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The Cost of a Bleed – A Retrospective Analysis of Non-Variceal Upper Gastrointestinal Bleeding in Hospital-Inpatients

By

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Keywords: Anticoagulants, Antithrombotic Agents, Gastrointestinal Hemorrhage, Health Care Economics and Organizations, Hospitalization

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ACADEMIC INTEGRITIY DECLARATION

I certify that this thesis:

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

2. and 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 by: James Alexander Sallis

Signed: J.Sallis

Date: 15/08/2024

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And finally, to my finance Erin Randall. Thank you for everything. You encourage me to be the best I can be.

ETHICS STATEMENT

Ethics approval was sought individually and gained from both the Southern Adelaide Local Health Network (SALHN) Human Research Ethics Committee (HREC) for the Flinders Medical Centre (FMC) cohort, and the Central Adelaide Local Health Network (CALHN) HREC for the Queen Elizabeth Hospital (QEH) cohort. A wavier of consent for acquisition of patient data was requested and approved from both HRECs. Justifications were that the work was retrospective in nature, would not interfere with patient's medical care, dealt with a predominantly elderly population with a high mortality rate and reasonably high patient numbers could be expected – especially during the early stages of casemix extraction.

The final approval and subsequent extensions from both the SALHN and CALHN HREC are available for viewing in *Attachment 1 – SALHN – Email Confirmation of Ethics Exemption , Attachment 2 – SALHN Email Confirmation of Ethics Extension, Attachment 3 – CALHN – Authorisation of Ethics Approval* and *Attachment 4 – CALHN Authorisation of Ethics Extension* respectively.

TERMS LIST

AAA – Abdominal Aortic Aneurysm

AF – Atrial Fibrillation

AHR – Adjusted Hazard Ratio

CABG – Coronary Artery Bypass Grafting

CALHN – Central Adelaide Local Health Network

CKD – Chronic Kidney Disease

CHA_2DS_2-VASc[1] – A clinical scoring tool that assists with long-term stroke risk stratification for atrial fibrillation patients. Includes: age, sex, congestive heart failure, hypertension, stroke/ TIA/ thromboembolism history, vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) and diabetes history.

CrCl – Creatinine Clearance

DAPT – Dual Antiplatelet Therapy

DOAC – Direct Oral Anticoagulant

DRG – Diagnosis-Related Group

DVT – Deep Vein Thrombosis

eGFR – Estimated Glomerular Filtration Rate

EMR – Electronic Medical Record

[1]A clinical scoring tool that assists with long-term stroke risk stratification for atrial fibrillation patients. Includes: age, sex, congestive heart failure, hypertension, stroke/ TIA/ thromboembolism history, vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) and diabetes history.

FMC – Flinders Medical Centre

GIB – Gastrointestinal Bleeding

HAC – Hospital Acquired Complication

HAS-BLED – A clinical scoring tool that estimates risk of major bleeding for patients treated with anticoagulation, to assess risk-benefit in atrial fibrillation care.

HR – Hazard Ratio

HREC – Human Research Ethics Committee

IHD – Ischemic Heart Disease

ICCU – Intensive and Critical Care Unit

ICD-10 – International Statistical Classification of Disease and Related Health Problems, 10th edition

IQR – Interquartile Range

LGIB – Lower Gastrointestinal Bleeding

LHN – Local Health Network

LOS – Length of Stay

NSQHS – National Safety and Quality Health Service

NSTEMI – Non – ST – Elevation Myocardial Infarction

NVUGIB – Non-Variceal Gastrointestinal Bleeding

PBS – Pharmaceutical Benefits Scheme

PC – Presenting Complaint

PCI – Percutaneous Coronary Intervention

PPI – Proton Pump Inhibitor

SALHN – Southern Adelaide Local Health Network

SAPT – Single Antiplatelet Therapy

SD – Standard Deviation

SPSS – Statistical Package for the Social Sciences

STEMI – ST – Elevated Myocardial Infarction

TQEH – The Queen Elizabeth Hospital

UGIB – Upper Gastrointestinal Bleeding

UR – Unit Record

COST BUCKET DEFINITIONS

Allied - Allied Health Services

Clinical - Clinical Services

Critical - Critical Care Areas

Deprec – Depreciation Costs

ED - Emergency Department

Hotel – Hotel Goods and Services

Imag - Imaging

Nonclinical - Non-Clinical Costs

Oncost – Labor (staff) oncosts, all stay types

OR - Operating Theatres

Other - Other Services

Pat Travel – Patient Travel

Path - Pathology Department

PayTax - Payroll Tax

Pharm - Pharmacy Department

Pharmacy PBS – PBS Pharmaceuticals (e.g. High Cost and S100)

Pros – Prosthetics

SPS - Special Procedure Suits

WardMed - General Ward Areas - Medical

WardNurs - General Ward Areas - Nursing

WardSupplies - General Ward Areas - Supplies

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ABSTRACT

Despite improvements in medical and surgical management in recent years, non-variceal upper gastrointestinal bleeding (NVUGIB) remains an expensive medical emergency with a high mortality rate. In this clinical landscape, antithrombotics (antiplatelets and anticoagulants) present unique and consequential challenges both prior and following a NVUGIB. These medications are essential for the treatment and prevention of a variety of serious and debilitating cardiovascular conditions. However, these agents undoubtedly increase the risk of recurrent gastrointestinal bleeding.

This thesis focuses on the costs associated with NVUGIB management and the real-world management of antithrombotics following acute NVUGIB, at two hospital networks in South Australia, with a comparison to contemporaneous recommendations in the literature. Variation between real and recommended management may signify an opportunity to reduce the future incidence, clinical severity and financial burden of NVUGIB.

The literature surrounding NVUGIB and antithrombotics indicated that the reinitiation of this therapy following a NVUGIB is largely beneficial, decreasing mortality and thrombosis, despite increasing bleeding risk. Primary prevention, especially in the elderly, should be ceased following a bleed and secondary prevention should be restarted when clinically appropriate. If indication allows, anticoagulation should be swapped to apixaban, given its superior safety profile (especially when compared to rivaroxaban and warfarin). Proton pump inhibitors (PPIs) should be initiated and continued upon discharge – with duration largely dictated by the duration of antithrombotics therapy.

When examining 358 eligible cases of NVUGIB, it was clear that real-world practice differed from literature in several important ways. Only 27 (60%) of primary prevention therapy cases were ceased upon discharge. Secondary prevention was ceased in 16 (13.9%) cases. Despite

adequate CHA2DS2-VASc scoring, 19 (15.1%) AF cases had their anticoagulation ceased upon discharge. Of the 62 AF cases that had anticoagulation continue upon discharge, there were 19 (30.1%) not treated with apixaban. PPI therapy was not prescribed in 23 (6.4%) cases where an antithrombotic was prescribed at point of discharge.

Following NVUGIB, the treating team's evaluation as to the ongoing benefits and risks of antithrombotics is essential. Documentation of these insights in the electronic medical record and discharge summary is essential to guide ongoing treatment and to inform future discussions between the patient and their families and health professionals providing care in the community. In 66.9% of anticoagulant and 73.4%% of antiplatelet cases, there were no such statements made in the patient's medical discharge summary.

Of the eligible 358 cases, costing analysis was undertaken on 85 cases, with a median total costing of $11,227.01 (IQR $6,434.71 – $19,637.09) per presentation. In those that presented to hospital with a NVUGIB, a strong and positive Pearson Correlation was found between the Total Cost and a patient's length of stay (0.663, p = <0.001). The estimated HAC costing had a wide variance, with a mean value of $2,099.31.

An analysis of case costing buckets revealed that staff labour, ward medical costs and ward nursing costs were consistently among the highest costing areas of NVUGIB cases. Drivers of cost appeared largely consistent and well portioned between high and low costing groups, as revealed by a K-means cluster analysis. The overall impression from this costing analysis was that unless length of stay can be meaningfully reduced, cost savings will be difficult without preventing the NVUGIB itself.

The reported research findings suggest there is scope to improve real-world patient care and to reduce the costing burden of NVUGIB by altering antithrombotic and PPI prescribing at the point of patient discharge. Communication within medical discharge summaries can be

improved. The research methods used could be applied to other real-world settings to inform improvement actions in other local contexts.

CHAPTER 1: INTRODUCTION

This research was motivated by a combination of clinical concern and academic curiosity, rooted in the practical experience of a hospital clinical pharmacist. The study emerged from direct observation and interactions with prescribers managing antithrombotic therapies in patients recovering from severe, often life-threatening, gastrointestinal bleeds (GIB).

Variations in prescribing practices and inconsistencies in medical documentation at the point of patient discharge were identified. These observations raised critical questions regarding the definition of best practices in this context and highlighted the need for evidence-based strategies to enhance patient care and outcomes.

The management of antithrombotics – antiplatelets and anticoagulants, present unique and consequential challenges. These medications are essential for the treatment and prevention of potentially lethal and debilitating conditions but increase the risk for developing, and may directly contribute, to recurrent complications of gastrointestinal bleeding. Therefore, the management of this therapy following a GIB can impact the patient's risk of mortality and morbidity, as well as their likelihood of re-presenting to hospital for either gastrointestinal rebleeding or thrombosis.

The investigation was narrowed specifically to Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB), guided by the knowledge that it is costly to the healthcare system and is often caused by antithrombotics.

The aim of this investigation was to investigate and estimate capacity to improve the prescribing patterns of antithrombotic therapy and related medical documentation, to improve patient outcomes, and reduce health service costs related to NVUGIB.

CHAPTER 2: LITERATURE REVIEW

2.1 METHODOLOGY

A literature search, limited to publications in the English language, was undertaken on 17th November 2021. Publications were included from January 2015 to the time of the search. A detailed search strategy (*Appendix 1*) was developed following a preliminary literature review. The search strategy was reviewed by a Southern Adelaide Local Health Network (SALHN) Reference Librarian prior to execution to ensure completeness. Once the strategy was finalised by the principal investigator, the search was undertaken by the librarian with approval from the Primary Supervisor. PubMed (National Centre for Biotechnology Information), EMBASE and Cochrane were searched [1-4]. The references of included papers were also hand searched.

Once the databases were searched, the results were downloaded into *EndNote*®, with duplicates removed. These citations were then uploaded into *Covidence*®, an online workflow platform that facilitates systematic reviews, accessible through Flinders University. Initially studies had their title and abstracts reviewed separately by the principal investigator and a randomised supervisor to ensure relevancy to the investigation. Full texts were then reviewed by the principal investigator. Consensus was then reached between the principal investigator and supervisors (JK, CP and GR).

Studies may have been excluded for the following: poor research question or hypothesis, significant sampling issues (small or unrepresentative sample size or selection bias) or flawed methodology (such as insufficient or inappropriate use of statistical methods). Sixteen studies fulfilled all criteria.

Literature Search

The study selection process captured 2539 studies being originally extracted from the databases. There were 2538 studies reviewed based on their title and abstract review. A subsequent 209 studies were approved for full text review, with a total of 64 studies being included in the final extract.

There were 16 studies included in addition to the Covidence extraction. Five from a preliminary literature review which included literature from outside of the initial date range, eleven cited within the extracted studies themselves (*Figure 1*).

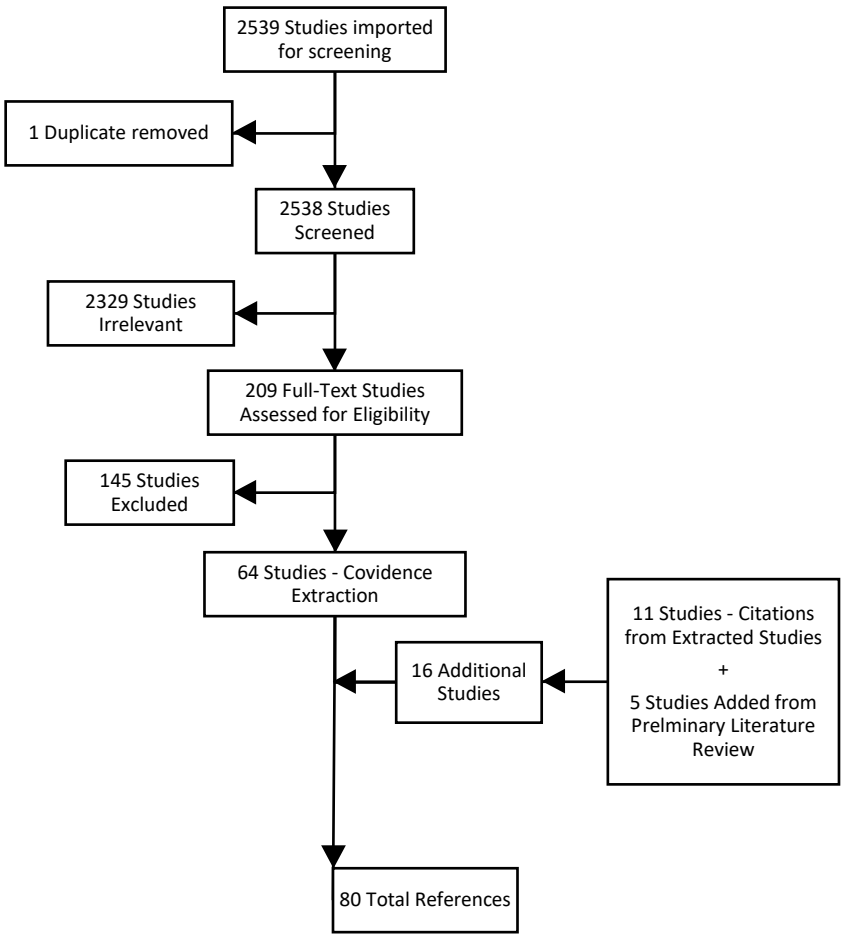

Figure 1 – Literature Search Flow Chart

2.2 GASTROINTESTINAL BLEEDING

Gastrointestinal bleeding (GIB) is considered a medical emergency and represents the most common cause of hospitalisations associated with digestive diseases in most countries [5-7]. Clinically GIB is classified as either upper (UGIB) or lower (LGIB). The former is defined as bleeding that originates above the ligament of Treitz, which includes the oesophagus, stomach or proximal duodenum. The later includes bleeding that originates below the ligament of Treitz. [1,6,8,9][2]

Although the overall incidence of UGIB is relatively low, it is a serious medical condition often requiring hospitalisation and causes significant costs to the healthcare system. The annual incidence of hospitalisation for acute UGIB in the general population is approximately 100 per 100,000 individuals [1].

Over the past 20 years the management and outcomes of UGIB have changed considerably. A large nationwide analysis of UGIB between 2002 to 2012 in the United States from Wuerth et al., [10] showed a decreased relative rate of hospitalisation and all-cause inpatient mortality following condition onset – 21% and 28% respectively. These changes include the addition of medication that suppresses acid secretion (e.g., proton pump inhibitors), the recognition and treatment of Helicobacter pylori (*H. pylori*), better awareness of Non-Steroidal Anti-inflammatory Drugs (NSAID) adverse effects and improved diagnostic and therapeutic endoscopy practices, more restrictive blood transfusion policies and improved critical and geriatric care [5,6,8,9,11].

UGIB can be further classified as variceal (VUGIB) or non-variceal UGIB (NVUGIB). These conditions are distinct due to differing causes, medical management and clinical outcomes.

[2] References stated outside of sentence, at end of paragraph, are applicable for all statements issued following the last referencing number.'

NVUGIB has a considerable mortality risk and has an incidence five times higher than VUGIB in most countries. VUGIB is caused by dilated submucosal veins (varices), both oesophageal or gastric in nature and is usually associated with both chronic liver disease and portal hypertension. [6,8]

In the community NVUGIB has a variety of causes. Peptic ulcers account for approximately 60% of all UGIB presentations [1,9]. These occur where the mucosal barrier breaks down and exposes the submucosa to harmful pepsin and acid within the gastroduodenal lumen, disturbing blood coagulation [1,6]. Peptic ulcers are most commonly caused by either bacterial *H. pylori* infection, the use of NSAIDs and/or aspirin. Other causes include anticoagulants and other antiplatelet agents [1,6]. Peptic ulcer bleeding may signal a general decline in health, as a marker of other co-existing comorbidities [12]. Evidence for this is the potential excess long-term mortality following a peptic ulcer, which include not only rebleeding but cardiovascular disease, respiratory disease and cancer [12]. Other causes of NVUGIB include gastroduodenal erosion, oesophagitis or oesophageal ulcers, vascular lesions, vascular ectasias, Mallory-Weiss tears and less often neoplastic lesions [1,5,6].

Symptoms of NVUGIB may include vomiting of blood (hematemesis), blood in stools (melena), abdominal pain and cramping, chest pain, burning, fatigue, dizziness, palpitations and diarrhoea [5,6,8,9,13]. NVUGIB can have a significant impact on an individual's quality of life (QOL) as well as their family [6,14]. This impact can occur during the acute event, the hospitalisation and beyond discharge from hospital [6,14]. Aside from the immediate symptoms (which can be painful and distressing), following discharge patients are commonly left with anaemia which can be associated with fatigue, heart palpitations, pallor, and shortness of breath [6]. Major intestinal bleeding can reduce QOL for up to nine months post bleed [15].

It is difficult to measure bleeding-related mortality due to NVUGIB as the condition often coexists among multiple comorbidities and acute conditions [6,8,15]. The majority of those afflicted by NVUGIB die from non-bleeding-related causes, their exact relationship to the bleeding event uncertain. The mortality rate varies widely in studies and target population (2-10%) [6,8,15]. During hospitalisation, NVUGIB has a four-fold increase in mortality compared to general community background mortality and often occurs in association with other serious conditions [6]. These can include neurological, renal, cardiac, pulmonary, metabolic, traumatic or septic conditions and can lead to haemodynamic instability and development of further bleeding [6]. A major bleeding event can also increase the risk of further thrombotic events due to a collection of compensatory mechanisms [6].

A complication following an acute GIB is recurrent bleeding. Like the index bleed, this can vary in severity and outcomes, potentially leading to rehospitalisation and death [16]. The index site (UGIB or LGIB) will affect the patient's short and long-term risks of rebleeding[16].

There are a variety of risk factors for the development of UGIB. Some of these are modifiable, including medication use (such as antithrombotics, NSAIDs, serotonin reuptake inhibitors, metamizole, calcium channel blockers and aldosterone antagonists), concomitant *H. pylori* infection, a history of dyspepsia and smoking [5,15].

Increased age is correlated with increased UGIB incidence, related morbidity and mortality. Approximately 70% of UGIB cases occur in those aged ≥60 years. This phenomenon is likely explained by age related physiological alterations of the GI tract, increasing comorbidities (such as cardiovascular diseases, respiratory and renal failure) and increasing use of prescribed medications including antithrombotics [1,6,11,17,18].

Oral anticoagulants (OAC) and low dose aspirin (LDA) are used in the treatment of cardiovascular disease and can contribute additional risks for developing UGIB [6,8,11,19,20].

Using a combination – both an antiplatelet and an anticoagulant, further increases the risk of UGIB by 60% compared to the background risk experienced by the general population [17].

The use of antithrombotics, in patients who develop NVUGIB, has been associated with a greater need for hospitalisation, transfusion and re-bleeding events when compared to non-users [21]. However, for peptic ulcers, regardless of background antithrombotic use, there is no difference in mortality for NVUGIB [19,20].

2.3 ANTIPLATELET THERAPY

Antiplatelets are endorsed worldwide as first-line treatment for cardiovascular disease. Indications include acute coronary syndrome, thrombosis prevention following cardiac stenting, peripheral vascular disease and transient ischemic attack (TIA) or stroke. However, adverse effects include GIB. Low dose aspirin (LDA) is the most commonly used antiplatelet, especially amongst the elderly population. Throughout this review, LDA refers to a single daily dose of 75-100mg unless otherwise specified. [1,5,9,22,23]

Antiplatelets can be used as single agents or in combination. Using two antiplatelets simultaneously is commonly referred to as dual-antiplatelet therapy (DAPT), and usually consists of LDA and a P_2Y_{12} platelet receptor inhibitor such as clopidogrel, prasugrel or ticagrelor. DAPT is recommended following acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI). DAPT (aspirin with clopidogrel) is recommended for a 90-day period for secondary prevention of ischaemic stroke, with a single antiplatelet continuing lifelong thereafter. These combinations are commonly prescribed in the elderly population, as there is increasing prevalence of stroke, acute coronary syndrome, and peripheral artery disease with age. [1]

Despite its efficacy DAPT has an associated additive risk of GIB when comparted to LDA, with UGIB being more common than LGIB (for aspirin and clopidogrel). Risk factors for DAPT-related GIB include older age, comorbidities, alcohol use, non-white race, anticoagulant use, renal disease, male gender. [16,17,22,24-26]

The term ‘triple therapy’ refers to the prescribing of DAPT along with an anticoagulant. Patients who have ACS (with or without cardiac stenting) and atrial fibrillation (AF) with significant stroke risk, will require DAPT therapy for at least 12 months and an anticoagulant

long-term. These patients are considered to be at considerable risk for both GIB and thrombosis. [27,28]

In Australia and a number of other countries, aspirin is available as an over-the-counter product in a variety of doses. At higher doses aspirin can be used as an anti-inflammatory and analgesic. LDA is available on the Pharmaceutical Benefits Scheme (PBS) General Schedule for cardiovascular disease, both as a singular agent and in combination with other antiplatelets (clopidogrel or dipyridamole). P_2Y_{12} platelet receptor inhibitors - clopidogrel, ticagrelor and prasugrel have more narrowly approved uses within the PBS. Under the PBS these agents are only approved for specific indications, or as substitutes for aspirin therapy in those that have an intolerance or allergy that will prevent its required use. [29]

Aspirin can be used as either 'primary prevention' or 'secondary prevention'. Primary prevention refers to use in patients who are of a high risk of developing, but are not currently diagnosed with, cardiovascular disease. The goal of this therapy is to prevent cardiovascular disease from occurring. Secondary prophylaxis is treatment in a patient who has suffered a myocardial infarction or particular types of cerebrovascular events, to prevent a secondary event from occurring. [24]

Primary prevention, as a strategy, has declined in recent years with recent data supporting the notion that it is may be more harmful than beneficial in the elderly, especially in those over 70 years. The contention is that aspirin will increase GIB without providing a meaningful survival benefit through decreasing potential cardiovascular events [1,24,30]. Compared with non-users, LDA increases the risk of developing NVUGIB by two-fold [6].

Secondary prevention is encouraged as appropriate first-line therapy and compared to primary prevention, offers a better benefit to risk ratio. The number needed to treat (NNT) to prevent

myocardial infarction, stroke or vascular death being 67, compared to 1745 in primary prevention. [8,31-33]

Through systematic antiplatelet effects, antiplatelets (such as aspirin and clopidogrel) increase the risk of GIB. Aspirin, unlike clopidogrel, has a topical mechanism that promote peptic ulcers and GIB [23]. There are limited studies that compare the prevalence of UGIB between aspirin and clopidogrel users [17].

The literature review produced numerous studies exploring the differences in GIB risk between the different antiplatelets. The key outcomes and recommendations are displayed in *Table 1* below.

