Antiplatelet and anticoagulant therapy in patients with acute coronary syndromes and atrial fibrillation

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Abstract

Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 receptor antagonist, is the standard of care following an acute coronary syndrome (ACS) presentation, and oral anticoagulation (OAC) is standard of care for stroke prevention in atrial fibrillation (AF) patients. In patients with AF who present with an ACS, it is not clear whether the combination of DAPT and OAC, known as triple therapy (TT), should be the preferred treatment strategy, or whether DAPT alone is optimal.

The first two studies in this thesis examined contemporary antiplatelet/anticoagulant management in New Zealand. The first study examined management of 93 ACS patients with AF from a single-centre. We found DAPT was the preferred treatment regimen, and no TT use was observed. Decisions regarding therapy did not appear to be based on assessments of stroke or bleeding risk. In the second study, we utilised the national ANZACS-QI registry, and examined pharmacy prescription data for 610 ACS patients who underwent percutaneous coronary intervention (PCI) with a history of AF. In this cohort DAPT was again the most common discharge regimen followed by TT, and their use was not driven by stroke risk (CHA2DS2VASc scores). Rates of DAPT and TT declined markedly over the 12 months following the ACS event. On the basis of these two studies we concluded that no consistent treatment strategy was evident for the management of ACS patients with AF.

A systematic literature review was then undertaken to identify optimal therapy. We selected papers describing treatment regimens and one-year outcomes for patients with AF and either ACS or PCI. The inclusion of stable PCI patients was necessary as the majority of literature featured mixed cohorts of ACS or stable coronary disease undergoing PCI. The identified literature was entirely observational in nature and the overall quality was poor. The largest studies reported that TT offered significant reductions in stroke over DAPT, and a consistent increase in bleeding associated with TT was reported.

On the basis that the available literature did not offer clear guidance on when the benefits associated with stroke reduction with TT would be greater than the harm
associated with excess bleeding, we constructed a decision analysis model. This model addressed likely thresholds at which TT stroke reduction may exceed harm from bleeding. Under most modelled scenarios TT was not preferred above DAPT at CHA\textsubscript{2}DS\textsubscript{2}VASc 2, and only outperformed DAPT when stroke risk was high in the CHA\textsubscript{2}DS\textsubscript{2}VASc 3-5 range.

Given the importance of bleeding in determining the net clinical benefit of DAPT versus TT we examined how accurately bleeding events could be predicted in a cohort of 1000 acute myocardial infarction patients. We examined the ACS bleeding scores CRUSADE and ACTION as well as low platelet reactivity (LPR) to predict one-year TIMI major and minor bleeding. We found that neither score nor LPR accurately predicted one-year bleeding events.

The clinical problem of optimal antiplatelet/anticoagulant therapy in ACS patients with AF remains significant. Our data suggests that at low stroke risks DAPT is probably the treatment of choice, with TT becoming more acceptable at higher stroke risk. Accurate classification of bleeding risk in this population is needed to minimise potential harms associated with TT.
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Abbreviations

ACS – acute coronary syndromes

ACS-AF - acute coronary syndrome patients with atrial fibrillation

ACTION - Acute Coronary Treatment and Intervention Outcomes Network registry

ACTIVE-A - Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events – A trial.

ACTIVE-W - The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events

ADP – adenosine diphosphate

AF – atrial fibrillation

AFASAK - Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study

AHA – American Heart Association

AMIS – Aspirin Myocardial Infarction Study

ANZACS-QI – All New Zealand Acute Coronary Syndrome – Quality Improvement registry

APPRAISE-2 - Apixaban for Prevention of Acute Ischemic Events 2 study

ARISTOTLE - Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

ASA – acetylsalicylate acid

ATLAS ACS 2-TIMI 51 - Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndromes – Thrombolysis in Myocardial Infarction study

ATRIA - anaemia, renal disease, age ≥75, prior haemorrhage, hypertension [bleeding score]

AU – aggregation units

AUC – area under curve
AVERRORES - Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment

BARC - Bleeding academic research consortium

BMI – body mass index

CAD – coronary artery disease

CABG – coronary artery bypass graft

CAPRIE – Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events

CHF – congestive heart failure

COX1 - Cyclooxygenase-1

CURE – Clopidogrel in Unstable angina to prevent Recurrent Events trial

CRUSADE – Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines

DAP – data access proposal

DAPT – dual antiplatelet therapy

EAFT – European Atrial Fibrillation trial

ECG – electrocardiogram

ED – emergency department

eGFR – estimated glomerular filtration rate

ESC – European Society of Cardiology

GRACE – Global Registry of Acute Coronary Events

HAS-BLED - Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drug or Alcohol [bleeding score]

ICD – international classification of disease

INR – international normalised ratio

ISIS-2 – Second International Study of Infarct Survival
LAA – left atrial appendage
LPR – low platelet reactivity
MACE - major adverse cardiovascular events
MI – myocardial infarction
mOBRI - modified Outpatient Bleeding Risk Index
NHI – national health index
NOAC - non-vitamin K oral anticoagulant
NSTEACS – non-ST-segment elevation acute coronary syndrome
NSTEMI – non-ST-segment elevation myocardial infarction
OAC – oral anticoagulant
OR – odds ratio
PCI – percutaneous coronary intervention
PIONEER-AF PCI - Open-Label, Randomized, Controlled, Multi-centre Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention
PLATO – Platelet Inhibition and Patient Outcomes study
QALY – quality-adjusted life year
RCT – randomised control trial
REACH - Reduction of Atherothrombosis for Continued Health
RE-DUAL PCI - Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
RE-LY - Randomized Evaluation of Long-Term Anticoagulation Therapy
ROC – receiver operator characteristic curve
ROCKET AF - The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR – relative risk

SPAF I – Stroke Prevention in Atrial Fibrillation trial

STEMI – ST-segment elevation myocardial infarction

TRITON-TIMI 38 - Trial to Assess Improvement in therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction

TIA – transient ischaemic attack

TIMI – thrombolysis in myocardial infarction

TT – triple therapy

UA – unstable angina

VIEW – vascular informatics using epidemiology and the web

VKA - vitamin K antagonist

WOEST - What is Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary STenting
1 Introduction
1.1 Acute coronary syndromes

An acute coronary syndrome (ACS) is a potentially life-threatening condition that occurs most commonly when transient or permanent thrombotic occlusion of the coronary vasculature results in myocardial ischaemia and/or infarction. The term ACS specifically refers to a spectrum of clinical conditions that increase in severity from unstable angina (UA), to non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) in its most high-risk form ¹.

1.1.1 Pathophysiology

ACS is the unstable manifestation of coronary artery disease (CAD). The underlying pathophysiology of CAD is atherosclerosis, a dynamic and ongoing process of plaque formation and stenosis within artery walls. Two key processes, namely endothelial dysfunction and inflammatory response, are crucial to the development of atherosclerotic lesions and therefore ACS. Traditional CAD risk factors including hyperlipidaemia, hypertension, diabetes and smoking, cause damage to the endothelium ². Under normal conditions the endothelium maintains a delicate balance of anti and pro thrombotic, inflammatory, atherogenic and coagulant functions, and when damage ensues one or more of these functions are lost resulting in endothelial dysfunction ³. Now the vasculature is predisposed to a vasoconstrictive state, platelet aggregation and adhesion, thrombosis, impaired coagulation, and vascular inflammation ⁴.

In addition to endothelial dysfunction, a highly specific series of cellular and molecular inflammatory responses also contribute to the development of atherosclerotic lesions ². Once the endothelium has been damaged, leukocytes bind and migrate to the sub-endothelial space where they digest oxidised low density lipoprotein cholesterol that has also crossed the artery wall. The artery walls now store large amounts of cholesterol with a yellow appearance- the constituent of an atherosclerotic plaque ⁵. A fibrous cap isolates the contents of the plaque from the circulatory system however further inflammatory responses degrade the integrity of this cap thereby creating an
environment conducive to plaque rupture. Inflammatory activation also increases the production of tissue-factor, a potent activator of the clotting cascade, which on plaque rupture will trigger thrombus formation and potentially occlude the coronary artery. Despite the chronic nature of atherosclerotic lesion development, the acute presentation often occurs spontaneously and without warning.

1.1.2 Burden of disease

Internationally ACS is a significant healthcare problem. CAD has been the leading cause of mortality globally for the past 15 years. Rates of CAD related deaths continue to rise and approximately half occur as a result of ACS. In 2000, 6.88 million deaths from CAD were recorded, increasing most recently to 8.75 million deaths in 2015. This increase is equivalent to 112 deaths per 100,000 in 2000, to 119 deaths per 100,000 in 2015. Cardiovascular disease is also the leading cause of mortality in New Zealand. Annually cardiovascular disease accounts for 33% of all deaths and, of these, 49% are attribute to CAD. For Maori males and non-Maori males CAD is the leading cause of mortality, and this is true for non-Maori females also. For Maori females CAD is the second highest cause of death behind lung cancer.

CAD also carries significant morbidity for the New Zealand population. Heart disease is the leading cause of health loss (loss of healthy years lived) in New Zealand. Among New Zealand males CAD is the leading cause of quality years lost and accounts for 10% of all health loss. For females CAD is the second most common cause, accounting for 6% of all health loss. Despite advances in CAD therapies, ACS results in persistent mortality, medical, social and economic burden.

1.1.3 Clinical treatment of ACS

There are two main goals for the management of an ACS. This first is to reduce myocardial necrosis and in doing so preserve cardiac function, particularly left
ventricular function. Treatment is dependent on where the patient falls on the ACS spectrum. Diagnosis of STEMI requires timely reperfusion therapy to restore blood flow through the coronary arteries and limit infarct size. Percutaneous coronary intervention (PCI) is the preferred treatment of choice when it can be performed with 90 minutes of first medical contact and this strategy successfully restores coronary artery flow in approximately 90% of patients. If time to PCI is expected to exceed 90 minutes, often due to geographical factors, then fibrinolysis should be administered as time delay negates the benefit of PCI over immediate fibrinolytic therapy. Patients with non-ST-segment elevation acute coronary syndromes (NSTEMI) are recommended to receive angiography with coronary revascularisation (PCI or coronary artery bypass graft [CABG]) as appropriate. Adjunct therapies to manage the acute phase may also include oxygen, nitro-glycerine, analgesia, antiplatelet agents, beta-blockers, anticoagulation, and angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers.

The second goal in the management of an ACS is to limit disease progression through secondary prevention strategies and risk management. This is critically important as after an ACS event patients remain at high risk of recurrent ischaemic events. Long-term patient adherence to cardioprotective medications is necessary and includes therapies such as antiplatelet agents, statins, ACE inhibitors/angiotensin II receptor blockers and beta-blockers. Intensive risk factor modification is also required and may include antihypertensive therapy, glucose-lowering therapy for diabetics and lifestyle changes (e.g. smoking cessation, diet modifications and physical activity). Referral to cardiac rehabilitation services is also an effective strategy to aid patient compliance as well as assisting in their transition to chronic self-management after an ACS event.

1.1.4 Platelets in ACS

The integrity of the circulatory system is maintained by haemostatic processes. When vessel walls are compromised, like in the instance of plaque rupture or erosion, circulating platelets are recruited to the site of injury where they are integral to healing.
As part of normal regulatory processes platelets play a key role in thrombus formation, and when an artery is sufficiently occluded by a thrombus an ACS event is initiated \(^{21}\).

In the setting of plaque disruption two distinct pathways activate platelets: one generated by exposed collagen, the other by exposed tissue factor. Collagen from the sub-endothelium binds to platelet glycoprotein VI facilitating platelet adhesion. In addition, glycoprotein VI is a major agonist for platelet activation and granule release. Amongst other compounds, adenosine diphosphate (ADP) and thromboxane A\(_2\) are both released during degranulation and both are potent platelet agonists, further perpetuating the cycle. Collagen also binds to von Willebrand factor, and this complex binds to platelet glycoprotein Ib-V-IX resulting in further platelet adhesion, or ‘rolling’ of platelets on the vessel wall \(^{22}\). Tissue factor on the other hand binds with factor VIIa (activated factor VII), and this complex activates factor IX, initiating a cascade that generates thrombin. Thrombin acts to further stimulate platelets, but also ensures stability by cleaving fibrinogen to fibrin- the insoluble mesh encapsulating the platelet plug \(^{23}\) (Figure 1-1).
Figure 1-1 Platelet activation after vascular injury

Endothelial damage results in platelet exposure to collagen and other extracellular membrane (ECM) proteins, facilitating platelet adhesion to the substratum. The adherent platelets then aggregate and release potent platelet agonists including adenosine diphosphate (ADP) and thromboxane A2. Following activation the platelets produce thrombin which initiates the coagulation cascade. This leads to the generation of fibrin, a mesh-like deposition that stabilises the platelet plug. Figure reproduced with permission from the rights holder, Springer Nature 24.
1.1.5 Thrombosis in ACS

The small amount of thrombin generated by the tissue factor-factor VIIa complex as outlined above is considered the initiation phase of coagulation and is very inefficient. This is because the activated forms of factors VIII and V (pro-cofactors) are not yet available. However, once thrombin is formed it acts to convert these pro-cofactors to factor VIIIa and factor Va respectively, leading to a burst of thrombin generation. As a measure of amplification, the thrombin generation with factor V is less than 1% the rate compared when factor Va is present. Pathophysiologically thrombi formed in the arterial system, like those in ACS, are predominantly platelet rich or ‘white clots’. In contrast, thrombi formed in other body systems (e.g. low-pressure systems such as the venous system or cardiac atria) are fibrin rich or ‘red clots’.

In the context of ACS platelets play an important role in the process of thrombus formation. The platelet therefore is a logical therapeutic target to prevent further coronary artery occlusions and this is achieved through the administration of antiplatelet agents.

1.1.6 History of Aspirin

1.1.6.1 Salicylic acid

Today, daily aspirin as an antiplatelet medication is a mainstay preventative treatment after an ACS event, proven to reduce secondary events in a safe and efficacious manner. However, arriving at this point is the product of a long and rich history.

Aspirin is one of the worlds most prescribed drug and originates from the Salicaceae family of plants. The Salicaceae are a willow family of flowering plants, and the willow tree itself has an abundantly watery bark with a high salicylic acid component; the organic compound for which willow gets its medicinal effects. The therapeutic use of Salicaceae plants dates back thousands of years, its earliest recorded use occurring in prehistoric times.
In March 2017 a study of Neanderthal dental plaque from an abscessed jawbone, dating from around 42,000 to 50,000 years ago, identified genetic material from the poplar tree (also of the Salicaceae family), indicative of therapeutic use. Historical evidence in the form of markings on clay tablets has indicated that ancient Egyptians of the Sumerian period (5500 – 4000 BC) used willow bark to alleviate rheumatic pain. Observations by Greek physician Hippocrates around 400 BC testified to the antipyretic and analgesic properties of salicylic tea, and this was later echoed by Galen in 200 AD who recorded the anti-inflammatory, analgesic and antipyretic effects of willow bark. These observations, although anecdotal, indicate that the therapeutic use of salicylic acid has a very long and enduring history until integration into modern medicine.

The first scientific description of willow bark is attributed to the Reverend Edward Stone in 1763. Stone wrote a letter to the President of the Royal Society of London describing the use of powder derived from willow bark to treat ague (fever) in 50 patients. His interest in Willow was acknowledged as being due to the ancient Doctrine of Signatures which dated from the time of Galen, and may go some way towards explaining the modernisation of salicylic acid. The doctrine details that clues to the treatment of a disease will be found in the cause of the disease. According to Stone:

As this tree delights in a moist or wet soil, where agues chiefly abound, the general maxim that many natural maladies carry their cures along with them or that their remedies lie not far from their causes was so very apposite to this particular case that I could not help applying it.

In the 19th century developments in chemical techniques led to a flurry of activity in characterising the components of willow bark. In 1826 Henri Leroux, a French pharmacist, isolated a crystalline compound, later to be called salicin for the first time. Two years later Johann Buchner, a German Professor of Pharmacology, purified the same compound and named it the Latin translation of willow, salicin. In 1838 an Italian chemist named Raffaele Piria resolved the chemical structure of salicin as a glucosidic salicyl alcohol. Then Piria oxidized salicyl alcohol in a pioneering move to generate salicylic acid. In 1853 French chemist Charles Gerhardt was the first to perform acetylation of salicylic acid to create acetylsalicylic acid (ASA). Later this development was acknowledged as a momentous modification for user experience;
unfortunately for Gerhardt he did not use or market this modified version of salicylic acid \textsuperscript{36}. In 1859 Hermann Kolbe, a German chemist, succeeded in artificially creating salicylic acid’s chemical structure and this allowed for industrial scale production and an end to the willow bark powder era. By 1874 artificial salicylic acid was being sold at a tenth of the price of extracted willow bark and physicians began to prescribe the medication for pain relief with good effect \textsuperscript{37}.

Despite the therapeutic advantages of salicylic acid administration, side effects, predominantly gastric irritation and unpleasant taste, were common. Approaching the turn of the century, Felix Hoffman, a German chemist working for the Bayer Company set to the task of finding a more palatable alternative; it is generally accepted that Hoffman’s father was suffering side effects from taking salicylic acid for rheumatism. In 1897, nearly half a century after Gerhardt, Hoffman through acetylation created ASA, named and branded as Aspirin \textsuperscript{38}. Aspirin was indeed more palatable and far gentler on the stomach. After this breakthrough the Bayer Company performed what is believed to be the first mass-marketing of any drug. Information about aspirin was sent to 30,000 doctors and by 1914 Bayer was reaping large profits from this wonder drug \textsuperscript{39}.

However Hoffman’s development of Aspirin had more untapped potential which would not be realised for many more years; the acetylation of salicylic acid is what allows aspirin to inhibit platelet activation and aggregation and therefore prevent cardiovascular events \textsuperscript{39}.

\textbf{1.1.6.2 Aspirin the antiplatelet}

Despite the widespread use of aspirin in the early 20\textsuperscript{th} century its role in cardiovascular health was unknown. In 1945, questions begun to surface regarding the interaction between salicylates and haemostasis; this was born out of observations that salicylate administration (not ASA) was associated with increased prothrombin time, but not increased rates of bleeding. Stirrings were enough that the Wisconsin Alumni Research Foundation (creators of Warfarin) were prompted to apply for a patent for a combined salicylic acid and vitamin K tablet; the incorrect assumption being that vitamin K might
be compensatory in this context. What is now known is that despite the increased prothrombin time, the absence of increased bleeding events was due to lack of acetylation - the key to aspirin’s therapeutic effectiveness in the setting of cardiovascular disease.

During the 1950’s the theory of aspirin having a role in myocardial infarction (MI) prevention got more traction due to the publications of a Californian general practitioner named Dr Lawrence Craven. In 1950 Craven reported higher rates of haemorrhage following tonsillectomy when Aspergum (chewable aspirin) was prescribed for pain relief, sometimes so severe, patients were re-hospitalised and in each instance the laboratory reported a prolonged coagulation time. Further, given the dose of aspirin was far less than what would be prescribed for rheumatic conditions Craven suspected the surgical wound to be of particular pertinence to this observation. Craven hypothesised that the drug might be of value as a preventative of vascular thrombotic conditions, including coronary thrombosis. He finished by declaring that for two years he had been advising his male patients aged 40-65 years to take ASA daily, and that with more than 400 doing so, none has suffered a coronary thrombosis. Thus, the seed was planted into the medical community. Later in 1950 Craven reiterated similar findings, this time with 600 male patients prescribing to daily aspirin with great effect. Craven’s 1953 publication reported on his self-administration of high dose aspirin (12 tablets/day, for 5 days) which resulted in profuse nose bleeding; he repeated this three times and implored to scientific community to perform clinical trials on the basis of his observations. Craven’s final publication shortly before his death was powerful; according to Craven:

To date, approximately 8,000 men have adopted a regime calling for from 5 to 10 gr. of aspirin daily, with a surprising result. Not a single case of detectable coronary or cerebral thrombosis has occurred.

During this time gastric bleeding was attributed to direct mucosal irritation from ingesting aspirin, however similar observations after intravenous administration suggested a systemic effect on haemostasis. In the late 1960s Dr Harvey Weiss asked the next logical question, does aspirin affect platelets? Weiss theorised that aspirin associated bleeding might result from defective platelet aggregation. After conducting
experiments in 20 patients (10 case, 10 control) he reported that aspirin significantly prolonged bleeding time and significantly decreased platelet aggregation, the latter attributed to impaired intrinsic ADP release. Moreover the aggregation of platelets with added ADP was not affected in subjects taking aspirin. Weiss was also the researcher who performed experiments confirming the importance of acetylation; by comparing ASA with sodium salicylate Weiss found that unlike ASA, sodium salicylate did not impair platelet aggregation nor inhibit ADP release. This mechanism of action discovery was confirmed shortly thereafter by other research groups and was a key step in the progression of cardiovascular preventative medicine.

Around the same time in a seemingly unrelated area of research, Sir John Vane through the use of bioassays discovered the release of prostaglandins and “rabbit aorta contracting substance” (to be later named thromboxane A2) during anaphylaxis. In further studies Vane found that aspirin antagonised the release of “rabbit aorta contracting substance” and prostaglandins in a dose-dependent manner. Support for Vane’s findings were soon published with one study isolating and stimulating platelets from patients on aspirin, concluding that prostaglandin synthesis was specifically inhibited by aspirin. The enzyme inhibited by aspirin was later revealed as cyclooxygenase-1 (COX1). Collectively the results from many years of research revealed that aspirin’s effect on platelet aggregation results from the inhibition of COX1 which reduces thromboxane A2 synthesis, and, inhibits the response to thromboxane which is dependent on ADP for amplification. In 1982 Vane was jointly awarded the Nobel prize for physiology or medicine alongside Sune Bergstrom and Bengt Samuelsson, for their discoveries of prostaglandins and related biologically active substances, with particular mention made regarding Vane’s discovery of the inhibitory effect of aspirin on prostaglandins.
1.1.7 Aspirin’s therapeutic evidence

With biochemical mechanisms more readily understood concentrated research of aspirin as a secondary preventative measure commenced. In the 1970s six double-blind, placebo-controlled randomised trials examined the efficacy of aspirin for secondary prevention after MI (definitions here forth pertain to the vernacular of the time and are not necessarily consistent with contemporary definitions) (see Table 1-1). All reports except one (the Aspirin Myocardial Infarction Study [AMIS] trial 54) showed a trend in favour of aspirin but firm conclusions could not be drawn. None of the studies demonstrated a statistically significant difference between the aspirin intervention and placebo control groups for total mortality. In retrospect, it is evident that the aspirin doses administered in these trials were relatively high, with five of the six trials using daily doses in excess of 900mg. Side-effects or bleeding complications were not reported well in these studies, with the exception of the PARIS study which reported significantly higher rates in the aspirin intervention arm compared with placebo of, hematemesis/melaena (6.4% vs. 2.5%, p=0.002) and symptoms of peptic ulcer/gastritis (18.1% vs. 13.2%, p=0.02) 55.
Table 1-1 Early *aspirin versus placebo* randomised control trials: total mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient cohort</th>
<th>Aspirin</th>
<th>Mean duration</th>
<th>Mortality (%) Placebo arm</th>
<th>Mortality (%) Aspirin arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elwood et al (1974)</td>
<td>Men with prior MI (n=1239)</td>
<td>300 mg/day</td>
<td>12 months</td>
<td>9.8</td>
<td>7.6</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary drug project aspirin study (1976)</td>
<td>Prior MI (n=1529)</td>
<td>972 mg/day</td>
<td>22 months</td>
<td>8.3</td>
<td>5.8</td>
<td>0.07</td>
</tr>
<tr>
<td>German-Austrian multicentre prospective clinical trial (1979)</td>
<td>Prior MI (n=626)</td>
<td>1500 mg/day</td>
<td>24 months</td>
<td>7.1</td>
<td>4.1</td>
<td>0.14</td>
</tr>
<tr>
<td>Elwood &amp; Sweetnam (1979)</td>
<td>Prior MI (n=1725)</td>
<td>900 mg/day</td>
<td>12 months</td>
<td>14.5</td>
<td>12.2</td>
<td>0.18</td>
</tr>
<tr>
<td>AMIS (Aspirin myocardial infarction study) (1980)</td>
<td>Prior MI (n=4524)</td>
<td>1000 mg/day</td>
<td>40 months</td>
<td>9.7</td>
<td>10.8</td>
<td>0.22</td>
</tr>
<tr>
<td>PARIS (Persantine aspirin reinfarction study (1980)</td>
<td>Prior MI (n=2026)</td>
<td>972 mg/day or</td>
<td>41 months</td>
<td>12.8</td>
<td>10.5</td>
<td>0.27</td>
</tr>
</tbody>
</table>

MI = myocardial infarction
1.1.7.1 Aspirin for secondary prevention

The 1980s saw further randomised control trials (RCT) conducted with a focus on secondary prevention. During this period the dosing of aspirin was greatly reduced (75mg-325mg/day) when compared to trials from the 1970’s and results in favour of aspirin’s efficacy emerged (Table 1-2). Of particular importance was the 1988 landmark trial, the Second International Study of Infarct Survival (ISIS-2)\(^\text{60}\). Preceding ISIS-2, two smaller studies by Lewis et al (1983)\(^\text{61}\) and Cairns et al (1985) \(^\text{62}\) produced strikingly similar results in UA patients. Both studies found daily aspirin resulted in a respective 50% and 51% relative risk reduction in the composite endpoint of death/nonfatal MI, and therefore a therapeutic benefit for secondary prevention was first observed. With regard to adverse effects Cairns et al did not present data, and Lewis et al reported no detectable difference although their measurements are somewhat irregular (as they were conducted at any time within the trial period of 12 weeks).

When ISIS-2 was conducted 417 hospitals enrolled 17,187 patients within 24 hours of suspected MI symptom onset. Patients were randomized to receive: 1) 1 month of 160mg/day aspirin; 2) 1-hour intravenous infusion of 1.5 million units of streptokinase; 3) both; 4) neither. Focusing on the aspirin only group, at 5 weeks treatment with aspirin resulted in a 23% relative risk reduction in vascular mortality (9.4% vs. 11.8% placebo, \(p<0.0001\)), and despite small convergence this survival benefit remained at 15 months (\(p<0.001\)). Aspirin therapy versus placebo also resulted in fewer nonvascular deaths (0.3% vs. 0.5%) and therefore when combined with vascular death, all-cause mortality was also significantly reduced with aspirin in the first 5 weeks (\(p<0.001\)). Aspirin was also associated with significantly less non-fatal reinfarctions (1% vs. 2%) and non-fatal stroke (0.3% vs. 0.6%), and was not associated with significant increases in cerebral haemorrhages or haemorrhages requiring blood transfusion. ISIS-2 also examined streptokinase alone which resulted in an excess of non-fatal reinfarctions, however this was not observed in the streptokinase-aspirin arm. After ISIS-2 the role of aspirin for secondary prevention was further supported by smaller studies confirming its ability to prevent MI in the days post ACS \(^\text{63}\), and to prevent MI and death in the months post ACS \(^\text{64}\).
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient cohort</th>
<th>Intervention</th>
<th>Mean duration</th>
<th>Major findings</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al (1983) 61</td>
<td>Men with UA (n=1266)</td>
<td>324mg aspirin/day vs. placebo</td>
<td>12 weeks</td>
<td>Aspirin resulted in a 50% RR reduction for the combined endpoint of death/nonfatal MI (5% vs. 10.1%, p=0.0005)</td>
<td>No difference found for the outcome measures: 1) Hg drop; 2) stool test for occult blood.</td>
</tr>
<tr>
<td>Cairns et al (1985) 62</td>
<td>UA patients (n=555)</td>
<td>325mg aspirin q.i.d. vs. placebo (±200mg sulfinpyrazole)</td>
<td>18 months</td>
<td>Aspirin resulted in a 51% RR reduction for the combined endpoint of cardiac death/nonfatal MI (8.6% vs. 17%, p=0.008) (No observed benefit from sulfinpyrazole)</td>
<td>No haemorrhage or side effect data</td>
</tr>
<tr>
<td>ISIS-2 (1988) 60</td>
<td>Suspected MI (n=17187)</td>
<td>160mg aspirin/day vs. placebo</td>
<td>5 weeks</td>
<td>5 weeks: 23% RR reduction in total vascular mortality with aspirin (9.4% vs. 11.8%, p&lt;0.0001). 15 months: survival benefit persisted (p&lt;0.001).</td>
<td>No difference in haemorrhage or bleeds requiring transfusion (0.4% aspirin vs. 0.4% placebo). Small increase (0.6%) in absolute number of bleeds on aspirin (p=0.01)</td>
</tr>
<tr>
<td>Theroux et al (1988) 63</td>
<td>UA patients (n=239)</td>
<td>325mg aspirin b.i.d. vs. placebo</td>
<td>6 days</td>
<td>Aspirin resulted in a 29% RR reduction in MI compared with placebo (3.3% vs. 11.9%, p=0.012)</td>
<td>Total bleeding similar across both arms (aspirin 3.3% vs. 5.1% placebo)</td>
</tr>
<tr>
<td>The RISC group (1990) 64</td>
<td>Men with UA or non-Q-wave MI (n=796)</td>
<td>75mg aspirin/day vs. placebo</td>
<td>3 months</td>
<td>Aspirin resulted in 36% RR reduction for the combined endpoint of death/MI 3 months: (6.5% vs. 17.1%, p&lt;0.0001) RR 0.36</td>
<td>Negligible side effects recorded</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; Hg = haemoglobin; MI = myocardial infarction; q.i.d. = four times daily; RR = relative risk; UA = unstable angina.
1.1.7.2 Meta-analyses of antiplatelet data

With a large body of aspirin research having been conducted the synthesis of all results proved to be a valuable tool. Where, in the 1970’s, studies were indicative but not conclusive, these results were considered in addition to more recent research of the 1980’s and 1990’s, to provide high-level evidence of aspirin’s ability to prevent secondary cardiovascular events.

The Antiplatelet Trialists’ Collaboration first published in 1988 and included meta-analyses of 25 randomised trials of antiplatelet medication. Twelve of these studies pertained to MI (10) and UA (2) patients of which ten analysed aspirin, either alone or in conjunction with sulphinpyrazone or dipyridamole. The regimen most studied was 300-325 mg aspirin. When all trials were considered together antiplatelet therapy (predominantly aspirin) resulted in a significant 25% relative risk reduction in the MI trials, and a significant 36% relative risk reduction in the UA trials, for the combined endpoint of stroke, MI and vascular death \(^{65}\). From this publication until the early 2000’s aspirin endured as the mainstay preventative therapy for secondary MI and UA, as comparisons of aspirin and dipyridamole, or aspirin and sulfinpyrazone, failed to provide evidence that either therapy was more effective than 75-325mg doses of aspirin alone \(^{62,66,67}\).

