TICAGRELOR IN ACUTE CORONARY SYNDROMES

BY

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Abstract

The PLATO trial demonstrated significantly lower mortality and myocardial infarction in acute coronary syndrome (ACS) patients treated with ticagrelor and aspirin compared to clopidogrel and aspirin. Ticagrelor is a direct acting $P2Y_{12}$ receptor antagonist, and is a more potent inhibitor of platelet reactivity than clopidogrel, and this is believed to be the main cause of its superior efficacy in the PLATO trial. A range of factors have been associated with high on-treatment platelet reactivity (HOTPR) on clopidogrel, including genetic factors, drug interactions and clinical risk factors. HOTPR on clopidogrel has been associated with a higher risk of adverse outcomes following ACS. On the basis of the PLATO trial results, and the theoretical limitations associated with clopidogrel, ticagrelor was funded by PHARMAC in July 2013, and has been recommended for use in patients with ACS in New Zealand.

This thesis examined the use of ticagrelor in a real world ACS population being managed through Wellington Hospital cardiology department. We examined platelet reactivity in patients treated with ticagrelor compared to clopidogrel, factors associated with clinician choice to use ticagrelor versus clopidogrel and the incidence of side effects of ticagrelor that may have implications for compliance with the drug outside the setting of a randomized controlled trial.

We found that ticagrelor significantly reduced both platelet reactivity (30.3 AU ± 17.5 versus 43.7 AU ± 24.8, p= 0.0001) and the proportion of patients classified as having HOTPR (15.9% versus 37.7%, p= 0.0001), in comparison to clopidogrel. The clinical variables associated with HOTPR differ between clopidogrel and ticagrelor, suggesting that different factors were driving residual platelet reactivity on the two agents.

Over a 2 year period, clopidogrel (68%) was used more commonly than ticagrelor (42%), and in a different cohort of patients. Patients treated with ticagrelor were younger (61 years ± 10 versus 65 years ± 12, p=0.0001), less likely to present with STEMI (12% versus 31%, p=0.0001), less likely to have a history of prior

myocardial infarction (15.8% versus 22.7%, p=0.05), and had lower GRACE (98 ± 24 versus 108 ± 28, p=0.0001) and CRUSADE (25 ± 9 versus 28 ± 12, p=0.001) risk scores compared to those treated with clopidogrel. Prescription of ticagrelor was therefore not driven by clinical risk. Antiplatelet prescription varied significantly according to the patients' admitting hospital.

Bleeding rates on ticagrelor and clopidogrel within 30 days of study enrolment were low and were not significantly different. There was 1 patient on clopidogrel who had the drug discontinued due to bleeding. At 30 day follow up, significantly more patients treated with ticagrelor reported dyspnoea (43.3% versus 27.1%, p=0.001), however discontinuation of the drug due to dyspnoea on ticagrelor was infrequent (1.7%).

In this real world cohort of ACS patients, we observed that ticagrelor was associated with more potent platelet inhibition than clopidogrel, but was not associated with factors leading to increased discontinuation at 30 days. Despite the proven benefits of ticagrelor compared to clopidogrel, the majority of patients, including the highest risk patients appear to be preferentially treated with clopidogrel. The causes contributing to underuse of ticagrelor need to be examined and addressed.

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Science is nothing but perception.

- Plato

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Abbreviations

ACS- acute coronary syndrome

ACUITY- Acute Catheterisation and Urgent Triage strategy

ADAPT-DES- Assessment of Dual AntiPlatelet Therapy with Drug Eluting Stents

ADP- adenosine diphosphate

ARTIC- Assessment by a double Randomisation of a conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation one year after stenting

AU- arbitrary units

BARC- Bleeding Academic Research Consortium

BMI- body mass index

CABG- coronary artery bypass grafting

CAD- coronary artery disease

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

CCB- calcium channel blocker

CHF- congestive heart failure

CKMB- creatine kinase myocardial band

CLARITY-TIMI- CLopidogrel as Adjunctive ReperfusIon TherapY- Thrombolysis In Myocardial Infarction

COMMIT- ClOpidogrel and Metoprolol in Myocardial Infarction Trial

COX-1- cyclooxygenase-1

CREDO- Clopidogrel for the Reduction of Events During Observation

CRUSADE- Can Rapid risk stratification of Unstable Angina patients Supress ADverse outcomes with Early implementation of the ACC/AHA guidelines

CURE- Clopidogrel in Unstable angina to prevent Recurrent Events

CURRENT-OASIS- Clopidogrel and aspirin optimal Usage to Reduce Recurrent EveNTs- Organisation to Assess Strategies in Ischaemic Syndromes

CYP- cytochrome p450

DAPT- dual antiplatelet therapy

DES- drug-eluting stent

DISPERSE-2- Dose confIrmation Study assessing antiPlatelet Effects of AZD6140 vs clopidogRel in non-ST-segment Elevation myocardial infarction-2

ECG- electrocardiogram

GP- glycoprotein

GRACE- Global Registry of Acute Caronary Events

GRAVITAS- Gauging Responsiveness with A VerifyNow assay Impact on Thrombosis And Safety

HOTPR- high on-treatment platelet reactivity

HR- hazard ratio

ISAR-CHOICE- Intracoronary Stenting and Antithrombotic Regimen: Choose between 3 High Oral doses for Immediate Clopidogrel Effect

LD- loading dose

LTA- light transmittance aggregometry

LVF- left ventricular function

MACE- major adverse cardiac event

MADONNA- Multiple electrode Aggregometry in patients receiving Dual antiplatelet therapy tO guide treatmeNt with Novel platelet Antagonists

MD- maintenance dose

MEA- multiple electrode aggregometry

MI- myocardial infarction

MRI- magnetic resonance imaging

NSTEMI- non-ST-elevation myocardial infarction

NZ- New Zealand

OR- odds ratio

PCI- percutaneous coronary intervention

PEGASUS-TIMI- Prevention of cardiovascular Events in patients with a prior heart attack usinG ticAgrelor compared to placebo on a backgroUnd of aSpirin-Thrombolysis In Myocardial Infarction

PGE$_1$- prostaglandin E$_1$

PHARMAC- PHARmaceutical Managemency AgenCy

PLATO- PLATlet inhibition and patient Outcomes

PPI- proton pump inhibitor

PRBC- packed red blood cells

PRI- platelet reactivity index

PRU- P2Y$_{12}$ reaction unit

RESPOND- Response to ticagrelor in clopidogrel nonresponders and RESPONDers and effect of switching therapies

ROC- receiver-operator characteristic

SNP- single nucleotide polymorphism

STEEPLE- SafeTy and Efficacy of Enoxaparin in Percutaneous coronary intervention patients, an internationaL randomised Evaluation

STEMI- ST-elevation myocardial infarction

TIA- transient ischaemic attack

TIMI- Thrombolysis In Myocardial Infarction

t_{max}- maximum concentration

TRIGGER-PCI- Testing platelet Reactivity In patients underGoinG Elective stent placement on clopidogRel to guide alternative therapy with prasugrel- Percutaneous Coronary Intervention

TRILOGY ACS- TaRgetted platelet Inhibition to cLarify the Optimal strateGY to medically manage Acute Coronary Syndromes

TRITON-TIMI- TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel- Thrombolysis In Myocardial Infarction

UA- unstable angina

VASP-P- vasodilator-stimulated phosphoprotein phosphorylation

Chapter 1- Introduction

1.1 Atherosclerosis

Atherosclerosis is the underlying pathophysiology in the majority of coronary artery disease (CAD) cases. Coronary atherosclerotic lesions are characterized by the adaptive intimal thickening of the coronary artery due to the accumulation of lipids and endothelial, smooth muscle and immune cells. The evolution of an initial lesion to a complex vulnerable plaque impinging on the coronary vessel lumen and impeding blood flow, is illustrated in Figure 1.1 [1]. The mechanical force of blood flow can rupture atherosclerotic plaques, exposing the necrotic core that activates platelet adhesion, thrombosis and vasospasm [2].

1.1.1 Platelet involvement in atherosclerosis

Myocardial infarction (MI) is most commonly caused by plaque rupture and subsequent coronary artery thrombosis, in which platelets have a central role. Platelets primarily function to stop haemorrhage after tissue trauma and vascular injury, by preserving vascular integrity. A ruptured atherosclerotic plaque causes endothelial damage that platelets adhere to and aggregate. This forms a prothrombotic surface, which promotes clot formation and subsequent vascular occlusion. The occlusion of blood flow in coronary arteries leads to subsequent myocardial ischaemia and infarction. The central role platelets play in acute MI is demonstrated by the ability of antiplatelet agents to reduce the associated rate of mortality and morbidity [3].

Platelets are essential for primary haemostasis and to repair damaged endothelium, but they also contribute to the development of acute coronary syndromes (ACS) and the formation and extension of atherosclerotic plaques. Platelets adhere to blood vessel walls at sites of endothelial-cell activation, contributing to the development of chronic atherosclerotic lesions. The rupture of these lesions triggers the acute onset of arterial thrombosis [4].
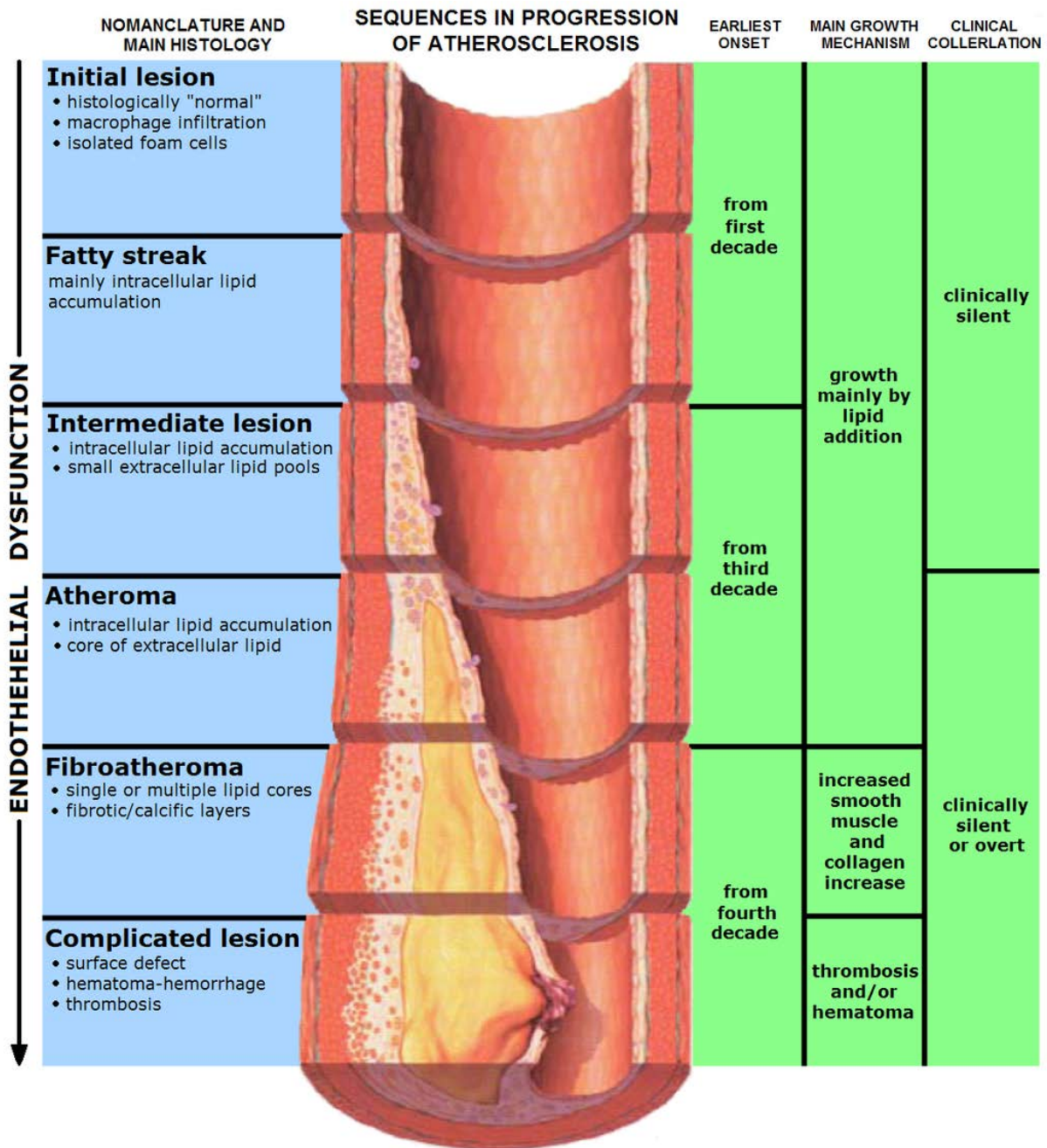
Figure 1.1 Progression of an atheroclerotic plaque.

Schematic depiction of the stages in the progression of atherosclerosis. Development of the lesion is illustrated, with the accompanying histology findings, approximate age of onset, dominant mechanism of growth and subsequent clinical manifestation. Image reproduced with permission from Creative Commons Attribution-Share Alike 3.0 Unported.

Atherosclerosis without blood flow limiting thrombosis is a slow, progressive disease. Erosion of the endothelial surface or atherosclerotic plaque disruption, initiates thrombosis, the mechanism responsible for the sudden transition from a stable, often clinically silent disease to a symptomatic life-threatening condition. Platelet activation occurs at vulnerable sites of the atherosclerotic plaque, where the thin fibrous cap separating the lipid-rich core from the lumen disintegrates, tears or breaks. This doesn't necessarily trigger an ACS, the majority of acute vascular lesions resolve spontaneously through a repair process similar to haemostasis. Haemorrhage into plaque fissures and sealing of the disrupted surface by platelets, contributes to the dynamic, unpredictable and nonlinear, but repeated progression of coronary atherosclerotic lesions. Repeated episodes of platelet activation over the persistently thrombogenic surface of a disrupted plaque eventually progresses to persistent thrombosis [5].

1.2 Acute coronary syndromes (ACS)

An ACS is the unstable and potentially life-threatening clinical manifestation of CAD. While atherosclerotic lesions may obstruct blood flow and cause symptoms classified as angina pectoris, they rarely cause a fatal event alone. Myocardial ischaemia and subsequent infarction are caused by vulnerable atherosclerotic plaques activating platelets, initiating an occluding thrombus on the culprit atherosclerotic plaque [6]. Vulnerable plaques often have a thin fibrous cap making them susceptible to rupture, exposing the lipid core to arterial blood flow. The plaque core is highly thrombogenic, containing factors that accelerate coagulation. The thrombus initially forms in the plaque, expanding and extending into the arterial lumen [7]. Plaque rupture or erosion is not enough to cause an ACS [8]. A combination of factors such as the thrombogenicity of the exposed plaque material, local blood flow dynamics and systematic thrombotic predisposition create a perfect storm scenario resulting in myocardial ischaemia and infarction [2].

1.2.1 Clinical treatment of ACS

ACS are a spectrum of clinical conditions ranging from undifferentiated chest pain, unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI), represented in Figure 1.2.
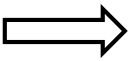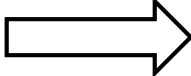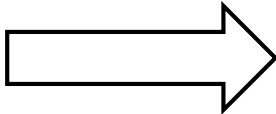
Unstable angina (UA)	Non-ST-segment elevation myocardial infarction (NSTEMI)	ST-segment elevation myocardial infarction (STEMI)
	(Increasing severity)	
	⇨ ⇨ ⇨	
Anginal pain that: → Has a more severe onset → Worsens in severity/length of episode → Occurs at rest/with minimal exertion	Clinical features of unstable angina: → + elevation of blood cardiac biomarkers (troponin, CKMB) → +/- ST segment depression and T wave flattening/inversion	Clinical features of myocardial infarction: → + ST-segment elevation.

Figure 1.2 Spectrum of Acute Coronary Syndromes (ACS).

Schematic table differentiating the clinical manifestation of ACS by UA, NSTEMI and STEMI. Adapted from Boateng et al. [9] with permission from Elsiever.

Myocardial infarction is most commonly caused by atherosclerotic plaque rupture, erosion, ulceration, fissuring or dissection causing intraluminal coronary thrombus. This results in decreased myocardial blood flow or distal platelet emboli and myocyte necrosis defined as MI type 1. MI can also be caused by an imbalance between myocardial oxygen supply and demand (MI type 2). This can be a result of coronary vasospasm, endothelial dysfunction, fixed atherosclerosis or a supply-demand imbalance alone. Revascularization procedures, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), can also cause MI (types 4a and 5, respectively). Stent thrombosis or restenosis following PCI are considered MI type 4b [10].

Symptoms of myocardial ischaemia can include various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest. Ischaemic equivalent symptoms include dyspnoea (shortness of breath) or fatigue. Discomfort caused by an ACS usually lasts longer than 20 minutes and may be accompanied by diaphoresis (sweating), nausea or syncope (loss of consciousness) [10].

Treatment of ACS aims to reduce the amount of myocardial necrosis to preserve left ventricular function. Reperfusion therapy aims to restore coronary blood flow to ischaemic myocardium to limit infarct size. PCI using stents and balloons is the preferred treatment strategy. PCI restores coronary artery blood flow in >90% of patients under optimal circumstances. Guidelines advise STEMI patients to undergo primary PCI within 90 minutes of hospital presentation, by a skilled provider in a well-equipped facility. If this cannot be achieved, fibrinolytic therapy is recommended. Adjunct therapies in both ACS and stable CAD include: oxygen, nitroglycerin, analgesia, antiplatelet agents, anticoagulants, antihypertensive medications and statin therapy [11].

1.2.2 Burden of ACS

CAD was the leading cause of death globally in 2010, responsible for 7.0 million deaths [12]. In 2011, CAD was the second leading cause of death in New Zealand, after cancer, accounting for 18.3% of all deaths. Acute myocardial infarction comprised 46% of deaths attributed to CAD [13]. A significant number of New Zealanders have an ACS every year. A snapshot audit conducted over a 2 week period in May 2012 found 1007 New Zealanders were admitted to hospital with suspected or definite ACS, equating to an annual rate of around 26,000 ACS presentations. During that 2 week study 17 patients died in hospital, and other deaths would have occurred prior to hospital admission or post discharge that were not captured in the study [14]. Over a two year period between 2007 and 2009, 42,920 New Zealanders were hospitilised with an ACS. A fifth (20.6%) of

patients died within a year of their ACS hospital admission, 46.2% within 28 days, giving case fatality rates of 9.5% at 28 days and 12.3% at one year. Case fatality increased with age and differed according to ethnicity. Maori had the highest age-standardised 28 day and one year case fatality rates (14.6% and 17.8%, respectively), followed by Pacific Islanders (12.5% and 16.3%), then European and other ethnicities (9% and 12-13%) [15].

1.3 Antiplatelet agents

The standard medical therapy for ACS includes the use of dual anti-platelet agents, aspirin and a $P2Y_{12}$ inhibitor, which has previously been clopidogrel. These agents are given to decrease the formation of thrombus within the coronary vasculature [16]. Aspirin irreversibly inhibits cyclooxygenase (COX-1) in the arachidonic acid pathway. This subsequently blocks the production of the platelet agonist thromboxane A_2, which stimulates thromboxane A_2 receptors to release adenosine diphosphate (ADP). ADP binds to the $P2Y_{12}$ ADP receptor on the platelet to inhibit the anti-aggregatory effects of adenylate cyclase, thus escalating aggregation. Thienopyridines, such as clopidogrel and prasugrel prevent ADP from binding to the $P2Y_{12}$ receptor, by irreversibly binding to the $P2Y_{12}$ receptor themselves. Inhibiting these mechanisms, reduces thrombus formation [17].

1.3.1 Aspirin

Aspirin is the cornerstone antiplatelet therapy of recurrent ischaemic events in ACS patients [18]. A meta-analysis of 16 trials, comprising 17,000 patients at high risk of occlusive vascular events (previous MI, stroke or transient ischaemic attack, TIA), compared long-term aspirin therapy to no aspirin therapy for the secondary prevention of recurrent ischaemic events. Aspirin therapy for secondary prevention resulted in an absolute reduction of serious vascular events (6.7% vs 8.2% per year, p<0.0001), stroke (2.08% vs 2.54% per year, p=0.002) and in coronary events (4.3% vs 5.3%, p<0.0001). In pooled analysis of the 6 trials comprising only patients with a previous MI, aspirin therapy reduced serious

vascular events (6.6% vs 8.3%, p<0.00001), non-fatal MI (2.2% vs 3.1%, p=0.00003), coronary heart disease death (3.6% vs 4.1%, p=0.04) and major coronary events (6.0% vs 7.4%, p=0.00003). However, aspirin therapy did not significantly reduce the incidence of stroke (0.6% vs 0.8%, p=0.06) [19].

Low dose aspirin (75-150 mg daily) is an effective long term antiplatelet agent. In the setting of an acute MI where an immediate antithrombotic effect is required, a loading dose of 150-300 mg is necessary to provide rapid and complete inhibition of thromboxane mediated platelet aggregation [20]. The benefit of early administration of aspirin in ACS has been consistently shown in unstable angina (UA) and NSTEMI patients [21, 22] and STEMI patients [23]. The important role of aspirin in ACS is emphasized by the nearly two-fold (OR 1.82, p<0.00001) increased risk of adverse events in patients with an ACS or stable CAD discontinued or non-compliant with aspirin therapy [20]. Furthermore, laboratory defined aspirin resistance has been associated with a higher risk of recurrent ischaemic events (odds ratio, OR, 3.8), ie "clinical resistance" [24].

1.3.2 Clopidogrel

Clopidogrel efficacy was first evaluated in the CAPRIE trial, which compared clopidogrel and aspirin monotherapy in the secondary prevention of atherothrombotic disease. The population studied comprised of 19,185 patients with atherosclerotic vascular disease, with similar proportions of patients suffering recent ischaemic stroke, recent MI or symptomatic peripheral arterial disease. The primary endpoint, a composite outcome of ischaemic stroke, MI or vascular death, was modestly reduced with clopidogrel treatment (5.32% vs 5.83%), with a relative risk reduction of 8.7% (p=0.043). Bleeding rates were similar between groups (9.27% vs 9.28%), as were severe bleeding events (1.38% vs 1.55%) [25].

The CURE trial was the first to investigate dual antiplatelet therapy (DAPT), with clopidogrel and aspirin, compared with placebo and aspirin. Patients presenting

with an ACS without ST-elevation treated with clopidogrel experienced a lower incidence of the primary outcome, a composite of death from cardiovascular causes, MI or stroke (9.3% vs 11.4%, p<0.001). However, this benefit was at the expense of major bleeding, with more patients treated with clopidogrel experiencing a major bleeding event (3.7% vs 2.7%, p=0.001). Life threatening episodes of bleeding were not significantly different (2.2% vs 1.8%), although the incidence of transfusion of two or more units of blood was higher with clopidogrel (2.8% vs 2.2%, p=0.02). The risk of minor bleeding was also higher amongst the clopidogrel group (5.1% vs 2.4%, p<0.001) [26]. In a substudy of patients pretreated prior to PCI in the CURE trial (PCI-CURE), the clopidogrel group experienced a significant reduction in the incidence of the primary end point within 30 days of PCI (4.5% vs 6.4%, p=0.03). This was achieved without a significant difference in major bleeding rates or the incidence of blood transfusions [27].