Literature Evaluation

From the available literature it would be reasonable to conclude that LDA increases the risk of UGIB, especially in the initial months of therapy and at higher doses. Among LDA users, primary prevention appears to present a higher risk of UGIB with little benefit, and this is clearly age-related. LDA when combined with NSAIDs, as part of DAPT, or with OAC worsen the incidence of UGIB. Among the P_2Y_{12} platelet receptor inhibitors, prasugrel appears to have a higher risk of causing an UGIB. However, when used in DAPT, it is unclear if the choice of P_2Y_{12} agent influences the overall risk of developing a major GIB. PPI therapy appears to decrease the risk of developing an UGIB in patients prescribed DAPT.

Despite the evidence and recommendations put forward from international guidelines, the PBS is currently restrictive with PPI use. PPIs in Australia (pantoprazole, esomeprazole, omeprazole, rabeprazole and lansoprazole) are only eligible for Streamlined Authority when used in the initial treatment of known peptic ulcers, not as preventative therapy [29].

Table 1 – Summary of Literature – Antiplatelets and GIB Risk

Study Type	Authors and Referencing	Key Findings and Recommendations
Umbrella Review – Systematic Reviews and Meta-Analysis	Veronese et al [34] .	Primary Prevention LDA – decreased cardiovascular disease incidence by 17% but was associated with a 34% increased relative risk of bleeding (major GI and intracranial). This included a higher risk of both UGIB and LGIB.
Systematic Review and Meta-Analysis	Guo et al. [35]	GIB risk substantially varied between P_2Y_{12} platelet receptor inhibitors. Prasugrel and ticagrelor - associated with greater overall GIB risk (RR 1.28, 95% CI 1.13 – 1.46) and UGIB (RR 1.32, 95% CI 1.05 – 1.67) compared to clopidogrel. Compared to clopidogrel, prasugrel had the highest UGIB risk (RR 1.40, 95% CI 1.10 – 1.77).
Meta-Analysis	Cardoso et al. [36]	Patients prescribed PPI therapy with DAPT decreased risk of an UGIB (OR 0.31, p=0.002) compared to those without PPI therapy.
Cohort Study – with Nested Case-Control Analysis	Rodriguez et al.[37]	LDA was associated with increased risk for UGIB (adjusted OR 1.53, 95% CI, 1.34 – 1.75). Greatest risk ≤ 3 months of initiation. Dose associated risk with aspirin and UGIB, with 75mg/day having adjusted OR 1.50 (95% CI, 1.31 – 1.71) and >75mg/day dosing OR 2.02 (95% CI 1.47 – 2.78). Primary prevention aspirin had a higher risk of UGIB compared to secondary prevention – adjusted OR 1.62 (95% CI, 1.38 – 1.90) vs 1.16 (95% CI, 0.89 – 1.50). Higher UGIB risk with DAPT (aspirin and clopidogrel) - adjusted OR 3.69 (95% CI 2.59 – 5.26). Higher UGIB risk when LDA combined with warfarin had an increased risk of UGIB –adjusted OR 3.22 (95% CI, 1.93 – 5.39). Increased international normalised ratio (INR) of ≥3, associated with ~5-fold increased risk of UGIB (OR 5.67, 95% CI 2.82 – 11.39). Associated UGIB risk factors with LDA: haemodialysis, a history of peptic ulcer, NSAIDs, DAPT and warfarin.
Retrospective Observational Cohort Study	Laredo et al. [38]	. In this study, the authors analysed 1327 patients taking DAPT (with clopidogrel, ticagrelor or prasugrel) and found no difference between DAPT types for the risk of major GIB (adjusted HR 0.996, 95% CI 0.497 – 1.966).

2.4 ANTICOAGULANT THERAPY

Anticoagulants are currently used for a variety of cardiovascular indications. These conditions include venous thromboembolism (VTE) treatment and prophylaxis (following joint replacement procedures), pulmonary embolism (PE), embolic stroke prevention in AF, and in the case of warfarin (a vitamin K antagonist) for prophylactic anticoagulation following insertion of mechanical heart valve prosthesis. Uniquely, low dose rivaroxaban is also used for stable chronic peripheral vascular and coronary artery disease. As aging populations grow, it is expected that OAC use will increase substantially in years to come. [1,5,7,9,39]

Currently only warfarin and direct oral anticoagulants (DOAC) apixaban, dabigatran and rivaroxaban are widely available in Australia. Warfarin is available on the PBS without restriction. DOACs are restricted by Streamline Authority for non-valvular AF and treatment and prevention of deep vein thrombosis (DVT) and PE. Low-dose rivaroxaban (2.5mg) has recently acquired a Streamline Authority for the treatment of chronic stable atherosclerotic disease. [29]

For the treatment of AF (unlike DVT or PE) the clinical scoring system of CHA_2DS_2-VASc can indicate the approximate risk of thrombosis (stroke) if left untreated [29,33]. The former calculates thrombosis risk based on congestive heart failure, hypertension, age (>65 and ≥75 years), diabetes and previous stroke/transient ischemic attack [40]. A CHA_2DS_2-VASc scoring of ≥ 2 for men and ≥ 3 for women (due to differential scoring of sex) was deemed a substantial risk of thrombus, therefore justifying the use of oral anticoagulation which aligns with international guidelines [28,33].

When evaluating AF, clinicians can often use scoring systems such as HAS-BLED for the prediction of major bleeding risk – usually in conjunction with CHA_2DS_2-VASc scoring. HAS-BLED presents bleeding risk in the form of a numerical score based on hypertension, abnormal

renal and liver function, stroke, prior bleeding, labile INRs, age (>65 years), drug and alcohol use [40]. However, HAS-BLED should not be used as justification to withhold or cease anticoagulation, instead it should prompt prescriber review of modifiable factors to decrease bleeding risk. This key message has been forwarded by numerous authorities, including the American Heart Association the European Society of Cardiology and the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand who all state that the decision to anticoagulate a patient with AF should be made from evaluating both benefit and risk [28,33,41]. It should be noted that in most patients with AF, there is a larger comparative risk of suffering a stroke compared to experiencing a serious bleed. They have clearly proposed that the HAS-BLED score be used as a warning to clinicians to address potentially modifiable risk factors. An example of this would be acute uncontrolled systolic hypertension (≥160 mmHg) (not merely a past medical history of hypertension). Where treating this would reduce the ongoing risk of bleeding for the patient (while also lowering stroke risk).

Historically, warfarin therapy has been the preferred option in patients with compromised renal function. This is due to the majority of DOAC landmark trials having excluded patients with CrCl <30 ml/min (< 25ml/min for apixaban) (RE-LY – dabigatran, ROCKET-AF – rivaroxaban, ARISTOTLE – apixaban, ENGAGE-AF TIMI 48 – edoxaban). Presently there is great inconsistency between the international AF guidelines for what stage of renal dysfunction justifies a preference for warfarin. In the absence of clear guidance, many clinicians will follow the more stringent and inflexible dosing guide provided by the manufacturer. [31]

In more recent years, warfarin use has decreased and been replaced with the newer DOACs due to their standardised dosing, no necessity for ongoing monitoring such as INR with warfarin and fewer drug interactions. However, warfarin remains the only proven and indicated anticoagulant following a mechanical heart valve replacement. [1,42]

There have been attempts to study DOAC use following a mechanical heart valve replacement. The RIWA study, a proof-of-concept, open-label, randomized clinical trial showed similar incidences of thromboembolic and bleeding events between warfarin and rivaroxaban cohorts but was hugely underpowered for these endpoints[43]. A trial comparing apixaban to warfarin with On-X® mechanical valves was attempted, with the trial stopping early due to excessive thromboembolic events being observed in the apixaban group[44]. Dabigatran is currently contraindicated in those with mechanical heart valves, due to it demonstrating failure to prevent thromboembolic events[45].

The most significant adverse effect of anticoagulation is undoubtedly major bleeding, and one that commonly concerns both clinicians and patients [7,14]. Data regarding the all-cause mortality and specific causes of death after a major OAC-associated bleed are limited, however the 30-day mortality risk is substantial - estimated to be 11-12% based on several of studies [7]. GIB accounts for almost half of all OAC-related major bleeding events, and OAC use is a known risk factor specifically for NVUGIB [1,6,7,14]. Evidence also suggests that for both UGIB and LGIB, a patient is of highest risk developing a bleed following the initiation of the OAC, with this risk decreasing over time [7]. The incidence of GIB among OAC randomised trials varies for those treated for VTE, ranges between 0.5 –1.6/100 patient-years and in those treated for AF, it ranges between 0.8 –1.9/100 patient-years [7]. For warfarin treatment, GIB is the most common site of bleeding, with an incidence three times higher than the general population (approximately 5.8/1000-person years) [15].

There are many risk factors for OAC-associated GIB. Some appear generic for all OAC, others unique to a particular class – either warfarin or DOACs. A prior history of GIB is a significant risk factor, regardless of the type of OAC [7,46,47]. It is estimated from trial data that those with a GIB history have a 2-3-fold increased risk of suffering a major GIB when compared to

those without [7]. Additional risk factors for OAC related GIB include baseline anaemia, sleep apnoea, NSAID and antiplatelet use (either aspirin or others), presence of *H. Pylori*, increased age, history of heart failure, increased body mass index and smoking [7,17,46,47].

For those prescribed warfarin therapy – older age (≥65 years), liver cirrhosis, lipid-lowering agents (for UGIB), or presence of diverticulosis are associated with increased risk of GIB [17]. For those prescribed DOAC therapy, increased GIB risk has been associated with older age (≥75 years) and comorbidities including renal impairment (creatinine clearance ≤50ml/min). Drug interactions through both the cytochrome P450 metabolism and P-glycoprotein efflux transporter systems can also increase drug levels and subsequently bleeding risk. [17,47,48]

When comparing classes, meta-analyses have demonstrated that DOACs do not pose an increased risk of major GIB compared to warfarin [48,49]. However, there is evidence to suggest that the individual DOACs possess variable risks in causing major GIB, both in comparison to warfarin and to one another [13,49,50]. DOACs have not been compared directly to one another in randomised trials. Due to the lack of comparative data,, it is hard to draw firm conclusions regarding the relative efficacy and safety of individual DOACs, among variable indications and doses. [7,13,48]

This literature review identified studies that explored the differences in GIB risk between the different classes of OAC, and between the individual DOACs. The key findings and recommendations are displayed in *Table 2*.

Literature Evaluation

In evaluating this evidence, there is no randomised controlled trials that explore the benefits and risks of OAC directly against one another. However, based on this literature it would be reasonable to deduce that warfarin and DOACs as a class may have a comparative GIB risk.

Irrespective of indication, the evidence suggests that apixaban is the safest OAC and rivaroxaban the most harmful. Based on this, it may be reasonable for high-risk patients requiring DOAC therapy to be preferentially prescribed apixaban and to avoid rivaroxaban wherever possible. It is also reasonable for protective medications (PPIs) to be prescribed when clinically appropriate, and risk factors such as *H. pylori*, NSAIDs and harmful drug interactions addressed proactively. Warfarin-treated patients experiencing high INRs or higher dose DOAC therapy in those with impaired renal function also presents additional risks for GIB.

Table 2 – Summary of Literature – Anticoagulants and GIB Risk

Study Type	Authors and Referencing	Key Findings and Recommendations
Systematic Review and Meta-Analysis – Randomised Controlled Trials	Aloysius et al. [51]	As a class, DOACs had similar GIB risk compared to warfarin therapy (RR 1.04, 95% CI 0.85 – 1.27) but had a lower risk of fatal GIB (RR 0.39, 95% CI 0.15 – 0.82). A major determinant of warfarin's fatal GIB risk was found to be poor INR control (time in therapeutic range (TTR) <60%).
Systematic Review and Network Meta-Analysis	Radadiya et al. [42]	The following DOACs had a higher bleeding risk when compared to warfarin – rivaroxaban (47% increase), dabigatran at standard dosing (150mg twice daily) (40% increase), and edoxaban (22% increase). Apixaban was the only agent not showing increase bleeding rates compared to warfarin. Apixaban (at standard 5mg dose, twice daily) also had a lower major GIB risk when compared to dabigatran (odds ratio (OR) 0.63, 95% CI 0.44 – 0.88) and rivaroxaban (OR 0.60, 95% CI, 0.43 – 0.83). Apixaban had the best safety profile for GIB and should be considered in high-risk patients. DOAC dosing should be tailored to the individual patient profile to appropriately balance benefits and risks.
Meta-Analysis – Four prospective randomised controlled trails (RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48)	Vingogradova et al. [52]	DOAC agents had substantial differences in their association with GIB. As a class, DOACs were associated with a higher GIB risk than warfarin (RR 1.23, CI 95% 1.03 –1.46, p=0.01). Rivaroxaban (RR 1.46, CI 95% 1.2 – 1.8, p<0.001), high-dose edoxaban (RR 1.22, CI 95% 1.01 – 1.47, p=0.038) and dabigatran (RR 1.50, CI 95% 1.20 – 1.88, p<0.001) were found to significantly increase GIB with nil association being found with apixaban.
Systematic Review	Anghel et al. [48]	Compared to warfarin: • Apixaban had the lowest risk of GIB, HRs varied from 0.45 (95% 0.34 – 0.59) to 1.13 (95% CI 0.79 – 1.63). • Dabigatran had either lower or nil significant difference, HRs varied from 0.58 (95% CI 0.47 – 0.71) to 1.43 (95% CI 1.07 – 1.90). • Rivaroxaban had a similar or higher GIB risk compared to warfarin, HRs varied from 1.00 (95% CI 0.87 – 1.16) to 1.38 (95% CI 1.12 – 1.54).
Cohort Study	Vinogradova et al. [50]	Compared to warfarin: • Apixaban was associated with a decreased risk of major bleed (adjusted HR (AHR) 0.66. 95% CI 0.54 – 0.79) and intracranial bleeding (AHR 0.40, 95% CI 0.25 – 0.64). • Dabigatran was associated with decreased risk for intracranial bleeding (AHR 0.45, 95% CI 0.26 – 0.77). • Rivaroxaban at any dose was associated with an increased risk of all-cause mortality (AHR 1.19, 95% CI 1.09 – 1.29). NNT (i.e., to avoid a major bleed) for each DOAC in comparison to warfarin therapy. Over a six-month period, apixaban resulted in the lowest NNT for those with AF (182, 95% CI 137 – 299) and those without (138, 95% CI 102 – 207).

		NNH (i.e., to observe an added death) was established for each DOAC in comparison to warfarin therapy. The most concerning agent, with the lowest NNH over the 6-month period, was rivaroxaban – both for those with AF (202, 95% CI 131 – 410) and those without (61, 95% CI 47 – 82).
Retrospective Cohort Study	Ray et al. [53]	Rivaroxaban had the greatest incidence of UGIB hospitalisations when compared to apixaban (incidence rate ratio (IRR) 1.97, 95% CI 1.73 – 2.25), dabigatran (IRR 1.19, 95% CI, 1.08 – 1.32) and warfarin (IRR 1.27, 95% CI 1.19 – 1.35). When comparing apixaban to rivaroxaban, the greatest difference in bleeding rate was observed in the high bleeding risk cohort. Concomitant PPI therapy was associated with lower hospitalisation (IRR 0.66, 95% CI 0.62 – 0.69) and lower rates of UGIB.
Population-Based Cohort Study	Komen et al. [54]	AF cohort – treated with DOACs, the use of PPIs was associated with a 25% decreased risk of developing UGIB. This protective benefit was greatest in the elderly (≥75 years), those at high bleeding risk (HAS-BLED ≥3) and those prescribed antiplatelets. The benefits of PPI therapy were only present in those taking apixaban or dabigatran, not those taking rivaroxaban.
Retrospective Propensity Cohort Study	Abraham et al. [55]	AF population, incidence of GIB rates – expressed as events/ 100 patient years: • Dabigatran – 2.29/ 100 patient years (95% CI 1.88 – 2.79). • Warfarin had an incidence of 2.87/ 100 patient years (95% CI 2.41 – 3.41). • Rivaroxaban 2.84/ 100 patient years (95% CI 2.30 – 3.52). Study did not include apixaban patients. GIB risk was increased significantly with older age (≥65 years). Prescribers should use caution when prescribing dabigatran or rivaroxaban in those aged over 75 years of age.
National Population-Based Cohort Study	Ingason et al. [56]	Comparing the rates of GIB among DAOCs – apixaban, dabigatran and rivaroxaban users. • Rivaroxaban had a higher major GIB rate than apixaban – 1.9 vs 1.4 events / 100 person years (95% CI 1.00 – 2.24). • Rivaroxaban also had a higher UGIB rate when compared to both apixaban (HR 1.30, 95% CI 0.74 – 2.27) and dabigatran (HR 3.75, 95% CI 1.32 – 10.71).
Retrospective Cohort Study	Youn et al. [57]	PPI agents, when used prophylactically, may reduce the risk of UGIB in patients receiving DOACs and with additional risk factors (e.g. history of UGIB, peptic ulcers or concomitant antiplatelet use)
Review Article – Key AF Trials	Xu et al. [7]	Incidence and distribution of GIB was compared within 12 key AF trials. Compared to warfarin: • Dabigatran (150mg twice daily), rivaroxaban (20mg once daily), and edoxaban (60mg once daily) had an increased bleeding risk. • Nil increased risk seen in standard apixaban dosing (5mg twice a day) or reduced edoxaban (30mg once daily). While trials do exist comparing the variable dosages of DOACs and their relative efficacy and safety profile, they do not address this issue in the context of post GIB.

2.5 POST BLEED MANAGEMENT

The decision to recommence an antithrombotic following a major GIB relies on a careful evaluation of the short and long-term risks of thromboembolism, recurrent GI bleeding (with or without antithrombotics) and the consequences to the patients including death. The decision to restart or cease therapy should involve a multidisciplinary team and the patient. [1,6,7,13,14,16].

Most clinicians are aware of the cyclical relationship between bleeding and thrombosis, particularly among those treated with antithrombotics who are of high risk of both events. A thrombotic event will lead to treatment with antithrombotics, increasing the patient's risk of bleeding. Bleeding events can trigger a prothrombotic response, further increasing the acute risk of thrombosis. A bleeding event may cause the temporary or permanent cessation of antithrombotic therapy, increasing the risk for future thrombotic events. [22]

Reintroducing antithrombotics following a GIB appears to be met with an overall survival benefit. This is unsurprising when considering mortality following the event is more often caused by underlying comorbidities (especially cardiovascular disease) as opposed to the bleed itself. The key findings from the literature, including clinical recommendations, are displayed in *Table 3.*

Table 3 – Summary of Literature – Antithrombotic Resumption Following GIB

Study Type	Authorship and Referencing	Key Findings and Recommendations
Antithrombotics		
Population-Based Cohort Study	Komen et al. [58]	The 90-day mortality in AF patients following a major GIB was 10.9% for those treated with DOACs, and 11.4% for warfarin. Those treated with antiplatelet therapy only, no particular antiplatelet agent had worse outcomes.
Nationwide Observational Cohort Study	Staerk et al. [59]	Investigated long-term outcomes in patients taking antithrombotics (warfarin, dabigatran, rivaroxaban, aspirin, clopidogrel, prasugrel or ticagrelor), hospitalised GIB patients and comorbid AF who were subsequently discharged. At 2 years, the cumulative incidence of all-cause mortality was 39.9% (95% CI 38.4 – 41.3). Restarting or modifying treatment to a single anticoagulant was associated with the lowest rate of all-cause mortality (HR 0.39, 95% CI 0.34 – 0.54) and thromboembolism (HR 0.41, 95% CI 0.31 – 0.54) when compared to all other treatment strategies (including cessation of therapy).
Observational Cohort Study	Sostres et al. [60]	The discontinuation of antithrombotics following a GIB had both short-term (90-days post event) and long-term increased risk of death and thromboembolic events compared to those that resumed therapy. Noteworthy is that for those with UGIB receiving OAC – resuming OAC was associated with lower ischaemic event rate when compared to not resuming therapy, HR 0.385 (95% CI, 0.172 – 0.864) but a marked increase in recurrent bleeding HR 4.350 (95% CI, 1.294 –14.628).
Observational Cohort Study	Hosni et al [61]	Resumption of antithrombotics (cardiovascular indications only) following GIB was protective against mortality (HR 0.53, 95% CI 0.31 – 0.92, p=0.023).
Retrospective Cohort Study	Sengupta et al. [62]	Among patients receiving DOAC therapy and hospitalised for GIB, in a 90-day post index bleed analysis, rivaroxaban had the highest rate of recurrent bleeding compared to other DOACs (log rank, p=0.4)
Antiplatelets		
Systematic Review and Meta-Analysis	Hashash et al. [63]	Following NVUGIB, resuming aspirin was associated with reduced mortality (HR 0.20, 95% CI 0.06 – 0.63) and increasing rebleeding risk (HR 1.90, 95% CI 0.60 – 6.00).
Systematic Review and Meta-Analysis	Wu et al. [64]	Compared clopidogrel (with and without PPI therapy) to aspirin with PPI therapy – for secondary prevention in those with histories of UGIB, peptic ulcer or preformation. No significant differences in the rates of recurrent UGI events were found between aspirin with PPI therapy and clopidogrel with PPI therapy. Commentary included assessment that aspirin plus PPI therapy is more cost effective and should be considered first choice compared to clopidogrel (± PPI).
Parallel Randomised, Placebo-Controlled Noninferiority Trial	Sung et al. [65]	Low dose aspirin, compared with placebo, was associated with high rebleeding rates but lower all-cause mortality within a 30-day period. • Placebo cohort – recurrent bleeding rate 5.4% and all-cause mortality 12.9%. • Aspirin cohort – recurrent bleeding rate 10.3% and all-cause mortality 1.3%. Differences in mortality were seen in cardiovascular, cerebrovascular, and gastrointestinal complications.

