro sites adopted ECR transfer for eligible patients with ELVO as standard of care (outside of clinical trials) in 2015, but sites included in the early DIDO study paper showed improved DIDO times while the other two (Frankston and Geelong) showed DIDO times similar to where others started off in earlier years. Increased awareness brought about by the earlier study at these sites may have contributed to their improvement despite no

formal quality improvement effort. The PSC to CSC travel times were remarkably similar across all metro sites (except Geelong), confirming DIDO is the ideal target for efficient transfer of ELVO patients in metro areas. On multivariate analysis, the use of the same ambulance crew, and IVT are associated with shorter DIDO times. This suggests patients transferred for primary ECR were associated with longer DIDO. The reason for this is unclear. At least some of these patients, being excluded from IVT, may have more complex medical problems (recent major surgery, multiple co-morbidities with unclear short and medium term prognosis.. etc) and requiring longer decision-making time.

Site	Number of patients	Primary ECR	Door to CT time	DNT	PSC to CSC travel time	DIDO (2017 – 2018)	DIDO (2015-2016)
Box Hill	85	30	10.5 (6 – 16)	50 (37 – 59.5)	22 (19 – 26)	82 (65 – 113)	103 (75 – 116)
Sunshine	64	25	25 (21 – 43)	88 (73 – 109)	22.5 (18.8 – 27)	107 (84 – 145)	131 (91.5 – 171)
Geelong	55	32	22 (16 – 32)	75 (57 – 107)	57 (51.5 – 62)	131 (100 – 159)	N/A
Northern	48	21	17 (12.3 – 25.8)	57.5 (47.3 – 85)	30 (27 -34)	97 (83 – 127)	135 (94 – 169.5)
Frankston	17	9	15 (6 – 22.5)	79 (55.5 – 89)	32 (27 – 36)	146 (131 – 187)	N/A

Table 6: DIDO times in Melbourne metropolitan PSCs in 2017 - 2018

176 regional transfers were included from 19 sites, 11 sites had less than 10 transfers with the rest ranging from 10 to 23 transfers per site over the study period. The same proportion of patients in regional sites were transferred for primary ECR, 43.2% vs 43.7% in metro and the overall median DIDO was longer at 132 minutes (IQR 108 – 167). Although there is no directly comparable study in the literature to compare this figure to, withstanding the difference in health system and geography, this median is very similar to data in Texas, United States, reported by Wu et al.[67]

In contrast to metro sites, shorter DIDO was associated with worse stroke severity on presentation in this cohort. Longer DIDO was associated with air transfer, but if a site is over 250km by road from the CSC, the faster outbound air travel time compared to road means air transfer is the faster way to get the patient from PSC to CSC despite longer DIDO for air transfers. Different challenges faced by regional sites compared to metro were discussed in the paper. For example, interventions such as using the same ambulance crew to transfer the patient for their outbound journey was neither feasible nor practical. For some of the smaller regional sites, taking an ambulance away from the town would deprive the town of the only active ambulance crew on duty. This study also showed that simple, but important quality improvement targets, such as door to CT time, despite being a variable collected by AuSCr, is not available for any of the patients transferred from regional sites.

All these metrics for ELVO transfers were not visible to any stakeholders involved prior to this paper. Similar data should be examined in different telestroke networks, in particular for sites where both road and air transports are reasonable options.[68] Without this real-world data it would be difficult to streamline and design a robust fit-for-purpose hyperacute stroke transfer system for ELVO patients.

This manuscript was published in 2023 but the data reported was from 2017 to 2018. The COVID-19 pandemic, complexity of the data linkage and the multiple organisations involved in the project all contributed to the delay in publication. DIDO times were missing for almost half of all regional transfers compared to 14% of metropolitan ones. This was despite meticulous data linkage with all available data sources. High proportion of missing data were also encountered by other stroke researchers in countries with similar health systems.[69] The ECR referral system in Victoria has evolved organically since its inception in 2015 with sporadic stakeholder involvement. For a service that is exclusively publicly

funded, mandatory reporting and monitoring of treatment metrics for this high-cost, high-value intervention is a reasonable way to provide quality assurance and helps identify areas for quality improvement. A state-wide, or national registry, would facilitate this.

Table 7 is a summary of DIDO papers published to date with papers in Chapter 3 included for context. The time sensitive nature of reperfusion therapy means fast DIDO should be associated with patient outcome and data from McTaggart et al supports this.[70] Australian data is lacking so far and we are in the process of preparing a manuscript to review the outcomes of all ELVO transfers at BHH from 2015 to 2022 in relation to DIDO times.

The paper was published in 2023 in *BMJ Open*. It was the first paper in the literature to recognise the differences faced by regional sites in ELVO ECR transfer. A difference recognised by the National Stroke Targets which proposed different DIDO targets: <60 minutes for metropolitan sites and <75 minutes for regional sites, to be achieved by 2030.[71]

YEAR PUBLISHED	AUTHOR	NUMBER OF PATIENTS	DIDO IN MINUTES (MEDIAN, IQR)	SETTING & COMMENTS
2017	Kodankandath et al [72]	N = 21, pre N = 31, post.	37, pre 26, post	16 PSCs to 1 CSC in New York. Single EMS system. Comparing two 3 month periods before and after a 1 year quality improvement program. “Transport time 1” + “ED time” would be equivalent to DIDO and presented here. Only 13 out of 52 patients received thrombectomy, unexplained. Exact year of study uncertain.
2017	McTaggart et al [54]	N = 48, partial N = 22, full	104 (78 - 121) 64 (51 - 88)	14 PSCs to 1 CSC in Rhode Island, New York over 11 months from July 2015. Pre and post a new ELVO diagnosis and transfer protocol (partial vs full).
2017	Ng et al ***(Chapter 3.1)***	N = 67	128 (107 – 164)	3 PSCs to 1 CSC in Melbourne, Australia over a 20-month period from January 2015.
2018	McTaggart et al [70]	N = 130	85 (68 – 111)	Same setting as McTaggart’s 2017 paper but covered 23 months from July 2015.
2019	Al Kasab et al [73]	N = 87	111 (92 – 157)	Two CSC with two telestroke networks in southeastern U.S with over 56 sites combined. Seven months from March 2017.

2019	Choi et al ***(Chapter 3.2)***	N = 133	86 (65 – 111)	1 PSC to 2 CSCs in Melbourne, Australia over a 46-month period from January 2015. 42 by air, 20 by road.
2020	Gangaharan [74]	N = 62	214 (171 – 247)	6 rural telestroke sites to 1 CSC (John Hunter Hospital, NSW, Australia). Cases between April 2013 and October 2019.
2021	Tiu et al [64]	N = 55	120.5 (98 – 150)	Regional tertiary PSC (Geelong) to one CSC over 30 months from July 2016.
2021	Scheving et al [75]	N = 111	99 (71 – 139)	1 CSC in Middle Tennessee (VUMC), patients from 36 different EDs. Median ED length of stay reported, likely the same/similar to DIDO time. Longest time is from CT to transfer request.
2021	Wu et al [67]	N=103	131 (93 – 187)	8 CSCs in the state of Texas with 46 spokes sites from December 2016 to May 2019. 54% via ground ambulance, the rest air.
2021	Van Meenen et al [69]	N = 198	85 (70 – 113)	3 PSC to 1 CSC from 2014-2021 in the Netherlands. 288 transferred but no EMS data on 68. Transfer time of 28 minutes (PSCs are near by).

2021	Boss et al [76]	N = 37	92 (69 – 110)	DIDO examined over a 3-month period only in a mandatory quality assurance registry of the state of Hesse, Germany with 8 PSCs and 6 CSCs covering the metropolitan Frankfurt Rhine Main.
2021	Prabhakaran et al [77]	N = 191	148 (106 – 207.8)	3 PSCs to 3 CSCs in Chicago from February 2018 to January 2020.
2022	Hassan et al [78]	N = 28, pre N = 35, post	202 (110 – 269) 114 (58 – 147)	Patients from a single PSC in Texas, 22 months prior to November 2018 and 20 months following using AI software (Viz LVO) for identification and communication.
2022	Gaynor et al [79]	N = 27	45 (41 – 55)	Single regional PSC with 243 beds in Dublin from October 2018 to January 2021 after a quality improvement program. Main feature was for ambulance crew to stay behind for outbound leg.
2022	Pérez de la Ossa et al[80]	N = 467	78 (63 – 97)	RACECAT trial. Six CSCs, 15 telestroke centres and 8 PSCs in Catalan, Spain.
2023	Wong et al ***(Chapter 3.3)***	N = 455	Metro: 107 (84 – 145) Regional: 132 (108 – 167)	3 CSCs, 7 metro sites and 17 regional sites in the state of Victoria, Australia from January 2017 to December 2018.

2023	Chung et al [81]	N = 27	72 (38 – 114)	One PSC 43km from a CSC in Icheon, South Korea from March 2019 to January 2020.
2023	Kuc et al [82]	N = 511	Mean 137.8	Registry of ELVO patients from 9 CSCs in northeast United States. Number of PSC or telestroke centres unknown. Mean (SD) DIDO was 138.2 (93.1) for female, and 137.5 (80/9) for male.
2023	van de Wijdeven et al [83]	N = 133	66 (52 – 83)	6 PSCs with 1 CSC in one Dutch ambulance region from October 2019 to November 2020.
2023	Stamm et al [84]	N = 21690	132 (97 – 189)	GWTG-Stroke registry study from January 2019 to December 2021. 108,913 patients from 1925 referring hospitals. DIDO reported here are those transferred for endovascular therapy.
2023	Sigal et al [85]	N=434	Mean 132.1 (SD 86.7)	9 healthcare systems in Northeastern United States (OPUS-REACH registry). 56% of patients had vascular imaging prior to transfer. Study period not reported.

Table 7: PSC DIDO published in the literature, search limited to English

1.6.4 The role of Primary Stroke Centre (PSCs) in the acute stroke care system

Apart from the Mobile Stroke Unit, which uses a miniaturised CT scan to definitively identify ELVO, another way of predicting ELVO in the prehospital setting is the use of prehospital stroke scales by paramedics driving normal ambulance.[86, 87] These scales, including the Hunter-8 and ACT-FAST algorithms developed by Australian researchers are widely used by various emergency medical services.[88, 89] The rationale for the use of these scales is that most patients with severe strokes, with either confirmed or suspected ELVO, would benefit from bypassing the local PSC, and instead directly transported to a CSC. This premise is challenged by data generated from robust modelling methods using real world data, as well as RCT involving a range of PSCs in Spain showing similar patient outcomes between the bypass model and "drip and ship" model.[80, 90] Further, the opportunity cost of bypassing PSC to patients with ELVO who would not have benefited from ECR due to other factors, and the hidden and long term cost to PSCs of these bypass strategies, are under-investigated.

The ACT-FAST algorithm was introduced to AV paramedics in late 2019. The intention was to bypass PSCs in the metro Melbourne area if the patient was assessed to be ACT-FAST positive in the field. Eastern Health's catchment was in principle excluded due to strong opposition from the stroke team at BHH. The main argument was our fast DIDO times would negate any potential benefit of bypass. Against this background, the paper in Chapter 3.4 examines the practical utility of the ACT-FAST triage algorithm from a PSC perspective over a 12-month period from January 2020. There were three important findings:

Misclassification by paramedics in the field

1216 patients presented with ongoing neurological symptoms on arrival and were assessed by the stroke team. 88 of these were classified as ACT-FAST positive by an experienced ASN based on examination findings in the medical records. The documentation of ACT-FAST status was not consistent and overall 54 patients were identified as ACT-FAST positive by paramedics. This included some of the 88 patients but 21 out of the 54 patients thought to be ACT-FAST positive by paramedics were misclassified as they did not fit the "eligibility screen" in Step 3 of ACT-FAST.

Only 35% of ACT-FAST positive patients required transfer to a CSC

49 of 88 of ACT-FAST positive patients had ELVO, 24 of 88 had intracranial haemorrhages (ICH) and the rest had no ELVO or were stroke mimics. 28 of 49 ELVO patients, and 3 of 24 ICH patients were transferred to a CSC for further treatment management. 57 of 88 (65%) ACT-FAST positive patients remained at the PSC with 18 commencing on the palliation pathway immediately after assessment on arrival.

Previously reported time saving of bypass PSC is exaggerated

Based on modelling, with a CSC-arrival-to-arterial-access time in transferred patients of 24 minutes and a median DIDO of 50 minutes (IQR 41-63) in this cohort, the average time saving of bypass would be 15 minutes. This compares to a time saving of 52 minutes reported by Zhao et al in 2021 using historic DIDO data.[89]

Studies in pre-hospital stroke scales have mainly focused on the performance of these scales in detecting ELVO, and real-world reliability data is lacking. Data from this paper confirms while ACT-FAST includes a section (Step 3) attempting to assess the “eligibility for ECR”, the information that is needed to make that assessment is either difficult to get or unreliable at the time of the assessment by paramedics.

This is the first study to show only about one third of ACT-FAST positive ELVO patients would benefit from care at a CSC. This suggests PSC has an important role in caring for most acute stroke patients in the hyperacute phase, and in ensuring patients who would not benefit from ECR can be cared for closer to home at their local hospital. This argues strongly for continued investment and quality improvement at PSCs in parallel to improving access to ECR for eligible ELVO patients. The median DIDO time at BHH further decreased to 45 minutes in 2022, suggesting any ELVO bypass strategies, either clinical or imaging (on the MSU), may not actually be beneficial overall if all PSCs improve their treatment metrics. Bypassing ACT-FAST patients, based on our data, would overwhelm existing CSC stroke teams and inadvertently delay the treatment to ELVO patients who would benefit from ECR. Finally, this paper confirms the importance of having up-to-date data in workflow modelling.

There is also local evidence that a higher proportion of code strokes presenting to PSCs (Sunshine and Northern Hospitals) are more complex, as patients with obvious and severe clinical deficits are now directly transferred to the CSC. The impact of ELVO bypass strategies on PSC stroke team staffing, acute stroke assessment and treatment efficacy, staff morale, and more importantly patient outcome, requires further investigation.

This paper was published in the third quarter of 2022 in *BMJ Neurology Open.* The argument that not all PSC should be bypassed for ELVO stroke was noted and cited by *Advances in Stroke: A Focus on Health Policy Literature from 2022* in the journal *Stroke*, published in September 2023.[91]

1.7 Anticoagulants as a barrier to intravenous thrombolysis (IVT)

1.7.1 Reperfusion therapies in patients treated with vitamin K antagonists (VKA)

Intravenous thrombolysis is considered contraindicated in fully anticoagulated patients presenting with acute ischaemic stroke. In the vitamin K antagonists (VKA) treated patient, an international normalised ratio (INR) of ≤1.7 is generally considered safe and acceptable for IVT. This has been supported by the AHA guideline since 2007 with no specific literature cited for the 1.7 cut-off.[92] Subsequent analysis from the GWTG-Stroke Registry (n=23437, 1802 with median INR 1.2, IQR 1.07-1.4, year 2009-2011), and Safe Implementation of Thrombolysis in Stroke (SITS)-International Stroke Thrombolysis Register (ISTR) (n=45074, 768 with INR<1.7, median not reported, year 2002 to 2011) found IVT in these patients were not associated with increased risk of symptomatic ICH.[93, 94] However, given the lack of randomised controlled trial data, the argument against,[95] and supporting the 1.7 cut-off remains.[96, 97] In practice, for VKA treated patients, clinicians can take the patient's INR result into account when assessing the risk and benefit of IVT. INR level is a reasonable marker for a patient's bleeding risk under normal situations, particularly in values >4, but is only one of the many factors involved in the acute IVT decision making process.[98] INR is a standard test available in any hospital pathology laboratory and point-of-care INR testing device with fast turn-around-time (≤ 2 minutes) has been available for over 20 years.

The main barriers to efficient reperfusion therapy for VKA treated patients presenting with acute ischaemic stroke emerge if the INR is not processed in a timely manner, or if the INR is >1.7. In the latter, if a proximal ELVO is identified, then primary ECR may be considered. High quality data supporting the relative safety of this approach is scant except for a recent analysis from GWTG-Stroke registry data between 2015 to 2020. The study focused on IVT and/or ECR in vitamin K antagonists (VKA) treated patients, direct presenters to CSC within 6 hours of onset with NIHSS >6.[99] It suggests slightly higher odds of symptomatic ICH in this specific cohort (INR>1.7, median and IQR not reported) compared to those who received primary ECR but not on a VKA (n=763 vs n=6338; 7.6% vs 5.0%; adjusted OR, 1.58 [95% CI, 1.08-2.30]; adjusted risk difference, 2.60% [95% CI, 0.30-4.89]). Indeed, higher odds of serious systemic haemorrhage <36 hours (adjusted OR, 3.27 [95% CI, 1.36-7.90]) was also observed. However, there are no differences in other secondary endpoints such as in-hospital mortality, discharge to home, hospice, inpatient rehab facility or nursing facility.

1.7.2 Direct oral anticoagulants (DOAC) in the acute ischaemic stroke patient

Direct oral anticoagulants (DOAC) are increasingly preferred over VKA in patients with non-valvular atrial fibrillation (AF) and venous thromboembolism. Patients on a DOAC remain at risk of ischaemic stroke. The residual stroke risk for AF patients anticoagulated after an index stroke is high, with a cumulative incidence at 1 year of 7% (95% CI, 5.2-8.7).[100] Routine laboratory monitoring of DOAC level was not required by the product label when they were approved in the early 2010s. Since the mid 2010s to the present time, most general hospital laboratories were either inexperienced or had no equipment to perform DOAC plasma drug level testing.[101]

The Australian Stroke Guidelines in 2017 was the first amongst major international guidelines to suggest utilisation of DOAC level in IVT decision making. However, patients with DOAC as their routinely prescribed medication typically are still not considered for IVT given the unavailability or long turn around time of DOAC level results (~60-90 minutes).[102] The exception to this being patients on dabigatran, where a normal thrombin time (TT), part of a standard coagulation panel and widely available, excludes the presence of dabigatran.[103] Dabigatran was approved in 2010 while the antidote idarucizumab was

approved in 2015. Early literature suggested the “reverse and lyse” strategy with idarucizumab was used with or without reference to the TT.[104] In 2018, BHH’s haematology pathology service was one of the first in Melbourne to process routine DOAC plasma drug level requests.

Pooled analysis of multiple international cohort studies suggested about one fifth of patients who had an ischaemic stroke were treated with an anticoagulant prior to their stroke onset.[105] Previous work at our hospital suggested that among patients who presented with acute stroke and were also prescribed a VKA, one third were thrombolysed as their INR were ≤1.7, yet only one out of 19 DOAC patients was treated with IVT.[102] DOAC plasma level testing was not available during that period. Was increased availability of DOAC level testing associated with increased IVT? We sought to understand the extent to which DOAC use may be a barrier to efficient reperfusion in the paper presented in Chapter 4.1.

1.7.3 Are DOACs a barrier to IVT?

The type of anticoagulants prescribed to ischaemic stroke and TIA patients presented to BHH with stroke symptoms reflects the worldwide trend of increasing DOAC use compared to warfarin.[106] At BHH, the percentage of patients on warfarin decreased from 60% during 2012 to 2017, and to 27% by 2018 to 2020. The study in Chapter 4.1 included 276 patients from the BHH departmental stroke database. These patients had an admission diagnosis of ischemic stroke, TIA or intracerebral bleed and all had an oral anticoagulant as their normal medication prior to their presentation with stroke symptoms. The focus was on the 103 patients who presented within 9 hours from stroke symptom onset based on the extended time window for IVT for selected patients with favourable CT perfusion changes (Figure 9).

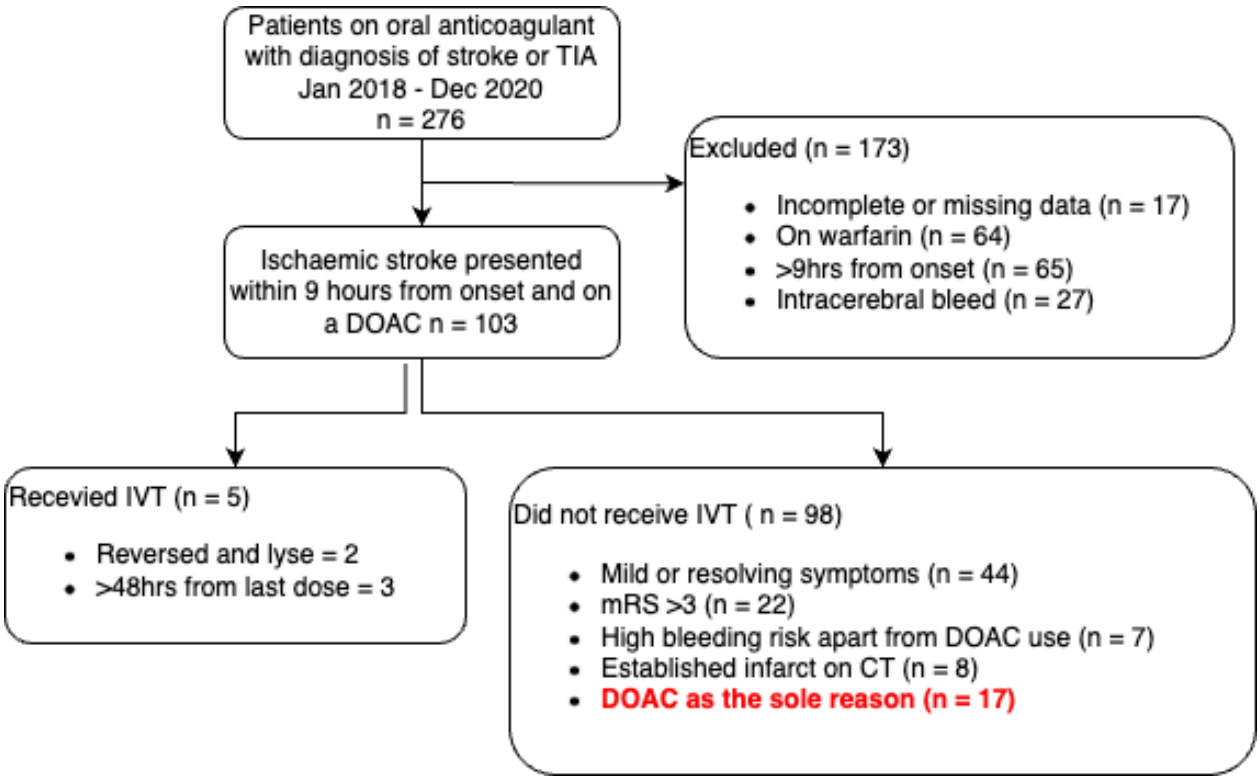

Figure 9: Patients on DOAC as exclusion criteria for thrombolysis - study flow diagram

DOAC level was performed in 15 out of the 103 DOAC treated ischaemic stroke patients presented within 9 hours from symptoms onset. 12 of the 15 patients had plasma levels above the threshold considered safe for IVT as per the Australian Stroke Guidelines. DOAC use was the sole reason noted as a contraindication for IVT for 17 patients on initial assessment. Plasma DOAC level was performed in only 8 of 17 patients and 2 had DOAC level deemed safe for IVT, yet neither received IVT on reassessment (one had mild symptoms by the time the DOAC level was back and there was potential for other differential diagnosis in the other). No clear reason was identified for their lower than expected DOAC levels.