In 1994 the Antiplatelet Trialists’ Collaboration published an updated collaborative overview of randomised trials of antiplatelet therapy. This analysis now involved 145 randomised trials and included 100,000 patients, of which 70,000 were high risk (defined as patients with acute MI, prior MI, prior stroke/transient ischaemic attack [TIA], or other relevant cardiovascular history e.g. UA). This meta-analysis differed from the 1988 precursor analysis in that only trials that assessed prolonged antiplatelet therapy (one month or more) were eligible for inclusion. Once again, the most widely tested therapy was aspirin (75-325 mg). For secondary prevention, overwhelmingly antiplatelet therapy was found to be superior to control treatment for the protection against vascular events (non-fatal MI, non-fatal stroke or vascular death) in acute MI patients (10% vs. 14%, p<0.00001), prior MI patients (13% vs. 17%, p<0.00001) and UA patients (9% vs. 14%, p<0.00001). When the results from the acute MI subset are
examined alone (as a surrogate for ACS patients) antiplatelet therapy consistently resulted in significant relative risk reductions for the endpoints of combined vascular events (29%), non-fatal MI (54%), vascular death (22%) and death from any cause (23%). The expansion to 145 trials also resulted in more variation of antiplatelet agents (e.g. the additional of ticlopidine and sulocdtidil) however analysis of aspirin only trials (n=49) found aspirin alone persisted to significantly reduce vascular events by demonstrating a 25% relative risk reduction. The investigation into low risk patients (primary prevention) yielded no clear evidence that antiplatelet therapy was beneficial for routine use. The clinical implications of this meta-analysis were that for secondary prevention antiplatelet therapy protects patients against vascular events, and no other regimen was more effective at preventing MI, stroke or death than aspirin at doses ranging from 75-325mg

The most recent meta-analysis of the Antithrombotic Trialists' Collaboration (previously Antiplatelet Trialist’ Collaboration) was published in 2002 and results can be seen in Figure 1-2. Where this paper differed from previous reports was that its focus was on high-risk patients only (acute MI, previous MI, UA, stable angina, acute ischaemic stroke, previous ischaemic stroke, peripheral artery disease or atrial fibrillation). This analysis included 287 studies of 135,000 patients comparing antiplatelet therapy to control, and once again the primary outcome was serious vascular events (non-fatal MI, non-fatal stroke or vascular death). Aspirin remained as the most widely studied antiplatelet drug, this time at 75-150mg daily and follow up ranged from 1 to 27 months. Overall antiplatelet therapy had a 22% relative risk reduction in serious vascular events when compared to control groups (10.7% vs. 13.2%, p<0.0001).

When the trials were subdivided into categories of high risk patients it was evident that the effect of antiplatelet medication differed among them, largely due to the effect on patients with acute stroke. That is, in the previous MI, acute MI, previous stroke and other high-risk groups, antiplatelet therapy reduced the primary endpoint by one quarter to one third, with a combined risk reduction of 25% (11.7% vs. 14.8%, p<0.0001). However in the acute stroke subgroup alone the risk reduction was by 11%, although still significant (8.2% vs. 9.1%, p=0.0009). The greatest benefit was observed in the acute
MI subgroup with a risk reduction of 30% (p<0.0001). What’s more, in each of the high-risk categories the absolute benefits substantially outweighed the absolute risks of major extracranial bleeding. Other measures of bleeding were not included in this analysis. What this meta-analysis added was that 75-150mg doses of aspirin daily were as effective as higher doses (160-325mg and 500-1500mg), and that this regimen is suitable for the long-term secondary protection against vascular events in high-risk patients, including those with acute MI.
### Proportional effects of antiplatelet therapy on serious vascular events

**Figure 1-2 Meta-analysis of antiplatelet therapy effect on serious vascular events**

Proportional effects of antiplatelet therapy on serious vascular events (non-fatal MI, non-fatal stroke or vascular death) in high risk categories. Stratified odds ratios are plotted for each group of trials (black square) along with its 99% confidence interval (horizontal line). Meta-analyses of results for all trials (and 95% confidence interval) are represented by an open diamond. Figure reproduced with permission from the rights holder, BMJ publishing group Ltd ⁶⁹.
1.1.8 Thienopyridines

Platelets can be activated by multiple pathways. While aspirin blocks platelet activation mediated by thromboxane A2 it does not block platelet activation by ADP, another important platelet activation pathway. The specific blocking of ADP is therefore a sensible target to induce further platelet inhibition. Thienopyridines are a class of drug that selectively and irreversibly inhibit the binding of ADP to P2Y₁₂ receptors on platelets. ADP is also a key factor in the activation of the glycoprotein IIb-IIIa complex, the main receptor for fibrinogen on the surface of the platelet and therefore thienopyridines possess antithrombotic effects beyond inhibition of ADP-induced aggregation alone. The first P2Y₁₂ receptor inhibitor, Ticlopidine was identified in the 1970’s and showed greater antithrombotic efficacy over aspirin in many clinical settings including patients with previous stroke/TIA, peripheral artery disease, ischaemic heart disease and those at high risk of thrombosis. Unfortunately ticlopidine was not well tolerated with approximately 50% of patients experiencing adverse side effects including nausea, vomiting and diarrhoea. Furthermore, within the first 3 months of ticlopidine use some patients experienced rare yet serious toxic side effects including leucopenia, thrombocytopenia, agranulocytosis and pancytopenia. This led health authorities to enforce haematological and clinical monitoring during the first three months of ticlopidine prescription, but also made way for clopidogrel, a newer P2Y₁₂ receptor inhibitor with a more favourable side effect profile and better activity/toxicity ratio in humans.

1.1.8.1 Clopidogrel

Clopidogrel is a prodrug that requires hepatic biotransformation into its active metabolite. Approximately 85% of the drug is metabolised into an inactive carboxylic acid metabolite and excreted from the body while the remaining 15% undergoes biotransformation. The active metabolite binds to the P2Y₁₂ receptor irreversibly blocking ADP binding and receptor activation. After cessation of oral administration, platelet inhibition is still detectable at a rate consistent with platelet turnover.
days) which is consistent with the permanent effects of clopidogrel on platelets and allows a once a day dosing regimen. Clopidogrel is well tolerated when compared to ticlopidine and for the most part side effects centre on increases in minor bleeding and gastric irritation. Remarkably clopidogrel was discovered by chance when scientists went in search of new thienopyridine derived anti-inflammatory drugs. In 1972 it was observed that after oral administration to rats of (the compound later to be named) clopidogrel, despite the absence of any anti-inflammatory profile, unexpected antiplatelet and antithrombotic activities were displayed. Preclinical development of clopidogrel did not take place until 1987, and after 10 years of development and large scale clinical trials this new and improved P2Y₁₂ inhibitor was approved for use in 1997 for the secondary prevention of cardiovascular disease, and in 2011 was named the second best-selling drug of all time. Interestingly, some commentators believe that clopidogrel could not be discovered today. This is because clopidogrel requires biotransformation into an active metabolite, its metabolite is very unstable and cannot be stored, its structure cannot be predicted by rational drug design, and its detection is only possible through in vivo screening which is rarely used by the pharmaceutical industry in the present day.

The major efficacy and safety analyses that preceded the approval of clopidogrel occurred in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial. CAPRIE was a large randomised trial of over 19,000 patients at high risk of ischaemic events and the primary endpoint was a composite of ischaemic stroke, MI or vascular death. Treatment with clopidogrel resulted in a significant relative risk reduction of 8.7% for the primary endpoint and fewer gastrointestinal haemorrhages (0.49% vs. 0.71%, p=0.05). Other safety and tolerability measures showed clopidogrel was at least as good as aspirin with no differences in rates of neutropenia and thrombocytopenia like that of its predecessor ticlopidine. Furthermore, secondary analyses of the CAPRIE trial showed that greater benefit was gained from clopidogrel administration in the high-risk subgroups including patients with a medical history of MI, ischaemic stroke or diabetes mellitus, or prior cardiac surgery.
1.1.9 Dual antiplatelet therapy

The combination of aspirin and a P2Y\(_{12}\) receptor inhibitor is known as dual antiplatelet therapy (DAPT). Due to their differing mechanism of action the addition of a P2Y\(_{12}\) receptor inhibitor to aspirin was in theory a sensible therapeutic option to potentiate antiplatelet effects. However, it was not known if DAPT would result in a reduction in ischaemic events or whether any benefit would be outweighed by increases in bleeding events. The 2001 breakthrough Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial set out to establish the efficacy and safety of DAPT with clopidogrel and aspirin, compared to aspirin alone in 12,562 ACS patients without ST elevation.\(^8^3\)

The CURE study demonstrated that for the primary endpoint of cardiovascular death, nonfatal MI and stroke, patients randomised to the DAPT arm had a 20% relative risk reduction (9.3% vs. 11.4%, \(p<0.001\)). A relative risk reduction of 14% was also demonstrated with DAPT for the secondary endpoint of cardiovascular death, nonfatal MI, stroke and refractory ischaemia (16.5% vs. 18.8%, \(p=0.001\)). For both the primary and secondary composite endpoints the benefit observed with DAPT therapy was largely driven by the 23% relative risk reduction in rates of MI. With regards to safety analyses treatment with DAPT resulted in a significantly higher rate of major bleeding (3.7% vs. 2.7%, \(p=0.001\)), and this was driven by increases in gastrointestinal bleeds (1.3% vs. 0.7%) and arterial puncture site bleeding (0.6% vs. 0.3%). There were no differences detected between the arms with regards to fatal bleeding, life-threatening bleeding or haemorrhagic stroke. Rates of minor bleeding were also higher with DAPT (5.1% vs. 2.4%, \(p<0.001\)).

In a sub study of CURE patients who received PCI (PCI-CURE), benefit from DAPT was also observed with the primary endpoint (composite of cardiovascular death, MI, or urgent target-vessel revascularisation within 30 days of PCI) occurring less often in the DAPT arm (4.5% vs. 6.4%, \(p=0.03\)), without increases in major bleeding.\(^8^4\)
1.1.9.1 Dual antiplatelet therapy integration into guidelines

The results from the above trials resulted in DAPT with clopidogrel and aspirin, being integrated into international guidelines as the recommended therapy after an ACS, replacing aspirin alone. Subsequent studies of DAPT further enhanced its therapeutic profile with benefit demonstrated in patients presenting with STEMI, those managed with PCI, as well as exhibiting a mortality benefit over aspirin alone in a RCT of 45,852 acute MI patients. Current ACS guidelines including but not limited to those from the American Heart Association (AHA), the European Society of Cardiology (ESC), and locally from the Cardiac Society of Australia and New Zealand all recommend DAPT after an ACS for 12 months and this is strongly supported (Level of Evidence A). For patients considered to be at high risk of recurrent ischaemic events extending DAPT beyond 12 months is reasonable also.

1.1.9.2 Newer P2Y₁₂ inhibitors

Despite the success of treatment with clopidogrel in ACS and post PCI, the drug has important limitations. The most important of which is the considerable variability in the level of platelet inhibition observed in patients treated with clopidogrel and aspirin following ACS. Those patients with high platelet reactivity on treatment clopidogrel have been shown to have an increased risk of death, MI and stent thrombosis. Subsequently newer P2Y₁₂ inhibitors were developed which were more potent and had a more consistent pharmacodynamic effect.

Prasugrel, like clopidogrel is a prodrug that requires biotransformation into its active form however unlike clopidogrel its metabolism is highly predictable. Prasugrel also irreversibly blocks P2Y₁₂ receptors but exhibits faster and more profound inhibition than clopidogrel. In the TRITON-TIMI 38 (Trial to Assess Improvement in therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) trial for ACS patients with a scheduled PCI, treatment with a combination of prasugrel and aspirin was found superior to treatment with clopidogrel and aspirin in reducing the primary endpoint, a combination of cardiovascular death, non-fatal MI or
non-fatal stroke, but also carried significantly higher rates of major bleeding including fatal bleeding. This trial also showed that DAPT with prasugrel resulted in net harm for patients with prior stroke/TIA and therefore prasugrel is contraindicated for this patient subgroup in clinical guidelines. For patients over 75 years of age or body weight less than 60kgs no added benefit from prasugrel was observed 98.

Ticagrelor is a reversible, direct acting, non-thienopyridine P2Y12 inhibitor. Because of this ticagrelor has a much faster onset of action and must be taken twice daily, unlike the once a day dosing of clopidogrel and prasugrel 99. DAPT with ticagrelor was compared to DAPT with clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial of ACS patients. The ticagrelor arm was found to be superior to the clopidogrel arm with regard to the primary end point of cardiovascular death, MI or stroke (9.8% vs. 11.7%, p<0.001). The rates of death from any cause (4.5% vs. 5.9%, p<0.001) and MI (5.8% vs. 6.9%, p=0.005) were also lower with ticagrelor. No difference was detected between the treatment groups with regard to major bleeding (ticagrelor 11.6% vs. clopidogrel 11.2%, p=0.43), however ticagrelor did result in significantly higher levels of non-CABG related bleeding (4.5% vs. 3.8%, p=0.03) including fatal intracranial haemorrhage (0.1% vs. 0.01%, p=0.02) 100.

On the basis of the above results both STEMI and NSTEACS guidelines recommend 12 months of DAPT (or more) for the prevention of secondary cardiovascular ischaemic events however a hierarchy of preference with regard to P2Y12 inhibitors has emerged. In general, ticagrelor or prasugrel is preferred over clopidogrel, however prasugrel’s use is limited given it is only recommended post PCI and is contraindicated in certain subgroups 1,88-91. In New Zealand both clopidogrel and ticagrelor are funded by PHARMAC for patients who have experienced an ACS event 101,102. Prasugrel is only available funded for patients who have received PCI and have a clopidogrel allergy, or who have had stent thrombosis while on clopidogrel in New Zealand, and this therefore limits its accessibility to a large degree 103,104.
1.2 Atrial Fibrillation

Atrial Fibrillation (AF) is the most commonly sustained arrhythmia and is characterised by a loss of coordinated atrial systole with irregular ventricular response. Chaotic electrical impulses in the atria, as a result of re-entry circuits and enhanced automaticity, overwhelm the AV node and result in irregular ventricular depolarisation. The rate of ventricular response is dependent on the rate at which atrial electrical impulses are generated, and the conduction and refractory properties of the AV node. The various categories of AF are defined by duration (Table 1-3). Patients with AF may be asymptomatic but when cardiac output is sufficiently reduced, clinical manifestations including fatigue, palpitations, hypotension, dyspnoea, syncope and heart failure manifest. However, the most well-established health risk for patients with AF is risk of thromboembolic stroke \cite{105}.

<table>
<thead>
<tr>
<th>Table 1-3 Definitions of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paroxysmal AF</strong></td>
</tr>
<tr>
<td><strong>Persistent AF</strong></td>
</tr>
<tr>
<td><strong>Long-standing persistent AF</strong></td>
</tr>
<tr>
<td><strong>Permanent AF</strong></td>
</tr>
</tbody>
</table>
1.2.1 Pathophysiology

It is generally accepted that the mechanisms that cause AF are not completely understood and as such AF is a phenotype which represents diverse pathophysiological processes. Abnormal impulse formation occurs when electrophysiological and structural abnormalities cause alterations to atrial tissue, and the mechanisms that initiate and sustain this are multifactorial. Electrophysiological abnormalities that trigger AF are complex and it is likely that multiple factors are present in any given patient. Structural abnormalities that sustain AF most commonly occur in the setting of heart disease. Conditions such as heart failure, hypertension, CAD, valvular heart disease and cardiomyopathies result in increases in left atrial pressure, which over time cause atrial dilation, inflammation, fibrosis and hypertrophy. Infiltrative diseases such as amyloidosis, sarcoidosis and hemochromatosis also contribute to structural changes that promote AF 106.

1.2.2 Burden of Atrial Fibrillation

The prevalence of AF increases with age and ranges from 1% in those under 60 years of age to 9% in those over 80 107. The incidence of AF is expected to rise over time in part due to better detection strategies 108-110 but mostly due to the fact that the populations mean age is increasing 111, with numbers expected to increase 2.5-fold by 2050 112. AF is independently associated with a 2-fold increase in all-cause mortality for women and 1.5-fold for men, particularly cardiovascular death. In addition, AF is independently associated with increased morbidity from heart failure, reduced quality of life, longer hospitalisations, cognitive decline, but for the most part morbidity from stroke. The risk of stroke in patients with AF is 5-fold that of the general population and strokes are more often fatal. When AF patients survive stroke they experience greater disability, have longer hospital stays are less likely to be discharged to their own home 113.
1.2.3 Mechanisms of stroke in atrial fibrillation

The processes that contribute to thrombus formation in an AF patient reflect the criteria of Virchow’s triad of thrombogenesis: 1) structural abnormalities and endothelial damage; 2) abnormal blood stasis; 3) abnormal blood constituents.

1.2.3.1 Prothrombotic atrial anatomy

The left atrial appendage (LAA) is the most common site of intra-atrial thrombus formation and this is due to its long, tubular and hooked morphology which promotes blood stasis in the absence of coordinated atrial contraction. In contrast the right atrial appendage is broad and triangular. Endothelial damage seen in the atria and LAA of AF patients has been well described and results in haemostatic disruption. This in turn contributes to thrombus formation by mediation of hypercoagulable state through the release of prothrombotic and proinflammatory molecules.

1.2.3.2 Abnormal blood stasis

Blood stasis in the setting of AF not only occurs due to loss of atrial systole but also due to the progression of left atrial dilatation. Left atrial dilatation is a key factor in thrombogenesis as left atrial size, once corrected for body surface area, is independently associated with stroke risk.

1.2.3.3 Abnormal blood constituents

It has been well documented that AF is associated with a hypercoagulable state as demonstrated by high levels of plasma fibrinogen, von Willebrand’s factor and fibrin D-dimer. Other prothrombotic factors including prothrombin fragments 1 and 2 and thrombin-antithrombin complexes are significantly higher in stroke patients with AF when compared to stroke patients with normal sinus rhythm, and these elevated levels persist in the absence of stroke when AF patients and healthy subjects are
compared. Associations between various prothrombotic factors and thrombus formation have also been described. D-dimer and von Willebrand’s factor have been shown to independently predict LAA thrombi on transoesophageal echocardiography. Markers of platelet activation (platelet factor 4 and beta-thromboglobulin) are also significantly higher in AF patients when compared to controls.

1.2.4 History of Warfarin

Warfarin has been the mainstay oral anticoagulant (OAC) for stroke prevention in AF patients for at least six decades. However the discovery of warfarin occurred by chance, with a fascinating set of circumstances that began in 1920s in the agricultural sectors of North America and Canada. Reports of otherwise healthy cattle dying from internal bleeding became frequent and no precipitating factors were apparent. This was an economic blow for farmers, especially with financial factors that contributed to the great depression also taking place. Two veterinarian scientists, Schofield and Roderick, took to investigating the cattle “bleeding disease”. Schofield noted that the characteristics appeared very similar to haemorrhagic septicaemia, however upon multiple attempts to establish causation, bacteria could not be found. In addition Schofield documented the absence of heat or pain in affected cattle which indicated the disease process was non-inflammatory, the absence of temperature, and the consistent presence of a weak and accelerated pulse. At the same time, repeated reports emerged of cattle in the same area being dehorned then dying 5-6 hours later. There was a lack of apparent pathogen or nutritional deficiency and therefore the diet of the livestock was examined with a common thread established- sweet clover silage.

Schofield and Roderick performed a basic experiment; three calves each fed for several weeks with hay, spoiled sweet clover and normal sweet clover respectively, before castration surgery was performed. The calf fed spoiled sweet clover died within hours of surgery while the other two made a healthy recovery. Sweet clover has a coumarin content that gives it a distinct sweet smell. Its use as silage was widespread in the 1920’s and a series of wet summers led to improper curing and storage. The sweet clover
became soiled with mould, however the economy of the time left farmers with little choice but to feed out the compromised silage; in more prosperous times silage of this quality would have been discarded. It was later discovered that certain moulds metabolised the coumarin into toxic dicoumarol – a potent vitamin K antagonist (VKA). By 1931 the pair had established that the disease now known as “sweet clover disease” was due to a plasma prothrombin defect but the biochemical agent was still unbeknownst ¹³².

In 1932, a decade after the first outbreak of haemorrhagic disease Professor Karl Link of the Wisconsin Alumni Research Foundation was unexpectedly confronted by an exasperated farmer one Saturday morning. As the story goes Link was the only person on site in the biochemistry lab when the farmer delivered a dead heifer, a can of unclotted blood, and 100 pounds of spoiled sweet clover, the only fodder he could afford. The farmer was frustrated with the repeated death of his stock and was reluctant to believe sweet clover, a silage that had been used for generations, could be the cause. Over the next six years Link, alongside one of his PhD students Mark Stahmann, set out to isolate the active principal in spoiled sweet clover, and through the use of an in-vitro clotting assay of rabbit plasma the pair isolated dicoumarol ¹³³. Dicoumarol was found to have a similar structure to vitamin K and when consumed by livestock inhibited vitamin K production, a necessity for the activation of prothrombin to thrombin and therefore clot formation. Link and colleagues also demonstrated that effects of dicoumarol in rabbits could be reversed by the administration of vitamin K, however it would be many years before the relationship between clotting time, dicoumarol and vitamin K were completely understood. Shortly after the chemical structure of dicoumarol was identified, synthesis of the compound saw it released into medical practice by 1941 ¹³⁴.

1.2.4.1 Dicoumarol to warfarin

Despite the novelty of being the first anticoagulant to treat thrombosis in humans, dicoumarol had many limitations. Dicoumarol’s narrow therapeutic window exposed
patients to abnormal rates of bleeding; and this was compounded by its 12-24-hour lag phase, long excretion time, and the cumulative effect of repeated administration. Link was suspicious that if not used properly dicoumarol administration was risky, and his concerns were justified as the anticoagulant gained a reputation of being dangerous due to episodes of uncontrolled bleeding. After a decade of fine-tuning through the development of vitamin K ready antidotes, and, through the thorough assessment of patient kidney and liver function, vitamin K status and prothrombin clotting time, dicoumarol remained the anticoagulant of choice until the mid-1950s.

In 1945 whilst staying in a sanatorium due to tuberculosis Link had the idea to use a coumarin derivative as a rodenticide. Believing dicoumarol would be a poor rodenticide due to its slow mechanism of action and the ability of rats to achieve a high vitamin K diet through natural grains, Link set out to find an analogue of dicoumarol, from the 150 compounds synthesised during the 1930s with his then PhD student Stahmann. Link selected the particularly active and more potent compound number 42, which was later named warfarin, “WARF” after the funding body (Wisconsin Alumni Research Foundation) and “-arin” after coumarin. Unlike dicoumarol warfarin was potent enough to kill rats despite the simultaneous ingestion of regular amounts of vitamin K, and in 1948 was first promoted as rat poison.

1.2.4.2 Therapeutic warfarin use in humans

Although warfarin toxicity and effectiveness had been studied extensively on various animals its application for use as an anticoagulant in humans was still unknown. However, in 1951 a then 22-year old army inductee attempted suicide through repeated warfarin ingestion over six days. The patient presented to hospital with severe flank (kidney) pain, generalised abdominal tenderness and a history of intermittent epistaxes. Over 48 hours the patient was transfused with whole blood and administered intravenous vitamin K. After 5 days it was considered that the patient had made a full recovery and this became the catalyst for investigations into warfarin therapy for humans.
Subsequent studies concluded that warfarin was more favourable than dicoumarol as it possessed a higher degree of predictability, ease of control, faster onset of action and increased safety due to its prompt counteraction by high dose vitamin K. Further, warfarin could achieve the desired therapeutic effect at a dose approximately one fifth that of dicoumarol and with all other things being equal this quality alone demonstrated its superiority 137,138. It is now well established that warfarin works by inhibiting the epoxide reductase enzyme which impedes the vitamin K oxidation-reduction reaction, thereby attenuating carboxylase production (Figure 1-3). The coagulation factors II, IX and X, prothrombin, as well as other regulatory factors require carboxylation for their pro-coagulant activity and therefore with warfarin administration the coagulation factors are produced, but have decreased functionality due to under-carboxylation 139. Therapeutic use of warfarin must be monitored, and doses adjusted accordingly. Specifically a measure of the patients’ prothrombin time is standardised to an international normalised ratio (INR) 140.
Figure 1-3 Warfarin mechanism of action

Warfarin antagonises epoxide reductase which impedes the vitamin K oxidation-reduction reaction. This results in decreased carboxylase production which is required to convert inactive coagulation factors (prothrombin, FVII, FIX and FX) to an active form. Figure reproduced with permission from the rights holder, Wolters Kluwer Health Inc. 141.

1.2.5 Warfarin for stroke prevention: the evidence

The late 1980s and 1990s was an era where the implications of thromboembolism for patients with AF became explicitly evident. The Framingham study published results in 1991 demonstrating that after following patients for 34 years, AF patients had a 5-fold increased chance of stroke when compared to patients without (p<0.001) 105 and this fact is consistently referenced within AF literature. At the same time results of RCTs examining anticoagulation with warfarin versus placebo for stroke prevention in AF emerged. During this period, it was still ethically appropriate to perform comparisons of warfarin with placebo, and overwhelming these studies demonstrated benefit from warfarin therapy for the prevention of stroke in patients with AF (Table 1-4). There was an associated increase in the rate of major and minor bleeding with warfarin also. Some of these trials, AFASAK (Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation
Study), SPAF I (Stroke Prevention in Atrial Fibrillation) and EAFT, also compared aspirin versus placebo but results were less convincing, with only SPAF I showing a non-significant trend in favour of aspirin over placebo. A specialised review of these RCTs in 1996 concluded that for the prevention of TIA and stroke, AF patients with any clinical risk factors including hypertension, age over 75 years, diabetes mellitus or previous stroke/TIA, should be administered dose-adjusted warfarin with a target INR of 2.0-3.0, and that aspirin is ineffective.\textsuperscript{142}
Table 1-4 Warfarin for stroke prevention: randomised placebo-controlled trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient cohort</th>
<th>Intervention</th>
<th>Mean follow-up</th>
<th>Efficacy outcomes</th>
<th>Safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK' (1989)</td>
<td>Chronic AF (n=1007)</td>
<td>Warfarin (INR 2.8-4.2) vs. placebo</td>
<td>2 years</td>
<td>Embolic events per year lower in the warfarin arm (2% vs. 5.5%, p&lt;0.05).</td>
<td>Warfarin: 21 nonfatal bleeding events Placebo: nil</td>
</tr>
<tr>
<td>BAATAF (1990)</td>
<td>Chronic AF (n=420)</td>
<td>Warfarin (INR 1.5-2.7) vs. placebo</td>
<td>2.2 years (terminated early)</td>
<td>86% RR reduction of stroke in warfarin arm (0.41% vs. 2.98%, p&lt;0.002)</td>
<td>No significant difference in major bleeding. Warfarin resulted in a 1.6-fold increase in 'other' bleeding.</td>
</tr>
<tr>
<td>SPAF I' (1991)</td>
<td>Chronic or intermittent AF (n= 1330)</td>
<td>Warfarin (INR 2-3.5) vs. placebo</td>
<td>1.3 years</td>
<td>67% RR reduction in annual rate of ischaemic stroke or systemic embolism in warfarin arm (2.3% vs. 7.4%, p=0.01)</td>
<td>Annual rate of major bleeding Warfarin: 1.5% Placebo: 1.6%</td>
</tr>
<tr>
<td>CAFA (1991)</td>
<td>Chronic AF (n=378)</td>
<td>Warfarin (INR 2-3) vs. placebo</td>
<td>2.5 years (terminated early)</td>
<td>Terminated early due to AFASAK and SPAF I results: non-significant 37 % RR reduction in stroke or systemic embolism with warfarin</td>
<td>Annual rate of fatal or major bleeding Warfarin: (2.5%) Placebo: (0.5%)</td>
</tr>
<tr>
<td>SPINAF (1992)</td>
<td>Men with chronic AF (n = 571)</td>
<td>Warfarin (INR 1.4-2.8) vs. placebo</td>
<td>1.7 years (terminated early)</td>
<td>Stroke rate per year significantly lower with warfarin (0.9% vs. 4.4%, p=0.001)</td>
<td>No difference detected with respect to major bleeding. Significant increase in minor bleeding with warfarin (14.5% vs. 10.5%, p&lt;0.04)</td>
</tr>
<tr>
<td>EAAF* (1993)</td>
<td>AF with recent TIA/stroke (n=1007)</td>
<td>Warfarin (INR 2.5-4) vs. placebo</td>
<td>2.3 years</td>
<td>62% RR reduction of stroke in warfarin arm</td>
<td>Major bleeds Warfarin: 2.8% Placebo: 0.7%</td>
</tr>
</tbody>
</table>

AF= atrial fibrillation; INR = international normalised ratio; RR = relative risk; TIA = transient ischaemic attack; *indicates aspirin versus placebo also examined in trial (results not shown).
1.2.5.1 Stroke prevention with warfarin and aspirin

Once the efficacy of warfarin had been established, further research was conducted to see if the additive effects of aspirin were beneficial. It was hypothesised that low-intensity, fixed-dose warfarin and aspirin (300-325mg/day) would exert sufficient efficacy but with less haemorrhagic side effects when compared to adjusted-dose warfarin (INR 2.0-3.0). In addition, this newer therapy would reduce the need for medical monitoring and overall be an easier regimen to follow. However the findings of AFASAK-2 \(^{149}\) and SPAF III \(^{150}\) which both examined this hypothesis found that dose-adjusted warfarin was the superior therapeutic option, and thus a low-dose warfarin plus aspirin therapy for stroke prevention was short lived.

1.2.5.2 Meta-analysis of warfarin data

In 2007 a seminal meta-analysis conducted by Hart et al \(^{151}\) convincingly established the efficacy of warfarin for the prevention of stroke in AF patients, despite its use over previous decades. One of the contributory factors that gave the meta-analysis authority was due to the inclusion of the valuable warfarin-placebo trials discussed earlier. The results showed that compared with placebo, dose-adjusted warfarin resulted in a 64% relative risk reduction of stroke (Figure 1-4). By comparison, antiplatelet therapy (predominantly aspirin) reduced stroke by only 22%. Direct warfarin-antiplatelet comparisons were also conducted and demonstrated that warfarin was superior, with a significant 37% relative risk reduction in stroke events (Figure 1-5). The meta-analysis also reported that the risk of major bleeding on warfarin was double that of antiplatelet therapy, but the study concluded that this was acceptable given that absolute rates of these adverse events were only 0.2% per year. The implication of this study was that additional trials were unlikely to change current estimates of warfarin; that is, for stroke prevention in AF, dose-adjusted warfarin was the treatment of choice.
Figure 1-4 Meta-analysis: warfarin versus placebo for stroke prevention

Adjusted-dose warfarin compared with placebo in six randomised trials. Treatment with warfarin resulted in a 64% (95% CI, 49% to 74%) relative risk reduction in stroke. Horizontal lines represent 95% confidence intervals around point estimates. Reproduced from Hart et al (2007)
Adjusted-dose warfarin compared with antiplatelet agents

AFASAK I
AFASAK II
Chinese
EAFT
PATAF
SPAF II
  Age ≤75 y
  Age >75 y
  Aspirin trials (n = 8)*
SIFA
ACTIVE-W
NASPEAF

All antiplatelet trials (n = 11)

Figure 1-5 Meta-analysis results: warfarin versus antiplatelet for stroke prevention

Adjusted-dose warfarin compared with antiplatelet agents in 11 randomised trials. Treatment with warfarin resulted in a 37% (95% CI, 23% to 48%) relative risk reduction in stroke. Horizontal lines represent 95% confidence intervals around point estimates. Reproduced from Hart et al (2007).

1.2.6 Stroke risk stratification tools

Given there is risk associated with oral anticoagulation, predominantly an increased risk of bleeding, is sensible to establish who will benefit from such therapy. Risk stratification tools are a method in which clinicians can perform stroke risk assessment and to date there have been over twelve schemas published with variable predictability and performance 152-154.