		This study is cited in most international guidelines as key evidence for the benefit of LDA continuation following an UGIB.
Anticoagulants		
Systematic Review and Meta-Analysis	Tapaskar et al. [66]	In those that resumed anticoagulation following a related GIB, the rates were higher (10.1%) compared to those that discontinued (5.3%). Anticoagulant resumption was associated with increased recurrent GIB (OR 1.646, 95% CI 1.035 – 2.617, p=0.035). However, resumption was associated with a significant decrease in thromboembolic events (OR 0.340, 95% CI 0.178 – 0.652, p=0.001) and reduction in mortality (OR 0.499, 95% CI 0.419 – 0.595, p<0.0001). The timing of OAC reinitiation was difficult to interpret due to the time until effect being radically different between classes of OAC.
Meta-Analysis	Little et al. [14]	Resuming anticoagulation following a related GIB was associated with an increased risk of recurrent GIB (RR 1.91, 95% CI 1.47 –2.48), a reduced risk of thromboembolism (RR 0.30, 95% CI 0.13 – 0.68) and decreased mortality risk (RR 0.51, 95% CI 0.38 – 0.70). This same overall trend for OAC recommencement was seen specifically in the UGIB patient cohort – with reduced thromboembolism (RR 0.19, 95% CI 0.08 – 0.45), reduced mortality (RR 0.70, 95% CI 0.53 – 0.91) and increased recurrent GIB risk (RR 1.69, 95% CI 1.05 – 2.71).
Prospective Observational Cohort Study	Sengupta et al. [67]	The continuation of anticoagulation (74% of patients prescribed warfarin) following a hospitalising GIB was associated with significantly lower rate of major thrombotic events within 90 days (HR 0.121, 95% CI 0.006-0.812, p=0.03). For patients who discontinued anticoagulation, the majority of thromboembolisms occurred in the following 2 weeks post hospital discharge.
Prospective Cohort Study	Qureshi et al. [68]	In patients treated for AF and who experienced a GIB, those that restarted a single anticoagulant (without an antiplatelet agent) had the lowest rates of all-cause mortality (HR 0.39, 95% CI 0.34-0.46) and thromboembolism (HR 0.41, 95% CI 0.31-0.54) but had a marked increase of major bleeding (HR 1.37, 95% CI 1.06-1.77).
Prospective Observational Study	Camm et al. [69]	Reducing dosages of DOACs in AF patients is associated with a higher risk of all-cause mortality (HR 1.24, 95% CI 1.04 – 1.48). A reduction of DOAC dosing below recommended dosages to decrease bleeding risk is unadvisable.
Multicentre Retrospective Cohort Study	Lee et al. [70]	In patients with AF and a history of peptic ulcer being treated with warfarin, the comparative benefits and risks of therapy can be greatly influenced by their time in therapeutic range (TTR), i.e., the average amount of time a patient's INR is between the aimed 2-3 range. A net clinical benefit model, a TTR≥ 65% yielded beneficial effects and a TTR≤55% harmful effects. Demonstrating that patients with poor INR management have an increased risk of adverse effects, including major bleeding. DOACs do not have the same issues with TTR as warfarin, and so pose a potential advantage in the post UGIB patient cohort who still require OACs.
Retrospective Observational Study	Ruiz et al. [71]	Investigated emergency re-presentations of elderly (≥65 years) patients with AF and OAC who had originally visited emergency for GIB. Study was underpowered to detect difference based on anticoagulation status upon discharge, they did discover that roughly 13% of patients re-presented within 30-days, indicating that short-term re-presentation is not uncommon.
Multicentre, Retrospective Cohort Study	Candeloro et al. [72]	Continuing anticoagulation post index GIB is associated with lower risk of thromboembolism (adjusted HR 0.34, 95% CI 0.21 – 0.55) and death (adjusted HR 0.50, 95% CI 0.36 – 0.68), but also a higher risk of major recurrent bleeding (adjusted HR 1.47, 95% CI 0.96 – 2.26). Recurrent bleeding risk was highest when anticoagulation was restarted within 7 days of index bleed (11%), compared to 14-21 days post bleed (8-9%).

Nationwide Observational Cohort Study	Lee et al. [73]	Patients with a history of UGIB (and were OAC naïve at the time), were prescribed an OAC (warfarin, rivaroxaban, dabigatran, apixaban or edoxaban) and then observed for a major GIB in a follow up period. Patients were also categorised according to PPI use. Among all OACs, rivaroxaban without PPI use had the highest crude incidence of major GIB (2.96 / 100 person-years). When compared to non-PPI users, those with OAC and PPI therapy had significantly lower risk of major GIB.
Nationwide Retrospective Observational Cohort Study	Kwon et al. [74]	Investigated ischaemic stroke and major bleeding in patients who had a history of GIB and were prescribed either warfarin or DOAC. Overall, DOAC use was associated with statistically significant decreased rates of ischaemic stroke (39%), lower major bleeding (27%) and composite outcomes (34%) when compared to warfarin. A lower risk of all-cause death (18%) was also associated with DOAC compared to warfarin. Of all DOACs, apixaban was associated with the lowest risk of major bleeding (HR 0.653, 95% CI 0.523 – 0.807). Only dabigatran (HR 0.762, 95% CI 0.576 – 0.989) and apixaban (HR 0.724, 95% CI 0.565 – 0.917) were associated with a lower risk of recurrent GIB when compared to warfarin. An additional finding was that apixaban, dabigatran and edoxaban were associated with a decreased risk of clinical events compared to rivaroxaban in AF patients with a history of GIB.
Retrospective Cohort Study	Tapaskar et al. [47]	In those treated for AF and hospitalised for a GIB, resuming OACs was associated with decreased risk of thromboembolism– warfarin (HR 0.61, 95% CI 0.39 – 0.96, p=0.033) and DOACs (HR 0.52, 95% CI 0.28 – 0.98, p=0.044). Resuming warfarin following index GIB was significantly associated with increased recurrent GIB (HR 2.12, 95% CI 1.43 – 3.14, p=0.0002) when compared to OAC cessation. DOACs resumption was not associated with increased recurrent GIB (HR 1.43, 95% CI 0.82 – 2.52, p=0.22) although this result was statistically underpowered. Among all DOAC therapy, only rivaroxaban was associated with recurrent GIB (HR 2.73, 95% CI 1.43 – 5.20, p=0.002).
Multicentre Retrospective Risk Modelling Analysis	Majeed et al. [75]	Analysis investigating how the timing of warfarin management, following an UGIB, would influence the relative risk of bleeding, thrombosis and mortality. Reinitiation of warfarin (on average) reduced the risk of thromboembolic events substantially (HR 0.19, 95% CI 0.07 – 0.55, p=0.002). However, this was also associated with an increased recurrent GI bleeding risk (HF 2.5, 95% CI 1.4 – 4.5, p=0.003). The multivariate analysis demonstrated that ceasing of warfarin therapy was associated with increased long-term mortality (HR 1.64, 95% CI 1.06 –2.56, p=0.03).
Statistical Analysis of Double-Blinded RCT	Garcia et al. [76]	Apixaban maintained superiority over warfarin (in stroke prevention, mortality and lower rates of major bleeding) in those who had previously experienced a prior GIB.

Literature Evaluation

In summary, there is a lack of robust high-quality evidence directing clinicians on the appropriate management of antithrombotic therapy following a NVUGIB. Most of the referenced literature was observational in nature, therefore the studies were subjected to unaccounted confounders and biases. Regarding confounders, many of the larger studies could not account for specific antithrombotic dosages, concomitant medications (such as PPIs and NSAIDs that may have included LDA) and variation in renal and hepatic functioning. Most studies that followed patients post hospital discharge were limited in their observation period, leaving longer term outcomes largely unaccounted for. Several of the studies attempted to reduce selection bias through propensity score matching, however the possibility for unobserved confounding still exists.

Another common flaw among numerous studies was data being sourced from national databases, with results and conclusions specific to ethnically heterogeneous populations (for example Japan, Korea and Denmark), therefore it is uncertain to what extent the results can be generalisable to other populations.

Although many studies were statistically powered to an adequate degree for measured outcomes, many of the individual studies fielded inadequate data, several producing results that were statistically significant which limited the conclusions that could be confidently drawn. The inclusion of thirteen meta-analyses may have provided evidence of a reasonable quality, with relevant cohorts and well applied statistic tests but these analyses depend on the individual studies having inherently similar cohorts.

However, from the available literature there are some reasonable conclusions that can be drawn. Firstly, the reinitiation of antithrombotics following a NVUGIB is largely beneficial, as seen in the decreased mortality and thrombosis observed in numerous studies, despite the frequently

reported increase in bleeding events. All antithrombotics should have indications assessed at the time of bleed, inappropriate therapy should be ceased but in consultation with a cardiologist when possible. Primary prevention LDA should be ceased, and secondary prevention LDA should be continued. Patients on DAPT should have LDA continued, and P_2Y_{12} platelet receptor inhibitors held and then recommenced in 3-5 days following haemostasis. Anticoagulants should be ceased until haemostasis can be achieved and then recommenced given the benefits found in the literature. The optimal timing of this recommencement is uncertain and will change according to agent. There is the potential for prescribers to change anticoagulant to apixaban, given the superior safety profile in those that have experienced a NVUGIB, especially compared to rivaroxaban and warfarin. All patients who suffer a NVUGIB should have PPI co-therapy to reduce the future risk of GIB, especially if they are continuing antithrombotics.

2.5.1 ANTIPLATELET THERAPY

The apparent benefits and risks of primary vs secondary prevention LDA, support the re-evaluation and discontinuation of primary prevention therapy. Secondary prevention (typically LDA) should be continued or reintroduced within three days for high-risk endoscopic lesions, once haemostasis has been achieved due to the associated decrease in mortality [6,8,16,77-79]. Most guidelines regarding the continuation or reinitiation of antiplatelet therapy following an acute UGIB, base recommendations on the available literature for LDA [41].

For those continuing on a single antiplatelet agent following an UGIB, a clinician may consider changing therapy, for example LDA to clopidogrel. This may be based on the belief that clopidogrel could be associated with a lower GIB risk compared to LDA and therefore could be associated with a lower rebleeding risk while maintaining cardiovascular protection. However, this strategy is without a conclusive evidence base, and although it receives mention in the literature, it is not endorsed by most contemporary guidelines. [17,23]

For DAPT patients not on clopidogrel, given that other P_2Y_{12} platelet inhibitors (ticagrelor and prasugrel) have been shown to have increased GIB risk when compared to clopidogrel alone, it may be reasonable for DAPT patients with these other agents to change to aspirin and clopidogrel following haemostasis to balance both benefits and risks of therapy. [35,80]

Usually for patients taking DAPT, aspirin is continued, and the P_2Y_{12} platelet receptor inhibitor is temporarily held for 5-7 days post haemostasis. The timing of this reinitiation is based on limited evidence. These patients are usually of a very high risk of future thrombotic events, especially those within 90 days of an ACS, recent coronary stent placement (<1 year for drug eluting stents or <1 month for bare metal stents), those with multiple stents or a history of stent occlusion. For these patients, treatment with DAPT is thought to be an imperative, despite the increased risk of GIB. [1,16,27,78,81]

For those on triple therapy, there is little evidence of what appropriate steps should be taken post haemostasis. Triple therapy corresponds to a very high bleeding risk as can be expected, regardless of the potential combination of chosen agents [22]. Depending upon thrombosis risk, a single antiplatelet agent and anticoagulant can be continued to lower future bleeding risk [27].

2.5.2 ANTICOAGULANT THERAPY

The American College of Cardiology [40] released a detailed report providing considerations when reinitiating anticoagulation following a major bleed. A key point raised by this report and other sources [6,8,16] was that prior to restarting OAC the indication should always be reviewed in the context of current guidelines. There is always the possibility that a patient is prescribed therapy inappropriately, or that the patient's clinical situation has changed so that the therapy is no longer required or justifiable. These could include a low calculated thrombosis risk, for AF patients this could be indicated by a low CHA_2DS_2-VAS_c and high bleeding risk as shown by HAS-BLED. However, it is crucial to appreciate that patients who have a high thrombotic risk will usually benefit from anticoagulation, even if they have high rebleeding risk. Other scenarios that could justify ceasing therapy include recovered acute stress cardiomyopathy, a first time VTE or a bioprosthetic valve placement that occurred more than 3 months ago. Temporary indications also exist such as post-surgical prophylaxis (e.g., hip or knee replacement).

Currently there is a wide variation in practice, with many clinicians permanently ceasing anticoagulation following a major GIB, despite a universal endorsement of OAC reinitiation from international guidelines [7]. These include the Joint Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) practice guidelines [82], the Asia-Pacific working group (2018 guideline) [83], Japanese

Society of Gastroenterology [77], European Society of Gastrointestinal Endoscopy (ESGE) [16] and the American College of Cardiology (ACC) [40].

OAC discontinuation following GIB is common. Among observational studies and the phase III DOAC trials (RE-LY, ROCKET-AF, ARISTOTELE and ENGAGE-TIMI 48), it was noted that OAC can be permanently discontinued in up to 50% of patients who experience a major GIB [7,14,84]. However, even amongst those that discontinue OAC, observational studies have suggested that these patients still have a 3-5% estimated risk of recurrent bleeding [7].

There is limited data to guide if restarting the same OAC or changing to another agent could be beneficial. When facing the decision to recommence anticoagulation following an NVUGIB, clinicians could consider changing therapy to another OAC, perhaps one with a reduced risk of causing recurrent GIB. It could be reasonable to change the agent to apixaban which may have a lower risk of GI rebleeding when compared to other OACs. [6,16,22,39,62,80,85]

Another difficult challenge for clinicians is the exact timing of OAC reinitiation. Warfarin, due to its delay in achieving therapeutic anticoagulation, may be started earlier than DOACs, which have a relatively short half-life and fast onset of action [16]. International guidelines mostly recommended immediate recommencement post haemostasis, and some recommend DOAC therapy is recommenced in 1-3 days [16,40,77,82,86].

2.5.3 PROTON PUMP INHIBITORS

Contemporary guidelines generally recommended that any patient who is on any antithrombotic therapy (either single antiplatelet therapy, DAPT, OAC or triple therapy) that continues following an UGIB is also prescribed a PPI to reduce potential reoccurrence [6,8,16,77,86]. There is a proposed mechanism of how PPI therapy could affect the action of

antiplatelet therapy, however no increased risk of adverse cardiovascular events has been found in with this drug combination in clinical studies [23].

CHAPTER 3: METHODOLOGY

The literature review informed a summary of relevant evidence on the use of antiplatelet and/ or anticoagulant agents following an acute NVUGIB. This chapter describes the methods used to undertake an empirical investigation of the management of NVUGIB in two South Australian public hospitals.

3.1 AIMS

I. Investigate the prescribing of both antiplatelet and/or anticoagulant agents following an acute NVUGIB (both as presenting complaints and HACs).

II. Investigate the prescribing of proton pump inhibitors following an acute NVUGIB (both as presenting complaints and HACs).

III. Investigate the frequency and types of communication contained within Medical Discharge Summaries relating to a patient's antithrombotic therapy.

IV. Estimate the costs of NVUGIB, both as a presenting hospital complaint and HAC.

3.2 HYPOTHESIS

There is capacity to significantly improve the prescribing patterns of antithrombotic therapy to reflect contemporary international guidance to improve patient outcomes and reduce health service costs related to NVUGIB.

3.3 STUDY POPULATION

Acute episodes of NVUGIB, either as presenting complaints to the Queen Elizabeth Hospital (TQEH) or Flinders Medical Centre (FMC) or as episodes that developed as a hospital acquired complication, through a retrospective casemix audit with the following inclusion and exclusion criteria.

3.4 INCLUSION CRITERIA

I. Patients admitted and discharged/ transferred from either:
    - TQEH between 01/01/2018 to 31/12/2020
    - FMC between 01/07/2021 to 31/08/2022 AND;

II. Patients who suffered an acute NVUGIB episode, either as a presenting complaint to hospital or that developed as a hospital acquired complication whilst admitted AND;

III. Were prescribed an oral antiplatelet and/or oral anticoagulant prior to their acute NVUGIB.

3.5 EXCLUSION CRITERIA

I. Patients aged <18 years at time of presentation.

II. Patients who had an admission complicated from a chronic gastrointestinal bleeding disorder – e.g., Crohn's Disease, Ulcerative Colitis, Diverticulitis. These conditions could complicate the diagnosis and treatment of an acute NVUGIB episode.

III. Patients who had a NVUGIB episode as a result of direct trauma. This could have formed the basis of the presenting complaint e.g., a motor vehicle accident, or could have occurred whilst in hospital, e.g., iatrogenic endoscopic perforations. Due to the cause of bleeding, there would be no clinical rationale to re-evaluate or change antithrombotic therapy.

IV. Patients who were undergoing haemodialysis. Direct Oral Anticoagulants (DOACs), such as apixaban, dabigatran and rivaroxaban, are dosed according to renal function and have not been extensively studied in patients undergoing haemodialysis. Generally, haemodialysis is seen as a contraindication to the prescribing of these agents. As this study was aimed to evaluate the prescribing patterns of these OACs, this condition was considered a significant confounder and was therefore excluded from investigation.

V. Patients who had a current diagnosis or history of cancer. Cancer is a pro-thrombotic state and will influence a prescriber's evaluation of the benefit and risk of continuing, holding, ceasing or substituting a patient's therapy. Some types of cancer also extenuate clotting mechanisms, making non-oral agents such as low molecular weight heparin (e.g., enoxaparin) a more attractive option due to their greater efficacy in treating and preventing thrombosis. This can heavily influence a prescriber's decision when evaluating their ongoing therapy, presenting a potential confounder.

VI. Patients who were engaged with palliative care services at the time of their discharge. Palliative care is a unique clinical pathway, where the prescribing of agents can be greatly influenced by factors such as a patient's condition, goals of care and life expectancy.

VII. Pregnancy was an exclusion. Due to a lack of human data, pregnancy is seen as a contraindication to the DOACs and warfarin (in most cases). Heparin is seen as the appropriate therapeutic alternative.

3.6 ICD-10 CODING

International Statistical Classification of Disease and Related Health Problems, 10th edition (ICD-10) coding was queried for primary or secondary diagnoses that aligned with a NVUGIB to identify patients.

ICD-10 codes used to identify UGIB were originally sourced from Montedori et al., [87]. Codes that included variceal bleeding were excluded, resulting in a finalised listing of ICD-10 codes (*Appendix 2).* An ICD-10 listing for exclusion criteria was also created (*Appendix 3*). A finalised listing of relevant ICD-10 codes was provided to the SALHN Casemix office to facilitate data extraction.

Casemix refers to a mix of types of patients treated by a hospital or other health care facility. It provides a consistent method of classifying patient based on shared characteristics. Using this, researchers can investigate data where the cases have been grouped through shared patient characteristics. [88]

A casemix extraction, based on the established inclusion criteria, was undertaken with a data collection period of three years (January 2018 – December 2020) for TQEH and 13 months (July 2021 – August 2022) for FMC.

3.7 DATA ACQUISITION AND MANAGEMENT

The Casemix Officer facilitated a casemix extraction in the format of *Microsoft Excel*®. This file was exclusively provided to the principal investigator. To ensure adherence to the ethics framework outlined from both the SALHN and Central Adelaide Local Health Network (CALHN) Human Research Ethics Committees (HREC), each identified case was assigned a Case Number within the Data Linking Spreadsheet (*Attachment 5*) and then deidentified and placed within a Data Collection Spreadsheet (*Attachment 6*).

Patient data from casemix included the assigned case number, patient UR, date of birth, patient age and gender. Admission details include presence of exclusion criteria with ICD-10 classification, date of hospital admission, date of hospital discharge, length of stay, use of blood products, presence of patient discharge or hospital transfer, in hospital death, if patient death was as a result of a bleeding episode, emergency presentation, hours within ED, admission from ED, ICCU admission, hours within ICCU admission, admitting ward, discharging ward. The principal diagnosis, additional diagnoses and procedures will be included with accompanying ICD-10 codes.

Patients with known exclusion criteria (through ICD-10 codes) were flagged, the remaining had their medical discharge summary screened through the Open Architecture Clinical Information System® (OACIS) by the principal investigator. If at any time a patient was found to possess exclusion criteria it would be noted within the Data Collection Spreadsheet and further investigation would cease.

The presence of pre-admission antiplatelet/ anticoagulant therapy was determined through evaluation of Sunrise EMR documentation – both the Medical Officer Admission Note and the pharmacy Medication History (if available). Details outlining any changes to existing therapy were collected from both the Medical Discharge Summary and the pharmacy Discharge Medications document (if available). Recorded details included the name of medication, its dose, and the frequency (*Attachment 7*). The prescriber's management of the antithrombotics and PPIs were recorded.

Once the casemix extraction was received, cases were screened based on the established criteria (*Appendix 2* for a detailed listing). To account for uncoded exclusion criteria, the principal investigator manually screened each remaining case using clinical documentation in the Sunrise EMR. Documentation included the Medical Discharge Summary and ward round notes authored by the treating team(s) and pharmacy documentation (where available) including the pharmacy Medication History and the Discharge Medications documents.

Additional exclusion criteria were developed during the manual screening of case notes – medical confirmation that GIB did not occur (inaccurate coding), the use of a non-oral anticoagulation, chronic gastrointestinal conditions (diverticulitis and ulcerative colitis), incomplete medical records, LGIB, Mallory-Weise Tears, trauma induced bleeding, variceal bleeding, and medical determination that an acute GIB did not occur. **Prior Antithrombotic Exposure**

After the remaining cases were reviewed for the presence of antithrombotic therapy, taken prior to the NVUGIB, investigators had eligible cases for examination. The term 'eligible cases' from this point onwards is in reference to the cases in which there was an absence of exclusion criteria, and an antithrombotic agent was prescribed prior to the NVUGIB.

Diagnostic Scoping

The presence of a scoping procedure (e.g., endoscopy, panendoscopy, colonoscopy) gives additional confidence to investigators for the accuracy of a NVUGIB diagnosis. In the absence of scoping, diagnoses cannot be verified, despite associated symptoms.

The appropriateness and timing of scoping is determined by the stratification of UGIB risk. Candidates for outpatient management, as compared to those that require acute services, can be indicated through clinical scoring systems such as the Glasgow Blatchford Score. This score incorporates clinical features such as systolic blood pressure, pulse, presence of melena, syncope, hepatic disease, cardiac failure, and laboratory parameters such as blood urea nitrogen and haemoglobin [89].

It was decided that the Glasgow Blatchford Score would not be collected during data acquisition given the scope and aims of this investigation.

Medical Discharge Summaries – Clinical Statements

Relevant statements within Medical Discharge Summaries were reviewed. To determine the treating team's perceived assessment of the patient's ongoing risk of thrombosis and bleeding. Advocation from the patient, their family or carers regarding their antithrombotic management was also recorded. These statements gave insight into clinical reasoning and allowed the investigators to assess how well continuity of care was being facilitated at point of discharge.

CHA_2DS_2-VAS_c Calculations

For the calculation of CHA_2DS_2-VASc, available ICD-10 codes were used. To validate this method a sample of 25 cases had CHA_2DS_2-VASc calculated using manual screening of Medical Discharge Summaries and using the provided ICD-10 codes from casemix.

Of the 25 cases, 22 of them produced identical scoring between the two methods. In two of the cases, the ICD-10 method resulted in inaccurate scoring – both had underscored CHA_2DS_2-VASc by not included hypertension, resulting in a total score of three. Although inaccurate, these scores would still indicate treatment with anticoagulation. In a single case the ICD-10 score was accurate, but the Medical Discharge Summary did not recount a prior NSTEMI, resulting in an inaccurate manual screen.

In summary the ICD-10 method resulted in 22 validated cases out of the 24 cases that were deemed accurate via manual screening, resulting in a 92% alignment between the methods. This was deemed high enough by the investigators to proceed with the ICD-10 method as the CHA_2DS_2-VASc scoring system for the entire AF cohort.

HAS-BLED

It was decided among investigators not to use clinical scoring systems such as HAS-BLED for the prediction of major bleeding risk with AF. As outlined in the literature review, HAS-BLED should not be used as justification to withhold or cease anticoagulation, instead it should prompt prescriber review of modifiable factors to decrease bleeding risk.

3.8 CHARLSON SCORING

The Charlson Comorbidity Index was utilised to improve the clinical understanding of the eligible cohort. This index incorporates patient age and prior medical history of myocardial infarction, COPD, chronic heart failure, peripheral vascular disease, cerebrovascular accident or transient ischaemic attack, AIDS, dementia, connective tissue disease, peptic ulcer disease,

liver disease, diabetes mellitus, hemiplegia and moderate to severe chronic kidney disease, presence of a solid tumour (localised and metastatic with graded scoring), leukemia and lymphoma. These factors are used to predict the 10-year survival in patients with multiple comorbidities. For example, within the original dataset used to develop this scoring index, 25% of those with a Charlson scoring of one died within a 10-year period, compared to 59% of those who scored equal or greater than three. [90]

Prior research has indicated that a strong association exists between a patient's non-gastrointestinal comorbidities (reflected in simplified Charlson scoring) and risk of NVUGIB occurrence [91]. Therefore, trends on Charlson scoring may explain variable bleeding rates independent of antithrombotics.