The CREDO trial demonstrated clopidogrel therapy for one year following PCI in patients with suspected CAD was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke. Patients pre-treated with clopidogrel at least 6 hours prior to PCI experienced a relative risk reduction of 38.6% for the composite end point, whereas this reduction was attenuated in patients pre-treated less than 6 hours prior to PCI. The risk of major bleeding over the year was numerically increased in the clopidogrel group (8.8% vs 6.7% with placebo after 28 days, p=0.07) [28].

The CLARITY-TIMI 28 trial compared clopidogrel to placebo in conjunction with fibrinolytic therapy in patients presenting with STEMI, achieving a 20% risk reduction in major adverse cardiac events (MACE) at 30 days. Clopidogrel therapy also reduced the rate and odds of death, recurrent MI or occluded infarct-related artery on angiography by 6.7% and 36% respectively. The rates of major bleeding were similar between the groups [29]. The COMMIT trial compared clopidogrel to placebo, in addition to aspirin, in 45,852 patients predominantly presenting with ST-segment elevation or bundle branch block (93%). Clopidogrel therapy in addition to standard therapy, significantly reduced the risk of death, reinfarction

or stroke (9.2% vs 10.1%, p=0.002). This benefit was not associated with an excess risk of bleeding [30].

On the basis of these clinical trials, DAPT with clopidogrel and aspirin became the international guideline recommended therapy following ACS [31-34]. The implementation of DAPT significantly improved patient outcomes, yet 8-10% of patients suffer a recurrent cardiovascular event within a year of ACS. The first study indicating variability in CAD patient response to the recommended doses of clopidogrel was published just one year after the CURE trial [35]. Gurbel and colleagues demonstrated response variability to clopidogrel in PCI patients loaded with 300 mg clopidogrel, followed by a 75 mg maintenance dose. Whilst initially clopidogrel non-responsiveness occurred in 31% of patients measured 1-5 days after their loading dose was given, this did fall to 15% by day 30 [36]. Higher loading doses of 600 mg clopidogrel have been associated with more potent platelet inhibition than a dose of 300 mg. Yet, a 600 mg clopidogrel loading dose is not able to overcome all response variance, which continues to persist [37]. Hence, the level of platelet reactivity following clopidogrel therapy is essentially unpredictable.

1.4 High on-treatment platelet reactivity (HOTPR)

The idea that patients who do not respond adequately to an antiplatelet agent that has clinical benefit in reducing thrombotic events, are at an increased risk for thrombotic events, is a logical one. There is a substantial amount of literature proposing clopidogrel nonresponsiveness as an etiology for thrombotic events following PCI [38]. A single treatment strategy against a single receptor cannot be expected to prevent any subsequent thrombotic events. Hence clinical treatment failure, the occurrence of an ischaemic event whilst undergoing clopidogrel therapy, is not indicative of clopidogrel resistance. The definition of resistance or nonresponsiveness to an antiplatelet agent should ideally be the failure of the antiplatelet agent to inhibit its target of action [39]. Initially, this was assessed by measuring patients' responsiveness to clopidogrel as the absolute or relative

change from baseline in platelet aggregation. Whilst this is a reliable measure of treatment effect, it does not necessarily identify patients at high risk. Baseline ADP-induced platelet aggregation is subject to significant interindividual variability, hence the absolute or relative measure of clopidogrel responsiveness and subsequent platelet inhibition may overestimate the ischaemic risk in nonresponders with low baseline platelet reactivity, whilst conversely underestimating the risk in clopidogrel responders who maintain high platelet reactivity during treatment. A measure that takes this into account is the absolute level of platelet reactivity whilst on-treatment and has been proposed as a superior measure of thrombotic risk [40, 41].

1.4.1 Prognostic significance of HOTPR

Meta-analyses have demonstrated high on-treatment platelet reactivity (HOTPR) is highly predictive of adverse ischaemic events [42]. In a meta-analysis of 20 studies comprising 9,187 patients, HOTPR was associated with a 3-fold increase in nonfatal MI ($p<0.00001$), a 4-fold increase in definite or probable stent thrombosis ($p<0.0001$) and a 3.4-fold increase in cardiovascular mortality, compared with patients within the therapeutic range of platelet reactivity. There was a 5-fold increase in the rate of a composite of ischaemic events ($p<0.00001$), made up of cardiovascular death, MI, ischaemic stroke, rehospitalisation for ACS or unplanned repeat revascularization [43].

1.4.2 Contributors to HOTPR

Clopidogrel is a prodrug that is converted via hepatic metabolism to its active metabolite, which exerts its therapeutic antiplatelet effect. However, this is an inefficient process as most absorbed clopidogrel (~85% to 95%) is hydrolysed by carboxylase in the blood into an inactive carboxylic metabolite SR26334. The remaining ~10% to 15% makes it to the liver where it is rapidly metabolized by the hepatic cytochrome (CYP) P450 family of isoenzymes in a two-step sequential process. CYP2C19, CYP2B6 and CYP1A2 oxidise clopidogrel to 2-oxo-clopidogrel.

CYP2C19, CYP2B6, CYP2C9 and CYP3A then hydrolyse 2-oxo-clopidogrel to a highly unstable active metabolite, R-130964, which specifically covalently binds to the platelet P2Y12 receptor during the platelet's passage through the hepatic circulation, illustrated in Figure 1.3. This is an irreversible reaction, hence it results in inhibition of ADP-induced platelet activation and subsequent aggregation for the lifespan of the platelet [44], which is 8-10 days in healthy subjects [45]. As such, new platelets released into the circulation after clopidogrel metabolism are not exposed to the active metabolite and its conferred inhibition until the next dose is administered [46].

Clopidogrel's reliance on hepatic metabolism to exert its therapeutic effect is a significant shortcoming. Variable and insufficient active metabolite generation is the leading explanation for both variability in patients' response to clopidogrel and non-responsiveness altogether [47]. Single nucleotide polymorphisms (SNP) upregulate the ABCB1 gene that encodes the p-glycoprotein drug-efflux transporter that is a physiologic intestinal barrier against the absorption of several drugs, including clopidogrel [48]. SNPs that compromise CYP450 isoenzymes' ability to metabolise clopidogrel, drug-drug interactions and other factors that interfere with P450 isoenzyme activity are all contributors to this variance in the levels of active metabolite generation and ability of the prescribed dosage of clopidogrel to exert its therapeutic effect [38].

Links have been established between genetic polymorphisms associated with insufficient clopidogrel active metabolite generation, elevated platelet function indicating decreased clopidogrel responsiveness, and adverse clinical outcomes. However, no single study has been able to decisively prove this in the same patient population. Furthermore, it is uncertain whether factors contributing to a poor response to clopidogrel are additive in compromising the antiplatelet therapy of clopidogrel and subsequent patient outcomes [38].
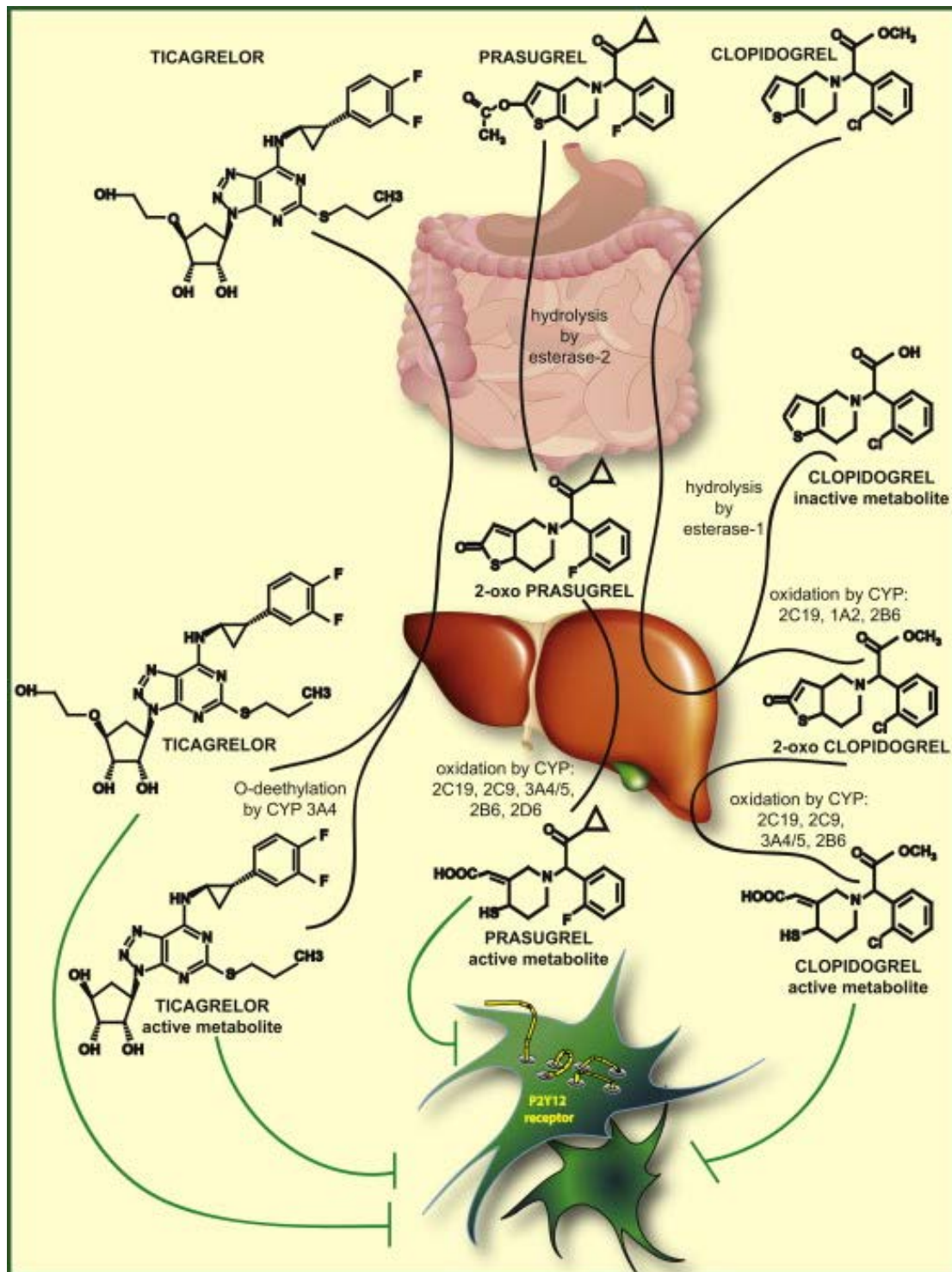
Figure 1.3 The metabolic pathways of P2Y$_{12}$ receptor antagonists clopidogrel, prasugrel and ticagrelor.

ADP= adenosine disphosphate; CYP= cytochrome P450. Figure reproduced from Siller-Matula et al. [49] with permission from Elseiver.

ABCB1 SNPs have been demonstrated to alter clopidogrel pharmacokinetics and pharmacodynamics. As a consequence, patients carrying a variant ABCB1 T allele have worse clinical outcomes [48]. Twelve percent of variability in clopidogrel response can be attributed to the CYP2C19*2 loss-of-function allele [38]. CYP2C19 is involved in both of the sequential steps to convert clopidogrel to its active metabolite. Patient carriage of any two CYP2C19 loss of function allele variants (*2, *3, *4 or *5) is linked to worse clinical outcomes [48]. Other studies comprising PCI patients also demonstrate a significant relationship between ischaemic risk and any loss-of-function allele carriers, for both homozygotes and heterozygotes [50, 51]. CYP2C19*2 variants were observed in 32% of a New Zealand (NZ) ACS population. There were significant differences in distribution by ethnicity, with 47% Maori and Pacific Islanders carrying the allele, compared to 26% in the NZ European population. CYP2C19*2 status was a significant predictor of platelet reactivity in multivariate analysis, along with diabetes and clopidogrel dose. However, only 20-21% of the variance in observed platelet reactivity was explained by a patients' genotype and clinical characteristics [52].

Drug interactions influence the metabolism of clopidogrel by stimulation, competition or inhibition of CYP450 isoenzyme activity. Rifampin and St. John's wort both stimulate CYP3A4 activity, while tobacco smoking that upregulates CYP1A2 activity, contribute to increased levels of clopidogrel's active metabolite and enhanced platelet inhibition. In contrast, agents that compete with clopidogrel for access to CYP450s or inhibit CYP450s altogether attenuate clopidogrel's antiplatelet therapy. Proton pump inhibitors (PPI), lipophilic statins and calcium channel blockers (CCB) metabolized by CYP2C19 and CYP3A4 have been associated with a diminished pharmacodynamic response to clopidogrel. Whilst reduced platelet inhibition from clopidogrel has been illustrated following co-administration of these agents, the ischaemic consequence of this remains controversial [38].

In addition to genetic polymorphisms and drug interactions, clinical characteristics have also been associated with a diminished antiplatelet response to clopidogrel. Age, diabetes, ACS, increasing body mass index (BMI), reduced left

ventricular function (LVF), renal failure, inflammation, sex, platelet count, fibrinogen levels, underdosing and patient compliance have all been associated with the variability of patient response to clopidogrel [49].

1.4.3 Measuring platelet reactivity

The predictive value of on-treatment platelet reactivity measurements for both periprocedural and longterm ischaemic event risk has been widely investigated. However, there is discord regarding both the optimal methodology to measure platelet reactivity and the threshold that defines HOTPR to ADP [38]. Different assays reflect distinct aspects of platelet biology, hence choosing the right assay depends on the purpose of testing [53].

Light transmittance aggregometry (LTA) evaluates the response of the platelets $P2Y_1$ and $P2Y_{12}$ receptors to ADP. Platelet-rich plasma is stirred in a cuvette between a light source and a photocell. ADP is added, stimulating the platelets to aggregate, detected by the photocell as greater light transmission [54]. LTA is not standardised between institutions and is subject to methodological variables that contribute to variance in the prevalence of nonresponders. These include the concentration of the agonist ADP, the anticoagulant used and the LTA value (maximal or late platelet aggregation). Furthermore LTA is time-consuming and technically demanding, contributing to its limited use [55].

VerifyNow is a point of care assay that measures the rate and extent of platelet aggregation in whole blood. It performs this by a turbidimetric measurement of platelet agglutination and aggregation to fibrinogen-coated micro beads. VerifyNow uses a combination of the agonists ADP and prostaglandin E_1 to specifically target the $P2Y_{12}$ receptor. Additionally, a separate well contains thrombin receptor activating peptide that provides a baseline platelet function measurement to give the degree of platelet inhibition on clopidogrel [55].

The vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) assay is the most specific assay to quantify the pharmacodynamics effect of clopidogrel. It uses flow cytometry to measure the inhibition of the P2Y12 receptor, clopidogrel's biological target, and its intracellular signaling, cyclic adenosine monophosphate-dependent phosphorylation of VASP, stimulated by PGE_1. Platelets are labeled with a primary monoclonal antibody against serine 239-phosphorylated VASP, followed by a secondary antibody that fluoresces. The platelet population are identified, fluorescence is measured and platelet reactivity index (PRI) calculated, which inversely correlates with the effect of clopidogrel treatment [53]. While VASP measures the extent of $P2Y_{12}$ receptor inhibition, it does not give a functionally relevant measure of platelet aggregation and hence fails to encompass the true extent of HOTPR [43].

The Multiplate assay uses multiple electrode aggregometry (MEA) to assess platelet function in whole blood by testing platelet aggregation with various agonists. Stimulated platelets aggregate and adhere to two independent electrode sets in a test cuvette and the change in electrical impedance is measured. The mean value of the two independent electrode pairs are expressed as the area under the curve of the aggregation tracing. This can be expressed as arbitrary aggregation units (AU x min) or as units (AU), which has caused some confusion in the literature, although 10 AU x min are equivalent to 1 AU. MEA is semiautomated, performs a dual measurement to serve as an internal control and eliminates potential disadvantages of LTA, including variable reproducibility, large sample volumes, time-consuming centrifugation and lengthy processing time [53]. However, residual platelet aggregation is markedly affected by the anticoagulant used and time delay between sampling and testing. Hirudin, a direct thrombin inhibitor, is the recommended anticoagulant as it preserves physiological calcium concentrations. A timeframe of 15-45 minutes from blood sampling to analysis has been suggested to minimize variability [56].

1.4.4 Measuring HOTPR

The LTA, VerifyNow, VASP-P and MEA assays' predictive ability rests on the establishment of a threshold definition of HOTPR. Receiver-operator characteristic (ROC) curve analysis is used to define the cutoff value of HOTPR that is associated with ischaemic risk with the greatest sum of sensitivity and specificity. HOTPR is defined according to the assay used: >46% maximal 5-µmol/l ADP-induced aggregation using LTA [57], >235 to 240 P2Y$_{12}$ reaction units (PRU) with VerifyNow [58], PRI >50% by VASP-P [59] and >468 AU/min in response to ADP using MEA [38, 60].

Aradi and colleagues conducted a review and meta-analysis on the prognostic significance of HOTPR measured by LTA, VASP-P, VerifyNow and MEA in 20 studies, comprising 9,187 stable CAD and ACS patients. Although there were large interstudy and intra-assay differences in the prevalence of HOTPR (6%-80%) due to different methodologies and definitions of the HOTPR threshold, the predicted risk for cardiovascular death, nonfatal MI and stent thrombosis in patients with HOTPR were not heterogenous between the studies. LTA had the highest predictive value for cardiovascular death and was significantly associated with MI and stent thrombosis (OR 4.18, 2.93 and 3.66 respectively, all p<0.0001). The VerifyNow assay predicted cardiovascular death and MI (OR 2.28, p=0.009 and 2.98, p<0.00001, respectively), but there was only a trend in predicting stent thrombosis (OR 4.17, p=0.09). MEA had the greatest power to predict MI and stent thrombosis (OR 4.03, p=0.03 and 13.89, p=0.002, respectively), though there was only a trend in predicting cardiovascular death (3.21, p=0.08). VASP-P was not predictive of cardiovascular death or stent thrombosis (1.84, p=0.08 and 1.48, p=0.64, respectively), although this was based on two small studies [43].

A study investigating the rate of HOTPR in a New Zealand ACS population demonstrated that 38% patients experienced HOTPR. In accordance with other studies, platelet reactivity was linked with clopidogrel dosing. Patients treated with low dose clopidogrel experienced significantly higher rates of HOTPR (45.4%) compared to patients on intermediate or high dose regimens (25.4% and

26.8%, respectively). Maori and Pacific Islanders had a higher rate of HOTPR compared with NZ Europeans (57% vs 35.9%, respectively). Patients with diabetes also had higher rates of HOTPR than non-diabetics (50% vs 34.8%). Maori and Pacific Islanders were observed to have higher rates of diabetes, which may have contributed to the ethnic disparity in clopidogrel response [61].

1.5 Bleeding

Adverse ischaemic outcomes are not the only concern. ACS patients who suffer from major bleeding have a five-fold higher incidence of 30 day mortality (hazard ratio, HR 5.37, p<0.0001) [62]. Blood transfusion is associated with a nearly four-fold increase in the adjusted risk of 30 day mortality for ACS patients (adjusted HR 3.94). Blood transfusion is a marker of more serious bleeding events but may also directly cause adverse outcomes by depleting nitric oxide, resulting in vasoconstriction, or decreasing the oxygen carriage of the blood [63]. The mechanisms responsible for the association between bleeding and mortality are complex. They include hypotension, anaemia, ineffective oxygen delivery, vasoconstriction, platelet dysfunction and subsequent discontinuation of antiplatelet or antithrombotic therapy [64].

Major bleeding events and MI have a similar impact on patient mortality within a year of an ACS. Major bleeding and MI accounted for 13% and 10% of deaths in the ACUITY trial. Even after accounting for baseline predictors of mortality, major bleeding and MI carried hazard ratios of 3.5 and 3.1 for mortality at one year. The risk of bleeding and MI peak at different time points. MI has a dramatic early risk of death, with hazard ratios of 17.6 within a day, 8.2 at one week, 2.9 at 30 days and 1.4 thereafter. Whereas bleeding has a more prolonged mortality risk, with hazard ratios of 5.5 within a day, 5.8 at one week, 5.6 at 30 days and 2.4 thereafter [65].

1.5.1 Therapeutic window

In contrast to the accumulation of ischaemic events in clopidogrel non-responders, dropping below a threshold value predicts major bleeding events. Sibbing and colleagues established a therapeutic window using ROC curve analysis of PCI patients' platelet reactivity measured by MEA [66]. While platelet reactivity measured by MEA >46 AU was associated with definite or probable stent thrombosis [60], platelet reactivity <19 AU with MEA was associated with in-hospital Thrombolysis In Myocardial Infarction (TIMI) defined major bleeding [67]. The concept of a therapeutic window of platelet reactivity is similar to the international normalized ratio range used to monitor warfarin therapy [39]. Bonello and colleagues established ≤16% PRI as a cutoff associated with increased bleeding risk in ACS patients undergoing PCI measured by VASP-P [68], while PRI >50% predicted ischaemic events in stable CAD PCI patients [59]. A lower cutpoint of 86 PRU has been used with the VerifyNow assay in stable CAD patients [69], while 208 PRU has been used as the upper threshold in PCI patients (stable CAD and ACS) in the ADAPT-DES and GRAVITAS trials [70, 71]. The therapeutic window for each assay is illustrated in Figure 1.4.

<85	VerifyNow-PRU	>208
<16%	VASP-PRI	>50%
<19	MEA-AU	>46
<31	TEG-MA_{ADP} (mm)	>47
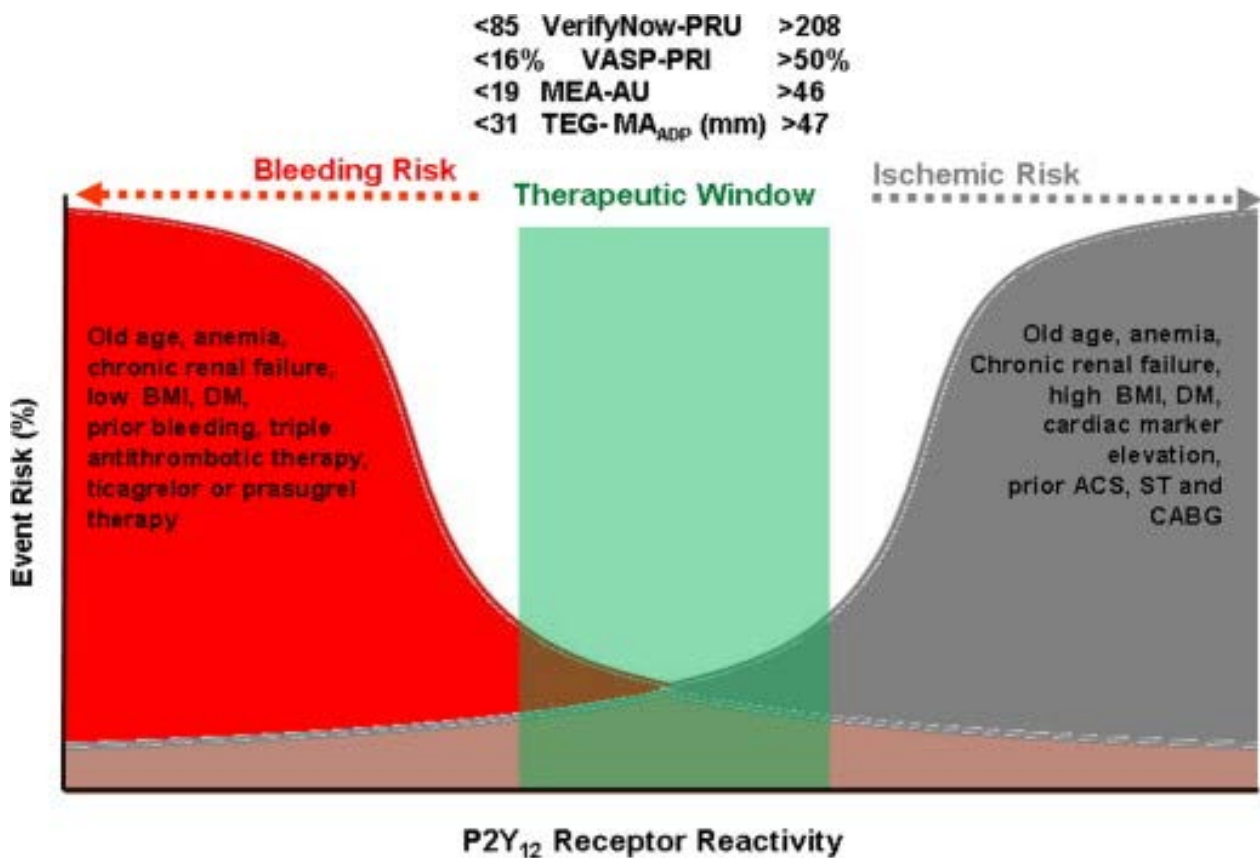
Figure 1.4 MEA, VerifyNow and VASP-P thresholds associated with increased bleeding or ischaemic risk, creating a therapeutic window.