In current times none has been more widely accepted and utilised than the CHA2DS2-VASc stroke risk assessment tool 155. The CHA2DS2-VASc schema was developed in 2009 and demonstrated modest predictive ability (c-statistic 0.606) in its derivation cohort. The components of CHA2DS2-VASc can be seen in Table 1-5 and stratify patients as low, intermediate or high risk of stroke. Prior to CHA2DS2-VASc the CHADS2 score, which was validated in 2001, was commonly used, and differed from the former as it did not include the risk factors of age (65-74 years), vascular disease and female sex 156. In the most recent comparative analyses CHA2DS2-VASc performed with similar predictive ability when compared with eight other risk stratification tools including its predecessor CHADS2, however it demonstrated superiority over other scores when identifying those patients at low-risk of stroke 157. There is consensus that a patient at low risk of stroke does not require oral anticoagulation and therefore the CHA2DS2-VASc score carries the advantage of identifying these patients with greater accuracy, therefore reducing the risk of bleeding that would have been received through oral anticoagulation administration. What’s more, the CHA2DS2-VASc schema does not differ depending on the type of non-valvular AF being assessed (paroxysmal, persistent or permanent), although there is a reasonable argument that stroke risk is not equal across these groups 158. These factors have seen the CHA2DS2-VASc schema adopted into guideline documents as a Class I recommendation to assess stroke risk in AF patients106,113.
### Table 1-5 CHAD_{2}S_{2}VASc schema

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Score</th>
<th>Stroke risk (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>2</td>
<td>Low risk (0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>Intermediate risk (1)</td>
</tr>
<tr>
<td>Stroke/TIA/embolism history</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
<td>High risk (2+)</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sex category female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Max total</strong></td>
<td><strong>9</strong></td>
<td></td>
</tr>
</tbody>
</table>

### 1.2.7 Limitations of warfarin

There are many limitations associated with warfarin use. Some commentators believe that if invented today, warfarin would not be adopted into clinical practice. The main adverse effect of warfarin is of course bleeding, and this is closely related to the pharmacodynamics of warfarin and its dosing. Warfarin has a very narrow therapeutic index and maintaining this can be problematic. This is partly due to high interpatient variability in its dose-response relationship\textsuperscript{159}, but also because the measurement of INR is invasively obtained via a blood test, and also has innate factors that may contribute to erroneous readings\textsuperscript{160}. This monitoring also comes at financial cost to health providers. Interpatient variability may be due to genetic factors including
impaired ability to metabolise warfarin (mutations in CYP2C9 gene) that lead to decreased elimination, and, mutations in the gene responsible for the epoxide reductase enzyme that leads to varying levels of inhibition by warfarin.

Warfarin, being a VKA is also highly susceptible to drug-drug and food-drug interactions. The Bristol-Myers Squibb produced patient information sheet lists 165 drugs and 29 natural remedies that interact with warfarin. Some drugs can reduce the absorption of warfarin (e.g. cholestyramine), some increase clearance (e.g. barbiturates) while others potentiate effects by inhibiting warfarin’s clearance (e.g. sulfinpyrazone or amiodarone). In a similar fashion the pharmacodynamics of warfarin may be affected by drugs that interfere with the cyclic interconversion of vitamin K (e.g. antibiotics). Fluctuating levels of dietary vitamin K predominantly derived from plant material also has implications; high dietary vitamin K will reduce response to warfarin while low dietary vitamin K will potentiate effects. Long term alcohol consumption may also increase warfarin clearance. In summary, although warfarin shows good efficacy for stroke prevention is not an easy drug to use. Bleeding is a common side effect, frequent and invasive monitoring is required, there is high interpatient variability and numerous food and drug interactions. For these reasons it is easy to appreciate why warfarin is the third most common drug (behind non-steroidal anti-inflammatory drugs and diuretics) to cause hospital admission through adverse effects. Despite these limitations warfarin remains the reference standard treatment for patients with AF and risk factors for stroke.

1.2.8 Non-vitamin K oral anticoagulants

In more recent time the development of non-vitamin K oral anticoagulants (NOACs), also known as novel oral anticoagulants, has provided alternative options for the prevention of thromboembolism. Through direct targeting of key coagulation factors such as activated thrombin and factor Xa (Figure 1-6), NOACs can inhibit clot formation without the need for frequent INR monitoring, dose adjustments and the excess food and drug interactions when compared with warfarin. Therefore, NOACs also have a more user-
friendly profile which is important given its use for chronic AF. In New Zealand to date three NOAC dugs have been approved for use in AF; dabigatran, a direct thrombin inhibitor, and apixaban and rivaroxaban, both factor Xa inhibitors. Phase III RCTs have been performed to compare NOACs with warfarin and results for NOACs are favourable.

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**Figure 1-6 NOAC agents and their targets in the coagulation cascade**

Dabigatran is a direct thrombin inhibitor; thrombin is required for the conversion of fibrinogen to fibrin. Apixaban and rivaroxaban are factor Xa inhibitors; factor Xa is required for the conversion of prothrombin to thrombin.
1.2.8.1 Dabigatran

In the RE-LY RCT (Randomized Evaluation of Long-Term Anticoagulation Therapy), dabigatran at two doses, 110mg and 150mg, were compared to warfarin with a primary endpoint of stroke or systemic embolism in 18,113 AF patients at risk of stroke (defined as previous stroke or TIA, heart failure [New York Heart Association class II or higher], ≥75 years of age, or 65-74 years with diabetes, hypertension or CAD). The 110mg dose of dabigatran was associated with annual rates of stroke and systemic embolism similar to that of warfarin (1.53% vs. 1.69%, p=0.34), but with significantly less major bleeding (2.71% vs. 3.36%, p=0.003). The 150mg dose of dabigatran was associated with significantly less stroke or systemic embolism (1.11% vs. 1.69%, p<0.001) and similar major bleeding rates (3.11% vs. 3.36%, p=0.31). In addition, rates of life-threatening bleeding and intracranial bleeding were significantly higher in the warfarin arm when compared to both doses of dabigatran (p<0.05 for all comparisons) 164.

1.2.8.2 Apixaban

The factor Xa inhibitor apixaban was compared to warfarin in the ARISTOTLE RCT (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) 165. The primary endpoint of stroke or systemic embolism was examined in a cohort of 18,201 patients with AF, who were randomly assigned to receive either apixaban (5mg, twice daily) or warfarin, over a median follow up period of 1.8 years. To be eligible for inclusion AF patients had to have at least one additional risk factor for stroke defined as ≥75 years of age, previous stroke/TIA/systemic embolism, heart failure, diabetes or medicated hypertension. Results were overwhelmingly in favour of apixaban with the NOAC demonstrating less stroke or systemic embolism (1.27% vs. 1.60%, p<0.001 for non-inferiority; p=0.01 for superiority), less major bleeding (2.13% vs. 3.09%, p<0.001) and lower rates of all-cause mortality (3.52% vs. 3.94%, p=0.047).
1.2.8.3 Rivaroxaban

Rivaroxaban was also compared to warfarin for non-inferiority, for the prevention of stroke and systemic embolism, in the ROCKET AF trial (The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)\textsuperscript{166}. In this study 14,264 AF patients at moderate to high risk of stroke (CHADS\textsubscript{2} score of 2 or more) were randomly assigned to receive either 20mg of rivaroxaban daily or warfarin. Rivaroxaban was found to be non-inferior to warfarin with one-year rates of stroke or systemic embolism similar across both groups (rivaroxaban 1.7\% vs. warfarin 2.2\%, p<0.001 for non-inferiority). There was no difference detected with regard to one-year rates of major or non-major clinically relevant bleeding (rivaroxaban 14.9\% vs. warfarin 14.5\%, p=0.44), however rivaroxaban resulted in significantly fewer intracranial and fatal bleeds (0.5\% vs. 0.7\%, p=0.02; 0.2\% vs. 0.5\%, p=0.003, respectively).

On the basis of these trials a 2013 meta-analysis concluded that for patients with non-valvular AF, NOACs decrease stroke or systemic embolism (odds ratio 0.82, 0.74-0.91, p<0.001) (Figure 1-7), hemorrhagic stroke (odds ratio 0.44, 0.30-0.66, p<0.001) and mortality (odds ratio 0.88, 0.82-0.95, p=0.001), and demonstrate similar risk of major bleeding compared to warfarin (odds ratio 0.85, 0.69-1.05, p=0.14) (Figure 1-8)\textsuperscript{167}. The authors concluded that NOACs approved by regulatory bodies should be the first-line therapies used for the antithrombotic management of patients with AF. In New Zealand Dabigatran (110mg and 150mg) is currently the only NOAC funded by PHARMAC\textsuperscript{168}.
Effect of NOACs versus warfarin on the primary endpoint of stroke or systemic embolism. The RE-LY trial examined dabigatran, the ROCKET AF trial examined rivaroxaban and the ARISTOTLE trial examined apixaban. Figure reproduced with permission from the rights holder, Elsevier.

Figure 1-7 NOACs versus warfarin meta-analysis: stroke or systemic embolism
Figure 1-8 NOACs versus warfarin meta-analysis: major bleeding

Effect of NOACs versus warfarin on the safety endpoint of major bleeding. The RE-LY trial examined dabigatran, the ROCKET AF trial examined rivaroxaban and the ARISTOTLE trial examined apixaban. Figure reproduced with permission from the rights holder, Elsevier 167.
1.2.9 AF guidelines

Internationally guidelines for the prevention of stroke in AF patients are generally consistent, of which the AHA and ESC are predominant authority bodies. Both organisations have a Class I recommendation that advocates the use of the CHA₂DS₂VASc score as the risk stratification tool of choice to assess annual stroke risk. In brief, the 2016 ESC guidelines for thromboprophylaxis in AF patients recommend no therapy for patients with a CHA₂DS₂VASc score of 0, consideration of OAC therapy for patients with a CHA₂DS₂VASc score of 1, and OAC therapy for those with a CHA₂DS₂VASc score of 2 or more, with OAC being in the form of VKA or NOAC. The exception to this is if the patient’s only risk factor is female gender (CHA₂DS₂VASc = 1), then they would also benefit from no therapy. The ESC continues that high bleeding risk is not reason enough to withhold anticoagulation, instead reversible factors contributing to bleeding risk should be corrected. The 2014 AHA guidelines are subtly different; for patients with a CHA₂DS₂VASc score of 1 they suggest no therapy or aspirin or OAC therapy, however this is based on weak evidence (level of evidence C). In contrast the ESC explicitly state that antiplatelet therapy cannot be recommended for stroke prevention due to it possessing similar bleeding risk to OAC therapy, but without the corresponding reduction in stroke events. New Zealand does not publish an AF guideline but are largely influenced by the ESC and AHA. In summary all patients with a CHA₂DS₂VASc score of two or more, and some with a CHA₂DS₂VASc score of 1, are indicated to receive VKA or NOAC therapy for stroke prevention.
1.3 ACS patients with AF

Patients who experience an ACS and have medical history of AF are high risk and difficult to manage; they tend to be older, have more co morbidities and worse outcomes. In acute MI populations up to 21% of patients will have AF and approximately 30% of all AF patients have vascular disease. In the SNAPSHOT study from Australia and New Zealand 15% of those presenting with ACS patients were found to have a prior history of AF. With the incidence of AF expected to rise overtime the absolute numbers of patients with AF who also experience an ACS will likely grow.

For AF and ACS, the recommended therapy for each condition is well validated, OAC and DAPT respectively. However, this rich evidence base falls away when AF and ACS are combined. Further, OAC therapy and DAPT are each alone insufficient protection for this patient group as established in earlier trials. In brief, OAC therapy with warfarin is superior to DAPT (aspirin and clopidogrel) for the prevention of stroke and systemic embolisation in AF patients, whilst DAPT is superior to OAC therapy for the prevention of recurrent cardiovascular events in patients presenting with ACS or managed with PCI. Therefore, the combination of DAPT and OAC, known as triple therapy (TT), in theory seems a logical solution for the treatment of ACS patients with AF as it provides both atherothrombotic and thromboembolic protection. However, to date no RCTs have been conducted that have specifically addressed optimal therapy for this patient group. This is also complicated by the fact that any protection achieved from TT is likely counter-balanced by an increased risk of bleeding.

Defining optimal medical therapy for ACS patients with AF is further complicated by the variety of drugs that can constitute triple therapy and the corresponding lack of clinical trials. VKAs, particularly warfarin, have traditionally been the OAC of choice, but the recently developed NOACs have shown superiority with regard to patient convenience and efficacy with no increase in bleeding events. For the treatment of ACS, aspirin and clopidogrel have been standard of care, but the introduction of the newer P2Y12 receptor antagonists, such as prasugrel and ticagrelor, have added complexity to DAPT in the context of TT. There have been a small number of trials assessing TT for the treatment of ACS to assess whether it was superior to DAPT at reducing ischaemic...
events, and these have yielded unfavourable results largely due to significant increases in bleeding risk, \textsuperscript{178-181} however these findings are not necessarily applicable to AF patients, and their unique antithrombotic requirements.

1.3.1 Guidelines for the treatment of ACS patients with AF

Guidance for the treatment of ACS patients with AF can be found in publications from different international societal bodies, and in each case the lack of evidence to guide recommendations is acknowledged. The trade-off between protection from ischaemic events and bleeding risk is always a key factor and no evidence based consensus is made across the different publications.

It is a challenge to synthesis the information across guideline and consensus documents due to their differing content. However, in general, the notion is that an ACS patient with AF is identified as either having high risk of stroke or low risk of stroke and treated accordingly. A patient with high stroke risk is believed to receive benefit from TT (of a variable duration) before transitioning to OAC and single antiplatelet. On the other hand, a patient at low risk of stroke does not require OAC therapy and is believed to receive benefit from DAPT alone. Overarching this is the belief that an ACS patient with AF who has unacceptably high bleeding risk would most likely benefit from DAPT. OAC monotherapy is recommended for all AF patients at 12 months post ACS event (Figure 1-9).
What is not consistent is how these patients (high stroke risk, low stroke risk and unacceptable bleeding risk) are identified (Table 1-6). The most recent American perspective for AF patients undergoing PCI does not put forward risk stratification tools to assess stroke and bleeding risk, but rather refers to a patient’s ratio of risk, without providing definition. For example, a patient deemed at high thrombotic risk/low bleeding risk is suggested to receive TT for 3-6 months\textsuperscript{182}. However, methods to quantify patient risk are not prescribed. Currently the AHA guideline for AF refers to CHA\textsubscript{2}DS\textsubscript{2}VASc to assess stroke risk, and suggests that those with a score of 2 or more should receive TT with warfarin (but not the newer NOACs), although duration is not defined (Level of Evidence C)\textsuperscript{106}. In addition the AHA guidelines for NSTEACS \textsuperscript{88} and STEMI \textsuperscript{89} suggest that if TT is used, then therapy should be administered for as shorter duration as possible. None of the American based guidelines define bleeding risk.
The Canadian Cardiac Society’s AF recommendations are different again and use a novel tool to assess stroke risk in the context of AF patients with NSTEACS or STEMI; High stroke risk is defined as age > 65 years or CHADS$_2$ ≥1, whereas low stroke risk is defined as age <65 years and a CHADS$_2$ score of 0. Utilising this schema some ACS patients with AF could indeed have a CHADS$_2$ score of 0 as vascular disease is not a component of this score. Patients at high risk of stroke are suggested to receive 3-6 months of TT. Consistent with the above no explicit detail is provided regarding bleeding risk $^{183}$.

In contrast the ESC consensus document for AF patients with ACS/PCI is very prescriptive. Stroke risk is determined using CHA$_2$DS$_2$VASc, with a CHA$_2$DS$_2$VASc of 1 an indication for TT, which qualifies all ACS patients given the 1 point received for vascular disease (as per Table 1-5). TT duration is variable and ranges from 1 to 12 months. Bleeding risk is defined using the HAS-BLED score (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drug or Alcohol), with a score of 3 or more being high risk $^{184}$. The ESC NSTEACS $^{90}$ are subtly different in that they refer to a CHA$_2$DS$_2$VASc score of 2 more as a consideration for TT, for as short a duration as possible, and this is echoed closely in the ESC STEMI guideline $^{91}$.

New Zealand guidelines regarding the ACS patient with AF are very brief. There is not a dedicated consensus document, but rather scant details can be found in NSTEACS $^{185}$ and STEMI $^{186}$ guidelines. The NSTEACS guidelines put forward that TT consisting of aspirin, P2Y$_{12}$ inhibitor (not prasugrel) and OAC, should be used for as short a period as possible but do not provide details as to the patient characteristics or level of risk this recommendation would apply to. The STEMI guidelines outlines TT for 1 month, followed by cessation of aspirin if long-term oral anticoagulation is indicated, e.g. CHA$_2$DS$_2$VASc score of 2 (Level of Evidence C). Once again bleeding risk is not adequately detailed.

Finally, the Australian position which is published in their ACS guidelines suggests a CHA$_2$DS$_2$VASc score of 1 as low risk of stroke, and ≥2 as high risk of stroke, with the duration of TT in the latter group (ranging from 1 -6 months), dependant on their bleeding risk as defined by HAS-BLED score $^1$. 

50
Table 1-6 Summary of guidelines for ACS patients with AF

<table>
<thead>
<tr>
<th></th>
<th>High stroke risk definition</th>
<th>Suggested duration of TT</th>
<th>High bleeding risk definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>American-based guidelines (incl. AHA)</td>
<td>Not defined</td>
<td>3-6 months</td>
<td>Not defined</td>
</tr>
<tr>
<td>ESC guidelines</td>
<td>CHA2DS2VASc =1</td>
<td>1-12 months</td>
<td>HAS-BLED ≥3</td>
</tr>
<tr>
<td>Canadian Cardiac Society guidelines</td>
<td>Age &gt; 65 years or CHADS2 ≥ 1</td>
<td>3-6 months</td>
<td>Not defined</td>
</tr>
<tr>
<td>New Zealand guidelines</td>
<td>Not defined</td>
<td>Not defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>Australian guidelines</td>
<td>CHA2DS2VASc ≥2</td>
<td>1-6 months</td>
<td>HAS-BLED ≥3</td>
</tr>
</tbody>
</table>

In summary, the above guidelines demonstrate inconsistencies regarding discharge therapies for ACS patients with AF, and this largely centres on variations in stroke and bleeding risk assessment. There also appears to be discordance between publications from the same societies, if to a lesser extent. Where risk stratification tools are suggested, that is CHA2DS2VASc, CHADS2 and HAS-BLED, these scores are validated in AF cohorts only and not in cohorts of ACS patients with AF, which adds further complexity to the matter. The implication is that there is confusion and lack of certainty regarding what optimal therapy is for ACS patients with AF, and indecision about which patients would benefit from TT given the broad interpretation that could occur from the above guidelines.
1.4 Overall aims

This thesis aimed to explore optimal therapy for patients with a medical history of AF who have experienced an ACS. Such patients are at high risk of repeat events and careful management is required. However, a lack of sufficient evidence-based research combined with the numerous therapeutic agents available have resulted in confusion and uncertainty about how to best treat this patient group.

Therefore, the overall aims of this thesis are:

1. To describe discharge prescription of antiplatelet and anticoagulant therapy in ACS patients with AF
2. To describe national prescription patterns of antiplatelet and anticoagulant therapies in ACS patients with AF
3. To examine whether prescribed therapies for this patient group were associated with one-year outcomes
4. To systematically review published literature to determine whether DAPT or TT is optimal therapy for ACS patients with AF
5. To construct a decision analysis model to evaluate bleeding and stroke risk in ACS patients with AF
6. To determine likely thresholds of stroke risk at which the benefits of TT may exceed harm from bleeding
7. To characterise in-hospital and one-year bleeding events in a real world MI cohort
8. To evaluate the ability of CRUSADE and ACTION bleeding risk scores to predict in-hospital and one-year bleeding events
9. To examine whether low platelet reactivity is predictive of in-hospital and one-year bleeding events
2 Management of ACS patients with AF from a single-centre setting

Publication arising from this chapter:

2.1 Introduction

The previous chapter has identified that international guidelines for the treatment of ACS patients with AF are inconsistent and lack clarity with regard to optimal antiplatelet and anticoagulant strategies. However, in general terms it is accepted that patients at high risk of stroke would likely be candidates for TT and those at low risk of stroke candidates for DAPT.

In our local setting, New Zealand guidelines offer very limited detail as to how best treat ACS patients with AF. The NSTEACS guidelines briefly mention TT may be used for as short a period as possible, but do not offer direction as to which patients to apply this recommendation to. The STEMI guidelines offer little more, suggesting TT for 1 month after PCI in patients with a CHA₂DS₂VASc score of 2, but do not describe any further supporting detail to aid decision making. Neither guideline adequately discusses stroke risk or considers bleeding risk. By comparison to other guideline documents, New Zealand guidelines are the least prescriptive, lack detail and therefore offer little guidance to clinicians.

Given this lack of detail we set out to describe current practice in prescribing antithrombotic therapies for ACS patients with AF, with particular focus on whether the use of oral anticoagulation was related to stroke or bleeding risk.

Therefore, the aim of this study was:

- To describe discharge prescription of antiplatelet and anticoagulant therapy in ACS patients with AF
2.2 Methods

2.2.1 Patient enrolment

Patients enrolled into the Wellington ACS study between January 2012 and February 2015, who also had a recorded medical history of AF were eligible for inclusion into the present study. Entry criteria for the Wellington ACS study were patients presenting to Wellington Regional Hospital with an ACS event that had been adequately pre-treated with DAPT (chronic therapy or loading doses) and who required angiography; the Wellington ACS study was set up to examine platelet reactivity and clinical outcomes, hence the above enrolment criteria.

Exclusion criteria for the Wellington ACS study and therefore the present study, were a platelet count <100 x 10^9/L, haemoglobin <100 g/L, and administration of a fibrinolytic agent within 24 hours prior to enrolment or glycoprotein IIb/IIIa antagonist within 1 week prior to enrolment. This study was approved by the Lower Regional South Ethics Committee (ref: LRS/11/09/035/AM01). All patients provided informed written consent at the time of enrolment.

2.2.2 Data collection

Patient demographics, clinical characteristics, clinical management, in-hospital outcomes and discharge information were recorded prospectively from patient medical records and from the cardiac catheterisation database. Clinical management, including discharge medication prescription was at the discretion of the attending physician.

2.2.3 Definitions

An ACS was defined as symptoms of myocardial ischaemia lasting > 10 minutes and either troponin elevation or acute electrocardiogram (ECG) changes (≥ 1mm of new ST segment deviation or T wave inversion in at least 2 contiguous leads). A patient was deemed to have AF if they either had a documented past medical history of AF, or no prior AF but who were in AF at the time their pre-angiogram enrolment ECG was performed. Patients who had new onset AF later during their hospital admission or post-
procedural AF were not included in this analysis. Adequate DAPT pre-treatment was defined as:

- chronic therapy with aspirin (≥75mg/day) and either clopidogrel (≥75mg/day) or ticagrelor (90mg/bd), or,
- loading doses of ≥300mg aspirin (at least 2 hours prior) and either ≥300mg clopidogrel (at least 6 hours prior) or 180mg ticagrelor (at least 1.5 hours prior)

Risk of stroke for AF patients was calculated on admission and at discharge (including index event) using the CHA\textsubscript{2}DS\textsubscript{2}VASc assessment tool\textsuperscript{155}; a score of ≥2 = high risk, 1 = intermediate risk and 0 = low risk (see Chapter 1, Table 1-5). Bleeding risk was calculated post-admission using the ACS bleeding score CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines)\textsuperscript{187}; a score of ≤20 = very low risk, 21-30 = low risk, 31-40 = moderate risk, 41-50 = high risk and >50 = very high risk (Table 2-1). Admission medication was defined as the patients’ regular medication prior to index admission. Discharge medication was defined as the medication prescribed at the time of discharge from Wellington Regional Hospital.

2.2.4 Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean and standard deviation. We compared characteristics of AF and non-AF patients using Chi squared tests for dichotomous data and independent t-tests for continuous data. Use of oral anticoagulants was examined for dichotomous data using binary logistic regression and continuous data using independent t-tests. Risk scores were analysed using Spearman rank tests. For all statistical analyses a p-value ≤0.05 was considered significant. All statistical tests were performed using SPSS version 22 (IBM, Armonk, NY).
Table 2-1 CRUSADE bleeding risk score

<table>
<thead>
<tr>
<th>Baseline haematocrit, %</th>
<th>Sex</th>
<th>Composite score determines bleeding risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥31</td>
<td>Male</td>
<td>≤20 = very low risk</td>
</tr>
<tr>
<td>31-33.9</td>
<td>Female</td>
<td>21-30 = low risk</td>
</tr>
<tr>
<td>34-36.9</td>
<td>CHF at presentation</td>
<td>31-40 = moderate risk</td>
</tr>
<tr>
<td>37-39.9</td>
<td>No</td>
<td>41-50 = high risk</td>
</tr>
<tr>
<td>≥40</td>
<td>Yes</td>
<td>&gt;50 = very high risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Creatinine clearance, * mL/min</th>
<th>Prior vascular disease**</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15</td>
<td>No</td>
</tr>
<tr>
<td>&gt;15-30</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt;30-60</td>
<td></td>
</tr>
<tr>
<td>&gt;60-90</td>
<td>No</td>
</tr>
<tr>
<td>&gt;90-120</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt;120</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>Systolic blood pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤70</td>
<td>≤90</td>
</tr>
<tr>
<td>71-80</td>
<td>91-100</td>
</tr>
<tr>
<td>81-90</td>
<td>101-120</td>
</tr>
<tr>
<td>91-100</td>
<td>121-180</td>
</tr>
<tr>
<td>101-110</td>
<td>181-200</td>
</tr>
<tr>
<td>111-120</td>
<td>≥201</td>
</tr>
<tr>
<td>≥121</td>
<td></td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.
*Creatinine clearance was estimated with the Cockcroft-Gault formula.
**Prior vascular disease was defined as history of peripheral artery disease or prior stroke.
2.3 Results

2.3.1 Patient selection

Between January 2012 and February 2015 a total of 1090 patients were enrolled into the Wellington ACS study. We identified 93 patients within this data set with AF, composed of 77 (83%) patients with a past history of AF, and 16 (17%) with no medical history who were in AF at the time of their enrolment ECG (Figure 2-1).

**Figure 2-1 Flow diagram of the patient selection process**

ACS-AF = acute coronary syndrome patients with atrial fibrillation; ECG = electrocardiogram.
2.3.2 Patient characteristics

Many characteristics of the AF cohort (n=93) differed compared to the non-AF patients (n=997) and this data is shown in Table 2-2. The AF cohort was older (mean age in years 69.8 ± 9.6 vs. 62.4 ± 11, p <0.001), however there was no difference seen in percentage female or body mass index between the two groups. The AF cohort had significantly higher rates of hypertension (83% vs. 60%, p <0.001), diabetes (31.2% vs. 18.5%, p=0.003), heart failure (6.5% vs. 2.3%, p=0.018), previous stroke/TIA (12.9% vs. 6.3%, p=0.017) and previous MI (36.6% vs. 23.2%, p=0.004). The non-AF cohort had significantly more current smokers (22.7% vs. 8.6%, p=0.002) and family history of CAD (37.5% vs. 26.9%, p=0.04). All AF patients were considered to have non-valvular AF as none had greater than mild valve disease and none had received valve replacement surgery.

In the AF cohort, the predominant presenting ACS was NSTEMI (75.3%) followed by STEMI (18.3%) and UA (6.5%) Overall, post angiography clinical management was as follows: medical therapy in 45.2%, PCI in 45.2%, and the remaining 9.7% received CABG surgery.
Table 2-2: Demographics and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>ACS-AF (n=93) Total n (%)</th>
<th>Non ACS-AF n=93 Total n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year, mean ± SD)</td>
<td>69.8 ± 9.6</td>
<td>62.4 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>29 (31.2)</td>
<td>298 (29.9)</td>
<td>0.800</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>30.1 ± 5.1</td>
<td>29.2 ± 5.6</td>
<td>0.130</td>
</tr>
<tr>
<td><strong>Stroke risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>12 (12.9)</td>
<td>63 (6.3)</td>
<td>0.017</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77 (83)</td>
<td>598 (60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6 (6.5)</td>
<td>23 (2.3)</td>
<td>0.018</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29 (31.2)</td>
<td>184 (18.5)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Vascular disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>34 (36.6)</td>
<td>231 (23.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>PAD</td>
<td>7 (7.5)</td>
<td>73 (7.3)</td>
<td>0.940</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>69 (74.2)</td>
<td>643 (64.5)</td>
<td>0.067</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8 (8.6)</td>
<td>226 (22.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Angina</td>
<td>29 (31.2)</td>
<td>238 (23.9)</td>
<td>0.106</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>15 (16.1)</td>
<td>147 (14.7)</td>
<td>0.723</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>9 (9.7)</td>
<td>68 (6.8)</td>
<td>0.305</td>
</tr>
<tr>
<td>Angiogram showing CAD</td>
<td>26 (28)</td>
<td>205 (20.6)</td>
<td>0.098</td>
</tr>
<tr>
<td>Family history CAD</td>
<td>25 (26.9)</td>
<td>374 (37.5)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

ACS-AF = acute coronary syndrome patients with atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SD = standard deviation.
2.3.3 Drug therapy

The use of OACs in the AF cohort was low. Of the patients with a known history of AF (n=77) a total of 15 (19.5%) patients were on an OAC at admission for the treatment of AF (not for any other clinical indication) and this was OAC alone in 12 (15.6%) patients, and an OAC-aspirin combination in 3 (3.9%) patients (Table 2-3). Admission OAC use was not related to risk of stroke as defined by the patients admission CHA₂DS₂VASc risk score (odds ratio = 1.3, [0.93-2], p=0.116).

Table 2-3 Pre-existing drug therapy prior to ACS admission

<table>
<thead>
<tr>
<th>CHA₂DS₂VASc risk (score)</th>
<th>Low (0) n = 5 (%)</th>
<th>Intermediate (1) n = 8 (%)</th>
<th>High (≥2) n = 64 (%)</th>
<th>Total n = 77 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OAC use</td>
<td>0</td>
<td>0</td>
<td>15 (23.4)</td>
<td>15 (19.5)</td>
</tr>
<tr>
<td>OAC alone</td>
<td>-</td>
<td>-</td>
<td>12 (18.8)</td>
<td>12 (15.6)</td>
</tr>
<tr>
<td>OAC + aspirin</td>
<td>-</td>
<td>-</td>
<td>3 (4.7)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>OAC + P2Y₁₂ inhibitor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OAC + DAPT (TT)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3 (60)</td>
<td>1 (12.5)</td>
<td>29 (45)</td>
<td>33 (42.9)</td>
</tr>
<tr>
<td>DAPT</td>
<td>0</td>
<td>0</td>
<td>6 (9.4)</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Aspirin + Clopidogrel</td>
<td>-</td>
<td>-</td>
<td>5 (7.8)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Aspirin + Ticagrelor</td>
<td>-</td>
<td>-</td>
<td>1 (1.6)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Nil</td>
<td>2 (40)</td>
<td>7 (87.5)</td>
<td>14 (22)</td>
<td>23 (29.9)</td>
</tr>
</tbody>
</table>

DAPT = dual antiplatelet therapy; OAC = oral anticoagulant; TT = triple therapy.
Based on admission CHA\textsubscript{2}DS\textsubscript{2}VASc calculations 6.5% of the AF cohort were at low risk of stroke (score of 0) and 10.4% were at intermediate risk of stroke (score of 1), and no OAC use was observed in either group. The remaining 83.1% were at high risk of stroke (score ≥2) and OAC use was seen in patients with a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 2, 3, 4 and 5. No OAC use was observed in patients with the highest risk of stroke, in this cohort a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 6 or 7 (Figure 2-2).

![Diagram showing admission OAC use by CHA2DS2VASc score](image)

**Figure 2-2 Admission data: OAC use by CHA2DS2VASc score**

No OAC use was observed in patients at low (CHA\textsubscript{2}DS\textsubscript{2}VASc = 0) or intermediate (CHA\textsubscript{2}DS\textsubscript{2}VASc = 1) risk of stroke at admission. OAC use was observed in patients at high risk of stroke for the CHA\textsubscript{2}DS\textsubscript{2}VASc scores 2 through 5 were, with CHA\textsubscript{2}DS\textsubscript{2}VASc 4 patients having the highest rate of admission OAC prescription at 7.8%. We did not observe OAC use in the patients at highest risk of stroke (CHA\textsubscript{2}DS\textsubscript{2}VASc scores 6-7).
OAC use in the AF cohort at discharge (n=93) was again low with 11 patients (11.8%) discharged on an OAC; this was OAC alone (2 patients), OAC and aspirin (4 patients), and OAC and P2Y₁₂ inhibitor (5 patients). No patient was discharged on OAC and DAPT (triple therapy) in this cohort (Table 2-4). Discharge OAC use was not related to discharge CHA₂DS₂VASc score, nor to any other clinical characteristic. However, discharge on an OAC was more likely in patients treated with an OAC prior to admission (odds ratio = 14, [3.4 – 58], p < 0.001) (Table 2-5). Of the 15 patients admitted on an OAC, 7 remained on an OAC at discharge.