It is worth noting that patients who died during their inpatient stay, or those engaged with palliative care services at point of discharge were excluded from the eligible cases. Therefore, those with very high Charlson scoring upon admission may have been removed from the eligible case analysis.

Charlson scoring was calculated through a series of formulae in Microsoft Excel®, utilising casemix ICD-10 coding.

3.9 REPEAT PRESENTATIONS

Following a NVUGIB, episodes of rebleeding can be a source of mortality, morbidity and can adversely impact a patient's quality of life. These episodes produce further burden upon our health care system through admission costs and resources.

In this investigation re-presentations were only recognised if the index presentation and sequel presentation fell into the data capture window (January 2018 – December 2020 for TQEH and July 2021 – August 2022 from FMC), giving a variable timeframe for each of the individual

cases. Patients would not be detected if they had a GIB outside this timeframe, re-presented to a different hospital. Re-presentations could be made ineligible for data collection if the patient acquired new exclusion criteria in the interim or were no longer prescribed antithrombotic therapy. Repeat presentations for thrombosis were not included in data collection (if NVUGIB was not coded for during presentation).

Repeat presentations (or re-presentations) were detected through the matching of patient unit record (UR) numbers. This process was undertaken once all patient data had been collected and eligible patients (those without exclusion criteria and antithrombotic agent prescribed) had been identified.

3.10 COSTING ANALYSIS

By estimating the magnitude and consistency of hospital costs, the value and certainty of potential interventions aimed at reducing the frequency of bleed events, can be predicted.

For the purposes of an individualised (per case) costing analysis, the SALHN costing centre provided a detailed costing report of the available eligible cases. These costing reports are in accordance with the Australian Hospital Patient Costing Standards (v4.1) [92-95].

The costing analysis of this report was undertaken with SPSS®.

The primary method of identifying potential associations in the Presenting Complaint cohort between costing and baseline patient factors was Pearson Correlations. This was undertaken because such associations could inform a targeting strategy for potential interventions.

If the costing of each available case was not normally distributed, it was decided that the data would undergo logarithmic transformation to ensure reliable regression modelling.

The costing report would include a breakdown of the different categories of health care spending. Again, for the PC cohort Pearson Correlations were used to investigate potential associations between these categories and aggregate costs. These associations may help explain variation in hospital costs.

Cluster analysis can be utilised to investigate certain baseline factors that could be associated with low- and high-cost clustering. For the available dataset a K-Means Cluster Analysis was determined to be most applicable.

NVUGIB re-presentation rates and costs were also investigated as a contributor to cost saving strategies that may reduce the rate of index bleeds.

Analysis of HAC associated costs can inform the value of interventions to reduce the frequency of HACs. The Independent Health and Age Care Pricing Authority's (IHACPA) National Weighted Activity Unit (NWAU) calculator was used and then repurposed to find the approximate costing of NVUGIB HACs. There were seven such HAC cases in the SALHN costing report, specifically admitted through the acute services stream. The original calculator could be used to determine the base costing for each of their presenting Diagnostic Related Groups (DRGs) [96].

A method was outlined in the IHACPA's National Pricing Model [97] for calculating the final safety and quality adjusted NWAU. Using each case's NWAU, Adjusted NWAU and the National Efficient Price determination ($6,032) [98] the approximate costing of each HAC was estimated.

CHAPTER 4: RESULTS

4.1 DATA SCREENING AND EXCLUSIONS

The casemix extraction produced a total of 2016 hospital presentations for investigation, with 1169 from TQEH and 847 from FMC. Comparable exclusion rates for both screening methods (ICD-10 and manual) were applied to the extraction from the two hospitals (TQEH 58.1%, FMC 61.4%).

A detailed summary for all excluded cases can be viewed in *Table 4*. Most cases excluded using ICD-10 coding were related to cancer (active or historical), either solely (137 cases) or in combination with other exclusion criteria (62 cases), to make 283 in total. Cancer, as an exclusion criterion, was predicted to affect many potential cases due to its high prevalence among the cohort – as the elderly are at heightened risk of suffering a NVUGIB and cancer risk increases with age. Tumours, in some instances, may also be a provoking factor for UGIB [99]. The involvement of palliative care (without the presence of additional exclusion criteria such as cancer) was coded to 50 cases, excluding 31 cases from TQEH and 19 from FMC. A minority of other cases were excluded due to haemodialysis, pregnancy and being under the age of 18 years.

The classification of LGIB led to 300 cases being excluded – 158 from TQEH and 142 from FMC. This classification was taken from the Medical Discharge Summary with the treating team explicitly stating the bleed was lower in origin. Cases where the treating team stating the bleeding site was unknown or could have been a combination of UGIB and LGIB were included in the case analysis.

As with coding, cancer continued to exclude high numbers of cases in the manual screening. There were 270 cases excluded solely due to the condition – 167 from TQEH and 103 from FMC.

Table 4 – Case Exclusion Details. N (%) unless otherwise stated

ICD-10 based exclusions	TQEH	FMC	TOTAL CASES
Cancer	74 (26.1)	63 (22.3)	137 (48.4)
Cancer and Haemodialysis	1 (0.4)	3 (1.1)	4 (1.4)
Dialysis	8 (2.8)	11 (3.9)	19 (6.7)
Palliative Care	31 (11.0)	19 (6.7)	50 (17.7)
Palliative Care and Cancer	37 (13.1)	21 (7.4)	58 (20.5)
Pregnancy	0	6 (2.1)	6 (2.1)
Under 18 years	0	9 (3.2)	9 (3.2)
Manual Screening based exclusions	TQEH	FMC	TOTAL CASES
Bleeding due to peripheral anticoagulant	3 (0.3)	0	3 (0.3)
Cancer	167 (18.0)	103 (11.1)	270 (29.2)
Cancer and Palliative Care	0	1 (0.1)	1 (0.1)
Chronic Gastrointestinal Bleeding	2 (0.2)	0	2 (0.2)
Dialysis	2 (0.2)	4 (0.4)	6 (0.7)
Incomplete Medical Records	35 (3.8)	23 (2.5)	58 (6.3)
Lower Gastrointestinal Bleed	158 (17.1)	142 (15.3)	300 (32.4)
Mallory-Weise Tear	4 (0.4)	4 (0.4)	8 (0.9)
Multifactorial Bleeding – Organ Failure	0	2 (0.2)	2 (0.2)
Nil Acute Gastrointestinal Bleed	116 (12.5)	72 (7.8)	188 (20.3)
Palliative Care	12 (1.3)	11 (1.2)	23 (2.5)
Patient Death	14 (1.5)	3 (0.3)	17 (1.8)
Trauma Induced Bleeding	15 (1.6)	12 (1.3)	27 (2.9)
Variceal Bleeding	11 (1.2)	11 (1.2)	22 (2.4)

A total of 188 cases were classified as not having an acute GIB. Similarly, LGIB classification was taken from documentation within the Medical Discharge Summary. In these incidences either another condition was suspected, or the patient was suffering from a chronic gastrointestinal condition.

Incomplete medical records led to 58 cases being excluded. In these cases, documentation was poor, incomplete, or missing to a degree that data collection would be made unreliable or impossible.

From the original casemix, it was identified that 32 patients died during their hospital admission. At the time of manual screening, 17 of the cases remained and were subsequently excluded as their antithrombotic therapy could not be reviewed upon discharge.

The remaining 805 cases were reviewed for the presence of antithrombotic therapy taken prior to the NVUGIB, providing investigators with a total of 358 cases in which antithrombotic therapy may have plausibly contributed to a NVUGIB, where the prescribing of these agents could be reviewed both prior and following the event. There were 208 such cases from TQEH and 150 from the FMC.

4.2 PATIENT DATA

As seen in *Table 5*, the monthly presentation rates varied considerably both when comparing hospitals and within the hospitals themselves. FMC had a notably higher monthly mean presentation rate compared to TQEH – 11.5 cases (SD ± 3.5) compared to 5.8 cases (SD ± 2.2) respectively. An independent samples T-Test of the two hospital's monthly presentation rate yielded a t-value of 6.91595 and a p-value of <0.00001. From this data we can conclude that the FMC had a significantly higher monthly presentation rate compared to TQEH.

Table 5 - Case Demographics

	Total Eligible Cohort	TQEH	FMC
Monthly Mean Presentation Rate	7.3 (SD ± 3.6)	5.8 cases (SD ± 2.2)	11.5 cases (SD ± 3.5)
Median Age (years)	80 (IQR 8)	81.5 (IQR 8.5)	78.3 (IQR 7.8)
Presenting Complaint - Median Age (years)	79.21 (IQR 8.3)	80.5 (8.5)	77.67 (7.2)
Hospital Acquired Complication – Median Age (years)	84 (IQR 4.8)	83.5 (4.3)	84.9 (3.4)
Gender (Male)	194 (58%)	107 (51.4%)	87 (58%)

Eligible cases were predominately elderly, with HAC cases being notably older than PC cases. Age was non-normal in its distribution, similar between the two hospitals and older in HAC

cases compared to PC. The eligible cohort was majority male, with small differences in gender split noted between the hospitals. The PC cohort were predominately male (55.31%) and the HAC cohort were predominantly female (55.26%).

4.2.1 PRESENTING COMPLAINT

The majority of eligible cases were from NVUGIB occurring as a presenting complaint, as opposed to a HAC – 320 (89.4%) cases compared to 38 (10.6%) respectively.

Appendix 2 lists the ICD-10 codes relating to a presenting complaint of NVUGIB. A total of 74 unique codes were used with *melaena* and *gastrointestinal haemorrhage unsp* being the most common (60 cases each). Other common codes included *chronic or unspecified duodenal ulcer with haem* (36 cases), *chronic or unsp gastric ulcer w haem* (27 cases), *iron deficiency anaemia dt blood loss* (14 cases), *haemtemesis* and *chronic or unsp duodenal ulcer w perf* (ten cases).

A wide variety of principal diagnoses were seen in those that acquired a NVUGIB as a HAC. There were 32 unique codes, including cardiovascular, such as *acute subdendocardial MI* and *congestive heart failure*, infections such as *cellulitis of lower limb, COPD with acute lower resp infection* and *sepsis, unspecified* and even endocrine related such as *Type 2 DM with unspecified neuropathy*. There were no noteworthy patterns found in the principal diagnosis codes between HAC cases.

4.2.2 LENGTH OF STAY

The length of stay (LOS) varied between subgroups for eligible cases.

The median LOS for all eligible cases was five days (IQR: 2 – 8). The median LOS for TQEH was greater than FMC, five days (IQR: 2 – 8.25) compared to four (IQR: 2 – 8).

The LOS (median) was greater in those that acquire NVUGIB as a HAC, when compared to those with the presenting compliant – 13 days (IQR: 7.25 – 21.75) as compared to four days (IQR: 2 – 7).

By grouping the cohort into 10-year age brackets, it was observed that the median LOS and the corresponding IQR appeared to increase with each age bracket. This can be seen in *Table 6.*

Table 6 - Length of Stay Per Age Bracket

Age Bracket	Number of Cases	Median LOS (Days)	IQR (Days)
18-59	34	3	2 – 6
60-69	38	3	2 – 7
70-79	104	4	2 – 8
80-89	125	6	3 – 10
90+	59	6	3 – 12

4.2.3 ADMISSION PATHWAYS

Emergency

Most eligible cases were admitted through the hospital emergency department (ED) – 85.2%. Those who presented with a NVUGIB, presented through the ED in 284 (88.8%) cases. Interestingly, of those that acquired a NVUGIB as a HAC (38 cases), only 24 (63.27%) presented to ED, this would seem to suggest that many HACs for NVUGIB occur in elective admissions or direct ward transfers from other health services.

ICCU

In 32 (8.94%) of eligible cases, the patient was admitted to ICCU. These units are typically high cost due to high staff to patient ratios, clinical and equipment demands. The minimum LOS was four hours and a maximum of 501 hours.

For those that were admitted to ICCU, the median LOS was 44.0 hours (IQR 20 – 73.3). Those who had a NVUGIB from a HAC had a higher median LOS in ICCU when compared to the

PC cohort – 67.0 hours (IQR: 56.5 – 123.5) compared to 36.0 hours (IQR:19.75 – 66.25). The difference in either cohort can be seen in *Figure 2*.

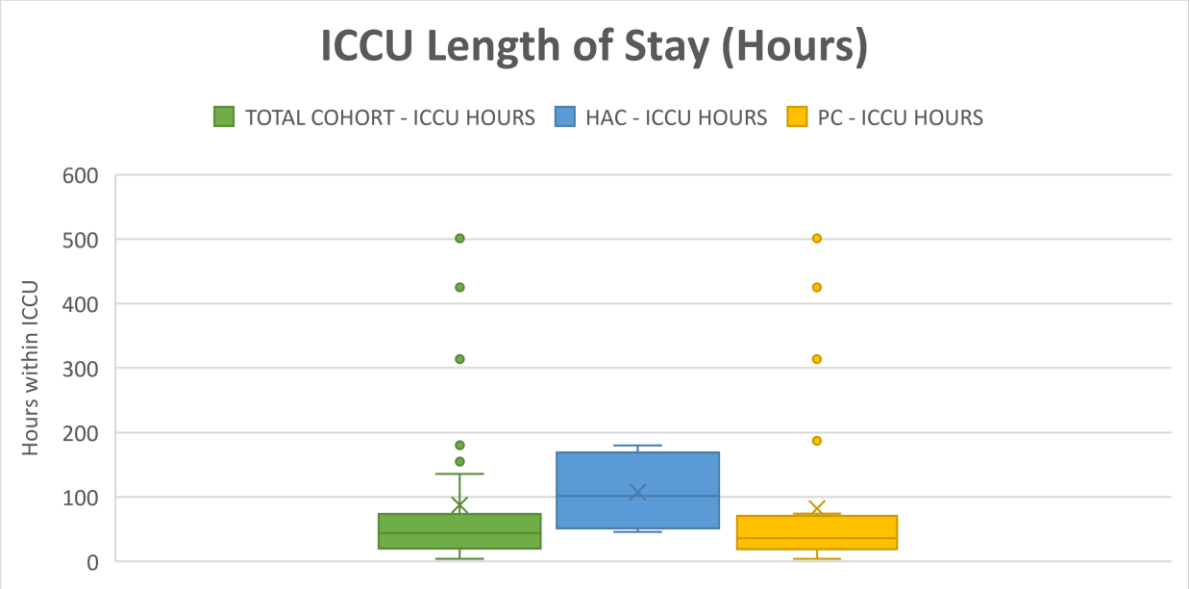

Figure 2 – ICCU Length of Stay

It was noted that there was a greater length of stay (hours) among ICCU admissions where bleeding had resulted from a HAC. A possible hypothesis for this could be that the patient may have been burdened by additional acute morbidity given their hospital admission, worsening their recovery from the NVUGIB.

4.2.4 CHARLSON SCORING

As visually displayed in *Figure 3*, the distribution of Charlson scoring was heavily negatively skewed, with a similar distribution showing for both the total cohort and each hospital cohort. The median Charlson Score was 1, with an IQR 0-1. The maximum Charlson score observed was 8 (single case).

A Chi-Square analysis revealed that there was no significant difference in the distribution of Charlson scoring between the two hospitals ($\chi^2 = 0.00014$, $p = \leq 0.05$).

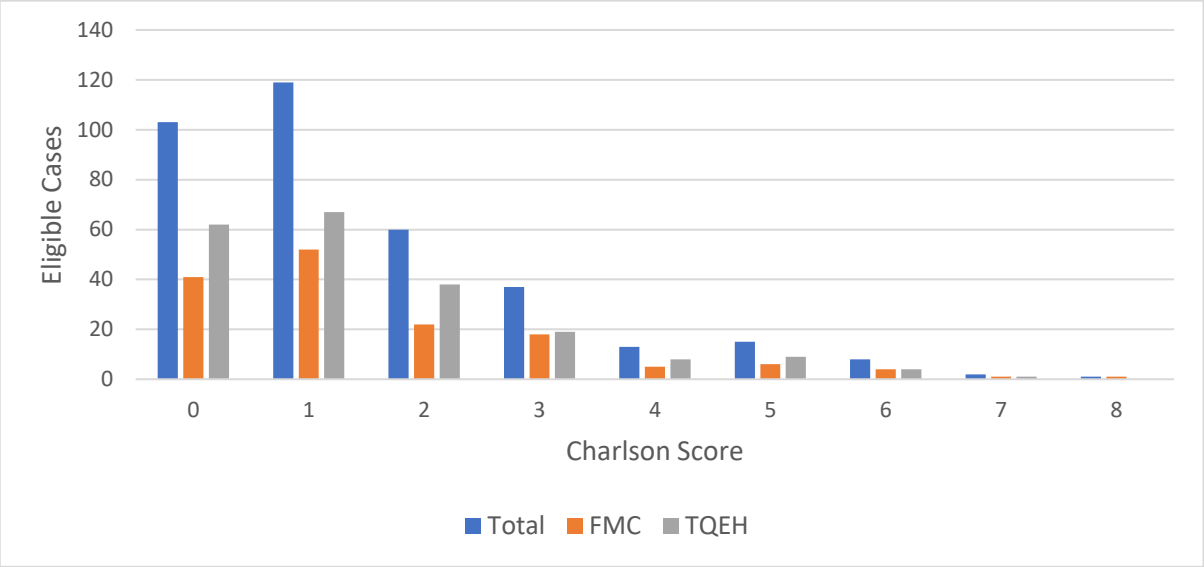

Figure 3 – Charlson Comorbidity Index Distribution

4.2.5 DIAGNOSTIC SCOPING

Patient Glasgow Blatchford Scores were not investigated during data collection and without it, interpreting the comparable rates of undertaking a scoping procedure between hospitals is difficult. Hepatic disease and cardiac failure differences would contribute to both Charlson and Glasgow Blatchford Scoring – however, as seen in *Section 1.1: Charlson Scoring*, significant differences in scoring were not found among the two hospital sites.

Older patients who are comorbid may decline or be denied scoping procedures (either diagnostic or treatment) due to the risk of adverse complications. However, the two cohorts did display a similar age distribution TQEH (median 81.5 years, IQR 73 - 90) and the FMC (median 78.29, IQR 70.49 – 86.09).

The presence or absence of scoping procedures was detected through recorded procedure codes. These codes included scoping that are both diagnostic (e.g., *panendoscopy to duodenum with biopsy*) and active treatment (e.g., *panendoscopy to duodenum with heater probe coagulation*).

The presence or absence of scoping procedures can be seen below in *Table* 7. Among the eligible cases, 214 (59.8%) received a scoping procedure during their inpatient stay. When comparing hospitals, FMC had 102 (68.0%) cases receiving scoping and TQEH had 112 (53.9%). When a Chi-Square test was used on the incidence of scoping procedures between the two hospitals, it was observed that FMC had a statistically significantly higher rate of scoping ($\chi^2 = 7.2612$, p=0.007).

Table 7 – Scoping Procedures. N (%) unless otherwise indicated.

	FMC (150)	TQEH (208)	Total Cases
Scoping Procedure	102 (68%)	112 (54%)	214 (59.8)
Nil scoping procedure	48 (32%)	96 (46%)	144 (40.2)

4.3 ANTIPLATELETS

4.3.1 PRESCRIBED AGENT(S)

In 218 eligible cases, an antiplatelet agent was prescribed – 126 (58%) from TQEH and 92 (42%) from FMC. The type of agent(s) and hospital of case origin are shown in *Table 8*. In 32 cases an antiplatelet was used in combination with anticoagulants, this is discussed here as well as included in *Section 5.2: Anticoagulation*.

Aspirin was most common antiplatelet agent. It was the leading SAPT agent (128) and was involved in all DAPT cases. Clopidogrel was the second most common, both in SAPT (32) and in DAPT. The third most common agent was ticagrelor – only within DAPT.

Table 8 – Antiplatelets Prior to Index Bleed. N (%) unless otherwise stated

	Total (218 cases)	FMC (92 cases)	TQEH (126 cases)
SAPT	160 (73.4)	69 (75.0)	91 (72.2)
Aspirin	128 (58.7)	52 (56.5)	76 (60.3)
Clopidogrel	32 (14.7)	17 (18.5)	15 (11.9)
DAPT	58 (26.6)	23 (25.0)	35 (27.8)
Aspirin + clopidogrel	38 (17.4)	14 (15.2)	24 (19.1)
Aspirin + dipyridamole (200 BD)	1 (0.5)	0 (0)	1 (0.8)
Aspirin + dipyridamole (25mg)	1 (0.5)	0 (0)	1 (0.8)
Aspirin + ticagrelor	18 (8.3)	9 (9.8)	8 (6.3)

4.3.2 INDICATIONS

Secondary prevention was the single largest cohort indication for the use of antiplatelet therapy (115 cases). This is to be expected as antiplatelets are universally regarded as first-line treatment following an ischemic event, with no clear substitutes. This cohort was further subdivided by a time frame of 12 months – those that were still within 12 months of their index thrombosis, and those who were beyond this timepoint. This was clinically noteworthy as the de-escalation from DAPT to SAPT would typically occur following this time point (in most

patients, given the literature at time of clinical review). Most secondary prevention cases had their NVUGIB occur in the greater than 12-month time frame, as opposed to within it – 78 cases compared to 37 respectively.

Primary prevention of cardiovascular disease with aspirin was a major contributor to NVUGIB – with 45 cases.

Both stroke and transient ischaemic attack (TIA) had small but notable case numbers – 16 and seven cases respectively. Both conditions having SAPT as their first line treatment.

There were five cases in which antiplatelets were being used in the treatment of AF. In all such cases the indication was explicitly documented in the medical record, as to not be confused with cases of primary prevention.

Antiplatelet indications were numerous, as shown in *Table 9*.

Table 9 – Antiplatelet Indications

Indications	Total	FMC	TQEH
Secondary Prevention (all cases)	115	50	65
Secondary Prevention: <12 months - Total	37	14	23
Secondary Prevention: >12 months - Total	78	36	42
Primary Prevention	45	15	30
Stroke	16	9	7
Peripheral Vascular Disease	11	5	6
TIA	7	1	6
AF	5	0	5
Analgesia	4	4	0
AAA - EVAR	4	1	3
DVT prophylaxis (joint replacement)	4	2	2
Heart Valve: AVR within 12 months	2	2	0
TAVI	1	0	1
Hypertrophic Obstructive Cardiomyopathy	1	0	1
Pericarditis	1	1	0
Vertebral arterial atheroma/ small incidental meningioma.	1	1	0

4.3.3 MEDICAL DISCHARGE SUMMARY – ANTIPLATELET STATEMENTS

From the 218 antiplatelet cases, 58 (26.6%) had statement(s) of clinical reasons within the Medical Discharge Summary and in 160 (73.4%) nil statement(s) were documented.

Ideally, a statement should contain an assessment of both bleeding and thrombosis risk to justify decisions made, especially when a change to therapy has occurred. In the 127 cases in which a change to antiplatelet therapy did occur, only 48 (37.8%) of them provided a clinical statement.