Factors associated with increased bleeding and/or ishcaemic risk are also included. Reproduced from Tantry et al. [72] with permission from Elseiver.

1.6 More potent platelet inhibition

1.6.1 Higher clopidogrel doses

The ISAR-CHOICE trial evaluated the absorption, metabolism and platelet inhibition of 300 mg, 600 mg and 900 mg clopidogrel loading doses (LD) in stable CAD patients. A 600 mg LD of clopidogrel results in higher plasma concentrations of clopidogrel, its active thiol metabolite (R-130964) and its inactive carboxyl

metabolite than 300 mg. This translates into lower values of platelet aggregation. Yet, increasing the loading dose to 900 mg does not further suppress platelet aggregation, reflected in a lack of increase in plasma concentrations of clopidogrel's active metabolite [73].

The CURRENT-OASIS 7 trial assessed the safety and efficacy of high vs standard dose clopidogrel (600mg LD and 150mg daily MD for 7 days, then 75mg daily thereafter vs 300mg LD and 75mg MD) in patients presenting with ACS scheduled for PCI. Furthermore, the investigators evaluated the safety and efficacy of high vs low dose aspirin (300-325 mg daily vs 75-100 mg daily) within each clopidogrel arm. No significant differences were found between high and standard dose clopidogrel in the rates of the primary outcome of cardiovascular death, myocardial infarction or stroke (4.2% vs 4.4%, p=0.30). Nor did the primary outcome differ according to high vs low aspirin dose (4.2% vs 4.4%, p=0.61). However, there was a nominally significant reduction in the primary outcome with high dose clopidogrel (3.9% vs 4.5%, p=0.036) in the 69% patients who underwent PCI. High dose clopidogrel also significantly reduced the secondary outcome of stent thrombosis in PCI patients (1.6% vs 2.3%, p=0.001) but this was at the expense of increased trial defined major bleeding incidence overall (2.5% vs 2.0%, p=0.01). Major bleeding incidence did not differ with high or low aspirin dosage (2.3% vs 2.3%, p=0.90) [74].

1.6.2 Prasugrel

The TRITON-TIMI 38 trial investigated efficacy of prasugrel, a third generation thienopyridine, in moderate to high risk ACS patients scheduled for PCI. In doing so, it tested the hypothesis that an antiplatelet agent that could produce higher and more consistent levels of platelet inhibition to ADP-induced platelet aggregation, would reduce ischaemic events [75]. The primary efficacy endpoint, a composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke occurred in 9.9% prasugrel patients, compared with 12.1% in clopidogrel patients (p<0.001), a 19% relative reduction. The key safety end point of TIMI major

bleeding occurred in 2.4% prasugrel patients vs 1.8% clopidogrel patients (p=0.03), a relative increase of 32%. The rate of life-threatening bleeding was greater with prasugrel (1.4% vs 0.9%, p=0.01), as was fatal bleeding (0.4% vs 0.1%, p=0.002). Net clinical benefit, the combined efficacy and safety endpoints, favoured prasugrel over clopidogrel (12.2% vs 13.9%, p=0.004). However, patients with a history of stroke or TIA suffered net harm from prasugrel treatment (HR 1.54, p=0.04). This was despite the exclusion of patients with a history of haemorrhagic stroke. Furthermore, patients 75 years and older and patients weighing less than 60 kg received no net benefit from prasugrel therapy [76].

Prasugrel achieves more rapid, potent and consistent platelet inhibition than 300 mg clopidogrel in healthy subjects. This was attributed to more efficient absorption and metabolism of prasugrel compared to clopidogrel toward their active metabolites [77]. The metabolic pathway of prasugrel is illustrated in Figure 1.3. Genetic polymorphisms in ABCB1, associated with a diminished response to clopidogrel, do not affect patient response to prasugrel [78]. Prasugrel also achieved higher and more consistent levels of platelet inhibition in patients with stable CAD than high dose clopidogrel (600 mg LD, followed by 150 mg MD) [79].

The efficacy of prasugrel in UA and NSTEMI patients treated medically (without revascularization) was investigated in the TRILOGY ACS trial. Prasugrel treatment did not significantly reduce the incidence of the primary end point, a composite of death from cardiovascular causes, myocardial infarction or stroke (13.9% vs 16.0%, p=0.21). Similar risks of bleeding were observed in both prasugrel and clopidogrel treated patients. It should be noted that patients with a history of TIA or stroke were excluded. The prasugrel dose was also reduced from 10 mg to 5 mg in patients aged 75 or older and who weighed less than 60 kg [80]. These 3 groups of patients suffered from net harm or no net benefit from prasugrel treatment in the TRITON-TIMI 38 trial [76].

1.7 Platelet function guided therapy

Platelet function testing has utility as a prognostic marker for PCI patients. The central role of platelets in the pathophysiology of atherothrombosis and clinical phenotypes is widely accepted. The association between HOTPR and subsequent ischaemic events has been consistently proven. Randomised clinical trials of more potent antiplatelet agents than clopidogrel have demonstrated reduced thrombotic event rates. Furthermore, the final mechanism of action between $P2Y_{12}$ receptor antagonists is all similar [72].

The GRAVITAS trial investigated whether treatment with high dose clopidogrel (600 mg LD, 150 mg MD), as opposed to standard dose clopidogrel (no further LD, 75 mg MD), was beneficial in patients experiencing HOTPR. The primary endpoint of cardiovascular death, MI or stent thrombosis at 6 months was not significantly different (2.3% vs 2.3%, p=0.97). Nor was the safety endpoint of severe or moderate bleeding (1.4% vs 2.3%, p=0.10). Clopidogrel undertreatment may explain these neutral results. Half of HOTPR patients had already been loaded with 600 mg clopidogrel prior to screening, 53.3% and 52.7% were randomised to high and standard dose clopidogrel respectively. High dose clopidogrel only modestly reduced on-treatment platelet reactivity and the rate of HOTPR by 22%. This was supported by a lack of excess severe or moderate bleeding events with high clopidogrel treatment. Treatment with a more potent antiplatelet agent may be more beneficial. Furthermore, the GRAVITAS population was primarily low risk. Only 10% of patients presented with MI, 60% were stable angina and the remainder UA. This contributed to a lower than accounted for event rate, which combined with a modest sample size, left the study underpowered [81].

The TRIGGER-PCI study sought to determine whether clopidogrel HOTPR could be corrected with prasugrel. Stable CAD patients were loaded with 600 mg clopidogrel. Of the patients screened, 19.0% experienced HOTPR. HOTPR was corrected in 94.1% of prasugrel patients, compared to only 29.6% of clopidogrel patients. However, this could not be related to the primary endpoint of cardiac death or MI at 6 months, which did not occur in the prasugrel arm and only once

in the clopidogrel arm. As such, the study was deemed futile and terminated. Whilst TRIGGER-PCI validated a key pre-requisite for demonstrating the utility of personalized antiplatelet therapy through platelet function testing, by demonstrating that HOTPR can be corrected with a more potent antiplatelet agent, it failed to link this to an improvement in clinical outcomes. The low event rate can in part be attributed to recruiting a cohort at low risk of adverse events. The TRIGGER-PCI approach may be warranted for high risk populations, such as an ACS population [82].

Aradi and colleagues sought to determine the efficacy and safety of intensifying antiplatelet therapy in PCI patients based on platelet reactivity testing by VerifyNow, MEA, VASP-P or LTA in a meta-analysis of 10 studies comprising 4,213 patients. Intensified antiplatelet therapy significantly reduced the risk of cardiovascular mortality, MI and stent thrombosis (OR 0.28, p=0.008; OR 0.47, p=0.006 and OR 0.38, p=0.006, respectively). The risk of a composite of the above was also reduced (OR 0.44, p<0.001). This benefit was not accompanied by an increase in the rate of major or minor bleeding (OR 0.81, p=0.44 and OR 1.15, p=0.24, respectively). The net clinical benefit favoured intensifying antiplatelet therapy (OR 0.50, p=0.0003). The net clinical benefit of intensified antiplatelet treatment was dependent on the risk of early stent thrombosis on standard dose clopidogrel (p=0.023), not on clinical presentation (ACS vs stable CAD). Hence the risk of stent thrombosis needs to be considered when interpreting results of platelet function tests [83].

Hazarbasanov and colleagues examined whether intensifying clopidogrel treatment according to platelet reactivity improved clinical outcomes in 192 PCI patients. In the tailored group of patients, platelet function was measured with MEA 24 hours post clopidogrel loading (stable angina patients 300 mg, 600 mg in ACS). Patients with HOTPR, defined as platelet reactivity >46 AU, were given an additional 600 mg clopidogrel and prescribed a MD of 150 mg daily for a month. Reloading non-responsive patients in the tailored group significantly lowered platelet reactivity (61.0 AU vs 21.5 AU, p<0.0001), an effect that was maintained throughout chronic therapy. The primary endpoint, a composite of cardiac death,

MI, ischaemic stroke or definite/probable stent thrombosis was significantly lower in the tailored therapy group, compared to standard care at 6 months (0% vs 5.3%, p=0.028). Only one TIMI major bleeding event occurred in the tailored group during 150 mg maintenance therapy, while none occurred in the control arm [84].

The MADONNA study examined whether personalized antiplatelet therapy with a more potent antiplatelet agent, prasugrel, or repetitive loading with clopidogrel was both an effective and safe treatment strategy. PCI patients were loaded with 600 mg clopidogrel and platelet reactivity measured by MEA. A group of non-guided PCI patients receiving standard of care treatment served as the control. HOTPR was defined as platelet reactivity ≥50 AU. This value was chosen as the mean of cut-offs previously proposed by Sibbing [60] and Siller-Matula [53], 47 AU and 54 AU respectively. Non-responders (26%), patients with HOTPR, were reloaded with 600 mg clopidogrel or loaded with 60 mg prasugrel if available. Stent thrombosis was reduced in the guided group (0.2% vs 1.9%, p=0.027), as was ACS (0% vs 2.5%, p= 0.001), although there was no difference in cardiovascular death (2% vs 1.3%, p= 0.422). Siller-Matula and colleagues also used ROC curve analysis to demonstrate ADP-induced platelet aggregation measured by MEA distinguished between patients with or without subsequent definite or probable stent thrombosis (p=0.004). MEA detection of definite stent thrombosis had sensitivity and specificity of 100%, while probable stent thrombosis had sensitivity and specificity of 63% and 85% respectively [85].

The ARTIC investigators explored antiplatelet therapy adjustment in PCI patients. 2,440 PCI patients were randomized to platelet function monitoring versus conventional treatment. Patients experiencing HOTPR to clopidogrel in the monitoring group (34.5%) were reloaded with 600 mg clopidogrel or 60 mg prasugrel and a glycoprotein (GP) IIb/IIIa inhibitor before the procedure, then assigned 150 mg clopidogrel or 10 mg prasugrel daily MD. At 14-30 days post stent implantation, patients with persistent HOTPR to clopidogrel had their MD increased by 75 mg or were switched to 10 mg prasugrel. Conversely patients taking 150 mg clopidogrel or 10 mg prasugrel with low platelet reactivity, were

switched to a MD of 75 mg clopidogrel. The primary endpoint was a composite outcome of death, MI, stent thrombosis, stroke, or urgent revascularization. At one year, the primary endpoint did not differ significantly between the monitored and the conventionally treated groups (34.6% vs 31.1%, p=0.10), nor did the incidence of major bleeding as defined by the STEEPLE trial (3.3% vs 2.3%, p=0.15). The primary endpoint was primarily driven by the incidence of MI [86].

The ADAPT-DES study examined the relationship between platelet reactivity on DAPT and clinical outcomes following drug-eluting stent (DES) implantation in 8,582 patients. PCI patients adequately loaded with clopidogrel (600 mg, 300 mg or ≥75 mg for ≥5 days) and aspirin (≥300 mg orally or ≥ 250 mg intravenously) were enrolled. Stable CAD patients comprised 48.3%, while ACS made up the remainder (14.6% NSTEMI, 9.5% STEMI and 27.6% UA). 42.7% patients experienced HOTPR. The primary endpoint was definite or probable stent thrombosis (0.8%). Other endpoints included all-cause mortality (1.9%), MI (3.1%) and clinically relevant bleeding (6.2%). HOTPR was strongly related to stent thrombosis (p=0.001) and MI (p=0.01), was inversely related to bleeding (p=0.002), but not mortality. HOTPR had the greatest influence on both ischaemic and bleeding events within the first 30 days, the time period when these events occur most frequently. Whilst platelet reactivity was able to reclassify patients according to the risk of developing stent thrombosis, MI or clinically relevant bleeding, beyond baseline clinical characteristics, the absolute magnitude of this difference was small [70].

In the ADAPT-DES study platelet reactivity was also associated with other known risk factors for mortality: age, diabetes, prior MI, ACS and anaemia. Furthermore, more than 40 baseline and procedural variables were associated with HOTPR. HOTPR was an independent predictor of stent thrombosis and MI one year after successful DES placement, yet was protective against clinically relevant bleeding events. Ischaemic and haemorrhagic complications were strongly related to all-cause mortality, although HOTPR was not an independent predictor of mortality. This may be due to the effects of ischaemic vs haemorrhagic complications on patient survival cancelling each other out. Bleeding occurred at a greater

frequency than stent thrombosis or MI and was associated with higher mortality. The inverse relationship between ischaemia and bleeding and their influence on mortality implies that to improve survival, we need to overcome HOTPR with more potent antiplatelet agents without an increase in prognostically important bleeding associated with greater platelet inhibition [70].

1.8 Ticagrelor

1.8.1 Absorption and metabolism

Ticagrelor is a direct acting, reversible binding, antiplatelet agent that rapidly and nearly completely inhibits platelet aggregation in response to ADP. Ticagrelor is rapidly absorbed in stable CAD patients, with an onset of antiplatelet effect approximately 30 minutes after administration [87]. In healthy subjects, ticagrelor reaches maximum concentrations (t_{max}) in the plasma at 1.5 hours post dosing. Ticagrelor's equipotent active metabolite AR-C124910XX reaches t_{max} 3 hours post dosing [88]. Ticagrelor and AR-C124910XX are illustrated in Figure 1.3.

Plasma concentrations of ticagrelor and its active metabolite increase linearly, proportional to dosage on the first day of treatment and are stable and at predictable concentrations after two weeks of treatment. After the variance in clopidogrel active metabolite generation previously discussed, this is advantageous. The extent of platelet inhibition is dependent on the concentration of antiplatelet agent available to bind to platelets, hence closely reflects plasma drug concentrations [89]. Ticagrelor and its active metabolite are constantly present in the plasma and are able to bind to and inhibit new platelets as they are released into the circulation, in accordance with their steady-state plasma levels [46]. Furthermore, direct $P2Y_{12}$ inhibitors such as ticagrelor may be able to inhibit $P2Y_{12}$ receptors that were previously internalized and not accessible to transient exposure to active thienopyridine metabolites [87]. While CYP3A4/5 isoforms metabolise ticagrelor, SNPs in CYP450s do not compromise ticagrelor therapy as ticagrelor binds directly to platelets without having to undergo bioactivation [88].

1.8.2 Platelet inhibition

Loading doses of 180 mg ticagrelor achieve greater platelet inhibition than 300 mg clopidogrel in both clopidogrel pre-treated and naïve ACS patients. This effect is maintained during maintenance therapy (90 mg twice daily) [46]. In stable CAD patients, ticagrelor platelet inhibition remained higher than with clopidogrel 24 hours after the last dose. This demonstrates that if a dose of ticagrelor is missed, platelet inhibition remains adequate and may alleviate concerns of the impact of suboptimal patient compliance on therapy with a reversible antiplatelet agent [89].

Within one hour of 180 mg ticagrelor loading, almost 80% of stable CAD patients achieved near maximal platelet inhibition. This was 1.6 times the effect 600 mg clopidogrel could achieve at 8 hours post loading. By 2 hours post loading, 90% of ticagrelor patients achieved greater than 50% platelet inhibition, in comparison to 31% of patients treated with clopidogrel. Furthermore, 90% of ticagrelor patients achieved greater than 70% platelet inhibition, compared to 16% of clopidogrel patients. The greater platelet inhibition of ticagrelor was maintained throughout therapy [87].

While ticagrelor also has a faster offset time in stable CAD patients, platelet inhibition achieved 24 hours post dose is still greater than with clopidogrel (58% vs 52%) due to its initial potency. Despite the large reduction in platelet inhibition 24 hours post dose, ticagrelor still maintains a superior antiplatelet effect than clopidogrel, again indicating missing a dose will not have a detrimental effect [87].

SNPs in the gene encoding the P2Y$_{12}$ receptor (P2RY$_{12}$) has been associated with variability in platelet reactivity. SNPs in the P2Y1 receptor (P2RY1) and part of the gene encoding the glycoprotein IIb/IIIa (ITGB3) have been linked to platelet reactivity to ADP. None of these SNPs influences ticagrelor's inhibition of ADP-induced platelet aggregation [90].

1.8.3 Efficacy

Ticagrelor's benefit over clopidogrel in 18,624 STEMI, NSTEMI and UA patients was demonstrated in the PLATO trial. The primary endpoint, a composite of death from vascular causes, MI or stroke, occurred in 9.8% of patients treated with ticagrelor, compared with 11.7% of clopidogrel patients (p< 0.001). The benefit with ticagrelor was derived from reduced incidences of MI alone (5.8% vs 6.9%, p=0.005) and death from vascular causes (4.0% vs 5.9%, p=0.001). Ticagrelor use resulted in an absolute and relative reduction of the rate of all cause mortality at one year (1.4% and 22% respectively) [91].

A substantial portion of ticagrelor's superior efficacy in the PLATO trial has been attributed to the enhanced platelet inhibition achieved with ticagrelor [92]. Ticagrelor is a more effective antiplatelet for ACS irrespective of CYP2C19 and ABCB1 genotype, associated with diminished antiplatelet effects of clopidogrel [93]. Ticagrelor may also have a pleiotrophic effect derived from its novel drug class cyclopentyltriazolopyrimidines, by blocking the reuptake of adenosine by red blood cells [94]. Inhibition of adenosine reuptake may provide cardiovascular benefit by reducing blood pressure, improving coronary blood flow and protecting against reperfusion injuries [95].

Ticagrelor achieved greater platelet inhibition than clopidogrel in stable CAD patients in the RESPOND study, which was essentially uniform in both patients who responded to clopidogrel and those who did not. Nearly all ticagrelor patients, irrespective of clopidogrel response status were within the therapeutic range of platelet reactivity. During switching of therapy, ticagrelor rapidly enhanced platelet inhibition, regardless of clopidogrel response status. Switching to clopidogrel treatment was associated with a reduction in platelet inhibition. This was despite reloading patients when switching with 180 mg ticagrelor or 600 mg clopidogrel, suggesting switching antiplatelet therapy may be a better strategy to reduce HOTPR than reloading with clopidogrel. The extremely low prevalence of HOTPR in ticagrelor patients provides a mechanism for the clinical benefit of ticagrelor in the PLATO trial [96].

The long-term benefit of ticagrelor in 21,162 high risk patients beyond one year post MI has also been demonstrated in the PEGASUS-TIMI 54 trial. This study was independent of the drug's manufacturer AstraZeneca. Doses of 90 mg and 60 mg twice daily were compared with placebo [97]. The primary efficacy end point, a composite of cardiovascular death, MI and stroke, occurred at 3 years in 7.85% of the 90 mg ticagrelor group, 7.77% in the 60 mg ticagrelor group and 9.04% in the placebo group (p=0.008 for 90 mg ticagrelor vs placebo, p=0.004 for 60 mg ticagrelor vs placebo) [98].

1.8.4 Safety

The superior efficacy of ticagrelor in reducing recurrent MI and death from vascular causes from enhanced platelet inhibition has not come at the expense of significantly increased overall bleeding. The rates of major or minor bleeding in NSTEMI patients in the DISPERSE-2 trial were not significantly different (90 mg bd ticagrelor 9.8% vs clopidogrel 8.1%, p=0.43) [99]. The rates of overall bleeding in the PLATO trial were also similar (11.6% vs 11.2%, p=0.43). While the incidence of major bleeding, fatal bleeding and blood transfusions were not significantly different, non-CABG related major bleeding (4.5% vs 3.8%, p=0.02) and non-procedure related major bleeding (3.1% vs 2.3%, p=0.05) were significantly different, primarily after 30 days of treatment [100].

Ticagrelor reduced the incidence of CABG related major bleeding, consistent with recovery of platelet function after the reversible binding of ticagrelor to the $P2Y_{12}$ receptor [99], despite the recommendation based on pharmacokinetic studies that ticagrelor only needed to be withheld for 24-72 hours, compared to 5 days for clopidogrel [87]. Ticagrelor's reduction in CABG related bleeding compensated for its increase in non-CABG related major bleeding. This allowed the net clinical benefit, a composite outcome of cardiovascular death, myocardial infarction, stroke and major bleeding (CABG and non-CABG related) to favour ticagrelor. Increasing age, decreasing creatinine clearance, haemoglobin, female sex and

ticagrelor use were all associated with higher non-procedure related major bleeding. Whilst some patient groups have a heightened risk of bleeding, such as renal insufficiency, they are also at risk from ischaemic events and may concomitantly benefit from ticagrelor's more potent platelet inhibition [100].

TIMI major bleeding was significantly higher in patients treated with ticagrelor 1-3 years post MI in the PEGASUS-TIMI trial. TIMI major bleeding occurred in 2.60% of 90 mg ticagrelor patients, 2.30% in 60 mg ticagrelor and 1.06% with placebo (p<0.001 for each dose vs placebo) [98].

1.8.5 Dyspnoea and discontinuation

Ticagrelor therapy has been associated with an increased incidence of reported dyspnoea in patients with stable CAD and ACS [89, 91, 99, 101]. Dyspnoea is more commonly reported early in the course of ticagrelor treatment, the majority occurring within 1 week or 30 days in patients with stable CAD and ACS, respectively. Episodes are predominantly mild or moderate in severity [101, 102]. Ticagrelor related dyspnoea has not been associated with congestive heart failure or bronchospasm, in both stable CAD and ACS patients [89, 99]. Dyspnoea reported in ticagrelor treated stable CAD patients did not result in changes to cardiac or pulmonary function measurements [101] and ticagrelor use in ACS patients has not been associated with changes in pulmonary function measurements [103].