The result of this study appears to show DOAC plasma level did not result in more DOAC treated stroke patients receiving IVT. In the 5 patients treated, DOAC level did not facilitate IVT and TT was also not checked prior to administration of reversal agent. However, it is important to note DOAC level was not ordered for the 9 out of 17 patients where DOAC was the sole contraindication to IVT. The reason DOAC level was not requested was unknown, but likely reflects the lack of knowledge of the assay availability. For context, it is unusual for INRs not to be tested in patients taking warfarin and presenting with an

ischaemic or haemorrhagic stroke. Of the 15 patients where DOAC level was measured, 12 had a level above the IVT threshold, yet it is impossible to know if the opportunity for IVT was missed in the 9 patients where DOAC level was not even ordered.

Similar studies examining the potential missed opportunity for IVT solely due to DOAC used at the time of stroke presentation is lacking. Austin et al from the Alfred Hospital in Melbourne presented a conference abstract at SSA in August 2023 showing 18 of 234 acute stroke patients presenting to their centre within 4.5hrs of onset (Jan 2021 to Dec 2022) had DOAC as their only contraindication for IVT.[107] No DOAC level testing was mentioned. Our figure (17/103) is not directly comparable to theirs as we used an IVT window of <9hrs rather than <4.5hrs.

Marsch et al published their experience in using DOAC level to facilitate IVT in late 2019.[108] The study included 522 OAC treated patients presenting with suspected stroke over a period of 4 years from 2014. 261 were on a DOAC, of which just less than 50% presented within 4.5hrs from symptom onset. 206 of 261 patients had a DOAC plasma level measured on admission. Levels were low (<50ng/ml) in 60 of the 206, intermediate (50-100ng/ml) in 47 of the 206 and high (>100 ng/ml) in 99 of the 206. 24 of the 261 DOAC patients were treated with IVT, 21 had low DOAC levels, and 2 had levels in the intermediate range. One received IVT without a level done. Safety outcomes were compared to the 30 VKA treated patients who received IVT (median INR 1.4, IQR 1.3 – 1.5). No differences were found between the two groups in symptomatic ICH, any ICH, median mRS at 3 months or favourable functional outcome (mRS 0-2) at 3 months. The median turnaround time for DOAC plasma was 39 minutes (IQR 35-46), faster than the median [71 minutes (IQR 46.5 – 143)] reported in our study. Further refinement to our protocols has improved the median time to about 30 minutes at BHH for urgent requests from the middle of 2023 onwards.

Currently, in the absence of widespread adoption of reperfusion protocols involving plasma DOAC level in acute reperfusion decision making, patients on DOAC presenting with ELVO would be considered for primary ECR without IVT. Safety data on this approach is limited but is probably at least comparable to VKA treated patients, if not safer.[109, 110]

The paper in Chapter 4.1 was published online in September 2022 and has one citation which is closely related to the paper presented in Chapter 4.2. The challenge of treating patients presenting with acute ischaemic stroke whilst on a DOAC is enormous and

topical. Emerging observational data, including ours and elsewhere, suggests IVT may be safe even in those with confirmed DOAC intake, however this approach remains controversial.[111] A debate session was dedicated to this topic at the SSA conference in August 2023.

1.8 Point of care DOAC testing in hyperacute stroke

The available literature suggests DOAC plasma level, if available in a timely fashion, may allow safe IVT in DOAC patients who would otherwise not be considered for IVT.[108] As discussed, despite guidance on the utility of DOAC plasma level in acute stroke decision making in Australian guidelines, testing of DOAC plasma level is far from routine. At the time of writing (early 2024), DOAC testing is not performed in hospital laboratories in any regional hospitals in Australia. DOASENSE™ is a urine dipstick that can exclude clinically relevant DOAC plasma level within 10 minutes (Figure 10). We are the first group in the world to publish our experience of using this assay in the hyperacute stroke setting. We sought to assess the reliability of this assay by comparing its results to conventional DOAC plasma level testing by the hospital pathology service. The acute arm consists of patients presenting with acute stroke symptoms for consideration of IVT, with the subacute arm in stroke inpatients following DOAC initiation for secondary prevention. This paper is presented in Chapter 4.2.

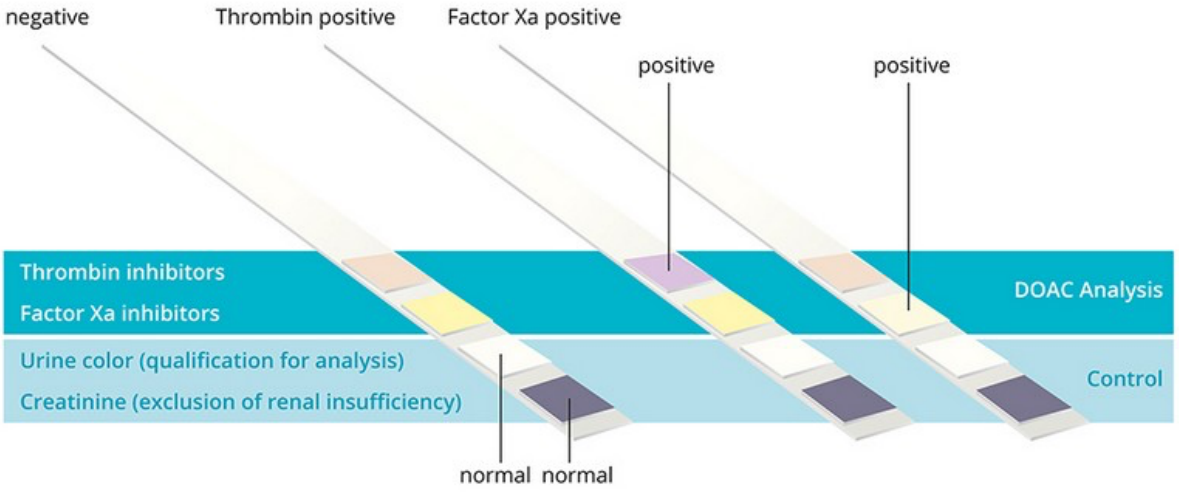

Figure 10: DOASENSE™ Dipstick with 4 different pads, two for quality control purposes, and one each containing reagent for detection of thrombin inhibitors and factor Xa inhibitors. The changes in colour can be identified visually or with the DOASENSE Reader.

The acute arm included 17 patients. Concurrent blood and urine samples were taken for DOAC plasma level assay and DOASENSE™ testing respectively. The median turnaround time for plasma DOAC level was 52 minutes (IQR 38 – 67) compared with 20 minutes (IQR 17-24) for DOASENSE™, the latter including urine acquisition time as well. One false positive case was noted where the rivaroxaban plasma level was <20 ng/ml but the DOASENSE™ returned a positive result. No false negative was noted in the acute arm. In the subacute arm, where 24 patients with recent stroke were started on a DOAC and both blood and urine samples were taken at 4 to 6 hours post first dose ingestion, 22 of 24 patients tested positive on DOASENSE™. The two false negative results corresponded to plasma level of 56 and 58 ng/ml.

Our results, together with the studies performed in other settings, suggest the result of DOASENSE™ is reliable in excluding the presence of clinically relevant DOAC level in the plasma and may be used to facilitate acute stroke decision making.[112, 113, 114, 115] This is particularly important for acute stroke patients presenting to regional hospitals where DOAC plasma level is either not available, or a rapid turnaround time is not feasible. Without some form of DOAC level assessment, it is likely DOAC use, or presumed DOAC use, in acute stroke patients presenting to regional hospitals will continue to be excluded from IVT. Although other point of care DOAC testings exists, DOASENSE™ is most studied and validated in the literature.[116]

Being able to consider IVT in DOAC treated stroke patients is particularly important for patients in regional areas. This is true for patients with or without identifiable proximal ELVO. Despite no data being available for recently anticoagulated patients, in non-anticoagulated patients with ELVO, about 10% would experience reperfusion before thrombectomy after IVT alone.[21] The reversal agent of anti-Xa inhibitors, andexanet alfa, gained Australian Therapeutic Goods Authority (TGA) approval in July 2023. Similar to the use of idarucizumab for dabigatran treated patients, it is expected clinicians may eventually consider the "reverse and lyse" strategy for stroke patients on anti-Xa inhibitors. From a cost perspective alone, it is reasonable for the absence or presence of DOAC to be determined prior to the administration of andexanet alfa, as each vial (200mg) cost AUD$3,250 at the time of writing. The recommended dosing regimen depends on the dose and the factor Xa inhibitor used, as well as the time since last dose. The recommended "low dose" would require 5 vials and "high dose" would require 10 vials.[117]

The paper in Chapter 4.2 was published in April 2023 in Stroke and was cited by a recently published consensus statement on the use of DOASENSE™.[118] A German feasibility study on DOASENSE™ in stroke patients, very similar to our work, was published in the middle of December 2023 in *Frontiers in Neurology.*[119] That paper, together with our work, underscore the relevance and emerging interest in improving access to reperfusion therapies in DOAC treated stroke patients. Based on the results of these pilot studies, planning for a multi-centre study involving all regional hospitals covered by the VST network in Victoria and Tasmania, as well as John Hunter Hospital and a few regional hospitals in NSW, is in progress.

This is the end of the Contextual Statement. Prior published works as part of this thesis are presented in Chapter 2 to 4 grouped by the three themes. The Concluding Commentary is presented in Chapter 5.

CHAPTER 2: BARRIERS TO FAST DOOR-TO-NEEDLE TIME

2.1. Are All Stroke Patients Eligible for Fast Alteplase Treatment? An Analysis of Unavoidable Delays.

Choi PM, Desai JA, Kashyap D, Stephenson C, Kamal N, Vogt S, Bohm V, Suddes M, Bugbee E, Hill MD, Demchuk AM, Smith EE.

Acad Emerg Med. 2016 Apr;23(4):393-9

Journal Impact Factor 2.925 in 2016, 4.4 in 2022, 13 citations and a Field-Weighted Citation Index (FWCI) of 1.27

Co-authorship statement: I completed this work during my 1.5-year stroke fellowship with the Calgary Stroke Program, Foothills Medical Centre, University of Calgary.

I contributed to the design and data collection, and am responsible for the overall project administration. I wrote the original draft and E Smith conceived the study and analysed the data. AM Demchuk, MD Hill and E Smith provided extensive editing input. JA Desai, C Stephenson and N Kamal were members of the stroke team with intellectual input into the project. D Kashyap, S Vogt, V Bohm, M Suddes and E Bugbee were collaborators with nursing and executive roles in the emergency department at Foothills Medical Centre.

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2.2. The quest to reduce stroke treatment delays at a Melbourne metropolitan primary stroke centre over the past two decades.

Park PSW, Frost T, Tan S, Wong J, Pope A, Dewey HM, Choi PMC.

Intern Med J. 2022 Nov;52(11):1978-1985

Journal Impact Factor 2.1 in 2022, 9 citations, FWCI of 2.16

Co-authorship statement:

P Park completed this work during his stroke fellowship as first author. S Tan and J Wong, stroke fellow in the year after and before P Park respectively, were involved in review and editing. A Pope, senior statistician provided statistical analysis. T Frost, ASN, provided data and was involved in reviewing. HM Dewey was involved with review and editing.

As senior author, I was involved in the conceptualisation, methodology, supervision, extensive review and editing of the draft manuscript.

Page 57 - 64, Supplemental Materials Page 65 - 70
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Page 57 - 64, Supplemental Materials Page 65 - 70
doi: 10.1111/imj.15429

2.3. Using body cameras to quantify the duration of a Code Stroke and identify workflow issues: a continuous observation workflow time study.

Wong JZW, Park PSW, Frost T, Stephens K, Newk-Fon Hey Tow FK, Garcia PG, Senanayake C, Choi PMC.

BMJ Open. 2023 Jan 25;13(1):e067816

Impact factor 2.7 in 2022

Co-authorship statement:

J Wong completed this work during his stroke fellowship as first author. P Park, T Frost, K Stephens, F Newk-Fon Hey Tow, P Garcia, C Senanayake were all members of the stroke team involved with data collection.

As senior author, I was involved in the conceptualisation, methodology, supervision, extensive review and editing of the draft manuscript.

BMJ Open

Using body cameras to quantify the duration of a Code Stroke and identify workflow issues: a continuous observation workflow time study

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ABSTRACT

Objective 'Code Stroke' (Code) is used in health services to streamline hyperacute assessment and treatment delivery for patients with ischaemic stroke. However, there are few studies that detail the time spent on individual components performed during a Code. We sought to quantify the time taken for each process during a Code and investigate associations with modifiable and non-modifiable factors.

Design Continuous observation workflow time study.

Setting and participants Recordings of 100 Codes were performed at a high-volume primary stroke centre in Melbourne, Australia, between January and June 2020 using a body camera worn by a member of the stroke team.

Main outcome measures The main measures included the overall duration of Codes and the individual processes within the Code workflow. Associations between variables of interest and process times were explored using linear regression models.

Results 100 Codes were captured, representing 19.2% of all Codes over the 6 months. The median duration of a complete Code was 54.2 min (IQR 39.1–74.7). Administrative work performed after treatment is completed (median 21.0 min (IQR 9.8–31.4)); multimodal CT imaging (median 13.0 min (IQR 11.5–15.7)), and time between decision and thrombolysis administration (median 8.1 min (IQR 6.1–10.8)) were the longest components of a Code. Tenecteplase was able to be prepared faster than alteplase (median 1.8 vs 4.9 min, p=0.02). The presence of a second junior doctor was associated with shorter administrative work time (median 10.3 vs 25.1 min, p<0.01). No specific modifiable factors were found to be associated with shorter overall Code duration.

Conclusions Codes are time intensive. Time spent on decision-making was a relatively small component of the overall Code duration. Data from body cameras can provide granular data on all aspects of Code workflow to inform potential areas for improvement at individual centres.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Body cameras are a novel method of capturing workflow data from Code Strokes.
⇒ The approach provides granular data regarding time points and staffing, with precision to the second, allowing for accurate measurement of all tasks performed during a Code.
⇒ Body cameras allow for more objective analysis of workflow and overcome the cost and working hour restrictions of human observers.
⇒ In this study, only one body camera was used at a time, limiting the ability to record tasks being performed in parallel off-screen.
⇒ Only 100 Codes were recorded, with few instances of uncommon delay factors such as intubation, ultrasound-guided cannulation and blood pressure management.

INTRODUCTION

Timely thrombolysis from stroke onset is associated with favourable functional outcomes, an effect which diminishes with every minute and hour delay.[1 2] Similarly, longer transfer time out of primary stroke centres to comprehensive stroke centres for endovascular thrombectomy (EVT) is associated with poorer functional outcomes for patients.[3] 'Code Stroke' (Code) streamlines hyperacute care for patients with ischaemic stroke in the emergency department (ED).[4 5] Codes facilitate rapid access to thrombolysis and/or EVT by implementing a combination of best-practice strategies to reduce door-to-needle time (DNT).[6]

Despite continued quality improvement initiatives at our centre resulting in sustained improvements in DNT, our median DNT has stagnated in recent years.[7] Time-and-motion studies are an effective way of characterising and quantifying potential workflow issues.[8] Results from these studies provide insights for teams to adjust and improve clinical practice and resource allocation. Video studies have been useful in a variety of time-critical

settings including emergency and resuscitation situations for review and training purposes.[9 10]

We sought to understand the workflow during a Code Stroke on a granular level by measuring the total duration of running a Code and to capture as many objective variables affecting workflow, such as the number of staff involved, and the time spent during a Code on performing key tasks, including decision-making.

METHODS

Setting

Box Hill Hospital (BHH) is a high-volume primary stroke centre in metropolitan Melbourne, Australia. It services a primary and secondary catchment of approximately 1.1 million people.[11] In 2020, the stroke team attended 1230 Codes, 75 patients received thrombolysis with 36 patients transferred to a comprehensive stroke centre for EVT.

Local stroke team processes

The Code response team at BHH comprises a neurology registrar or fellow (Australian postgraduate year (PGY) 4+) with an acute stroke nurse (ASN), a hospital medical officer ('HMO', Australian PGY 2+) and a research nurse typically being available during working hours. Working hours were defined as 08:00–17:00, evening shifts as 17:00–22:00 and overnight as 22:00–08:00. Codes could be activated by paramedics via pre-notification to the hospital, on arrival by a triage nurse or an ED doctor. Once a Code is activated, local protocols allow for the patient to be transported direct to CT without initial assessment from the neurology team to streamline patient care. A Code is considered 'stood down' once it is known that the patient will not receive hyperacute treatment for any reason. This can occur before, during or after CT imaging. Either the neurology registrar, fellow or neurologist has the authority to stand down the Code, including cancellation of perfusion imaging, if they find the patient to be ineligible for reperfusion therapy. The final treatment decision is discussed with the neurologist in-charge via telephone (not usually present at the Code).

Body camera video recording

We conducted a continuous observation workflow time study[8] of 100 Codes at BHH between January and June 2020. All adult cases where the registrar/fellow or ASN was called to assess a patient via a Code were eligible for inclusion in this study. This included after-hours and overnight Codes to provide a comparison for in-hours versus out-of-hours decision-making. The on-call neurology registrar/fellow or ASN (referred henceforth as the 'wearer') was provided with a portable body-worn camera (bodycam) capable of recording video and audio. The device is a Miufly EH15 bodycam with standard video and audio recording capability.[12] Purchase of the device was funded by the first and last authors. Only one member of the team wore the camera at a time. Each team member was encouraged to record as many consecutive Codes as possible during a shift. Not all Codes could be recorded due to simultaneous Codes or camera availability. Recordings could be stopped early at the discretion of the wearer for patients requiring sensitive discussion or planned withdrawal of care. These recordings were deleted and excluded from the study. A screening log was maintained for all recordings and Code Stroke activation was confirmed with the local stroke database. There were several reasons for excluding a recording including inappropriate setting (eg, palliative situation), contemporaneous Codes where there was only one camera in operation or inability to obtain consent (due to workload or patient discharged). The wearer was not required to document the reason for exclusion, which was at the discretion of the wearer. Codes involving the donning of personal protective equipment (PPE) in response to the global COVID-19 pandemic were excluded because it obscured the audio and video, and local infection control protocols did not permit our bodycam to be worn external to PPE. All recordings were reviewed within 30 days by at least one of the investigators. Once the data were collected, the recording was permanently deleted. No copies or transcripts of the recording were made.

Standard protocol approvals, registrations and patient consent

Each patient was informed of the recording on first contact and cases being recorded were indicated by a sign (see online supplemental methods). To ensure the patient's care was not compromised by the study, written informed consent for this study was only obtained after the patient had received all appropriate reperfusion treatment or the Code was stood down. For patients who were transferred for EVT, consent was obtained when they returned to BHH. For patients unable to consent, consent was obtained from an appropriate person responsible identified in accordance with local regulations. Patients or persons responsible who did not consent to the study were excluded and recordings deleted immediately.

All relevant staff members who could appear in the background (from the ED, radiology department and ambulance paramedics) were briefed on the confidentiality measures and opt-out procedure. These staff members were not required to sign study consent form. Recordings with staff who opted out were to be excluded from this study but no requests to opt out occurred during the study period.