**Table 2-4 Discharge drug therapies**

<table>
<thead>
<tr>
<th>CHA₂DS₂VASc risk score</th>
<th>Low (0) n = 0 (%)</th>
<th>Intermediate (1) n = 6 (%)</th>
<th>High (≥2) n = 87 (%)</th>
<th>Total n = 93 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OAC use</td>
<td>0</td>
<td>0</td>
<td>11 (12.7)</td>
<td>11 (11.8)</td>
</tr>
<tr>
<td>OAC alone</td>
<td>-</td>
<td>-</td>
<td>2 (2.3)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>OAC + aspirin</td>
<td>-</td>
<td>-</td>
<td>4 (4.6)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>OAC + P2Y₁₂ inhibitor</td>
<td>-</td>
<td>-</td>
<td>5 (5.7)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>OAC + DAPT (TT)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>1 (16.7)</td>
<td>13 (15)</td>
<td>14 (15.1)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0</td>
<td>0</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>DAPT</td>
<td>0</td>
<td>5 (83.3)</td>
<td>62 (71.3)</td>
<td>67 (72)</td>
</tr>
<tr>
<td>Aspirin + Clopidogrel</td>
<td>-</td>
<td>5 (83.3)</td>
<td>55 (63.2)</td>
<td>60 (65)</td>
</tr>
<tr>
<td>Aspirin + Ticagrelor</td>
<td>-</td>
<td>-</td>
<td>7 (8)</td>
<td>7 (7.5)</td>
</tr>
</tbody>
</table>

DAPT = dual antiplatelet therapy; OAC = oral anticoagulant; TT = triple therapy.
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>0.98 – 1.15</td>
<td>0.16</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.81</td>
<td>0.20 – 3.30</td>
<td>0.77</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke/TIA</td>
<td>0.65</td>
<td>0.08 – 5.55</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.17</td>
<td>0.97 – 1.28</td>
<td>0.19</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.54</td>
<td>0.16 – 14.55</td>
<td>0.71</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.3</td>
<td>0.35 – 4.86</td>
<td>0.69</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>0.87</td>
<td>0.8 – 1.05</td>
<td>0.31</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>0.65</td>
<td>0.33 – 8.24</td>
<td>0.54</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.07</td>
<td>0.12 – 9.64</td>
<td>0.95</td>
</tr>
<tr>
<td>History of angina</td>
<td>0.75</td>
<td>0.19 – 3.24</td>
<td>0.75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>0.41</td>
<td>0.05 – 3.46</td>
<td>0.42</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>1.65</td>
<td>0.33 – 8.24</td>
<td>0.54</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.54</td>
<td>0.16 – 14.55</td>
<td>0.71</td>
</tr>
<tr>
<td>OAC on admission</td>
<td>14</td>
<td>3.4 – 58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge CHA2DS2VASc</td>
<td>1.27</td>
<td>0.83 – 1.94</td>
<td>0.28</td>
</tr>
<tr>
<td>Discharge CRUSADE score</td>
<td>1.01</td>
<td>0.96 – 1.05</td>
<td>0.82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical management</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical management</td>
<td>2.35</td>
<td>0.64 – 8.66</td>
<td>0.20</td>
</tr>
<tr>
<td>PCI</td>
<td>0.23</td>
<td>0.05 – 1.15</td>
<td>0.07</td>
</tr>
<tr>
<td>CABG</td>
<td>2.40</td>
<td>0.43 – 13.26</td>
<td>0.32</td>
</tr>
</tbody>
</table>

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NSTEMI = non ST-segment elevation myocardial infarction; OAC= oral anticoagulant; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischaemic attack.
At discharge CHA\textsubscript{2}DS\textsubscript{2}VASc calculations included the index event and therefore no patient was at low risk of stroke, while 6.5% of patients were at intermediate risk of stroke and 93.5% at high risk of stroke. Discharge OAC use was observed in high risk patients only (CHA\textsubscript{2}DS\textsubscript{2}VASc ≥2) (Figure 2-3). The clinical management of each patient, be it medical therapy, PCI or CABG surgery, was not associated with the discharge use of OAC (Table 2-5).

**Figure 2-3 Discharge data: OAC use by CHA2DS2VASc score**

At discharge OAC use was observed in high risk patients only (CHA\textsubscript{2}DS\textsubscript{2}VASc ≥2). No OAC use was observed in the patients at highest risk of stroke (CHA\textsubscript{2}DS\textsubscript{2}VASc =7). Overall OAC use at discharge was low.
Of the patients admitted on an anticoagulant (n = 15) this was warfarin in 10 (66%) patients and dabigatran in 5 (33%) patients. For patients prescribed an anticoagulant at discharge (n = 11) this was warfarin in 9 (82%) patients and dabigatran in 2 (18%) patients.

At discharge DAPT was the most common treatment regime. A total of 67 (72%) patients in this cohort were discharged on DAPT, 83.3% of intermediate risk patients and 71.3% of high risk patients (Table 2-4).

2.3.4 Bleeding risk

CRUSADE bleeding scores were calculated for each AF patient after the index admission. Figure 2-4 shows a significant relationship between CRUSADE bleeding score and CHA2DS2-VASc score; that is, as risk of bleeding increases so does risk of stroke (r = 0.683, p = 0.01). Numerically this relationship is evident in Table 2-6 where all patients who are at moderate (22, 23.7%) or high/very high (21, 22.6%) risk of bleeding were also at high risk of stroke. However, there was a group of patients who were at high risk of stroke and low/very low risk of bleeding (n=44, 47.3%), who may have been suitable candidates for OAC therapy (see Table 2-6). Risk of bleeding based on CRUSADE scores was not related to whether a patient was discharged on an OAC (OR 1.01, CI 0.96 -1.05, p = 0.818) (Table 2-5).
Correlation between stroke risk (CHA$_2$DS$_2$VASc) and bleeding risk (CRUSADE) is statistically significant ($r = 0.683$, $p = 0.01$). A CHA$_2$DS$_2$VASc score of 1 indicates intermediate risk of stroke and a CHA$_2$DS$_2$VASc score of 2 or more indicates high risk of stroke.
Table 2-6 Composite bleeding and stroke risk

<table>
<thead>
<tr>
<th>CRUSADE bleeding risk (points)</th>
<th>CHA\textsubscript{2}DS\textsubscript{2}VASc risk of stroke (points)</th>
<th>Low (0)</th>
<th>Intermediate (1)</th>
<th>High (≥2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High/very high (≥41)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Moderate (31-41)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Low/ very low (≤30)</td>
<td></td>
<td>0</td>
<td>6</td>
<td>44</td>
</tr>
</tbody>
</table>
2.4 Discussion

There is limited information available about how patients with the combination of AF and ACS are being currently managed. There are many therapeutic options and decision making is complex in this group of patients. In our study of patients with ACS and AF we observed low use of OACs prior to hospital admission. Furthermore, OAC use at discharge was lower again, with DAPT being the predominant discharge regime. Decisions surrounding OAC use did not appear to be based on stroke or bleeding risk analysis, or any other identifiable clinical factors. The probability of being discharged on an OAC was substantially higher if the patient was on an OAC at admission.

At the time of hospital admission, only 19.5% of patients with a known history of AF were on an OAC. In the group classified as high risk on the basis of CHA₂DS₂VASc score only 23% were on an OAC. Both the AHA and the ESC recommended OAC therapy for AF patients with a CHA₂DS₂VASc score of 2 or more. Despite this, significant underutilisation of OACs in eligible AF patients has been widely reported, similar to that seen in our cohort. In addition, of those admitted on an OAC, most (10/15) were on warfarin treatment despite randomised trials demonstrating the superiority of NOACs when compared to warfarin therapy, and the availability of dabigatran through New Zealand government funding since 2011. Our study has not examined reasons for the low use of OACs in the AF patient group. It has previously been suggested that lack of knowledge of trials and guidelines, and overestimation of potential contraindications and risk, including fear of bleeding, may be contributory.

On discharge from hospital following an ACS event we observed an even lower rate of OAC prescription in AF patients at high risk of stroke. In our cohort only 12% of such patients were prescribed an OAC. Use of an OAC was not related to stroke risk (CHA₂DS₂VASc score) or bleeding risk (CRUSADE score), nor to any other clinical characteristic. This is despite consensus that decisions regarding OAC therapy should be based on careful considerations of stroke and bleeding risk. The only statistically significant factor contributing to discharge OAC prescription in our cohort was whether the patient was admitted on an OAC. We did identify a group of patients with high risk of stroke and low/very low risk of bleeding on the basis of risk scores, and in theory this
is the group who may have had greatest opportunity to benefit from OAC use with lowest risk of potential harm. When OACs were prescribed a variety of strategies were used, including with or without a single antiplatelet agent (aspirin or P2Y\textsubscript{12} inhibitor). No triple therapy was observed in this cohort.

DAPT was the predominant discharge regime and was prescribed to 72% of patients. Given that clinical guidelines advocate DAPT as best practice for post-ACS patients, and de-emphasize the use of OACs due to risk of bleeding, this result is not entirely surprising \textsuperscript{91}. While DAPT may offer some protection from stroke in AF patients, antiplatelet agents do not prevent the activation of coagulation factors that play a greater role in the development of fibrin-rich thrombi, as seen in AF \textsuperscript{197}, and are not as effective as OAC at preventing stroke \textsuperscript{198,199}.

In estimating bleeding risk, we have used an ACS based bleeding risk score (CRUSADE) rather than a bleeding score developed for AF patients on chronic OAC (such as HAS-BLED\textsuperscript{200}). Bleeding risk scores have been developed for either AF or ACS, but not the combination of AF and ACS. Use of an AF-based bleeding score may have identified a slightly different cohort as having low bleeding risk.

2.4.1 Limitations

Firstly, as enrolment criteria for the Wellington ACS study and therefore this study, included adequate pre-treatment on DAPT we may have introduced a selection bias in our AF cohort. AF patients on OAC may have been less likely to be given DAPT due to concerns regarding bleeding risk. If this was the case, then our cohort may under-represent the use of OAC in AF patients in our community. In addition the DAPT entry criteria has prevented any patients managed with an OAC and a single antiplatelet agent being included. Whilst this was not a guideline recommended therapy at the time of this study we cannot exclude this possibility.

Secondly, from our initial ACS study cohort 8.5% were identified as having a medical history of AF. Whilst this is within the expected range for ACS patients with AF based on
previous publications (6-21%), it is towards the lower bounds \textsuperscript{169}. Given that we know advancing age is a risk factor for AF \textsuperscript{201}, and that increasing age may deter invasive management \textsuperscript{202,203}, it is also possible that the angiography entry criteria has also resulted in fewer ACS patients with AF being eligible for inclusion into this study. The consequence of this is that our study has not described the prescription patterns for ACS patients with AF, managed without angiography, and this may account for the lower rate of AF seen in our ACS cohort.

Thirdly, we observed lower than anticipated use of OACs at discharge (12%). As a result, determining factors associated with discharge OAC use was statistically challenging. We identified OAC use on admission as the only independent driver of OAC use at discharge, however had OAC use at discharge been more prevalent we may have identified other factors due to greater statistical power.

Lastly, this study was performed opportunistically in a pre-existing Wellington ACS study. As a consequence the results detailed above only pertain to a single-centre and are not representative of New Zealand practice in its entirety. Further examination of nationwide practice would be advantageous to adequately characterise the discharge management of ACS patients with AF in New Zealand.

\section*{2.5 Conclusion}

This study suggests that for ACS patients with AF, the default discharge therapy is DAPT. What’s more, OAC use is minimal and does not appear to be driven by stroke or bleeding risk. However, given the limitations associated with selection bias in this cohort were significant, and data was representative of single-centre practice only, it is possible that our findings are not representative of overall patient management strategies in this patient group. In order to examine practice without selection bias, and at a national level, we chose to utilise the All New Zealand Acute Coronary Syndrome - Quality Improvement data registry to examine treatment strategies for ACS patients with AF. This approach is examined in Chapter 3.
3 Management of ACS patients with AF: a description of national practice
3.1 Introduction

In Chapter 2 we described management of a cohort of ACS patients with a medical history of AF from a single-centre study. We observed DAPT to be the most common discharge therapy for this patient group, with limited use of OACs regardless of CHA2DS2VASc score. Because this cohort was derived from a pre-existing study of ACS patients, one of the enrolment criteria was that patients were on DAPT at the time of angiography. This may have excluded patients who were managed with an OAC and a single antiplatelet agent. In addition, the cohort only represented practice at one centre.

In order to examine in more detail how ACS patients with AF were managed in New Zealand we chose to use the All New Zealand Acute Coronary Syndrome - Quality Improvement (ANZACS-QI) registry data set. ANZACS-QI was implemented with the primary aim of supporting evidence-based management of ACS patients in New Zealand, through both quality improvement and research. The ANZACS-QI programme is a nationalised collaboration between all publicly funded District Heath Boards (40 hospitals) that admit ACS patients, as well as 6 private hospitals that provide coronary angiography services, and aims to capture data on all patients treated in New Zealand for an ACS complaint. This registry collects information including patient demographics and clinical management during hospital admission for ACS. The registry data can then be linked to Ministry of Health datasets to examine patient outcomes and pharmaceutical dispensing data.

Therefore, the aims of this study were:

- To describe national prescription patterns of antiplatelet and anticoagulant therapies in ACS patients with AF
- To examine whether prescribed therapies were associated with one-year patient outcomes
3.2 Methods

3.2.1 Registry description

There are two complementary data sources within ANZACS-QI that generate two overlapping cohorts: 1) The ACS routine information cohort which captures patients aged 20 years or more who are admitted to hospital with an International Classification of Disease 10 (ICD-10) code consistent with ACS, and; 2) The ACS-CathPCI registry cohort which systematically collects data on coronary angiography and PCI procedures, including those undertaken in private hospitals.204,206

Once data has been entered into the ANZACS-QI registries patients are only identifiable by their National Health Index (NHI) number. Using encrypted NHI numbers it is then possible to link ANZACS-QI registry data with New Zealand Health databases collected by the Ministry of Health. These are the National Minimum Dataset, Pharmaceutical Collection and Mortality Collection and details can be seen in Table 3-1.204

To access data from ANZACS-QI we completed a Data Access Proposal (DAP) that was submitted to the ANZACS-QI governance board outlining the proposed study and analysis. This DAP was reviewed by that board, and approved under the umbrella ethical approval for the ANZACS-QI registries granted by the National Multi-Region Ethics Committee (MEC07/19/EXP). In order to access Ministry of Health Datasets, the DAP was then viewed by the Vascular Informatics using Epidemiology and the Web (VIEW) governance board, and this group approved access to this data under the VIEW ethical approval granted by the Northern Region Ethics Committee (AKY/03/12/314)204.
Table 3-1 National Databases linked with ANZACS-QI registries

<table>
<thead>
<tr>
<th>Name of dataset</th>
<th>Data collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Minimum Dataset</td>
<td>Admission related data: date of admission, date of discharge, ICD-coded discharge diagnoses, ICD-coded procedural diagnoses (including angiography, PCI, CABG). Demographic data Previous hospitalisations</td>
</tr>
<tr>
<td>Pharmaceutical Collection</td>
<td>Government subsidised medication dispensing claims from community pharmacies</td>
</tr>
<tr>
<td>Mortality Collection</td>
<td>Date of death and ICD-coded underlying and contributing causes of death</td>
</tr>
</tbody>
</table>

3.2.2 Data extraction

From 1st January 2012 through to the 31st of December 2015 a total of 19,295 patients with a final diagnosis of ACS were identified from the ANZACS-QI database. This registry does not currently record data on AF, although as a process of this DAP this has been recognised as an important missing piece of data and the next update of ANZACS-QI will add an AF data field. Patients with a history of AF were identified from the National Minimum Dataset as those having an ICD-10 discharge code of AF at any point in the preceding 10 years including the index admission. This identified 3,730 patients with a medical history of AF. Utilising the ACS-CathPCI registry 1101 of these patients received PCI and 610 of this group had one-year follow-up data available and defined the study cohort. The process of cohort identification can be seen in Figure 3-1.

Of the 610 patients in our target cohort demographic data (age, gender) and information regarding clinical presentation (STEMI, NSTEMI, UA) were extracted from the ACS routine information cohort. Information detailing past medical history and co-morbidities were obtained from the National Minimum Dataset. CHA$_2$DS$_2$VASc scores were calculated using data from both sources (Table 3-2). Data regarding therapies for
the 12 months post ACS were extracted from the Pharmaceutical Collection in quarterly blocks. This dataset provided information on prescriptions filled by patients during the quarter. Mortality data was sourced from the Mortality Collection and are based on underlying and/or contributory causes of death from a death certificate. Other one-year outcome data including ischaemic (stroke and MI) and bleeding events were extracted from the National Minimum dataset and are based on discharge coding following hospital admission.
Figure 3-1 Flow chart of cohort identification

ACS-AF = acute coronary syndrome with atrial fibrillation; PCI = percutaneous coronary intervention.
3.2.3 Definitions

Definitions used in the study are presented in Table 3-2. Prescription data was based on filled prescriptions within the quarter following the index admission for each patient and included oral antiplatelet agents (aspirin, clopidogrel, ticagrelor and prasugrel) and oral anticoagulants (warfarin, dabigatran, apixaban, rivaroxaban). DAPT was defined as the combination of aspirin and a P2Y\textsubscript{12} inhibitor. TT was the combination of aspirin, P2Y\textsubscript{12} inhibitor and any OAC. Single antiplatelet was the use of aspirin or P2Y\textsubscript{12} inhibitor alone.

3.2.4 Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean and standard deviation. We compared treatment groups using independent t-tests for continuous data and Chi squared tests for dichotomous data. Survival analysis was performed using the Kaplan-Meier method. For all statistical analyses a p-value ≤0.05 was considered significant. All statistical tests were performed using SPSS version 22 (IBM, Armonk, NY).
### Table 3-2 Definitions of data collected from national databases

<table>
<thead>
<tr>
<th><strong>Acute coronary syndrome</strong></th>
<th>Final diagnosis within ANZACS-QI dataset of UA, NSTEMI or STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>ICD-10 coded atrial fibrillation up to 10 years prior or during the index admission</td>
</tr>
<tr>
<td><strong>CHA₂DS₂VASc score</strong></td>
<td>Congestive heart failure or ICD-10 coded heart failure at any time in the past or Worst Killip class of 2, 3 or 4 recorded in ANZACS-QI during index admission</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>Dispensing of two or more blood pressure lowering medications the previous 6 months or SBP &gt;150 mmHg recorded in ANZACS-QI during index admission</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>As recorded in ANZACS-QI during index admission</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>As recorded in ANZACS-QI during index admission</td>
</tr>
<tr>
<td><strong>Previous stroke/TIA</strong></td>
<td>ICD-10 coded ischaemic stroke or TIA at any time in the past or Recorded in ANZACS-QI during index admission</td>
</tr>
<tr>
<td><strong>Vascular disease</strong></td>
<td>ICD-10 coded ACS, coronary procedure, PVD, or peripheral vascular procedure at any time in the past or Recorded in ANZACS-QI during index admission</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>As recorded in ANZACS-QI during index admission</td>
</tr>
<tr>
<td><strong>Bleeding events</strong></td>
<td>Any bleeding or ICD-10 discharge code from primary or secondary diagnosis for any bleeding</td>
</tr>
<tr>
<td></td>
<td>Intracranial bleeding or ICD-10 discharge code from primary or secondary diagnosis for intracranial bleeding</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal bleeding or ICD-10 discharge code from primary or secondary diagnosis for gastrointestinal bleeding</td>
</tr>
</tbody>
</table>

ICD = international classification of disease; NSTEMI = non-ST-segment elevation myocardial infarction; PVD = peripheral vascular disease; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischaemic attack; UA = unstable angina.
3.3 Results

3.3.1 Demographics

The demographic details of the 610 patients can be seen in Table 3-3. In our study cohort the mean age was 71.3 ± 10.7 years and 186 (30%) were female. Hypertension was the most common risk factor and was recorded in 530 (87%) of patients. A history of CHF was documented in 237 patients (39%), diabetes in 147 patients (24%) and prior stroke in 74 patients (12%). The presenting ACS was NSTEMI for 50% of cases, and STEMI and UA occurred in 37% and 13% of cases respectively. The average CHA\textsubscript{2}DS\textsubscript{2}VASc score for this cohort was 4.2 ± 1.6.

On the basis of the prescriptions filled in the first quarter, 469 patients (77%) were initially on either DAPT (370 patients, 61%) or TT (99 patients, 16%). The demographics of these two groups were compared and are given in Table 3-3. No significant difference was detected between TT and DAPT patients with regard to age, gender, presenting ACS or the clinical risk factors of CHF, hypertension or prior stroke. The only significant difference was that the TT group had a significantly higher rate of diabetes compared to DAPT patients (37% vs. 22%, p=0.002). The average CHA\textsubscript{2}DS\textsubscript{2}VASc score of the TT group was numerically higher than that of the DAPT group (4.3 vs. 4.1) however this was not statistically significant.
Table 3-3 Demographic data

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=610)</th>
<th>Triple therapy (n=99)</th>
<th>DAPT (n=370)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.3 (10.7)</td>
<td>71.3 (10.3)</td>
<td>70.8 (10.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>Female gender</td>
<td>186 (30%)</td>
<td>30 (30%)</td>
<td>115 (31%)</td>
<td>0.88</td>
</tr>
<tr>
<td>History of CHF</td>
<td>237 (39%)</td>
<td>40 (40%)</td>
<td>117 (32%)</td>
<td>0.10</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>530 (87%)</td>
<td>90 (91%)</td>
<td>311 (84%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes</td>
<td>147 (24%)</td>
<td>37 (37%)</td>
<td>82 (22%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>74 (12%)</td>
<td>10 (10%)</td>
<td>40 (11%)</td>
<td>0.84</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>4.2 (1.6)</td>
<td>4.3 (1.5)</td>
<td>4.1 (1.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>STEMI</td>
<td>226 (37%)</td>
<td>29 (29%)</td>
<td>139 (38%)</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>303 (50%)</td>
<td>54 (54%)</td>
<td>183 (49%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>81 (13%)</td>
<td>16 (16%)</td>
<td>48 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; DAPT = dual antiplatelet therapy; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment myocardial infarction.

3.3.2 Distribution of treatment strategies

For ACS patients with AF there were multiple variations of prescriptions filled in the 12 months (four quarters) post ACS event and these can be seen in Figure 3-2. Overall DAPT was the most commonly occurring therapy in each quarter but a steady decline over time was identified. In the first quarter 61% of patients received DAPT and this dropped to 34% in the fourth quarter. If the first quarter alone is examined we see that after DAPT, TT is the next most common prescription filled at 16%. This is followed by a close grouping of OAC + P2Y12 inhibitor (7.2%), single antiplatelet (6%), no therapy (5.5%) and OAC + aspirin (4%). The least common therapy in the first quarter was OAC alone at 0.2%.
Alongside declining DAPT rates over time it is also evident that TT rates decline over time. Starting at 16% in the first quarter this rate is halved by the second quarter (8%), and by the fourth quarter (3.3%) TT is the least common prescription filled.

In the first quarter 5.5% of patients did not have any prescriptions filled for either anticoagulants or antiplatelet agents. It is possible that some of these patients may have been transferred to palliative care settings and therefore not have had outpatient prescriptions filled. For quarters two through four, proportions of patients on each treatment were adjusted for the number alive at the start of the quarter. We observed rates of no therapy rise to 14% in the second quarter before reaching a high of 19% in both the third and fourth quarters. In the second and third quarters no therapy was the second most common treatment regimen behind DAPT. At 12 months no therapy was the third most common prescription filled behind DAPT (34%) and single antiplatelet therapy (23.5%).

OAC + aspirin and OAC + P2Y_{12} regimens displayed similar rates of prescription. Both showed a gradual rise over time with OAC + aspirin rising from 4% in the first quarter to 11.5% in the fourth quarter, while OAC + P2Y_{12} increased from 7% to 10% over the same time period. As mentioned OAC alone was the least prescribed therapy in the first quarter (0.2%) and this increased to 8.9% by the fourth quarter.
Figure 3-2 Distribution of treatment therapies by quarter

Graph plots treatment strategy (%) by time after ACS (Q); Q1 = 0-3 months, Q2 = 3-6 months, Q3 = 6-9 months, Q4 = 9-12 months.
3.3.3 Oral anticoagulant use

Initial therapy with an OAC (prescription of any OAC in the first quarter) was 27.5% The mean CHA$\text{2}$$\text{DS2VASC}$ score for patients with initial OAC therapy was $4.5 \pm 1.5$ and this was significantly higher than the mean score of $4.14 \pm 1.59$ for patients not on an OAC ($p=0.01$). Figure 3-3 demonstrates the number of patients at each CHA$\text{2}$$\text{DS2VASC}$ score for the cohort and the percentage that were initially treated with an OAC. OAC use was lowest at CHA$\text{2}$$\text{DS2VASC}$ 1 with 10% and this gradually increased to 36% at CHA$\text{2}$$\text{DS2VASC}$ 4. OAC use was similar at CHA$\text{2}$$\text{DS2VASC}$ 5 through 8 before peaking at 60% (3 patients out of 5) at CHA$\text{2}$$\text{DS2VASC}$ 9.
Figure 3-3 Percentage OAC use by CHA$_2$DS$_2$VASc score

Graph plots the number of patients for each CHA2DS2VASc score and the percentage that were initially treated with an OAC.
3.3.4 One-year outcomes

Overall there were 74 deaths (12%) at one-year follow up with mortality of 5% within the first month following the index event (see Figure 3-4). Based on death certificate coding 45 deaths (61%) were due to ischaemic heart disease, 8 (11%) to cancer, 1 (1.4%) to intracranial haemorrhage and the remaining 20 (27%) to various other causes. At one-year there were hospital admissions for non-fatal MI in 13 patients (2%), ischaemic stroke/TIA in 9 patients (1.5%) and intracranial bleeding in 3 (0.5%) patients.

Survival did not differ between initial treatments of DAPT or TT (6.3% vs. 8%, respectively, p=0.51) (Figure 3-4). With regard to one-year rates of non-fatal MI, stroke and bleeding events there was no significant difference between patients initially treated with TT or DAPT.

There was no difference in survival between those initially on OAC therapy compared to patients without OAC therapy. There was also no difference in MI or stroke rates between those on initial OAC therapy and those not on an OAC.

Hospital admissions for bleeding occurred for 22 patients (3.6%) and these patients were more likely to be on an OAC (7.1%) than not (2.2%, p=0.004). Fourteen patients were admitted to hospital for gastrointestinal bleeding (2.3%) and again these patients were more likely to be on OAC therapy (4.7% vs. 1.3%, p=0.01). Intracranial bleeding rates did not differ between treatment groups.
Kaplan-Meier graph shows patient survival rates (%) one-year post ACS event. Overall one-year mortality was 12%. Mortality did not differ between patients initially treated with DAPT or TT (6.3% vs. 8% respectively, $p=0.51$).
3.4 Discussion

In this analysis of patients with ACS and AF treated with PCI, we observed that DAPT was the most common initial treatment strategy, although the rate of DAPT declined significantly across the 12 months following ACS. TT was the second most common initial strategy, but also declined markedly over time. There was a small, but not significant difference in CHA$_2$DS$_2$VASc score between DAPT and TT groups, suggesting treatment options were not heavily driven by stroke risk. Overall initial OAC use was associated with a higher CHA$_2$DS$_2$VASc score, although OACs were not used in more than 50% of patients except at CHA$_2$DS$_2$VASc 9. The proportion of patients not on any OAC or antiplatelet therapy was high, with nearly 20% of patients during the period of 6-12 months post ACS not filling prescriptions for these therapies. Overall mortality in this group was high at 12% at one-year, and likely reflects the high-risk characteristics of this patient group.

The results of this study are consistent with the observations in Chapter 2 that DAPT is the preferred treatment after an ACS for patients with concurrent AF, and that this treatment strategy was not strongly influenced by stroke risk. The duration of DAPT was less than 12 months in almost half those initially prescribed this therapy. TT duration was less than 12 months in more than half those on this treatment initially. Some of the decline in these more intensive therapies is accounted for by an increase over time in either single antiplatelet therapy or OAC, but in addition there is an increase over time in the number of patients not filling prescriptions for either antiplatelet or oral anticoagulant drugs. Because this data is based on what prescriptions are filled, and not what prescriptions are written, we are not able to distinguish between patient non-compliance and clinician prescription choices. However, the observed treatments strategies are not consistent with current guidelines regarding optimal medical therapy in patients with ACS and PCI, regardless of AF $^{1,88-91}$.

Patients with higher CHA$_2$DS$_2$VASc scores were more likely to receive therapy that included OAC. However there was only a small amount of OAC use in this cohort, and the relationship with CHA$_2$DS$_2$VASc scores was not strong. It is possible that many of the patients included in our study were not in AF during the index admission. The way we
have identified AF is based on any hospital admission with AF within 10 years. The absence of observed AF during an ACS event could have contributed to the low observed use of OAC. However, a history of AF should have been noted for these patients, and AF is likely to become increasingly present for most patients over time, as AF begets more AF. It is also possible that some of the patients we have classified as having an AF history may represent coding error in the past.

The most common outcome of interest in this cohort at one-year was mortality, with a 12% rate and this did not differ by treatment. We observed a one-year stroke/TIA rate of 1.5% in this cohort, which is lower than expected based on the cohort’s mean CHA₂DS₂VASc score of 4.2. This may suggest that DAPT is providing a level of protection against stroke. It is also possible that there may have been stroke events contributing to mortality that have not been correctly identified in death certificate coding. In addition, particularly TIA events may not have resulted in hospital admission, as these may be treated in emergency department (ED) alone, and so some cases may have been missed. Given the low rate of stroke/TIA, we had insufficient statistical power to detect any relationship between treatment strategies and stroke events.

Hospital admissions for bleeding occurred at a rate of 3.6% in this cohort. All minor-moderate bleeding events that were treated in the community or ED were not part of this analysis. Patients on OAC were more likely to experience both any bleeding and gastrointestinal bleeding which is consistent with wider literature.

3.4.1 Limitations

In order to describe discharge therapy for ACS patients with AF on a national scale we were restricted to the parameters of the national databases utilised. Firstly, as mentioned in the methods section, ANZACS-QI does not collect information regarding AF and therefore identifying this subgroup had challenges. We chose to identify AF based on prior discharge coding of AF within the National Minimum Dataset. The accuracy of this coding is not clear, and patients with AF may have been missed, and we
cannot be certain that all patients coded as having AF did in fact have this arrhythmia. Secondly, the use of national data meant we could only extract information pertaining to prescriptions filled by patients, not what was prescribed to patients. The difference here is potentially a significant one.

Our ability to examine the relationship between treatment strategies and clinical outcomes was limited. While we requested this dataset at the end of 2016, we had not appreciated that the Ministry of Health datasets at that time were only complete until the end of 2015. This meant that almost 500 patients did not have one-year follow-up data available. In addition, the proportion of patients with ACS and AF undergoing PCI was lower than we anticipated (1101 out of 3730, 29%), and this resulted in a final cohort of only 610 patients. While this is large enough to describe national prescription behaviour reasonably it does limit our ability to look at outcomes by treatment. We identified multiple drug regimens with small event numbers that were all restricted to those requiring hospital admission, this has meant that differences in outcomes between therapies are not detectable and lack statistical power.