Ticagrelor prevents adenosine cellular uptake, increasing extracellular levels of adenosine in healthy subjects. Increased adenosine levels cause vasodilation, promoting myocardial perfusion, but can also induce dyspnoea not associated with bronchospasm. The drug's adenosine-mediated secondary mode of action may have contributed to its cardioprotective effects in the PLATO trial, but also the increased incidence of dyspnoea associated with its use [104].

Discontinuation of therapy due to adverse events occurred in a greater proportion of ticagrelor patients in the PLATO trial (7.4% vs 6.0%, p<0.001). While dyspnoea was reported in 13.8% and 7.8% of ticagrelor and clopidogrel patients respectively (p<0.001), 0.9% and 0.1% of ticagrelor and clopidogrel patients discontinued study medication due to dyspnoea (p<0.001) [91].

A greater proportion of ticagrelor patients discontinued therapy in the PEGASUS-TIMI 54 trial, 32.0% and 28.7% of patients in the 90 mg and 60 mg ticagrelor doses respectively, compared to 21.4% in the placebo group, primarily due to adverse effects. Dyspnoea was more prevalent in the ticagrelor groups, 18.93% and 15.84% of the 90 mg and 60 mg groups respectively, compared to 6.38% in the placebo group. Whilst the majority of episodes were mild or moderate in severity (58.1% and 36.9%, respectively), they led to discontinuation in 6.5% 90 mg ticagrelor, 4.55% 60 mg ticagrelor, but only 0.79% placebo patients. These rates of ticagrelor discontinuation due to dyspnoea are higher than in the PLATO trial. A proposed explanation for this was that the PLATO trial enrolled ACS patients where transient dyspnoea is frequently associated with their acute event, whereas, for stable patients 1 year post MI in PEGASUS, dyspnoea is more easily attributed to study medication, leading to its discontinuation [98].

1.9 Overall aims and objectives

This thesis explores the use of ticagrelor in a real world ACS population. Clinical trial populations are highly selective, enrolling patients at low risk of adverse events and non-compliance with therapy. Hence, the investigation of ticagrelor in an all-comers ACS population is warranted. We examined the extent to which ticagrelor reduced the incidence of HOTPR and whether clinical characteristics associated with HOTPR differed between patients treated with ticagrelor and clopidogrel. We explored factors influencing antiplatelet prescription including clinical risk factors and geographic elements. We determined the incidence of adverse effects associated with ticagrelor use including bleeding, dyspnoea and treatment discontinuation, in a real world ACS population.

Therefore the objectives of this thesis are:
- To examine the incidence and clinical characteristics associated with HOTPR in ACS patients treated with ticagrelor and clopiodgrel.
- To explore the clinical and geographic variables influencing the rate of ticagrelor and clopidogrel prescription.
- To determine the incidence of adverse effects associated with ticagrelor use by examining bleeding, dyspnoea and treatment discontinuation rates.

Chapter 2- High on-treatment platelet reactivity and associated clinical characteristics in acute coronary syndrome patients treated with ticagrelor and clopidogrel

2.1 Introduction

There is substantial variance in the level of platelet inhibition achieved with clopidogrel. A threshold of suboptimal platelet reactivity has been established that is associated with an increased risk of ischaemic events, above which patients are defined as having HOTPR [38]. HOTPR measured by MEA significantly predicts MI and stent thrombosis, with a trend towards predicting cardiovascular death in patients with CAD, including ACS [43].

Numerous factors have been linked to the presence of HOTPR in patients treated with clopidogrel. These include age, gender, BMI, diabetes, ACS, reduced LVF, renal insufficiency, inflammation, platelet count, underdosing, compliance, drug interactions and genetic polymorphisms [49]. In a New Zealand ACS population, 38% patients treated with clopidogrel experienced HOTPR [61].

Ticagrelor has been demonstrated as a superior drug compared to clopidogrel by its ability to reduce ischaemic events as shown in the PLATO trial [91]. Part of ticagrelor's benefit over clopidogrel has been attributed to more potent and consistent platelet inhibition [87, 92]. Ticagrelor is direct acting and is not affected by genetic polymorphisms that compromise clopidogrel bioavailability [93].

The rate of MEA measured HOTPR in ACS patients treated with ticagrelor has not been clearly defined in the literature to date. Clinical factors that may contribute to the rate of MEA measured HOTPR in ACS patients treated with ticagrelor is also unknown. Determining the rate of HOTPR in an ACS population treated with ticagrelor and what factors may contribute to this is important due to the ischaemic risk associated with HOTPR.

The aims of this study were:

1. To determine the incidence of HOTPR with ticagrelor in comparison to clopidogrel.

2. To investigate factors linked to HOTPR on ticagrelor and whether they differ from factors linked to HOTPR on clopidogrel.

2.2 Methods

2.2.1 Study population

Patients presenting to Wellington Regional Hospital with an ACS between 1st July 2013 and 30th June 2015 were eligible for inclusion in the study if coronary angiography (±PCI) was planned and they were adequately pretreated with ticagrelor or clopidogrel and aspirin.

An ACS was defined as symptoms suggestive of myocardial ischaemia lasting > 15 min with either troponin elevation or new electrocardiogram (ECG) changes consistent with myocardial ischaemia. ECG changes consistent with myocardial ischaemia included ≥ 1 mm of new ST segment deviation or T wave inversion ≥ 1 mm in at least 2 contiguous leads. Troponin was considered elevated if greater than 14 ng/L, with a rise and/or fall of 50% if 14-50 ng/L or 20% if >50 ng/L in a subsequent measure [10].

Adequate pretreatment was defined as chronic therapy (> 7 days) with aspirin (≥ 100 mg once daily) and ticagrelor (90 mg twice daily) or clopidogrel (≥ 75 mg once daily). If patients were not on chronic therapy with these agents then adequate pretreatment was defined as loading with aspirin ≥ 300 mg and ticagrelor 180 mg at least 2 hours, or clopidogrel ≥ 300 mg at least 6 hours, prior to enrolment followed by maintenance therapy.

Exclusion criteria included a known platelet function disorder, platelet count <100 x 10^9/L, haemoglobin <100 g/L, administration of a fibrinolytic agent within 24 hours of enrolment, administration of a glycoprotein IIb/IIIa receptor antagonist within a week prior to enrolment and inability to provide informed consent. The study was reviewed and approved by Lower South Regional Ethics Committee (ref: LRS/11/09/035/AM01).

2.2.2 Data collection

Patient demographics, prior medical history, clinical characteristics, admission medications, clinical management, procedural variables and in-hospital outcomes were obtained prospectively from review of medical records and cardiac catheterization database. Ethnicity was self-identified by the patient. Clinical management, including prescription of antiplatelet agent, was at the discretion of the attending physicians.

2.2.3 Blood collection and platelet function testing

Whole blood samples for platelet function testing were collected from either a peripheral vein using a 21-gauge needle before angiography or in the cardiac catheterisation laboratory from the arterial sheath immediately after insertion and prior to heparin administration. All samples were collected into tubes anticoagulated with hirudin (25 µg/ml, Dynabyte; Munich, Germany) and platelet function testing was performed 30 ± 15 min following collection as described below [56].

Platelet aggregation was measured in whole blood by MEA using the Multiplate analyser (Dynabyte; Munich, Germany), in accordance with the manufacturer's instructions. Briefly, whole blood was diluted 1:1 with 300 µL 0.9% NaCl solution in the test cell, which contained a teflon coated magnetic stirring bar. Following incubation at 37°C for 3 min, 20 µL of ADP was added to the test cuvette to a final concentration of 6.5 µM. ADP stimulates platelets to aggregate and adhere to the test cell electrodes, impeding the current between them. The increase in impedance due to the attachment of platelets to electrodes is detected for each sensor unit separately and recorded continuously for 6 min with the mean being transformed to arbitrary aggregation units (AU) that are plotted against time. This can be expressed as arbitrary aggregation units (AU x min) or as arbitrary units (AU), with 10 AU x min being equivalent to 1 AU [53].
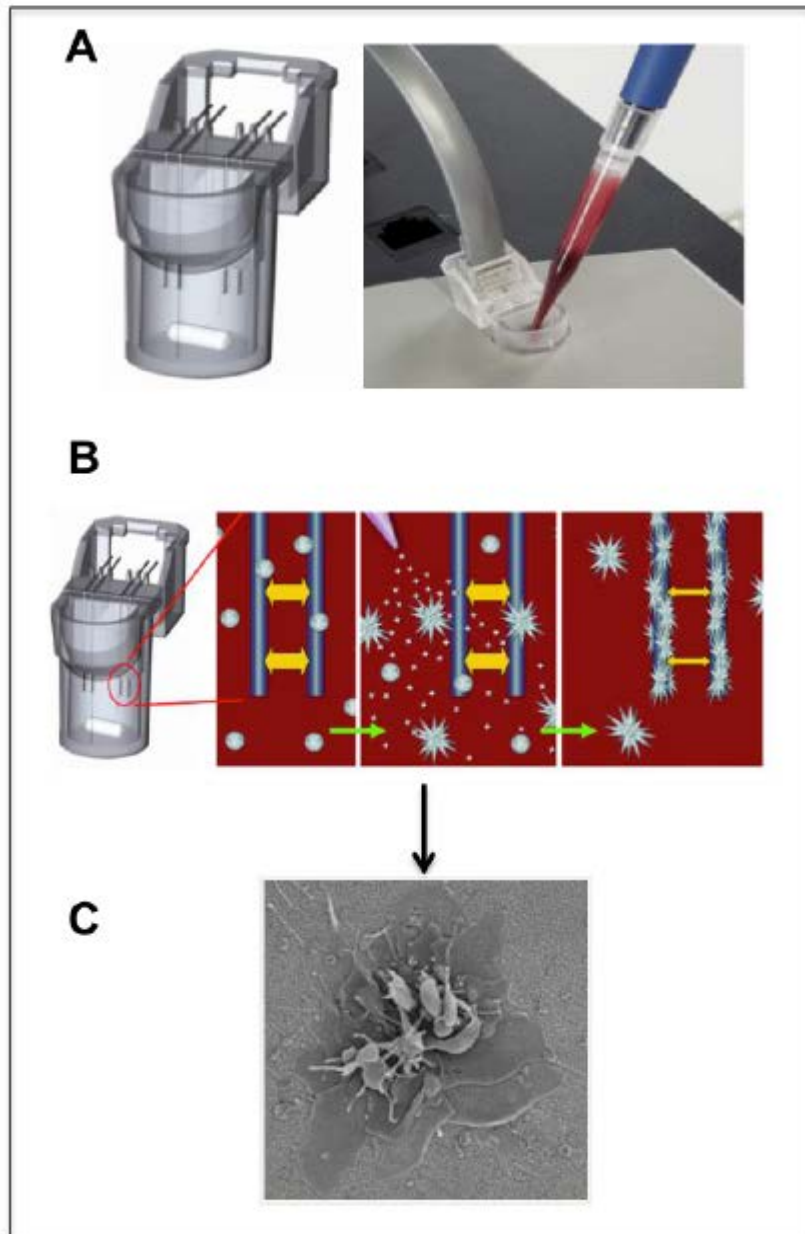
Figure 2.1 Multiple electrode aggregometry (MEA)

Whole blood and saline were added to a test cuvette using an automated pipette (A). Adenosine diphosphate (ADP), a platelet agonist, was added to stimulate platelets to aggregate on paired electrodes in each test cuvette, impeding the current (B). A scanning electron microscopy image of platelet aggregation on the surface of an electrode (C). The images are recreated from the Multiplate educational material, sourced from http://www.multiplate.net/en/detection.php.

2.2.4 Definitions

Clopidogrel dosing regimens were categorized as high, intermediate or low. A 600 mg loading dose followed by a 150 mg daily maintenance dose was defined as a high dosing regimen. Intermediate dosing regimens were defined as either a 600 mg loading dose coupled with a 75 mg daily maintenance dose or a 300 mg loading dose with a 150 mg maintenance dose. Low dose regimens were defined as a 300 mg loading dose with a 75 mg daily maintenance dose or chronic therapy with a 75 mg clopidogrel daily [61]. HOTPR was defined as platelet reactivity ≥ 47 AU [72].

2.2.5 Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables were tested for normality with the Kolmogorov-Smirnov normality test. All continuous variables were normally distributed and are expressed as means and standard deviations (mean ± SD). Chi-square tests were used to compare the proportion of ticagrelor patients with HOTPR by prior MI and the proportion of clopidogrel patients with HOTPR by renal insufficiency and clinical presentation. Student's *t*-test were used to compare absolute values of platelet reactivity by prior MI in ticagrelor patients and renal insufficiency, clinical presentation, platelet count and dosing regimen in clopidogrel treated patients. ANOVA was used to compare the proportion of clopidogrel patients with HOTPR by their dosing regimen classification. All statistical tests were performed using SPSS 22.0 (IBM; New York, USA).

2.3 Results

2.3.1 Baseline demographics

During the study period 538 patients with ACS met the inclusion criteria and were enrolled in the study. Their baseline demographics, clinical characteristics and laboratory data are shown in Table 2.1. The mean age was 63 ± 12 years with 71.9% being male and 18% having diabetes. The majority identified themselves as NZ European 88.1%, 8.7% as Maori or Pacific Islanders and the remaining 3.2% as other ethnicities. Patients predominantly presented with NSTEMI 76% and 24% as STEMI. Patients treated with ticagrelor were younger, more likely to be male, less likely to present with STEMI, have suffered a previous MI, experience atrial fibrillation and be taking proton pump inhibitors or calcium channel blockers.

2.3.2 Platelet reactivity and HOTPR prevalence

Patients who were administered ticagrelor demonstrated significantly lower platelet reactivity when stimulated with ADP compared to patients administered clopidogrel (30.3 AU vs 43.7 AU respectively, p<0.0001), shown in Table 2.2 and Figure 2.2. The proportion of patients with HOTPR was also lower in the ticagrelor group (15.9% vs 37.7% respectively, p<0.0001), shown in Table 2.2 and Figure 2.3.

Table 2.1 Patient demographics, clinical characteristics and laboratory data by antiplatelet agent

Demographics	All (n=538)	Ticagrelor (n=233)	Clopidogrel (n=305)	p value
Age (years)	63 ± 12	61 ± 10	65 ± 12	**<0.0001**
Male, n (%)	387 (71.9)	177 (76.0)	210 (68.9)	**0.027**
BMI	29.2 ± 5.5	29.3 ± 5.2	29.1 ± 5.7	0.695
Ethnicity				0.616
NZ European	474 (88.1)	202 (86.7)	272 (89.2)	
Maori or Pacific Islander	47 (8.7)	22 (9.4)	25 (8.2)	
Other	17 (3.2)	9 (3.9)	8 (2.6)	
Risk factors, n (%)				
Hypertension	319 (59.3)	129 (55.3)	190 (62.3)	0.105
Dyslipidaemia	336 (62.5)	145 (62.2)	191 (62.6)	0.926
Diabetes	95 (17.8)	38 (16.3)	57 (18.7)	0.473
Current Smoker	118 (21.9)	53 (22.7)	65 (21.3)	0.69
Medical history, n (%)				
Prior MI	107 (19.9)	37 (15.9)	70 (23.0)	**0.042**
Atrial fibrillation	30 (5.6)	7 (3.0)	23 (7.5)	**0.023**
Renal insufficiency	27 (5.0)	8 (3.4)	19 (6.2)	0.141
Clinical Presentation, n (%)				**<0.0001**
STEMI	129 (24.0)	30 (12.9)	99 (32)	
NSTEMI	409 (76.0)	203 (87.1)	206 (68)	
Laboratory findings				
Creatinine (μmol/L)	90 ± 26	90 ± 18	91 ± 31	0.536
Platelet count (10^9/L)	235 ± 64	237 ± 61	234 ± 66	0.526
Admission medication				
Statin	193 (35.9)	80 (34.3)	113 (37.0)	0.515
PPI	124 (23.0)	41 (17.6)	81 (26.5)	**0.014**
CCB	80 (14.9)	26 (11.2)	54 (17.7)	**0.034**
ACE-I	162 (30.1)	68 (29.2)	94 (30.8)	0.682

Abbreviations: BMI- body mass index; NZ European- New Zealand European; MI-myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI; PPI- proton pump inhibitor; CCB- calcium channel blocker; ACE-I- angiotensin-converting-enzyme inhibitor.

Table 2.2 Platelet reactivity and proportion of HOTPR by antiplatelet agent

Platelet reactivity	All (n=542)	Ticagrelor (n=233)	Clopidogrel (n=305)	p value
Platelet reactivity (AU)	37.8 ± 22.8	30.3 ± 17.5	43.7 ± 24.8	<0.0001
HOTPR	152 (28.3)	37 (15.9)	115 (37.7)	<0.0001

Abbreviations: HOTPR- high on-treatment platelet reactivity.
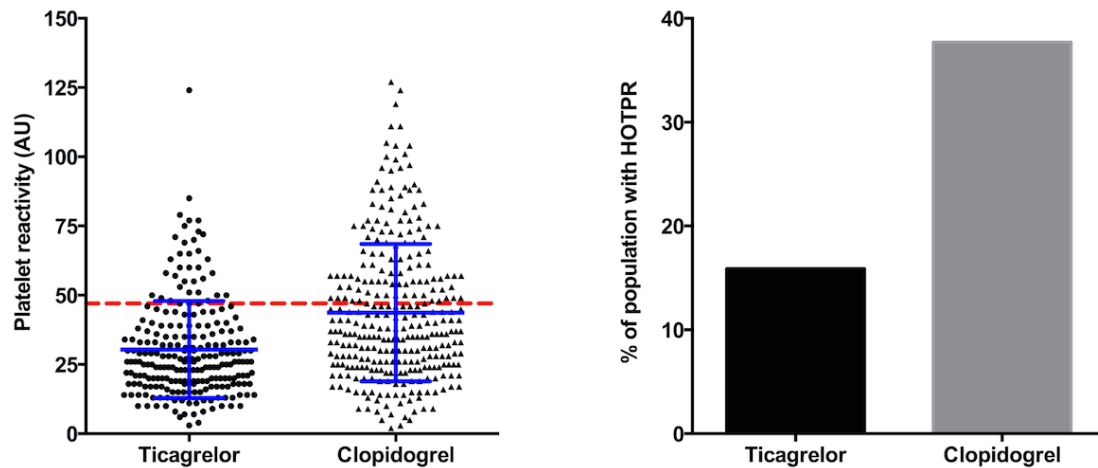
Figure 2.2 A) A) Platelet reactivity of patients treated with ticagrelor (n=233) and clopidogrel (n=305; p<0.0001, unpaired Students *t*-test). The red dotted line represents the 47 AU high on-treatment platelet reactivity (HOTPR) threshold. The mean and standard deviation are represented in blue. B) The rate of HOTPR in patients treated with ticagrelor and clopidogrel (p<0.0001, Chi-squared test).

2.3.3 Predictors of HOTPR

To investigate predictors of HOTPR in patients treated with ticagrelor, baseline demographics, clinical characteristics and laboratory data were tested against rates of HOTPR in a univariate analysis, shown in Table 2.3. A prior MI was the only factor significantly different in the ticagrelor group of patients with and without HOTPR (29.7% vs 13.3%, respectively, p=0.012), shown in Table 2.4 and Figure 2.3. However, the mean values of platelet reactivity between patients treated with ticagrelor with and without a history of MI were not significantly different (p=0.321).

Table 2.3 Ticagrelor group demographics, clinical characteristics and laboratory data by HOTPR

Demographics	Ticagrelor (n=233)	HOTPR (n=37)	No HOTPR (n=196)	p value
Age (years)	61 ± 10	62 ± 10	61 ± 10	0.511
Male, n (%)	177 (76.0)	31 (83.8)	146 (74.5)	0.225
BMI	29.3 ± 5.2	30.6 ± 5.4	29.0 ± 5.2	0.081
Ethnicity				0.25
NZ European	202 (86.7)	35 (94.6)	167 (85.2)	
Maori or Pacific Islander	22 (9.4)	2 (5.4)	20 (10.2)	
Other	9 (3.9)	0 (0)	9 (4.6)	
Risk factors, n (%)				
Hypertension	129 (55.3)	20 (54.1)	109 (55.6)	0.861
Dyslipidaemia	145 (62.2)	22 (59.5)	123 (62.8)	0.705
Diabetes	38 (16.3)	9 (24.3)	29 (14.8)	0.15
Current Smoker	53 (22.7)	7 (18.9)	46 (23.5)	0.545
Medical history, n (%)				
Prior MI	37 (15.9)	11 (29.7)	26 (13.3)	**0.012**
Atrial fibrillation	7 (3.0)	2 (5.4)	5 (2.6)	0.351
Renal insufficiency	8 (3.4)	1 (2.7)	7 (3.6)	0.79
Clinical Presentation, n (%)				0.899
STEMI	30 (12.9)	5 (13.5)	25 (13)	
NSTEMI	203 (87.1)	32 (86.5)	171 (87)	
Laboratory findings				
Creatinine (µmol/L)	90 ± 18	94 ± 20	89 ± 18	0.144
Platelet count (109/L)	237 ± 61	231 ± 51	238 ± 62	0.543
Admission medication				
Statin	80 (34.3)	14 (37.8)	66 (33.7)	0.625
PPI	41 (17.6)	5 (13.5)	36 (18.4)	0.477
CCB	26 (11.2)	5 (13.5)	21 (10.7)	0.62
ACE-I	68 (29.2)	11 (29.7)	57 (29.1)	0.937

Abbreviations: HOTPR- high on-treatment platelet reactivity; BMI- body mass index; NZ European- New Zealand European; MI- myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI; PPI- proton pump inhibitor; CCB- calcium channel blocker; ACE-I- angiotensin-converting-enzyme inhibitor.

Table 2.4 Platelet reactivity and proportion of HOTPR in the ticagrelor group in patients with or without a prior MI

Ticagrelor	Previous MI (n=37)	no previous MI (n=196)	P value
HOTPR (%)	11 (29.7)	26 (13.3)	**0.012**
Platelet reactivity (AU)	33 ± 19	30 ± 17	0.321

Abbreviations: HOTPR- high on-treatment platelet reactivity; MI- myocardial infarction.
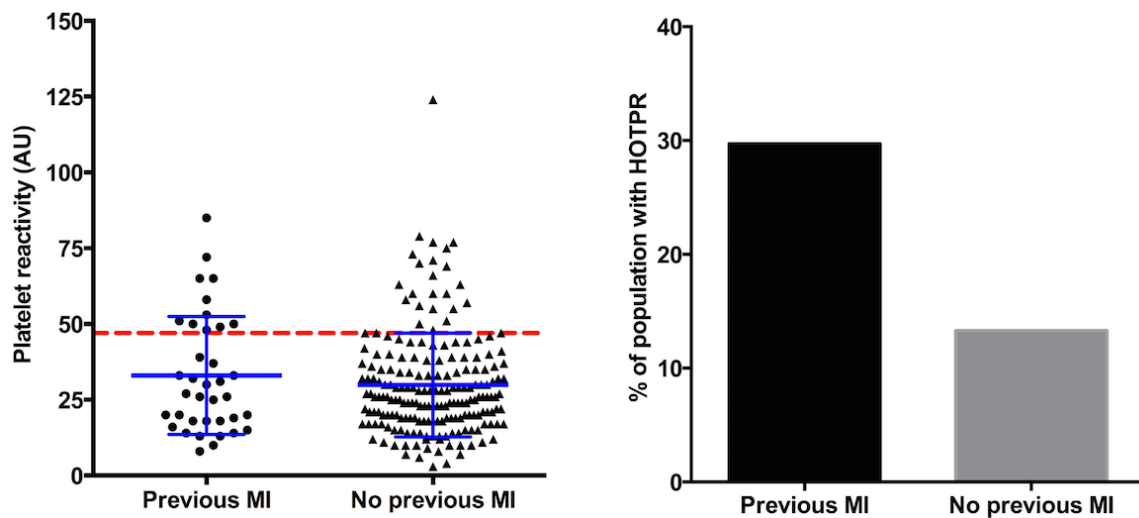
Figure 2.3 A) Platelet reactivity of patients treated with ticagrelor, with and without a prior MI (n=37 and n=196, respectively, p=0.321 unpaired Students *t*-test). The red dotted line represents the 47 AU high on-treatment platelet reactivity (HOTPR) threshold. The mean and standard deviation are represented in blue. B) The rate of HOTPR in the ticagrelor group, in patients with and without a prior MI (p=0.012, Chi-squared test).