Statistical analysis

Non-overlapping time points within the Code Stroke were chosen to illustrate the workflow as a single linear process reflective of the patient's journey in the ED. Examples of tasks performed in parallel within each interval are demonstrated in figure 1. All specified intervals and complete definitions of these are available in online supplemental table 1. Our main outcome measure was the 'team journey', defined as the total duration the

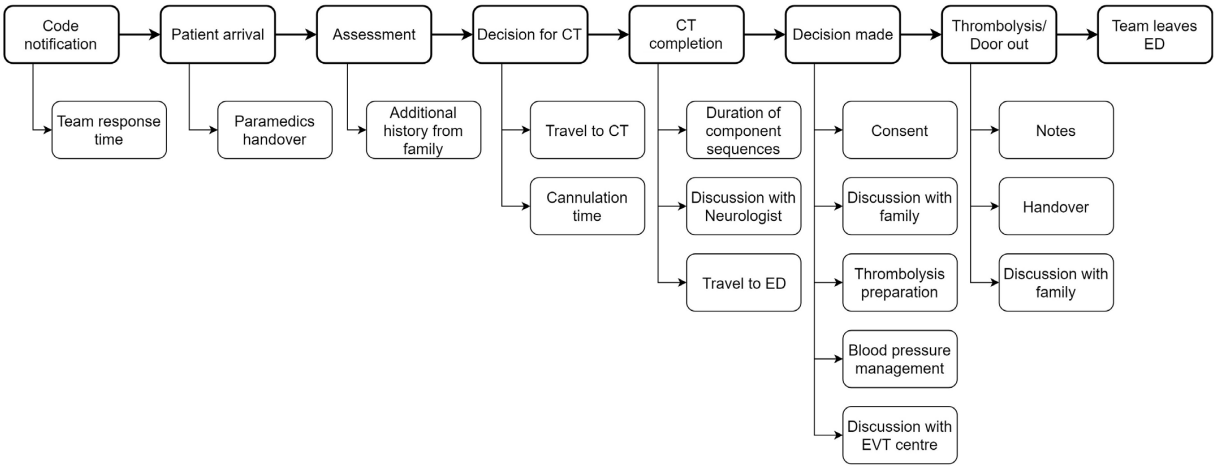

Figure 1 Sample representation of the patient journey during a Code Stroke with examples of component processes included during each time interval. The key processes in the top line are mutually exclusive, with its component processes able to occur in parallel and may overlap with other processes. ED, emergency department; EVT, endovascular thrombectomy.

team spent on a Code, calculated from the time of Code notification to the time the team leaves the ED.

The default process once a Code is activated is for the patient to undergo multimodal CT imaging (non-contrast CT, CT angiogram and CT perfusion). If the registrar/fellow was not able to assess the patient prior to transport to the CT scanner, the time to assessment and decision for CT was given a value of zero. For all other tasks which could be completed concurrently with a previous task, the duration was assigned a zero value for the purposes of statistical calculations, implying instantaneous completion of a task.

Descriptive statistics and regression models were performed in R studio V.4.0.5. Differences between categorical variables were assessed using the Kruskal-Wallis rank-sum test. Associations between variables of interest (see online supplemental table 2) and the duration of each task were examined using linear regression models. The final models were selected using the Akaike information criterion in a stepwise, forward selection process using the olsrr package in R. The models were assessed for multicollinearity and variables with variable inflation factor (VIF) larger than 5 were removed from the model and recalculated, resulting in VIF less than 2 in the final models.

Patient and public involvement

Outside of the panel members and laypersons comprising the ethics committee who provided feedback to the protocol in the initial ethics approval of the study, patients/members of the public were not involved in the design, conduct or reporting of this study.

RESULTS

A total of 19.2% of all Codes at BHH during the study period were recorded. A comparison of the bodycam cohort and overall Code Stroke population is shown in table 1.

Workflow

The median team journey was 54.2 min (IQR 39.1–74.7). This can be further stratified by treatment group as demonstrated in figure 2. Modifiable in-hospital factors, including number of staff, were not associated with a shorter team journey. A shorter team journey was however associated with two factors: decision to stand down the Code before imaging and prehospital intravenous cannulation (online supplemental table 3).

Median times of the component processes are visualised in figure 3. Key performance measures are summarised in table 2 with detailed timing of other processes shown in online supplemental table 4. Median duration of multimodal CT was 13.0 min (IQR 11.5–15.7) with the non-contrast portion being 3.7 min (IQR 3.0–4.4). Longer door-to-CT time was associated with the patient being offloaded in an ED cubicle prior to CT (35.0±8.3 min predicted delay, p<0.001). Conversely, shorter door-to-CT time was associated with pre-notification of the Code. No association was seen between duration of pre-notification and door-to-CT time.

Sixty patients arrived without an intravenous cannula in situ. Of these, 29 patients required cannula insertion by the team, which consumed a median 3.1 min (IQR 2.1–7.3). A total of 10.3% of cannulations (3 of 29) required portable ultrasound-guided insertion. With ultrasound, the time taken for cannulation ranged from 10.0 to 17.3 min. Treatment implementation was completed in a median of 8.1 min (IQR 6.1–10.9) (n=12). This included tasks such as obtaining consent for treatment, obtaining collateral history from family members, mixing the thrombolytic agent, phone calls to neurologists and blood pressure management. Tenecteplase

Table 1 Comparison of patient and Code Stroke characteristics between the study cohort and overall Code Stroke population at Box Hill Hospital during the study period (January–June 2020)

Characteristic	Bodycam cohort (n=100)	Overall (n=522)
Age, years (median (IQR))	75.5 (62–81)	76 (63–85)
Male, no (%)	53 (53)	275 (52.7)
NIHSS (median (IQR))	2 (0–5)	2 (0–6)
Baseline mRS, no (%)	(n=99)	
0	73 (74)	243 (54.4)
1	7 (7)	76 (17.0)
2	7 (7)	51 (11.4)
3	12 (12)	65 (14.5)
4	0	11 (2.5)
5	0	1 (0.2)
Pre-notified Codes, no (%)	62 (62)	370 (70.9)
Code initiator, no (%)		
Ambulance paramedic	68 (68)	437 (83.7)
ED triage/doctor	31 (31)	66 (12.6)
Inpatient	1 (1)	19 (3.6)
Code stood down, no (%)	87 (87)	477 (91.4)
Discharge diagnosis, no (%)		
Ischaemic stroke	47 (47)	193 (37.0)
Transient ischaemic attack	13 (13)	47 (9.0)
Haemorrhagic stroke	1 (1)	43 (8.2)
Stroke mimic	39 (39)	239 (45.8)
Received thrombolysis, no (%)	13 (13)	28 (5.4)
Transferred for EVT, no (%)	6 (6)	15 (2.9)
Enrolled in clinical trial, no (%)	9 (9)	14 (2.7)
Time of presentation, no (%)		
Working hours 08:00–17:00	75 (75)	338 (64.8)
Evening 17:00–22:00	20 (20)	105 (20.1)
Overnight 22:00–08:00	5 (5)	79 (15.1)
Day of presentation, no (%)		
Weekday	80 (80)	384 (73.6)
Weekend	17 (17)	120 (23.0)
Public holiday	3 (3)	18 (3.4)

ED, emergency department; EVT, endovascular thrombectomy; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

(n=7) was able to be prepared faster than alteplase (n=6) (median 1.8 vs 4.9 min, p=0.02).

The time after treatment is implemented or Code is stood down was considered as 'administrative work'. Tasks occurring during this time included typing notes, charting, handover and discussion or debrief with the patient and/or family. The median administrative work time for all Codes was 21 min (IQR 9.8–31.4). In univariable and multivariable analyses, the presence of a neurology HMO was associated with shorter administrative work time (median 10.3 vs 25.1 min, p<0.01). Conversely, if the research nurse was present, or during overnight Codes (where no HMO was present), the administrative work time was longer.

Staffing

All Codes were attended by a neurology registrar/fellow. There was at least one HMO present at 35% of Codes, but there was no HMO for overnight Codes. Stroke nurse attendance was 80.3% for Codes during weekday working hours. There was only one team member at 25% of Codes, two members in 49% of Codes, and 26% of Codes had three or more members present. The median response time between Code notification and arrival of the stroke team was 7.7 min (IQR 5.0–16.7) (n=89). Longer response times were seen overnight, on weekends and on public holidays. Our model predicted that the team would arrive an estimated 23.6±4.4 min later for overnight Codes compared with evenings (p<0.01).

Decision-making time

The first decision point identified was the decision to proceed with imaging or not. This occurred in a median 3.5 min (IQR 1.9–6.1) (n=84). This was found to be associated with the severity of the stroke, time of day and the presence of a neurology HMO (online supplemental table 3). The second major decision point was the decision for thrombolysis and/or EVT. Figure 2 demonstrates the median door-to-decision times for each situation stratified by imaging and treatment received. Treatment decision time was taken as the point the wearer confirmed verbally that they were proceeding with thrombolysis, EVT or standing down the Code. Door-to-decision time was defined as the time from patient arrival to the time a decision was made for thrombolysis, EVT or to stand down the Code. Public holidays and non-English-speaking background were associated with slower door-to-decision time, while more severe symptoms and prehospital intravenous cannulation shortened it (online supplemental table 3). There was no statistically significant difference in door-to-decision time with time of day, stroke nurse presence or Code pre-notification.

Ideal DNT

The data allowed us to calculate a theoretical ideal DNT of 21 min at our centre, visualised in figure 4. This model assumes the stroke team is pre-notified and has arrived before the patient; the decision to proceed with CT is performed instantaneously; clinical assessment is performed en route to CT; and the decision to thrombolyse can be made within the time to complete full multimodal CT imaging. Currently, thrombolysis is typically performed after perfusion and CT angiography, an addition which we have found to be only 10 min beyond the non-contrast CT.

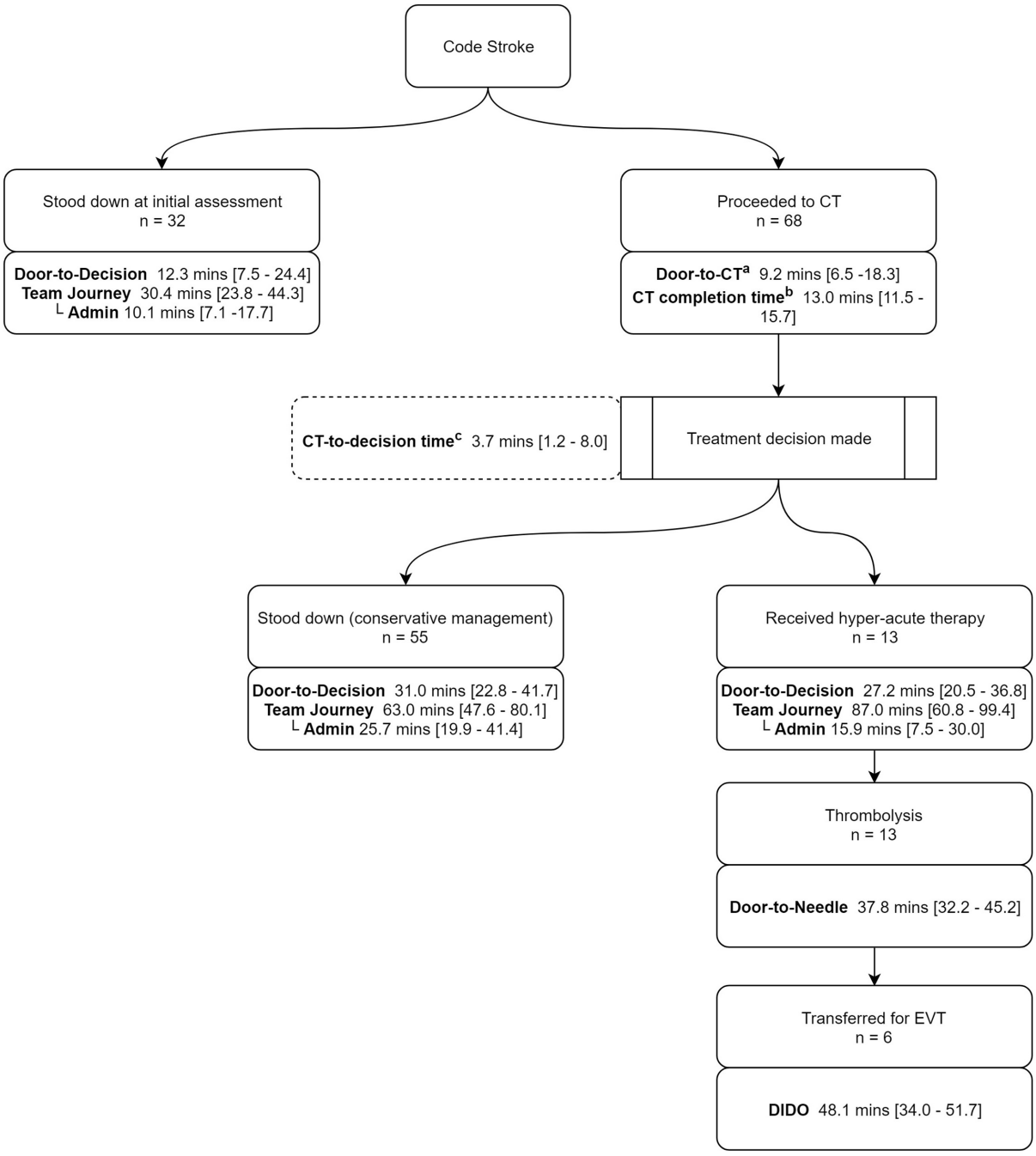

Figure 2 Decision-making and team journey metrics stratified by imaging and treatment group. Team journey is defined as the total time spent by the stroke team on a Code. [a]Door to CT (n=52). [b]CT completion time (n=50). [c]CT-to-decision time (n=59). Admin, administrative work (charting, notes, handover); DIDO, door-in-door-out time; EVT, endovascular thrombectomy.

DISCUSSION

The bodycam has allowed us to characterise our Code workflow and identify issues unique to our centre. Our findings show that Code Stroke is a time-intensive task, with a Code consuming a median of 54 min within the workday of the stroke team. A large proportion of this is spent on administrative work after reperfusion treatment is administered. Decision-making, however, only comprises a small part of the Code. The bodycam has also allowed us to capture non-standardised data such as time of decision, cannulation variables and number of staff, all with precision to the second. From this, we were

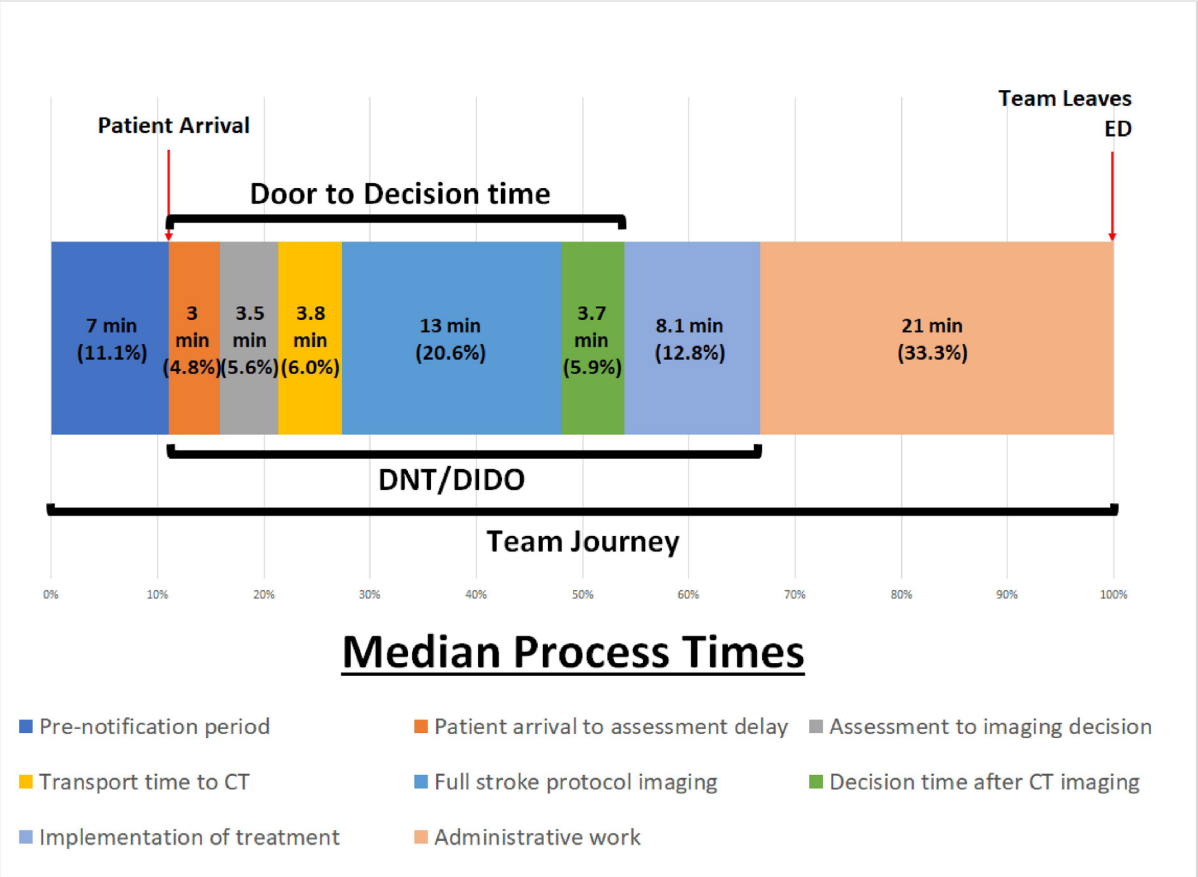

Figure 3 Timeline demonstrating the median time of each key process during a Code Stroke. The percentage values reflect the task duration as a proportion of the sum of all median process times. Team journey is defined as the total time spent by the stroke team on a Code. DIDO, door-in-door-out time; DNT, door-to-needle time; ED, emergency department.

able to quantify the time saved when using tenecteplase compared with alteplase; time to decision-making and an ideal DNT for our centre. These are powerful data that can be replicated at other centres to identify local bottlenecks and barriers to Code Stroke workflow.

Personal recording devices have now become readily accessible to the public and are easy to operate. Studies using these devices would allow researchers to obtain both time and location information not available to fixed camera set-ups.[13] Self-reported data are highly unreliable[8] and are unable to provide the level of detail required for our purposes. Trained human observers have been used in previous studies but labour costs and training are expensive and time-consuming. ED scribes are not routinely used in Australia. The cost of providing an observer outside of traditional work hours would be prohibitive. Video capture of Code Stroke also has the potential to reduce inter-rater variability by allowing the event of interest to be reviewed both remotely and during office hours. Furthermore, the ability to pause and rewind may reduce the likelihood of inaccurate or missing data when using human observers, especially when many tasks occur in parallel during a Code. It has also been shown that the physical presence of an observer can change the practice

Table 2 Summary statistics for key time metrics in this study

Time metric	n	Median (IQR) (min)	Range (min)
CT completion to decision made	59	3.7 (1.2–8.0)	0–31.5
Door-to-CT	52	9.2 (6.5–18.3)	4.3–117.2
Door-to-decision	83	25.2 (14.9–37.5)	4–115
Door-to-needle	13	37.8 (32.2–45.2)	25.0–63.0
Door-in-door-out	6	48.1 (34.0–51.7)	28.6–61.3

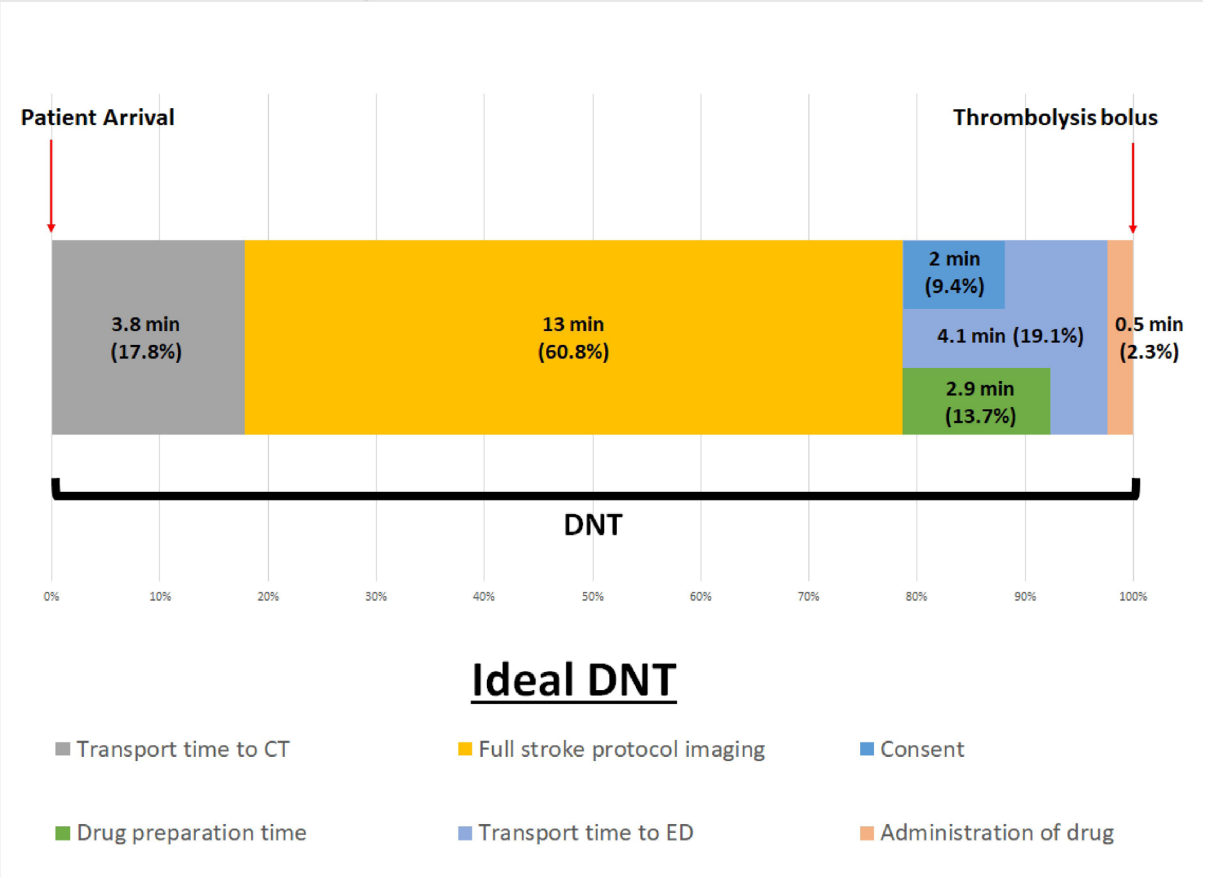

Figure 4 Timeline demonstrating the components of the ideal DNT at our centre of 21.4 min. The percentage values reflect the task duration as a proportion of the ideal DNT. DNT, door-to-needle time; ED, emergency department.

of the study subjects,[14] which could be minimised using personal recording devices.[13 15] Without the bodycam, we would not have been able to obtain these granular data as previous attempts with using trained observers have failed.