Finally, we chose to only look at ACS patients managed with PCI and therefore this cohort does not detail the management of ACS patients with AF, managed with medical therapy or CABG. Whilst this does add some limitation to our study, this was a deliberate step to overcome the difficulties of assessing those managed with CABG (CABG increases the risk of new AF occurring post-surgery, has bleeding risk associated with the operation, and it is unclear how commonly DAPT in used post-CABG in New Zealand). Limiting the cohort to those managed with PCI also eliminated the complexities of medically managed patients (e.g. very frail patients who may have contraindications to DAPT/OAC, or those without clear ACS) and ensures that these patients had obstructive coronary disease.
3.5 Conclusion

Through the utilisation of the ANZACS-QI registry we were able to describe prescriptions in a larger cohort of ACS patients with AF. Overall ACS patients with AF filled prescriptions for multiple drug regimens and rates were inconsistent and variable overtime. DAPT was the most common prescription filled in the 12 months post PCI and its use over TT was not driven by stroke risk, nor did it impact mortality. A growing number of patients were considered to be undertreated, filling prescriptions for either no therapy or single antiplatelet therapy. It is therefore evident that no clear treatment strategy was utilised for this patient group. To examine optimal therapy for ACS patients with AF a comprehensive review of clinical evidence is necessary. This is explored in Chapter 4.
4 Systematic literature review

Publication arising from this chapter:

4.1 Introduction

In the previous two chapters we have described the prescription rates for ACS patients with a medical history of AF. On the basis of current guidelines, it may have been reasonable to expect that for the most part, patients at high risk of stroke would be prescribed TT, and those at low risk of stroke or with excessive bleeding risk would receive therapy with DAPT. Instead we observed DAPT to be the most common strategy employed in both the single-centre and national cohorts, with TT was used minimally in the national cohort and not at all in the single-centre. What’s more, the use of these therapies did not appear to be based on assessments of stroke risk (Chapter 2 and 3) or bleeding risk (Chapter 2). We therefore concluded that in these cohorts, no clear treatment strategy was evident for the management of ACS patients with AF.

We have previously discussed the inconsistencies in clinical guidelines with regard to this patient group, particularly the brevity of New Zealand guidelines, and this may account for our observations in New Zealand practice. In addition, there is a lack of RCTs that specifically address therapy for ACS patients with AF, and this has unquestionably impacted guideline quality and clinical practice. However despite this lack of RCTs it may be possible to synthesise any observational studies for this patient group, with a view to establishing best practice. As DAPT and TT are guideline recommended therapies, yet the majority of ACS patients with AF receive DAPT, we set out to compare the safety and efficacy of DAPT and TT for the discharge management of this patient group.

Therefore, the aim of this study was to:

- Systematically review published literature to determine whether DAPT or TT is optimal therapy for ACS patients with AF
4.2 Methods

4.2.1 Search strategy

We electronically searched Medline, Medline pending, EMBASE and Evidence-Based Medicine Reviews (EBMR) databases, using the MeSH terms “atrial fibrillation” AND “acute coronary syndromes” (all fields), “anticoagulants” OR “platelet aggregation inhibitors” (all fields), and the key words “OAC”, “NOAC”, “warfarin”, “apixaban”, “rivaroxaban”, “dabigatran”, “darexaban”, “triple therapy” “dual antiplatelet therapy”, “clopidogrel”, “prasugrel”, “ticagrelor” and “antiplatelet” in all fields. Results were limited to English language and human populations. In addition, the reference lists of pertinent articles were manually screened for eligible articles. We limited the search strategy to results from 1st January 2000 to 31st December 2016.

4.2.2 Inclusion criteria

Studies had to meet all of the following criteria: (1) AF patients with an ACS or CAD undergoing intervention; (2) comparison of DAPT and TT; (3) inclusion of either ischaemic and/or bleeding outcomes. Studies that were based on mixed populations on anticoagulant therapy that were not purely an AF population were excluded. Where more than one study reported on the same patient population only the most recent report was included.

4.2.3 Data extraction

Abstracts were screened to assess eligibility. The full text article was examined for all potentially eligible studies.
4.3 Results

The search strategy identified 1888 titles. After the removal of duplicates 1599 abstracts were screened. A final set of 10 papers met the inclusion criteria (Figure 4-1) and details of these are given in Table 4-1. Where author groups published more than one study from largely the same patient population (Sambola et al\textsuperscript{214,215}, Lamberts et al\textsuperscript{199,216} and Fosbol et al\textsuperscript{217,218}) only the most recent study was included in the current review. There was considerable heterogeneity between studies with respect to outcomes, patient numbers in the DAPT and TT arms (range n=67 to n=5486) and follow-up periods (6 months – 42 months). Of the 10 studies, only Sambola et al (2016)\textsuperscript{214} and Rubboli et al (2014)\textsuperscript{219} were prospective in nature.

The proportion of patients with ACS ranged from 40\% in Suh et al (2014)\textsuperscript{220} to 100\% in Fosbol et al (2013)\textsuperscript{217}. In 6 of the 10 studies the proportion of patients with ACS was higher in the DAPT treatment arm than in the TT arm. Details of paroxysmal, persistent and permanent AF groups could not be determined and in all cases the term AF was used to collectively represent these groups. Allocation to DAPT or TT was at the discretion of the physician in 6 studies and not described in the remaining 4 studies (Table 4-1). When treatment was determined by a physician there were no reports of institutional protocols or schema to assist physician decision making. Nine studies had a follow up duration greater than or equal to 12 months and in these studies there were no statements regarding the duration of either DAPT or TT, or what therapy was adopted once DAPT or TT was discontinued.
Figure 4-1 Flow chart of study selection

ACS = acute coronary syndrome; AF = atrial fibrillation; DAPT = dual antiplatelet therapy; TT = triple therapy.
### Table 4-1 Overview of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Population</th>
<th>Design</th>
<th>Data Source</th>
<th>Groups</th>
<th>Allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sambola et al (2016) 214</td>
<td>12 months</td>
<td>AF + PCI</td>
<td>Prospective</td>
<td>Hospital database</td>
<td>DAPT (n=266)TT (n=319)</td>
<td>Physician allocated</td>
</tr>
<tr>
<td>De Vecchis et al (2016) 221</td>
<td>378 ± 15.9 days</td>
<td>AF + PCI</td>
<td>Retrospective</td>
<td>Hospital database</td>
<td>DAPT (n=19)TT (n=48)</td>
<td>Physician allocated</td>
</tr>
<tr>
<td>Kang et al (2015) 222</td>
<td>20.6 ± 7.4 months</td>
<td>AF + DES</td>
<td>Retrospective</td>
<td>Hospital database</td>
<td>DAPT (n=236)TT (n=131)</td>
<td>Physician allocated</td>
</tr>
<tr>
<td>Mennuni et al (2015) 223</td>
<td>12 months</td>
<td>AF + PCI</td>
<td>Retrospective</td>
<td>Hospital databases</td>
<td>DAPT (n=488)TT (n=371)</td>
<td>Physician allocated</td>
</tr>
<tr>
<td>Rubboli et al (2014) 219</td>
<td>12 months</td>
<td>AF + PCI</td>
<td>Prospective</td>
<td>Hospital databases</td>
<td>DAPT (n=162)TT (n=679)</td>
<td>Physician allocated</td>
</tr>
<tr>
<td>Suh et al (2014) 220</td>
<td>42.0 ± 29.0 months</td>
<td>AF + PCI</td>
<td>Retrospective</td>
<td>Medical centre database</td>
<td>DAPT (n=166)TT (n=37)</td>
<td>Physician allocated</td>
</tr>
<tr>
<td>Fosbol et al (2013) 217</td>
<td>12 months</td>
<td>AF + NSTEMI with PCI</td>
<td>Retrospective</td>
<td>CRUSADE registry and insurance database</td>
<td>DAPT (n=1200)TT (n=448)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lamberts et al (2013) 199</td>
<td>12 months</td>
<td>AF + MI and/or PCI</td>
<td>Retrospective</td>
<td>Not stated</td>
<td>DAPT (n=3590)TT (n=1896)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Ho et al (2013) 224</td>
<td>5.9 ± 5.0 months</td>
<td>AF + PCI</td>
<td>Retrospective</td>
<td>Not stated</td>
<td>DAPT (n=220)TT (n=382)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Maegdefessel et al (2008) 225</td>
<td>16.8 (2-68) months</td>
<td>AF + PCI</td>
<td>Retrospective</td>
<td>Hospital database</td>
<td>DAPT (n=103)TT (n=14)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

Length of follow up is in months ± standard deviation or months (range); AF = atrial fibrillation; DAPT = dual antiplatelet therapy; DES = drug eluding stent; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI – percutaneous coronary intervention; TT = triple therapy.
4.3.1 Composite Ischaemic outcomes

While it was common to report on a composite endpoint, the components of this endpoint differed across the 10 studies. In 7 studies adjusted composite endpoint results were given (Table 4-2). No individual study found a significant difference in composite endpoints between groups, although in 4 of the 7 studies there was a trend towards lower rates on TT (odds ratios ranged from 0.71 to 0.94) 199,217,223,224.

4.3.2 Mortality

While all studies reported unadjusted mortality only 3 studies reported adjusted results for mortality (Table 4-2). In Mennuni et al there was 8.6% 12 month mortality in the DAPT arm compared to a 7.1% rate on TT with an adjusted odds ratio of 0.62, (0.35-1.08). 223. In Lamberts et al the 12 month mortality rates for the DAPT and TT arms were 12% and 4% respectively, with adjusted all-cause mortality reduced with TT (odds ratio 0.61 [0.47-0.77]) 199. Ho et al reported a 6.8% mortality on DAPT compared to 6.5% on TT with an adjusted odds ratio of 0.96 (0.49-1.86) 224. In addition Kang et al reported propensity-score matched results and found a 3% mortality rate in the DAPT group compared to 7% in the TT group 222. In the remaining studies Fosbol et al reported mortality of 13.3% on DAPT versus 12.9% on TT without adjusted results being given 217, Suh et al reported 11.4% mortality on DAPT, with no deaths in the 37 patients treated with TT 220, and Rubboli et al reported 11% mortality rates in both groups 219. Sambola et al reported no difference in mortality with DAPT and TT arms with respect to patients with a CHA2DS2VASc of 1 (5.5% vs. 7.4%, respectively) and those with CHA2DS2VASc of 2 or more (10.6% vs. 9.2%, respectively) 214. DeVecchis et al reported 5 all-cause deaths, 1 in the DAPT group and 4 in the TT group 221 and Maegdefessel et al reported 4 cardiovascular deaths, 3 in the DAPT group and 1 in the TT group 225.
<table>
<thead>
<tr>
<th>Study</th>
<th>DAPT Patients</th>
<th>TT Patients</th>
<th>Composite Endpoint</th>
<th>OR Composite</th>
<th>OR Mortality</th>
<th>OR Stroke</th>
<th>OR Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sambola et al (2016)</td>
<td>N=266, 79% ACS</td>
<td>N=319, 68% ACS</td>
<td>Mortality, MI, stent thrombosis, repeat revascularisation.</td>
<td>1.05 (0.67-1.86)</td>
<td>-</td>
<td>-</td>
<td>2.97 (1.25-7.02)**</td>
</tr>
<tr>
<td>Kang et al (2015)</td>
<td>N=99, 73.7% ACS</td>
<td>N=99, 76.7% ACS</td>
<td>Mortality, MI, repeat revascularisation, stroke</td>
<td>1.57 (0.82-2.99)†</td>
<td>3% DAPT vs 7% TT†</td>
<td>0% DAPT vs 4% TT†</td>
<td>6.8 (1.98-23.6)**†</td>
</tr>
<tr>
<td>Mennuni et al (2015)</td>
<td>N=488, 57% ACS</td>
<td>N=371, 54% ACS</td>
<td>Mortality, MI, stroke</td>
<td>0.77 (0.52-1.14)</td>
<td>0.62 (0.35-1.08)</td>
<td>4.4 (0.45-42.3)</td>
<td>1.79 (1.11-2.89)*</td>
</tr>
<tr>
<td>Rubboli et al (2014)</td>
<td>N=162, 66% ACS</td>
<td>N=679, 54% ACS</td>
<td>Mortality, MI, stent thrombosis, revasc., stroke</td>
<td>1.17 (0.57-2.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fosbol et al (2013)</td>
<td>N=1200, 100% ACS</td>
<td>N=448, 100% ACS</td>
<td>Mortality, MI, stroke</td>
<td>0.94 (0.73-1.21)</td>
<td>-</td>
<td>-</td>
<td>1.29 (0.96-1.74)</td>
</tr>
<tr>
<td>Lamberts et al (2013)</td>
<td>N=3590, 72% ACS</td>
<td>N=1896, 53% ACS</td>
<td>MI, Coronary death</td>
<td>0.83 (0.68-1.0)</td>
<td>0.61 (0.47-0.77)*</td>
<td>0.67 (0.46-0.98)*</td>
<td>2.08 (1.64-2.65)*</td>
</tr>
<tr>
<td>Ho et al (2013)</td>
<td>N=220, 68% ACS</td>
<td>N=382, 71% ACS</td>
<td>Mortality, ischemic stroke, TIA</td>
<td>0.71 (0.37-1.38)</td>
<td>0.96 (0.49-1.86)</td>
<td>1.15 (0.21-6.35)</td>
<td>1.25 (0.6-2.6)‡</td>
</tr>
</tbody>
</table>

Odds ratios (OR) are given relative to DAPT; Statistically significant results are given by * p < 0.05, ** p < 0.01, *** p <0.001. † = results were propensity-score matched, not adjusted; ‡ Bleeding odds ratio was for the subgroup of patients with a CHADS2 score of greater than 2. ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; MI = myocardial infarction; TT = triple therapy.
4.3.3 Stroke

All 10 studies reported unadjusted stroke rates and these are given in Table 4-3. Stroke risk information (using CHADS$_2$\textsuperscript{226} or CHA$_2$DS$_2$VASc$^{155}$) were given in 8 of these studies. In 2 of the studies the TT group had higher stroke risk than the DAPT group (Mennuni et al CHADS$_2$ scores 2.9 vs. 2.5, $p<0.01$\textsuperscript{223}; Ho et al CHADS$_2$ scores 2.6 vs. 2.1, $p<0.001$\textsuperscript{224}), while in 1 the DAPT group had a higher stroke risk (Kang et al, CHADS$_2$ scores 2.06 vs. 1.68, $p=0.003$)\textsuperscript{222}. In the studies by Suh et al\textsuperscript{220}, Rubboli et al\textsuperscript{219} and Fosbol et al\textsuperscript{217} the TT and DAPT groups had no statistical difference in their stroke risk. Lamberts et al\textsuperscript{199} and Sambola et al\textsuperscript{214} did not report statistical comparison of stroke risks between treatment arms, but data given appear similar.

DeVecchis et al did not report stroke risk for the DAPT and TT arms, but reported 1 stroke event (2%) in the 48 patients in the TT arm and no strokes in the 19 patients in the DAPT arm\textsuperscript{221}. Maegdefessel et al also did not report stroke risk, and reported the highest stroke rate in the DAPT arm (8.7%), and reported no stroke in the 14 patients treated with TT\textsuperscript{225}.

In the other 8 studies the stroke rate varied between 0.2 and 5.3%. Of the 7 studies that performed statistical analyses only Sambola et al reported significantly different stroke rates based on unadjusted results, with 5.3% in the DAPT group and 1.7% in the TT group ($p=0.03$)\textsuperscript{214,217,219,220,222-224}.

Three studies presented adjusted results for stroke, with variable findings (Table 4-2). Lamberts et al reported that TT significantly reduced the risk of stroke compared to DAPT (odds ratio 0.67, [0.46-0.98])\textsuperscript{199}. Both Mennuni and Ho reported results favouring DAPT (odds ratio 4.4, [0.45-42.3]\textsuperscript{223} and odds ratio 1.15, [0.21-6.35]\textsuperscript{224} respectively), however neither of these results were statistically significant. In addition, Kang et al presented propensity-score matched stoke results, reporting no strokes in the DAPT group and 4% in the TT group\textsuperscript{222}. 

100
Table 4-3 Unadjusted stroke rates

<table>
<thead>
<tr>
<th>Study</th>
<th>DAPT Patients</th>
<th>DAPT Stroke Risk</th>
<th>DAPT Stroke Rate (%)</th>
<th>TT Patients</th>
<th>TT Stroke Risk</th>
<th>TT Stroke Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sambola et al (2016)</td>
<td>N=266</td>
<td>45% CHA(_2)DS(_2)VASc 2+</td>
<td>5.3*</td>
<td>N=319</td>
<td>56% CHA(_2)DS(_2)VASc 2+</td>
<td>1.7</td>
</tr>
<tr>
<td>DeVecchis et al (2016)</td>
<td>N=19</td>
<td>Not given</td>
<td>0</td>
<td>N=48</td>
<td>Not given</td>
<td>2</td>
</tr>
<tr>
<td>Kang et al (2015)</td>
<td>N=236, 77.4%</td>
<td>Mean CHADS(_2): 1.68*</td>
<td>2.1</td>
<td>N=131, 77.8%</td>
<td>Mean CHADS(_2): 2.06</td>
<td>3</td>
</tr>
<tr>
<td>Mennuni et al (2015)</td>
<td>N=488, 57%</td>
<td>Mean CHADS(_2): 2.5*</td>
<td>0.2</td>
<td>N=371, 54%</td>
<td>Mean CHADS(_2): 2.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Rubboli et al (2014)</td>
<td>N=162, 66%</td>
<td>Mean CHADS(_2): 2.1</td>
<td>4</td>
<td>N=679, 54%</td>
<td>Mean CHADS(_2): 2.3</td>
<td>2</td>
</tr>
<tr>
<td>Suh et al (2014)</td>
<td>N=166, 43%</td>
<td>Mean score: 1.95</td>
<td>3.6</td>
<td>N=37, 33%</td>
<td>Mean score: 1.81</td>
<td>2.7</td>
</tr>
<tr>
<td>Fosbol et al (2013)</td>
<td>N=1200, 100%</td>
<td>Median CHADS(_2)VASc: 4</td>
<td>2.2</td>
<td>N=448, 100%</td>
<td>Median CHADS(_2)VASc: 4</td>
<td>1.6</td>
</tr>
<tr>
<td>Lamberts et al (2013)</td>
<td>N=3590, 72%</td>
<td>90% CHA(_2)DS(_2)VASc 2+</td>
<td>4.2†</td>
<td>N=1896, 53%</td>
<td>90% CHA(_2)DS(_2)VASc 2+</td>
<td>1.8</td>
</tr>
<tr>
<td>Ho et al (2013)</td>
<td>N=220, 68%</td>
<td>Mean CHADS(_2): 2.1*</td>
<td>0.9</td>
<td>N=382, 71%</td>
<td>Mean CHADS(_2): 2.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Maegdefessel et al (2008)</td>
<td>N=103, 88%</td>
<td>Not given</td>
<td>8.7†</td>
<td>N=14, 72%</td>
<td>Not given</td>
<td>0</td>
</tr>
</tbody>
</table>

Statistically significant differences between treatment arms are indicated by * p <0.05. † statistical comparison of stroke rates not performed. ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; TT = triple therapy.
4.3.4 Bleeding

Different definitions of bleeding were used across the 10 studies (Table 4-4), and this resulted in differing rates of bleeding observed from no bleeding to a high of 16.7% bleeding. Bleeding risk, using either HAS-BLED 200 or ATRIA (anaemia, renal disease, age ≥75, prior haemorrhage, hypertension) 152 scores were reported in 7 of the 10 studies. In 5 of these studies there was no statistical difference in bleeding risk between treatment arms 217,219,220,222,223. Lamberts et al 199 and Sambola et al 214 did not perform statistical analysis however bleeding risk appears to be similar in both treatment arms.

Unadjusted bleeding rates were presented in all 10 studies and significant differences were observed in 3. Kang et al reported a 16.7% bleeding rate in the TT group, significantly higher than the 4.6% in the DAPT group 222, and Mennuni et al reported an 11.5% bleeding rate for TT group compared with 6.4% for DAPT 223. Sambola et al 214 also showed higher bleeding in the TT group (8.4%) when compared to the DAPT group (3.1%). Four studies (DeVecchis et al 221, Rubboli et al 219, Suh et al 220 and Ho et al 224) did not find significant differences between bleeding rates while 3 studies (Fosbol et al 217, Lamberts et al 199 and Maegdefessel et al 225) did not perform statistical analyses on unadjusted bleeding rates.

Adjusted bleeding results were presented in 6 studies (Table 4-1) and in 4 of these there was a statistically significant increase in bleeding associated with TT (Sambola et al odds ratio 2.97, [1.25-7.02] 214, Kang et al odds ratio 6.84, [1.98-23.6] 222, Lamberts et al odds ratio 2.08, [1.64-2.65] 199 and Mennuni et al odds ratio 1.79, [1.11-2.89] 223). The other 2 studies reported non-significant increases in bleeding with TT (Fosbol et al odds ratio 1.29, [0.96-1.74] 217, Ho et al odds ratio 1.25, [0.6-2.6]) 224.
<table>
<thead>
<tr>
<th>Study</th>
<th>DAPT Patients</th>
<th>DAPT Bleeding risk</th>
<th>DAPT Bleeding rate (%)</th>
<th>TT Patients</th>
<th>TT Bleeding risk</th>
<th>TT Bleeding rate (%)</th>
<th>Bleeding Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sambola et al (2016)</td>
<td>N=266, 79% ACS</td>
<td>HAS-BLED ≥3, 37%</td>
<td>3.1*</td>
<td>N=319, 68% ACS</td>
<td>HAS-BLED ≥3, 42%</td>
<td>8.4</td>
<td>TIMI Major</td>
</tr>
<tr>
<td>DeVecchis et al (2016)</td>
<td>N=19, 68% ACS</td>
<td>Not given</td>
<td>5.3</td>
<td>N=48, 69% ACS</td>
<td>Not given</td>
<td>8.3</td>
<td>Major bleeding – not defined</td>
</tr>
<tr>
<td>Kang et al (2015)</td>
<td>N=236, 77.4% ACS</td>
<td>HAS-BLED, mean 2.1</td>
<td>4.6*</td>
<td>N=131, 77.8% ACS</td>
<td>HAS-BLED, mean 2.2</td>
<td>16.7</td>
<td>Intracerebral or hemodynamic compromise</td>
</tr>
<tr>
<td>Mennuni et al (2015)</td>
<td>N=488, 57% ACS</td>
<td>HAS-BLED, mean 2.9</td>
<td>6.4*</td>
<td>N=371, 54% ACS</td>
<td>HAS-BLED, mean 2.9</td>
<td>11.5</td>
<td>BARC 2+</td>
</tr>
<tr>
<td>Rubboli et al (2014)</td>
<td>N=162, 66% ACS</td>
<td>HAS-BLED, mean 2.9</td>
<td>12</td>
<td>N=679, 54% ACS</td>
<td>HAS-BLED, mean 2.9</td>
<td>10</td>
<td>BARC 3 &amp; 5</td>
</tr>
<tr>
<td>Suh et al (2014)</td>
<td>N=166, 42% ACS</td>
<td>HAS-BLED, mean 2.0</td>
<td>0.6</td>
<td>N=37, 33% ACS</td>
<td>HAS-BLED, mean 1.9</td>
<td>2.7</td>
<td>Overt bleeding, need for transfusion, intracranial bleeding</td>
</tr>
<tr>
<td>Fosbol et al (2013)</td>
<td>N=1200, 100% ACS</td>
<td>ATRIA, median 3</td>
<td>11.9†</td>
<td>N=448, 100% ACS</td>
<td>ATRIA, median 3</td>
<td>14.4</td>
<td>Bleeding causing hospital admission</td>
</tr>
<tr>
<td>Lamberts et al (2013)</td>
<td>N=3590, 72% ACS</td>
<td>HAS-BLED ≥3, 24.3%</td>
<td>4.6†</td>
<td>N=1896, 53% ACS</td>
<td>HAS-BLED ≥3, 24.3%</td>
<td>6.2</td>
<td>Bleeding causing hospital admission or death</td>
</tr>
<tr>
<td>Ho et al (2013)</td>
<td>N=220, 68% ACS</td>
<td>No bleeding risk score</td>
<td>9.6</td>
<td>N=382, 71% ACS</td>
<td>No bleeding risk score</td>
<td>10.6</td>
<td>Bleeding requiring transfusion</td>
</tr>
<tr>
<td>Maegdefessel et al (2008)</td>
<td>N=103, 89% ACS</td>
<td>No bleeding risk score</td>
<td>1.9†</td>
<td>N=14, 72% ACS</td>
<td>No bleeding risk score</td>
<td>0</td>
<td>Not defined in methods – requiring transfusion stated in results</td>
</tr>
</tbody>
</table>

Statistically significant differences between treatment arms are indicated by * p <0.05. † statistical comparison of stroke rates not performed. ACS = acute coronary syndrome; BARC = Bleeding academic research consortium. TIMI = thrombolysis in myocardial infarction criteria.
4.4 Discussion

The quality of studies identified comparing clinical outcomes for patients with AF and ACS/PCI treated with DAPT or TT was poor. Eight of the ten studies included in this review were retrospective in nature, and none of the studies adequately described the basis of treatment allocation. Only one study was of a pure ACS population, the other nine containing a mix of stable coronary artery disease patients undergoing PCI and ACS patients. There was consistency in the observation that TT was associated with an increase in the rate of bleeding. While the largest study of the ten observed a reduction in stroke and in mortality associated with TT compared to DAPT, this was not a consistent finding.

This systematic review highlights a large gap in current literature. As we know up to 21% of patients with ACS may have concurrent AF, therefore this is a common clinical presentation. In addition, a number of studies have shown that patients with AF have worse clinical outcomes following ACS than those without AF. The absence of robust data on which to base treatment recommendations is therefore a significant concern and is reflected in the quality of guideline publications for this patient group (mostly expert consensus).

The studies included in this review were all observational, mostly retrospective, and some very small. A number of these studies incorporated treatment groups other than DAPT and TT although these have not been discussed here. The original intent of this review had been to limit the studies discussed to pure ACS with AF populations. However, this would have left only the study by Fosbol et al included. The change to a mixed ACS and stable coronary disease inclusion expanded the number of studies included, but at the risk of altering the characteristics of the patient population. Treatment allocation was inadequately described in all studies. While consensus documents suggest stratifying patient by risk to determine treatment regimen, none of the studies included in this review have stated that this was done. The similarity in stroke and bleeding risk scores between the treatment arms in the majority of studies supports this notion.
On the basis of the small number of studies in this systematic review it is evident that bleeding rates are significantly higher in patients treated with TT compared to DAPT. This was demonstrated consistently in the adjusted results, including the two largest studies, Fosbol et al 217 and Lamberts et al 199 with the former particularly pertinent as it was the only study to only include patients with ACS. Greater bleeding in TT groups was also supported in the majority of unadjusted results. There are some limitations that need to be noted here. Bleeding definitions used varied considerably, and the observed bleeding rates varied in part as a consequence of this. However, some of the studies that only included major bleeding reported higher rates of bleeding than others that had broader definitions of bleeding. It is possible that some bleeding was not captured in some of these studies due to the retrospective nature of most of the studies.

The bleeding results reported in this study are consistent with the data from RCTs conducted in ACS populations that have compared TT to DAPT. In ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndromes – Thrombolysis in Myocardial Infarction) patients were randomised to rivaroxaban low dose (2.5mg twice daily) or high dose (5mg twice daily) plus DAPT or DAPT alone 179. This study reported a reduction in cardiovascular and all-cause mortality associated with the low dose of rivaroxaban (but not the higher dose) and an increase in non-CABG related major bleeding but not fatal bleeding in both TT groups. The APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) study examined the addition of apixaban (5mg twice daily) to DAPT. This study was halted prematurely as there was no evidence of a reduction in the composite end point of cardiovascular death, MI or ischaemic stroke associated with TT, and a significant increase in major bleeding was observed in the apixaban group 178. In our own national cohort reported in Chapter 3 event numbers restricted our ability to detect differences between DAPT and TT arms, but despite this we found patients treated with an OAC were more likely to be hospitalised for bleeding events (7.1% vs. 2.2%, p=0.004) with no detectable difference in stroke/TIA rates.

A recent meta-analysis including the two phase III trials APPRIASE-2 and ATLAS ACS2-TIMI 51, and 5 phase II trials in ACS with DAPT and TT arms, reported an increased risk
of bleeding associated with TT (Hazard Ratio 2.34; 2.06-2.66) with a modest reduction in major adverse cardiovascular events (MACE) (HR 0.87;0.80-0.95 )\textsuperscript{232}. A similar association was described in a sub-study of the RE-LY trial, demonstrating that for warfarin and both 110mg and 150mg doses of dabigatran, addition of antiplatelet agents resulted in increased major bleeding \textsuperscript{233}. Furthermore, nationwide registry data from Denmark of 40,812 MI patients showed that risk of bleeding causing hospitalisation increased with the number of antithrombotic drugs used, with those on TT at highest risk (compared to aspirin, DAPT hazard ratio 1.47, [1.28-1.69], TT hazard ratio 4.05, [3.08-5.33]) \textsuperscript{176}. Taking the results from these studies together with the findings in this review, it seems highly likely that TT in AF and ACS patients will result in an increase in clinically important bleeding.

The efficacy of TT was less clear in the studies reviewed here. It might have been expected that the major benefit of TT would be seen in a reduction in the rate of stroke. This is based on meta-analysis of AF studies, showing superiority of warfarin to antiplatelet therapy for the reduction in stroke \textsuperscript{234}. Consistent with this, the largest study included in this review did observe a reduction in stroke associated with TT \textsuperscript{199}. However the second largest study, Fosbol et al reported a 2.2% rate of stroke on DAPT and a 1.6% rate on TT, which were not significantly different in unadjusted analysis. Three other studies reported a trend towards higher stroke rates on TT in adjusted analysis, although in none of these cases was a statistically significant result observed \textsuperscript{222-224}. These results suggest that the advantage of adding warfarin to DAPT for stroke prevention in the context of ACS in AF patients is not clear, but benefit may exist.

It is also unclear that there is a reduction in composite ischaemic endpoints or in mortality associated with TT, although in the case of mortality Lamberts et al did demonstrate a mortality advantage \textsuperscript{199}. Whilst it is conceivable that addition of and OAC to DAPT may reduce mortality related to thromboembolic events \textsuperscript{179}, it is also clear that major bleeding events in patients with ACS are associated with an increase in mortality\textsuperscript{235,236}.

As discussed in the introductory chapter, the ESC is the most prescriptive in its recommendations for the treatment of ACS patients with AF, and includes a structured
algorithm based on stroke risk and bleeding risk to determine the combination of antithrombotic and antiplatelet therapy \cite{184}. The associated ESC NSTEACS guidelines of 2015 \cite{90} presents a simplified version that does recommend TT for all ACS patients with AF undergoing PCI, for 1 month in those with high bleeding risk and 6 months for those with lower bleeding risk, followed by dual therapy (clopidogrel and anticoagulation) out to 12 months. Bleeding risk in this context is defined by HAS-BLED \cite{200}, and while this score has been well validated in AF, it has not been validated in AF and ACS. On the other hand, only the AHA guideline for AF references a CHA\textsubscript{2}DS\textsubscript{2}VASc $\geq$ 2 to indicate TT \cite{106}, whereas the associated NSTEMI and STEMI guidelines do not offer specific detail regarding stroke risk thresholds, and do not reference a bleeding score \cite{88,89}. The studies included in the current review showed similar bleeding scores in both treatment arms suggesting that bleeding risk was not strongly associated with treatment allocation. In three studies there was a higher stroke risk in the TT arm, which may indicate stroke risk was a factor in treatment allocation in at least some cases.

Within the ESC guidelines \cite{90,184} the term OAC is used and refers to either well-controlled warfarin or one of the newer NOACs. It is important to note that all of the studies in this review that used OACs were using a VKA, predominantly warfarin, and it is entirely possible that the use of NOACs would result in a different safety-efficacy ratio. Whilst there is lack of supporting evidence in this context, the superiority of the NOACs over warfarin for stroke prevention in AF patients has been demonstrated \cite{164-166,177} and therefore the ESC suggestion of anticoagulation using these agents may be logical. Current AHA guidelines limit comment to warfarin on the basis that data is lacking for the newer agents \cite{89}.