To investigate predictors of HOTPR in patients treated with clopidogrel, baseline demographics, clinical characteristics and laboratory data were tested against rates of HOTPR in a univariate analysis, shown in Table 2.5. Patients treated with clopidogrel with renal insufficiency had significantly higher absolute values of platelet reactivity and a greater incidence of HOTPR, shown in Table 2.6 and Figure 2.4. Patients treated with clopidogrel presenting with a STEMI had greater absolute values of platelet reactivity and an elevated HOTPR prevalence, shown in Table 2.7 and Figure 2.5. Increasing platelet count was associated with increased platelet reactivity, shown in Figure 2.6. HOTPR incidence was significantly different by clopidogrel dosing regimen, but not by absolute values of platelet reactivity, shown in Table 2.8 and Figure 2.7.

Table 2.5 Clopidogrel group demographics, clinical characteristics and laboratory data by HOTPR

Demographics	Clopidogrel (n=305)	HOTPR (n=115)	No HOTPR (n=190)	p value
Age (years)	65 ± 12	66 ± 13	65 ± 11	0.309
Male, n (%)	210 (68.9)	73 (63)	137 (72)	0.115
BMI	29.1 ± 5.7	29.8 ± 6.0	28.6 ± 5.5	0.075
Ethnicity				0.424
NZ European	272 (89.2)	101 (87.8)	171 (90.0)	
Maori or Pacific Islander	25 (8.2)	12(10.4)	13 (6.8)	
Other	8 (2.6)	2 (1.7)	6 (3.2)	
Risk factors, n (%)				
Hypertension	190 (62.3)	77 (67.0)	113 (59.5)	0.191
Dyslipidaemia	191 (62.6)	71 (61.7)	120 (63.2)	0.804
Diabetes	57 (18.7)	27 (23.5)	30 (15.8)	0.095
Current Smoker	65 (21.3)	25 (21.7)	40 (21.1)	0.887
Medical history, n (%)				
Prior MI	70 (23.0)	22 (19.1)	48 (25.3)	0.217
Atrial fibrillation	23 (7.5)	13 (11.3)	10 (5.3)	0.053
Renal insufficiency	19 (6.2)	12 (10.4)	7 (3.7)	**0.018**
Clinical Presentation, n (%)				**0.007**
STEMI	99 (32)	48 (41.7)	51 (26.8)	
NSTEMI	206 (68)	67 (58.2)	139 (73.2)	
Laboratory findings				
Creatinine (µmol/L)	91 ± 31	94 ± 40	89 ± 23	0.297
Platelet count (109/L)	234 ± 66	250 ± 68	224 ± 64	**0.001**
Admission medication				
Statin	113 (37.0)	39 (33.9)	74 (38.9)	0.378
PPI	81 (26.5)	33 (28.7)	48 (25.3)	0.511
CCB	54 (17.7)	25 (21.7)	29 (15.3)	0.151
ACE-I	94 (30.8)	33 (28.7)	61 (32.1)	0.532
Clopidogrel dosing				**0.026**
High	40 (13.1)	11 (9.6)	29 (15.3)	
Intermediate	130 (42.5)	42 (36.5)	88 (46.3)	
Low	135 (44.4)	62 (53.9)	73 (38.4)	

Abbreviations: HOTPR- high on-treatment platelet reactivity; BMI- body mass index; NZ European- New Zealand European; MI- myocardial infarction; STEMI-ST-elevation MI; NSTEMI- non-STEMI; PPI- proton pump inhibitor; CCB- calcium channel blocker; ACE-I- angiotensin-converting-enzyme inhibitor.

Table 2.6 Platelet reactivity and proportion of HOTPR in the clopidogrel group, in patients with and without renal insufficiency

Clopidogrel	Renal insufficiency (n=19)	no renal insufficiency (n=286)	p value
HOTPR (%)	12 (63.1)	103 (36.0)	**0.018**
Platelet reactivity	57 ± 28	43 ± 24	**0.013**

Abbreviations: HOTPR- high on-treatment platelet reactivity
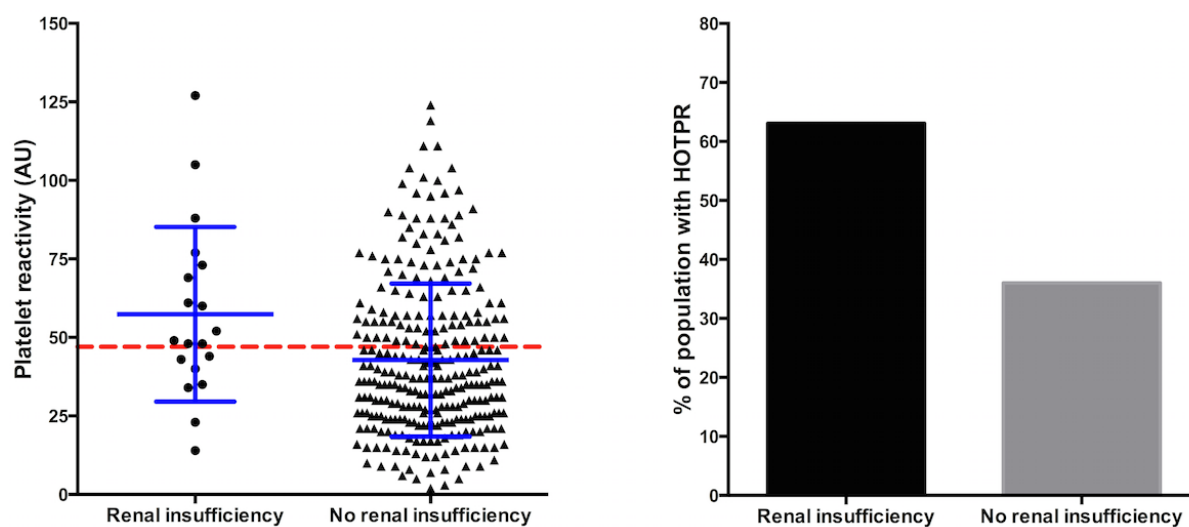
Figure 2.4 A) Platelet reactivity in the clopidogrel group, in patients with and without renal insufficiency (n=19, n=286, respectively, p=0.013, unpaired Students *t*-test). The red dotted line represents the 47 AU high on-treatment platelet reactivity (HOTPR) threshold. The mean and standard deviation are represented in blue. B) The rate of HOTPR in the clopidogrel group, in patients with an without renal insufficiency (p=0.018, Chi-squared test).

Table 2.7 Platelet reactivity and proportion HOTPR in the clopidogrel group, in patients presenting as STEMI or NSTEMI

Clopidogrel	STEMI (n=99)	NSTEMI (n=206)	p value
HOTPR (%)	48 (48.5)	67 (32.5)	**0.007**
Platelet reactivity	50 ± 25	41 ± 24	**0.003**

Abbreviations: HOTPR- high on-treatment platelet reactivity; STEMI- ST-elevation myocardial infarction; NSTEMI- non-STEMI.
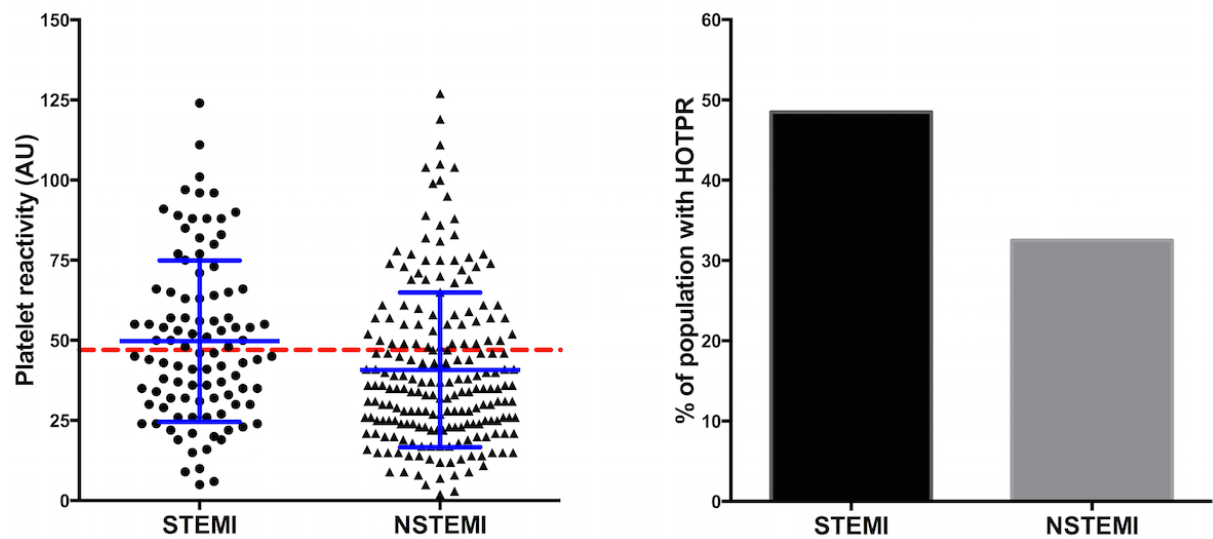
Figure 2.5 A) Platelet reactivity in the clopidogrel group, patients presenting as ST-elevation myocardial infarction (STEMI, n=99) and non-STEMI (NSTEMI, n=206; p=0.003, unpaired Students *t*-test). The red dotted line represents the 47 AU high on-treatment platelet reactivity (HOTPR) threshold. The mean and standard deviation are represented in blue. B) The rate of HOTPR in the clopidogrel group, in patients presenting as STEMI or NSTEMI (p=0.007, Chi-squared test).
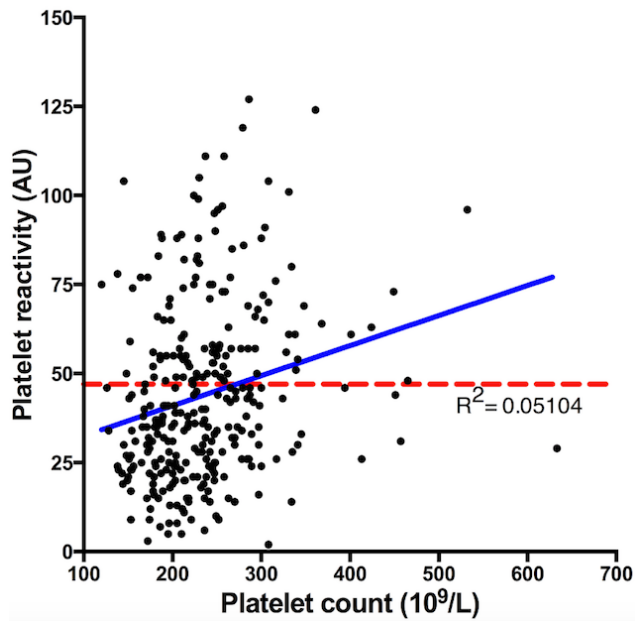
Figure 2.6 Correlation between residual platelet reactivity in patients treated with clopidogrel and platelet count (r²=0.051, p=0.001, Pearson correlation).

Table 2.8 Platelet reactivity and proportion of HOTPR in the clopidogrel group, by clopidogrel dosing regimen

Clopidogrel	High (n=40)	Intermediate (n=130)	Low (n=135)	p value
HOTP (%)	11 (27.5)	42 (32.3)	62 (45.9)	0.026
Platelet reactivity	39 ± 21	43 ± 26	46 ± 25	0.199

Abbreviations: HOTPR- high on-treatment platelet reactivity
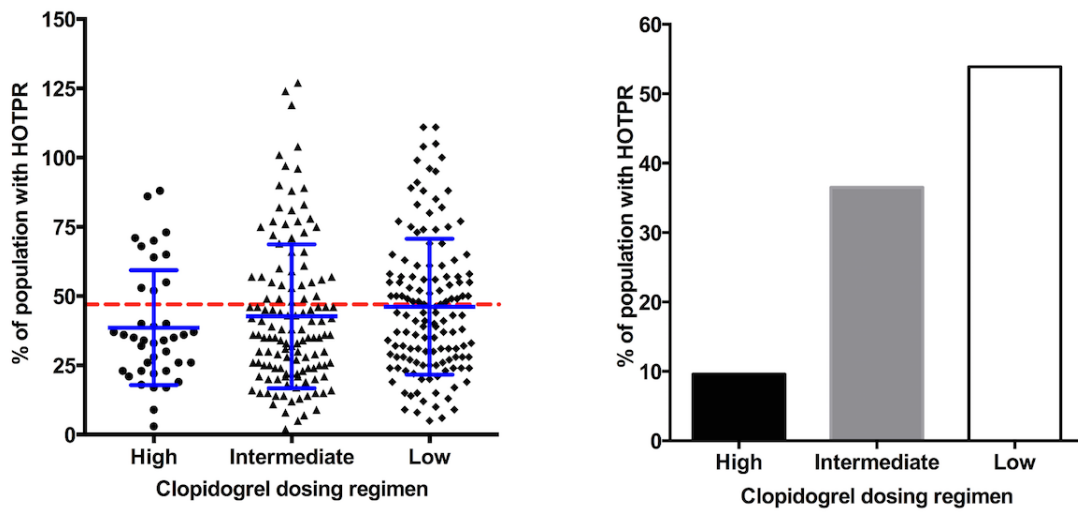
Figure 2.7 A) Platelet reactivity in the clopidogrel group, classified by high (n= 40), intermediate (n=130) and low (n=135) dosing regimens (p=0.199, one-way ANOVA). The red dotted line represents the 47 AU high on-treatment platelet reactivity (HOTPR) threshold. The mean and standard deviation are represented in blue. B) The rate of HOTPR in the clopidogrel group increased significantly with decreasing clopidogrel dosing regimen (p=0.026, Chi-square test).

2.4 Discussion

In the present study we have demonstrated that ticagrelor significantly reduces both the absolute level of platelet reactivity and the proportion of patients classified as having HOTPR, in comparison to clopidogrel. We have also demonstrated that the clinical variables associated with HOTPR differ between patients treated with clopidogrel and ticagrelor. Clopidogrel dosage, renal insufficiency, clinical presentation and platelet count appeared to contribute to the rate of HOTPR in clopidogrel treated patients. In contrast, only a history of prior MI was associated with the rate of HOTPR in patients treated with ticagrelor.

Ticagrelor exerted more potent residual platelet inhibition compared to clopidogrel (30.3 AU ± 17.5 vs 43.7 AU ± 24.8, p<0.0001). As a consequence of the more potent platelet inhibition, a reduced proportion of patients treated with ticagrelor experienced HOTPR (15.9% vs 37.7%, p<0.0001). Our absolute values of platelet reactivity and corresponding proportion of patients with HOTPR on ticagrelor are higher than reported for ACS patients in the literature using MEA [105-107]. Our study differs in the inclusion of both STEMI and NSTEMI patients treated with ticagrelor and a substantially larger sample size. A possible reason for our higher values of platelet reactivity on ticagrelor may be due to the optimization of our protocol in testing platelet function to reduce variability. We perform MEA between 15 and 45 minutes of sample collection as there is a significant reduction in platelet aggregation after 60 minutes [56]. Large interstudy and intrassay heterogeneity in the measurement of platelet reactivity has also been documented with clopidogrel, with HOTPR prevalence ranging from 6% to 80% [43].

Ticagrelor has been repeatedly shown to be a more potent antiplatelet agent than clopidogrel in both stable and acute coronary disease settings, using LTA, VerifyNow and VASP-P assays [89, 92]. Indeed, ticagrelor's mortality benefit has been in part attributed to more potent and consistent platelet inhibition in ACS patients [92]. A loading dose of ticagrelor achieves greater platelet inhibition, measured by LTA and VerifyNow assays, than both 300 mg and 600 mg loading

doses of clopidogrel. This treatment effect is maintained throughout chronic therapy in patients with both stable CAD and ACS [46, 87]. Ticagrelor's antiplatelet potency is reflected in its ability to reduce the proportion of patients experiencing HOTPR, measured by LTA, VerifyNow and VASP-P assays, in comparison to clopidogrel in patients with stable CAD [108]. Furthermore, ticagrelor can overcome clopidogrel HOTPR, measured by LTA, VerifyNow and VASP-P assays, in stable CAD patients, even when patients are reloaded with high dose clopidogrel [96]. This suggests different drivers to HOTPR on ticagrelor and clopidogrel, although none of these studies have measured HOTPR with MEA.

A prior MI was the only factor that was statistically associated with HOTPR in our cohort. The proportion of patients with a history of MI was 29.7% in patients with HOTPR, compared to 13.3% in patients within the therapeutic range. However, absolute values of platelet reactivity did not differ significantly between those with and without a prior MI, 33 ± 19 AU and 30 ± 17 AU, respectively. To our knowledge no other studies have demonstrated an association between prior MI and HOTPR on ticagrelor. Furthermore, we have no mechanistic explanation for this relationship. It is possible this relationship is due to a play of chance, as we have performed multiple comparisons in our data. Further study is required to investigate whether prior MI and ticagrelor HOTPR is a consistent relationship.

Delay in the antiplatelet effect of ticagrelor has been documented in STEMI patients, resulting in significant proportions of patients experiencing HOTPR measured by VerifyNow at the time of primary PCI [109]. In STEMIs treated with primary PCI, 31.8% of ticagrelor patients had HOTPR (≥46.8 AU) measured with MEA 2 hours post loading with 180 mg. The incidence of HOTPR reduced with time, occurring in 9.1% at 6 hours, 4.8% at 24 hours, to no patients with HOTPR after 5 days [105]. STEMI was not associated with HOTPR in our cohort, with STEMIs comprising 13.5% of patients experiencing HOTPR, compared to 13.0% of patients within the therapeutic range (p=0.899). STEMI patients receiving primary angioplasty were excluded from this study due to insufficient time between antiplatelet loading and PCI. The majority of STEMI patients in this study received clopidogrel (76.7%) due to guidelines recommending clopidogrel as

adjunctive antiplatelet therapy to fibrinolytic therapy and additionally not to administer ticagrelor within 24 hours of thrombolysis [110, 111]. Furthermore, we excluded patients who were switched from clopidogrel to ticagrelor 24 hours post thrombolysis due to clopidogrel's irreversible platelet inhibition [44], which may have an unknown impact on ticagrelor platelet function measurements. In the five ticagrelor STEMI patients with HOTPR, the minimum time between ticagrelor loading and platelet function testing was 8 hours. Hence insufficient time between ticagrelor loading and PCI did not appear to be contributing to HOTPR.

We have performed platelet function testing after a sufficient time period to allow for antiplatelet loading to reach its therapeutic effect. This is a measure of residual platelet reactivity. We have not performed baseline platelet function testing prior to antiplatelet therapy and therefore cannot comment on the magnitude of the antiplatelet effect of the two drugs. We were unable to take baseline measures of platelet function due to clinical logistics. The majority of patients in the study (69%) presented to referring hospitals and were therefore loaded on antiplatelet therapy before transfer to Wellington hospital for invasive management. Obtaining patient informed consent between the establishment of troponin rise/fall and antiplatelet loading in patients presenting to Wellington Hospital would have delayed patient care and was not logistically possible in this study. Furthermore, baseline ADP-induced platelet aggregation is subject to significant interindividual variability. Hence the absolute or relative measure of antiplatelet responsiveness may overestimate the ischaemic risk in nonresponders with low baseline platelet reactivity, whilst conversely underestimating the risk in clopidogrel responders who maintain high platelet reactivity during treatment. On this basis the measure of on-treatment absolute level of platelet reactivity has been proposed as a superior measure of thrombotic risk [44, 112].

The incidence of HOTPR on clopidogrel in this study (37.7%) was similar to that observed in a previous cohort of ACS patients treated with clopidogrel published by our research group, where 38% of the clopidogrel group experienced HOTPR as measured by MEA. Clinical factors associated with HOTPR in this cohort

included Maori ethnicity, diabetes, previous PCI and a low clopidogrel dosing regimen. Although the relationship did not reach statistical significance, there was a trend towards BMI being associated with HOTPR [61]. Further clinical factors associated with HOTPR in the literature include age, ACS, reduced LVF, renal failure, inflammation, gender, platelet count, fribrinogen levels, underdosing, compliance, gene polymorphisms and drug interactions [49]. Consistent with previous literature, in the present study we identified dosing regimen, renal insufficiency, STEMI and platelet count as drivers of HOTPR on clopidogrel. Higher BMI, diabetes and Maori ethnicity, which have all previously been associated with an increased incidence of HOTPR, had a numerically higher incidence of HOTPR in the clopidogrel group in our study but these differences were not statistically significant. This may have been due to a lack of statistical power.

In our study we identified an inverse relationship between clopidogrel dosing regimen and the proportion of patients with HOTPR. Over half (53.9%) of patients with HOTPR were prescribed a low clopidogrel dosing regimen, with 36.5% and 9.6% prescribed intermediate and high dosing regimens respectively (p=0.026). However, the absolute values of platelet reactivity were not significantly different (p=0.199). The wide variance in platelet reactivity analysed as a continuous variable may have left us underpowered to detect significant differences between the groups. Clopidogrel under-dosing is a pivotal cause of HOTPR, higher clopidogrel dosing regimens have been demonstrated to reduce platelet reactivity and the proportion of patients experiencing HOTPR [37].

HOTPR occurred in significantly more patients in the clopidogrel group with renal insufficiency (63.1%), in comparison to patients without renal insufficiency (36.0%, p=0.018). The impact of renal insufficiency on platelet reactivity is reflected in its inclusion in the PREDICT score that identifies patients with clinical factors influencing persistent platelet aggregation [113] and its predictive ability of MACE [114]. Platelet responsiveness to clopidogrel has been shown to be decreased in patients with chronic renal failure and is unable to be overcome by increasing clopidogrel dosage. The mechanisms proposed for platelet dysfunction

in CRF include an increased platelet turnover rate, impaired drug absorption and transportation and coagulation disorders [115].

STEMI patients in our study treated with clopidogrel had greater platelet reactivity (50 ± 25 AU) and HOTPR incidence (48.5%) than NSTEMI patients (41 ± 24 AU, p=0.003 and 32.5%, p=0.007 respectively). It is possible that this is due to a greater activation of platelets in STEMI than NSTEMI, or alternatively a reduced intestinal absorption of clopidogrel in STEMI patients [116, 117].

We observed a relationship between platelet count and HOTPR in patients treated with clopidogrel. Elevated platelet counts have been associated with HOTPR measured by both whole blood aggregommetry (Chronolog 590) [118] and PFA-100 cartridges [119]. Inflammation is a key driver in the progression of atherosclerosis and a greater degree of inflammation is associated with plaque instability [120]. Platelets and inflammation interact in a positive feedback loop, linking the haemostatic and inflammatory systems. Platelets release proinflammatory mediators, display surface molecules with inflammatory functions and interact with inflammatory cells, while inflammation itself induces platelet reactivity [121].