The current model in Melbourne allows for paramedics to activate a Code without detailed discussion with the receiving medical team. This results in a low proportion of patients being treated at Codes. This Code response increases staffing demands and the workload on individual clinicians. Around one-third of our Codes occur after hours and a quarter occur on weekends or public holidays. At a centre with a daily average of four Code Strokes, time spent on Codes can total nearly half the working hours of a standard shift. Even for Codes stood down on clinical assessment alone, the team would still be engaged in ED for a median of 30.4 min. Our data suggest that in centres with more than eight Codes per day, more than one stroke team may be required.

Contrary to anecdotal evidence, actual decision-making time once the information and imaging data have been gathered only represented 5.9% (3.7/63.1 min) of the overall Code Stroke process or 9.8% (3.7/37.8 min) of DNT. This time period represented the time spent in discussion with the neurologist. Instead, we have found that most of the time spent by the team at any Code is on administrative work. Surprisingly, administrative work for Codes which were stood down after imaging consumed the longest time despite not receiving treatment. One explanation is that this group is more likely to encompass stroke mimics or more complex decision-making scenarios, often requiring more time spent on handover and family discussions. Importantly, we did not find that purely increasing the number of staff attending a Code would reduce the team journey despite savings in administrative time. However, the extra team member could allow for tasks to be shared and the neurology registrar's time to be used more efficiently.

The benefit of reperfusion therapy in acute stroke is highly time sensitive but translation of this knowledge to real-world practice has been slow. Individual centres have reported significant improvements in treatment metrics over the last few decades, spearheaded by local stroke champions and region-wide programmes but it is clear we can improve on the status quo.[7 16 17] There is increasing interest in the benefits of mobile stroke units.[18 19] These

units undoubtedly shorten treatment times by bringing the scanner and thrombolytics to the patient, yet they are resource intensive. Before widespread deployment of these units, it would seem logical to improve and maximise the efficiency of care at existing primary stroke centres where these already exist.[20]

Through bodycam data, we have found that local efforts to improve Code Stroke protocols[7] have reduced the discrepancy between in-hours and after-hours decision-making time despite the team physically arriving later. Our data have informed us that patients not eligible for clinical trials requiring multimodal imaging could be thrombolysed 9 min faster based on non-contrast CT alone. Second, we calculated for our centre that the lack of prehospital intravenous cannulation and direct-to-CT protocol potentially adds 14 and 35 min of delay to workflow, respectively, confirming again the importance of these within the Code Stroke protocol.[7] Bodycam studies could be replicated at other centres to identify delays unique to each centre and to quantify resources required to optimise treatment delivery.

Limitations

There are several limitations to this study. First, the recordings were not made on consecutive Code Strokes and the proportion of overnight recordings was lower in the study cohort. Partly, this occurred due to the limited number of cameras and the limitations of handing over the cameras between shifts. Yet, the bodycam allowed us to record a good proportion of after-hours Codes (25%), which would otherwise have been difficult to obtain if using a human observer. Our recruitment method may also explain the higher proportion of patients enrolled in trials and receiving reperfusion treatment compared with the overall cohort (13% vs 5.4%). We have noted that, at our centre, the proportion of patients receiving thrombolysis has decreased over time as total Code Stroke activations have increased, due to a larger number of non-stroke diagnoses. The proportion of patients receiving thrombolysis ranged from 6% to 12% between 2016 and 2019.[7] As such, the number of reperfusion cases captured in this study is within the expected range.

Second, we did not examine associations between DNT/door-in-door-out and patient-related factors such as blood pressure management or need for sedation.[21] We found that these situations occurred infrequently with no patients in this cohort requiring intubation or sedation for CT imaging. Larger-scale bodycam studies would be able to examine associations between patient or logistical factors and treatment times. Although this was not included in our study, the bodycam can also be used to provide qualitative data from clinician interactions and the ability to review the dynamic decision-making in complex cases that are not reflected in mock scenarios. Multiple bodycams could also be used to record the activity of other stroke team members and capture if any duplication of tasks occurred. This would be particularly helpful to further time the micro-tasks performed within administrative work time. However, this work is resource intensive as over 84 hours of footage was reviewed to yield the data for 100 patients in this study.

CONCLUSION

Bodycams are a convenient and feasible method of collecting data on Code Strokes. Clinical practices vary between different centres and this is a useful tool for stroke teams to examine their workflow and identify areas for quality improvement initiatives.

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Contributors JZWW and PC conceived and designed the study. JZWW obtained ethics approval. JZWW, TF and KS were involved in training required staff for the study. JZWW, TF, KS, PSWP, FKN-FHT, PGG and CS were involved in data collection. JZWW and PSWP were involved in data linkage and analysis. JZWW and PC drafted and finalised the manuscript. PC is the guarantor of the study.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Eastern Health Human Research Ethics Committee (reference number: E19/020/58177). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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Online supplementary material

Contents

Supplemental methods

Script on contact

"This emergency assessment is being recorded by a small video camera for the sole purpose of quality improvement. Once we have finished assessing and given you the appropriate treatment, we will discuss this further, and formally ask for your consent to use the recording".

Bed sign

"Emergency assessment of acute stroke is being videoed for quality improvement purposes. Please speak to any member of the stroke team or the Nurse Unit Manager for further information"

Table S1. Definitions of all time periods captured in the study.

Key time periods are highlighted in yellow. ED, emergency department; EVT, endovascular thrombectomy

Process/Task/Time period (Example tasks which may occur during this period)	**Start definition**	**End definition**
Team journey = Total time team spent on the code	Time Code Stroke pager is sent	The recording is stopped by the team when physically leaving the ED
Pre-notification duration	Time Code Stroke pager is sent	Patient arrives in the ED
Team response/travel time	Time Code Stroke pager is sent	Team arrives where the patient is
Preparation time for team (accessing previous history)	Team arrives where the patient is	Patient arrives in the ED
Arrival to assessment time (see components below)	Patient arrives in the ED	Team starts assessing/talking to patient
→ Time before team starts speaking to paramedics for handover	Patient arrives in the ED	Paramedics start talking to stroke team
→ Handover time	Paramedics starts talking to stroke team	Team starts assessing/talking to patient
Assessment duration	Team starts assessing/talking to patient	Stroke team makes decision to move to CT OR Stand down Code
Cannulation time	Team starts to attempt the cannula	Cannula is ready to use

Transport time to CT	Stroke team makes decision to move to CT	Patient is physically on the CT table
Door to CT time	Patient arrives in the ED	Patient is physically on the CT table
Time taken to complete all scans (see components below)	Patient is physically on the CT table	All necessary scans are complete
→ Time to prepare for scout	Patient is physically on the CT table	First scout image is taken
→ Duration of non-contrast scan	First scout image is taken	All CT brain images are acquired
→ Time to prepare for CT perfusion scan	All CT brain images are acquired	First perfusion image is taken
→ Duration of CT perfusion scan	First CT perfusion image is taken	All CT perfusion images are acquired
→ Time it takes for automated software to send perfusion scans via email	All CT perfusion images are acquired	Email is received by one of the team
→ Time to prepare for CT angiogram scan	All CT perfusion images are acquired	First CT angiogram image is taken
→ Duration of CT angiogram scan	First CT angiogram image is taken	All CT angiogram images are acquired
Return transport time from CT	All necessary scans are complete	Time the patient arrives back in the ED cubicle
Time to make a decision after scans acquired (see components below)	All necessary scans are complete	Decision is made about treatment (thrombolysis, clot retrieval or conservative management)

→ Time taken to get additional history from patient or family, or examine the patient again	Team starts talking to a family member or goes back to talk/examine the patient	The conversation/examination is complete
→ Time before team calls the neurology consultant after scan (can occur before scans are finished)	All necessary scans are complete	Team starts speaking to the consultant
→ Time it takes consultant to make decision	Team starts speaking to the consultant	Decision is made about treatment (thrombolysis, clot retrieval or conservative management)
Time to enact the decision (see components below)	Decision is made about treatment (thrombolysis, clot retrieval or conservative management)	Stand down Code OR Thrombolytic agent bolus dose is given OR Patient is out the door for transfer to other hospital
→ Time between treatment decision and discussion with patient	Decision is made about treatment (thrombolysis or clot retrieval)	Team starts talking to patient about the treatment (thrombolysis/clot retrieval)
→ Time taken to obtain consent from the patient for thrombolysis/clot retrieval	Team starts talking to patient about the treatment (thrombolysis/clot retrieval)	Patient consents to the treatment (verbally)
→ Response time to opening thrombolysis	Patient consents to the treatment (verbally)	Team opens the box containing the thrombolytic agent
→ Time taken to draw up thrombolytic agent	Team opens the box containing the thrombolytic agent	Team finishes preparing the drug and it is ready in the syringe
→ Time taken to prepare to give the thrombolytic agent	Team finishes preparing the drug and it is ready in the syringe	Thrombolytic agent is given

→ Time delay between the bolus dose and connecting the infusion (alteplase)	Thrombolytic agent bolus dose is given	Infusion is connected to the patient
→ Time spent on treating blood pressure	Team identifies blood pressure is an issue and calls for treatment	Team decides blood pressure is at safe level to administer thrombolysis
→ Time delay between blood pressure under control and giving the thrombolytic agent bolus dose	Team decides blood pressure is at safe level to start thrombolysis	Thrombolytic agent bolus dose is given
→ Time delay to call the clot retrieval hospital (comprehensive stroke centre)	Decision is made about treatment (clot retrieval)	Team starts talking to the consultant at the clot retrieval site
→ Duration of the (first) clot retrieval phone call	Team starts talking to the consultant at the clot retrieval site	Team ends phone call with the clot retrieval team
→ Time it takes the consultant at clot retrieval centre accepts patient transfer	Team ends phone call with the clot retrieval team	Clot retrieval consultant gives verbal approval for transfer over phone
→ Time it took overall to get EVT centre to accept	Decision is made about treatment (clot retrieval)	Clot retrieval consultant gives verbal approval for transfer over phone
→ Delay between giving the thrombolytic agent bolus and patient is out the door	Thrombolytic agent bolus dose is given	Patient is out the door for transfer to other hospital
→ Time it takes to get patient out the door once EVT centre has accepted	Clot retrieval consultant gives verbal approval for transfer over phone	Patient is out the door for transfer to other hospital

→ Time between EVT centre accepting and the ambulance is called	Clot retrieval consultant gives verbal approval for transfer over phone	Someone is seen/heard calling for an ambulance
→ Duration of ambulance call	Someone is seen/heard calling for an ambulance	Ambulance phone call ends
→ Ambulance response time	Ambulance phone call ends	Paramedics physically arrive next to patient
→ Preparation time for crew to get patient into ambulance	Paramedics physically arrive next to patient	Patient is out the door for transfer
Time taken to consent for a trial	Team starts talking to patient about the trial	Patient consents to the trial (verbally or signed)
Administrative work (handover to ED or other teams, documentation/charting, discussions with patient/family)	Stand down Code OR Thrombolytic agent bolus dose is given OR Patient is out the door for transfer to other hospital	The recording is stopped by the team when physically leaving the ED
Door-to-needle time (DNT) Door-in-door-out time (DIDO)	Patient arrives in the ED Patient arrives in the ED	Thrombolytic agent bolus dose is given Patient is out the door for transfer to other hospital
Door-to-decision time	Patient arrives in the ED	Decision is made about treatment (thrombolysis, clot retrieval or conservative management)

Table S2. Independent variables included in the data collection tool and examined in the regression analyses.

ED, emergency department; HMO, hospital medical officer; EVT, endovascular thrombectomy; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

Patient-related factors	Non-modifiable	Age Sex Non-English speaking background Pre-morbid mRS Stroke severity (NIHSS) Weekday, weekend, public holiday Time of day of arrival
	Medical	Sedation required to perform CT Patient requiring intubation Blood pressure requiring treatment prior to thrombolysis Further history or examination required from patient or family If patient's family was immediately contactable
Process-related factors	Notification	Pre-notification of Code before arrival Code activated by ED, paramedics or inpatient
	Imaging	If patient went to CT If patient underwent full multi-modal CT imaging protocol Radiographer present when patient arrived at CT Number of radiographers present during CT imaging CT scanner occupied when patient arrived at CT
	Staffing	Total number of stroke team members present Acute stroke nurse presence Neurology HMO presence Research coordinator presence Neurology consultant presence
	Intra-department movement	If patient was offloaded into ED cubicle prior to CT If patient returned to ED on ambulance stretcher or ED bed

	IV access	Patient cannulated prior to arrival in ED Number of IV cannulation attempts Portable ultrasound required for cannulation
	Decision-making	Neurology consultant sub-specialty field (stroke or non-stroke) If neurology consultant was contacted to make decision If Code was stood down (no treatment given)
	Thrombolysis	If thrombolysis was administered Thrombolytic agent used (alteplase/tenecteplase) Person being consented for treatment (Patient/family/emergency)
	EVT centre	If patient was transferred for EVT Number of calls to EVT consultant Delay in image transfer to EVT centre
	Transport	If outbound ambulance crew is the same as inbound Number of calls to organise transport
	Clinical trials	Patient enrolment in clinical trial Person being consented for clinical trial (Patient/family/emergency)

Table S3. Regression models

1. Pre-notification duration

Variable	Estimate	Std. Error	t value	p value	
(Intercept)	4.29355	3.29053	1.305	0.1961	
NIHSS score	-0.05043	0.24262	-0.208	0.8359	
Pre-hospital IV cannulation (true)	4.68093	2.54996	1.836	0.0705	
Sex (male)	4.92112	2.58374	1.905	0.0608	
mRS score [linear]	-0.78882	3.12899	-0.252	0.8017	
mRS score [quadratic]	-2.11813	3.85896	-0.549	0.5848	
mRS score [cubic]	-2.63822	4.51699	-0.584	0.561	
Time of day (overnight)	12.31886	6.09359	2.022	0.0469	*
Time of day (working hours)	0.25985	3.07013	0.085	0.9328	

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05
Residual standard error: 10.78 on 73 degrees of freedom
(18 observations deleted due to missingness)
Multiple R-squared: 0.1719, Adjusted R-squared: 0.08113
F-statistic: 1.894 on 8 and 73 DF, p-value: 0.07384

In this model, overnight Codes were associated with a longer pre-notification duration (+12.3 minutes).

2. Team response time

Variable	Estimate	Std. Error	t value	p value	
(Intercept)	10.267	2.167	4.737	8.98E-06	***
Time of day - overnight	23.625	4.466	5.29	9.99E-07	***
Time of day - working hours	1.86	2.339	0.795	0.428894	
Code initiated by ED	-7.145	2.041	-3.5	0.000755	***
Code initiated as inpatient	-19.201	9.129	-2.103	0.03851	*
Day type - Weekend	7.074	2.539	2.786	0.006635	**
Day type - Public Holiday	10.928	5.241	2.085	0.040181	*

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05
Residual standard error: 8.761 on 82 degrees of freedom
(11 observations deleted due to missingness)
Multiple R-squared: 0.381, Adjusted R-squared: 0.3358
F-statistic: 8.414 on 6 and 82 DF, p-value: 4.066e-07

In this model, the team responded slower (+23.6 minutes) on overnight Codes compared to evenings, as well as on weekends (+7.1 minutes) and public holidays (+10.9 minutes) compared to weekdays. The team responded faster (-7.1 minutes) if the Code was initiated by ED rather than pre-notification by paramedics. Note, in the study cohort, there was only one inpatient Code, interpretation of this estimate is reserved.

3. Assessment duration

Variable	Estimate	Std. Error	t value	p value	
(Intercept)	4.27489	1.00427	4.257	5.93E-05	***
NIHSS score	-0.31318	0.07646	-4.096	0.000105	***
Time of day - Overnight	-1.63632	2.00015	-0.818	0.415892	
Time of day - Working hours	2.54264	1.00247	2.536	0.013281	*
Neurology HMO present	1.96034	0.91153	2.151	0.03473	*
Total number Stroke team members	-0.76594	0.42101	-1.819	0.072856	

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05
Residual standard error: 3.104 on 75 degrees of freedom
(19 observations deleted due to missingness)
Multiple R-squared: 0.2492, Adjusted R-squared: 0.1992
F-statistic: 4.979 on 5 and 75 DF, p-value: 0.0005436

This model estimates that a higher NIHSS score (more severe stroke) shortened time spent on patient assessment on arrival by 0.3 minutes for every point on the NIHSS score. Conversely, assessment duration was longer during working hours (+2.5 minutes) compared to evenings, and longer (+2.0 minutes) if a neurology HMO was present during the Code.

4. **Door-to-CT time**

Variable	Estimate	Std. Error	t value	p value	
(Intercept)	5.5915	16.5984	0.337	0.737977	
Patient offloaded to cubicle - True	35.0311	8.264	4.239	0.000129	***
Total number radiographers present	2.9054	3.9399	0.737	0.465166	
Code prenotification - True	-21.954	4.7823	-4.591	0.0000432	***
mRS score [linear]	-7.2558	6.1186	-1.186	0.242679	
mRS score [quadratic]	-3.339	6.6618	-0.501	0.618966	
mRS score [cubic]	-4.3862	7.7681	-0.565	0.575472	
Age	0.3644	0.1918	1.899	0.064736	
NIHSS score	-0.5816	0.3946	-1.474	0.148338	
Total number Stroke team members	-2.697	2.0649	-1.306	0.198968	

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05
Residual standard error: 14.2 on 40 degrees of freedom
(50 observations deleted due to missingness)
Multiple R-squared: 0.6566, Adjusted R-squared: 0.5793
F-statistic: 8.496 on 9 and 40 DF, p-value: 5.816e-07

In this model, offloading a patient into a cubicle before transferring to the CT scanner was associated with longer door-to-CT by 35.0 minutes. Pre-notification of the patient's arrival

was associated with a shorter door-to-CT time (-22.0 minutes). There were 52 patients who proceeded to CT imaging, hence only 2 observations were missing in this model.

5. Door-to-Decision time

Variable	Estimate	Std. Error	t value	p value	
(Intercept)	48.4805	4.0143	12.077	2.14E-12	***
Neurologist sub-specialty - non-stroke	-5.3068	4.6309	-1.146	0.261863	
Day type - Weekend	-0.2416	5.7817	-0.042	0.966975	
Day type - Public holiday	53.5842	12.6576	4.233	0.000238	***
NIHSS score	-0.7561	0.3577	-2.114	0.043884	*
Pre-hospital IV cannulation - True	-14.7702	4.4519	-3.318	0.002601	**
Non-English speaking background - True	33.7146	13.5151	2.495	0.019027	*

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05
Residual standard error: 11.71 on 27 degrees of freedom
(66 observations deleted due to missingness)
Multiple R-squared: 0.647, Adjusted R-squared: 0.5685
F-statistic: 8.247 on 6 and 27 DF, p-value: 3.986e-05

This model found that longer door-to-decision time was associated with public holidays (+53.6 minutes) compared to weekdays, and non-English speaking patients compared to native English speakers (+33.7 minutes). Conversely, a more severe stroke by NIHSS score reduced the door-to-decision time by 0.8 minutes for every 1 point on the NIHSS score. Pre-hospital cannulation was associated with faster (-14.8 minutes) door-to-decision time.

Many observations were dropped due to missing data for neurologist sub-specialty. However, the Akaike information criterion was lowest for this model compared to other models excluding this variable.

6. Administrative work

Variable	Estimate	Std. Error	t value	p value	
(Intercept)	15.9423	9.4878	1.68	0.10444	
Neurologist sub-specialty - non-stroke	-4.0278	6.2244	-0.647	0.52303	
NIHSS score	0.7927	0.6358	1.247	0.22318	
Neurology HMO present	-24.901	6.8838	-3.617	0.00121	**
Time of day - Overnight	42.3263	11.8296	3.578	0.00134	**
Time of day - Working hours	15.3625	9.4063	1.633	0.11403	
Non-English speaking background - True	25.5312	19.7798	1.291	0.20773	
Research coordinator present	16.1996	7.5575	2.144	0.04124	*
Enrolment in trial - True	-13.618	7.9495	-1.713	0.09816	

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05
Residual standard error: 14.82 on 27 degrees of freedom
(64 observations deleted due to missingness)
Multiple R-squared: 0.5446, Adjusted R-squared: 0.4097
F-statistic: 4.036 on 8 and 27 DF, p-value: 0.002909

Administrative work is predicted to take the longest time on overnight Codes (+42.3 minutes) compared to evenings. The presence of a research coordinator was also associated with longer administrative work time (+16.2 minutes). The presence of a neurology HMO was associated with a shorter administrative work time (-24.9 minutes).

Again, many observations were dropped due to missing data for neurologist sub-specialty. However, this model was also selected using the lowest Akaike information criterion.