Table 10 – Antiplatelets Clinical Statements Summary. N (%) unless otherwise stated

Types of Statements	Thrombosis risk	Bleeding risk	Thrombosis and bleeding risk	Advocation Statement(s)	Nil Statements Made
Total Count (218 cases)	43 (19.7)	42 (19.3)	27 (12.4)	0	160 (73.4)
Ceased (63 cases)	18 (28.6)	19 (30.2)	14 (22.2)	0	39 (62.0)
Continued (91 cases)	9 (9.9)	4 (4.4)	3 (3.3)	0	81 (89.0)
DAPT to SAPT (38 cases)	14 (36.8)	14 (36.8)	9 (23.7)	0	19 (50.0)
Dose Decrease (2 cases)	0	0	0	0	2 (100)
Held: With Restart Date (11 cases)	0	2 (18.2)	0	0	9 (81.2)
Held: Unknown Outcome (3 cases)	0	0	0	0	3 (100.0)
Switch (11 cases)	2 (18.2)	3 (27.3)	1 (9.1)	0	7 (63.6)

Statements regarding thrombosis risk was mentioned in 43 (19.7%) cases. Statements regarding bleeding risk was mentioned in 42 (19.3%) cases. Only 27 (12.4%) cases mentioned both thrombosis and bleeding risk. No statements regarding advocation for the patient or their

family/ carers were present in the Medical Discharge Summaries reviewed by investigators as it pertains to antiplatelet therapy.

As seen in *Table 10*, clinical statements were more frequently made when therapy was ceased or if therapy was deescalated from DAPT to SAPT. Few statements were made when antiplatelet agents were switched – making it difficult to determine if the decision to change therapy was based on an evaluation of bleeding or thrombosis.

4.3.4 MANAGEMENT UPON DISCHARGE

The assessment of antiplatelet management was organised by agent indication to provide a clinical management framework.

The indications that were identified for in-depth analysis were primary prevention, secondary prevention, and stroke/ TIA (the latter two were merged due to similarity in clinical presentation and treatment). These indications were selected because this was the basis of clinical management seen in the literature review. The other indications were niche, with small patient numbers, and would require a per-patient analysis without the possibility of generalisation.

The overall frequency of prescribing, both prior and following the NVUGIB is outlined under each separate indication.

I. Primary Prevention

Of the 45 cases of primary prevention, all were treated with SAPT and all but one, was treated with aspirin – as seen in *Table 11*. Following the NVUGIB, 27 (60%), of these cases had antiplatelet therapy discontinued.

In every case where primary prevention was continued, there was a complete lack of documentation underpinning this clinical reasoning. There was nil mentioning of bleeding or thrombosis risk within the Medical Discharge Summary.

Table 11 – Primary Prevention Prescribing Timeline

Type of Agent	Prior	Post Bleed
Total SAPT	45	18
Aspirin	44	18
Clopidogrel	1	0

When antiplatelet status changed the treating teams were more likely to document their clinical rationale, as opposed to when therapy continued. In cases where primary prevention was ceased, there were eight examples in which the treating team documented an interpretation of both ongoing thrombosis and bleeding risk. There was a single case in which bleeding risk was solely mentioned. However, with only eight cases (29.6% of cessations) mentioning the bleeding and thrombosis risk, many cases could be left to interpretation by community prescribers and primary prevention restarted despite the ongoing risks.

II. Secondary Prevention

In the 115 cases of secondary prevention, 69 (60%) were treated with SAPT and 46 (40%) with DAPT prior to the NVUGIB.

The proportion of antiplatelet therapy (prescribed upon admission) that was SAPT, appeared to change significantly when dividing the cohort into more or less than 12 months since the index thrombosis. For cases within the 12-month time frame (37 patients) – six (16.2%) were being treated with SAPT and 31 (83.8%) with DAPT. For cases beyond the 12-month period (78 patients) – 63 (80.8%) were being treated with SAPT and 15 (19.2%) with DAPT.

In secondary prevention (both within and past the 12-month time frame), there were occasionally additional clinical details available in Medical Discharge Summaries that would indicate the precise type of ACS. This included CABG, STEMI, NSTEMI and PCI or in combination with either a bioprosthetic atrial or ventricular valve repair. Although an analysis was planned for these groups – only 26 of the total secondary prevention cohort had these details available, making analysis with further stratification with 12-month time frame not possible. The details of how antiplatelets in secondary prevention were managed are seen in *Table 12*. In 59 (51.3%) of secondary prevention cases, the original antiplatelet therapy continued. In cases where therapy was continued – only four (6.8%) of these statements were regarding bleeding risk, nine (15.3%) were regarding thrombosis risk and three (5.1%) with both.

Table 12 – Antiplatelet Management Per Indication

Therapy Changes	Secondary Prevention (Total)	Secondary Prevention <12 months	Secondary Prevention >12 months
Ceased	16	2	14
Continued	59	15	44
DAPT -> SAPT	28	18	10
Dose Decrease (aspirin 300mg to 100mg)	2	1	1
Held: Recorded Restart Date	3	0	3
Held: Unknown Outcome	2	1	1
Switch	5	0	5

There were 56 (48.7%) cases in which the original antiplatelet(s) were changed in some manner (non-continued cases). Of these that changed 18 (31.6%) had a statement regarding bleeding risk, 15 (26.3%) on thrombosis risk and nine (15.8%) on both.

There were 16 (13.9%) cases in which therapy ceased, including two cases where the ACS had occurred within 12 months (the highest risk period for another ACS event). An additional three (2.6%) had their therapy held without a specified duration.

In the five cases in which therapy was switched, only one contained a statement of thrombosis risk and three had mentioning of ongoing bleeding risk as their rationale.

In the 28 cases in which therapy was changed from DAPT to SAPT, ten (35.7%) had statements regarding bleeding risk, 11 (39.3%) regarding thrombosis risk and seven (25.0%) with both.

III. Stroke/ TIA

Of the 23 cases indicated for TIA or stroke, 17 were treated with SAPT (12 with aspirin, 5 with clopidogrel) and six treated with DAPT (four with aspirin and clopidogrel, with two case each for aspirin with dipyridamole (200mg BD and 25mg)). Most patients, 14 (60.9%) in total, were discharged with an antiplatelet agent upon discharge. Only six (26.1%) of them continued their original agent, with three switching to another antiplatelet.

For those that switched, two changed from aspirin to clopidogrel, and one from clopidogrel to aspirin as seen in *Table* 13. None of the four cases treated with aspirin and clopidogrel remained on this therapy following discharge, with all of them changing to clopidogrel as SAPT.

Table 13 – Antiplatelet Management TIA/ Stroke

Therapy Changes	TIA and Stroke
Ceased	6
Continued	6
DAPT -> SAPT	4
Dose Decrease (aspirin 300mg to 100mg)	0
Held: Recorded Restart Date	3
Held: Unknown Outcome	1
Switched	3

In all stroke/ TIA cases – only four had a statement regarding thrombosis, five bleeding risk and three with containing both. For cases in which thrombosis risk was mentioned, two were regarding therapy being ceased and two were in the context of DAPT to SAPT. The only additional cases that mentioned bleeding risk had therapy restarting a week following discharge.

There were only three out of the 23 (13.0%) cases in which there was a clinical statement on both bleeding and thrombosis risk.

IV. Atrial Fibrillation

In the five cases in which AF was being treated with antiplatelets, four of them were being treated with aspirin and a single case was being treated with aspirin and clopidogrel. Only one of the SAPT patients had their therapy ceased, with three of them continuing therapy for this indication.

Only the DAPT case, that was ceased and apixaban was commenced under the recommendation of cardiology, had clinical statements made in the Medical Discharge Summary – acknowledging the ongoing thrombosis risk as the justification for therapy change.

4.4 ANTICOAGULANTS

4.4.1 TYPES OF AGENTS

In 172 eligible cases, an anticoagulant was prescribed prior to the NVUGIB, 93 (54.1%) cases by way of TQEH and 79 (45.9%) cases from FMC. The types of agents prescribed, and hospital of case origin are shown in *Table 14*, with percentages in reference to the cohort (total, FMC or TQEH).

As a class of drugs, DOACs were prescribed more frequently when compared to warfarin. A total of 120 (69.8%) cases had a DOAC prescribed prior to the NVUGIB as compared to 52 (30.2%) cases for warfarin. The FMC had a nominally higher proportion of DOAC to warfarin cases (59 to 20 respectively), as compared to TQEH (61 to 32 respectively). Apixaban was the most prescribed anticoagulant, both in terms of total cases and per hospital with 80 total cases. Warfarin had 52 cases, dabigatran nine cases and rivaroxaban 31 cases.

Table 14 - Anticoagulant Prior to Index Bleed. N (%) unless otherwise stated

	Total (172 cases)	FMC (93 cases)	TQEH (79 cases)
Warfarin	52 (30.2)	20 (21.5)	32 (40.5)
DOAC	120 (69.8)	59 (63.4)	61 (77.2)
Apixaban	80 (46.5)	33 (35.5)	47 (59.5)
Dabigatran	9 (5.2)	5 (5.4)	4 (5.1)
Rivaroxaban	31 (18.0)	21 (22.6)	10 (12.7)

4.4.2 INDICATIONS

Like with antiplatelets, the assessment of anticoagulants is organised by indication. There were a variety of indications observed as seen in *Table 15*.

AF was the most common indication, with a total of 126 cases (with a single case of shared indication with a tissue AVR). PE was indicated in 13 cases, DVT in 11 cases and three cases in which these indications were treated concurrently.

Mechanical heart valves accounted for 14 cases and will not be evaluated for potential changes to existing anticoagulation as warfarin is the only permittable choice. In every one of these cases warfarin was prescribed on both admission and on discharge as expected.

Table 15 – Anticoagulant Indications

Indication	Total	FMC	TQEH
AAA - EVAR Grafting	2	0	2
Atrial Fibrillation	125	57	68
Atrial Fibrillation and Tissue AVR	1	0	1
DVT	11	6	5
Mechanical Heart Valve (All locations)	14	6	8
Mitral Valve Repair (Bioprosthetic)	1	0	1
Pulmonary Embolism	13	7	6
Pulmonary Embolism and DVT (concurrently)	3	1	2
R) brachial and R) subclavian artery thrombectomy	1	1	0
Inappropriate taking of medicines (overdose on partner's medication)	1	1	0

4.4.3 MANAGEMENT UPON DISCHARGE

Investigators limited their evaluation of therapy to the AF, DVT and PE cohorts (153 cases). Anticoagulation for mechanical cardiac valves cannot be permanently ceased and can only be managed with warfarin. The clinical framework surrounding the treatment of these conditions is well established, along with clinical tools to approach benefit and risk of therapy. Evidence for anticoagulant management was provided through the literature review, providing a basis of evidence for investigators to propose optimisation strategies.

Additional factors that could have influenced decision making in these cohorts was the presence of drug allergies and renal function.

Drug allergies

There was a single incidence in which drug allergy influenced prescribing. This patient had a recorded allergy to apixaban. They were being treated for AF with dabigatran, and following the bleed were changed to warfarin for ongoing treatment.

Renal function

Only 117 cases (68.0% of AF, DVT & PE cohort) had available creatinine levels. The CrCl could not be calculated in many patients, despite it potentially being a more accurate clinical marker, as the patient's height/ weight was inconsistently recorded. For this reason, eGFR was used as a determinate of a patient's renal function. This cohort's eGFR can be seen in *Table 16*.

Table 16 – Renal Function (AF, DVT & PE Cohort). N (%) unless otherwise stated.

	Total Cohort	TQEH	FMC
Cases with available creatinine	117 (100)	67 (67.3)	50 (42.7)
eGFR ≥30ml/min/ 1.73m^2	92 (78.6)	52 (44.4)	40 (34.2)
eGFR <30ml/min 1.73m^2	25 (21.4)	15 (12.8)	10 (8.6)
eGFR 15-29ml/min 1.73m^2	21 (18.0)	13 (11.1)	8 (6.8)
eGFR <15ml/min 1.73m^2	4 (3.4)	2 (1.7)	2 (1.7)

This information would have been made available to clinicians within the clinical EMR. The patient's eGFR is generated from SA Pathology, which uses the CKD-EPI formulae (4 formulae encompassing separate formulae for males and females at different creatinine thresholds) for calculated eGFR and has done since September 2017.

Among the 117 cases in which renal function would be evaluated, only 25 (21.4%) of cases had an eGFR <30ml/min/1.73m^2. Among this cohort – six had their therapy ceased (or held for an unknown duration), five of them for the treatment of AF and one for PE. Only six of these cases were discharged with warfarin, four of them were continued on pre-existing warfarin and two had switched from a DOAC.

I. Atrial Fibrillation

A. CHA_2DS_2-VASc Scoring - AF

A total of 126 patients were being treated with oral anticoagulants for AF (this included the single case with AF and bioprosthetic MVR as the indication). Within the AF cohort, no cases had a CHA_2DS_2-VASc score that would indicate anticoagulation would be inappropriate (≥ 2 for men and ≥ 3 for women). Therefore, in cases where anticoagulation was ceased, it could not be feasibly based on an inadequate CHA_2DS_2-VASc score, and therefore an evidence-based determination of low thrombosis risk.

B. Management of Anticoagulation - AF

In AF, apixaban was the most common agent prescribed prior to the NVUGIB (66 cases). Rivaroxaban and warfarin had substantial numbers (30 and 25 respectively) and dabigatran was in only nine cases as seen in *Table 17*.

From the available literature, in patients who have an adequate CHA_2DS_2-VASc score, anticoagulation should persist to reduce mortality following the NVUGIB. In 19 (15.1%) cases, anticoagulation was ceased and another four held with an unknown review date or outcome.

A total of 74 AF patients had an eGFR of >30ml/min/1.73 m^2, with 62 of them discharging with an anticoagulant – i.e., therapy not ceasing or being held for an unknown duration.

Table 17 – AF Anticoagulation Management

	Total	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Prior to Bleed	126	62	9	30	25
Continued	70	38	2	12	18
Ceased	19	11	1	5	2
Dose Decrease	7	7	0	0	0
Held (but restarted)	7	2	1	2	2
Held (unknown outcome)	4	4	0	0	0
Switched from this agent	N/A	0	5	11	3
Switched to this agent	N/A	16	0	0	3

II. DVT/ PE

A total of 27 cases were identified in which patients were treated for either past DVTs and/or PE prior to the index NVUGIB.

Regarding renal function, there were two cases in the DVT/ PE cohort that had an eGFR of ≤ 30mL/min – one of these patients switched to warfarin from apixaban, the other had their therapy ceased. There were also no allergies against anticoagulants being listed among the DVT/ PE that would have influenced prescribing.

From the DVT/ PE cohort there was a 29.6% discontinuation rate, that affected both apixaban and warfarin cases. The details of anticoagulation management in the DVT/ PE cohort can be seen in *Table 18*. Only 19 patients were prescribed anticoagulation upon discharge, seven of which were on warfarin. Considering only one of these patients had renal dysfunction, the remaining six could have changed to apixaban to optimise rebleeding risk.

Table 18 – DVT/ PE Anticoagulation Management

	Total	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Prior to Bleed	27	17	0	1	9
Continued	9	6	0	0	3
Ceased	8	5	0	0	3
Dose Decrease	2	2	0	0	N/A
Held (but restarted)	2	1	0	0	1
Held (unknown outcome)	0	0	0	0	0
Switched FROM this agent	N/A	3	0	1	2
Switched TO this agent	N/A	3	0	0	3
Count Post Bleed	19	12	0	0	7

III. Combination Therapy

There were 32 cases in which both antiplatelets and anticoagulants were co-prescribed.

Most of the antiplatelet prescribing was in the form of SAPT (30 cases). This was expected as triple therapy (DAPT + anticoagulation) is quite clinically rare and acknowledged to be promoting of high bleeding risk. The anticoagulation was more evenly divided, as seen in *Table 19.*

Table 19 – Agents in Combination Therapy

Antiplatelets	Cases	Anticoagulants	Cases
Aspirin	19	Apixaban	16
Clopidogrel	11	Dabigatran	1
Aspirin + clopidogrel	2	Rivaroxaban	7
		Warfarin	8

The indications for these cases appeared to be primarily secondary prevention for antiplatelet agents and AF for anticoagulants, as seen in *Table 20*. It was observed that in the cases of combination therapy, a higher rate of discontinuation was seen following the NVUGIB – with often only one of the therapies continuing.

Table 20 – Indication of Agents

Antiplatelet Indication	Cases	Anticoagulant Indication	Cases
AAA – EVAR	2	AAA – EVAR	2
Analgesia	1	AF	25
AVR	1	Mechanical Valve	1
Primary Prevention	1	PE	3
PVD	2	PE + DVT	1
Secondary Prevention (total)	24		
Secondary Prevention (< 12 months)	3		
Secondary Prevention (>12 months)	21		
Stroke	1		

4.4.4 MEDICAL DISCHARGE SUMMARY - ANTICOAGULANT STATEMENTS

From the 172 anticoagulant cases, 57 (33.1%) had at least one statement of clinical reasons within the Medical Discharge Summary, and in 115 cases (66.9%) nil statement(s) were made. There were 10 (5.8%) statements regarding thrombosis risk, 55 (32.0%) regarding bleeding risk, nine (5.2%) statements regarding both thrombosis and bleeding risk and six (3.5%) statements regarding advocation. These details can be seen in *Table 21*.

Table 21 – Anticoagulants - Clinical Statements in Medical Discharge Summaries. N (%) unless otherwise stated.

Types of Statements	Thrombosis risk	Bleeding risk	Thrombosis and bleeding risk	Advocation Statement(s)	Nil Statements Made
Total Count (172)	10 (5.8)	55 (32.0)	9 (5.2)	6 (3.5)	115 (66.9)
Ceased (28)	9 (32.1)	23 (82.1)	9 (32.1)	4 (14.3)	5 (17.9)
Continued (97)	1 (1.0)	3 (3.1)	0	1 (1.0)	92 (95.0)
Dose Decreased (9)	0	7 (77.8)	0	0	2 (22.2)
Held: With Restart Date (11)	0	4 (36.4)	0	1 (9.1)	7 (63.6)
Held: Unknown outcome (2)	0	1 (50.0)	0	0	1 (50.0)
Switched (25)	0	17 (68.0)	0	0	8 (32.0)

From the 106 cases where the original anticoagulant was continued (or held with a known restart date), there was one case (0.9%) in which clinical reasoning was issued regarding thrombosis risk, seven (6.6%) regarding bleeding risk, nil statements for both bleeding and thrombosis risk and two statements (1.9%) regarding advocation. In 92 (95%) of these continued (or held with known restart date) cases, there were nil statements made.

From the 30 cases in which therapy was ceased (including held with unknown restart date) – nine cases (30.0%) contained clinical reasoning on thrombosis risk, 24 (80.0%) regarding bleeding risk, nine cases (30.0%) for both bleeding and thrombosis and four cases (13.3%) in which statements regarding advocation. In six (20.0%) of these cases, nil statements were made.

Anticoagulation was switched in 25 cases. Only 17 (68.0%) of these cases gave statements on bleeding risk, and there were nil cases in which thrombosis risk or advocation was mentioned. This resulted in eight (32.0%) cases where nil statements were made.

Dose reduction occurred in nine cases (all apixaban). Seven (77.8%) cases contained statements regarding bleeding risk and there were nil statements made regarding thrombosis risk or advocation. There were two (22.2%) cases where nil statements were made.

4.5. PROTON PUMP INHIBITORS

From the total 358 eligible cases, 185 had a PPI prescribed to the patient upon admission, and 328 had a PPI prescribed at point of discharge.

The most common PPI prescribed, both prior to the patient admission and upon discharge was pantoprazole. Pantoprazole accounted for 69.7%% of all PPIs prescribed on admission and 86.3% of all PPIs upon discharge. Pantoprazole was newly initiated as PPI of choice in 99.5% of cases. This is likely due to pantoprazole being the only PPI available via intravenous administration. Pantoprazole was also listed on the SA Medicines Formulary and would have been on ward imprest in almost all clinical areas for ease of access.

There were 30 patients who did not discharge with a PPI, seven of them discharged with nil antithrombotic agent, seven of them left with an antiplatelet agent, and 16 were prescribed an

anticoagulant. Among the total eligible cohort, PPI therapy was not prescribed in 23 (6.4%) cases where an antithrombotic was prescribed at point of discharge.

4.6 REPEAT PRESENTATIONS

Following a NVUGIB, episodes of rebleeding can be a source of mortality, morbidity and can adversely impact a patient's quality of life. These episodes produce further burden upon our health care system through admission costs and resources.

Repeat presentations (or re-presentations) were detected through the matching of patient unit record (UR) numbers. This process was undertaken once all patient data had been collected and eligible patients (those without exclusion criteria and antithrombotic agent prescribed) had been identified.

Additional datasets from other institutions or from differing time periods, to detect re-presentation patterns amongst eligible cases, were not sought. As a result, a patient could have had a GIB prior or following this established period that would remain undetected. Patients who re-presented to a different hospital (public or private) would have not been detected through this method as ethics approval was only sought for the FMC and TQEH.

Due to this method of identifying repeat presentations, the depth of information and conclusions that can be made are limited. Those who re-presented with exclusion criteria did not have their antithrombotic status noted and those that were not prescribed an antithrombotic upon presentation did not have further information recorded as per our established method of data collection.

Only cases possessing an ICD-10 code corresponding to a potential GIB would have appeared within the casemix extraction. As stated within the literature search, a major complication from

the cessation or inappropriate modification of antithrombotics is thrombus formation. These presentations would remain undetected if they did not coincide with a GIB episode.

Among the eligible cohort, 41 index bleeds (11.5%) resulted in a total of 60 repeat presentations. There were 23 (56.1%) cases that presented to TQEH and 18 (43.9%) cases from FMC. Among the 60 re-presentations, there was 33 (55%) from TQEH and 27 (45%) from FMC.

The number of repeat presentations generated from an index bleed varied. The majority (29 (70.1%) cases) of these index bleeds generated a single repeat presentation. Ten (24.4%) of the index bleeds generated two re-presentations. A single (2.4%) case generated three re-presentations, and another case (2.4%) generated eight re-presentations.

Among both index bleeds and re-presentations, most had NVUGIG as a presenting complaint as opposed to a HAC. For index bleeds the rate of presenting complaint was 92.7% and among re-presentations it was 90.6%.

Among the 60 re-presentations to hospital, only 31 of them were considered eligible cases – the remainder either had exclusion criteria or were not prescribed an antithrombotic. By focusing on the 25 index bleeds that led to these eligible case re-presentations, there was a re-presentation rate of 9.5% with a mean time to re-presentation of 197 days.

Table 22 – Indications of Index Bleed Antithrombotics

Antiplatelet Indications	Frequency	Anticoagulant Indications	Frequency
AAA - EVAR	1	AAA - EVAR Grafting	1
Analgesia	1	AF	14
Primary Prevention	4	DVT	3
PVD	1	Mech Valve	5
Secondary Prevention (total)	11	PE	1
Secondary Prevention <12 months	5		
Secondary Prevention >12 months	6		
TIA	1		

The prescribing of antithrombotics was evaluated among the index bleeds – with 19 of them prescribed antiplatelet agents and 24 prescribed anticoagulants, which included two cases of combination therapy. The indication of these agents can be seen above in *Table 22*.