Diabetes has been repetitively demonstrated to contribute to the presence of HOTPR [113, 114, 122]. Our research group has demonstrated diabetes as a driver of HOTPR in a previous cohort of ACS patients treated with clopidogrel [61]. While diabetes was numerically increased in the patients in the clopidogrel group with HOTPR in the present study (23.5% vs 15.8%), it did not reach statistical significance (p =0.095). While we had more patients than Johnson and colleagues, the proportion of patients with diabetes was lower, which may have left us underpowered.

2.4.1 Limitations

We only performed a single measurement of platelet reactivity prior to angiography. Clinical logistics meant we were unable to measure patients' baseline platelet reactivity prior to administration of antiplatelet agents.

Therefore we can only comment on patients' residual platelet reactivity after treatment, not their response to antiplatelet therapy. However, patients' residual platelet reactivity has been proposed as a superior measure of clinical risk than the response to antiplatelet therapy [44]. Furthermore, clinical logistics also dictated that platelet reactivity measurements prior to angiography were not at standard time points after symptom onset or antiplatelet therapy commencement. The prevalence of HOTPR has been shown to reduce over time [36]. However, our single measurement is in the period of greatest ischaemic risk. The hazard ratio of a recurrent MI is 17.6 within 2 days of the original infarction and 8.2 within a week [65].

The choice and dose of antiplatelet agent was at the clinicians' discretion. Genetic testing was not undertaken, so the effect of genetic polymorphism on patient phenotype could not be assessed. Furthermore, the observational nature of our study does not allow us to investigate the mechanism behind the factors we have identified that are associated with platelet reactivity. Our study does not include STEMI patients treated with primary PCI due to insufficient time between clopidogrel or ticagrelor loading and PCI. The STEMI patients in this study were predominantly thrombolysed in referring hospitals. Reasons for withholding thrombolysis were if they were late presenting to hospital (> 12 hours after symptom onset) or their ST-elevation resolved shortly after hospital presentation.

2.4.2 Conclusion

This study demonstrates that ticagrelor provides more potent platelet inhibition than clopidogrel measured by MEA. This is reflected in ticagrelor's ability to reduce the proportion of ACS patients experiencing HOTPR. Different clinical factors contribute to HOTPR in ACS patients treated with ticagrelor or clopidogrel. Clopidogrel dose, renal insufficiency, clinical presentation and platelet count are linked to clopidogrel HOTPR. In contrast, only a history of myocardial infarction is associated with ticagrelor HOTPR.

Chapter 3- Clinical factors associated with ticagrelor prescription in real world patients with acute coronary syndromes

3.1 Introduction

Variability in the residual antiplatelet effect of clopidogrel, factors contributing to this and the subsequent ischaemic consequences have been well documented [38]. Ticagrelor offers a therapeutic alternative with a different mechanism of action that is able to overcome factors linked to clopidogrel variability, giving more potent and predictable platelet inhibition [96]. This translates into the increased efficacy of ticagrelor over clopidogrel in reducing ischaemic events. Whilst this wasn't coupled with a significant increase in overall bleeding, patients treated with ticagrelor experienced higher rates of non-CABG related bleeding [91]. Based on the PLATO trial, national and international guidelines recommend using ticagrelor in intermediate to high risk NSTEMI patients [16, 123] and STEMI patients 24 hours post thrombolysis [110, 111].

Several risk prediction tools are used in clinical practice to balance the efficacy and safety of antithrombotic therapy by predicting patient risk of mortality/ ischaemia and bleeding. This balance is important as MI and major bleeding events have a similar impact on patient mortality within a year of an ACS [65]. The GRACE score is used to estimate a patient's risk of 6 month mortality following hospital discharge [124]. The CRUSADE score is used to estimate a patient's risk of a major bleeding event in hospital [125].

PHARMAC publically funded ticagrelor for use in NSTEMI and STEMI patients in July 2013. However, delayed adoption of new therapeutics introduced into clinical practice has repeatedly been demonstrated [126, 127]. This study explored factors associated with ticagrelor prescription, in particular clinical risk, and the rate of ticagrelor adoption into clinical practice.

The aims of this study were:
1) To determine which factors were associated with ticagrelor prescription.
2) To examine the prescription rates of ticagrelor by time.

3.2 Methods

3.2.1 Study population

Patients presenting to Wellington Regional Hospital with an ACS between 1 July 2013 and 30 June 2015 were eligible for inclusion into the study if coronary angiography (± PCI) was planned and they were adequately pretreated with ticagrelor or clopidogrel and aspirin. This time period was chosen as ticagrelor was funded for use in NSTEMI and STEMI patients 24 hours post thrombolysis by PHARMAC from 1 July 2013.

ACS and adequate pretreatment was previously defined in chapter 2.2.1. Exclusion criteria was as previously defined in chapter 2.2.1, with the exception of patients treated with more than one $P2Y_{12}$ inhibitor, who were included in this study.

The study was reviewed and approved by Lower South Regional Ethics Committee (ref: LRS/11/09/035/AM01).

3.2.2 Data collection

Patient demographics, prior medical history, clinical characteristics, admission medications and clinical management, were obtained prospectively from review of medical records and the cardiac catheterization database. Ethnicity was self-identified by the patient. Clinical management, including prescription of antiplatelet agent, was at the discretion of the attending physicians.

3.2.3 Definitions

The GRACE score was calculated using the algorithm that weighted nine variables predictive of 6 month mortality. These included age, a history of congestive heart failure (CHF), a prior MI, resting heart rate, systolic blood pressure, ST-segment depression, initial serum creatinine, elevated cardiac enzymes and no in-hospital PCI. The algorithm is shown in Table 3.1 [124].

The CRUSADE score was calculated using an algorithm that weighted eight variables predictive of in-hospital major bleeding. These included baseline haematocrit, creatinine clearance, heart rate, gender, signs of CHF at presentation, prior vascular disease, diabetes mellitus and systolic blood pressure. Creatinine clearance was estimated using the Cockcroft-Gault formula. Prior vascular disease was defined as a previously documented history of peripheral artery disease or prior stroke. The algorithm is shown in Table 3.2 [125].

3.2.4 Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables were tested for normality with the Kolmogorov-Smirnov normality test. All continuous variables had normal distribution and were expressed as means and standard deviations. Linear regression was performed on the correlation between the GRACE and CRUSADE risk scores using GraphPad Prism 6 (GraphPad Software Inc.; California, USA). Antiplatelet prescription by hospital and risk factors in ticagrelor and clopidogrel patients were compared using the unpaired Student's t-test and chi-squared test for continuous and categorical variables, respectively, using SPSS 22.0 (IBM).

Table 3.1 Algorithm used to determine the risk score of GRACE all-cause mortality from hospital discharge to 6 months [124]

Risk factor	Division	Point allocation
Age	≤39	0
	40-49	18
	50-59	36
	60-69	55
	70-79	73
	80-89	91
	≥90	100
History of CHF	Yes	24
	No	0
History of MI	Yes	12
	No	0
Resting Heart Rate (beats/min)	≤49.9	0
	50-69.9	3
	70-89.9	9
	90-109.9	14
	110-149.9	23
	150-199.9	35
	≥200	43
Systolic Blood Pressure (mm Hg)	≤79.9	24
	80-99.9	22
	100-119.9	18
	120-139.9	14
	140-159.9	10
	160-199.9	4
	≥200	0
ST-Segment Depression	Yes	11
	No	0
Initial Serum Creatinine (µmol/L)	0-35.3	1
	35.4-70	3
	71-105	5
	106-140	7
	141-176	9
	177-353	15
	≥354	20
Elevated Cardiac Enzymes	Yes	15
	No	0
No In-Hospital PCI	Yes	14
	No	14

Table 3.2 Algorithm used to determine the risk score of CRUSADE in-hospital major bleeding [125]

Risk factor	Division	Point allocation
Baseline haematocrit, %	<31	9
	31-33.9	7
	34-36.9	3
	37-39.9	2
	≥40	0
Creatinine clearance, mL/min	≤15	39
	>15-30	35
	>30-60	28
	>60-90	17
	>90-120	7
	>120	0
Heart rate (bpm)	≤70	0
	71-80	1
	81-90	3
	91-100	6
	101-110	8
	111-120	10
	≥121	11
Gender	Male	0
	Female	8
Signs of CHF at presentation	No	0
	Yes	7
Prior vascular disease	No	0
	Yes	6
Diabetes mellitus	No	0
	Yes	6
Systolic blood pressure, mm Hg	≤90	10
	91-100	8
	101-120	5
	121-180	1
	181-200	3
	≥201	5

3.3 Results

3.3.1 Baseline demographics

During the study 530 patients with ACS met the inclusion criteria and were enrolled in the study. Their baseline demographics, clinical characteristics and laboratory data are shown in Table 3.3. The average age was 64 ± 10 years with 72.1% being male and 18% having diabetes. The majority identified themselves as New Zealand European 87.5%, 9.1% as Maori or Pacific Islanders and the remaining 3.4% as other ethnicities. Patients predominantly presented with NSTEMI 76.4% and 23.6% as STEMI. There were a number of significant differences between those initially treated with ticagrelor and those treated with clopidogrel. Patients treated with ticagrelor were younger, less likely to present with STEMI and have a history of prior myocardial infarction and had lower GRACE and CRUSADE scores shown in Table 3.3.

There was a modest correlation between the GRACE and CRUSADE risk scores when plotted for the whole cohort, as demonstrated in Figure 3.1.

Table 3.3 Patient demographics, clinical characteristics and laboratory data by antiplatelet agent.

Demographics	All (N=530)	Ticagrelor (n=221)	Clopidogrel (n=309)	p value
Age (years)	64 ± 11	61 ± 10	65 ± 12	**<0.0001**
Male, n (%)	382 (72.1)	168 (76.0)	214 (69.3)	0.087
BMI	29.1 ± 5.5	29.2 ± 5.2	29.1 ± 5.8	0.735
Ethnicity				0.38
NZ European	464 (87.5)	189 (85.5)	275 (89.0)	
Maori or Pacific Islander	48 (9.1)	22 (10.0)	26 (8.4)	
Other	18 (3.4)	10 (4.5)	8 (2.6)	
Risk factors, n (%)				
Hypertension	315 (59.4)	125 (56.1)	191 (61.8)	0.187
Dyslipidaemia	329 (62.1)	135 (61.0)	194 (62.8)	0.691
Diabetes	95 (18.0)	38 (17.4)	57 (18.4)	0.711
Current Smoker	117 (22.1)	50 (22.6)	67 (21.7)	0.797
Medical history, n (%)				
Prior MI	105 (19.8)	35 (15.8)	70 (22.7)	**0.052**
Atrial fibrillation	32 (6.0)	9 (4.1)	23 (7.4)	0.108
Renal insufficiency	26 (4.9)	7 (3.2)	19 (6.1)	0.117
Clinical Presentation, n (%)				**<0.0001**
STEMI	125 (23.6)	28 (12.7)	97 (31.4)	
NSTEMI	405 (76.4)	193 (87.3)	212 (68.6)	
Risk scores				
GRACE	104 ± 27	98 ± 24	108 ± 28	**<0.0001**
CRUSADE	26 ± 11	25 ± 9	28 ± 12	**0.001**

Abbreviations: BMI- body mass index; NZ European- New Zealand European; MI-myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI; GRACE-Global Registry of Acute Coronary Events; CRUSADE- Can Rapid risk stratification of Unstable angina patients Supress Adverse outcomes with Early implementation of the ACC/AHA guidelines

Figure 3.1 Ischaemic versus haemorrhagic risk, the GRACE and CRUSADE risk scores.

Abbreviations: GRACE- Global Registry of Acute Coronary Events; CRUSADE- Can Rapid risk stratification of Unstable angina patients Supress Adverse outcomes with Early implementation of the ACC/AHA guidelines.

3.3.2 Antiplatelet prescription by hospital

The prescription of antiplatelet agents differed markedly depending upon which hospital patients presented to (p<0.0001). The percentage of patients prescribed ticagrelor varied from 65% at Wellington Hospital to 8% at Wanganui Hospital, shown in Figure 3.2. The lowest rates of ticagrelor prescription occurred in the 2 hospitals without resident cardiologists, Wanganui and Wairarapa Hospitals. The difference in use of agents was not due to a significant difference in patient risk scores (GRACE or CRUSADE) across hospitals, as demonstrated in Table 3.4. There were some differences in the Wellington Hospital cohort, particularly with a lower proportion of STEMI patients. As Wellington Hospital was the only PCI capable hospital, STEMI patients presenting to Wellington requiring primary PCI went directly to angiography and were not eligible for enrolment within our ACS registry.
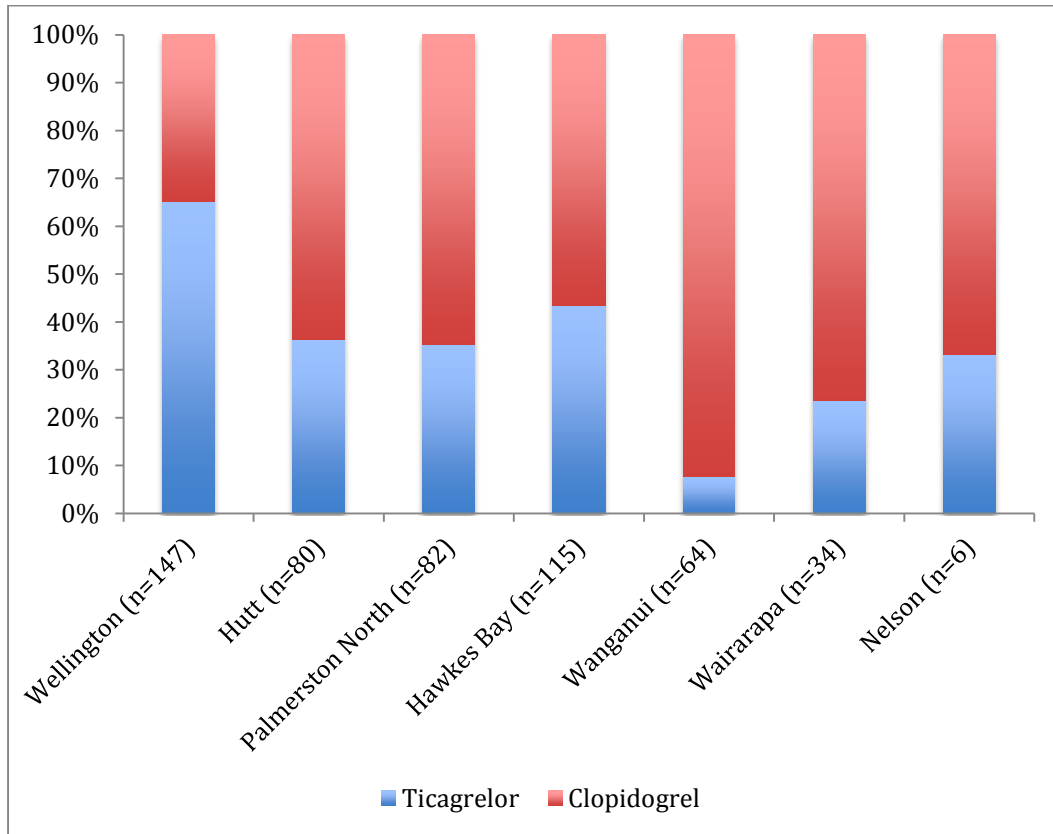
Figure 3.2 Proportion of antiplatelet prescription by initial hospital

We performed a sub-analysis of patients presenting to Hutt, Palmerston North and Hawkes Bay hospitals, shown in Table 3.5. Wellington Hospital was excluded due to its alternative treatment of STEMIs. Wanganui Hospital was excluded because of its consistently low prescription rate of ticagrelor (7.8%). Wairarapa Hospital was excluded because of its small sample size (n=34). Nelson Hospital was excluded because patients are not routinely transferred to Wellington for intervention. Additionally, prescription of antiplatelet agents at Wanganui and Wairarapa Hospitals are by general physicians, not cardiologists as in Wellington, Hutt, Palmerston North and Hawkes Bay. Patients prescribed clopidogrel in this subgroup of hospitals were older, more likely to present with STEMI and have higher GRACE and CRUSADE scores (Table 3.5), consistent with the findings of our overall analysis.

Table 3.4 Risk factors of patients by initial admitting hospital

Risk factors	Wellington (n=146)	Hutt (n=80)	Palmerston North (n=82)	Hawkes Bay (n=115)	Wanganui (n=64)	Wairarapa (n=34)	p value
Age (years)	64 ± 11	63 ± 12	62 ± 11	64 ± 10	64 ± 13	64 ± 11	0.873
Male, n (%)	108 (74.0)	58 (72.5)	58 (70.7)	85 (73.9)	42 (65.6)	25 (73.5)	0.880
Prior MI	25 (17.1)	19 (23.8)	11 (13.4)	23 (20.0)	20 (31.3)	4 (11.8)	0.066
STEMI	7 (4.8)	19 (23.8)	31 (37.8)	31 (27.0)	19 (29.7)	14 (41.2)	**<0.0001**
GRACE	104 ± 27	104 ± 30	100 ± 24	104 ± 24	108 ± 29	104 ± 23	0.549
CRUSADE	26 ± 10	27 ± 11	25 ± 12	26 ± 10	28 ± 13	23 ± 13	0.469

Abbreviations: MI- myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI; GRACE- Global Registry of Acute Coronary Events; CRUSADE- Can Rapid risk stratification of Unstable angina patients Supress Adverse outcomes with Early implementation of the ACC/AHA guidelines
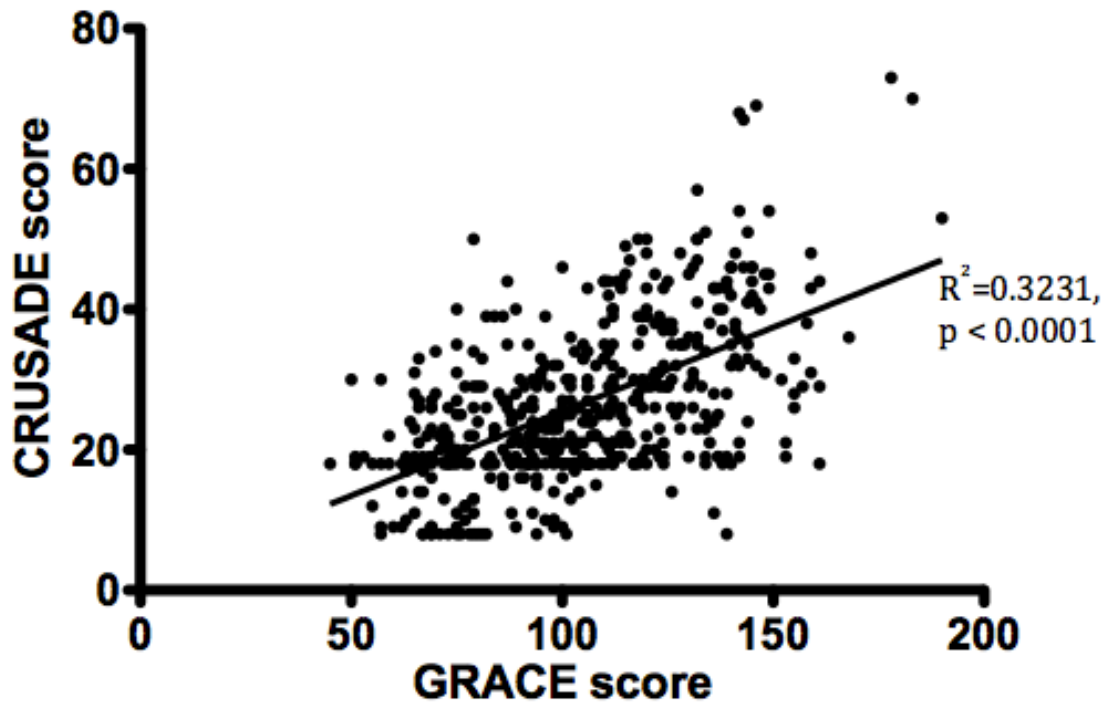
Risk factors	All (N=277)	Ticagrelor (n=108)	Clopidogrel (n=169)	p value
Age (years)	63 ± 11	60 ± 9	66 ± 12	**<0.0001**
Male, n (%)	201 (72.6)	83 (76.9)	118 (69.8)	0.201
Prior MI	53 (19.1)	17 (15.7)	36 (21.3)	0.251
STEMI	69 (24.9)	14 (13.0)	55 (32.5)	**<0.0001**
GRACE	102 ± 26	94 ± 23	108 ± 26	**<0.0001**
CRUSADE	26 ± 11	24 ± 9	28 ± 12	**0.002**

Abbreviations: MI- myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI; GRACE- Global Registry of Acute Coronary Events; CRUSADE- Can Rapid risk stratification of Unstable angina patients Supress Adverse outcomes with Early implementation of the ACC/AHA guidelines

3.3.3 Antiplatelet switching

Antiplatelet switching from one agent to the other prior to angiography was not common, and occurred in 4.5% of patients (Table 3.6). Patients were predominantly switched from clopidogrel to treatment with ticagrelor (91.7%). Consistent with higher risk patients being prescribed clopidogrel, patients who were switched had lower GRACE and CRUSADE risk scores (p=0.042 and p=0.019 respectively), shown in Table 3.6. Age, gender, prior MI and STEMI were not significantly associated with antiplatelet switching.

Table 3.6 Risk scores in patients with antiplatelet switching

Risk factors	Unchanged (n=506)	Switched (n=24)	p value
Age (years)	63 ± 11	61 ± 6	0.24
Male, n (%)	362 (71.5)	20 (83.3)	0.208
Prior MI	101 (20.0)	4 (16.7)	0.692
STEMI	119 (23.5)	6 (25.0)	0.867
GRACE	104 ± 27	93 ± 24	**0.042**
CRUSADE	27 ± 11	21 ± 9	**0.019**

Abbreviations: MI- myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI; GRACE- Global Registry of Acute Coronary Events; CRUSADE- Can Rapid risk stratification of Unstable angina patients Supress Adverse outcomes with Early implementation of the ACC/AHA guidelines

3.3.4 Antiplatelet prescription over time

Prescription of ticagrelor varied over the two year time period of this study, as shown in Figure 3.3. In the last two periods (January-March 2015 and April-June 2015), use of ticagrelor increased to 49% and 57%, relative to the preceding 6 periods of time, where between 34% and 41% of patients were prescribed ticagrelor.
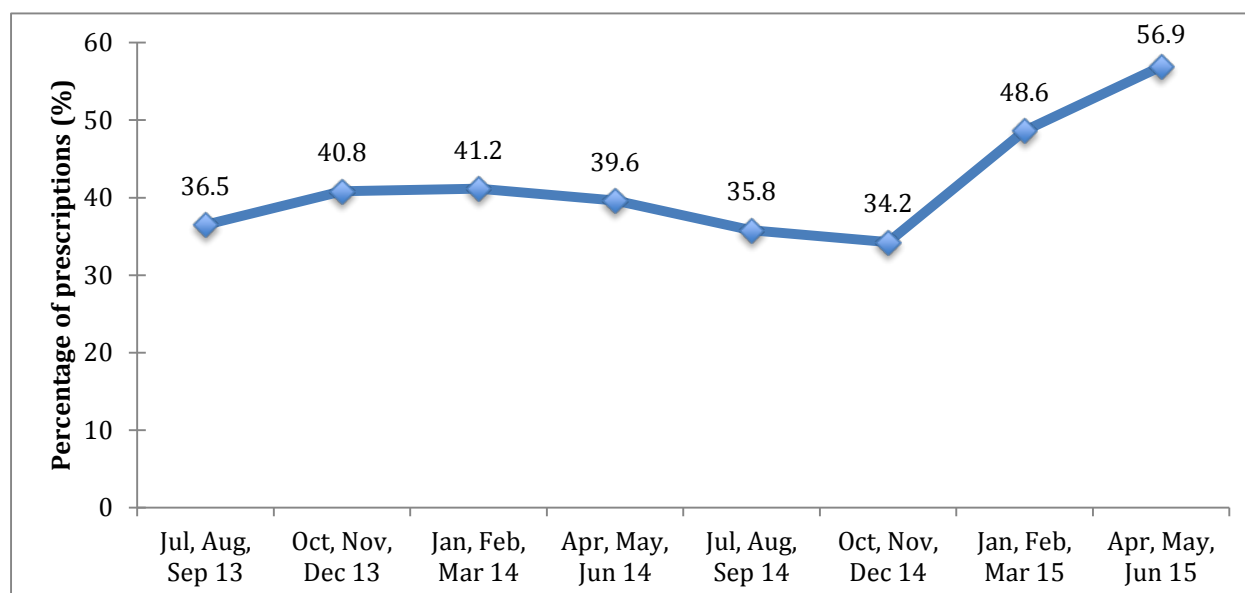
Figure 3.3 Prescription of ticagrelor by quarter from July 2013 to June 2015

3.4 Discussion

We have demonstrated that patients prescribed ticagrelor were younger, less likely to present with STEMI, less likely to have a history of prior MI and had lower GRACE and CRUSADE risk scores. Prescription of ticagrelor was therefore not driven by increased clinical risk. Antiplatelet prescription varied significantly according to the patients' admitting hospital. More patients were prescribed clopidogrel overall, but the proportion of ticagrelor prescription increased over the two year study period.