7. Team journey

Variable	Estimate	Std. Error	t value	p value	
(Intercept)	53.9571	10.9062	4.947	0.00000458	***
Went for CT imaging - True	32.7998	5.3262	6.158	3.48E-08	***
NIHSS score	-0.3581	0.5365	-0.668	0.5065	
Code stood down - True	-23.9189	8.335	-2.87	0.00535	**
mRS score [linear]	3.2745	5.0992	0.642	0.52276	
mRS score [quadratic]	-7.1235	6.4875	-1.098	0.27575	
mRS score [cubic]	-5.5954	7.958	-0.703	0.48419	
Code prenotification - True	15.4062	4.7095	3.271	0.00163	**
Pre-hospital IV cannulation - True	-11.1479	5.1982	-2.145	0.03527	*
Acute stroke nurse present	6.1515	4.2085	1.462	0.14806	
Neurology HMO present	-8.047	4.8569	-1.657	0.10179	

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05
Residual standard error: 18.7 on 74 degrees of freedom
(15 observations deleted due to missingness)
Multiple R-squared: 0.5364, Adjusted R-squared: 0.4738
F-statistic: 8.563 on 10 and 74 DF, p-value: 4.077e-09

The Team journey is defined as the total time the team spent in ED on the Code. In this model, Codes where the patient was brought to CT imaging was associated with a longer Team Journey (+32.8 minutes). The team is also predicted to spend a longer duration in ED (+15.4 minutes) when the Code is pre-notified. There was an association of shorter team journey when patients had pre-hospital IV cannulation (-11.1 minutes).

Codes stood down were associated with shorter team journeys (-23.9 minutes). A proportion of these would not have proceeded to CT imaging, however the variance inflation factors in this model were <2 and did not indicate multi-collinearity in this model.

Table S4. Results of key time periods as represented in eFigure 1.

Time metric	n	Median (mins)	Inter-quartile range (mins)	Minimum (mins)	Maximum (mins)
Pre-notification duration	87	7.0	0 - 14.3	0	56.1
Team response time	89	7.7	5.0 - 16.7	0	52.9
Arrival to assessment time	77	3.0	0.6 - 12.6	0	88.8
Assessment duration	84	3.5	1.9 - 6.0	0	21.3
Transport time to CT	51	3.8	2.9 - 4.5	1.8	11.6
CT completion time	57	12.7	11.0 - 15.6	3.0	27.0
Return transport time from CT	50	4.1	3.6 - 5.0	2.9	9.6
Decision to treatment implementation	12	8.1	6.1 - 10.9	3.2	17.8
Thrombolysis drawing up time	8	2.9	2.0 - 4.9	1	7.3
Administrative work	87	21.0	9.8 - 31.4	0.6	68.1
Team journey	89	54.2	39.1 - 74.7	16.6	126.8

CHAPTER 3: DOOR-IN-DOOR-OUT TIME FOR ELVO AT PRIMARY STROKE CENTRE

3.1 Deconstruction of Interhospital Transfer Workflow in Large Vessel Occlusion: Real-World Data in the Thrombectomy Era.

Ng FC, Low E, Andrew E, Smith K, Campbell BCV, Hand PJ, Crompton DE, Wijeratne T, Dewey HM, Choi PM.

Stroke. 2017 Jul;48(7):1976-1979

Journal Impact Factor 6.239 in 2017, 8.3 in 2022, 73 citations , FWCI of 4.41

Co-authorship statement:

F Ng completed this work during his first year neurology training as first author. E Low, E Andrew and K Smith were collaborators at Ambulance Victoria providing data. B Campbell and P Hand were collaborators from the Royal Melbourne Hospital providing data. D Crompton and T Wijeratne were collaborators from the Northern Hospital and Western Hospital respectively, also providing data. HM Dewey was involved with reviewing and editing.

As senior author, I was involved in the conceptualisation, methodology, supervision, extensive review and editing of the draft manuscript.

doi: 10.1161/STROKEAHA.117.017235

3.2 Door-in-Door-Out Time of 60 Minutes for Stroke With Emergent Large Vessel Occlusion at a Primary Stroke Center.

Choi PMC, Tsoi AH, Pope AL, Leung S, Frost T, Loh PS, Chandra RV, Ma H, Parsons M, Mitchell P, Dewey HM.

Stroke. 2019 Oct;50(10):2829-2834

Journal Impact Factor 7.19 in 2019, 8.3 in 2022, 25 citations, FWCI of 1.3

Co-authorship statement:

As first author, I was involved in the conceptualisation, methodology, supervision, extensive review and editing, and wrote the first draft of the manuscript. S Leung assisted with data collection. A Tsoi was a resident and involved with data collection and presented the findings of this study at a departmental meeting. A Pope performed advanced statistical analysis. T Frost and P Loh are BHH stroke team personnel and were involved with reviewing the manuscript. R Chandra, H Ma, M Parsons and P Mitchell were collaborators from other stroke centres and involved with reviewing the manuscript. H Dewey was involved with review and editing as head of department.

doi: 10.1161/STROKEAHA.119.025838

3.3. Door-in-door-out times for patients with large vessel occlusion ischaemic stroke being transferred for endovascular thrombectomy: a Victorian state-wide study

Wong JZW, Dewey HM, Campbell BCV, Mitchell PJ, Parsons M, Phan T, Chandra RV, Ma H, Warwick A, Brooks M, Thijs V, Low E, Wijeratne T, Jones S, Clissold B, Ngun MY, Crompton D, Sriamareswaran RK, Rupasinghe J, Smith K, Bladin C, Choi PMC.

BMJ Neurol Open. 2023 Jan 17;5(1):e000376

Journal impact factor 2.9 in 2022

Co-authorship statement:

J Wong completed this work during his two years at Box Hill Hospital, first as a fellow and later as first year advanced trainee. All other authors apart from H Dewey and myself were collaborators from other health services. They provided data as well as involvement with reviewing the manuscript. H Dewey was involved with review and editing.

As senior author, I was involved in the conceptualisation, methodology, supervision, extensive review and editing of the draft manuscript.

BMJ Neurology Open

Door-in-door-out times for patients with large vessel occlusion ischaemic stroke being transferred for endovascular thrombectomy: a Victorian state-wide study

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ABSTRACT

Background Time to reperfusion is an important predictor of outcome in ischaemic stroke from large vessel occlusion (LVO). For patients requiring endovascular thrombectomy (EVT), the transfer times from peripheral hospitals in metropolitan and regional Victoria, Australia to comprehensive stroke centres (CSCs) have not been studied.

Aims To determine transfer and journey times for patients with LVO stroke being transferred for consideration of EVT.

Methods All patients transferred for consideration of EVT to three Victorian CSCs from January 2017 to December 2018 were included. Travel times were obtained from records matched to Ambulance Victoria and the referring centre via Victorian Stroke Telemedicine or hospital medical records. Metrics of interest included door-in-door-out time (DIDO), inbound journey time and outbound journey time.

Results Data for 455 transferred patients were obtained, of which 395 (86.8%) underwent EVT. The median DIDO was 107 min (IQR 84–145) for metropolitan sites and 132 min (IQR 108–167) for regional sites. At metropolitan referring hospitals, faster DIDO was associated with use of the same ambulance crew to transport between hospitals (75 (63–90) vs 124 (99–156) min, p<0.001) and the administration of thrombolysis prior to transfer (101 (79–133) vs 115 (91–155) min, p<0.001). At regional centres, DIDO was consistently longer when patients were transported by air (160 (127–195) vs 116 (100–144) min, p<0.001). The overall door-to-door time by air was shorter than by road for sites located more than 250 km away from the CSC.

Conclusion Transfer times differ significantly for regional and metropolitan patients. A state-wide database to prospectively collect data on all interhospital transfers for EVT would be helpful for future study of optimal transport mode at regional sites and benchmarking of DIDO across the state.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Shorter transfer time between peripheral hospitals and comprehensive stroke centres has been associated with improved clinical outcomes in patients with large vessel occlusion stroke requiring endovascular thrombectomy.

WHAT THIS STUDY ADDS

⇒ The median door-in-door-out time in Victoria was 107 min for metropolitan sites and 132 min for regional sites. Air transfer may save overall transport time for sites located more than 250 km from the nearest comprehensive stroke centre.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study reveals the value of system-wide databases to capture interhospital patient transfer metrics. Such data will help with the planning of patient transfers by optimising the choice of transport mode and increasing the precision of patient arrival times.

INTRODUCTION

The effectiveness of endovascular thrombectomy (EVT) for large vessel occlusion (LVO) ischaemic stroke is time sensitive. Any delay in transfer would theoretically result in poorer outcomes as infarct size increases. This hypothesis is supported by data which demonstrate worsening functional outcomes with greater reperfusion delays, especially in patients for whom complete reperfusion was not achieved.[1–3]

In Australia, patients presenting with acute stroke are generally assessed at the nearest regional or metropolitan hospital. Most of

these are hospitals that do not have an on-site EVT service. Victorian Stroke Telemedicine (VST) was first established in 2013 and now provides 24/7 telehealth consultations for patients with suspected stroke. The service operates across 17 Victorian regional hospitals and provides access to a stroke physician.[4] If appropriate, patients are then transferred to a comprehensive stroke centre (CSC) after discussion between the CSC neurologist, neurointerventionalist and the VST clinician. Victoria has two designated state-wide CSCs and one additional CSC also receives external transfers for EVT. Two additional metropolitan centres provide EVT for patients presenting to their service but do not routinely accept external transfers for EVT. There are no privately funded CSCs in Victoria.

The transfer time from peripheral hospitals without on-site EVT capability to CSCs has not been studied in Victoria. We sought to examine the patient journey for those with LVO stroke, with particular interest in door-in-door-out time (DIDO) and interhospital transfer times from both metropolitan and regional hospitals across the state of Victoria.

METHODS

Patients who were transferred from a public hospital in Victoria, Australia to a CSC for consideration of EVT between January 2017 and December 2018 were included. All sites are guided by the state-wide service protocol for transfers of patients requiring EVT.[5] The imaging of all transferred patients is reviewed by the neurointerventionalist at the CSC. The final decision to transfer is agreed between the referring and CSC clinicians. Patients transferred between hospitals but who did not ultimately undergo the procedure were also included in the study.

The study was designed to focus on the transfer processes between public hospitals and high-volume EVT centres. The EVT centres included in this study were The Royal Melbourne Hospital, Monash Medical Centre and the Austin Hospital. The following regional sites were included (figure 1): Mildura, Swan Hill, Horsham, Echuca, Bendigo, Hamilton, Warrnambool, Ballarat, Werribee, Shepparton, Wangaratta, Albury, Warragul, Traralgon, Wonthaggi, Sale and Bairnsdale. Metropolitan sites included were Box Hill Hospital, Maroondah Hospital, University Hospital Geelong, Frankston Hospital, Sunshine Hospital, Footscray Hospital and the Northern Hospital.

Data linkage

All patients transferred from an external hospital with ischaemic stroke were identified from the departmental stroke databases at the CSCs. These records were reviewed to confirm the presence of LVO and intention to transfer for EVT. These data were then matched with records from Ambulance Victoria and metropolitan hospitals. VST provided data from their consultation database which is separate from the medical record of the regional hospitals. To maintain patient confidentiality, identifying data were only shared between hospitals involved in the patient's care to match cases for this study. Patients were then assigned study codes for later identification and analysis. The study was registered at the respective ethics and research offices as a quality improvement project and patient consent was not required.

Definitions

LVO was defined as occlusion of the intracranial or extracranial internal carotid artery, M1 or M2 middle

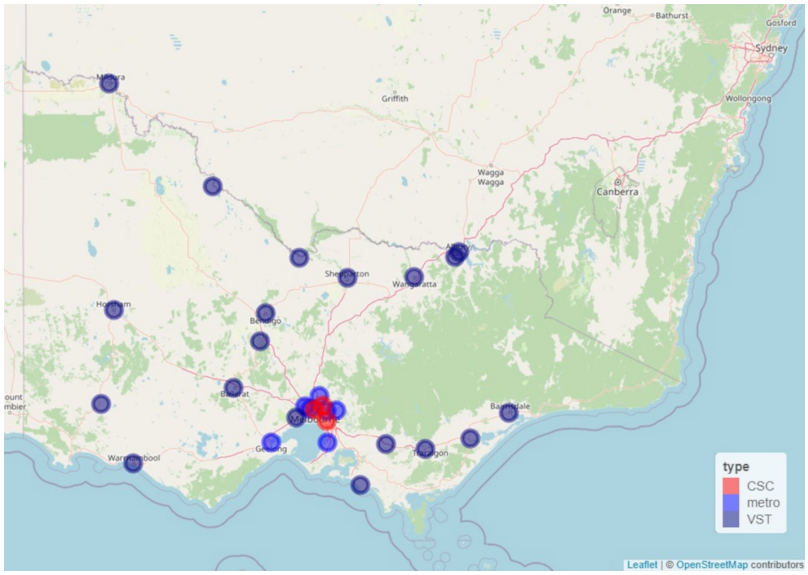

Figure 1 Map showing geographic distribution of all stroke centres included in this study. CSC, comprehensive stroke centre; metro, metropolitan sites; VST, Victorian Stroke Telemedicine sites.

cerebral artery or basilar occlusion. 'Inbound' refers to events or transport occurring prior to arrival at the first hospital. 'Outbound' refers to events or transport occurring between the referring hospital en route to the CSC. DIDO was calculated as the time between arrival at the first hospital and departure from that hospital as obtained from ambulance records. Arrival and departure times documented by Ambulance Victoria were chosen as they had fewer missing data and were more reflective of the patient's true arrival and departure times at the emergency department. In cases where these data were missing, the documented triage time obtained from the medical record was used. Door-to-door time (D2D) is defined as the time between patient arrival at the first hospital and patient arrival at the CSC. This represents the sum of the DIDO and travel time between referring hospital and CSC. The CSC arrival time was also obtained from Ambulance Victoria records unless missing from the data.

'Air transfer' refers to fixed-wing or helicopter transfers, but this distinction was not available retrospectively in individual case files. Any outbound transfer involving two or more crews was considered a 'multi-leg journey'. This included air transfers where an additional road crew was required to transport the patient from the referring hospital to the aircraft, and/or aircraft to the CSC.

Statistical analysis

Statistical analysis was performed in RStudio V.4.0.5. Comparisons between groups were assessed using χ^2 or Kruskal-Wallis tests as appropriate. Multivariable analysis with variables of interest was performed using linear regression models with controls for patient age, sex, premorbid function, time of day and time of week. Missing data were excluded from analysis using a pairwise deletion method. Statistically significant variables were further selected using a stepwise forward selection method based on the Akaike information criterion.

RESULTS

Records for 491 patients were found during the 2-year period, with 455 included in the study (figure 2). Records were complete for only 38% of patients. Incomplete records were either missing data from the inbound journey, outbound journey, primary stroke centre (PSC) metrics or a combination of these. Thirteen patients from private hospitals and nine patients from other public hospitals were identified in the study. These transfers were not included in the scope of the study. All of these records were also missing part or all ambulance data.

Three hundred and ninety-five patients (89.8%) underwent EVT after transfer. There was one posterior cerebral artery occlusion, two proximal M3 occlusions and one vertebral artery occlusion included in the final cohort. Baseline demographics of the patients stratified by metropolitan and regional referral locations are shown in table 1. There were no significant differences in patient

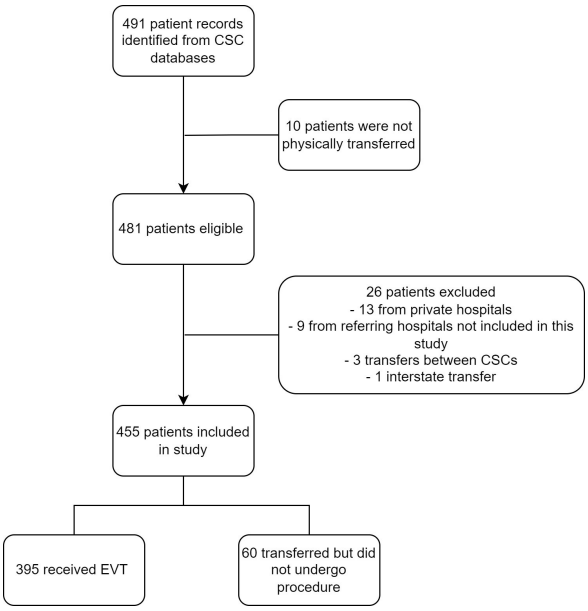

Figure 2 Flow chart summarising the inclusion and exclusion of patients for the study. CSC, comprehensive stroke centre; EVT, endovascular thrombectomy.

baseline demographics between metropolitan and regional sites. A higher proportion of patients in regional centres required transfer by air or had multileg outbound journeys en route to the CSC. The outbound journey was much longer for patients coming from regional centres as expected for the increased distance from CSCs. Inbound metrics for patients arriving by ambulance to the first hospital are shown in table 2.

DIDO and interhospital transport times for individual sites are listed in online supplemental tables 1 and 2. Median DIDO was longer at regional sites than metropolitan sites (132 (108–167) vs 107 (84–145) min, p<0.001). DIDO for regional patients transported by air was longer than DIDO for patients transported by road crew only (160 (127–195) vs 116 (100–144) min, p<0.001). For regional patients, multivariable linear regression showed an association of shorter DIDO with worse stroke severity by the National Institutes of Health Stroke Scale score, whereas longer DIDO was associated with air transfers and less urgent ambulance dispatch (code ≥2 'not lights and sirens') (R^2=0.347, p<0.001).

At metropolitan sites, univariable analysis showed an association between shorter DIDO and the use of the same transporting crew for the outbound transfer (median DIDO 75 vs 123.5 min, p<0.001). However, this association was not seen at regional centres (figure 3). Use of the same crew occurred in 53/189 (28%) of cases at metropolitan PSCs and 20/101 (19.8%) of cases at regional centres. In multivariable analysis of metropolitan transfers, use of the same outbound crew (75 (63–90) vs 124 (99–156) min, p<0.001) and patients receiving thrombolysis (101 (79–133) vs 115 (91–155) min, p<0.001)

Table 1 Comparison of demographic data and key transfer times within the study cohort

	Regional (N=176)	Metropolitan (N=279)	Overall (N=455)	P value
Sex, n (%)				0.519
Female	72 (40.9)	124 (44.4)	196 (43.1)	
Male	104 (59.1)	155 (55.6)	259 (56.9)	
Age (years)				0.273
Median (Q1, Q3)	72.0 (64.0, 78.0)	73.0 (64.0, 81.0)	73.0 (64.0, 80.0)	
NIHSS score on first assessment				0.151
Median (Q1, Q3)	15.0 (9.00, 19.0)	16.0 (10.0, 20.0)	15.0 (10.0, 20.0)	
Missing, n (%)	16 (9.1)	31 (11.1)	47 (10.3)	
Premorbid mRS, n (%)				0.071
0	131 (74.4)	180 (64.5)	311 (68.4)	
1	17 (9.7)	44 (15.8)	61 (13.4)	
2	8 (4.5)	9 (3.2)	17 (3.7)	
≥3	4 (2.3)	11 (4.0)	15 (3.2)	
Missing	16 (9.1)	35 (12.5)	51 (11.2)	
Arrival mode, n (%)				0.009
Ambulance	164 (93.2)	253 (90.7)	417 (91.6)	
Inpatient	3 (1.7)	20 (7.2)	23 (5.1)	
Self-present	9 (5.1)	6 (2.2)	15 (3.3)	
Thrombolysis, n (%)				0.597
Yes	100 (56.8)	142 (50.9)	242 (53.2)	
No	76 (43.2)	122 (43.7)	198 (43.5)	
Missing	0	15 (5.4)	15 (3.3)	
Transport by air, n (%)				<0.001
Yes	83 (47.2)	3 (1.1)	86 (18.9)	
No	76 (43.2)	271 (97.1)	347 (76.3)	
Missing	17 (9.7)	5 (1.8)	22 (4.8)	
Multileg outbound journey, n (%)				<0.001
Yes	82 (46.6)	2 (0.7)	84 (18.4)	
No	71 (40.3)	256 (91.8)	327 (71.9)	
Missing	23 (13.1)	21 (7.5)	44 (9.7)	
DIDO (min)				<0.001
Median (Q1, Q3)	132 (108, 167)	107 (84, 145)	114 (91.0, 150)	
Missing, n (%)	85 (48.3)	38 (13.6)	123 (27)	
Outbound journey time (min)				<0.001
Median (Q1, Q3)	90.0 (73.0, 105)	26.0 (20.0, 36.5)	33.5 (23.0, 75.0)	
Missing, n (%)	69 (39.2)	56 (20.1)	125 (27.5)	

P values shown for Kruskal-Wallis test. A multileg outbound journey refers to any transfer involving two or more ambulance crews between the referring hospital and comprehensive stroke centre, including any transfers to and from an aircraft.
DIDO, door-in-door-out time; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

were associated with shorter DIDO (multivariable linear regression R^2=0.13, p=0.02). We did not find any association between DIDO and patient age, sex, severity of stroke, premorbid function, weekday versus weekend, working hours versus after hours or PSC case volume in univariable or multivariable analyses across the overall or metropolitan cohorts. Full detail of the analyses can be found in online supplemental tables 3 and 4, and online supplemental figure 1.