Using the re-presentation data, a Kaplan-Meier curve was generated using SPSS®, the result can be viewed in *Figure 4.* Overall, when comparing the re-presentations of those who discharged with and without prescribed antithrombotics, there was little difference between the two cohorts. A Chi-Square test of equality of survival distributions was generated at the end of the data collection period for the two groups was not statistically significant (χ^2=0.344, p=0.558). This lack of significance could be explained by the small absolute numbers of re-presentations in the cohorts.

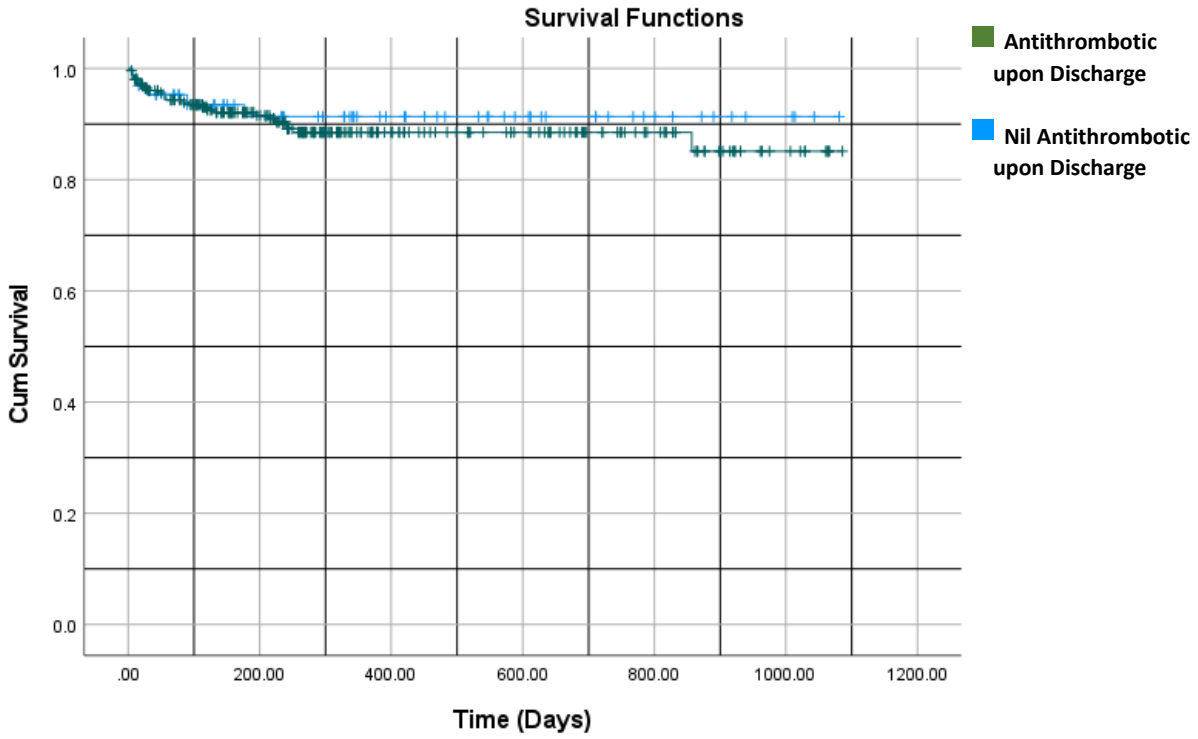

Figure 4 – Repeat Presentation Kaplan-Meier Curve

CHAPTER 5: COSTING ANALYSIS

As outlined in *Section 3.10: Costing Analysis*, the cost analysis of NVUGIB (both as a PC and a HAC) is necessary to inform potential future strategies.

Due to the release schedule of costing reports, the SALHN costing centre was able to provide individualised (per case) costing for 85 of the eligible SALHN cases instead of the entire cohort.

This costing report provided a Total Cost per case – i.e., the summarised cost attributed to this episode of inpatient care. It also included a breakdown of costing based on individual costing buckets. These buckets were stratified – with costing being divided through departments, i.e. medical, nursing, allied health and pharmacy, resource utilisation and clinical areas. The de-identified costing report, as issued by the SALHN patient costing officer is available for viewing in *Attachment 8 – SALHN Costing Report*.

The original report divided most costing buckets into both direct and indirect costing. For the sake of aiding statistical analysis, both the direct and indirect costing was merged into a combined costing bucket for this report.

Investigators were advised by the SALHN costing team that costing weight and classifications may differ due to differing clinical models and admit/ counting rules, the availability of data and differences in the resource availability to support the patient costing process. Statistical analysis of the clinical and costing data was performed using Microsoft Excel® (version 2302) and SPSS® (version 29).

5.1 TOTAL COST (PER CASE)

Aggregate admission costs were divided into costing buckets of $5,000, starting with the lowest recorded total admission costing of $572.45 to a maximum recorded cost of $95,981.02. The

median of these total costs was calculated at $11,227.01 (IQR $6,434.71 – $19,637.09) and a mean value of $16,721.05 (SD ±$16,212.18).

The distribution of all Total Cost (per case) was noted to follow a non-normal distribution, with heavy positive skewing – as seen in *Figure 5* below. This indicates that most patients had relatively low costing presentations, with a small minority being remarkably expensive to the hospital system.

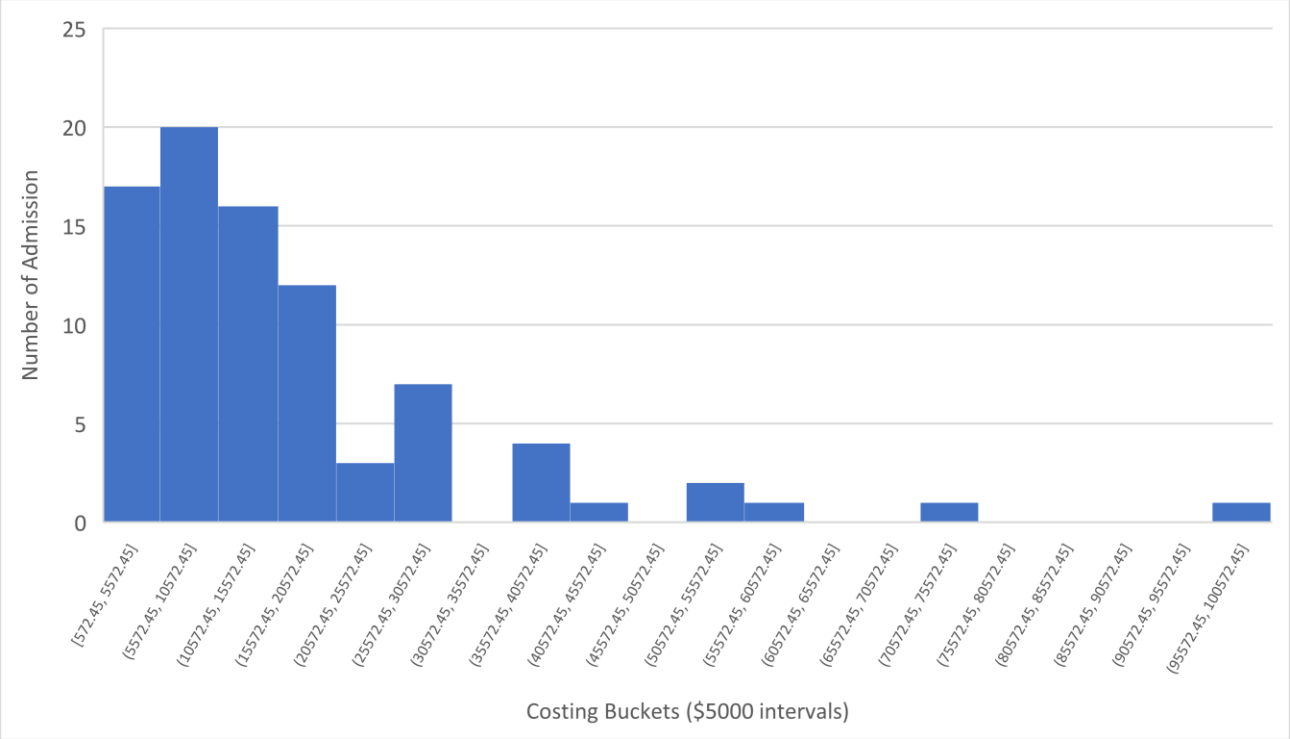

Figure 5 – Distribution of Total Cost (per case)

As seen in *Table 23*, several differences could be seen in the Total Cost (per case) and various patient cohorts.

The NVUGIB HAC cohort had a notably higher median Total Cost per case and IQR ($44,407.67, $25,693.58 - $53,670.82) that was both more expensive and broader in range when compared to the presenting complaint cohort (median $10,920.7, IQR $6,194.72 - $18,359.93). This indicates a higher average cost and a greater degree of costing variance.

Table 23. Patient Cohorts and Total Cost (per case)

Cohort	Sub cohort (n)	Median Costing	Interquartile Range	Mean Costing	Standard Deviation
Presenting Complaint	NVUGIB Presenting Complaint (78)	$10,920.7	$6,194.72 - $18,359.93	$14,487.82	$13,914.39
	NVUGIB HAC (7)	$44,407.67	$25,693.58 - $53,670.82	$41,605.68	$20,192.43
Gender	Male (52)	$11.313.16	$6,921.88 - $22,010.24	$17,791.21	$15,705.17
	Female (33)	$10,941.56	$5,634.12 - $15,785.82	$15,034.74	$17,089.34
Scoping	Scoping Procedure (56)	$11,313.16	$6,688.14 - $18,904.11	$16,552.11	$16,753.54
	Nil Scoping Procedure (29)	$11,035.20	$5,731.93 - $22,517.37	$17,047.29	$15,394.76
Antithrombotic Agent Prescribed	Antiplatelet (41) Cases	$10,425.68	$6,140.33 - $19,637.09	$14,503.05	$12,008.78
	Anticoagulant (35) Cases	$11,720.05	$8,828.07 - $18,956.57	$17,474.18	$17,682.13
	Combination Therapy (9) (Antiplatelet & Anticoagulant)	$13,532.95	$6,357.87 - $27,987.62	$23,896.45	$24,985.96

Interpretation of these result should be done with caution however, as there are only seven HAC cases included in this costing report. However, key that the NVUGIB would be in addition to presenting condition, it would be reasonable to expect HAC cases to be more expensive than the presenting cases.

The median Total Cost per patient was approximately equivalent when comparing genders ($11,313.16 for males and $10,941.56 for females). However, males appeared to have an IQR which was broader and with a notably higher third quartile when compared to females – $6,921.88 - $22,010.24 and $5,634.12 - $15,785.82 respectively.

The median Total Cost for those who had a scoping procedure ($11,313.160) was similar to those without ($11,035.20), however the scoping cohort had a notably lower third quartile. A possible explanation for this could be that the non-scoping cohort could have contained two separate groups of patients – those with less severe bleeding who may have been discharged quickly (costing less) and those with severe bleeding but due to advanced age/ significant

comorbidities/ patient preference they could have not received scoping for diagnosis or active treatment, extending LOS and potential increase in costing.

The median Total Cost was similar when comparing those prescribed antiplatelet(s), an anticoagulant or combination therapy prior to their bleed – $10,425.68, $11,720.05, and $13,532.95 respectively. However, the IQR was broader for combination therapy ($6,357.87 - $27,987.62) when compared to either antiplatelet(s) ($6,140.33 - $19,637.09) or anticoagulant ($8,828.07 - $18,956.57) separately. This larger IQR could have been a result of more clinical variability – from a cohort with more morbidities (assumably from more antithrombotic indications or could have been an artefact from the low cohort numbers (9 cases).

Sections 5.2 to *5.6* present detailed cost analyses investigating correlations between costs and patient and admission characteristics and cost drivers. These analyses are only presented for the cohort who were admitted due to the experience of a NVUGIB. The results of these analyses are not presented for the cohort experiencing a NVUGIB as a HAC because it is not possible to distinguish costs associated with the diagnosis for which these patients were admitted, and costs associated with a NVUGIB.

5.2 TOTAL COSTING – CORRELATIONS

Statistical analysis was employed to the determine the type and strength of any correlation (or lack of) in the PC cohort between the Total Cost (per case) and the LOS, presenting complaint (NVUGIB or other), Charlson scoring, patient age and gender. Because of a difference in predicted costing patterns, and low case numbers, Pearson Correlations were not performed with the HAC cases.

Hours spent within ED, admissions to ICCU and hours spent within ICCU were also included in this analysis – as they could be proxies of clinical severity.

Table 24. Pearson Correlations - Total Cost (log_{10}) and Patient Factors

	Presenting Complaint Cohort (78 cases)	
	Pearson Correlation	Sig (2-tailed)
Length of Stay	0.663**	<0.001
Charlson Score	0.306**	0.006
Scoping Procedure (diagnostic/ treatment)	0.181	0.114
Patient Age	0.103	0.370
Hours within ED	0.176	0.145
Hours within ICCU	0.307**	0.006

***p = ≤ 0.01, *p = ≤ 0.05.*

Given the non-normal distribution of Total Cost (per case), it was decided to use the log_{10} value of the Total Cost (per case) to create reliable regression modelling. This was processed with SPSS®, with a univariate Person Correlation being produced as seen in *Table 24*.

5.2.1 LENGTH OF STAY

The first potential correlation in the PC cohort that was investigated was the Total Cost (per case) and the patient's LOS, with the results being strong in correlation and positive in nature (0.662, p=<0.001). This relationship appears logically consistent, and justifiable from a health economics standpoint – the longer a patient remains in hospital, the more resources they will inevitably consume, and the higher costs will become.

LOS has been established as a key driver of hospital costs and can affect the capacity of the health care system and a prolonged hospital stay can increase the risk of complications, worsen the patient's quality of life, and consume valuable resources [100].

It is possible that for many patients, costs are front loaded into their admission, i.e., most costly resources such as surgery are utilised in the first days of the admission. However, with the available data this hypothesis cannot be assessed.

In either case, based on this available data, a potential health economic strategy that reduces the LOS may reduce the Total Cost (per case), either directly or indirectly. It should be noted that reducing LOS may also have secondary benefits, such as aiding hospital bed flow.

5.2.2 OTHER CLINICAL FACTORS

Among the other tested factors scoping, patient age, hours with ED and hours within ICCU, none of these had significant correlation observed. This is likely due to either a poor connection between total cost and these factors and/ or the limited sample size.

5.3 LENGTH OF STAY – CORRELATIONS

To determine any potential relationship between the patient LOS and other clinical factors, another series of Pearson Correlations were undertaken with SPSS®– as seen in *Table 25.*

Table 25. Pearson Correlations PC Cohort – LOS and Patient Factors

	Pearson Correlation	Sig (2-tailed)
Charlson Score	.342*	0.002
Scoping Procedure (diagnostic/ treatment)	-0.051	0.658
Patient Age	.230*	0.043
Hours within ED	0.143	0.239
Hours within ICCU	.285*	0.012

***p = ≤ 0.01, *p = ≤ 0.05.*

There appeared to be a statistically significant, yet weak positive correlation between LOS and Charlson Score (0.342, p=0.002). It could be assumed that a patient with a high Charlson Score has a greater morbidity burden, is more clinically unwell and will likely require additional prolonged medical services.

Patient age appears to have a weak and statistically significant positive correlation that did not reach statistical significance (0.230, p=0.043). This was expected to be stronger in correlation, as the elderly often suffer from a higher morbidity burden, require longer recovery periods. In addition, they often required prolonged admissions to facilitate placement and respite.

Hours spent within ED did not show a statistically significant correlation found in total cases or either cohort. However, hours in ICCU was positive and statistically significant (0.285, p=0.012).

5.4 COSTING BUCKET ANALYSIS

As seen in *Table 26*, there was a wide variance in the median and IQR between costing buckets. Indicating that associated costing per patients was highly variable.

Table 26 – NVUGIB PC Cohort - Costing Bucket Breakdown

Costing Buckets	Median Costing	IQR	Mean	Standard Deviation
Total Cost	$10,920.70	$6,194.72 - $18,359.93	$14,487.82	$13,914.39
Allied Health	$380.09	$196.33 - $733.95	$682.65	$950.50
Critical	$0	$0 – $0	$921.55	$3,928.32
ED	$157.50	$85.91 - $336.48	$270.01	$318.64
Hotel	$218.42	$120.71 - $370.89	$308.72	$299.11
Imaging	$83.11	$0.05 - $829.43	$492.66	$1,024.78
NonClinical	$459.68	$251.16 - $772.21	$632.55	$657.25
Oncosts	$1,039.49	$563.63 - $1,677.82	$1,364.81	$1,313.62
OR	$263.56	$7.71 - $1,326.95	$928.78	$1,343.97
Pathology	$567.90	$149.60 - $1,062.79	$832.63	$937.02
Pharm	$108.93	$63.31 - $173.29	$178.41	$443.25
Pros	$0	$0 - $0	$61.41	$351.04
SPS	$0	$0 - $906.01	$602.56	$956.54
Ward Med	$1,718.68	$963.21- $3,035.15	$2,543.59	$2,661.40
Ward Nurse	$2,038.08	$997.26 - $4,213.93	$3,079.89	$3,092.27
Ward Supplies	$621.75	$334.11 - $1,041.02	$953.05	$1,345.49
Pharm PBS	$12.71	$0 - $251.70	$130.25	$192.39
PatTravel	$2.24	$1.24 - $3.79	$16.51	$97.11

NVUGIB, Non-Variceal Upper Gastrointestinal Bleed; PC, Presenting Complaint; Pat-Travel, Patient Travel

There were three costing buckets that had a median costing of >$1,000 – oncosts ($1,039.49), ward med ($1,718.68) and ward nurse ($2,038.08). These three costing buckets had a high IQR, indicating large variability between individual cases. Only six cases included costing associated with Critical care. The median costing for these cases was $9,764.97 (IQR $6,702.11 - $12,047.98). Despite having few case numbers overall, it was clear that costing associated

with critical care is expensive and if required during an admission will likely increase Total Cost to a large degree.

It appears that the distribution of costs was spread among numerous costing buckets. This is important to consider for any who wish to reduce admission costs with potential interventions. Although a correlation between LOS and Total Cost was noted, correlation between the LOS and the specific costing buckets was not as clear or conclusive – as seen in *Table 27*.

Table 27 –Pearson Correlations – PC Cohort – LOS and Costing Buckets

Costing Buckets	Pearson Correlation	Sig (2- tailed)
Allied Health	0.357**	0.001
Critical	-0.010	0.929
ED	-0.036	0.757
Hotel	0.160	0.161
Image	0.015	0.895
Non Clinical	0.116	0.312
Oncosts	0.153	0.182
OR	-0.026	0.823
Path	0.113	0.324
Pharm	0.285*	0.011
Pros	-0.073	0.527
SPS	-0.057	0.621
Ward Med	0.118	0.303
Ward Nurse	0.183	0.108
Ward Supplies	0.177	0.121
Pharm PBS	0.247*	0.029
PatTravel	-0.027	0.815

***p = ≤ 0.01, *p = ≤ 0.05. Note: All costing buckets (like total cost) were transformed into a Z score (log_{10}) due to the wide-ranging disparity between associated costs.*

Prior to this analysis, it was expected that many of the individual costing buckets would have a linear relationship between cost accumulation and LOS. However, as seen below, the only statistically significant correlations found were Allied Health (0.357, p=0.001) and Pharm (0.285, p=0.011). The correlation with the Allied Health costing is curious, with a potential reciprocal relationship existing between it and LOS. An elderly patient with a prolonged hospital stay may require services such as occupational therapy and physiotherapy as part of

rehabilitation following a NVUGIB to facilitate discharge. It may also be true that the reason as to why patients would have an extended LOS would be the facilitate of services such as social work who may be employed to facilitate respite planning prior to discharge. The association between LOS and Pharm could be explained by a selection bias in the patient cohort – those that present with a NVUGIB and a likely contributing, potentially high-risk (i.e., an anticoagulant) medication would certainly be prioritised for pharmacy history taking, pharmaceutical review, medication counselling and discharge planning.

5.5 CLUSTER ANALYSIS

A K-Means cluster analysis was utilised in SPSS® to identify patient clusters for costing in the PC cohort, using standardised values of costing buckets (Z-scores) . The costing buckets for Depreciation and Payroll Tax were excluded.

Both two and three clusters resulted in an iteration history with a value of zero being reached after only three iterations. As can been seen in *Figure 6* two clusters resulted in a clear distinction of low and high-cost patients. When three clusters were created, it resulted in the mid cluster only containing a single case – without a clear clinical distinction that could be identified. Therefore, two clusters appeared to be optimal. The F-Ratio observed for many of the costing buckets was reasonable and significance was reached with most values (see *Appendix 4 – K-Means Cluster Analysis: ANOVA Table* for details). Less significant buckets included ED, Pros and SPS.

The high-cost cohort (cluster 1) appeared to have large variation across most of the costing categories, compared to the low-cost group (cluster 2) that appeared to be more homogenous, with low Z-scores for almost all costing categories.

The high-cost cluster contained seven cases (9.1%), out of a total of 77 cases within the costing report that had a presenting complaint of NVUGIB. Combining their Total Costs per case of these high-cost cases resulted in a total of $202,702.72, totalling approximately 18.1% of all Total Costs (per case) for the PC cohort.

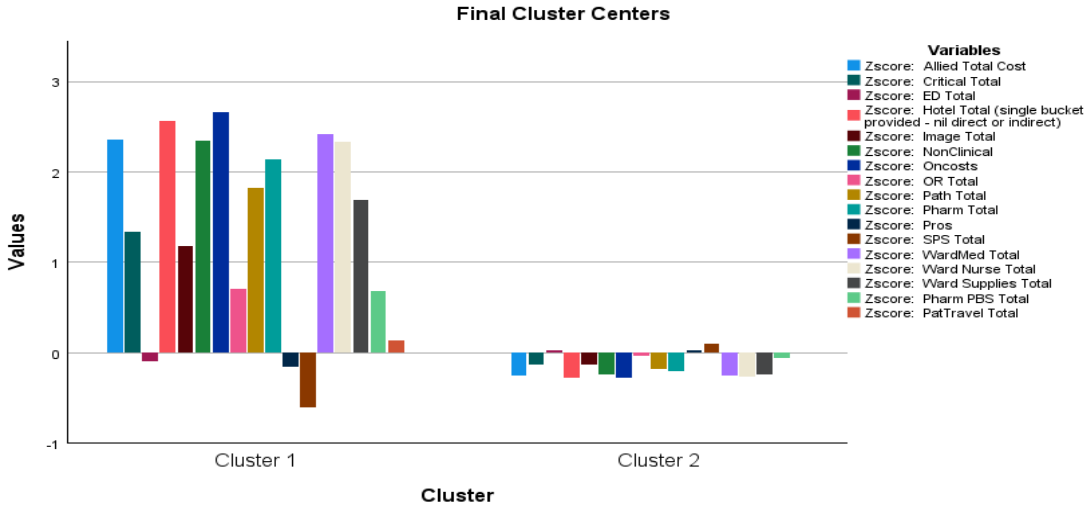

Figure 6 – Full Cohort: K-Means Cluster Analysis: 2 Clusters

The cost buckets for PC cases can be observed in *Table 28*. The SD for most cost buckets (across cohorts) was approximate to, or greater than the mean values – indicating a non-normal distribution, much like to distribution observed in the Total Cost (per case) data. The median costing between the two cohorts was sizeable – with the high-cost cohort having a value of $17,475.68 and the low-cost cohort having $10,919.27. Among the high-cost cohort, the median values were higher in nearly all costing buckets when compared to the low-cost cohort – with the only exception being OR.