Patients initially treated with clopidogrel were significantly older than those given ticagrelor, were more likely to have had a prior MI, and had higher GRACE scores. Increasing age is a powerful predictor of worse clinical outcomes. For every 10 year increase in patient age, there is a 75% increase in hospital mortality [128]. This is accounted for in the GRACE risk score with weighting ranging from 18 to 100 and is the factor that has the greatest influence over the total GRACE risk score. A prior MI is also weighted with 12 points in the GRACE score [124]. These two factors contributed to the higher GRACE score in the clopidogrel group. Patients treated with clopidogrel also had slightly higher CRUSADE scores than those treated with ticagrelor [125]. While the average CRUSADE risk scores for patients treated with ticagrelor and clopidogrel were significantly different (p=0.001), they are both within the low risk CRUSADE risk category, 25 and 28 respectively.

As the GRACE and CRUSADE risk scores share 3 clinical factors, the two risk scores correlate modestly well, as demonstrated in the present study. An implication of this is that it is difficult to identify a group of patients with high mortality/ischaemic risk (GRACE score) who do not also have a high bleeding risk (CRUSADE score). It is possible that factors associated with an elevated risk of bleeding are influencing clinician choice of antiplatelet agent more strongly than factors associated with increased ischaemic risk (GRACE score). This is despite ticagrelor's benefit shown in the PLATO trial in ACS patients with both high

mortality/ischaemic risk and bleeding risk, such as those with diabetes and renal impairment, being consistent with those of the main cohort [129, 130].

This pattern of prescription conflicts with published national and international guidelines for the management of NSTEMI patients. Ticagrelor has been recommended in European NSTEMI guidelines for all patients at moderate-to-high risk of ischaemic events. This is regardless of the initial treatment strategy and including patients initially treated with clopidogrel [16]. Whilst the 2012 American NSTEMI guidelines do not give preference to ticagrelor or clopidogrel [131], the 2014 update prefers ticagrelor in patients treated with an early invasive or ischaemia-guided strategy [132]. Ticagrelor has been recommended in the New Zealand NSTEMI guidelines as the preferred $P2Y_{12}$ inhibitor since 2012, a year before ticagrelor was funded by PHARMAC [123].

Hesitation to prescribe evidence based therapies to the elderly is not a novel finding. While both cardiovascular and bleeding complications are more prevalent in the elderly who have greater risk profiles and experience greater in hospital mortality, they less frequently receive the standard of care [128, 133].

Elderly patients aged 75 and older experienced substantially higher event rates, yet received a diminished benefit from prasugrel over clopidogrel in the TRITON-TIMI 38 trial. Coupled with their higher non-CABG related TIMI major bleeding events and an excess of spontaneous fatal haemorrhages, the net clinical benefit of prasugrel was eliminated in the elderly [76]. Yet, in a prespecified subanalysis of the PLATO trial, the findings in elderly patients aged 75 and older were consistent with those in the main PLATO cohort. The clinical benefit of ticagrelor over clopidogrel was not significantly different in the elderly and there was no increase in the PLATO trial defined overall major bleeding [134].

This hesitation to prescribe ticagrelor may reflect heightened bleeding concerns following the introduction of the last anti-thrombotic agent to New Zealand. Dabigatran was introduced in July 2011 without prescription restrictions. Approximately 7000 patients commenced treatment in the first two months,

resulting in 78 bleeding events during this period. Contributing clinical factors were increased age, impaired renal function and prescriber error [135].

While there is evidence that patients with increasing age, GRACE and CRUSADE risk scores can be safely treated with ticagrelor, evidence is lacking for combining ticagrelor with fibrinolytic therapy. Whilst 38% of the PLATO trial population were STEMIs [91] these patients exclusively received primary PCI [136] as fibrinolytic therapy, either planned or within 24 hours, was part of the exclusion criteria [137]. A significantly greater proportion of STEMI patients are treated with clopidogrel based on the international guidelines for using clopidogrel as adjunctive antithrombotic therapy to fibrinolytic therapy. This is based on the CLARITY and COMMIT trials [110, 138]. Post thrombolysis, the European guidelines recommend ticagrelor or prasugrel with aspirin for chronic therapy, while the American guidelines recommend clopidogrel or prasugrel [110, 138]. The New Zealand guidelines recommend clopidogrel as adjunctive antithrombotic therapy to fibrinolytic therapy before switching the patient to ticagrelor 24 hours post thrombolysis [111].

We have demonstrated that prescription of antiplatelet agent was in part determined by the hospital patients initially presented to. The proportion of patients prescribed ticagrelor ranged from 65.3% in Wellington, a tertiary centre, to 7.8% in Wanganui, a secondary provincial hospital staffed by physicians, not cardiologists. The patient populations presenting to the different hospitals were not significantly different, except for the proportion of STEMIs. This is due to Wellington's alternate treatment pathway for STEMIs as an interventional centre able to perform primary PCI. In the three secondary hospitals staffed by cardiologists, Hutt, Palmerston North and Hawkes Bay hospitals, increasing age, GRACE and CRUSADE risk scores and presenting as a STEMI, were associated with clopidogrel prescription. Hence Wellington and Wanganui's oppositional treatment strategies do not significantly influence the results. Higher risk patients were still being systematically treated with clopidogrel.

Antiplatelet switching was not common, occurring in 4.5% of patients. Antiplatelet switching predominantely involved switching patients from clopidogrel to ticagrelor treatment (91.7%). Consistent with our previous results, patients who were switched had significantly lower GRACE and CRUSADE risk scores. Furthermore, there was not a significant association between STEMI patients and antiplatelet switching. Again, this antiplatelet switching pattern conflicts with published guidelines for moderate to high risk NSTEMIs to be prescribed ticagrelor and STEMIs initially loaded on clopidogrel to be switched to ticagrelor 24 hours post thrombolysis [16, 110, 111, 123]. The low rate of antiplatelet switching prior to angiography observed in our cohort may represent system inertia.

In this study there was little change in the proportion of patients receiving ticagrelor between July 2013 and December 2014. Only from January 2015 was there a detectable increase, and only from April 2015 were more than half the ACS patients being treated with ticagrelor. This study was not designed to examine the cause of the increase in ticagrelor prescriptions observed over this time period. However, it is reasonable to speculate that the introduction of local guidelines on ticagrelor use in November 2014, with accompanying educational programmes between November 2014 and May 2015, may have contributed to the observed increase in ticagrelor adoption. Slow adoption of ticagrelor has also been shown in a US registry, with an increase in quarterly ticagrelor prescription from 1.8% to 14.4% over a two year period from January 2012-2014. Ticagrelor was also prescribed in this registry to younger patients with less comorbidities than patients treated with clopidogrel. The rate of ticagrelor prescription is lower than ours as prasugrel is also available in America [139].

Delayed adoption of new therapies in clinical practice is problematic, especially as clinical decision making is strongly influenced by factors other than clinical evidence. An eight year delay between the introduction of a new therapeutic agent and its adoption into Australian prescription practice demonstrates this inertia [126]. Adoption times differ from drug to drug and in different localities. Drugs with a novel mechanism of action or in a therapeutic class with limited

alternatives are adopted more readily than drugs with adequate alternatives, again demonstrating system inertia. While efficacy and side effect profile are taken into account, colleagues and pharmaceutical representatives influence practice patterns [127]. The presence of inertia suggests the flow of new evidence into clinical practice and the subsequent rate of change of prescribing practices are important factors that determine how closely clinical decision making reflects the perception of drug efficacy and safety [126]. Given that this process is essentially a diffusion one, it is not surprising that uptake is faster in tertiary centres and slower in secondary centres that are not staffed with specialists, such as Wanganui Hospital.

3.4.1 Limitations

Our study did not capture every patient prescribed DAPT. We only enrolled patients presenting to or referred to Wellington Hospital for invasive management who had been adequately pre-treated with DAPT. Patients undertaking angiography in secondary centers with cardiac catheterisation facilities (Hawkes Bay and Palmerston North hospitals) not referred for PCI were not captured in this study. Patients were not captured if there was insufficient time between transfer patient arrival and angiography to obtain patient informed consent. Furthermore patients were not captured if they met our exclusion criteria. While this means we have missed some of the highest risk patients (STEMIs undergoing primary PCI), the majority of other patients where an invasive strategy was not undertaken were likely to have had relatively lower risk.

3.4.2 Conclusion

Patients prescribed ticagrelor were younger, less likely to present with STEMI and had lower GRACE and CRUSADE risk scores. As GRACE and CRUSADE risk scores correlate well, clinicians may have been prioritizing bleeding concerns over ischaemic risk. Patients prescribed clopidogrel were essentially higher risk, contrasting with national and international NSTEMI guideline recommendations for prescription of ticagrelor in high risk patients. Ticagrelor's slow uptake over the two year study period demonstrates system inertia in adopting new therapeutic agents.

Chapter 4- Safety and tolerability of ticagrelor in real world acute coronary syndrome patients

4.1 Introduction

Ticagrelor's greater efficacy over clopidogrel in reducing the ischaemic events was demonstrated in the PLATO trial. While this was not coupled with a significant increase in overall bleeding, ticagrelor use was associated with a significant increase in non-CABG related bleeding. Ticagrelor patients also reported a significantly greater incidence of dyspnoea and ticagrelor was discontinued more frequently than clopidogrel due to adverse effects [91]. This led to concerns about the impact of bleeding, dyspnoea and ticagrelor's twice daily dosing outside the controlled environment of a highly selective clinical trial population, at low risk of adverse events and therapy non-compliance.

As we have demonstrated in Chapter 3, clinicians have been prioritizing bleeding concerns over ischaemic risk by prescribing ticagrelor to patients with both lower CRUSADE and GRACE scores. This has contributed to ticagrelor's slow adoption into New Zealand clinical practice. As the flow of new evidence into clinical practice contributes to the rate of change in prescribing patterns [126] we sought to investigate both the safety and tolerability of ticagrelor in a real world New Zealand ACS population by analyzing the rate of clinical outcomes throughout index hospital admission and between hospital discharge and 30 day follow up.

The aims of this study were:
1. To examine bleeding incidence in ACS patients treated with ticagrelor or clopidogrel during hospital admission and at 30 day follow up.
2. To determine the incidence of dyspnoea in ACS patients treated with ticagrelor and clopidogrel at 30 day follow up.
3. To determine whether adverse events contributed to therapy discontinuation in ACS patients treated with ticagrelor and clopidogrel, during index hospital admission and at 30 day follow up.

4.2 Methods

4.2.1 Study population

Patients presenting to Wellington Regional Hospital with an ACS between 1 July 2013 and 30 June 2015 were eligible for inclusion into the study if coronary angiography (± PCI) was planned and they were adequately pretreated with ticagrelor or clopidogrel and aspirin. Exclusion criteria was as previously defined in chapter 2.2.1, with the exception of patients treated with more than one $P2Y_{12}$ inhibitor, who were included in this study. Eight patients (1.9%) with incomplete follow up were excluded from the analysis of 30 day follow up outcomes. The study was reviewed and approved by Lower South Regional Ethics Committee (ref: LRS/11/09/035/AM01). All patients provided written informed consent.

4.2.2 Data collection

Patient demographics, prior medical history, clinical characteristics, admission medications, clinical management, procedural variables and in-hospital outcomes were obtained prospectively from review of medical records and the cardiac catheterization database. Patient outcomes between hospital discharge and 30 days post study enrolment were obtained via telephone call. Ethnicity was self-identified by the patient. Clinical management, including prescription of antiplatelet agent, was at the discretion of the attending physicians.

4.2.3 Definitions

ACS and adequate pretreatment were defined as previously stated in chapter 2.2.1. The primary endpoint of combined MACE was defined as a composite outcome of death, non-fatal MI, ischaemic stroke and stent thrombosis. MI was defined according to the 3rd Universal Definition of Myocardial Infarction [10]. Stent thrombosis was defined according to the Academic Research Consortium [140]. Bleeding was classified according to both the TIMI and BARC bleeding definitions, as shown in Tables 4.1 and 4.2. PLATO defined bleeding is shown in

Table 4.3, as it is referred to. Bleeding events and MI were adjudicated by a clinician blinded to the antiplatelet agent.

Table 4.1 TIMI bleeding definition [76, 141, 142]

Non-CABG related bleeding	Definition
Major	• Intracranial bleeding (excluding microhaemorrhages <10 mm evident only on gradient-echo MRI). • Clinically overt haemorrhage with associated haemoglobin drop ≥ 5 g/dL. • Fatal bleeding (bleeding directly resulting in death within 7 days).
Minor	• Clinically overt (including imaging) with associated haemoglobin drop 3 to <5 g/dL.
Requiring medical attention	Overt sign of haemorrhage that meets one of the following criteria, but not major or minor criteria: • Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing dose of medication). • Leading to or prolonging hospitalisation. • Prompting evaluation (unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging).
Minimal	• Any overt bleeding event that does not meet above criteria.

Abbreviations: TIMI- Thrombolysis in Myocardial Infarction; non-CABG- non-coronary artery bypass grafting; MRI- magnetic resonance imaging.

Table 4.2 Bleeding Academic Research Consortium (BARC) definition

Bleeding class		Definition
Type 0		No bleeding.
Type 1		- Non actionable bleeding. - Patient does not seek treatment or evaluation. - May lead to self-discontinuation of therapy without medical consultation.
Type 2		Overt, actionable haemorrhage that does not meet type 3, 4 or 5 thresholds, but: 1. requires nonsurgical, medical intervention and/or 2. hospitalization or increased care and/or 3. prompts evaluation.
Type 3	A	- Overt bleeding with related haemoglobin drop 3 to <5g/dL (corrected for intracurrent transfusion: 1 unit of packed red blood cells (PBRC) or whole blood increases haemoglobin by 1g/dL). - Any transfusion with overt bleeding.
	B	- Overt bleeding with related haemoglobin drop ≥5g/dL. - Cardiac tamponade. - Bleeding requiring surgical intervention to control (excluding nasal/dental/skin/haemorrhoid). - Bleeding requiring intravenous vasoactive agents.
	C	- Intracranial haemorrhage (includes intraspinal, excludes microbleeds and haemorrhagic transformation). - Intraocular bleed compromising vision. - Subcategories confirmed by autopsy, imaging, or lumbar puncture.
Type 4		Coronary Artery Bypass Grafting (CABG)-related bleeding - Perioperative intracranial bleeding <48 hours. - Reoperation after closure of sternotomy to control bleeding. - Transfusion of ≥5 units of whole blood or PRBC <48 hours. - Chest tube output ≥2L <24 hours.
Type 5	A	Fatal bleeding Probable: no autopsy or imaging confirmation but clinically suspicious.
	B	Definite: overt bleeding, autopsy or imaging confirmation.

Table 4.3 PLATO trial bleeding definition [91]

Bleeding class	Definition
Major life-threatening	• Fatal • Intracranial • Intrapericardial with cardiac tamponade • Hypovolemic shock or severe hypotension requiring pressors or surgery. • Clinically overt or apparent bleeding with a related haemoglobin drop >5g/dL. • Requiring transfusion of ≥4 U whole blood or PRBCs.
Other major	• Significantly disabling • Related haemoglobin drop of 3 to 5g/dL • Requiring transfusion of 2-3 U whole blood or PRBCs.
Any major	Any one of above criteria.
Minor	Requiring medical intervention to stop or treat bleeding.
Minimal	All others not requiring intervention or treatment.

Abbreviations: PLATO- PLATelet inhibition and patient Outcomes; PRBCs- packed red blood cells.

4.2.4 Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables were tested for normality with the Kolmogorov-Smirnov normality test and found to be normally distributed. Continuous variables are expressed as means and standard deviations. GRACE and CRUSADE risk scores were calculated using Microsoft Excel software. The unpaired Student's t-test was used for all continuous variables by antiplatelet agent. The chi-squared test was used for all categorical variables by antiplatelet agent. All statistical tests were performed using SPSS 22.0 (IBM).

4.3 Results

4.3.1 In hospital outcomes

4.3.1.1 Baseline demographics

During the study 530 patients with ACS met the inclusion criteria and were enrolled in the study. Their baseline demographics, clinical characteristics and laboratory data are shown in Table 4.4. The mean age was 64 ± 11 years with 72.1% being male and 18.0% having diabetes. The majority identified themselves as NZ European 87.5%, 9.1% as Maori or Pacific Islanders and the remaining 3.4% as other ethnicities. Patients predominantly presented with NSTEMI (76.4%) with the remainder presenting with STEMI (23.6%). Patients treated with ticagrelor were younger, less likely to present with STEMI and have a history of prior MI and had lower GRACE and CRUSADE scores.

In the study cohort overall, radial access was used in 88.1% of patients, 29.8% were treated medically, 55.3% were treated with PCI and 14.9% were treated with CABG. Patients treated with ticagrelor and clopidogrel had similar management strategies and procedural details, shown in Tables 4.5 and 4.6.

Table 4.4 Baseline demographics and clinical characteristics by antiplatelet agent

Demographics	All (N=530)	Ticagrelor (n=221)	Clopidogrel (n=309)	p value
Age (years)	64 ± 11	61 ± 10	65 ± 12	**<0.0001**
Male, n (%)	382 (72.1)	168 (76.0)	214 (69.3)	0.087
BMI	29.1 ± 5.5	29.2 ± 5.2	29.1 ± 5.8	0.735
Ethnicity				0.38
NZ European	464 (87.5)	189 (85.5)	275 (89.0)	
Maori/ PI	48 (9.1)	22 (10.0)	26 (8.4)	
Other	18 (3.4)	10 (4.5)	8 (2.6)	
Risk factors, n (%)				
Hypertension	315 (59.4)	125 (56.1)	191 (61.8)	0.187
Dyslipidaemia	329 (62.1)	135 (61.0)	194 (62.8)	0.691
Diabetes	95 (18.0)	38 (17.4)	57 (18.4)	0.711
Current Smoker	117 (22.1)	50 (22.6)	67 (21.7)	0.797
Medical history, n (%)				
Prior MI	105 (19.8)	35 (15.8)	70 (22.7)	**0.052**
Atrial fibrillation	32 (6.0)	9 (4.1)	23 (7.4)	0.108
Renal insufficiency	26 (4.9)	7 (3.2)	19 (6.1)	0.117
Clinical Presentation, n (%)				**<0.0001**
STEMI	125 (23.6)	28 (12.7)	97 (31.4)	
NSTEMI	405 (76.4)	193 (87.3)	212 (68.6)	
Risk scores				
GRACE	104 ± 27	98 ± 24	108 ± 28	**<0.0001**
CRUSADE	26 ± 11	25 ± 9	28 ± 12	**0.001**

Abbreviations: BMI- body mass index; NZ European- New Zealand European; PI-Pacific Islander; MI- myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI, GRACE- Global Registry of Acute Coronary Events; CRUSADE- Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines.

Table 4.5 Angiographic procedural details by antiplatelet agent

Procedural details	All (N=530)	Ticagrelor (n=221)	Clopidogrel (n=309)	p value
Access site				0.373
Radial	467 (88.1)	198 (89.6)	269 (87.1)	
Femoral	63 (11.9)	23 (10.4)	40 (12.9)	
Management strategy				0.121
Medical	158 (29.8)	58 (26.2)	100 (32.4)	
PCI	293 (55.3)	123 (55.7)	170 (55.0)	
CABG	79 (14.9)	40 (18.1)	39 (12.6)	

Abbreviations: PCI- percutaneous coronary intervention; CABG- coronary artery bypass grafting.

Table 4.6 Procedural details for patients treated with PCI by antiplatelet agents

PCI	All (N=293)	Ticagrelor (n=123)	Clopidogrel (n=170)	p value
Number lesions treated	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	0.687
Number vessels treated	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	0.173
Number of stents	1.4 ± 0.6	1.4 ± 0.6	1.3 ± 0.6	0.797
BMS	0.1 ± 0.3	0.1 ± 0.2	0.1 ± 0.3	0.686
DES	1.3 ± 0.7	1.3 ± 0.7	1.3 ± 0.7	0.687

Abbreviations: PCI- percutaneous coronary intervention; BMS- bare metal stent; DES- drug eluting stent

4.3.1.2 Adverse ischaemic events

Patients treated with ticagrelor experienced significantly lower rates of MACE in hospital when compared to those treated with clopidogrel (4.5% vs. 10.0%, p=0.019), shown in Table 4.7. There was one cardiac death in a clopidogrel treated patient, who suffered an ischaemic stroke.

The difference in MACE between the groups was driven by the higher rates of MI and ischaemic stroke in patients treated with clopidogrel. However, the differences in the rates of MI and ischaemic stroke between the two groups were not significant alone. The majority of recurrent myocardial infarctions occurred peri-procedurally (32). There were only 2 recurrent myocardial infarctions in-hospital that weren't related to procedures. There were no cases of definite stent thrombosis.

Table 4.7 In hospital ischaemic outcomes by antiplatelet agent

Hierarchial MACE	All (N=530)	Ticagrelor (n=221)	Clopidogrel (n=309)	p value
Total MACE	41 (7.7)	10 (4.5)	31 (10.0)	**0.019**
Death	1 (0.2)	0	1 (0.3)	0.397
MI	34 (6.4)	9 (4.1)	25 (8.1)	0.064
Ischaemic stroke	6 (1.1)	1 (0.5)	5 (1.6)	0.211
Stent thrombosis	0	0	0	1

Abbreviations: MACE- major adverse cardiac event; MI- myocardial infarction

4.3.1.3 Non-CABG related bleeding events

There was no significant difference in the non-CABG related bleeding rates between the ticagrelor and clopiodgrel groups when classified by either the TIMI or BARC criteria (Table 4.8). Non-CABG related major bleeding events were rare, with no fatal bleeding events. There were 2 TIMI major bleeds both of which occurred in the clopidogrel group. These comprised of one intracranial haemorrhage and one gastrointestinal bleed associated with a haemoglobin drop ≥ 5 g/dL requiring transfusion. A haemoglobin drop between 3 and 5 g/dL occurred in 2 patients, 1 from in each group.