Data were available for eight sites which used eitherroad transport alone or combined air and road transport (Geelong, Ballarat, Bendigo, Wangaratta, Shepparton, Hamilton, Warrnambool and Bairnsdale). Total DIDO and outbound travel times for these sites

Table 2 Comparison of inbound metrics for ambulance-transported patients at regional and metropolitan centres

	Regional (N=176)	Metropolitan (N=279)	Overall (N=455)	P value
Symptom onset to call (min)				0.369
Median (Q1, Q3)	29.0 (9.00, 82.5)	35.5 (11.0, 110)	31.0 (9.00, 101)	
Missing, n (%)	76 (43.2)	179 (64.2)	255 (56.0)	
Dispatch response time (min)				0.889
Median (Q1, Q3)	10.0 (8.00, 15.0)	10.0 (8.00, 15.0)	10.0 (8.00, 15.0)	
Missing, n (%)	53 (30.1)	75 (26.9)	128 (28.1)	
Extrication time (min)				0.037
Median (Q1, Q3)	21.0 (16.0, 25.0)	18.0 (13.0, 26.0)	19.0 (14.0, 25.8)	
Missing, n (%)	55 (31.3)	78 (28.0)	133 (29.2)	
Inbound travel time (min)				0.077
Median (Q1, Q3)	16.0 (8.00, 34.0)	19.0 (13.8, 26.0)	19.0 (12.0, 29.0)	
Missing, n (%)	55 (31.3)	79 (28.3)	134 (29.5)	

P values shown for Kruskal-Wallis test.

are shown in figure 4. DIDO was longer at all these sites when patients were transferred by air compared with road transport. However, overall D2D was numerically shorter when transferred by air if road transport distance exceeded 250 km (Hamilton, Warrnambool and Bairnsdale) or if the median calculated D2D by road transport exceeded 250 min (Shepparton, Hamilton, Warrnambool and Bairnsdale) based on visual comparison in figure 4.

DISCUSSION

This is the first report of transfer time metrics at a state level in Australia for patients with LVO transferred from a peripheral referring hospital to a CSC. Metrics such as DIDO are an ideal target for quality improvement and have been shown to correlate with stroke outcomes.[3]

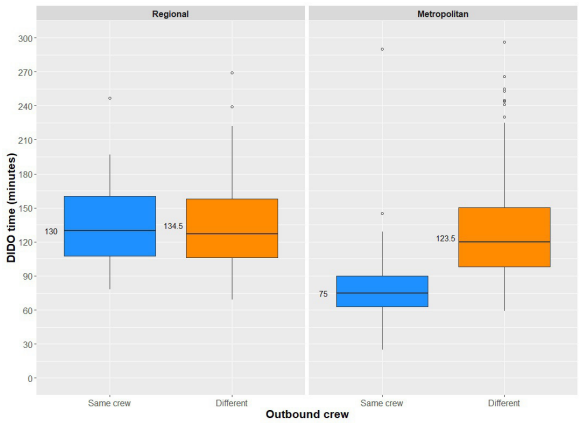

Figure 3 Boxplots comparing DIDO and use of the same outbound crew, stratified by regional and metropolitan sites. The difference was found to be statistically significant at metropolitan sites in univariate and multivariate analyses. DIDO, door-in-door-out time.

These time metrics are important as they serve as objective measures of the overall performance of a complicated process currently involving multiple organisations.[6 7] In Victoria, air transport of patients may be organised by either Ambulance Victoria or Adult Retrieval Victoria depending on the clinical status of the patient. Regardless of the agency involved, the same pool of aircraft is used for all acute and non-acute transfers of patients within the state. In our cohort, up to four separate ambulance crews may be involved in air transfers between regional sites and CSCs.

The inbound time metrics suggest ambulance performance is similar in metropolitan and regional settings. Importantly, time from crew dispatch to arrival at the scene was similar (median 10 min). There was a small difference observed in extrication time at the pick-up address (median 21 vs 18 min), but this was not statistically significant once applying a Bonferroni correction for multiple comparisons and is probably of little clinical significance. Despite the similar response and arrival times for crews in regional compared with metropolitan areas, there continues to be a discrepancy in DIDO between metropolitan and regional hospitals. However, there is still scope for improvement in DIDO at metropolitan sites. In a cluster-randomised trial involving high-efficiency PSCs in non-urban areas of Catalonia, Spain,[8] the median DIDO was 78 min between 2018 and 2020, shorter than the best performing metropolitan site in this study (82 min).

In metropolitan centres, use of the same ambulance crew to transport the patient between PSC and CSC reduced DIDO, consistent with previous findings.[7] This is impractical to replicate in regional sites largely due to crew availability as the regional road ambulance crew would be out of service for a median of 180 min to cover the return journey between regional PSC and CSC. In fact, we did not find the use of the same

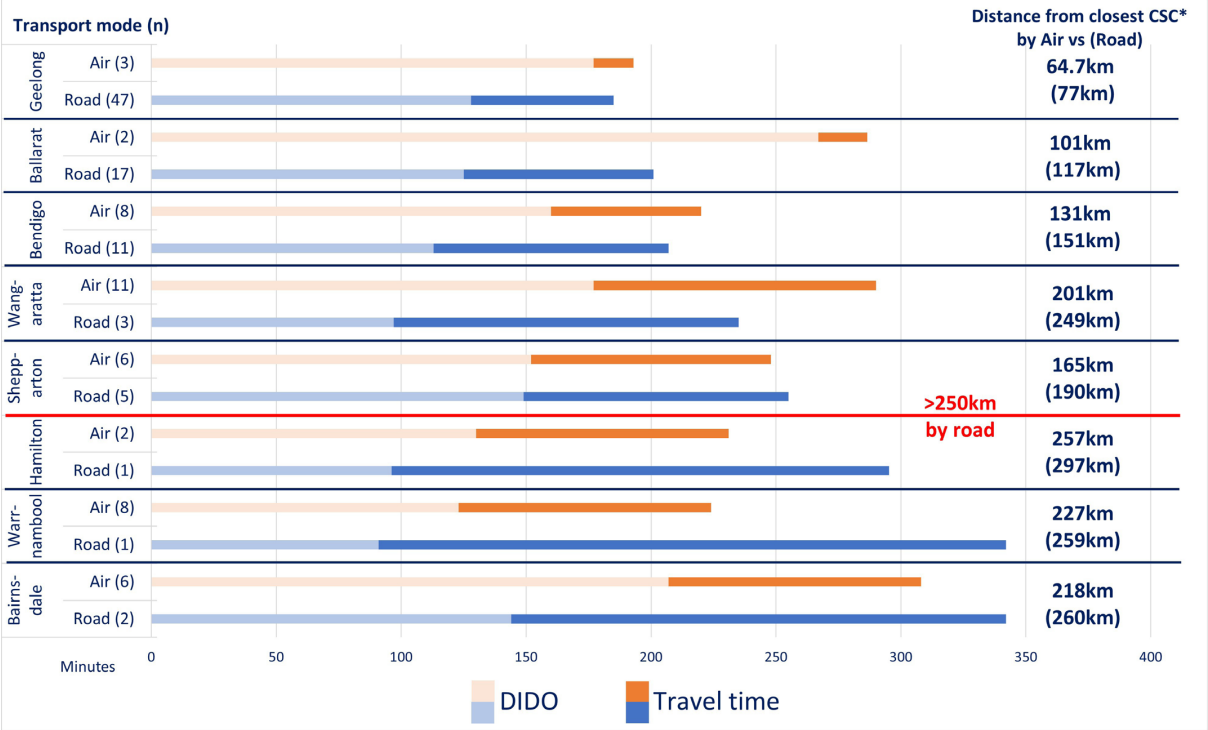

Figure 4 Graph comparing road and air transport at regional sites which used both modes of transport. Not all transfers occurred to the closest CSC for that site and these data were excluded from the graph. University Hospital Geelong is considered a metropolitan primary stroke centre within the Victorian system. It is the only metropolitan site which used air and road transport. CSC, comprehensive stroke centre; DIDO, door-in-door-out time.

ambulance road crew to be associated with shorter regional DIDO, possibly reflective of the additional time required to coordinate such a transfer. Regional patients receiving thrombolysis were not found to have longer DIDO, although patients with more severe stroke were associated with shorter DIDO. Also, ambulances dispatched as less urgent 'not lights and sirens' were associated with longer DIDO. This would indicate that other factors within local patient transfer protocols or logistic factors within the state ambulance service, that were not captured within this study, need to be further examined and improved. Although we did not adjust for multiple comparisons, the α levels of the reported statistically significant associations were <0.001.

DIDO was consistently longer when transporting patients by air, an observation seen elsewhere in Australia.[9] Our data suggest that for regional Victorian sites located more than 250 km by road from their closest PSC, the longer DIDO spent arranging for air transfer is offset by the saving in outbound travel time. Conversely, sites closer than 250 km should preference road-only transport to avoid prolonging DIDO due to logistical delays of air transfer. We suggest that distance, being a non-modifiable factor, could be used to guide the choice for mode of transport until sustained improvements in regional DIDO are able to change the equation.

Victoria is the smallest mainland Australian state and the difference between the shortest (Werribee) and longest (Mildura) distances between a regional site and a CSC is 450 km. Given the relatively few transfers from individual regional sites over the study period, our data from individual regional sites are imprecise for clinical or modelling purposes. However, these data can act as a guide for clinicians involved in the care of these patients. At state-wide referral sites, there can often be patients requiring EVT requiring transfer simultaneously. With such data, receiving hospitals can account for DIDO and travel time in preparing for patient arrival. The data can be portrayed in an easily accessible, interactive format as shown in this link (https://jowo92.shinyapps.io/DIDOmap/).

The main limitation of this study is the high proportion of missing data. This is despite our best efforts in matching patient identifiers across databases from different health services. Our experience of the current difficulties in identifying patients transferred for EVT from existing routine data and local hospital stroke databases strongly argues for the establishment of a prospective state-wide database with key variables of interest relating to LVO stroke transfers and outcomes. This should include the smaller EVT centres

and private hospitals that were omitted in this study as the uptake of EVT increases. Also, we were unable to assess if DIDO across Victoria has improved since 2019 and the authors acknowledge that more contemporary data may show different findings. Quality improvement initiatives at the PSC level have been shown to dramatically decrease DIDO.[10–12] At one metropolitan Melbourne PSC, DIDO has improved from 82 min from 2017 to 2018 in this study to 50 min in 2021.[10] The very resource intensive nature of modern stroke interventions should justify the effort and investments of establishing such a database. Monitoring of DIDO at a system level and benchmarking with other sites may assist with local quality improvement initiatives. A shift to an underlying 'Formula 1 pit stop' or 'grab and go' mentality needs to be instilled while addressing local process-related delays to achieve sustained improvement in DIDO across the state. Such a database could also be linked to the interactive map for up-to-date data of transfer times across the state.

In conclusion, regional sites in Victoria have longer DIDO than metropolitan hospitals. Investment in the development of a state-wide database for patients transferred for EVT will support improvements in overall treatment efficiency of patients with LVO stroke. Such data can further refine DIDO and travel time estimates, which can inform decisions on the optimal mode of transport to ultimately shorten the time to reperfusion.

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Contributors JZWW and PMCC conceived the study. JZWW, HMD, BCVC, PJM, MP, TP, RVC, HM, MB, VT, TW, BC, DC, JR, KS, CB and PMCC designed and planned the data collection and linkage methods. JZWW, BCVC, TP, HM, VT, EL, TW, SJ, BC, MYN, DC, RKS, JR and PMCC were responsible for ethics applications and governance at each site. JZWW, BCVC, TP, AW, EL, SJ, BC, MYN, RKS, KS and CB performed data collection from their respective organisations. JZWW finalised the linkage, and prepared and analysed the data. JZWW and PMCC drafted the manuscript. All authors contributed to editing of the manuscript and approved the final submission. PMCC is the guarantor of the overall study.

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Supplementary table 1. Complete data for individual metropolitan sites.

Metropolitan Sites	Box Hill (N=85)	Frankston (N=17)	Geelong (N=55)	Maroondah (N=1)	Northern (N=48)	Sunshine (N=64)	Western (N=9)	Overall (N=279)
Sex								
Female	40 (47.1%)	8 (47.1%)	26 (47.3%)	1 (100%)	20 (41.7%)	25 (39.1%)	4 (44.4%)	124 (44.4%)
Male	45 (52.9%)	9 (52.9%)	29 (52.7%)	0 (0%)	28 (58.3%)	39 (60.9%)	5 (55.6%)	155 (55.6%)
Age (years)								
Median [Q1, Q3]	74 [65, 82]	77 [72, 80]	71 [62.5, 77]	83 [83, 83]	70.5 [64.8, 81.3]	70 [64, 80]	68 [64, 80]	73 [64, 81]
NIHSS score on first assessment								
Median [Q1, Q3]	17 [11, 22]	16 [11, 19]	14 [70, 18]	NA	12 [9, 18]	17 [10, 20]	14 [11, 17]	15.5 [10, 20]
Missing	0 (0%)	2 (11.8%)	1 (1.8%)	1 (100%)	13 (27.1%)	11 (17.2%)	3 (33.3%)	31 (11.1%)
Pre-morbid mRS								
0	57 (67.1%)	13 (76.5%)	37 (67.3%)	0 (0%)	14 (29.2%)	51 (79.7%)	8 (88.9%)	180 (64.5%)
1	25 (29.4%)	1 (5.9%)	8 (14.5%)	1 (100%)	2 (4.2%)	6 (9.4%)	1 (11.1%)	44 (15.8%)
2	2 (2.4%)	0 (0%)	4 (7.3%)	0 (0%)	3 (6.3%)	0 (0%)	0 (0%)	9 (3.2%)
≥3	1 (1.2%)	1 (5.9%)	1 (1.8%)	0 (0%)	6 (12.5%)	2 (3.1%)	0 (0%)	11 (4%)
Missing	0 (0%)	2 (11.8%)	5 (9.1%)	0 (0%)	23 (47.9%)	5 (7.8%)	0 (0%)	35 (12.5%)
Inbound travel time (mins)								
Median [Q1, Q3]	19 [13.5, 24]	23.5 [19.5, 28.8]	20.5 [12, 28.8]	NA	16 [14, 25.8]	21.5 [13, 27]	22.5 [19.3, 25.8]	19 [14, 26]
Missing	18 (21.2%)	3 (17.6%)	21 (38.2%)	1 (100%)	18 (37.5%)	12 (18.8%)	7 (77.8%)	80 (28.7%)
Door to CT time (mins)								
Median [Q1, Q3]	10.5 [6, 16]	15 [6, 22.5]	22 [16, 32]	38 [38, 38]	17 [12.3, 25.8]	25 [21, 43]	40 [32.5, 62.5]	19 [11, 28]
Missing	3 (3.5%)	1 (5.9%)	2 (3.6%)	0 (0%)	10 (20.8%)	3 (4.7%)	2 (22.2%)	21 (7.5%)

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Metropolitan Sites (continued)	Box Hill (N=85)	Frankston (N=17)	Geelong (N=55)	Maroondah (N=1)	Northern (N=48)	Sunshine (N=64)	Western (N=9)	Overall (N=279)
Thrombolysis								
Yes	55 (64.7%)	7 (41.2%)	22 (40%)	0 (0%)	18 (37.5%)	37 (57.8%)	3 (33.3%)	142 (50.9%)
No	30 (35.3%)	9 (52.9%)	32 (58.2%)	0 (0%)	21 (43.8%)	25 (39.1%)	5 (55.6%)	122 (43.7%)
Missing	0 (0%)	1 (5.9%)	1 (1.8%)	1 (100%)	9 (18.8%)	2 (3.1%)	1 (11.1%)	15 (5.4%)
Door to Needle time (mins)								
Median [Q1, Q3]	50 [37, 59.5]	79 [55.5, 89]	75 [57, 107]	NA	57.5 [47.3, 85]	88 [73, 109]	85 [83, 94.5]	62 [50, 88]
Missing	30 (35.3%)	10 (58.8%)	33 (60%)	1 (100%)	30 (62.5%)	27 (42.2%)	6 (66.7%)	137 (49.1%)
Door in Door out time (mins)								
Median [Q1, Q3]	82 [65, 113]	146 [131, 187]	131 [100, 159]	107 [107, 107]	97 [83, 127]	117 [97, 148]	105 [105, 106]	107 [84, 145]
Missing	3 (3.5%)	3 (17.6%)	1 (1.8%)	0 (0%)	9 (18.8%)	16 (25%)	6 (66.7%)	38 (13.6%)
Multi-leg outbound journey, n (%)								
TRUE	0 (0%)	0 (0%)	1 (1.8%)	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	2 (0.7%)
FALSE	85 (100%)	17 (100%)	44 (80%)	1 (100%)	37 (77.1%)	63 (98.4%)	9 (100%)	256 (91.8%)
Unknown	0 (0%)	0 (0%)	10 (18.2%)	0 (0%)	11 (22.9%)	0 (0%)	0 (0%)	21 (7.5%)
Outbound transport involving air transfer, n (%)								
TRUE	0 (0%)	0 (0%)	3 (5.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.1%)
FALSE	85 (100%)	17 (100%)	47 (85.5%)	1 (100%)	48 (100%)	64 (100%)	9 (100%)	271 (97.1%)
Unknown	0 (0%)	0 (0%)	5 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (1.8%)
PSC to CSC travel time (mins)								
Median [Q1, Q3]	22 [19, 26]	32 [27, 36]	57 [51.5, 62]	33 [33, 33]	30 [27, 34]	22.5 [18.8, 27]	17 [16, 20]	26 [20, 35]
Missing	19 (22.4%)	4 (23.5%)	12 (21.8%)	0 (0%)	15 (31.3%)	8 (12.5%)	0 (0%)	58 (20.8%)

Supplementary table 2. Complete data for individual regional sites.

Regional sites A-H	Albury (N=22)	Bairnsdale (N=9)	Ballarat (N=23)	Bendigo (N=21)	Castlemaine (N=1)	Echuca (N=10)	Hamilton (N=3)	Horsham (N=1)
Sex								
Female	10 (45.5%)	2 (22.2%)	8 (34.8%)	7 (33.3%)	1 (100%)	3 (30%)	1 (33.3%)	0 (0%)
Male	12 (54.5%)	7 (77.8%)	15 (65.2%)	14 (66.7%)	0 (0%)	7 (70%)	2 (66.7%)	1 (100%)
Age (years)								
Median [Q1, Q3]	73.5 [68, 81]	76 [67, 79]	69 [58, 75.5]	76 [68, 79]	89 [89, 89]	72.5 [67.3, 77.8]	77 [65, 79.5]	71 [71, 71]
NIHSS score on first assessment								
Median [Q1, Q3]	16 [11.3, 19]	5 [2, 17]	17 [11, 24]	11 [7, 18]	NA	16 [15, 17]	18 [15, 18.5]	14 [14, 14]
Missing	0 (0%)	0 (0%)	8 (34.8%)	0 (0%)	1 (100%)	1 (10%)	0 (0%)	0 (0%)
Pre-morbid mRS								
0	16 (72.7%)	7 (77.8%)	12 (52.2%)	19 (90.5%)	0 (0%)	6 (60%)	3 (100%)	1 (100%)
1	3 (13.6%)	2 (22.2%)	2 (8.7%)	1 (4.8%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)
2	3 (13.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
≥3	0 (0%)	0 (0%)	1 (4.3%)	1 (4.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	8 (34.8%)	0 (0%)	1 (100%)	1 (10%)	0 (0%)	0 (0%)
Inbound travel time (mins)								
Median [Q1, Q3]	12 [7, 13]	28 [14, 36]	16 [8.75, 40.8]	9 [7, 29]	NA	5 [4, 8.50]	17 [14.5, 19.5]	NA
Missing	17 (77.3%)	2 (22.2%)	3 (13%)	4 (19%)	1 (100%)	3 (30%)	1 (33.3%)	1 (100%)
Door to CT time (mins)								
Median [Q1, Q3]	NA	NA	NA	NA	NA	NA	NA	NA
Missing	22 (100%)	9 (100%)	23 (100%)	21 (100%)	1 (100%)	10 (100%)	3 (100%)	1 (100%)

Regional sites A-H (continued)	Albury (N=22)	Bairnsdale (N=9)	Ballarat (N=23)	Bendigo (N=21)	Castlemaine (N=1)	Echuca (N=10)	Hamilton (N=3)	Horsham (N=1)
Thrombolysis								
Yes	13 (59.1%)	3 (33.3%)	9 (39.1%)	11 (52.4%)	0 (0%)	6 (60%)	2 (66.7%)	1 (100%)
No	9 (40.9%)	6 (66.7%)	14 (60.9%)	10 (47.6%)	1 (100%)	4 (40%)	1 (33.3%)	0 (0%)
Door to Needle time (mins)								
Median [Q1, Q3]	NA	NA	NA	NA	NA	NA	NA	NA
Missing	22 (100%)	9 (100%)	23 (100%)	21 (100%)	1 (100%)	10 (100%)	3 (100%)	1 (100%)
Door in Door out time (mins)								
Median [Q1, Q3]	NA	170 [156, 207]	137 [106, 179]	121 [105, 166]	NA	164 [145, 211]	130 [114, 145]	NA
Missing	22 (100%)	4 (44.4%)	8 (34.8%)	9 (42.9%)	1 (100%)	3 (30%)	1 (33.3%)	1 (100%)
Multi-leg outbound journey, n (%)								
TRUE	16 (72.7%)	8 (88.9%)	1 (4.3%)	9 (42.9%)	0 (0%)	8 (80%)	3 (100%)	0 (0%)
FALSE	0 (0%)	1 (11.1%)	18 (78.3%)	10 (47.6%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)
Unknown	6 (27.3%)	0 (0%)	4 (17.4%)	2 (9.5%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
Outbound transport involving air transfer, n (%)								
TRUE	18 (81.8%)	7 (77.8%)	2 (8.7%)	8 (38.1%)	0 (0%)	10 (100%)	2 (66.7%)	0 (0%)
FALSE	0 (0%)	2 (22.2%)	18 (78.3%)	11 (52.4%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)
Unknown	4 (18.2%)	0 (0%)	3 (13%)	2 (9.5%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
PSC to CSC travel time (mins)								
Median [Q1, Q3]	NA	95.5 [84.5, 115]	74 [67.3, 79.8]	92.5 [87.8, 94.8]	NA	80.5 [53.3, 92.8]	105 [101, 152]	NA
Missing	22 (100%)	5 (55.6%)	7 (30.4%)	7 (33.3%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)