With regard to DAPT therapy all of the studies in this review are referring to an aspirin and clopidogrel combination. The ESC guidelines advocate the use of aspirin and clopidogrel to constitute DAPT in the context of AF, but not the newer P2Y\textsubscript{12} receptor inhibitors prasugrel and ticagrelor, based on no proven benefit in the AF and ACS population. Both prasugrel and ticagrelor have both been shown to be superior to clopidogrel on the basis of the ACS trials TRITON-TIMI 38 \cite{237} and PLATO \cite{238} respectively. However, these agents were both associated with increased risks of non-CABG related
bleeding compared to clopidogrel. The absence of even observational data describing outcomes in AF and ACS patients treated with the NOACs and antiplatelet agents is striking and further demonstrates the paucity of data to guide clinical decision making in treating this group of patients.

The ongoing MUSICA-2 trial of DAPT (aspirin and clopidogrel) versus TT (aspirin, clopidogrel and VKA) in patients with AF and low to moderate thromboembolic risk undergoing PCI, when completed may provide more guidance regarding optimal pharmacological therapy, however does not include the newer antithrombotic agents, nor directly addresses ACS patients with AF.

This review has focused exclusively on the comparison of DAPT and TT. However, the combination of OAC and a single antiplatelet agent for AF and ACS patients may be important to consider. Lamberts et al included both aspirin and warfarin, and aspirin and clopidogrel treatment arms in their study, and found both resulted in significantly less bleeding than TT, without any difference in rates of stroke. Examining the utility of an oral anticoagulant and a single antiplatelet agent may therefore have merit. This area is now considerably more complex, as the newer NOACs and antiplatelet drugs provide an increased range of possible therapeutic combinations, at a range of dosing options, that adds to the confusion in how best to treat AF patients with ACS.

### 4.4.1 Study limitations

We excluded a number of studies that were based on populations on OAC therapy at the time of ACS event. These studies would have included mostly AF patients, mixed with a smaller proportion of patients with mechanical valves, deep vein thrombosis/pulmonary embolism, or other indications for anticoagulation. Our rationale for this exclusion was that the non-AF patients included have quite a different risk profile, and that many patients with AF and ACS may not have been on an anticoagulant at the time of the ACS. We did choose to include studies that were not in
pure ACS patients, as had we not done so, only one study would have been included in the review.

Meta-analyses were not performed due to heterogeneity of eligible studies and absence of RCTs. As a result, we have not been able to further synthesise our observations with regard to the increased bleeding risks demonstrated with TT. Further, due to the variations in bleeding definitions used across studies, we cannot characterise the increased risk of bleeding on TT with accuracy (e.g. increases in major bleeding, minor bleeding etc.).

Information regarding the duration of either DAPT or TT, or what default therapy was once DAPT or TT was discontinued was inadequately described in all studies; therefore, we were unable to draw inferences about optimal duration of therapy on the basis of our results.

4.5 Conclusions

The existing literature comparing DAPT to TT for this patient group was poor in quality, consisting predominantly of retrospective studies with mixed ACS and PCI patients. There was a lack of detail on treatment allocation, and important differences in the clinical characteristics of DAPT and TT treatment arms were often not accounted for. There was not consistent evidence of reduced stroke or composite ischaemic endpoints associated with TT, however the largest study indicated that TT offered significant reductions in mortality and stroke. Where adjusted results were presented, TT was consistently associated with an increase in bleeding risk. Due to the heterogeneity of bleeding endpoints utilised we remain uncertain as to the characteristics of the increased bleeding seen with TT. It also remains unclear how the increases in bleeding associated with TT are offset by reductions in thromboembolic events or mortality for ACS patients with AF. Therefore, we believe a decision analysis model may provide guidance regarding the thresholds at which TT results in benefit from stroke prevention that will outweigh harm from bleeding. This approached is explored in Chapter 5.
5 Decision analysis model: balancing bleeding risk with stroke prevention on TT
5.1 Introduction

Chapter 4 demonstrated that the evidence base that informs clinicians when managing ACS patients with AF is poor. To date only 10 studies have compared DAPT and TT in pure AF with ACS/PCI populations, and these were mostly retrospective in design. However despite the small number of studies examined in the previous chapter we consistently observed that use of TT in this patient group was associated with increased rates of bleeding, and this has previously been identified as an independent driver of mortality after an ACS event. With regard to stroke prevention with TT, the largest study saw a significant reduction in stroke endpoints on the basis of adjusted results. This was also supported by 6 smaller studies that presented lower stroke rates with TT, however, these were not all statistically significant. To further describe this trade-off between increased bleeding risk and decreased stroke risk with TT, additional investigation is required.

On the basis of clinical guidelines for the management of ACS patients with AF, patients at high risk of stroke are suggested to receive TT; in this context TT is likely to offer protection against stroke that exceeds the increased harm from bleeding, and is therefore beneficial. Conversely, patients at high risk of bleeding are suggested to receive DAPT over TT; in this instance TT would likely result in harm from bleeding that exceeds benefit from stroke prevention, and is therefore harmful. Accurately defining the thresholds to indicate TT use is challenging, and currently there is not consensus across guideline publications regarding the definitions of high risk of stroke and high risk of bleeding as outlined in Chapter 1 of this thesis.

In the absence of RCTs, a decision analysis model may be a useful tool as it provides a theoretical, systematic and transparent approach to clinical decision making. In brief, a decision analysis model utilises quantitative inputs from published literature to construct a decision tree, taking into account the associated probabilities and utilities of possible health outcomes, and in doing so provides a logical framework to compare treatment strategies. Similar challenges have arisen in AF alone populations where the administration of OAC is required for thromboprophylaxis, but also results in excess bleeding that could cause harm. Decision models have been used previously to
determine circumstances that favour OAC therapy for AF patients requiring protection
from stroke who are at risk of intracranial haemorrhage \(^{243}\), upper gastrointestinal
bleeding \(^{244}\) or those at risk of bleeding from falls \(^{245}\). Decision models have also been
used to determine the tipping point between different antithrombotic therapies for AF
patients by taking into account both risk of stroke and risk of bleeding \(^{246,247}\).

Using a similar approach to that seen in AF cohorts we set out to construct a decision
analysis model to examine the use of TT and DAPT in ACS patients with AF. Our model
was constructed to identify the theoretical tipping points at which TT would result in
benefit from stroke protection that outweighed the harm from excess bleeding. Health
outcomes were evaluated with regard to quality-adjusted life years (QALY) and risk of
mortality.

Therefore, the aims of this study were:

- To construct a decision analysis model to evaluate bleeding and stroke risk in ACS
  patients with AF
- To determine likely thresholds of stroke risk at which the benefits of TT may
  exceed harm from bleeding
5.2 Methods

The utilisation of a decision analysis model is a theoretical approach to evaluating the potential outcomes of clinical decisions and therefore must be custom built. We constructed this decision analysis model utilising LabVIEW 8.5 software (National Instruments, Austin, Texas). The decision analysis model was used to determine the tipping point, the stroke risk threshold at which the benefit of TT exceeds harm from bleeding, for ACS patients with AF in the 12 months post ACS event. We explored these tipping points at varying levels of stroke and haemorrhagic risk. A schematic of the decision analysis model can be seen in Figure 5-1. The decision model was run in the first instance to represent a base case scenario. Following this the model was run an additional two times, once for worst case stroke distribution and once for worst case stroke utilities, as found in published literature respectively.
Figure 5-1 Schematic of the decision analysis model
Flow diagram of the components of the decision model. Bleeding events categorised as fatal, non-fatal intracranial, major and minor. Stroke events categorised as fatal, major disability, moderate disability and minor disability. Model outputs were evaluated with regard to total quality adjusted life years (QALYs) and total mortality for both stroke and bleeding events.
5.2.1 Baseline conditions

Baseline conditions for the model were a patient’s one-year risk of bleeding and one-year risk of stroke. For both conditions level of risk was determined from published literature with respect to DAPT. Defining bleeding rates in ACS populations is difficult, largely due to the heterogeneity of bleeding definitions available and the challenges of accurately recording low acuity bleeding events. Therefore literature that reports any bleeding rates in ACS cohorts are likely to offer greater accuracy (see the CURE and APPRAISE-2 trials in Table 5-1). On the basis of this we entered one-year risk of bleeding (on DAPT) into the model at 7.5%. In addition, we modelled bleeding rates both lower and higher than this, at 5% and 10%, to cover a range of probable circumstances (Table 5-1).

Table 5-1 Bleeding rates of patients from contemporary ACS trials

<table>
<thead>
<tr>
<th>ACS Trial</th>
<th>Bleeding definition</th>
<th>Total rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE 83</td>
<td>Any bleeding</td>
<td>6.8%</td>
</tr>
<tr>
<td>PCI-CURE 84</td>
<td>Study criteria: Major bleeding (incl. blood transfusion) Minor bleeding</td>
<td>7.4%*</td>
</tr>
<tr>
<td>TRITON TIMI-38 237</td>
<td>TIMI major and minor bleeding</td>
<td>4%†</td>
</tr>
<tr>
<td>PLATO 238</td>
<td>TIMI major or minor bleeding</td>
<td>10.1%‡</td>
</tr>
<tr>
<td>ATLAS ACS 2-TIMI 51 179</td>
<td>TIMI major or minor bleeding</td>
<td>6.3%‡</td>
</tr>
<tr>
<td>APPRAISE -2 178</td>
<td>Any bleeding</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

* Indicates bleeding rates from DAPT arm only. †Bleeding rates do not include lower acuity events (e.g. TIMI minimal or similar) as indicated by bleeding definitions presented.
One-year risk of stroke (on DAPT) was entered into the model at 2.2%, 3.2%, 4.0%, 6.7% and 9.8% and these values equate to the annual risk of stroke for CHA\textsubscript{2}DS\textsubscript{2}VASc scores 2 through to 6\textsuperscript{209}. The CHA\textsubscript{2}DS\textsubscript{2}VASc risk stratification tool was originally derived from non-anticoagulated AF patients, and therefore the risk percentages are not strictly transferrable to annual stroke risk on DAPT, given antiplatelet medication will provide a level of protection against stroke. The consequence of using CHA\textsubscript{2}DS\textsubscript{2}VASc rates as a surrogate for risk of stroke on DAPT, is that the model will overestimate the risk of stroke for any given CHA\textsubscript{2}DS\textsubscript{2}VASc score in this study. As benefit from TT is driven by stroke risk this was a deliberate step to ensure TT was not at a disadvantage in the model. For ease of interpretation, when the condition one-year risk of stroke is mentioned hereafter it is most commonly referred to by its corresponding CHA\textsubscript{2}DS\textsubscript{2}VASc score.

### 5.2.2 Adjustment to baseline conditions by therapy

Baseline conditions were adjusted on the basis of treatment strategy. One-year risk of bleeding was unadjusted in the DAPT arm of the model, but increased in the TT arm. When bleeding rates for TT and DAPT are compared, most studies reports significant increases in bleeding on TT; the strongest evidence of this has emerged from RCTs of ACS patients (Table 5-2). Taking this in account, bleeding on TT was entered into the model at two values, relative risks of 2 and 2.5 fold that of DAPT.

Similarly, one-year risk of stroke was unadjusted in the DAPT arm of the model, but decreased in the TT arm, representing increased stroke protection from TT. Estimating the benefit TT offers over DAPT with regard to stroke protection was more challenging as overall there is less literature available to quantify this. The APPRAISE-2 and ATLAS ACS 2-TIMI 51 RCTs did not demonstrate significant reductions in ischaemic stroke with TT, however these were cohorts of ACS patients, and not ACS patients with AF who by comparison have increased stroke risk. The observational study of 12,165 AF patients with MI/PCI, conducted by Lamberts et al, found TT significantly reduced ischaemic stroke when compared to DAPT, reporting an odds ratio of 0.67 (0.46-0.98) (Table 5-2); to date this is the best evidence available for stroke prevention in AF patient with ACS.
Overall there is less certainty as to the level of protection TT offers over DAPT with regard to protection from ischemic stroke. Therefore we modelled varying degrees of protection with TT in the form of odds ratios (0.65, 0.7, 0.75, and 0.8). An odds ratio of 0.65 represented TT at its most protective, and an odds ratio of 0.8 represented TT at its least protective.

Table 5-2 Summary of TT versus DAPT studies examining stroke and bleeding endpoints

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>RR of bleeding with TT</th>
<th>OR of ischaemic stroke with TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPRAISE -2 178</td>
<td>Randomised control trial: ACS cohort</td>
<td>2.59 (1.5-4.46)*</td>
<td>0.68 (0.4-1.15)</td>
</tr>
<tr>
<td>ATLAS ACS 2-TIMI 51</td>
<td>Randomised control trial: ACS cohort</td>
<td>3.96 (2.46-6.38)*</td>
<td>0.97 (0.64-1.47)</td>
</tr>
<tr>
<td>Lamberts et al 199</td>
<td>Observational registry data: AF patients with MI/PCI</td>
<td>2.08 (1.64-2.65)*</td>
<td>0.67 (0.46-0.98)*</td>
</tr>
</tbody>
</table>

Information obtained from these studies pertains to DAPT in the form of aspirin and clopidogrel, and TT in the form of aspirin, clopidogrel and OAC (VKA or NOAC). * indicates statistical significance, p<0.05. MI= myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RR = relative risk.
5.2.3 Distribution of events by severity

With the rates of stroke and bleeding established for each treatment arm, the distribution of events by severity were calculated. Bleeding events were defined using the TIMI criteria as fatal bleeding, non-fatal intracranial bleeding, major bleeding and minor bleeding, and all were non-CABG related. Bleeding event distribution for the base case was taken from a cost-effectiveness analysis of randomised trials pertaining to ACS patients on DAPT (Table 5-3).

Stroke events were defined using the modified Rankin score (mR) and stratified as fatal (mR 6), major disability (mR 5), moderate disability (mR 3-4) and minor disability (mR 0-2). For the base case, the distribution of stroke events was taken from a cost-effectiveness analysis of randomised trial data regarding thromboprophylaxis in over 23,000 AF patients (ARISTOTLE and AVERRORES [Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment] cohorts) (Table 5-3).

5.2.4 QALY weighting (utility) by severity

Each event was then allocated a corresponding QALY weighting, also known as a utility measure. A utility of zero equates to death, and a utility of 1 equates to perfect health. The utility measures for bleeding events were taken from the same cost-effectiveness analysis that bleeding distribution was sourced from; these utilities in turn were sourced from multiple previous ACS decision models. For the base case, stroke utilities were taken from the same cost-effectiveness analysis that stroke distribution was taken from, these utilities originated from the EQ-5D health assessment tool which is a standardised measure of quality of life (Table 5-3).
### Table 5-3 Model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
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<th>QALY weight (utility)</th>
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<td></td>
<td></td>
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<td>Worse case</td>
<td>Base case</td>
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<tr>
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<td></td>
<td>0.11</td>
<td>0.232</td>
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<td>Major disability</td>
<td></td>
<td>0.15</td>
<td>0.219</td>
<td>0.5141</td>
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<tr>
<td>Moderate disability</td>
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<td>Reference</td>
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<td><strong>Bleeding</strong></td>
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<tr>
<td>Fatal bleeding</td>
<td></td>
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<td></td>
<td>-</td>
</tr>
<tr>
<td>Non-fatal intracranial bleeding</td>
<td></td>
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<td>0.96</td>
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**Annual risk of stroke according to CHA2DS2-VASc score**

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Risk</th>
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<tr>
<td>1:</td>
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<tr>
<td>3:</td>
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<td>4:</td>
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<tr>
<td>5:</td>
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<td>6:</td>
<td>9.8%</td>
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<tr>
<td>8:</td>
<td>6.7%</td>
</tr>
<tr>
<td>9:</td>
<td>15.2%</td>
</tr>
</tbody>
</table>
5.2.5 Model outputs

The final step in the decision model was to generate model outputs on the basis of the above-mentioned stroke and bleeding event rates, distributions and utilities. For each set of input parameters the model was iterated 1000 times to generate the model outputs in the form of total QALY or total mortality measures.

Total QALY outputs were calculated for each treatment arm and took into account all stroke events (fatal, major, moderate and minor) and all bleeding events (fatal, intracranial and major). We explored this for the range of baseline bleeding and stroke risks, across all adjustment by therapy parameters, to determine the tipping points. Under each combination of variables the therapy, DAPT or TT, which maximised QALY was determined as the treatment of choice.

Mortality outputs were fatal bleeding risk and fatal stroke risk. All models for mortality were generated using a 7.5% one-year rate of bleeding, and base case distributions and utilities. The therapy with the lowest mortality risk was selected as treatment of choice. Benefit was calculated as the absolute difference when compared to the higher risk therapy. In addition to this, pooled mortality risk was calculated by combining fatal bleeding risk and fatal stroke risk for each treatment arm.

5.2.6 Modifications to stroke distribution and utility

After the base case scenario the decision analysis model was run an additional two times, to test TT under a set of parameters where it had potential to be most useful. The second run of the model substituted in worst case stroke distribution as found in published literature, and this was identified in a cost-effectiveness analysis of DAPT for stroke prevention in AF patients\(^{254}\), and was based on the ACTIVE-A (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events–A) trial\(^{256}\). Compared to the base case this change in parameters saw an increase in strokes that were fatal or resulted in major disability (Table 5-1). The third run of the model returned stroke event distribution back to base case settings, but substituted in worst case stroke utilities,
which were found in a utility elicitation study where AF patients were interviewed about
their quality of life. This change to parameters saw the utility of major and moderate
disability strokes decrease, however the utility of stroke with minor disability remained
the same, as per the base case (Table 5-3).

5.2.7 Model assumptions

Firstly, DAPT either alone or as part of TT, is the recommended preventative measure
for secondary cardiovascular ischaemic events (e.g. MI, stent thrombosis). On
consideration of TT versus DAPT literature, the model assumes that the addition of OAC
to DAPT to form TT is dependent on stroke/bleeding consequences, but independent of
secondary cardiovascular ischaemic events; predominantly there are no differences in
secondary cardiovascular ischaemic events when TT and DAPT are compared
and therefore these events were not included in the model.

Secondly, patient age was not entered into the model. As the clinical dilemma in
question pertains to the first 12 months post ACS event, the consequence of the model
does not extend beyond this time frame; the assumption being both arms are equal
after 12 months and return to routine therapy.

Thirdly, for simplicity the model assumed that all stroke and bleeding events occurred
at the same time, essentially on day one post index event. This is because the inputs for
risk of stroke and risk of bleeding were not modified to account for changes in risk over
the 12 month period. For similar reasons the model also assumed no transition between
health states; in reality a patient is likely to have medication changes should they
experience either a stroke or bleeding complication within the 12 months post ACS and
it is unlikely that these circumstances could be replicated in a model with certainty.

Lastly, a utility for minor bleeding was not entered into the model as the consequences
of these events are transient and near negligible.
5.3 Results

5.3.1 Total QALY – base case

The results from the base case model can be seen in Table 5-4 and this iteration takes into account all events (stroke: fatal, major, moderate and minor; bleeding: fatal, intracranial and major). The treatment which maximise QALY for each set of conditions is displayed. Under all conditions for patients with a CHA\(_2\)DS\(_2\)VASc score of 2 or less, treatment with DAPT is preferred over TT. The implication at this level is that TT results in bleeding harm that exceeds benefit from stroke protection. On the other hand, when stroke risk increases to a CHA\(_2\)DS\(_2\)VASc score of 6, under all conditions treatment with TT is preferred. In this instance TT results in benefit from stroke protection that exceeds harm from bleeding. The tipping point at which benefit from TT outweighs the associated harm lies between the CHA\(_2\)DS\(_2\)VASc scores of 2 and 6, and depends upon the risk parameters applied.

When we consider the 7.5% one-year risk of bleeding we observe that all patients with a CHA\(_2\)DS\(_2\)VASc score of 3 have QALY maximised with DAPT. For these patients the tipping point in favour of TT occurs at a CHA\(_2\)DS\(_2\)VASc score of 4 at a minimum, if not a CHA\(_2\)DS\(_2\)VASc score of 5 and less often 6. However if one-year bleeding risk is lower at 5% the tipping point in favour of TT also lowers and occurs most commonly at CHA\(_2\)DS\(_2\)VASc scores 3-4. Where one-year bleeding risk is higher at 10%, we see a clear indication that for all conditions, patients with CHA\(_2\)DS\(_2\)VASc scores of 4 have QALY maximised with DAPT. The increased annual risk of bleeding seen here has resulted in bleeding harm from TT that exceeds stroke protection until at least CHA\(_2\)DS\(_2\)VASc 5 and sometimes 6.
### Table 5-4 Base case total QALY outputs

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc</th>
<th>TT Stroke OR</th>
<th>TT bleeding relative risk = 2</th>
<th>TT bleeding relative risk = 2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.65 0.7 0.75 0.8</td>
<td>0.65 0.7 0.75 0.8</td>
<td>0.65 0.7 0.75 0.8</td>
</tr>
</tbody>
</table>

#### 5% One-year bleeding risk

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc</th>
<th>TT Stroke OR</th>
<th>TT bleeding relative risk = 2</th>
<th>TT bleeding relative risk = 2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>DAPT DAPT DAPT DAPT</td>
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<td>DAPT DAPT DAPT DAPT</td>
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<tr>
<td>3</td>
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<td>DAPT DAPT DAPT DAPT</td>
</tr>
<tr>
<td>4</td>
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<td>TT TT DAPT DAPT</td>
<td>TT TT DAPT DAPT</td>
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<tr>
<td>5</td>
<td>TT TT TT TT</td>
<td>TT TT TT TT</td>
<td>TT TT TT TT</td>
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<tr>
<td>6</td>
<td>TT TT TT TT</td>
<td>TT TT TT TT</td>
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</table>

#### 7.5% One-year bleeding risk

<table>
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<th>TT bleeding relative risk = 2</th>
<th>TT bleeding relative risk = 2.5</th>
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<tbody>
<tr>
<td>1</td>
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#### 10% One-year bleeding risk

<table>
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<th>TT bleeding relative risk = 2.5</th>
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<tr>
<td>6</td>
<td>TT TT TT TT</td>
<td>TT TT TT TT</td>
<td>TT TT TT TT</td>
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</table>

DAPT = dual antiplatelet therapy; OR = odds ratio; TT = triple therapy.
5.3.2 Total QALY – worst case stroke distribution

The decision analysis model was run a second time according to worst case stroke distributions as found in published literature. The proportion of fatal and major strokes were increased to 23.2% and 21.9% respectively, while moderate and minor stroke proportions decreased to 21.0% and 33.9% respectively. The outcomes from this model can be seen in Table 5-5. Despite large changes in the rate of fatal and major strokes there was little change in treatment recommendations when compared to the base case scenario. All changes (white boxes) were in favour of TT where DAPT had been previously.

In only one circumstance did a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 2 result in benefit from TT that exceeded harm, and that was when all variables assumed TT to be at its most favourable, with a one-year bleeding risk of 5%, the lowest relative risk of bleeding lowest (relative risk 2) and the greatest stroke protection (odds ratio 0.65). For all other conditions a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 2 resulted in DAPT as the preferred therapy. Consistent with the base case, under every set of conditions a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 6 resulted in benefit from TT. Although the distribution of stroke is at its worse in this model, we have once again observed that for TT, the tipping point to indicate stroke prevention benefit that exceeds harm from excess bleeding, occurs around a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 3-5.
Table 5-5 Total QALY model outputs - worst case stroke distribution

<table>
<thead>
<tr>
<th>TT Stroke OR</th>
<th>0.65</th>
<th>0.7</th>
<th>0.75</th>
<th>0.8</th>
<th>0.65</th>
<th>0.7</th>
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One-year bleeding risk

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</tbody>
</table>

DAPT = dual antiplatelet therapy; OR = odds ratio; TT = triple therapy. White boxes indicate a change from the base case as seen in Table 5-4.
5.3.3 Total QALY – worst case stroke utilities

The third iteration of the model was run using worse case stroke utilities. This saw a large reduction in major stroke utility (from 0.51 to 0.11) and moderate stroke utility (from 0.56 to 0.39), while minor stroke utility remained constant (0.62). The results from this can be seen in Table 5-6. With the post-stroke quality of life utilities greatly reduced there were moderate changes in therapeutic recommendations (white boxes), all in favour of TT over DAPT when compared to the base case.

On the basis of 7.5% one-year bleeding risk, the tipping points to indicate TT occurred most commonly at scores of CHA₂DS₂VASc 3-5, where in the base case the tipping points were most commonly higher at CHA₂DS₂VASc 4-6. However, consistent with the base case, a CHA₂DS₂VASc of 2 or less results in DAPT still being preferable. If one-year bleeding risk increased to 10% the tipping points alter moderately, with a CHA₂DS₂VASc score of 5 for the most part necessary to favour TT, and in one circumstance a CHA₂DS₂VASc of 4 resulted in TT (when TT offered greatest stroke protection with an odds ratio of 0.65). When we consider the lowest one-year risk of bleeding, 5%, we see that treatment with TT is recommended more so. For all CHA₂DS₂VASc scores of 1, DAPT is the preferred therapy however, benefit from TT exceeds harm for a range of circumstances at CHA₂DS₂VASc 2, 3 and most of CHA₂DS₂VASc 4.
Table 5-6 Total QALY model outputs - worst case stroke utilities

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>TT Stroke OR</th>
<th>0.65</th>
<th>0.7</th>
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DAPT = dual antiplatelet therapy; OR = odds ratio; TT = triple therapy. White boxes indicate a change from the base case as seen in Table 5-4.
5.3.4 Mortality

Probabilities of stroke mortality and bleeding mortality were generated from the decision model using base case parameters and a 7.5% rate of one-year bleeding. Table 5-7 displays probabilities of fatal stroke and fatal bleeding. When mortality from stroke alone is considered, we observe that with increasing CHA$_2$DS$_2$VASc scores, the associated stroke mortality increases also. Across the range of risk reductions associated with TT (odds ratios 0.65-0.8) there is a proportional decrease in stroke mortality compared to DAPT, but the absolute reduction in stroke mortality from TT was greatest at CHA$_2$DS$_2$VASc 6 (Table 5-7). In this model, bleeding risk was held constant and the relative risk of bleeding associated with TT was modelled; we see this reflected in mortality outputs where fatal bleeding remains constant on DAPT, and is 2 or 2.5 times higher in the respective TT arms (Table 5-7).

Figure 5-2 displays preferential therapy with respect to fatal bleeding risk, fatal stroke risk and combined mortality risk for each CHA$_2$DS$_2$VASc score. These outputs were generated under base case conditions, and with TT offering greatest protection from stroke (odds ratio 0.65) and lowest relative risk of bleeding lowest (relative risk 2). When absolute differences were considered, bleeding mortality risk favours treatment with DAPT for each CHA$_2$DS$_2$VASc score. Stroke mortality risk favours TT for every CHA$_2$DS$_2$VASc score and absolute differences increases as stroke risk increases; at CHA$_2$DS$_2$VASc 2 the absolute difference favours TT by 0.065% and increases to 0.302% at CHA$_2$DS$_2$VASc 6. With respect to combined mortality, DAPT is the preferred treatment from CHA$_2$DS$_2$VASc 2 to 5, and at CHA$_2$DS$_2$VASc 6 combined mortality tips to favour TT. Numerically, at CHA$_2$DS$_2$VASc 2 combined mortality risk favours DAPT by 0.16% and this diminishes to 0.019% at CHA$_2$DS$_2$VASc 5. At CHA$_2$DS$_2$VASc 6 overall mortality favours TT by 0.077%.
### Table 5-7 Mortality outputs

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<th>Bleeding Mortality (%)</th>
<th>Stroke Mortality (%)</th>
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DAPT = dual antiplatelet therapy; OR = odds ratio; TT = triple therapy.
Chance of mortality is presented as the absolute difference in mortality risk (%) when compared to the higher risk therapy. The light blue bars represent the therapy that is preferred when risk of fatal bleeding and risk of fatal stroke are considered separately. The dark blue bars represents the therapy that is favoured when risk of fatal bleeding and risk of fatal stroke are considered together. As stroke risk (CHA$_2$DS$_2$VASc) increases overall favour with DAPT diminishes until CHA$_2$DS$_2$VASc 6 where combined mortality tips to favour TT.
When the risk of mortality from bleeding or stroke was pooled we found that DAPT generated less mortality risk than TT for CHA$_2$DS$_2$VASc scores 2 to 5 (Figure 5-3). At CHA$_2$DS$_2$VASc 2, 3 and 4 there is a clear delineation between DAPT and TT with respect to pooled mortality risk (0.41% vs. 0.59%, 0.5% vs. 0.65% and 0.58% vs. 0.71%, respectively). At CHA$_2$DS$_2$VASc 5 pooled mortality risk begins to converge with DAPT still carrying less pooled mortality risk (0.81% vs. 0.88%). At CHA$_2$DS$_2$VASc 6, pooled mortality risk was comparable between the two treatments however, at this level TT generated slightly less risk (1.075% vs. 1.08%) and was therefore the tipping point between DAPT and TT.
Figure 5-3 Pooled fatal bleeding and fatal stroke mortality risk

Plots represent the pooled risk of death from bleeding or stroke at each CHA\textsubscript{2}DS\textsubscript{2}VASc score. DAPT carries a lower pooled annual mortality risk for CHA\textsubscript{2}DS\textsubscript{2}VASc scores 2 through 5, and at CHA\textsubscript{2}DS\textsubscript{2}VASc 6 favour tips to TT.
5.4 Discussion

This study was designed to determine the likely tipping points at which treatment with TT resulted in benefit from stroke protection that outweighed harm from bleeding. When total QALY was considered we found the tipping point to be higher than a CHA$_2$DS$_2$VASc score of 2, and lower than a CHA$_2$DS$_2$VASc score of 6, and was dependent upon the risk parameters applied. When the model was repeated with worst case stroke parameters the results only moderately changed. When we assumed lower one-year bleeding risk and worst case stroke parameters, on occasion a CHA$_2$DS$_2$VASc score 2 was the tipping point to indicate TT. However under most conditions excess bleeding with TT will cause more harm than benefit until stroke risk is higher; somewhere in the vicinity of CHA$_2$DS$_2$VASc score 3, 4 and 5.

The quality of model inputs sourced from available literature directly impacts the quality of model outputs. The distribution and utility of bleeding events were derived from a cost-effectiveness analysis of patients on DAPT, which was centred on the all-important ACS trials, CURE 83, TRITON-TIMI 38 237, and PLATO 238; we consider these ACS trials to be high-quality, large-scale and contemporary and therefore a reliable source of information for bleeding in our model. For the base case bleeding on DAPT was estimated at 7.5% per annum and this equated to a fatal bleeding rate of 0.225% per annum and an intracranial bleeding rate of 0.225%. When compared to the above mentioned DAPT trials we see that our distribution of fatal bleeding and intracranial haemorrhage (ICH) is not dissimilar (CURE: fatal bleeding 0.2%, ICH 0.1%; TRITON-TIMI 38: fatal bleeding 0.1-0.4%, ICH 0.3%; PLATO: fatal bleeding 0.3%, ICH 0.2-0.3%). The 7.5% annual bleeding rate also generated a non-CABG TIMI major bleeding event rate of 3.75% in our model and although there was slightly less consistency between this and DAPT trials, rates were not largely different (CURE: 2.7-3.7%; TRITON-TIMI 38: 1.8-2.4%; PLATO: 2.2-2.8%). Overall, we consider the 7.5% annual bleeding rate entered into the model to be a reasonable proxy, and with the addition of the low bleeding risk (5%) and higher bleeding risk (10%) iterations, an accurate estimate of real-world conditions is likely represented within our model.
The increased risk of bleeding on TT compared to DAPT is large and consistently recorded throughout published literature. The APPRAISE-2 \textsuperscript{178} and ATLAS ACS 2-TIMI 51 \textsuperscript{179} trials mentioned above resulted in significantly more TIMI major bleeding with TT (hazard ratios 2.59 [1.5-4.46] and 3.96 [2.46-6.38] respectively). In addition, multiple observational studies of AF patients with ACS/PCI demonstrate increases in bleeding with TT over DAPT with statistically significant odds ratios ranging from 1.79-2.97 \textsuperscript{199,214,223}. We entered the relative risk of bleeding with TT to be 2-2.5 fold that of DAPT and it is possible that this may be a conservative estimate, and by extending this RR this would have disadvantage TT more so.