The high-cost cohort had significant costing differences observed among most costing buckets – with higher medians and IQR when compared to the low-cost cohort. Indicating that costs remained distributed among many services and was highly variable among cases. A visual

representation of the mean values for each of the costing buckets, separately for both the high and low-cost clusters is shown in *Figure 7*.

For both clusters, costing associated with Ward Nurse and Ward Med were the two highest contributors– both contributing to approximately 40% of overall costing. For the high-cost cohort, the third highest contributor was Critical (15%) and for the low-cost cohort it was OnCosts (10%).

Table 28 – NVUGIB PC Cohort - Costing Cohorts (High and Low) – Costing Bucket Breakdown

	High-Cost Cohort				Low-Cost Cohort			
	Median	IQR	Mean	Standard Deviation	Median	IQR	Mean	Standard Deviation
Total Cost	$17,475.68	$7,292.63 - $36,710.86	$28,957.53	$34,406.66	$10,919.27	$6,249.10 - $17,713.75	$13,061.23	$9,407.42
Allied Health	$1,048.16	$468.06 - $2,339.77	$1,477.29	$1,490.64	$374.07	$198.01 - $676.73	$604.31	$856.72
Critical	$0.00	$0.00 - $0.00	$4,150.01	$10,979.89	$0.00	$0.00 - $0.00	$603.25	$2,344.41
ED	$229.10	$128.87 - $272.05	$318.28	$359.14	$143.18	$85.91 - $369.70	$265.25	$316.82
Hotel	$372.36	$148.95 - $843.90	$576.25	$646.49	$217.64	$121.34 - $352.75	$282.34	$233.94
Imaging	$89.30	$0.07 - $1,048.47	$773.25	$1,268.05	$77.06	$0.05 - $795.47	$465.00	$1,004.35
NonClinical	$807.79	$321.68 - $2,034.94	$1,336.06	$1,515.47	$459.03	$255.46 - $748.07	$563.20	$473.22
OnCosts	$1,581.45	$701.42 - $3,260.13	$2,710.33	$3,320.28	$1,028.99	$568.28 - $1,667.82	$1,232.15	$868.52
OR	$1,086.56	$217.36 - $1,226.32	$1,497.15	$2,271.44	$252.85	$0.00 - $1,305.17	$872.75	$1,228.47
Pathology	$1,375.15	$327.88 - $2,865.13	$1,754.99	$1,716.78	$567.74	$154.38 - $1,002.80	$741.69	$787.22
Pharm	$213.33	$103.56 - $406.89	$264.42	$245.81	$106.14	$61.26 - $162.37	$169.93	$458.40
Pros	$0.00	$0.00 - $0.00	$13.87	$36.71	$0.00	$0.00 - $0.00	$66.10	$367.67
SPS	$0.00	$0.00 - $449.82	$429.83	$812.89	$0.00	$0.00 - $925.11	$619.59	$972.91
Ward Med	$3,161.66	$1,185.63 - $7,898.81	$5,356.06	$6,246.31	$1,693.08	$957.63 - $2,875.95	$2,266.31	$1,891.59
Ward Nurse	$4,226.08	$1,767.23 - $7,993.91	$5,566.17	$5,610.24	$2,036.87	$336.98 - $3,522.29	$2,834.76	$2,672.34
Ward Supplies	$1,106.84	$433.44 - $2,453.23	$1,581.05	$1,658.27	$619.33	$336.98 - $944.65	$891.13	$1,308.56
Pharm PBS	$77.14	$8.14 - $252.51	$132.04	$140.17	$4.10	$0.00 - $251.70	$130.08	$197.56
Pat Travel	$3.73	$1.46 - $7.94	$11.30	$20.36	$2.23	$1.24 - $3.45	$17.03	$101.67

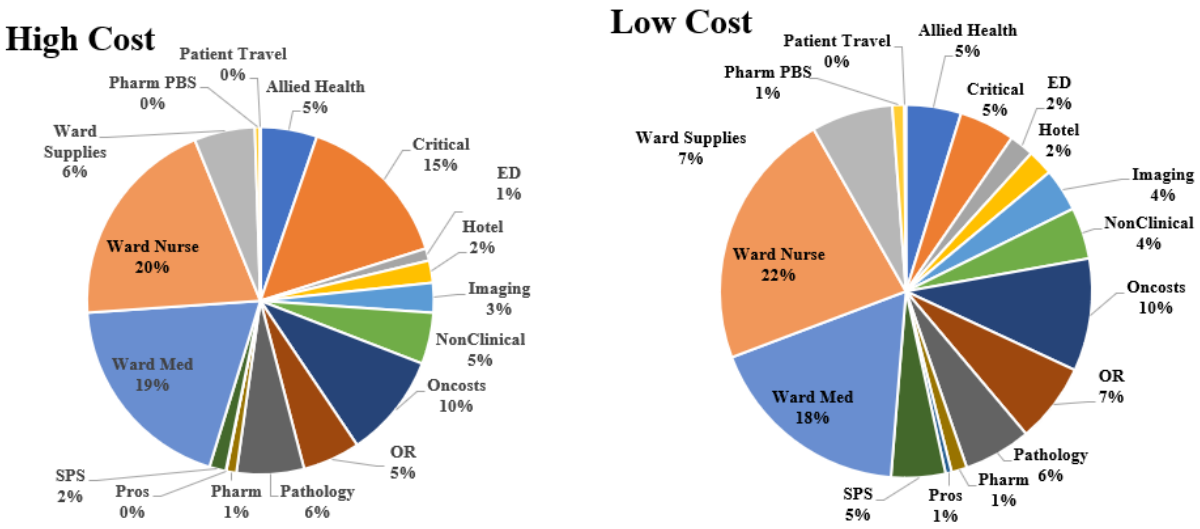

Figure 7 – PC Cohort – Mean Cost Bucket Values – Per Cluster

Upon analysis it was revealed that these high-cost cases were the oldest seven patients in the SALHN NVUGIB PC costing cohort (median age of 94.37 years and IQR 93.57 – 94.57 years). This is an interesting observation, given that Total Cost ($\log_{10}$) did not have a statistically significant positive correlation with patient age (0.103, p=0.370).

5.6 REPEAT PRESENTATION COSTING

As referenced in *Section 4.6: Repeat Presentations*, among the eligible cohort there were 25 index bleeds that led to 31 re-presentation cases, with a 9.5% re-presentation rate among the eligible cohort within the data capture period. This represents a large financial burden upon the hospital, and although precise costing figures are not available due to not all representations being in the SALHN costing report – the mean Total Cost of the PC cases was calculated at $14,487.82. If we multiply this by 31, a result of $449,122.42 is found.

Within *Chapter 4*, it was identified that several patients could have had changes to their antithrombotic therapy, in alignment with the best available evidence for reducing rebleeding rates while accounting for thrombosis risk. These evaluations were made from the available detail recorded in the medical record. Investigators cannot preclude the possibility that in some instances these changes would not have been appropriate for those patients.

There is a temptation to suggest that by making alternative prescribing decisions upon patient discharge, which align with evidence to reduce rebleeding rates, sizeable cost savings could be made by a reduction in re-presentation rates. However, for this to be done robustly there needs to be firm evidence of comparative NVUGIB rebleeding rates between the relevant antithrombotic agents in an elderly population. There appears to be emerging evidence in relation to rebleeding rates, but the data is limited, especially in comparing NOAC agents are variable dosing in the elderly population.

The available re-presentation data could not be used to show a statistically significant difference in re-presentation rates between those prescribed antithrombotics at discharge and those without.

It is the investigator's opinion, after reviewing the literature and our available data that a costing projection of altered rebleeding rates with differing antithrombotic prescribing is not currently

possible. However, the comparative bleeding rates among antithrombotic agents for index UGIB rates is far more robust – and may provide a basis for a new prescribing strategy – as discussed in *Chapter 6: Discussion – Future Strategies.*

5.7 HOSPITAL ACQUIRED COMPLICATIONS

Within the SALHN costing report there were seven cases in which patients experienced NVUGIB as a HAC. Investigation was undertaken to estimate the approximate cost of these bleeds – as outlined in *Section 3.10: Costing Analysis Methodology*.

Regarding the maximum funding adjustment under the National Pricing Model – all cases, except for case 5, either had GIB as the sole experienced HAC or had or GIB as the HAC with the maximum adjustment value. Case 5 experienced GIB, delirium, and renal failure as HACs during their admission – with renal failure claiming the maximum adjustment value of 19.8%.

The Estimated HAC Costing had wide variance, with a mean value of $2,099.31.

This mean value indicates that the estimated HAC costs represent only a small portion of the Total Admission Cost. This is despite the literature stating that experiencing a GIB while in hospital greatly increases mortality rates, admissions costs, extend LOS and decrease patient QOL. Despite this, the available models would indicate that the additional costing burden is small in scale. The results of these calculations, as well as their inputs can be seen in *Table 29*.

Table 29 – HAC Price Modelling

Case	1	2	3	4	5	6	7
Total Admission Cost	$15,785.82	$22,517.37	$28,869.78	$44,407.67	$51,328.71	$56,012.93	$72,317.48
HAC with maximal adjustment value	GIB	GIB	GIB	GIB	Renal Failure	GIB	GIB
DRG 11	J65A	E62A	F14A	J65A	T60A	T60A	L63A
Charlson Score	2	6	1	0	1	1	3
NWAU Value	1.4585	1.7243	6.8197	1.4585	4.6114	4.6114	1.3633
Total Complexity Score	48.9342	55.6405	52.288	39.7181	26.4067	46.8743	55.6043
Complexity Group	Low	Low	Low	Low	Low	Low	Low
Maximum Adjustment	9.00%	9.00%	9.00%	9.00%	19.80%	9.00%	9.00%
Dampening	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Final Adjustment	9.00%	9.00%	9.00%	9.00%	19.80%	9.00%	9.00%
Adjusted NWAU	1.3272	1.5691	6.2059	1.3272	3.7445	4.1964	1.2406
National Efficient Price	$6,032	$6,032	$6,032	$6,032	$6,032	$6,032	$6,032
Estimated HAC Costing	$792.01	$936.17	$3,702.44	$792.01	$5,229.14	$2,503.28	$740.13

CHAPTER 6: DISCUSSION

This investigation was successful in its pursuit in the evaluation of real-world management of both antiplatelet, anticoagulant and proton pump therapy, following an acute NVUGIB, in comparison to contemporary practice as shown in the literature. As shown, there are numerous areas in which prescribing could be altered to better suit contemporary practice.

However, there are limitations of this investigation that should be acknowledged.

6.1 LIMITATIONS

Medical Coding

The inaccuracy of medical coding was a limitation of this investigation. The inaccuracy and incompleteness of coding was highlighted in the manual screening of case notes for exclusion criteria, where it led to more than double the rate of exclusions when compared to ICD-10 codes.

Human error in the process of clinical coding must also be understood as a potential source of inaccuracy, as is insufficient detail in the medical record limiting appropriate coding at times. Error may have occurred if casemix officers omitted cases possessing coded exclusion criteria from the casemix extractions. This is unlikely as all extractions included coded exclusion cases; however, it is possible that oversights occurred.

The inaccuracy of medical coding is well established in the literature.

A systematic review undertaken by Burns and colleagues [101] investigated the accuracy of hospital discharge coding compared to manual review of case notes. Coding upon discharge had an overall median accuracy of 83.2% (IQR: 67.3 – 92.1%). Median diagnosis accuracy being lower than median procedure accuracy (80.3% (IQR:63.3 – 94.1%) compared to 84.2% (IQR: 68.7 – 88.7%) respectively).

In a systematic review by Campbell et al. [102] investigated the accuracy of medical coding within the UK, the accuracy of hospital coding varied greatly between hospitals. For ICD coding, the median accuracy of medical coding varied from 53 to 93% depending upon the dataset.

On a smaller scale, Tsopra et al. [103] investigated the accuracy of diagnoses recorded in discharge summaries in the UK among three different respiratory wards. From a total of 107 discharge summaries the mean inaccuracy rate per discharge summary was 55% (95% CI: 52-58%), with primary diagnoses being incorrectly recorded or often missing.

Clinical Data

Data was collected from two different hospitals, from differing LHNs. However, this is still a limited investigation, with practices within other South Australian hospital undetermined. The generalisability of the findings of this investigation may be limited.

The lack of clinical data such as a patient's Glasgow Blatchford score limits the conclusions that can be drawn from the statistically significant difference scoping rates that was observed between the two hospitals.

Costing Data

Due to the release schedule of costing data, not all eligible SALHN cases had costing data available for analysis. This limited the investigations that could be made concerning representations costing and may have improved the statistical significance of numerous calculations.

6.2 CLINICAL INTEPRETATIONS

6.2.1 PRESENTATION RATES

From the casemix extraction, it became apparent that the FMC had a higher presentation/ HAC rate for apparent UGIB. This is perhaps explained by FMC possessing more medical/ surgical units and treating patients who are more likely to be prescribed antithrombotic therapy – such as the cardiology (including interventional cardiology), stroke, respiratory medicine, vascular surgery, orthopaedic surgery and the cardiothoracic surgical unit. Patients with prior history of care at these units would likely present to FMC for the management of an UGIB. Another contributing factor for varying presentation rates could be a difference in the referral pathways for SA Ambulance Services for UGIB.

6.2.2 PATIENT AGE

The median age of eligible cases was 80 years (IQR 72 – 88). This was unsurprising, given that the literature reported that increased age correlates with UGIB incidence and that approximately 70% of UGIB cases occurring in those aged ≥60 years [1,6,11,17,18].

6.2.3 DIAGNOSTIC SCOPING

In *Section 4.2.5: Diagnostic Scoping*, it was noted that FMC had a higher and statistically significant rate of scoping procedures compared to TQEH. Possible interpretations include changes in clinical scoring and scoping criteria between the hospitals or across the two separate time periods (Jan 2018- Dec 2020 for TQEH and Aug 2021- Aug 2022 for FMC). FMC may have received higher acuity patients through the data capture period or experienced greater service availability to conduct scoping procedures, as compared to TQEH, explaining the higher frequency of scoping procedures.

6.2.4 ANTIPLATELETS

As shown in *Section 4.3.1: Prescribed Agents*, the eligible cohort had more SAPT cases than DAPT cases. As SAPT is prescribed at a higher frequency, often for lifelong duration, across more indications, this was unsurprising. The ratio of DAPT to SAPT cases is likely higher than their overall relative prescribing rates, given that DAPT has a comparably higher risk of causing UGIB. It was also unsurprising to see ticagrelor only prescribed within DAPT – given the Pharmaceutical Benefits Scheme (PBS) indication.

Primary Prevention

The high usage of aspirin for primary prevention, 45 cases, was understandable for several reasons. Aspirin as a therapy has been widely available, without prescription, for a long duration. Primary prevention was accepted and even encouraged until recent revision in clinical guidelines. Therefore, the promotion of primary prevention aspirin is likely engrained practice for many clinicians. Clopidogrel, in comparison, is restricted on the PBS for select indications and has not been as widely available, for as long.

The majority (60%) of primary prevention cases did not cease therapy upon discharge. To reiterate conclusions reached from the literature review – primary prevention appears to be (on balance) a poor justification for antiplatelet therapy, due to the therapy creating a GIB risk that outweighs the potential avoidance for coronary and cerebral ischemia, especially for the elderly. Upon review it was found that of those who did not cease primary prevention therapy, the median age was 75.9 years.

Considering that those who have suffered a NVUGIB are of increased risk of a rebleeding episode, the downside of primary prevention only increases following the index bleed. Having 40% of patients persist with primary prevention is not ideal and could be improved upon. Given that a NVUGIB is a notable event and a trigger for antithrombotic review it may be presumed

that those on inappropriate aspirin primary prevention who present without a bleeding event would be discontinued at a lower rate.

Secondary Prevention

According to the available literature, secondary prevention should have continued to minimise ongoing mortality and morbidity – however it was discontinued in 13.9% of cases, with an additional 2.6% of cases having their therapy held with no mentioning of restarting.

When reviewing the secondary prevention cohort (*Section 4.3.2*), it was discovered that most patients had a NVUGIB more than 12 months from their index thrombosis, as opposed to within 12 months – 78 cases compared to 37 cases respectively. This can be potentially explained by several contributing factors. Most patients would live beyond 12 months from their index thrombosis – making a larger over 12-month cohort of potential bleeding cases. However, DAPT poses a greater risk of GIB as compared to SAPT and the greatest period of risk for GIB is in the months following initiation. This would explain why the >12-month cohort has higher case number, but the ≤12-month cohort still presented a sizeable number of cases.

As displayed in *Section 4.3.4*, in patients treated for secondary prevention, there was a distinct difference in the proportion of SAPT and DAPT prescribing when the cohort was classified according to time since the index thrombosis – at the 12-month timeframe. A higher DAPT proportion was noted within the 12-month period (83.3%), which changed to a higher proportion of SAPT (80.3%) when beyond 12 months. This trend was expected, given that DAPT would typically deescalate to SAPT following 12 months of therapy (in most cases). Patients changed to either aspirin or clopidogrel monotherapy, and as per the literature review, the choice of aspirin/ clopidogrel did not affect rebleeding rates if a PPI was co-prescribed [64].

More contemporary clinical evidence has shown that a shorter duration of DAPT following ACS may be feasible in some cases, reducing from a 12-month duration to 3-6 months [104,105]. However, when evaluating the available evidence, it is apparent that many of the more modern studies were powered to detect bleeding outcomes and not ischemia, and the patient populations were highly selective. The European Society of Cardiology in a 2023 guideline [106] commented that the use of these regimens could be considered as an alternative to the default 12-month DAPT duration, however it will be highly dependent upon the patient's bleeding and ischaemic risks.

Other modern strategies to reduce bleeding risk include initially prescribing the more potent $P2Y_{12}$ inhibitors for DAPT (namely prasugrel or ticagrelor) and then deescalating to DAPT with clopidogrel. [106]

It would be very difficult to evaluate the prescribing choices seen in the secondary prevention cases against these more complex modern regimens. The potential ceasing, switching or continuation of antiplatelet(s) would be near impossible to evaluate without a great deal more patient data, in particular cardiac histories.

AF

It was unusual to see antiplatelets being used in five cases for the treatment of AF, given that the class of drugs are generally regarded as inadequate for treating this condition. It was disappointing that three of these cases had this therapy continue upon discharge.

The recent 2024 ESC Guidelines for the Management of Atrial Fibrillation [107], reiterates that antiplatelet agents (including DAPT) are not a suitable alternative to anticoagulants and can lead to harm, especially in the elderly.

Stroke/ TIA

Of the 23 eligible cases treated for stroke or TIA, 14 (60.9%) were discharged on an antiplatelet.

There is universal agreement from the Australian and New Zealand Living Clinical Guidelines for Stroke Management [108], European Stroke Organisation [109] and the American Heart Association/ American Stroke Association [25], that long term SAPT antiplatelet therapy is still recommended as secondary prevention to reduce the risk of recurrent strokes.

However, the evidence for continuation, change, or discontinuation of antiplatelet agent(s) following a NVUGIB is not as strong within the TIA/ stroke population as compared to either primary or secondary prevention. The choice to continue an antiplatelet following a NVUGIB is clinically complex and would vary depending upon the patient's clinical presentation and other risk factors.

Of the four cases that were treated with DAPT (aspirin and clopidogrel), all of them changed to SAPT (clopidogrel) upon discharge. As stated in *Section 2.3: Antiplatelet Therapy*, the recommended duration of DAPT following a stoke/ TIA (at the time of literature review) was 90-days. The recommended duration of DAPT has reduced since the time of the investigator's literature review, with more contemporary guidelines recommending a duration of 21-30 days (in most patient cohorts) [110-112].

Based new recommended duration, and the ongoing risk of recurrent GIB from these eligible cases, the changing from DAPT to SAPT was likely appropriate for these patients.

6.2.5 ANTICOAGULANTS

FMC had a higher proportion of rivaroxaban cases than TQEH (as seen in *Section 4.4.1: Types of Agents*), likely a reflection of the higher DOAC prescribing and that rivaroxaban has an elevated risk of causing UGIB as compared to agents such as apixaban or warfarin.

There were many incidences in which continuing anticoagulation was switched to apixaban – this occurred in 16 cases within the AF cohort and 12 cases within the DVT/ PE cohort. This is encouraging, as it would indicate that many prescribers were aware at the time of clinical review that apixaban held some superiority as an anticoagulant when compared to warfarin and other DOACs. It is likely that the rate of switching to apixaban continued to increase as awareness of apixaban's superiority in regarding to bleeding risk has become more widely known.

AF

I. Renal Functioning

Only 117 (68.0%) cases within the AF/ DVT/ PE cohort had available eGFR to evaluation renal function. Ideally, given the available literature at the time, all AF cases in which eGFR was >30ml/ min/1.73m^2 the patient would have been discharged from hospital with apixaban to minimise the risk of rebleeding and thrombosis. From this cohort of 62 cases, 19 (30.1%) cases did not discharge with apixaban and therefore did not have their therapy optimised.

Recently there is evidence that apixaban may be used safely and effectively in CKD patients – including Stage 4 (GFR 15-29ml/min/ 1.73m^2) and Stage 5 (GFR <15ml/ min/ 1.73m^2). This has occurred following the period of case data accumulation. A recent systematic review – *Safety and Efficacy of Apixaban vs Warfarin in Patients with Stage 4 and 5 Chronic Kidney Disease*, showed the overall efficacy of apixaban was equivalent to warfarin (across indications) and a safety profile that was equivalent (and in some studies superior) in regard to bleeding risk [32].

There were a minority of patients – 25 cases, in which eGFR was < 30ml/min/1.73m^2. Of these, there were six patients who were prescribed warfarin upon discharge. With modern literature, it would be possible for many of these patients to continue with dose-adjusted apixaban.

Additional considerations, such as therapeutic drug monitoring with apixaban serum level, could be used to ensure safe and appropriate prescribing. This could further reduce the reliance on warfarin therapy over apixaban – improving patient rebleeding rates.

II. CHA_2DS_2-VASc

All the 126 AF cases had a CHA_2DS_2-VASc score (through ICD-10 coding) that would justify the ongoing use of oral anticoagulation. And yet despite this, therapy was ceased in 19 (15.1%) cases, with the available literature indicating that these patients will likely experience a higher rate of mortality as an ongoing result.

DVT/ PE

The decision to continue or cease anticoagulation therapy for a DVT or PE following a NVUGIB, is clinically complex, multifaceted and without firm guidance in available literature. Anticoagulant selection, therefore, was only evaluated in those therapy was not ceased following the bleed. For patients who persisted with anticoagulation, ideally, they would have been changed to dose appropriate apixaban once the bleeding had been treated to minimise the risk of ongoing rebleeding and thrombosis.

Of the 19 eligible cases, that were treated for DVT/ PE and that continued anticoagulation following discharge, twelve (63.2%) were prescribed apixaban. It was curious to see that in three cases therapy was switched from apixaban to another agent, and in three cases another agent was switched to apixaban. This may indicate that prescribers may have been altering therapy for other reasons that perceived rebleeding risk, such as patient preference or drug-drug interactions.