Regional sites A-H (continued)	**Albury (N=22)**	**Bairnsdale (N=9)**	**Ballarat (N=23)**	**Bendigo (N=21)**	**Castlemaine (N=1)**	**Echuca (N=10)**	**Hamilton (N=3)**	**Horsham (N=1)**
Thrombolysis								
Yes	13 (59.1%)	3 (33.3%)	9 (39.1%)	11 (52.4%)	0 (0%)	6 (60%)	2 (66.7%)	1 (100%)
No	9 (40.9%)	6 (66.7%)	14 (60.9%)	10 (47.6%)	1 (100%)	4 (40%)	1 (33.3%)	0 (0%)
Door to Needle time (mins)								
Median [Q1, Q3]	NA	NA	NA	NA	NA	NA	NA	NA
Missing	22 (100%)	9 (100%)	23 (100%)	21 (100%)	1 (100%)	10 (100%)	3 (100%)	1 (100%)
Door in Door out time (mins)								
Median [Q1, Q3]	NA	170 [156, 207]	137 [106, 179]	121 [105, 166]	NA	164 [145, 211]	130 [114, 145]	NA
Missing	22 (100%)	4 (44.4%)	8 (34.8%)	9 (42.9%)	1 (100%)	3 (30%)	1 (33.3%)	1 (100%)
Multi-leg outbound journey, n (%)								
TRUE	16 (72.7%)	8 (88.9%)	1 (4.3%)	9 (42.9%)	0 (0%)	8 (80%)	3 (100%)	0 (0%)
FALSE	0 (0%)	1 (11.1%)	18 (78.3%)	10 (47.6%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)
Unknown	6 (27.3%)	0 (0%)	4 (17.4%)	2 (9.5%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
Outbound transport involving air transfer, n (%)								
TRUE	18 (81.8%)	7 (77.8%)	2 (8.7%)	8 (38.1%)	0 (0%)	10 (100%)	2 (66.7%)	0 (0%)
FALSE	0 (0%)	2 (22.2%)	18 (78.3%)	11 (52.4%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)
Unknown	4 (18.2%)	0 (0%)	3 (13%)	2 (9.5%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
PSC to CSC travel time (mins)								
Median [Q1, Q3]	NA	95.5 [84.5, 115]	74 [67.3, 79.8]	92.5 [87.8, 94.8]	NA	80.5 [53.3, 92.8]	105 [101, 152]	NA
Missing	22 (100%)	5 (55.6%)	7 (30.4%)	7 (33.3%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)

Regional sites M-Wa	Mildura (N=3)	Sale (N=6)	Shepparton (N=12)	Swan Hill (N=1)	Traralgon (N=14)	Wangaratta (N=14)	Warragul (N=7)	Warrnambool (N=9)
Sex								
Female	1 (33.3%)	6 (100%)	5 (41.7%)	0 (0%)	5 (35.7%)	9 (64.3%)	2 (28.6%)	3 (33.3%)
Male	2 (66.7%)	0 (0%)	7 (58.3%)	1 (100%)	9 (64.3%)	5 (35.7%)	5 (71.4%)	6 (66.7%)
Age (years)								
Median [Q1, Q3]	64 [59, 67]	75 [67.5, 79.5]	72.5 [56, 80.5]	72 [72, 72]	68.5 [62, 72.8]	74.5 [68.3, 82]	69 [66, 73]	66 [41, 75]
NIHSS on arrival								
Median [Q1, Q3]	19 [9.50, 20]	11 [6.25, 21.8]	7 [2.50, 12.5]	12 [12, 12]	12.5 [7, 22.8]	17 [13, 21]	13 [11, 15]	7 [2, 15]
Missing	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	3 (21.4%)	0 (0%)	0 (0%)
Pre-morbid mRS								
0	3 (100%)	6 (100%)	8 (66.7%)	1 (100%)	11 (78.6%)	6 (42.9%)	7 (100%)	9 (100%)
1	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	3 (21.4%)	2 (14.3%)	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	2 (14.3%)	0 (0%)	0 (0%)
≥3	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	3 (21.4%)	0 (0%)	0 (0%)
Inbound travel time (mins)								
Median [Q1, Q3]	50 [50, 50]	5 [4, 17.5]	12 [8, 32]	16 [16, 16]	20 [10, 29]	25 [5, 36]	10 [7.50, 10]	41.5 [19.5, 49]
Missing	2 (66.7%)	3 (50%)	3 (25%)	0 (0%)	1 (7.1%)	1 (7.1%)	4 (57.1%)	1 (11.1%)
Door to CT time (mins)								
Median [Q1, Q3]	NA	NA	NA	NA	NA	NA	NA	NA
Missing	3 (100%)	6 (100%)	12 (100%)	1 (100%)	14 (100%)	14 (100%)	7 (100%)	9 (100%)

Regional sites M-Wa (continued)	Mildura (N=3)	Sale (N=6)	Shepparton (N=12)	Swan Hill (N=1)	Traralgon (N=14)	Wangaratta (N=14)	Warragul (N=7)	Warrnambool (N=9)
Thrombolysis								
Yes	2 (66.7%)	3 (50%)	8 (66.7%)	1 (100%)	9 (64.3%)	8 (57.1%)	6 (85.7%)	5 (55.6%)
No	1 (33.3%)	3 (50%)	4 (33.3%)	0 (0%)	5 (35.7%)	6 (42.9%)	1 (14.3%)	4 (44.4%)
Door to Needle time (mins)								
Median [Q1, Q3]	NA	NA	NA	NA	NA	NA	NA	NA
Missing	3 (100%)	6 (100%)	12 (100%)	1 (100%)	14 (100%)	14 (100%)	7 (100%)	9 (100%)
Door in Door out time (mins)								
Median [Q1, Q3]	239 [239, 239]	123 [123, 123]	149 [136, 166]	204 [204, 204]	118 [112, 125]	142 [121, 182]	144 [111, 144]	123 [91, 141]
Missing	2 (66.7%)	5 (83.3%)	6 (50%)	0 (0%)	3 (21.4%)	5 (35.7%)	4 (57.1%)	2 (22.2%)
Multi-leg outbound journey								
TRUE	2 (66.7%)	2 (33.3%)	7 (58.3%)	1 (100%)	1 (7.1%)	12 (85.7%)	0 (0%)	9 (100%)
FALSE	0 (0%)	2 (33.3%)	4 (33.3%)	0 (0%)	11 (78.6%)	2 (14.3%)	5 (71.4%)	0 (0%)
Unknown	1 (33.3%)	2 (33.3%)	1 (8.3%)	0 (0%)	2 (14.3%)	0 (0%)	2 (28.6%)	0 (0%)
Outbound transport involving air transfer								
TRUE	3 (100%)	3 (50%)	6 (50%)	1 (100%)	1 (7.1%)	11 (78.6%)	0 (0%)	8 (88.9%)
FALSE	0 (0%)	2 (33.3%)	5 (41.7%)	0 (0%)	12 (85.7%)	3 (21.4%)	5 (71.4%)	1 (11.1%)
Unknown	0 (0%)	1 (16.7%)	1 (8.3%)	0 (0%)	1 (7.1%)	0 (0%)	2 (28.6%)	0 (0%)
PSC to CSC travel time (mins)								
Median [Q1, Q3]	162 [162, 162]	65 [65, 65]	103 [99.8, 111]	115 [115, 115]	90 [82.8, 97.8]	125 [101, 136]	64 [55, 73]	103 [98.5, 123]
Missing	2 (66.7%)	5 (83.3%)	4 (33.3%)	0 (0%)	2 (14.3%)	4 (28.6%)	2 (28.6%)	1 (11.1%)

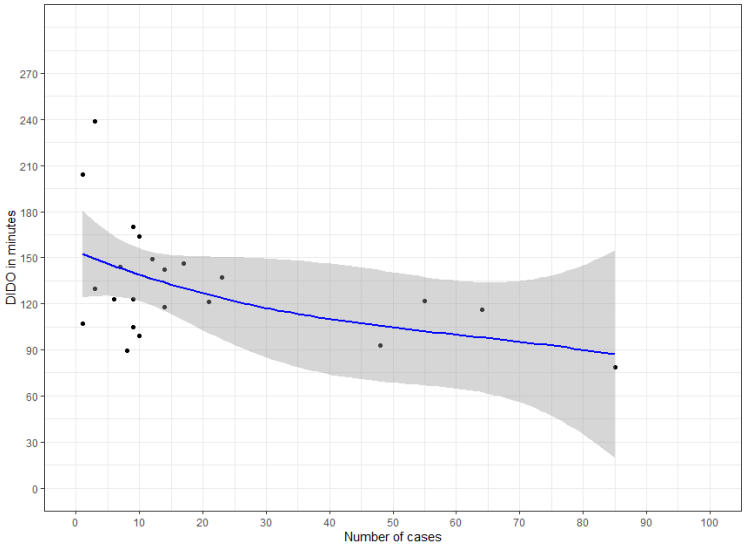
Regional sites We-Wo	Werribee (N=8)	Wodonga (N=1)	Wonthaggi (N=10)	Overall (N=176)
Sex				
Female	6 (75%)	0 (0%)	3 (30%)	72 (40.9%)
Male	2 (25%)	1 (100%)	7 (70%)	104 (59.1%)
Age (years)				
Median [Q1, Q3]	75 [69.3, 79]	59 [59, 59]	73.5 [67, 75.8]	72 [64, 78]
NIHSS on arrival				
Median [Q1, Q3]	11.5 [4.25, 16.5]	15 [15, 15]	12.5 [8.25, 13.8]	14 [7, 19]
Missing	2 (25%)	0 (0%)	0 (0%)	16 (9.1%)
Pre-morbid mRS				
0	6 (75%)	1 (100%)	9 (90%)	131 (74.4%)
1	0 (0%)	0 (0%)	0 (0%)	17 (9.7%)
2	0 (0%)	0 (0%)	1 (10%)	8 (4.5%)
≥3	0 (0%)	0 (0%)	0 (0%)	4 (2.3%)
Missing	2 (25%)	0 (0%)	0 (0%)	16 (9.1%)
Inbound travel time (mins)				
Median [Q1, Q3]	15 [11, 24.8]	56 [56, 56]	17 [10.5, 24.5]	16 [8, 34]
Missing	4 (50%)	0 (0%)	3 (30%)	55 (31.3%)
Door to CT time (mins)				
Median [Q1, Q3]	NA	NA	NA	NA
Missing	8 (100%)	1 (100%)	10 (100%)	176 (100%)

Regional sites We-Wo (continued)	Werribee (N=8)	Wodonga (N=1)	Wonthaggi (N=10)	Overall (N=176)
Thrombolysis				
Yes	4 (50%)	0 (0%)	9 (90%)	100 (56.8%)
No	4 (50%)	1 (100%)	1 (10%)	76 (43.2%)
Door to Needle time (mins)				
Median [Q1, Q3]	NA	NA	NA	NA
Missing	8 (100%)	1 (100%)	10 (100%)	176 (100%)
Door in Door out time (mins)				
Median [Q1, Q3]	89.5 [78.8, 104]	NA	99 [92.5, 114]	132 [108, 167]
Missing	4 (50%)	1 (100%)	3 (30%)	85 (48.3%)
Multi-leg outbound journey				
TRUE	0 (0%)	1 (100%)	1 (10%)	82 (46.6%)
FALSE	8 (100%)	0 (0%)	8 (80%)	71 (40.3%)
Unknown	0 (0%)	0 (0%)	1 (10%)	23 (13.1%)
Outbound transport involving air transfer				
TRUE	0 (0%)	1 (100%)	1 (10%)	83 (47.2%)
FALSE	8 (100%)	0 (0%)	8 (80%)	76 (43.2%)
Unknown	0 (0%)	0 (0%)	1 (10%)	17 (9.7%)
PSC to CSC travel time (mins)				
Median [Q1, Q3]	28 [26, 43]	NA	77 [73.5, 79.5]	90 [73, 104]
Missing	3 (37.5%)	1 (100%)	3 (30%)	70 (39.8%)

Supplementary Table 3. Univariable analysis (Kruskal-Wallis χ^2) of variables of interest and DIDO

Variable	n	χ2	p-value
Outbound crew – metropolitan patients only	189	6.869	1.33e-15
Outbound crew – regional patients only	101	0.13966	0.7086
Thrombolysis – metropolitan patients only	264	6.688	0.0097
Thrombolysis – regional patients only	176	0.36086	0.5480
Transport mode (air or ground) – regional patients only	159	16.62	4.566e-05
Outbound ambulance dispatch code – metropolitan patients only	234	11.258	7.926e-4
Outbound ambulance dispatch code – regional patients only	114	7.9584	0.0048

Supplementary figure 1. Association between PSC case volume/site experience and DIDO.



There was a trend towards lower DIDO with higher case volume in univariable analysis (see Figure below), however this did not reach statistical significance (Spearman's rho for non-parametric data = -0.357, p = 0.102). PSC case volume was included in the multivariable regression analysis for regional and metropolitan sites (see Supplementary Table 2), but no statistically significant association was found.

Supplementary Table 4. Regression model results after forward selection of significant variables

Variables included in all initial linear regression models were: Age, sex, NIHSS score at PSC, baseline mRS score, thrombolysis, weekday/weekend, time of day (working hours/after hours), ambulance dispatch code, outbound ambulance crew, case volume (total number of transfers made by that PSC during the study period). The models were refined by identifying the most significant variables using the Akaike Information Criterion and included in the final models below.

1. Overall DIDO for all patients

	Estimate	Std. Error	t value	p value	
(Intercept)	51.4792	59.9625	0.859	0.39152	
Outbound crew (different)	53.6718	17.3654	3.091	0.00225	**
mRS score [linear]	-10.1559	67.0592	-0.151	0.87976	
mRS score [quadratic]	9.2704	57.7877	0.16	0.87269	
mRS score [cubic]	-35.2313	75.4497	-0.467	0.64099	
NIHSS score at PSC	-1.5377	1.134	-1.356	0.17646	
Ambulance dispatch code (Category >2 (less urgent))	38.892	22.259	1.747	0.08197	.
Thrombolysis (yes)	-47.5743	16.7369	-2.842	0.00489	**
Patient age	1.1021	0.6968	1.582	0.11517	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
Residual standard error: 118.1 on 224 degrees of freedom
(220 observations deleted due to missingness)
Multiple R-squared: 0.1096, Adjusted R-squared: 0.06986
F-statistic: 2.758 on 10 and 224 DF, p-value: 0.003164

This model suggests that using a different ambulance crew to transport the patient between PSC and CSC adds 53.7 minutes to DIDO, while the patient receiving thrombolysis reduced DIDO by 47.6 minutes. Note that 220/455 patients were missing data. This result was not reported in the main manuscript as the model is skewed towards metropolitan patients.

2. DIDO for metropolitan patients only (n=279)

	Estimate	Std. Error	t value	p value	
(Intercept)	13.6487	81.6609	0.167	0.8675	
Outbound crew (different)	71.7545	25.0856	2.86	0.00486	**
mRS score [linear]	-21.265	80.9472	-0.263	0.79316	
mRS score [quadratic]	45.757	78.5526	0.583	0.56114	
mRS score [cubic]	-33.7884	94.4443	-0.358	0.72105	
NIHSS score at PSC	-1.3686	1.738	-0.787	0.43229	
Ambulance dispatch code (Category >2 (less urgent))	25.5126	43.4557	0.587	0.55806	
Thrombolysis (yes)	-68.8786	24.94	-2.762	0.0065	**
Patient age	1.3837	0.9779	1.415	0.15924	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
Residual standard error: 140.8 on 144 degrees of freedom
(124 observations deleted due to missingness)
Multiple R-squared: 0.1334, Adjusted R-squared: 0.07317
F-statistic: 2.216 on 10 and 144 DF, p-value: 0.01993

This model using metropolitan patient transfers only suggest that using a different ambulance crew to transport the patient adds 71.8 minutes to DIDO, while the patient receiving thrombolysis reduced DIDO by 68.9 minutes.

3. DIDO for regional patients only (n=176)

	Estimate	Std. Error	t value	p value	
(Intercept)	121.1917	16.8446	7.195	4.00E-10	***
NIHSS score at PSC	-1.9105	0.6709	-2.848	0.00568	**
Ambulance dispatch code (Category >2 (less urgent))	25.3655	12.1908	2.081	0.040876	*
Transport mode (Air transfer)	45.9438	11.6238	3.953	0.000173	***
PSC case volume	1.7071	0.8655	1.972	0.052259	.

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
Residual standard error: 42.9 on 75 degrees of freedom
(96 observations deleted due to missingness)
Multiple R-squared: 0.3472, Adjusted R-squared: 0.3124
F-statistic: 9.972 on 4 and 75 DF, p-value: 1.59e-06

Mode of transport was included in the multivariable regression analysis for regional patients. There were too few (n=3) air transfers in the metropolitan cohort.

3.4 Practical utility of the ACT-FAST triage algorithm from a primary stroke centre perspective.

Tan S, Stephens K, Gao L, Tan E, Frost T, Choi PMC

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Co-authorship statement:

S (Peter) Tan completed this work during his two years at Box Hill Hospital, first as a fellow and later as first year advanced trainee. K Stephens was involved with data collection and reviewing the draft manuscript. L Gao and E Tan provided support with analysis. T Frost was involved with reviewing.

As senior author, I was involved in the conceptualisation, methodology, supervision, extensive review and editing of the draft manuscript.

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Practical utility of the ACT-FAST triage algorithm from a primary stroke centre perspective

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ABSTRACT

Background: Rapid reperfusion in ischaemic stroke with emergent large vessel occlusion (ELVO) reduces morbidity and mortality. Limited distribution of endovascular clot retrieval (ECR) capable comprehensive stroke centres (CSCs) necessitates development of pre-hospital models of care to provide equitable and economical access to reperfusion therapy. We examine the time metrics of the traditional secondary transfer strategy in comparison to the direct bypass strategy and the potential utility of the ACT-FAST prehospital triage algorithm on a large volume Melbourne primary stroke centre (PSC).

Method: Retrospective analysis of consecutive patients presenting to a PSC from 1 January 2020 to 31 December 2020. Clinical records were interrogated for ACT-FAST positive patients. Time metrics were established using Google Maps traffic modelling and local/published door-to-needle, door-in-door out and door-to-groin data.

Results: 88 patients during the study period were ACT-FAST positive. Of these, 49/88 (56%) cases had ELVO ischaemic strokes, 24/88 (27%) cases had intracranial haemorrhages and the remaining 15/88 (17%) had non ELVO ischaemic strokes or mimics (seizure, complex migraine, etc). 28/88 (32%) cases met indication for and were subsequently transferred to a CSC for consideration of ECR. The modelled median scene to groin time for the direct bypass strategy is 94 min whereas the median scene to groin time for the secondary transfer strategy is 109 min, giving a difference of 15 min.

Conclusion: Time savings to groin puncture for the direct bypass strategy is substantially less than previous estimates and suggests that the secondary transfer strategy continues to be a viable pathway for a high efficiency PSC.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Access to reperfusion therapy, in particular endovascular clot retrieval, is limited. Prehospital models of care are being continuously revised to optimise access to therapy while maintaining cost-effectiveness.

WHAT THIS STUDY ADDS

⇒ This study highlights the three models of care currently available in Melbourne, Australia and examines the hypothetical effect of pre-hospital paramedic triaging at a high efficiency primary stroke centre (PSCs). It finds a majority of patients do not benefit from direct bypass to a comprehensive stroke centre and the delay to groin access for endovascular clot retrieval at our centre is much less than previously suggested in previous studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that secondary transfer is still a viable pathway if workflows are optimised to reduce door-in-door out times. There remains a considerable role that high performing PSCs can play in the overall stroke systems of care.

BACKGROUND

Time is brain. Although intravenous thrombolysis is widely available at primary stroke centres (PSCs), the availability of endovascular clot retrieval (ECR) is limited to a few comprehensive stroke centres (CSCs) located in the major capital cities of Australia. This necessitates interhospital transfer of emergent large vessel occlusion (ELVO) patients both in the metro and regional settings to these CSCs for ECR.

Currently, there are three distinct pathways an ELVO stroke patient within metropolitan Melbourne may arrive at a CSC. First, and historically, all suspected stroke patients are initially transported for assessment at the nearest hospital from the scene with 24/7 thrombolysis service, regardless of PSC or CSC designation. These patients are then transferred to CSC for consideration of ECR if appropriate. Since late 2017, with the commission of the first Australian Mobile Stroke Unit Ambulance (MSU), a second option became available during 08:00–18:00 hours, Monday to Friday operating within 20 km from the city centre.[1] Eligible patients are given intravenous thrombolysis on the MSU and if a ELVO is identified by the on-board CT angiography, transferred directly to a CSC. Finally, in 2019, a city-wide PSC bypass strategy was

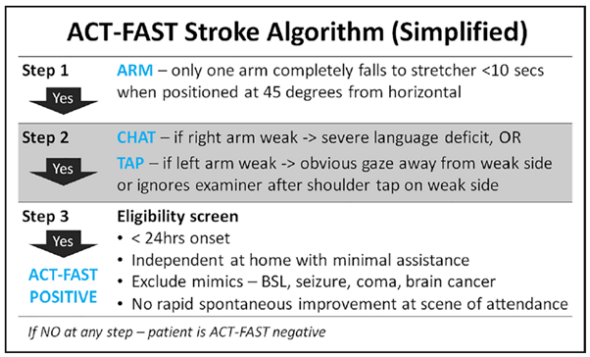

Figure 1 ACT-FAST algotithm. BSL - Blood sugar level

implemented by Ambulance Victoria using the ACT-FAST tool (figure 1). This pathway involved ACT-FAST positive patients being taken directly to the nearest CSC for assessment, bypassing PSC along the way.