In estimating stroke parameters, the distribution and utilities were based on predominant randomised control trials of therapy for AF, namely ARISTOTLE \textsuperscript{165}, AVERROES \textsuperscript{252} and ACTIVE-A \textsuperscript{256}. Research of this calibre does not yet exist for ACS patients with AF, but the use of this quality AF data as a surrogate does provide satisfactory confidence in the stroke inputs we utilised.

Estimating the degree of stroke protection from TT compared to DAPT was more challenging. The RCTs APPRAISE-2 \textsuperscript{178} and ATLAS ACS 2-TIMI 51 \textsuperscript{179} added NOAC therapy to standard ACS management (80\% DAPT and 93\% DAPT, respectively) and neither study found TT to significantly reduce ischaemic stroke (APPRAISE-2: odds ratio 0.68, [0.40-1.15]; ATLAS ACS 2-TIMI 51: odds ratio 0.97, [0.64-1.14]). However, it is important to note that these studies were of ACS patients that did not necessarily have significant risk factors for stroke. Beyond this we considered lesser-quality observational studies of AF patients with PCI and/or ACS. The largest was a study of over 12,000 AF patients with ACS/PCI which reported TT significantly increased stroke protection over DAPT (odds ratio 0.67, [0.46-0.98]) \textsuperscript{199}. Another two studies showed benefit from TT with odds ratios of 0.71 and 0.76 and however these were unadjusted and neither reached statistically significance \textsuperscript{217,220}. On the basis of the ACTIVE-W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) we also know that warfarin alone is superior to DAPT for protection against ischaemic stroke in AF patients (without ACS) (odds ratio 0.46, [0.32-0.66]) \textsuperscript{198}, and this may provide a signal towards the TT-DAPT dynamic for stroke protection.
As we were less certain about the stroke protection received with TT we ran the model with varying degrees of protection when compared to DAPT, with odds ratios ranging from 0.65-0.8; how accurate this is remains unknown due to the quality of the source literature. This variable has impacted largely on the outputs of the model, and contributes greatly to the lack precision with regard to tipping points. Had we more confidence in the degree of stroke prevention with TT, our model outputs may have been more exact in defining thresholds where benefit from TT exceeds harm. However despite these challenges it remains evident that stroke protection from TT is relatively small compared to the increased risk of bleeding that accompanies this therapy, and hence the tipping points for the most part exceed a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 2.

This model was designed to examine the benefit-harm ratio for 12 months after ACS however long term implications also warrant discussion. We may have inadvertently introduced a bias into our model on the basis that the long term effects of bleeding events are in general terms less permanent than those of stroke events. With this in mind it is important to consider the mortality outputs, as by definition fatal endpoints have zero utility and therefore no ongoing consequence. Under base case parameters we observed that TT consistently resulted in more harm from fatal bleeding, than benefit from fatal stroke prevention, for all CHA\textsubscript{2}DS\textsubscript{2}VASc scores 2 to 5. Only at a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 6 did DAPT result in greater harm from mortality, and therefore this was the tipping point to indicate treatment with TT. Therefore, irrespective of any potential long term bias the message is consistent; TT results in excess harm from bleeding that is greater than the benefit of reduced stroke until higher CHA\textsubscript{2}DS\textsubscript{2}VASc scores.

On the basis of our results the model indicates that as CHA\textsubscript{2}DS\textsubscript{2}VASc scores increase, TT is likely to become a better treatment option for ACS patients with AF. However, neither the single-centre study (Chapter 2) nor the ANZACS-QI study (Chapter 3) demonstrated that elevated CHA\textsubscript{2}DS\textsubscript{2}VASc scores were strongly influencing clinician use of TT. Across both the single-centre and ANZACS-QI studies TT use was low, not only for patients with lower CHA\textsubscript{2}DS\textsubscript{2}VASc scores where the model indicates this is appropriate, but for all
CHA\textsubscript{2}DS\textsubscript{2}VASc scores, including those at very high risk of stroke who would benefit from TT.

The results of this model, taken together with the TT prescription rates outlined above, highlight the need for further prospective work examining the use of TT in ACS patients with AF. As we have covered in previous chapters there is inconsistency across clinical guidelines as to the definition of *high risk of stroke*, and therefore inconsistency as to when TT is indicated. The New Zealand and American guidelines do not define a threshold however the ESC suggest CHA\textsubscript{2}DS\textsubscript{2}VASc score of 1, the Australian guidelines suggest a CHA\textsubscript{2}DS\textsubscript{2}VASc ≥2, and Canadian Cardiac Society uses a threshold akin to CHA\textsubscript{2}DS\textsubscript{2}VASc 2 (CHADS\textsubscript{2} ≥ 1 or age over 65). On the basis of our decision model it is evident that despite the discrepancies between guidelines, in all instances the TT threshold is likely too low. Whilst this model lacks precision in being able to define an exact threshold to indicate benefit from TT, it does provide valuable hypothesis generating information, and indicates that future RCTs would be well place to test a TT threshold around CHA\textsubscript{2}DS\textsubscript{2}VASc scores 3 -5.

### 5.4.1 Model assumptions

In the construction of this model we implemented deliberate assumptions to ensure TT was not disadvantaged when compared to DAPT. Firstly, we used absolute CHA\textsubscript{2}DS\textsubscript{2}VASc stroke rates as a surrogate for annual stroke risk on DAPT. In doing so, this did not take into account any thromboprophylaxis as a result from DAPT, thereby enhancing the relative stroke protection from TT. Secondly, we may have been conservative with our estimate of the relative risk of bleeding on TT. Lastly, we ran the model additional times to implement the worst case stroke rate distribution and worst case stroke utilities, in effect to examine scenarios where TT would be most beneficial. Whilst doing this made some adjustments to the model outputs, the overall message remained constant- that the tipping point between DAPT and TT did not occur until higher CHA\textsubscript{2}DS\textsubscript{2}VASc scores. We did not perform worst case bleeding rates and utilities for bleeding as this would have only favoured DAPT more so.
Another major assumption within the model is that DAPT and TT treatment strategies are neutral with regard to recurrent ischaemic events in the 12 months post ACS event. This assumption was driven largely by the fact that both arms receive DAPT, the standard of care for secondary prevention, however, it could be argued that TT may provide a greater level of protection due to the thromboprophylaxis attributed to oral anticoagulation. With regard to disease pathophysiology it is important to note that thrombi formed in the arterial system, like those in ACS are predominantly platelet rich, in contrast to thrombi formed in low pressure systems (e.g. atria) which are fibrin rich. Therefore any efficacy in recurrent ischaemic events attributed to OAC is likely to be inconsistent and variable.

5.4.2 Limitations

Firstly, the construction of this decision model was based largely on inputs from observational studies that were not the quality we would have ideally wanted. Ideally all utilities and probabilities used in this model would have been derived from detail-rich, randomised trials of pure AF with ACS populations however currently no such information is available. Therefore probabilities and utilities were derived from best quality cost-effectiveness analyses and/or utility elicitation studies in either AF populations (for stroke information) or ACS populations (for haemorrhagic information). Whilst we are confident that the inputs utilised were the best available from published literature, the quality of the source studies adds limitations to the interpretation of our results as discussed above. Fundamentally we imposed a level of confidence on every parameter entered into the model of which we cannot be certain of accuracy.

Secondly, our utilisation of CHA$_2$DS$_2$VASc for annual stroke risk, whilst practical from a clinical perspective does add limitations to the interpretation of results. Not all components of the CHA$_2$DS$_2$VASc risk stratification tool carry equal weight, therefore equal CHA$_2$DS$_2$VASc scores may indeed carry variable stroke risks depending on the factors that compose the score. What’s more, other patient characteristics that are linked with stroke risk such as atrial fibrosis and left atrial appendage morphology are
not included in the CHA\textsubscript{2}DS\textsubscript{2}VASc score and would impact a patient’s actual stroke risk \cite{258,259}.

Lastly, we did not enter a variable for age into our decision model and therefore outputs do not account for consequences extending beyond 12 months. The construction of this model was complex as it was made up of multiple variables and resulted in hundreds of model outputs; as discussed previously this was largely driven by the need to model multiple scenarios. The addition of another variable, age, which is subject to utility changes over time, would have added further complexity to the model with unknown benefit. The clinical dilemma in question pertains to a 12 month period hence this was the duration modelled. As a consequence we cannot extrapolate our total QALY outputs to represent time-frames beyond this.

### 5.5 Conclusion

Our theoretical decision model has demonstrated that bleeding from TT impacts greatly on the overall risk-benefit balance for ACS patients with AF. For the most part bleeding from TT will do more harm than good unless stroke risk is sufficiently high, around CHA\textsubscript{2}DS\textsubscript{2}VASc scores 3 to 5. The consequences of bleeding with TT seen in this model highlight the need for clinicians to accurately predict patients at risk of experiencing a haemorrhagic event, as this is a fundamental consideration of prescribing TT. Whether contemporary bleeding risk tools accurately predict post ACS bleeding events is examined in Chapter 6.
6 Evaluating the ability of ACS bleeding risk scores to predict bleeding events
6.1 Introduction

In the previous chapter we established that TT results in bleeding harm which impacts largely on the overall risk-benefit ratio after an ACS event. Under many circumstances the administration of TT results in bleeding risk that exceeds any benefit gained from stroke prevention. As such, careful assessment of bleeding risk is a strategy that may be effective at identifying patients with an increased bleeding risk profile, and in turn may help to mitigate the risks associated with antithrombotic therapy. Consistent with this, most guidelines favour DAPT over TT in patients with high bleeding risk. However, assessment of bleeding risk will only be an effective strategy if the assessment tools are accurate.

Among ACS bleeding risk stratification tools available, the CRUSADE \(^{187}\) and ACTION (Acute Coronary Treatment and Intervention Outcomes Network registry) \(^{260}\) bleeding scores are commonly used, and were developed and validated in large-scale cohorts. However, these scores were designed to be predictive of in-hospital bleeding events, yet previous studies have shown that the majority of bleeding events occur following discharge from hospital after an ACS \(^{261}\). Therefore, accurate prediction of bleeding events for the out-of-hospital phase is also important, particularly when we consider that patients may be on multiple antithrombotic agents for up to one-year following an ACS event.

In addition to bleeding risk scores, there is emerging evidence that identification of low platelet reactivity (LPR) by platelet function testing may be predictive of bleeding events both in-hospital and at one-year. However, most observational studies have been in patients undergoing PCI and findings have been variable \(^{262}\). It is also unknown whether platelet function testing provides additive prognostic information to existing bleeding scores.

To optimise outcomes for patients after an ACS accurate assessment of bleeding risk is essential. It may also help to mitigate bleeding harm in patients eligible for therapies with increased bleeding risk, such as TT. In this chapter we set out to characterise bleeding events in-hospital and up to one-year, in a real-world MI cohort. We then
investigated the performance of the CRUSADE and ACTION risk scores to predict in-hospital bleeding and one-year major bleeding events in patients with MI undergoing an invasive approach. In addition, we assessed the predictive value of platelet function testing to establish whether this added value to existing risk scores.

Therefore, the aims of this study were:

- To characterise in-hospital and one-year bleeding events in a real world MI cohort
- To evaluate the ability of CRUSADE and ACTION bleeding risk scores to predict in-hospital and one-year bleeding events
- To examine whether LPR is predictive of in-hospital and one-year bleeding events
6.2 Methods

6.2.1 Study design and population

In this prospective, single-centre, cohort study we enrolled 1000 patients between January 2012 and May 2015. Patients with acute MI undergoing invasive management, who were adequately pre-treated with DAPT, were eligible for enrolment. Patients were excluded if they had a platelet count <100 x 10^9/L, a known platelet function disorder, administration of a fibrinolytic agent within 24 hours prior to enrolment or a glycoprotein IIb/IIIa antagonist within 1 week prior to enrolment. Patient management was at the discretion of the attending physician. This study was approved by the Lower Regional South Ethics Committee (LRS/11/09/035/AM01). Written informed consent was obtained from all subjects.

6.2.2 Data Collection

Patient demographics, clinical characteristics, clinical management, procedural variables and in-hospital outcomes were collected prospectively from review of medical records and the cardiac catheterisation database. Follow up data was collected from the National Admissions Database and telephone calls at 30 days and one-year. Where necessary, a review of case notes was performed and the appropriate general practitioner contacted to further classify clinical outcomes.

6.2.3 Definitions

Acute MI was defined according to the third universal definition of myocardial infarction. Adequate pre-treatment on DAPT was defined as administration of aspirin (chronic therapy with ≥75mg/day or a loading dose with ≥300mg) with either clopidogrel (chronic therapy ≥75mg/day or ≥300mg loading dose) or ticagrelor (chronic therapy 90mg/bd or 180mg loading dose). Bleeding was defined using the TIMI major and minor criteria.

263
(Table 6-1) The primary endpoint of this study was the combination of non-CABG related TIMI major and minor bleeding at one-year.

Clinical risk factors and characteristics were defined according to the American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. Anaemia was defined as haemoglobin <12g/dL for women, and <13g/dL for men. When the CRUSADE bleeding risk score was applied patients were categorised as very low risk (score ≤20), low risk (score 21-30), moderate risk (score 31-40) or combined high/very high risk (score 41-100) (see chapter 2, Table 2-2). Likewise when the ACTION bleeding risk score was applied patients were categorised as very low risk (score ≤20), low risk (score 21-30), moderate risk (score 31-40) or combined high/very high risk (score 41-100) (Table 6-2). Within the ACTION risk score 2 points are attributed to patients with home warfarin use; for the purposes of this analysis patients on NOACs were also scored 2 points.
<table>
<thead>
<tr>
<th>Non-CABG TIMI bleeding</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIMI Major</strong></td>
<td>Any intracranial bleeding (excluding micro-haemorrhages &lt;10 mm evident only on gradient-echo MRI). Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL. Fatal bleeding (bleeding that directly results in death within 7 days).</td>
</tr>
<tr>
<td><strong>TIMI Minor</strong></td>
<td>Clinically overt (including imaging), resulting in haemoglobin drop of 3 to &lt;5 g/dL. No observed blood loss: ≥4 g/dL decrease in haemoglobin. Any overt sign of haemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above: Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug); Leading to or prolonging hospitalisation; Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging).</td>
</tr>
<tr>
<td><strong>TIMI Minimal</strong></td>
<td>Any overt bleeding event that does not meet the criteria above.</td>
</tr>
</tbody>
</table>

MRI = magnetic resonance imaging
Table 6-2 ACTION bleeding score

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Systolic Blood Pressure</th>
<th>Heart rate on admission</th>
<th>Heart Failure ± Shock on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40</td>
<td>0</td>
<td>≤90</td>
<td>4</td>
</tr>
<tr>
<td>41-50</td>
<td>1</td>
<td>91-100</td>
<td>3</td>
</tr>
<tr>
<td>51-60</td>
<td>2</td>
<td>101-120</td>
<td>2</td>
</tr>
<tr>
<td>61-70</td>
<td>3</td>
<td>121-140</td>
<td>1</td>
</tr>
<tr>
<td>71-80</td>
<td>4</td>
<td>141-170</td>
<td>0</td>
</tr>
<tr>
<td>81-90</td>
<td>5</td>
<td>171-200</td>
<td>1</td>
</tr>
<tr>
<td>≥91</td>
<td>6</td>
<td>≥201</td>
<td>2</td>
</tr>
<tr>
<td>≤40</td>
<td>0</td>
<td>≤90</td>
<td>4</td>
</tr>
<tr>
<td>41-60</td>
<td>2</td>
<td>91-100</td>
<td>3</td>
</tr>
<tr>
<td>61-70</td>
<td>3</td>
<td>101-120</td>
<td>2</td>
</tr>
<tr>
<td>71-80</td>
<td>4</td>
<td>121-140</td>
<td>1</td>
</tr>
<tr>
<td>81-90</td>
<td>5</td>
<td>141-170</td>
<td>0</td>
</tr>
<tr>
<td>≥91</td>
<td>6</td>
<td>171-200</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Serum Creatinine (mg/dl)</th>
<th>Baseline haemoglobin (g/dl)</th>
<th>121-130</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.8</td>
<td>0</td>
<td>131-150</td>
<td>12</td>
</tr>
<tr>
<td>0.8-1.59</td>
<td>1</td>
<td>≥151</td>
<td>14</td>
</tr>
<tr>
<td>1.6-1.99</td>
<td>2</td>
<td>121-130</td>
<td>11</td>
</tr>
<tr>
<td>2.0-2.99</td>
<td>4</td>
<td>131-150</td>
<td>12</td>
</tr>
<tr>
<td>3.0-3.99</td>
<td>6</td>
<td>≥151</td>
<td>14</td>
</tr>
<tr>
<td>4.0-4.99</td>
<td>8</td>
<td>121-130</td>
<td>11</td>
</tr>
<tr>
<td>5.0-5.99</td>
<td>10</td>
<td>121-130</td>
<td>11</td>
</tr>
<tr>
<td>≥6</td>
<td>11</td>
<td>121-130</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Gender</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50</td>
<td>Female</td>
<td>No</td>
</tr>
<tr>
<td>51-70</td>
<td>Male</td>
<td>No</td>
</tr>
<tr>
<td>101-120</td>
<td>Male</td>
<td>Yes</td>
</tr>
<tr>
<td>≥140</td>
<td>Female</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Home warfarin use</th>
<th>121-140</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>≥140</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
6.2.4 Platelet function testing

On-treatment platelet reactivity to ADP was quantified using the Multiplate analyser (Roche Diagnostics, Rotkreuz, Switzerland), a multiple electrode impedance aggregometer that assesses platelet function in whole blood as previously described. Briefly, whole blood was added to the test cuvettes, diluted (1:2 with 0.9% NaCl solution), stirred and warmed to 37 °C. ADP was added to a final concentration of 6.4 mM and aggregation was then continuously recorded for 6 min. Aggregation values are quantified as area under the aggregation curve expressed as aggregation units × minutes (AU). All material used for platelet function testing was obtained from the manufacturer (Roche Diagnostics, Rotkreuz, Switzerland). Thresholds for LPR were defined as <19 AU.

6.2.5 Statistical analysis

Continuous variables are presented as mean ± standard deviation, and comparisons between groups were performed using independent sample t-tests. Categorical variables are presented as frequency (percentage) and chi-square analyses were used to compare groups. In univariate analysis (those with non-CABG bleeding compared to those without) variables with p-values <0.05 were included in the multinomial model. All p-values were 2-sided and a value <0.05 was considered statistically significant. Receiver operator characteristic (ROC) curve analysis was used to examine the relationship between risk scores and the primary endpoint and reported as area under the curve measures (AUC). All statistical tests were performed using SPSS version 22 (IBM, Armonk, NY).
6.3 Results

The demographics and clinical characteristics of the 1000 acute MI patients enrolled in this study were typical of an ACS population and can be seen in Table 6-3. This group had an average age of 63 ± 11 years, 27.7% were female and 19.4% had diabetes. NSTEMI was the presentation in 80.6% of patients and STEMI in 19.4%. Clinical management was PCI in 60.5%, CABG surgery in 14.3% and medical management in 25.2%. All patients were on DAPT at the time of enrolment with 84.1% being discharged on DAPT. DAPT at discharge was aspirin and clopidogrel in 628 patients (74.6%), and aspirin and ticagrelor in 213 patients (25.4%).

The primary endpoint of non-CABG TIMI major and minor bleeding at one-year occurred in 133 (13.3%) of subjects (Table 6-3). Of the 133 bleeding events, 46 (34.5%) occurred in-hospital and 87 (65.4%) occurred between discharge and one-year. Seven of the bleeding events (5.3%) were TIMI major bleeds, and this consisted of 1 intracranial haemorrhage occurring in-hospital, and 6 clinically overt bleeds with a haemoglobin drop of >5g/dL, all occurring out-of-hospital. No fatal bleeding events occurred. The remaining 126 bleeding events (94.7%) were categorised as TIMI minor. Thirteen of these were clinically overt with a haemoglobin drop 3-5g/dL (5 occurred in-hospital and 8 out-of-hospital), and 113 required medical attention (40 in-hospital events vs. 73 out-of-hospital events) (Table 6-4).

A total of 143 (14.3%) patients in the study were managed with CABG surgery, and in this group 14 patients experienced TIMI major CABG related bleeding. There were 4 cases where reoperation to control bleeding was required, and 10 cases where the patient received ≥5 units of blood products. In this group there were 4 perioperative deaths, but none of these was due to bleeding. There were no cases of intracranial bleeding associated with CABG (Table 6-4).
## Table 6-3 Demographics and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=1000)</th>
<th>Bleeding (n=133)</th>
<th>No bleeding (n=867)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63 ± 11</td>
<td>65 ± 10</td>
<td>63 ± 11</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>277 (27.7)</td>
<td>48 (36.1)</td>
<td>229 (26.4)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>86 ± 18</td>
<td>85 ± 17</td>
<td>86 ± 18</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>BMI &lt;20/underweight</strong></td>
<td>24 (2.4)</td>
<td>3 (2.3)</td>
<td>21 (2.4)</td>
<td>0.907</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>854 (85.4)</td>
<td>113 (85.0)</td>
<td>741 (85.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Maori + PI</td>
<td>112 (11.2)</td>
<td>19 (14.3)</td>
<td>93 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>34 (3.4)</td>
<td>1 (0.8)</td>
<td>33 (3.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>611 (61.1)</td>
<td>92 (69.2)</td>
<td>519 (59.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>692 (69.2)</td>
<td>90 (67.7)</td>
<td>602 (69.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Diabetes</td>
<td>194 (19.4)</td>
<td>28 (21.1)</td>
<td>166 (19.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>227 (22.7)</td>
<td>27 (20.3)</td>
<td>200 (23.0)</td>
<td>0.175</td>
</tr>
<tr>
<td>Previous MI</td>
<td>238 (23.8)</td>
<td>35 (26.3)</td>
<td>203 (23.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>68 (6.8)</td>
<td>11 (8.3)</td>
<td>57 (6.6)</td>
<td>0.47</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>54 (5.4)</td>
<td>12 (9)</td>
<td>42 (4.8)</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>eGFR (mL/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 +</td>
<td>829 (82.9)</td>
<td>111 (83.5)</td>
<td>718 (82.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>46-59</td>
<td>123 (12.3)</td>
<td>14 (10.5)</td>
<td>109 (12.6)</td>
<td></td>
</tr>
<tr>
<td>31-45</td>
<td>30 (3.0)</td>
<td>6 (4.5)</td>
<td>24 (2.8)</td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>18 (1.8)</td>
<td>2 (1.5)</td>
<td>16 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>122 (12.2)</td>
<td>21 (15.8)</td>
<td>101 (11.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Low platelet reactivity</td>
<td>174 (17)</td>
<td>20 (15)</td>
<td>154 (17.8)</td>
<td>0.431</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>194 (19.4)</td>
<td>23 (17.3)</td>
<td>171 (19.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>806 (80.6)</td>
<td>110 (82.7)</td>
<td>696 (80.3)</td>
<td></td>
</tr>
<tr>
<td>CRUSADE score</td>
<td>22 ± 10</td>
<td>23 ± 10</td>
<td>22 ± 10</td>
<td>0.20</td>
</tr>
<tr>
<td>ACTION score</td>
<td>23 ± 6.6</td>
<td>24 ± 6.7</td>
<td>23 ± 6.5</td>
<td>0.44</td>
</tr>
<tr>
<td>GRACE score</td>
<td>124 ± 31</td>
<td>125 ± 32</td>
<td>124 ± 31</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Clinical management</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>252 (25.2)</td>
<td>28 (21.1)</td>
<td>224 (25.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>605 (60.5)</td>
<td>100 (75.2)</td>
<td>505 (58.2)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>143 (14.3)</td>
<td>5 (3.8)</td>
<td>138 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Discharged on DAPT</td>
<td>841 (84.1)</td>
<td>123 (92.5)</td>
<td>718 (82.8)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

BMI = body mass index; eGFR = estimated glomerular filtration rate; PI = Pacific Islander.
### Table 6-4 Bleeding events by TIMI criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>In-hospital</th>
<th>Out-of-hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint: Non-CABG TIMI Major &amp; Minor</strong></td>
<td>46 (34.5%)</td>
<td>87 (65.4%)</td>
<td>133 (100%)</td>
</tr>
<tr>
<td><strong>TIMI Major</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Clinically overt †</td>
<td>-</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td><strong>TIMI Minor</strong></td>
<td>45</td>
<td>81</td>
<td>126</td>
</tr>
<tr>
<td>Clinically overt †</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Requiring medical attention</td>
<td>40</td>
<td>73</td>
<td>113</td>
</tr>
<tr>
<td><strong>TIMI CABG Bleeding</strong></td>
<td>14 (100%)</td>
<td></td>
<td>14 (100%)</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Perioperative intracranial bleeding</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Reoperation to control bleeding</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Transfusion of ≥ 5 units blood</td>
<td>10</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>Chest tube output &gt;2L within 24 hours</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

† Clinically over with haemoglobin drop ≥5g/dL; ‡ Clinically overt with haemoglobin drop 3-5g/dL.
6.3.1 Predictors of Non-CABG bleeding

The demographics and clinical characteristic of those with non-CABG bleeding compared to those without are shown in Table 6-3. In univariate analyses a number of factors were associated with an increased risk of non-CABG related TIMI major or minor bleeding at one-year. These were increasing age (per 10-year increments) (odds ratio 1.21, [1.02-1.43]), female gender (odds ratio 1.57, [1.07-2.31]), history of hypertension (odds ratio 1.51, [1.02-2.23]), history of renal dysfunction (odds ratio 1.95, [1.00-3.80]), PCI (odds ratio 2.2, [1.43-3.3]) and DAPT at discharge (odds ratio 2.55, [1.31-4.98]); all were significant to a level p<0.05. In multinomial analysis both female gender (odds ratio 1.5, [1.01-2.2], p=0.044) and clinical management with PCI (odds ratio 1.96, [1.2-3.1], p=0.005) remained as independent predictors of bleeding.

6.3.2 CRUSADE bleeding score

Using the CRUSADE scoring criteria to assess for bleeding risk, most patients were categorised as very low risk (46.8%), followed by low risk (33.2%), moderate risk (16%) and high/very high risk (4%). Within each of these risk categories bleeding rates were 13%, 12%, 15.6% and 17.5% respectively (Table 6-5). At one-year most non-CABG related bleeding events occurred in those at very low risk of bleeding (n=61) and low risk (n=40) and this is likely reflective of the large number of patients in these groups.

When looking at the ability to predict the primary endpoint of non-CABG related TIMI major or minor bleeding, our analysis found no difference in mean CRUSADE scores for patients who had a bleeding event compared with those who did not (23 ± 10 vs. 22 ± 10, p=0.20). ROC curve analysis to assess the relationship between CRUSADE scores and non-CABG related TIMI major or minor bleeding was performed and with an AUC of 0.533 (p=0.226) and was therefore not predictive of bleeding in our cohort (Figure 6-1). Analysis of in-hospital bleeding events only, showed CRUSADE to have modest predictive ability with an AUC of 0.610 (p=0.012). This was also evident as patients who had an in-hospital bleed had significantly higher mean CRUSADE scores compared to
those who did not (26.0 ± 10.4 vs. 22.1 ± 10.0, p=0.01). With regard to out-of-hospital bleeding, once again CRUSADE was not predictive of bleeding events using both ROC curve analysis (AUC=0.487, p=0.679) and mean CRUSADE scores (out-of-hospital bleeding event vs. no bleeding event, 21.9 ± 9.9 vs. 22.4 ± 10.0 respectively, p=0.71).

**Table 6-5 Bleeding events by risk stratification**

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>TIMI Major (%)</th>
<th>TIMI Minor (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRUSADE score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low (n=468)</td>
<td>3 (0.6)</td>
<td>58 (12.4)</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Low (n=332)</td>
<td>1 (0.3)</td>
<td>39 (11.7)</td>
<td>40 (12)</td>
</tr>
<tr>
<td>Moderate (n=160)</td>
<td>3 (1.9)</td>
<td>22 (13.8)</td>
<td>25 (15.6)</td>
</tr>
<tr>
<td>High/very high (n=40)</td>
<td>-</td>
<td>7 (17.5%)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td><strong>ACTION score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low (n=366)</td>
<td>1 (0.3)</td>
<td>48 (13.1)</td>
<td>49 (13.4)</td>
</tr>
<tr>
<td>Low (n=489)</td>
<td>3 (0.6)</td>
<td>55 (11.2)</td>
<td>58 (11.9)</td>
</tr>
<tr>
<td>Moderate (n=136)</td>
<td>3 (2.2)</td>
<td>23 (16.9)</td>
<td>26 (19.1)</td>
</tr>
<tr>
<td>High/very high (n=9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 6-1 ROC curves showing predictive ability of CRUSADE bleeding risk score

The ROC curves are graphs of sensitivity (y-axes) versus 1-specificity (x-axes). CRUSADE was not predictive of one-year bleeding events (A) or out-of-hospital bleeding events (C). CRUSADE was modestly predictive of in-hospital bleeding (B).
6.3.3 ACTION bleeding score

When the action bleeding score was applied the distribution of patients into risk categories was different to that of CRUSADE. Nearly half the patients were categorised as being at low risk of bleeding (48.9%), followed by very low risk (36.6%), moderate risk (13.6%) and high/very high risk (0.9%). There was some variability in bleeding event rates between the risk categories. The moderate risk group had the highest bleeding event rate (19.1%), followed by the very low risk group (13.4%) and low risk group (11.9%). No bleeding events occurred in the high/very high risk patients. At one-year most non-CABG related bleeding events occurred in the low risk (n=58) and very low risk (n=49) groups, and once again this is probably reflective of the large patient numbers in these groups (Table 6-5).

The predictive ability of the ACTION risk score was also assessed (Figure 6-2). The mean ACTION score for patients who experienced a non-CABG TIMI major or minor bleed was not different to the non-bleeders (24 ± 6.7 vs. 23 ± 6.5, 0.44). ROC curve analysis also showed that the ACTION risk score was not predictive of these bleeding events (AUC=0.522, p=0.414). ACTION had very modest predictive power with regard to in-hospital bleeding events with an AUC value of 0.583 (p=0.056), however the mean ACTION scores for these patients did not reach statistical significance (in-hospital bleeding event vs. no bleeding event, 25 ± 6.6 vs. 23 ± 6.5, p=0.075). ACTION did not exhibit any ability to predict out-of-hospital non-CABG TIMI major or minor bleeding events, with equal mean ACTION scores in both the out-of-hospital bleeding and no bleeding groups (23 ± 6.6 vs. 23 ± 6.5, p=0.688), and a AUC value of 0.486 (p=0.662).
Figure 6-2 ROC curves showing predictive ability of ACTION bleeding risk score

The ROC curves are graphs of sensitivity (y-axes) versus 1-specificity (x-axes). ACTION was not predictive of one-year bleeding events (A) or out-of-hospital bleeding events (C). ACTION was only modestly predictive of in-hospital bleeding (B).
6.3.4 Low on-treatment platelet reactivity

When examining the relationship between LPR and non-CABG related TIMI major and minor bleeding there was no statistically significant difference in the frequency of LPR in those who had a bleeding event compared to those who did not, either in-hospital (8.7% vs. 17.9%, p=0.11), out-of-hospital (18.4% vs. 17.4%, p=0.81) or overall at one-year (15% vs. 17.8%, p=0.43) (Table 6-6). The ability of residual platelet reactivity to predict bleeding events for patients was also examined using ROC curve analysis. We found that platelet reactivity was not predictive of non-CABG related TIMI major and minor bleeding events either in-hospital (AUC=0.5, p=0.991), out-of-hospital bleeding (AUC=0.506, p=0.858) or overall at one-year (AUC=0.504, p=0.876) (Figure 6-3).