Combination Therapy

For those prescribed combination therapy, unfortunately there is limited clinical evidence of which therapy should be pursued following a NVUGIB. Hypothetically the benefits should remain for continuing the therapy as the antiplatelets and anticoagulants will treat the separate conditions without much cross-over efficacy due to their distinct mechanism(s) and site(s) of action. However, it must be acknowledged that (as shown in the literature review) this combination therapy does increase rebleeding risk – so the discontinuation of a single form of therapy may be understandable although clinical evidence is not available to endorse it as advisable.

6.2.6 MEDICAL DISCHARGE SUMMARY STATEMENTS

Poor or incomplete medical documentation, including sparce mentioning of clinical reasoning, could potentially compromise patient outcomes in the future. Community prescribers need clear communication at points of patient transfer to ensure continuity of care can be achieved and changes to therapy can be understood for themselves and explained to their patients.

Incomplete documentation and lacking communication were seen from the treating clinical teams within the Medical Discharge Summary. Statements made for the patient's ongoing risk for thrombosis or bleeding risk were inconsistent, and rarer for statements mentioning both. There were no statements made in the Medical Discharge Summaries in relation to a patient/ family or carer preference for therapy, illustrating that the choice surrounding ongoing therapy was made unilaterally by the treating team.

The Australian NSQHS Standards [113] given clear guidance regarding the reviewing and documentation change to patient medication. Medication safety standard (action 4.10) - a health service organisation has processes '*to perform medication reviews for patients, in line with evidence and best practice*' and that '*medicine-related problems are minimised by conducting medication reviews and documenting the outcomes in partnership with patients.*'

The Australian Government Department of Health and Aged Care, in their 2022 report [114] *Achieving Continuity in Medication Management* outlined in *Guiding Principle 9: Collaborating and communicating medicines-related information with other healthcare professionals* that healthcare professionals need to '*ensure complete, accurate, and timely medicines-related information is shared with relevant healthcare services*'. Specifically, within this report it highlights the requirement for '*explanations of the changes to therapy during the episode of care*.'

The Australian Commission on Safety and Quality in Health Care provided National Quality Use of Medicines Indicators [115], specifically number 5.3 '*Percentage of discharge summaries that include medication therapy changes and explanations for changes.*'

Continuity in Medication Management: A Handbook for South Australia Hospitals [116] outlines in Guiding Principle 9 – Communicating Medicines Information, '*when a patient is transferred to another episode of care, the transferring health care professional(s) should supply comprehensive, complete and accurate information to the health care professional(s) responsible for continuing the patient's medication management in accordance with their Medication Action Plan.'* It is acknowledged within this document that poor communication can contribute to medication related adverse events and unintended hospital re-admissions.

Antiplatelets

Every case in which primary prevention was continued, there was a complete lack of documentation outlining bleeding or thrombosis risk. Investigators interpreted this as primary prevention not being evaluated closely by the treating team and/ or poor documentation.

There were no statements regarding patient, carer, or family advocacy towards antiplatelet therapy in secondary prevention. Considering the variety of management choices and the likely consequences to patient morbidity and mortality that it could bring, it was disappointing to see

nil statements of advocacy. One must question if patients were being consulted regarding changes to therapy and educated as to the potential consequences of continuation or change.

Anticoagulants

In over two thirds (66.9%) of all anticoagulant cases there were nil statements made in relation to a patient's ongoing thrombosis or bleeding risk or advocation of therapy within their Medical Discharge Summary. The clinical documentation and communication of patient of bleeding risk, thrombosis risk and patient/ carer/ family advocation could be improved upon. Overall, statements of bleeding risk were more prevalent than thrombosis risk, both as a total and within every type of management outcome (continued, ceased, etc.). Statements of both thrombosis and bleeding risk only occurred when therapy had ceased, and this was in the minority (32.1%) of these cases. When therapy had switched, nil statements were made in 32.0% of cases.

6.2.7 PROTON PUMP INHIBITORS

As outlined in *Section 4.5*, there were 23 (6.4%) cases in which the patient was prescribed an antithrombotic and no PPI at point of discharge. Contemporary guidelines strongly recommend that any patient who is on antithrombotic therapy, and continues such therapy following a UGIB, is prescribed a PPI to reduce potential reoccurrence [6,8,16,23,77,86].

There was no recording of allergies, patient preference or drug interactions that would contradict PPI therapy. Potential reasons for the lack of PPI therapy could be clinician oversight, poor documentation of existing PPI therapy in the original medication history, patient self-discharge, patient refusal or allergies that were clinically discussed by not documented. Ensuring that patients who experience a NVUGIB, either as a presenting complaint or hospital acquired complication discharge with a PPI could lower future rebleeding rates.

6.2.8 REPEAT PRESENTATIONS

Due to the methodology used to identifying repeat presentations, the depth of information and conclusions that can be made are limited. Those who re-presented with exclusion criteria did not have their antithrombotic status noted and those that were not prescribed an antithrombotic upon presentation did not have further information recorded as per our established method of data collection. Therefore, it is expected that the re-presentations rates shown through this investigation are conservative and may in turn downplay rebleeding risk.

There is no certainty that with altered prescribing of antithrombotics, the repeat presentations (as presented in *Section 4.6*) may not have eventuated. However, the evidence available in the literature suggests that appropriate prescribing will balance the risk of rebleeding and thrombosis while limiting rebleeding episodes.

When investigating the use of antithrombotics in the index bleeds that preceded repeat presentations, there were nine (22.0%) index cases in which altered prescribing upon discharge (as informed by the literature) could have reduced rebleeding rates while balancing the risk of thrombosis. In the treatment of AF and DVT there were six cases in which therapy could have reasonably changed to apixaban but were not. These included two rivaroxaban and four cases of warfarin – in only one of these cases was the patients eGFR $\leq$ 30ml/min (it was 15ml/min). From the 41 index bleeds, there were three cases in which PPI were not prescribed at point of discharge.

The five cases of warfarin being prescribed for mechanical heart valves could not have been altered at the time of this clinical decision making. All cases of primary prevention therapy were ceased at point of discharge. There were several cases for which a change in prescribing would not be advocated. All the DAPT cases were treating a case of secondary prevention, within 12 months of the thrombus. Nil changes in prescribing would have been advised

following the index bleed considering the high risk of thrombus formation during this treatment period.

Tracking changes to therapy between admissions was difficult, due to many of the re-presentation cases possessing exclusion criteria (hence preventing prescribing data from being collected).

Re-presentation rates are clearly time dependent. Candeloro et al. [14] measure the cumulative incidence of recurrent bleeding (among other outcomes) in those hospitalised with a GIB, increased as time progressed. The cumulative incidence (percentage) was reported at 5.27 (95% CI, 3.96 – 6.84) at 30 days, 10.48 (95% CI, 8.6 – 12.57) at 90 days, 13.59 (95% CI, 11.45 – 15.92) at 180 days, 18.84 (95% CI, 16.32 – 21.5) at 365 days and 25.26 (95% CI, 22.31 – 28.32) upon 730 days.

As stated repeatedly in the literature, antithrombotic therapy increases the risk of suffering a NVUGIB [6,8,11] and increases rebleeding rates [19,22,61]. There were 174 antiplatelet index bleeding cases with 12 re-presentations (re-presentation rate of 6.9%), 122 anticoagulant index bleeding cases with 18 re-presentations (re-presentation rate of 14.8%) and 31 index bleeding cases with both antiplatelet and anticoagulant prescribed with a single re-presentation (re-presentation rate of 3.2%).

6.3 FUTURE STRATEGIES

LOS was identified as a positive corollary to total admission cost in this study, however, effective strategies to reduce LOS are limited. Obvious existing strategies include down transferring the patient to another site of lower acuity or discharging the patients with additional medical/ social supports. However, this will only reduce the end portion of a hospital stay. Some evidence suggesting however that shortening LOS by the last day in hospital does not

produce meaningful cost savings [117]. It should be noted that reducing occupied bed days can improve patient flow throughout a hospital.

As outlined in *Chapter 2*, the two strategies backed by cited evidence were the ceasing of primary prevention aspirin, especially in the elderly (>65 years) and the switching of anticoagulants rivaroxaban, dabigatran, and warfarin (where renal function allows) for the treatment of AF, PE and DVT to the agent apixaban, which has a lower bleeding risk. If attempting a pre-emptive approach to stopping or mitigating the risk of NVUGIB index bleeds, a strategy would need to consider the overall impact a change of therapy would ultimately cause.

A meta-analysis of randomised clinical trials and observational studies from Valkhoff et al. [118], focusing on the risk of UGIB and low dose aspirin, provided useful data for this estimation. The person-years weighted average number of additional UGIB cases associated with aspirin was 1.2/1000 patients per year (95% CI, 0.7 – 1.8). The calculated number needed to harm (NNH) was 816 (95% CI, 560 – 1500). Given that the eligible cohort consisted of 45 primary prevention cases, with 41 of these presenting with a NVUGIB, by using this predicted NNH, it would take the ceasing of aspirin in approximately 36,720 cases to prevent these admissions from occurring. The mean total cost of presenting NVUGIB cases with antiplatelets prescribed at admission was $14,503.05. If this averaged costing was multiplied by the 41, a total approximate costing of $594,625.05 would be realised.

Vingogradova et al. [52] were able to produce the NNH/ NNT to measure the relative benefits or risks of the different DOAC agents in comparison with warfarin. Over a 24-month period, in an AF cohort, the NNT (changing from warfarin to apixaban) to avoid major bleeding was 60. In the non-AF cohort, over the same time span, the NNT would be 96 to avoid an UGIB. Among those eligible cases that presented with a NVUGIB, there were 21 warfarin cases for

AF and 12 cases for non-AF (non-mechanical heart valve) indications. To avoid these presenting cases, a total of 1,260 cases from the AF cohort and 1,152 from the non-AF cohort would need therapy changed to apixaban. The mean Total Cost of cases presenting with a NVUGIB and prescribed an anticoagulant was $17,474.18. If we multiple this costing by the 33 cases (AF and non-AF), we get a total approximate costing of $576,647.94.

Evidence presented by Hilton et al. [119] suggests that reduced dosing in DOAC therapy for AF patients aged over 80 years or with a BMI <30kg/m^2 may reduce bleeding outcomes while not impacting mortality or thrombosis risk. As clinical evidence gathers, it is likely that populations with increased risk for NVUGIB will be further identified, and appropriate dosing strategies developed that extend further than the current manufacturer's guidelines.

The more recent evidence of apixaban in those with advanced chronic kidney disease is encouraging, hopefully extending this agent's use to a larger cohort can minimise their recurrent GIB risk. The use of therapeutic drug monitoring for apixaban may give prescribers the confidence necessary to employ these drugs in such a population – and guide dosing for optimal benefits. [108]

Electronic medical records such as South Australia's Sunrise® EMR & PAS platform could be used as part of an impactful, state-wide strategy. The clinical application of Sunrise® allows for the live identification of patient cohorts.

A patient's electronic record details their past medical history, which can be combed for both antithrombotics indications and contributing risk factors for future bleeding events. Historical drug orders (i.e., medications that the patient was known to be taking prior to their admission) are available for viewing – with antithrombotics being readily identifiable.

As we enter a new digital age, it is not difficult to imagine automated clinician support systems that nudge prescriber behaviour. Relevant information could be displayed in real time through dashboards and reports, medication re-evaluation could be prompted by an automated system based on patient details. Encouraging the prescribing of apixaban over alternative agents (where clinically justifiable), the discontinuation of primary prevention aspirin and the use of PPI therapy (where appropriate) discharge are all possibilities and would likely provide sustained benefit.

Ideally hospitals will implement strategies that could both limit cases in which patients present with a NVUGIB (both for index bleeds and rebleeding episodes) and NVUGIB that occur as a HAC.

In the future, clinical screening programs may be deployed through the Sunrise® EMR to detect patients of high risk of developing a NVUGIB, either during their inpatient stay or when discharged into the community. These patients could be identified though a mixture of past medical history, presenting complaints, patient demographics, medication history and current treatment. Clinical decision support could trigger at the point of patient review, encouraging clinicians to apply evidence-based treatment and monitoring strategies. Computer analysis of bleed panels could inform clinicians of early signs of GIB such as haemoglobin/ platelet changes could be utilised. A system that could influence nudge prescribing in a manner that accounts for both bleeding and thrombosis risk could create scalable and sustainable impact across our health care system. Prompting upon discharge for protective therapy such as PPIs to be prescribed (where appropriate) could also be considered.

CHAPTER 7: CONCLUDING STATEMENTS

Through this investigation several conclusions are possible.

Both FMC and TQEH have had sizable numbers of patients both that present to hospital with, and or have developed NVUGIB through a hospital acquired complication. Many of these patients were on antithrombotic therapy prior to the index bleed.

The clinical evidence suggests that evidence-based alteration of prescribed therapy can reduce the likelihood of a rebleeding episode while addressing the ongoing risks of thrombosis. From the available data, it appears that both hospitals could potentially improve outcomes by switching anticoagulants, deprescribing primary prevention aspirin and prescribing proton pump inhibitors upon discharge.

Changes to therapy may reduce rebleeding rates, and while strategies can be implemented or continued for limiting NVUGIB HACs, the impact may be modest in scope and effectiveness in terms of cost savings.

It should be noted that the strict exclusion criteria used to create a refined patient cohort, thereby making the accuracy of analysis in regard to prescribing patterns possible, also worked to reduce the generalisability and perhaps scope of this investigation's costing projections.

As we look to the future care, the pre-emptive evaluation of antithrombotic therapy to potentially avoid index bleeds through automated clinician support systems should be investigated – both within South Australia and broader territories. The ability to pre-screen patients at greater risk of bleeds early and change therapy, where appropriate, could undoubtedly improve cost savings for hospitals and improve patient outcomes.

CHAPTER 8: REFERENCES

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ATTACHMENTS

Attachment 1 – SALHN – Email Confirmation of Ethics Exemption

Attachment 2 – SALHN – Email Confirmation of Ethics Extension

Attachment 3 – CALHN – Authorisation of Ethics Approval

Attachment 4 – CALHN – Authorisation of Ethics Extension

Attachment 5 – Data Linking Spreadsheet

Attachment 6 – Data Collection Spreadsheet

Attachment 7 – Case Data Spreadsheet

Attachment 8 – SALHN Costing Report

APPENDICES

Appendix 1 – The Cost of a Bleed – Literature Search Strategy

Appendix 2 – Principal Diagnosis

Appendix 3 – Exclusion Criteria

Appendix 4 – K-Means Cluster Analysis: ANOVA Table

Appendix 1 – The Cost of a Bleed – Literature Search Strategy

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to November 24, 2021

Search Strategy:

#	Searches	Results
1	Gastrointestinal Hemorrhage/	43457
2	Peptic Ulcer Hemorrhage/	7266
3	upper.ti,ab.	365223
4	(1 or 2) and 3	7990
5	exp Upper Gastrointestinal Tract/	204841
6	(gastrointestinal or GI or esophageal or oesophageal or duodenal).ti,ab,kf.	462014
7	(5 or 6) and 3	45768
8	hemorrhage/	76967
9	haemorrhag*.ti,ab,kf.	55272
10	hemorrhag*.ti,ab,kf.	232778
11	bleeding.ti,ab,kf.	220610
12	injury.ti,ab,kf.	729226
13	blood.ti,ab,kf.	2056953
14	or/8-13	3066105
15	and/7,14	15128
16	UGIB.ti,ab,kf.	692
17	peptic ulcer*.ti,ab,kf.	34977
18	Stomach Ulcer*.ti,ab,kf.	2358
19	Duodenal ulcer*.ti,ab,kf.	20837
20	or/16-19	52669
21	***(gastrointestinal or GI or esophageal or oesophageal or duodenal).ti.***	***180634***
22	***(hemorrhage* or haemorrhage* or bleeding or injury or blood).ti.***	***835872***
23	***and/21-22***	***17792***
24	or/4,15,20,23	77169
25	antithrombins/ and oral administration/	454
26	(oral* adj3 (antithromb* or antiplatelet*)).ti,ab,kf.	1500
27	Anticoagulants/	81906
28	Anticoagulant*.mp.	118362
29	warfarin/	20465
30	Warfarin.mp.	32090
31	Vitamin K Antagonist.mp.	3217
32	Apixaban.mp.	4559
33	edoxaban.mp.	1866
34	thrombin inhibitor.mp.	3109
35	thrombin antagonist.mp.	55
36	Rivaroxaban/	3972

37	rivaroxaban.mp.	6985
38	Dabigatran/	3494
39	dabigatran.mp.	6065
40	Factor Xa inhibitor/	5526
41	Factor Xa inhibitor.mp.	1313
42	Aspirin/	46690
43	Aspirin.mp.	70449
44	Acetylsalicylic Acid.mp.	10241
45	Clopidogrel/	9530
46	Clopidogrel.mp.	15514
47	Ticagrelor/	1991
48	Ticagrelor.mp.	3465
49	Prasugrel Hydrochloride/	1596
50	Prasugrel.mp.	2748
51	Cangrelor.mp.	640
52	Platelet aggregation inhibitors/	38774
53	Platelet aggregation inhibitor*.mp.	39391
54	Vorapaxar.mp.	353
55	or/25-54	221834
56	and/24,55	2965
57	exp animals/ not (exp animals/ and exp humans/)	4919146
58	exp children/ not (exp children/ and exp adults/)	1294878
59	(child* or paediatric* or pediatric* or infant* or adolescen* or teen* or baby or neonate*).ti.	1348622
60	***case reports.pt.***	***2227510***
61	***"Single-Case Studies as Topic"/***	***87***
62	or/57-61	8765014
63	56 not 62	2519
64	limit 63 to (english language and yr="2015 -Current")	684
65	("28272736" or "32680646" or "33227428" or "27190077" or "26572685" or "29671413").ui.	6
66	64 and 65	5

Appendix 2 – Principal Diagnosis

ICD – 10 CODES FOR UGIB

ICD-10	Description
K25	**Gastric ulcer**
K25.0	Acute gastric ulcer with hemorrhage
K25.1	Acute gastric ulcer with perforation
K25.2	Acute gastric ulcer with both haemorrhage and perforation
K25.3	Acute gastric ulcer without haemorrhage or perforation
K25.4	Chronic or unspecified gastric ulcer with haemorrhage
K25.5	Chronic or unspecified gastric ulcer with perforation
K25.6	Chronic or unspecified gastric ulcer with both haemorrhage and perforation
K25.7	Chronic gastric ulcer without haemorrhage or perforation
K25.9	Gastric ulcer, unspecified as acute or chronic, without haemorrhage or perforation
K26	**Duodenal Ulcer**
K26.0	Acute duodenal ulcer with haemorrhage
K26.1	Acute duodenal ulcer with perforation
K26.2	Acute duodenal ulcer with both haemorrhage and perforation
K26.3	Acute duodenal ulcer without haemorrhage or perforation
K26.4	Chronic or unspecified duodenal ulcer with haemorrhage
K26.5	Chronic or unspecified duodenal ulcer with perforation
K26.6	Chronic or unspecified duodenal ulcer with both haemorrhage and perforation
K26.7	Chronic duodenal ulcer without haemorrhage or perforation
K26.9	Duodenal ulcer, unspecified as acute or chronic, without haemorrhage or perforation
K27	**Peptic ulcer, site unspecified**
K27.0	Acute peptic ulcer, site unspecified, with haemorrhage
K27.1	Acute peptic ulcer, site unspecified, with perforation
K27.2	Acute peptic ulcer, site unspecified, with both haemorrhage and perforation
K27.3	Acute peptic ulcer, site unspecified, without haemorrhage or perforation
K27.4	Chronic or unspecified peptic ulcer, site unspecified, with haemorrhage
K27.5	Chronic or unspecified peptic ulcer, site unspecified, with perforation
K27.6	Chronic or unspecified peptic ulcer, site unspecified, with both haemorrhage and perforation
K27.7	Chronic peptic ulcer, site unspecified, without haemorrhage or perforation
K27.9	Peptic ulcer, site unspecified, unspecified as acute or chronic, without haemorrhage or perforation
K28	**Gastrojejunal ulcer**
K28.0	Acute gastrojejunal ulcer with haemorrhage

K28.1	Acute gastrojejunal ulcer with perforation
K28.2	Acute gastrojejunal ulcer with both haemorrhage and perforation
K28.3	Acute gastrojejunal ulcer without haemorrhage or perforation
K28.4	Chronic or unspecified gastrojejunal ulcer with haemorrhage
K28.5	Chronic or unspecified gastrojejunal ulcer with perforation
K28.6	Chronic or unspecified gastrojejunal ulcer with both haemorrhage and perforation
K28.7	Chronic gastrojejunal ulcer without haemorrhage or perforation
K28.9	Gastrojejunal ulcer, unspecified as acute or chronic, without haemorrhage or perforation
K92	**Other diseases of digestive system**
K92.0	Hematemesis
K92.1	Melena
K92.2	Gastrointestinal haemorrhage , unspecified

Appendix 3 –Exclusion Criteria

ICD – 10 CODES for Exclusion Criteria

Exclusion Criteria	Casemix Description
Cancer	any with a 'C' code
< 18 years	less than 18 years old
Haemodialysis	Proc Code 13100-00
Haemodialysis & C Code (Cancer)	Proc Code 13100-00 or C code
Haemodialysis & O Code (Pregnancy)	Proc Code 13100-00 or O code
Haemodialysis & Z515 code (Palliative Care)	Proc Code 13100-00 or Z515 code
Pregnancy	any with an 'O' code
Pregnancy	any with Z33 - 35 code
History of Cancer	any with Z85 code
Z515 code & C Code (Palliative Care & Cancer)	any with Z515 or C Code
Yes: Z515 code (Palliative Care)	any with Z515 code

Appendix 4 – K-Means Cluster Analysis: ANOVA Table

ANOVA

	Cluster		Error			
	Mean Square	df	Mean Square	df	F	Sig.
Zscore: Allied Total Cost	43.460	1	.413	76	105.105	<.001
Zscore: Critical Total	13.799	1	.878	76	15.715	<.001
Zscore: ED Total	.093	1	1.022	76	.091	.763
Zscore: Hotel Total (single bucket provided - nil direct or indirect)	51.512	1	.354	76	145.320	<.001
Zscore: Image Total	10.957	1	.882	76	12.427	<.001
Zscore: NonClinical	42.982	1	.478	76	89.849	<.001
Zscore: Oncosts	55.013	1	.320	76	171.821	<.001
Zscore: OR Total	3.448	1	1.029	76	3.350	.071
Zscore: Path Total	25.675	1	.732	76	35.082	<.001
Zscore: Pharm Total	35.050	1	.640	76	54.796	<.001
Zscore: Pros	.218	1	1.099	76	.198	.658
Zscore: SPS Total	3.137	1	1.037	76	3.025	.086
Zscore: WardMed Total	45.673	1	.433	76	105.508	<.001
Zscore: Ward Nurse Total	42.798	1	.440	76	97.190	<.001
Zscore: Ward Supplies Total	23.834	1	.309	76	77.168	<.001
Zscore: Pharm PBS Total	3.499	1	1.011	76	3.460	.067
Zscore: PatTravel Total	.126	1	1.102	76	.115	.736

The F tests should be used only for descriptive purposes because the clusters have been chosen to maximize the differences among cases in different clusters. The observed significance levels are not corrected for this and thus cannot be interpreted as tests of the hypothesis that the cluster means are equal.