The ACT-FAST tool is designed to identify patients with ELVO in the field using clinical features alone based on a three-step algorithm.[2] The first step assesses for unilateral arm weakness using the NIHSS (National Institutes of Health Stroke Scale) method of arm drift and is fulfilled when one arm drifts to the stretcher in <10 s. The second step of ACT-FAST depends on which arm is weak. If the right arm is weak, paramedics are instructed to look for dysphasia. If the left arm is weak, paramedics are instructed to assess for left sided neglect. The third step is to determine eligibility for ECR therapy including that time of onset <24 hours, that deficits are not pre-existing, good premorbid functional level and to rule out common stroke mimics. A patient is considered ACT-FAST positive if a patient fulfils all three steps of the algorithm (figure 1).

The catchment area of the Eastern Health network—located in the east of Melbourne with Box Hill Hospital (BHH) as the network PSC was in principle not included in the ACT-FAST bypass strategy. We aim to examine the potential utility of the ACT-FAST prehospital triage tool in expediting treatment times and appropriately triaging suspected stroke patients in our catchment area.

METHODS

Departmental stroke databases were interrogated for patients who presented via ambulance with ongoing neurological symptoms for stroke team assessment from 1 January 2020 to 31 December 2020. Patient medical records were reviewed by an acute stroke nurse to determine if they met ACT-FAST criteria based on paramedic or medical assessment. ACT-FAST diagnostic accuracy was then compared with CT-angiogram imaging for the presence of ELVO (ICA, M1, M2, basilar artery occlusion). Variables collected included: age, sex, postcode, premorbid modified Rankin score, presence and location of ELVO on CTA, hyperacute therapy received, door to needle time (DTN) and door-in-door-out (DIDO) times and discharge diagnosis.

Potential direct bypass strategy time savings were estimated using google maps-based traffic modelling. Using the postcode of each patient as the on-scene location reference, travel time to BHH and then onwards to the usual referral CSC (The Royal Melbourne Hospital) was compared with the travel time if the patient was transported direct to the nearest CSC (The Royal Melbourne Hospital or Monash Medical Centre). Travel times were modelled for both day and night-time traffic. The median time from these traffic models was then used for further analysis, representing an estimated median time saved regardless of the time of the day. Analysis was performed using Microsoft Excel 365 and Stata (V.17.0).

RESULTS

Number of ELVO, non-ELVO ischaemic strokes, intracranial haemorrhage and mimics

A total of 1216 presentations were included with 88/1216 (7%) presentations ACT-FAST positive (table 1). Of these, 49/88 (56%) cases had ELVO ischaemic strokes, 24/88 (27%) cases had intracranial haemorrhages (ICHs) and the remaining 15/88 (17%) had non EVLO ischaemic strokes or mimics (seizure, complex migraine or functional etc). Of 88, 28 (32%) cases met indication for and were subsequently transferred to a CSC for consideration of ECR. Four additional patients during the study period were ACT-FAST negative but had ELVO amendable to ECR, these were also transferred to a CSC for ECR. In total, 19/ (28+4) (59%) of ECR cases received thrombolysis prior to transfer. Of 88, 18 (20%) cases were palliated on arrival after clinical and neuroimaging assessment. Of the ICH cases, only 3/24 (12.5%) of these required transfer to a neurosurgical centre during their admission (figure 2).

ACT-FAST had 92% sensitivity and 97% specificity for ELVO. Negative predictive value (NPV) was 99.7%, while positive predictive value (PPV) was 55.7%.

Where data were available, of 54 patients flagged as ACT-FAST positive by paramedics, as noted in ambulance documentation, 21 (40%) were in fact not positive based on step 3 eligibility criteria.

Time metrics

The median scene to BHH time in our cohort was 15 min (IQR 8.5–21). The modelled median time to transfer patients in our cohort directly from scene to the closest CSC (The Royal Melbourne Hospital or Monash Medical Centre) was 24 min (IQR 20–28).

The median DIDO time for ECR transfer, and door-to-needle (DTN) time were 50 min (IQR 41–63 min) and 45 min (IQR 35–62 min) respectively for this cohort. The median outbound transport time from BHH to The Royal Melbourne Hospital (the main referral CSC for our centre) was 20 min.

Table 1 Patient characteristics

	ACT-FAST positive patient characteristics (n=88)
Age	Median=80 (IQR 71–86)
Gender	50% Male
Pre-mRS	0=59 (67%) 1=19 (22%) 2=10 (11%)
Final diagnosis	ELVO stroke=49 ► M1=38 ► M2=8 ► Basilar=2 ► ICA=1 Non ELVO stroke=10 ICH=24 Mimic unable to excluded on scene=5

ELVO, emergent large vessel occlusion; ICH, intracranial haemorrhage; mRS, Modified Rankin Scale.

The time metrics used for comparison were derived from a consecutive sample of 460 ECR cases during the calendar years 2018–2019 (prior to the implementation of ACT-FAST triage bypass) from the two designated Victorian state-wide ECR centres (The Royal Melbourne Hospital and Monash Medical Centre). CSC-arrival-to-arterial-access times in direct-presenting patients is 70 min compared with 24 min for metropolitan secondary transfer patients.[3] The discrepancy between the times is due to the fact that direct presentations still require a full workup including history, examination, multimodal CT imaging and activation of the catheter laboratory prior to ECR whereas secondary transfer patients can be taken directly to the preactivated catheter laboratory. BHH secondary transfer patients would fall under the subset of metropolitan secondary transfer patients.

Therefore, in the Eastern Health catchment area the median scene to groin time for the direct bypass strategy is 94 min (Transfer time from scene to nearest CSC of 24 min+door to groin time of 70 min). The median scene to groin time for the secondary transfer strategy is 109

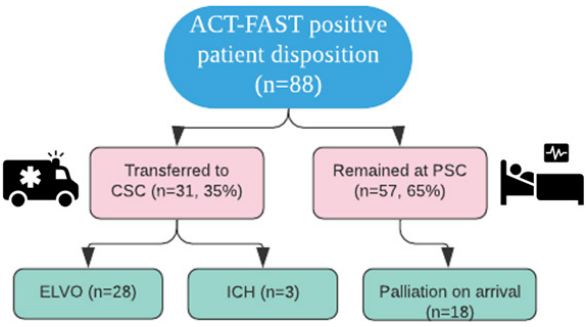

Figure 2 Disposition flow chart of ACT-FAST positive patients. CSC, comprehensive stroke centre; ELVO, emergent large vessel occlusion; ICH, intracranial haemorrhage; PSC, primary stroke centre.

Figure 3 Comparison of direct bypass and secondary transfer strategy timeline estimates.

min (Transfer time to BHH of 15 min+median DIDO of 50 min+BHH to CSC transfer time of 20 min+door to groin time of 24 min) (figure 3).

DISCUSSION

Within the Eastern Health catchment area, the time saving to ECR observed with the direct bypass strategy as compared with the secondary transfer strategy was substantially less than previous research estimates across metropolitan Melbourne (15 min vs 52 min).[3] Moreover, the majority of patients who were transferred on to the CSC from our PSC for ECR received thrombolysis prior to transfer, which given the study period DTN time of 45 min equates to median therapy administration time of 60 min from scene (Transfer time to BHH of 15 min+DTN time of 45 min). Pending the results of ongoing trials, the use of IV thrombolysis prior to thrombectomy remains the standard of care for eligible ELVO cases. It is associated with higher rates of successful reperfusion before thrombectomy (2.4% vs 7.0%) and overall successful reperfusion (79.4% vs 84.5%).[4] To date, primary ECR has not been shown to be superior and its non-inferiority is still up for debate. Further, the precise temporal relationship between bridging thrombolysis and ECR in respect to final patient outcomes is not entirely clear.

Previous studies in the Australian setting have found conflicting conclusions regarding the functional outcomes of patients undergoing the direct bypass strategy as compared with the secondary transfer strategy. A 2018 Victorian observational study showed that there was no difference in regard to 90-day functional outcomes between the two groups, but the study risks selection bias as no time metrics were analysed.[5] A more recent 2020 observational study from New South Wales out of Liverpool Hospital, a CSC, revealed 93 min longer stroke onset to groin puncture time, worse 90-day functional outcomes (39.6% vs 61.0% of MRS 0–2) and higher mortality (25.3% vs 6.8%) in the secondary transfer group.[6] Results from the 2022 RACECAT randomised control trial based in the Catalonia region of Spain, with 1401 patients randomised, showed that there was no significant difference in the rate of good (MRS 0–2) 90-day outcomes (32.8% in secondary transfer vs 33.4% direct bypass) or mortality (37.3% in secondary transfer vs 35.8% direct bypass) between direct bypass and secondary transfer groups.[7]

Although 90-day functional outcomes have not been shown to be conclusively different between the two transfer strategies, we acknowledge that the effectiveness of reperfusion therapy is highly time sensitive. Meretoja *et al* attempted to model the additional benefit of ECR on

top of thrombolysis with respect to timing. It found that on average, 4 days of disability free days were gained with every 1 min reduction to ECR reperfusion. This finding was relatively static with modelling of ECR at both 45 min and 90 min post thrombolysis.[8] Therefore, at the individual patient level the estimated 15 min delay between the two strategies study could be clinically significant, equating to 2 months of disability free days lost.

Our data suggest only one-third of ACT-FAST positive patients would have benefited from the direct bypass strategy. In a resource limited environment, we do need to consider the economic and human cost of bypassing the PSC for all ACT-FAST positive patients. For example, over triage and burdening of the CSC with ACT-FAST positive cases not eligible for ECR may reduce workflow efficiency which may impact treatment metrics for actual ECR candidates. Additionally, human factors such as increased distance to family support, increased distance to follow-up appointments and the disorientating effect of unfamiliar surroundings should also be considered in a patient's stroke journey from hyperacute therapy to recovery or palliation. The literature on this important opportunity cost is scant and any significant reorganisation of stroke service must take these factors into account.

The difference in time savings from previous estimates seen in our study can largely be attributed to the relatively fast DIDO times achieved at our PSC compared with other services. Since 2015, there has been a continuous quality improvement programme to reduce delay factors at our centre for both DTN and DIDO times.[9] The trend reveals there has been a 55% reduction in the DIDO time from 2015 to 2021 (111 min to 50 min). This has been achieved with a combination of interventions including streamlining the referral process to the CSC by granting the neuro-interventionalist PSC imaging access as well as systematically streamlining the code stroke process by setting up a task force to identify and resolve delay factors involving key partners such as the stroke team, emergency department, CT radiographers and the ambulance crew. Even in the presence of a bypass strategy, it is imperative for PSCs to maintain and improve hyperacute treatment metrics as not all patients with ELVO present with high NIHSS or are ACT-FACT positive.

There is currently one MSU in operation in Melbourne, in the first 365 days of operation between 2017 and 2018, it was reported that the MSU facilitated 42 patients for ECR.[1] More recent data are not publicly available. Results from two pivotal randomised controlled trials, B PROUD and BEST-MSU have shown that compared with conventional prehospital stroke care, MSU care led to improved functional outcomes.[10 11] We; therefore, expect there to be a growing role of the MSU in prehospital stroke care. However, given the resource intensive nature of MSUs, its operational capacity (currently only Monday to Friday during normal working hours), cost-effectiveness and applicability in non-urban or resource-limited settings is still under investigation.

This study affirms that the ACT-FAST algorithm has good sensitivity, specificity and NPV for ELVO. The PPV of 55.7% is similar to previous validation studies and is higher than other field validated scales such as the Rapid Arterial Occlusion Evaluation Scale at 42% and Los Angles Motor Scale at 36%.[2] The algorithm only missed four cases of ELVO stroke during the study period.

A large proportion of the false positive ACT-FAST cases were ICH, the vast majority did not require time sensitive neurosurgical intervention despite significant clinical deficits from mostly small to moderate size bleeds. Apart from 3 cases, the rest were all managed in our PSC stroke unit.

Our data also suggest information required in 'step 3' of the algorithm may be challenging to acquire on scene by paramedics. Therefore, the number of false positives is likely higher in practice. It is assumed all paramedics have undergone training to use the algorithm.

The main limitation of our study is the observational retrospective nature with time analysis done using google maps software modelling. In addition, we did not consider extra possible delays out of our scope and ability to measure, for instance, ambulance transport factors such as trolley loading and parking. Another limitation of our study is the use of the latest published but nonetheless non-contemporaneous time assessment data for time metric comparison. Unfortunately, workflow metrices are not routinely measured or collected at stroke centres in Australia. The data used for comparison was collected prior to COVID-19 and thus given the shift in some aspects of workflow post COVID-19 it is possible the time difference between the transfer strategies has changed. Anecdotal experience suggests secondary transfer cases may have an additional time advantage during the pandemic as rapid COVID-19 PCR testing done at the PSC may help expedite the procedural workflow at the CSC. Direct health economic calculations and quantitative analysis of human factors was out of the scope of this study.

Although the findings from this study are specific to our PSC the challenges faced are not unique, the overall reality is that the most clinically beneficial and cost-effective strategy of identifying and triaging potential ELVO stroke patients eligible for hyperacute therapy is still contentious. Certainly, the implementation of a continuous quality improvement programme to improve workflow efficiency at a PSC level can be replicated locally and abroad. We contend that there remains a considerable role high performing PSCs can play in the overall stroke systems of care.

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CHAPTER 4: DOAC AS A BARRIER TO DNT AND THE UTILITY OF A POINT OF CARE DOAC ASSAY

4.1 Trends in direct oral anticoagulant use in patients presenting with acute stroke

Teow KH, Tan PS, Frost T, Dewey HM, Borosak M, Choi PMC

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Co-authorship statement:

K Teow carried out this work as a final year medical student at Box Hill Hospital. As first author, she was involved with data collection, performed preliminary analysis and writing of the draft manuscript. P Tan and T Frost were involved with reviewing the manuscript. M Borosak provided information on the test assays and was involved with review and editing.

As the senior author and Kang's research supervisor, I was involved in the conceptualisation, formal analysis, methodology, supervision, extensive review and editing of the draft manuscript.

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4.2 Assessment of Direct Oral Anticoagulant Status Using the DOASENSE Dipstick in Thrombolysis Eligible Patients With Stroke: Proof-of-Concept Study

Tan PS, Park PSW, Cody R, Frost T, McNamara B, Borosak M, Choi PMC

Stroke. 2023 Apr;54(4):e142-e144

Journal Impact Factor 10.17 in 2022, 3 citations, FWCI 2.57

Co-authorship statement:

P Park started this work as a stroke fellow and applied for ethics. P Tan took over the project from P Park and collected most of the data, performed preliminary analysis and drafted the manuscript as first author. R Cody, T Frost, B McNamara and M Borosak were involved with reviewing the draft manuscript.

As the senior author, and P Park, S Tan and R Cody's primary clinical and research supervisor, I was involved in the conceptualisation, formal analysis, methodology, supervision, extensive review and editing of the draft manuscript.

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CHAPTER 5: CONCLUDING COMMENTARY

5.1 Summary

Increased access to reperfusion therapies, and faster treatment if eligible, have the potential for substantial population impact on outcome following stroke. Because cerebral infarction occurs progressively over time, the efficacy of reperfusion treatments are highly time dependent. Stroke systems of care must continue to evolve so the maximum number of acute stroke patients can access the benefits associated with the effective acute therapies that now exist. This thesis includes a selection of published works which examined how barriers to fast DNT and DIDO in a busy PSC were identified. The findings from this body of work have informed policy statements, service delivery, and importantly, provide the scientific basis to the recently released Australian National Targets for Acute Stroke treatment. Original contributions to the existing literature are summarised here.

Firstly, we have shown factors that are associated with faster DNT over two decades in a typical Australian PSC setting. The benefit of directly transporting the patient from triage to the CT scanner is quantified. The association of ASN presence with faster DNT was also shown for the first time. The “engine” behind the successful implementation of various strategies is the weekly reperfusion meeting, with timely feedback to the wider team and prompt trouble shooting. We are the first stroke team in the world to report that it is feasible to use body camera in understanding the Code Stroke workflow. We have shown the data collected may be used to set site-specific targets and to allow for adequate stroke team workforce resourcing.

Secondly, we are one of the first groups to examine PSC DIDO. We have raised awareness of the DIDO as a metric in ELVO stroke both locally and internationally as evidenced by the increasing number of publications on DIDO in the years since 2016. We have systematically studied and reported the factors associated with improving DIDO at a metropolitan PSC. The use of the same ambulance crew for

both the inbound and outbound journey was consistently shown to be associated with faster DIDO time. Subsequently, we expanded our research to include understanding DIDO at a state level, including all metro and regional sites. We have shown in Victoria, air transfer resulted in faster transfer time for sites located more than 250km from a CSC when currently either road or air transport maybe used for these sites based on aircraft availability. The final paper in Chapter 3 critically examines the performance of one of the many pre-hospital triage tools designed to be used by paramedics to bypass PSC for suspected ELVO stroke. We highlighted the important role of PSC in the stroke ecosystem of care; and the risk of over-triage to CSC, which may inadvertently compromise the care for patients with ELVO.

Finally, this thesis addressed one of the most topical problems in acute stroke medicine – improving access of IVT to the anti-coagulated patient, or at times, a presumed anti-coagulated patient presenting with acute ischaemic stroke. The extent of this problem in the DOAC era is outlined. A novel proof-of-concept pilot study was conducted to show the feasibility and utility of incorporating or including a point-of-care assay in the acute stroke decision making process.

5.2 Future direction

Overcoming the barriers to providing reperfusion therapies to acute ischaemic stroke patients requires a systematic approach to improving the status quo. There is now a confluence of factors that may finally allow a nation-wide effort to improvement in hyper acute stroke care in Australia. The new national targets, released in August 2023, and the Stroke Unit Certification Pilot Program in place since late 2022, are two key initiatives that outlined the vision for stroke care in Australia by 2030.[71, 120] The challenge to improve workflow at each PSC in Australia should however not be under-estimated. Targets, certification program, and even the data generated from this thesis are unlikely to result in the desired and sustained changes if attention is not paid to the implementation side of the ledger across sites in Australia.

Jeffrey Braithwaite, founding director of the Australian Institute of Health Innovation based at Macquarie University in Sydney, proposed a "*nuanced appreciation of change*" and emphasised "*change is always unpredictable, hard won, and takes time, it is often tortuous, and always needs to be tailored to the setting*".[121] His last point affirms the value of approaches such as the body cam study in Chapter 2.3 which provide detailed information on local pathways. While PSCs in Australia share similar organisational structures along metro and regional groupings, understanding the enablers, and barriers, to improving DNT and DIDO specific to the individual PSC by examining the workflow in real-life, has never been performed before.

The literature is not short on different implementation science methods, and in fact these tools have been employed to improve the rate of IVT, but studies specific to improving DNT are lacking.[122] The quality improvement work conducted at BHH evolved organically and did not follow any specific prescribed framework. A closer examination however reveals the issues discussed and addressed at the weekly reperfusion meeting at BHH closely align with the "Quality and Safety in Europe by Research" (QUASER), a research-based tool used to reflect on and develop quality improvement strategies.[123] Future work on improving DNT and DIDO at different sites may benefit from formally incorporating established implementation science framework such as QUASER to maximise the chance of successful outcomes.[124]

The difficulty in obtaining comprehensive data on patients treated with ECR, in particular from regional sites, highlighted the need for a state or national ECR registry. Utilisation of existing systems for quality improvement work requires manual data collection and duplication of data collection, and these are problems also encountered by other registries such as the Victorian Cardiac Outcomes Registry.[125] Evolution of technology and platforms used by the AuSCr may be able to overcome some of these issues by closer integration with hospital electronic medical record systems. This, in turn, would allow real-time data feedback to individual stroke centres.

Questions remain about how generalisable our experiences are. The majority of stroke patients, including a subset of patients with ELVO, only need stroke unit care at a PSC.[126] As shown in the data from AuSCr, PSCs have struggle to improve their

reperfusion metrics. The response to long DNT and ECR for ELVO in Melbourne and elsewhere internationally has been the MSU. However, we must critically evaluate the effect of any significant changes to workflow such as the MSU at a systems level. Should other Australian cities invest in having MSU and if so, what factors determine the number of MSU for any city? For example, a high value is placed on the number of patients treated within the “golden hour” using the MSU, but how may the MSU have changed the case mix of patients presenting to metropolitan PSCs and therefore maintenance of their skillset? PSCs are still expected to treat patients efficiently if a patient with ELVO present to a PSC first, as is the case when an ELVO patient is brought to the ED by family members or AV, or for inpatient stroke. In this thesis, an alternative is proposed. It would appear with highly efficient metropolitan PSCs, the benefit of Mobile Stroke Unit may be minimal and there might even be signal of harm.

Lastly, further research into the value of performing DOAC level in the acute stroke setting is urgently needed. Despite the argument that DOAC level assay is no more complicated than an INR test, DOAC level testing is still not widely available in most general hospital laboratories.[127] The ideal treatment approach to DOAC treated patient presenting with acute stroke needs to balance maximising access to fast reperfusion with minimising risk of bleeding. Planning for a prospective study involving VST sites, based on the pilot in Chapter 4.2 and utilising point of care DOAC testing with concurrent drug plasma level sampling, is currently underway. Parallel to this, research exploring whether in fact DOAC level testing confers additional benefit is also needed given recent observational data.[111]

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