Table 6-6 Low platelet reactivity by bleeding event

<table>
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<tr>
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<th>Low platelet reactivity</th>
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<td>n (%)</td>
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<td>(n=46)</td>
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<td>Out-of-hospital bleeding</td>
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<td>(n=87)</td>
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<td>No out-of-hospital bleeding</td>
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<tr>
<td>(n=913)</td>
<td>158 (17.4)</td>
<td></td>
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<tr>
<td>One-year bleeding</td>
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<td></td>
</tr>
<tr>
<td>(n=133)</td>
<td>20 (15)</td>
<td>0.43</td>
</tr>
<tr>
<td>No bleeding at one-year</td>
<td>154 (17.8)</td>
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Figure 6-3 ROC curves showing predictive ability of platelet reactivity

The ROC curves are graphs of sensitivity (y-axes) versus 1-specificity (x-axes). Platelet reactivity was not predictive of one-year bleeding (A), in-hospital bleeding (B) or out-of-hospital bleeding (C).
6.3.5 PCI subgroup analysis

A total of 605 patients (60.5%) were managed with PCI and non-CABG related TIMI major or minor bleeding occurred in 100 of these patients (16.5%). Of these, in-hospital bleeding events occurred in 35 patients and out-of-hospital bleeding events in 65 patients. Five of these bleeding events were defined as TIMI major (1 in-hospital and 4 out-of-hospital), and 95 as TIMI minor (34 in-hospital and 61 out-of-hospital).

Those managed with PCI in the in-hospital bleeding group had a significantly higher mean CRUSADE score compared to those without bleeding (24.8 ± 10.0 vs. 21.2 ± 9.6, p=0.033). ROC curve analysis showed the CRUSADE risk score had a modest ability to predict in-hospital bleeding events for those managed by PCI (AUC=0.608, p= 0.032). With regard to out-of-hospital bleeding events CRUSADE was not predictive (AUC=0.503, p=0.928), nor were mean CRUSADE scores statistically different in those with bleeding compared to those without bleeding (21.5 ± 9.8 vs. 21.4 ± 9.7, p = 0.917). For overall non-CABG related TIMI major and minor bleeding at one-year again the CRUSADE score was not predictive of events (AUC=0.545, p=0.155), and mean CRUSADE scores in those with bleeding compared to those without bleeding were very similar (22.7 ± 9.9 vs. 21.2 ± 9.6, p=0.155) (Figure 6-4).

The predictability of the ACTION risk score for patients managed with PCI was also examined. We found that ACTION was not predictive of bleeding events for in-hospital bleeding (AUC=0.572, p=0.152), out-of-hospital bleeding (AUC=0.509, p=0.830) or overall non-CABG bleeding events at one-year (AUC=0.534, p=0.280). Likewise no statistical difference was found between mean ACTION scores comparing those with bleeding to those without for in-hospital bleeding (24.4 ± 6.8 vs. 22.9 ± 6.5, p=0.171), out-of-hospital bleeding (23.1 ± 6.5 vs. 23.0 ± 6.5, p= 0.855) and all non-CABG related TIMI major and minor bleeding (23.6 ± 6.6 vs. 22.8 ± 6.5, p=0.312) (Figure 6-5).
Figure 6-4 PCI subset - predictive ability of CRUSADE bleeding risk score

The ROC curves are graphs of sensitivity (y-axes) versus 1-specificity (x-axes). In the PCI subset (n=605) CRUSADE was not predictive of one-year bleeding events (A) or out-of-hospital bleeding events (C). CRUSADE was modestly predictive of in-hospital bleeding in those managed with PCI (B).
Figure 6-5 PCI subset - predictive ability of ACTION bleeding risk score

The ROC curves are graphs of sensitivity (y-axes) versus 1-specificity (x-axes). In the PCI subset (n=605) ACTION was not predictive of one-year bleeding (A), in-hospital bleeding (B) or out-of-hospital bleeding (C).
In addition, for those managed with PCI there was no statistical difference in the frequency with which people were classified as having LPR in those with bleeding compared to those without bleeding either in-hospital (8.6% vs. 17.5%, \( p=0.17 \)), out-of-hospital (20% vs. 16.7%, \( p=0.5 \)) or overall at one-year (17% vs. 17%, \( p=0.76 \)). The predictability of residual platelet reactivity for patients managed with PCI was also examined using ROC curve analysis. We found that platelet reactivity was not predictive of non-CABG related TIMI major and minor bleeding events either in-hospital (AUC = 0.483, \( p=0.746 \)), out-of-hospital bleeding (AUC = 0.517, \( p=0.647 \)) or overall at one-year (AUC= 0.506, \( p=0.858 \)) (Figure 6-6).
A) One-year bleeding  
B) In-hospital bleeding  
C) Out-of-hospital bleeding

Figure 6-6 PCI subset – predictive ability of platelet reactivity

The ROC curves are graphs of sensitivity (y-axes) versus 1-specificity (x-axes). In the PCI subset (n=605) platelet reactivity was not predictive of one-year bleeding (A), in-hospital bleeding (B) or out-of-hospital bleeding (C).
6.4 Discussion

In this prospective real-world cohort we found a 13.3% rate of non-CABG TIMI major or minor bleeding within one-year following MI, with the majority of these events occurring following discharge from hospital. The CRUSADE score but not the ACTION score or LPR was predictive of in-hospital bleeding. However, neither bleeding score nor LPR was predictive of out-of-hospital bleeding or overall bleeding at one-year. The predictive ability of CRUSADE in-hospital was modest with the majority of bleeding events occurring in patients classified as low risk.

The incidence of bleeding after ACS varies depending on the population studied, the time frames examined and the definitions used. The more recent utilisation of intensive antithrombotic drugs also lend themselves to increased bleeding rates \(^{237,238}\). Keeping in mind the variability in these parameters the rate of major bleeding in the wider literature is reported anywhere between 2-12\% \(^{237,241,269-273}\). The overall one-year rate of TIMI major or minor non-CABG related bleeding in this cohort was 13.3% and was comparable with other ACS cohorts utilising the same TIMI bleeding definitions. The PLATO trial reported TIMI major or minor bleeding rates of 11.4% and 10.9% in the ticagrelor and clopidogrel arms respectively\(^{238}\). The slightly higher rate seen in our study may reflect the broader patient population enrolled in this registry when compared to a clinical trial.

Whatever the definitions employed it is clear that bleeding after an ACS event has a negative impact on prognosis \(^{235,274-277}\). We also know that bleeding events (fatal, intracranial or major) impact heavily on the overall risk-benefit balance for ACS patients with AF, as demonstrated in the previous chapter. It is therefore sensible that NSTEACS and STEMI specific guidelines suggest altering treatment on the basis of bleeding risk \(^{88-91}\). However, to achieve this clinicians require accurate tools to assess bleeding risk. Two bleeding scores that are used commonly are the CRUSADE and ACTION bleeding scores. These have been shown to perform better when compared to other bleeding risk scores \(^{273,278,279}\). The CRUSADE and ACTION scores were both developed and validated in very large cohorts of NSTEMI patients to quantify the risk of in-hospital major bleeding events and were found to be reasonably predictive (AUC 0.72 and 0.73 respectively).
CRUSADE and ACTION were developed to predict in-hospital events, patients discharged on antithrombotic regimens are still at risk from bleeding long after their hospital admission.

In our study CRUSADE and ACTION were only very modestly predictive of in-hospital non-CABG related bleeding events. This may be because we enrolled a mixed population. However, when we looked at a PCI population alone the predictive ability did not increase significantly. An alternative explanation may be that clinical practice has changed significantly from the time when these scores were derived. In particular there is less use of glycoprotein IIb/IIIa inhibitors and greater use of radial access. These factors may impact on the predictive value of these scores. Neither the CRUSADE nor the ACTION scores were predictive of bleeding post discharge or overall at one-year. This may be because the drivers for bleeding may differ pre- and post-discharge.

Despite enrolling a broad range of patients into the study relatively few patients were classified as being at high risk of bleeding by the CRUSADE and ACTION scores. As a result most bleeding occurred in those classified as being at low to moderate bleeding risk. The implications being that we need better risk stratification tools to target bleeding avoidance strategies, or alternatively we must use bleeding avoidance strategies that can be applied to the whole ACS population. What’s more, in the context of patients at increased risk of bleeding, such as ACS patients with AF prescribed TT, CRUSADE and ACTION are likely ineffective assessment tools, and therefore will not help to mitigate harm from bleeding through accurate prediction of bleeding events.

As mentioned, guidelines frequently advocate that we should consider both bleeding risk and ischaemic risk when deciding on therapeutic strategies. Whilst this is sound in theory, the practicalities of achieving this are challenging. An additional factor that makes this challenging in clinical practice is the fact that bleeding and ischaemic risk are linked with many of the independent risk factors for bleeding also being independent risk factors for recurrent ischaemic events. The GRACE score (Global Registry of Acute Coronary Events) is a predominant risk profile tool designed to predict 6 month readmission and mortality for patients admitted with an ACS, and consists of 8 predictors. Four of the predictors from GRACE are also present in CRUSADE (heart
rate, systolic blood pressure, renal function [creatinine/creatinine clearance] and heart failure at admission), while 6 predictors are also present in ACTION (age, heart rate, systolic blood pressure, creatinine, ST-segment deviation and heart failure at admission). Indeed this overlap is emphasized in a recent study of 1,587 ACS patients comparing GRACE and CRUSADE, and their ability to predict major bleeding events. When CRUSADE bleeding definitions were applied both scoring systems performed equally well (AUC = 0.79 vs 0.79, p=0.921), but when BARC major bleeding definitions were used the GRACE score outperformed CRUSADE (AUC = 0.80 vs. 0.73 respectively, p=0.028). This finding in addition to our current results, highlight the fact that bleeding risk scores derived in large-scale studies may not be applicable to daily routines that are currently guiding therapeutic decision making.

As major bleeding events have proven difficult to predict accurately even using a combination of traditional bleeding risk factors, alternative approaches are required. Platelet function testing may represent an alternative approach to help stratify bleeding risk and ischaemic risk. However, the value and accuracy of LPR to predict bleeding events in patients exposed to P2Y₁₂ inhibitors is not as clearly established as for HPR and stent thrombosis, with both positive and negative studies published so far. A meta-analysis of seventeen studies including 20 839 patients found that those with LPR had a significant, 1.7-fold higher risk of major bleeding in comparison to those with platelet reactivity in the optimal range (relative risk 1.74, [1.47–2.06], p < 0.00001). In the current study we did not find a statistically significant difference in the frequency of LPR in those who had a bleeding event compared to those who did not, either in-hospital, out-of-hospital, or overall at one-year. There are a number of important differences in our study when compared to those included in the meta-analysis. All studies included in the meta-analysis were performed on patients undergoing PCI with only a minority of patients presenting with ACS. The meta-analysis included studies using a variety of bleeding definitions, a variety of platelet function tests and follow-up durations between 1 and 17 months which may have also influenced findings.
Recently, a novel risk score, the PRECISE-DAPT score (age, creatinine clearance, haemoglobin, white blood cell count and previous bleeding)\textsuperscript{293}, was developed for the prediction of out-of-hospital bleeding during treatment with DAPT. This retrospective study included patients with both stable CAD (44%) and ACS (56%) who were treated with PCI, largely from previously performed clinical trials. The score was reasonably predictive with an AUC for out-of-hospital TIMI major or minor bleeding of 0.73 (95% CI 0.61–0.85). Whether the score predicted in-hospital bleeding was not examined. This score is a relatively simple five-item risk score, which can be calculated on-line. One of the components included in this risk score is “a history of spontaneous bleeding” and in fact is by far the most predictive element. As we did not collect information on whether or not patients had a history of spontaneous bleeding we could not examine this score in our cohort.

6.4.1 Limitations

Our study has inherent limitations associated with being an observational study; as such it may be susceptible to bias or confounding influences we could not control for. Our results rely heavily on the data collection of patient details and bleeding events, of which we cannot be certain of accuracy.

Weak relationships between bleeding scores were challenging to identify and may have been more evident in a larger cohort, however this was beyond the constraints of this thesis. However, given we found TIMI major or minor bleeding occurred in 13% of patients, a rate higher than some larger ACS cohorts, it is also possible that a larger cohort would not have helped to identify relationships if they are truly negligible. Furthermore, the usefulness of weak relationships is questionable and will likely offer little value in the setting of clinical assessment. It is also possible that our study was underpowered to detect small associations between LPR and bleeding events, however our cohort of 1000 MI patients was larger than many previous studies to examine this relationship\textsuperscript{286,287,294-301}. 
As we discussed earlier there is vast heterogeneity across bleeding definitions in wider literature; both CRUSADE and ACTION used study derived bleeding criteria. We designed this study to examine bleeding using the TIMI bleeding criteria as it frequently used in published literature, especially in predominant ACS trials, and we considered it to be a reasonable common endpoint for both scoring systems and platelet reactivity. Utilisation of CRUSADE’s and ACTION’s respective bleeding criteria may have resulted in findings that demonstrated predictability, however, we would have not been able to compare the performance of scores. What’s more, this study was designed to evaluate the accuracy of bleeding scores used in clinical settings, and the usefulness of CRUSADE and ACTION to predict their own study criteria would have not been of value.

In the time since we completed this study the PRECISE-DAPT bleeding score has been developed as previously discussed. This scoring system demonstrated ability to predict TIMI major or minor bleeding and it is possible that this may be of value moving forward. Like CRUSADE and ACTION, PRECISE-DAPT was derived from a large cohort (14,963 patients) and we do not know its predictive ability in smaller real-world cohorts like ours. We were unable to calculate PRECISE-DAPT as “a history of spontaneous bleeding”, a component of the score, was not collected in our study database.

6.5 Conclusion

In our real world cohort we found a 13.3% rate of clinically significant bleeding within one-year of MI. Two common ACS bleeding risk scores, CRUSADE and ACTION, were analysed and despite being predictive in large populations, performed poorly in our patient cohort. CRUSADE demonstrated a very modest ability to predict in-hospital bleeding events, but neither score was predictive of out-of-hospital events up to one-year. Platelet reactivity has been suggested as an alternative risk stratification tool however it did not demonstrate predictive ability in our cohort. An accurate risk assessment tool that predicts bleeding events for the duration of antithrombotic therapy is needed to optimise therapy for all ACS patients.
7 Summary and future directions
7.1 Summary

In this thesis, the aim of the first study was to describe the discharge prescription of antiplatelet and anticoagulant therapy in ACS patients with AF. We found DAPT to be the preferred discharge regimen, and OAC use was very low despite most patients being at high risk of stroke. Discharge OAC use was not associated with stroke risk as assessed by CHA$_2$DS$_2$VASc score, bleeding risk as assessed by CRUSADE score, nor any other clinical characteristic. The only predictor of OAC use at discharge was prehospital use of OAC. We also identified a large group of patients characterised by high stroke risk and low bleeding risk whom may have been suitable candidates for OAC therapy.

The aims of the second study were to describe national prescription patterns of antiplatelet and anticoagulant therapies in ACS patients with AF, and to examine whether therapies were associated with one-year outcomes. Despite expanding our patient cohort to include those treated nationwide, we found no clear treatment strategy for the 12 months post ACS event. Consistent with study one we found DAPT to be the most common regimen prescribed. TT was the second most prescribed therapy at discharge, and the use of DAPT compared with TT was not driven by stroke risk. Event rates were unexpectedly low and therefore we could not detect differences in outcomes between therapies due to a lack of statistical power. Overtime, treatment with DAPT and TT decreased and therapy with a single antiplatelet agent or no therapy increased, resulting in many patients being undertreated when compared to well-established ACS guidelines. Patients with higher CHA$_2$DS$_2$VASc scores were more likely to receive OAC therapy, however overall OAC use was low.

On the basis of the first and second study no clear treatment strategy for ACS patients with AF was evident. Therefore in the third study we aimed to systematically review published literature in an attempt to determine whether DAPT or TT was optimal therapy for ACS patients with AF. Studies of pure AF patients with ACS or coronary artery disease undergoing intervention, which compared DAPT and TT, and published ischaemic and/or bleeding endpoints were included in the review. We found that overall the quality of literature was poor with most studies being retrospective analyses on smaller single-centre cohorts. We concluded that TT was consistently associated
with increases in bleeding risk. There was not consistent evidence of reduced stroke or
composite ischaemic endpoints associated with TT, however the largest study indicated
that TT offered significant reductions in mortality and stroke. We therefore remained
uncertain as to whether the increase in bleeding seen with TT was associated with a
decrease in stroke endpoints.

The aims of the fourth study were to construct a decision analysis model to evaluate
bleeding and stroke risk in ACS patients with AF, and, to determine likely thresholds of
stroke risk at which the benefits of TT may exceed harm from bleeding. We found that
risk of bleeding with TT impacted heavily on the overall benefit-risk balance. As a result
the trade-off between increased stroke protection and excess bleeding events only
favoured TT when stroke risk was high, in most instances at a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 3-
5, dependant on the risk parameters applied. This theoretical approach generated the
hypothesis that current thresholds to indicate TT (CHA<sub>2</sub>DS<sub>2</sub>VASc ≥1 [ESC], CHA<sub>2</sub>DS<sub>2</sub>VASc
≥ 2 [Australian] and CHADS<sub>2</sub> ≥ 1 or age over 65 [Canadian], are all likely too low.

With the systematic literature review and the decision model both highlighting the
significant impact of bleeding events with TT we set out to explore whether we could
accurately predict bleeding events in those presenting with ACS. Therefore, the aims of
our final study were to: characterise in-hospital and one-year bleeding events in a real
world MI cohort; evaluate the ability of CRUSADE and ACTION bleeding risk scores to
predict in-hospital and one-year bleeding events; and, examine whether LPR is
predictive of in-hospital and one-year bleeding events. We found the one-year bleeding
rate of non-CABG related TIMI major or minor bleeding to be 13%, and identified female
gender and management with PCI as independent predictors of bleeding. The CRUSADE
bleeding score showed modest ability to predict in-hospital events but ACTION and LPR
did not. Neither bleeding score nor LPR was predictive of out-of-hospital bleeding or
overall bleeding at one-year. The majority of bleeding events occurred in patients
classified as low risk. We concluded that at the individual patient level, contemporary
ACS bleeding scores and LPR were not effective at predicting one-year bleeding events.

Taken together these studies reflect a large amount of clinical uncertainty for the
treatment of ACS patients with concurrent AF. Both in single-centre and nationwide
settings no clear treatment strategy was evident and did not appear to be based on assessments of risk. It is likely that the poor quality of literature identified in the systematic literature review has contributed to this confusion; that is, the absence of high-quality prospective trials has resulted in prescribing patterns that are not guided by a scientifically rigorous evidence base. During the course of this thesis we have also identified that bleeding risk with TT impacts largely on the overall stroke prevention-bleeding risk balance. Accurate prediction of bleeding events would be useful to help mitigate haemorrhagic consequences for ACS patients with AF, particularly those eligible for TT. However, better tools are required as the contemporary ACS bleeding risk scores, CRUSADE and ACTION, as well as platelet reactivity, lack predictive accuracy in a real-world setting.

7.2 Limitations

Throughout this thesis there have been certain limitations that may have influenced our findings and these have been acknowledged within respective chapters. However, there are also overarching limitations that must be acknowledged.

Where drug therapies have been investigated we have primarily examined a DAPT or TT paradigm as these are the current guideline recommendations. However it is entirely possible that other drug combinations have value in this setting, for example OAC + single antiplatelet therapy. There has been a small amount of research conducted on OAC + single antiplatelet regimens which are worth mentioning. The WOEST (What is Optimal antplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary STenting) trial compared OAC + single antiplatelet (clopidogrel) versus TT, but in a slightly different population (69% AF and only 25-30% ACS) and found favour with the former (less bleeding complications with no difference in thrombotic events) \(^{303}\).

The PIONEER-AF PCI study was an open-label, randomized, controlled, multi-centre study exploring assessing the risk of bleeding complications in AF patients undergoing PCI (50% ACS) with three different treatment regimens: rivaroxaban 15 mg once daily plus clopidogrel 75 mg daily for 12 months (a WOEST trial–like strategy), or rivaroxaban
2.5 mg twice daily (with DAPT for 1 to 12 months, an ATLAS trial–like strategy), or dose-adjusted VKA once daily (with DAPT for 1 to 12 months, traditional triple therapy). This study demonstrated that treatment with either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1 to 12 months was associated with a lower rate of clinically significant bleeding when compared to therapy with a vitamin K antagonist plus DAPT. The rates of death from cardiovascular causes, MI or stroke were similar in the three groups but the study was not powered for this endpoint.\textsuperscript{304,305}

Most recently, the RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) compared OAC + single antiplatelet therapy (dabigatran with P2Y12 inhibitor) to TT (with warfarin, P2Y12 inhibitor and aspirin) in patients with AF undergoing PCI (approximately 60% ACS). An OAC + antiplatelet resulted in significantly less bleeding and was non-inferior to TT with respect to thrombotic events.\textsuperscript{306} It is evident that these trials indicate potential value in a NOAC + P2Y12 inhibitor combination. However these studies were not conducted exclusively in our interest group of ACS patients with AF and did not perform comparisons with DAPT. Therefore, while an OAC + single antiplatelet regimen looks promising, as yet superiority over DAPT has not been demonstrated.

It is also difficult to know what drugs optimally make up OAC + single antiplatelet. There are a myriad of possible drug combinations that could constitute this regimen (Figure 7-1), particularly when the combinations of dosing (e.g. high dose vs. low dose), patient characteristics (e.g. variations in kidney function) and patient risk (e.g. stroke and bleeding risk) are considered. In actuality, even less research has been conducted on these alternative drug regimens when compared to DAPT and TT, and this likely explains their omission from guidelines and consensus documents at the commencement of this thesis. On balance, while we cannot rule out OAC + single antiplatelet as a valid treatment strategy for ACS patients with AF, we also cannot be certain of its efficacy-safety profile in this patient group as yet.
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**Figure 7-1 Possible combinations of OAC + single antiplatelet regimens**
Another major limitation that may have affected our findings is the quality of data used from the observational registries. We have used both a single-centre study (Wellington) and a nationwide (ANZACS-QI) ACS registry to detail the treatment of ACS patients with AF, however neither registry was designed to study this patient group specifically. With regard to the ANZACS-QI registry we cannot be certain as to the degree of accuracy that AF data has been recorded, and it is clear that improvements are greatly needed to better capture AF status. Moving forward, improvements to ACS registries would ensure greater confidence in AF-related research, and this is integral if we look to these registries in the absence of RCTs. The limitations of the ANZACS-QI registry design with regard to AF status have been a catalyst for change; as a direct result of the research conducted within this thesis, modifications to the ANZACS-QI database are occurring presently, with data fields specifically pertaining to AF being added. This has the potential to provide an accurate nationwide cohort of ACS patient with AF that will overcome the limitations we have experienced with capturing AF status. Further, it will provide a reliable data source as we look to determine better bleeding and stroke risk models which are desperately needed.

Lastly, we were not able to further define AF into the categories of paroxysmal, persistent and permanent. The current consensus is that stroke risk in AF patients is independent of AF classification and this is based largely on findings that AF patterns do not correspond well to AF burden. What’s more, no stroke risk stratification tool, including the widely used CHA$_2$DS$_2$VASc score, includes AF pattern in its assessment of patients. This has resulted in clinical guideline recommendations that selection of antithrombotic therapy should be based on risk of stroke irrespective of whether the AF pattern in paroxysmal, persistent or permanent. In contrast to this there have been some findings suggesting that AF pattern may influence stroke risk however this evidence is generally weak and guidelines suggest that this should not be a major factor in deciding the usefulness of an intervention. Furthermore, a 2016 meta-analysis found that when compared to paroxysmal AF, non-paroxysmal AF is associated with a highly significant increase in thromboembolism (adjusted HR 1.4, [1.2–1.6] p<0.001), with no detectable difference in bleeding. On the basis of the above, grouping all AF categories together as we have done may not be problematic in the
current AF setting; but we cannot exclude the possibility that stroke risk is indeed different across the different AF categories and had we been able to separate out our AF cohorts our findings may have been different.

7.3 Future directions

The findings of this thesis demonstrate that optimal therapy for ACS patients with AF remains unresolved. This has led to a large amount of clinical uncertainty that must be addressed given the number of ACS patients with concurrent AF is substantial and is expected to rise further over time. On the basis of our findings two avenues for future research are apparent.

Firstly, further prospective testing of DAPT and TT treatment regimens would be advantageous. The foundations for this have been established within this thesis, with the following points identified:

- There is no clear treatment strategy for ACS patients with AF
- TT is associated with excess bleeding risk compared to DAPT
- Stroke protection achieved from TT will be outweighed by excess haemorrhagic risk unless stroke risk is high, around a CHA₂DS₂VASc score of 3-5.

The design of prospective studies would be complex and it is likely that significant preliminary work would be needed to establish what OAC and P2Y₁₂ inhibitor would accompany aspirin in the TT arm. The range of possible combinations is vast when the options for OAC (warfarin, dabigatran, rivaroxaban or apixaban) and P2Y₁₂ inhibitor (clopidogrel, prasugrel or ticagrelor) and various doses are considered. It is sensible to suggest that the DAPT arm would consist of an aspirin-ticagrelor combination due its demonstrated superiority over an aspirin-clopidogrel combination in the PLATO trial, and its wide availability through New Zealand government funding (unlike prasugrel)²³⁸. Whatever the components, the proposed TT and DAPT regimens would also need to receive widespread acceptance from practicing clinicians which in itself brings about a set of challenges.
We believe there is genuine equipoise regarding optimal therapy for patients with a CHA₂DS₂VASc score of 3-5 and therefore a trial to address this would have merit. A simplified schematic of a prospective trial to assess DAPT versus TT can be seen in Figure 7-2. It would be advantageous to conduct this across multiple centres, not necessarily limited to New Zealand centres, as large patient numbers would be needed in each treatment arm. A suitable primary efficacy end point would be combined cardiovascular death, stroke and MI at one-year and a suitable primary safety endpoint would be TIMI major bleeding at one-year. It is also possible for net clinical benefit calculations to be performed for the treatment arms at CHA₂DS₂VASc 3, 4 and 5, to establish the tipping point that would overall favour TT.

With regard to patient population we suggest pure ACS patients with a medical history of AF, not the mixed stable and acute coronary populations seen in trials such as WOEST, PIONEER-AF PCI and RE-DUAL PCI. This is because patients with stable coronary disease have different risk features than those presenting with an acute coronary event. We also propose restricting patients to those managed with PCI to ensure a uniform ACS patient group with obstructive disease. Whilst optimal therapy for all ACS patients’ needs to be defined, select issues associated with CABG surgery and those medically managed would likely introduce complexities that may be difficult to control for. In brief, patients managed with CABG require interruption of antithrombotic therapy prior to surgery and are subject to periprocedural complications including new-onset AF, thrombosis and bleeding. Patients who are medically managed do not always have obstructive disease (rather mild or extensive diffuse disease), and may have frailty issues that alter their thrombotic and bleeding risk, and consequently deter management with PCI. Restricting the study cohort to PCI patients attempts to make the patient group as homogenous as possible and would be favourable given treatment effect is easier to identify when other variability has been reduced. Subsequent investigation into ACS patients managed medically or with CABG surgery would be well placed to occur after the proposed study, where findings regarding a PCI cohort can be taken into account during the study design phase.
Patients with active bleeding, recent spontaneous bleeding, previous intracranial bleeding, platelet function disorders, coagulopathies, alcohol dependence, mechanical valves and mitral stenosis would be excluded due to obvious safety concerns. However, we propose that a high bleeding risk exclusion criteria may not be reasonable given the lack of validated scores in this patient group, and the inaccuracy of pre-existing scores. The inference is that patients incorrectly deemed to be at high risk of bleeding maybe excluded from the trial, and patients incorrectly deemed to be at low risk of bleeding likely included. Should bleeding risk be erroneously assessed this may confound results to an unknown degree and undermine study findings. Further work would need to be done to develop or refute this idea.

Subgroup analysis would also provide valuable information moving forward. Within the CHA\textsubscript{2}DS\textsubscript{2}VASc 3, 4 and 5 treatment arms we may be able to evaluate the treatment effects for a specific endpoint (efficacy or safety), in subgroups of patients defined by a common baseline characteristic. That is, the tipping point for TT may vary across different patient groups. This may be of particular value when identifying subgroups of patients who experience excess harm from bleeding. On completion of a trial such as this, subsequent comparisons can be made with other treatment regimens (e.g. OAC + single antiplatelet) in an attempt to further refine optimal therapy for ACS patients with AF.
Figure 7-2 Simplified scheme of future prospective work examining DAPT and TT

Diagram displays a basic schematic of a prospective study designed to assess CHA$_2$DS$_2$VASc 3, 4 and 5 as thresholds between DAPT and TT.
The second avenue for future research centres on the development of bleeding risk models for ACS patients with AF. Accurate prediction of bleeding risk in this patient group is desperately needed. Both the systematic review (Chapter 4) and the decision model (Chapter 5) highlighted the impact of bleeding risk, when the stroke protection/bleeding risk balance was evaluated. Chapter 6 also established that the contemporary ACS scores of CRUSADE and ACTION were not predictive of bleeding events. Clinicians are therefore trying to manage a group of patients at risk of bleeding, without accurate tools to predict bleeding events. The utilisation of AF based bleeding scores does not seem a feasible solution to model risk in ACS patients with AF. No AF bleeding score accounts for changes in risk profile when a patient presents acutely unwell, as in the case in ACS, nor have these scores been validated in an ACS setting. This is also supported by a 2014 study that examined the predictive ability of the AF bleeding scores HAS-BLED, ATRIA and mOBRI (modified Outpatient Bleeding Risk Index), as well as REACH (Reduction of Atherothrombosis for Continued Health), in a cohort of AF patients undergoing PCI (57% for ACS), with the authors concluding “the performance of ATRIA, HAS-BLED, mOBRI, and REACH scores in predicting bleeding complications in this high-risk patient subset was useless” (pg. 1) 310.

However, mitigation of bleeding risk for ACS patients with AF is crucial. We must therefore look to the development of newer risk models. The above-mentioned prospective trial would provide an ideal setting to develop bleeding risk stratification models. However should a trial such as this not occur or be substantially delayed, the use of pre-existing registry data may be a suitable second-tier option. As mentioned previously, forthcoming improvements to the pre-existing ANZACS-QI registry make this a feasible alternative. In Chapter 3 we outlined that over a 3-year period a total of 3,730 patients were identified as having ACS and AF from the ANZACS-QI registry (see Chapter 3, Figure 3-1) (as we chose to examine the PCI subgroup only, and all the one-year follow up data was not available this was reduced to a final cohort of 610). With the addition of an AF data field to the ANZACS-QI registry it is anticipated that the prospective data collection for ACS patients with AF will be more accurate and reliable. With 3,730 patients over 3-years as a proxy expectation, within a matter of years we may be well-placed to derive novel bleeding risk stratification models from a New Zealand cohort of
ACS patients with AF. By comparison, CHADS\textsubscript{2} was derived in 1,733 patients\textsuperscript{156}, CHA\textsubscript{2}DS\textsubscript{2}-VASc in 1,084 patients\textsuperscript{155} and HAS-BLED in 3,978 patients\textsuperscript{200}. Should it be decided that the development of a bleeding risk model should be restricted to those managed with PCI only, data collection would naturally take longer.

Patients with ACS and AF are common and absolute numbers are expected to rise overtime. These patients are high risk and as such careful management is required. Despite this there is an absence of quality prospective data on therapy in this patient group, and this has led to a lack of clarity in clinical guidelines and clinical practice. Ensuring adequate stroke protection without excess bleeding harm is multifaceted and complex. As such, high quality prospective trials are desperately needed to define optimal care for ACS patients with AF.