When bleeding was classified using the BARC definition there were 4 BARC 3 bleeds with one occurring in the ticagrelor group and 3 in the clopidogrel group (Table 4.8). BARC 2 bleeding, which is relatively minor bleeding, occurred more frequently in ticagrelor treated patients (4.1% vs 1.3%, p=0.041). However, overall BARC bleeding rates were similar. Bleeding related to the arterial access site was responsible for the majority (70.6%) of bleeds (Table 4.9).

Table 4.8 In hospital non-CABG related bleeding by antiplatelet agent

non-CABG bleeding	All (N=530)	Ticagrelor (n=221)	Clopidogrel (n=309)	p value
Fatal bleeding	0	0	0	1
Intracranial haemorrhage	1 (0.2)	0	1 (0.3)	0.397
Haemoglobin (Hb) drop ≥ 5 g/dL	1 (0.2)	0	1 (0.3)	0.397
Overt with Hb drop >3, <5 g/dL	2 (0.4)	1 (0.5)	1 (0.3)	0.811
Transfusion	1 (0.2)	0	1 (0.3)	0.397
TIMI classification	7 (1.3)	3 (1.4)	4 (1.3)	0.950
Major	2 (0.4)	0	2 (0.6)	0.231
Minor	5 (0.9)	3 (1.4)	2 (0.6)	0.404
BARC classification	17 (3.2)	10 (4.5)	7 (2.3)	0.146
2	13 (2.5)	9 (4.1)	4 (1.3)	**0.041**
3A	2 (0.4)	1 (0.5)	1 (0.3)	0.811
3B	1 (0.2)	0	1 (0.3)	0.397
3C	1 (0.2)	0	1 (0.3)	0.397

Abbreviations: non-CABG- non-coronary artery bypass grafting; Hb- haemoglobin; TIMI- Thrombolysis in Myocardial Infarction; BARC- Bleeding Academic Research Consortium

Table 4.9 Site of in hospital bleeding events by antiplatelet agent

non-CABG bleeding	All (N=17)	Ticagrelor (n=10)	Clopidogrel (n=7)	p value
Site of bleeding				0.200
Intracranial	1 (5.9)	0	1 (14.3)	
Gastrointestinal	1 (5.9)	0	1 (14.3)	
Retroperitoneal	1 (5.9)	0	1 (14.3)	
Access site	12 (70.6)	8 (80.0)	4 (57.1)	
Other	2 (11.8)	2 (20.0)	0	

Abbreviations: non-CABG- non-coronary artery bypass grafting

4.3.1.4 In hospital discontinuation and switching of antiplatelet therapy

The rate of DAPT discontinuation between patients treated with ticagrelor and clopidogrel was not significantly different (22.6% vs 16.2%, p=0.062) and is shown in Table 4.10. Discontinuation of DAPT was primarily due to patient management strategies, patients either undergoing CABG, starting anticoagulation or receiving a final diagnosis other than an ACS. However, in one patient clopidogrel was stopped following a TIMI minor bleeding event. The reasons for DAPT discontinuation were similar between the ticagrelor and clopidogrel groups.

Switching between antiplatelet agents post angiography occurred in 5.5% of patients. Significantly more patients were switched from clopidogrel to ticagrelor post angiography (7.1%) than from ticagrelor to clopidogrel (3.2%, p=0.049). Patients were switched from ticagrelor to clopidogrel post angiography due to the perception of lower clinical risk (1.4%), following CABG (0.9%) or adverse effects (0.9%). Adverse effects included a rash and reported dyspnoea coupled with a need for anticoagulation. 22 patients were switched from clopidogrel to ticagrelor following angiography at the discretion of the physician. No reason was documented for this switch, but as 86% of these cases received intervention, it may be reasonable to suggest that angiographic evidence of significant coronary disease was a contributing factor.

Table 4.10 Proportion and rationale of in hospital DAPT discontinuation

Discontinuation	All (N=530)	Ticagrelor (n=221)	Clopidogrel (n=309)	p value
Total	100 (18.9)	50 (22.6)	50 (16.2)	0.062
Reason for discontinuation	**N= 100**	**n=50**	**n=50**	0.737
CABG	61 (61.0)	32 (64.0)	29 (58.0)	
Anticoagulant started	4 (4.0)	2 (4.0)	2 (4.0)	
Alternate diagnosis	34 (34.0)	16 (32.0)	18 (36.0)	
Bleeding	1 (1.0)	0	1 (2.0)	

Abreviations: DAPT- dual antiplatelet therapy; CABG- coronary artery bypass grafting.

4.3.2 Patient outcomes between hospital discharge and 30 days post enrolment

4.3.2.1 Baseline demographics

Of the 530 patients prescribed DAPT in hospital, 422 were discharged on DAPT. Their enrolment baseline demographics, clinical characteristics and laboratory data are shown in Table 4.11. The average age was 64 ± 11 years with 71.3% being male and 16.6% having diabetes. The majority identified themselves as NZ European 87.0%, 8.8% as Maori or Pacific Islanders and the remaining 4.3% as other ethnicities. Patients predominantly presented with NSTEMI (76.1%) with the remainder presenting with STEMI (23.9%). Patients discharged on ticagrelor were younger, had a higher BMI, were less likely to present with STEMI and have a history of prior myocardial infarction.

Table 4.11 Baseline demographics and clinical characteristics of patients discharged on DAPT

Demographics	All (N=422)	Ticagrelor (n=183)	Clopidogrel (n=239)	p value
Age (years)	64 ± 11	61 ± 10	66 ± 12	**<0.0001**
Male, n (%)	301 (71.3)	132 (72.1)	169 (70.7)	0.749
BMI	29.2 ± 5.5	29.8 ± 5.2	28.8 ± 5.7	**0.048**
Ethnicity				0.522
NZ European	367 (87.0)	156 (85.2)	211 (88.3)	
Maori/ PI	37 (8.8)	17 (9.3)	20 (8.4)	
Other	18 (4.3)	10 (5.5)	8 (3.3)	
Risk factors, n (%)				
Hypertension	255 (60.4)	105 (57.4)	150 (62.8)	0.262
Dyslipidaemia	266 (63.0)	111 (60.7)	155 (64.9)	0.376
Diabetes	70 (16.6)	27 (14.8)	43 (18.0)	0.376
Current Smoker	98 (23.2)	48 (26.2)	50 (20.9)	0.201
Medical history, n (%)				
Prior MI	82 (19.4)	27 (14.8)	55 (23.0)	**0.034**
Atrial fibrillation	26 (6.2)	7 (3.8)	19 (7.9)	0.081
Renal insufficiency	23 (5.5)	7 (3.8)	16 (6.7)	0.198
Clinical Presentation, n (%)				**<0.0001**
STEMI	101 (23.9)	24 (13.1)	77 (32.2)	
NSTEMI	321 (76.1)	159 (86.9)	162 (67.8)	

Abbreviations: DAPT- dual antiplatelet therapy; BMI- body mass index; NZ European- New Zealand European, PI- Pacific Islander; MI- myocardial infarction; STEMI- ST-elevation MI; NSTEMI- non-STEMI.

4.3.2.2 Adverse ischaemic events

MACE between discharge and 30 days was infrequent, with only 0.9% of patients experiencing MACE (Table 4.12). The rate of hierarchical MACE was similar in both the ticagrelor and clopidogrel groups. There was one death, in a ticagrelor patient who suffered a NSTEMI and subsequent cardiac failure. As this is hierarchical MACE, only his death is recorded. A further 3 patients suffered repeat non-fatal MIs, 1 ticagrelor patient and 2 clopidogrel patients. There were no documented cases of ischaemic stroke or definite stent thrombosis.

Table 4.12 Adverse events between hospital discharge and follow up at 30 days post enrolment

Hierarchial MACE	All (N=422)	Ticagrelor (n=183)	Clopidogrel (n=239)	p value
Combined MACE	4 (0.9)	2 (1.1)	2 (0.8)	0.788
Death	1 (0.2)	1 (0.5)	0	0.253
Non fatal MI	3 (0.7)	1 (0.5)	2 (0.8)	0.725
Stroke	0	0	0	1
Stent thrombosis	0	0	0	1

Abbreviations: MACE- major adverse cardiac event; MI- myocardial infarction.

4.3.2.3 Adverse bleeding events

Major adverse bleeding events were rare, with no fatal bleeding events or intracranial haemorrhages (Table 4.13). The incidence of documented TIMI or BARC defined bleeding was also rare at 1.7% and 2.8%, respectively (Table 4.13). The rates of bleeding on ticagrelor compared to clopidogrel as classified by the TIMI definition (2.2% vs 1.3%, p=0.458) and BARC definitions (3.3% vs 2.5%, p=0.638) were similar (Table 4.13). There was one TIMI major bleed from the gastrointestinal tract associated with a haemoglobin drop of 5 g/dL and requiring transfusion in the clopidogrel group. None of the bleeds classified as TIMI minor had a haemoglobin drops >3 g/dL but required investigation or intervention and included gastrointestinal, genitourinary, epistaxis and access site bleeds, along with a bleed into a knee joint.

Table 4.13 Bleeding events between hospital discharge and follow up at 30 days post enrolment

non-CABG bleeding	All (N=422)	Ticagrelor (n=183)	Clopidogrel (n=239)	p value
Fatal bleeding	0	0	0	1
Intracranial haemorrhage	0	0	0	1
Haemoglobin (Hb) drop ≥ 5 g/dL	1 (0.2)	0	1 (0.4)	0.381
Overt with Hb drop >3, <5 g/dL	0	0	0	1
Transfusion	1 (0.2)	0	1 (0.4)	0.381
TIMI classification	7 (1.7)	4 (2.2)	3 (1.3)	0.458
Major	1 (0.2)	0	1 (0.4)	0.381
Minor	6 (1.4)	4 (2.2)	2 (0.8)	0.246
BARC classification	12 (2.8)	6 (3.3)	6 (2.5)	0.638
2	11 (2.6)	6 (3.3)	5 (2.1)	0.448
3A	0	0	0	1
3B	1 (0.2)	0	1 (0.4)	0.381
3C	0	0	0	1

Abbreviations: non-CABG- non-coronary artery bypass grafting; Hb- haemoglobin; TIMI- Thrombolysis in Myocardial Infarction; BARC- Bleeding Academic Research Consortium

Table 4.14 Site of bleeding events between hospital discharge and follow up at 30 days post enrolment

non-CABG bleeding	All (N=11)	Ticagrelor (n=6)	Clopidogrel (n=5)	p value
Site of bleeding				0.279
Gastrointestinal	3 (27.3)	1 (16.7)	2 (40.0)	
Genitourinary	2 (18.2)	1 (16.7)	1 (20.0)	
Access site	2 (18.2)	2 (33.3)	0	
Epistaxis	1 (9.1)	1 (16.7)	0	
Cutaneous	2 (18.2)	0	2 (40.0)	
Other	1 (9.1)	1 (16.7)	0	

Abbreviations: non-CABG- non-coronary artery bypass grafting

4.3.2.4 Dyspnoea

Dyspnoea following hospital discharge was common (34.1%). Patients treated with ticagrelor reported dyspnoea more frequently (43.3%) than patients treated with clopidogrel (27.1%, p<0.0001), shown in Table 4.15. In a subgroup of patients asked "is this a change to how your breathing was prior to your admission?" (n=286), 52 (41.9%) patients treated with ticagrelor reported new or worsened dyspnoea as a change since hospital admission compared to 35 (21.6%) of patients treated with clopidogrel (p<0.0001). Discontinuation of therapy due to dyspnoea was rare and only occurred in ticagrelor patients (1.7%, p=0.046).

Table 4.15 Incidence of dyspnoea between hospital discharge and follow up at 30 days post enrolment

Dyspnoea	All (N=416)	Ticagrelor (n=180)	Clopidogrel (n=236)	p value
Dyspnoea	142 (34.1)	78 (43.3)	64 (27.1)	**0.001**
	N=286	**n=124**	**n=162**	
Worse since hospital admission	87 (30.4)	52 (41.9)	35 (21.6)	**<0.0001**
Leading to discontinuation	3 (0.7)	3 (1.7)	0	**0.046**

4.3.2.5 Discontinuation

DAPT discontinuation between hospital discharge and 30 days post enrolment occurred in only 4.0% of patients and was not significantly different between ticagrelor and clopidogrel treated patients, as show in Table 4.16. Therapy was primarily discontinued primarily because of patient management strategy: anticoagulation, CABG, other surgery or an alternate diagnosis (76.5%). Discontinuation due to adverse effects including dyspnoea and tinnitus was less frequent (23.5%), occurring in patients treated with ticagrelor, who were subsequently switched to clopidogrel. There was no antiplatelet discontinuation due to bleeding. Reasons for ticagrelor or clopidogrel discontinuation were not significantly different and were all the decision of a medical practitioner.

Table 4.16 Proportion of DAPT discontinuation between hospital discharge and follow up at 30 days post enrolment

Discontinuation	All (N=421)	Ticagrelor (n=182)	Clopidogrel (n=239)	p value
Total	17 (4.0)	9 (4.9)	8 (3.3)	0.409
Reason	N=17	n=9	n=8	0.195
Bleeding	0	0	0	
Dyspnoea	3 (17.6)	3 (33.3)	0	
Other adverse effect	1 (5.9)	1 (11.1)	0	
Anticoagulation started	1 (5.9)	0	1 (12.5)	
CABG	10 (58.8)	4 (44.4)	6 (75.0)	
Other surgery	1 (5.9)	0	1 (12.5)	
Alternate diagnosis	1 (5.9)	1 (11.1)	0	
Decision made by				1
Medical practitioner	17 (100)	9 (100)	8 (100)	
Patient	0	0	0	

4.4 Discussion

We have demonstrated in a real world cohort of ACS patients that bleeding rates on ticagrelor and clopidogrel within 30 days of study enrolment were low and were not significantly different. At 30 day follow up, significantly more patients treated with ticagrelor reported dyspnoea, however discontinuation of the drug due to dyspnoea was infrequent. Ticagrelor and clopidogrel therapy is primarily discontinued due to patient management strategies rather than adverse events associated with therapy. These findings suggest the safety and tolerability of ticagrelor in a real world ACS population is similar to that of clopidogrel.

In hospital bleeding

The rate of total TIMI bleeding in hospital was similar between ticagrelor and clopidogrel treated patients (1.4% vs 1.3%, respectively, p=0.950). Whilst numerically greater, the rate of total BARC classified bleeding in hospital in ticagrelor (4.5%) versus clopidogrel (2.3%) patients was not significantly different (p=0.146). However, the incidence of BARC type 2 bleeding was significantly greater in ticagrelor treated patients (4.1% vs 1.3%, p=0.041). Increased BARC type 2 bleeding without TIMI major or BARC type 3b/3c bleeding events, suggests that many documented ticagrelor bleeding events were fairly minor in nature. The significantly lower CRUSADE scores of the ticagrelor group (25 ± 9 vs 28 ± 12, p=0.001) may have contributed to reduced bleeding severity, although the average CRUSADE scores for both the ticagrelor and clopidogrel groups were within the low risk bleeding risk category.

The in-hospital bleeding rates in both groups in our cohort were relatively low. In the GRAPE ACS registry of PCI patients, BARC classified in hospital bleeding events occurred in 8.8% of patients [144]. Our lower bleeding incidence may be due to the exclusion of patients administered GP IIb/IIIa antagonists within 7 days of enrolment, as these agents are associated with increased bleeding risk in ACS patients [100]. Furthermore, in our study the majority of angiography (88.1%)

was performed via a radial route, and this has also been associated with a decreased bleeding risk in ACS patients [145].

In the PLATO trial the rate of non-CABG related TIMI major bleeding was significantly higher in ticagrelor vs clopidogrel treated ACS patients (2.8% vs 2.2%, respectively, p=0.02). This led to concerns that in a real world population, more bleeding may be seen in those treated with ticagrelor. We did not observe this in the present study. Our results are consistent with the GRAPE registry of ACS patients undergoing PCI, which reported in-hospital BARC ≥2 bleeding rates that were not significantly different between clopidogrel and ticagrelor or prasugrel treated patients [146]. An Australian ACS registry of PCI patients has also reported lower rates of TIMI major and minor bleeding with ticagrelor than in the PLATO trial. Lower bleeding rates in registries reflects the prescription of ticagrelor selectively in the real world, where clinicians avoid prescribing ticagrelor to patients with higher bleeding risk in accordance with guidelines and bleeding risk scores [147].

Bleeding between hospital discharge and 30 day follow up

The rate of total TIMI bleeding between hospital discharge and 30 day follow up was not significantly different between ticagrelor and clopidogrel treated patients (2.2% vs 1.3%, respectively, p=0.458). Nor was the rate of bleeding as defined by BARC classification, occurring in 3.3% of ticagrelor patients and 2.5% of clopidogrel patients (p=0.638). Although the TIMI and PLATO trial bleeding definitions are slightly different, our results are consistent with the rates of non-CABG related major bleeding within 30 days not being significantly different between the ticagrelor and clopidogrel groups (2.5% vs 2.2%, respectively, p=0.23) in ACS patients in the PLATO trial [100]. The bleeding incidence was much greater in the GRAPE ACS registry of PCI patients, where BARC classified bleeding events occurred in 17.3% of patients between hospital discharge and 30 day follow up. However, the prevalence of bleeding was driven by BARC type 1 bleeding [144]. We excluded BARC type 1 bleeding from our analysis because it is not clinically meaningful. However, analysis of bleeding between hospital

discharge and 30 day follow up is problematic as it is self-reported and subject to individual thresholds of what a patient considers serious enough to seek medical attention. This affects bleeding classification.

Dyspnoea between hospital discharge and 30 day follow up

Dyspnoea following hospital discharge was common and was reported in significantly more patients treated with ticagrelor than clopidogrel (43.3% vs 27.0%, respectively, p=0.001). Due to the frequency with which patients were describing dyspnoea, we introduced a second question asking patients to state whether this was new or worse since their hospital admission. Significantly more patients treated with ticagrelor (41.9%) than clopidogrel (21.6%, p<0.0001) experiencing dyspnoea reported that it was new or worse. However, discontinuation of therapy due to dyspnoea was rare and only occurred in ticagrelor patients (1.7%, p=0.046).

Dyspnoea occurred in 14.5% of the ticagrelor group and 8.7% of the clopidogrel group in the PLATO trial of ACS patients, leading to treatment discontinuation in 0.9% and 0.1% of patients respectively. Much of the excess dyspnoea associated with ticagrelor use occurred early in the first month of treatment and was mild or moderate in intensity [102]. Our rates of reported dyspnoea for both ticagrelor and clopidogrel are 3-fold higher than reported in the PLATO trial. Other studies on real world ACS patients undergoing PCI treated with ticagrelor have also reported a higher incidence of dyspnoea than the PLATO trial (22.6% vs 14.5%) and subsequent withdrawal of ticagrelor (9.1% vs 0.9%, respectively). Yet while 22.6% of patients suffered from dyspnoea, ticagrelor was responsible for dyspnoea in only 16.7% of patients [148]. Dyspnoea is the third most common reported symptom in internal medicine and is experienced in 15-18% of adults ≥40 years and 25-37% of adults aged ≥70 years [149]. As the majority of dyspnoea we observed was not new or worse since patients admission, it is important not to attribute all dyspnoea in patients treated with ticagrelor to the drug. This is reflected in the low rate of ticagrelor discontinuation due to dyspnoea.

In hospital antiplatelet discontinuation

Discontinuation of ticagrelor and clopidogrel during hospital admission was common, occurring in 22.6% and 16.2% of patients respectively. The proportion and rationale for in hospital antiplatelet discontinuation was not significantly different. Ticagrelor and clopidogrel were predominantely discontinued due to patient management strategy. This most commonly involved CABG (61.0%) or an alternate diagnosis other than ACS (34.0%). There was only one case of therapy discontinuation due to an adverse event, where clopidogrel was discontinued after a patient suffered a TIMI minor bleeding event during hospital admission.

Our rates of antiplatelet discontinuation are not directly comparable to the PLATO trial and real world registries due to different treatment protocols and inclusion criteria. The PLATO clinical trial protocol recommended that the study drug be restarted as soon as possible after CABG and prior to hospital discharge [150]. Furthermore, the PLATO trial excluded ACS patients with a need for oral anticoagulation and stricter inclusion criteria coupled with classification according to investigators initial not final diagnosis, minimized study drug discontinuation [137]. Real world ACS registries are often comprised solely of PCI patients [144, 146, 147], which reduces antiplatelet discontinuation due to CABG or alternate diagnoses.

Switching antiplatelet agents post angiography was infrequent, occurring in 5.5% of patients. Significantly more patients were switched from clopidogrel to ticagrelor (7.1%) than from ticagrelor to clopidogrel (3.2%, p=0.049). Patients treated with ticagrelor were switched to clopidogrel because of management strategy (2.3%) or adverse effects (0.9%) which included tinnitus and reported dyspnoea coupled with a need for anticoagulation. The reason for switching clopidogrel patients to ticagrelor was not documented, but it may be reasonable to suggest that angiographic evidence of significant coronary disease was a contributing factor. In the GRAPE ACS PCI registry, antiplatelet switching occurred in 35.5% of patients. Patients were predominately switched from clopidogrel, 90.4%, with 50.3% switched to ticagrelor and 40.1% switched to prasugrel which

is available in Greece [144]. Our low rates of patient switching from clopidogrel to ticagrelor treatment post angiography are consistent with our rates of antiplatelet switching pre angiography in Chapter 2. This suggests ticagrelor switching is being under-utilised in our cohort.

Discontinuation between hospital discharge and 30 day follow up

Discontinuation of ticagrelor and clopidogrel between hospital discharge and 30 day follow up occurred in 4.0% of patients and was not significantly different between the drugs (4.9% vs 3.3%, respectively, p=0.409). Antiplatelet therapy was primarily discontinued because of patient management strategy (76.5%) including a need for anticoagulation, CABG, other surgery or an alternate diagnosis. Discontinuation due to adverse events was less frequent, 23.5%. Discontinuation due to dyspnoea occurred in three ticagrelor patients and ticagrelor was discontinued in one patient with tinnitus. These patients were all switched to clopidogrel. There was no discontinuation due to bleeding and all antiplatelet discontinuation was at the discretion of a medical practitioner.

The higher rate of non-CABG related bleeding and dyspnoea reported with ticagrelor seen in the PLATO trial, coupled with ticagrelor's bi-daily dosing regimen [91] led to concerns about the impact of this on patient compliance with therapy and the clinical consequences. The PARIS study of PCI patients demonstrated that DAPT disruption due to bleeding or patient non-compliance occurred in 2.1% of patients at 30 day follow up. Antiplatelet disruption between 0 and 7 days had a MACE hazard ratio of 7.04 (p<0.0001), while antiplatelet disruption between 8 and 30 days had a MACE hazard ratio of 2.17 (p=0.06) [151]. In the present study there was no antiplatelet discontinuation due to bleeding between hospital discharge and 30 day follow up and all antiplatelet discontinuation was at the discretion of a medical practitioner.

We have demonstrated low rates of bleeding in patients treated with ticagrelor, both in hospital and between hospital discharge and 30 day follow up that does not contribute to ticagrelor discontinuation. While ticagrelor use is associated

with significantly more reported dyspnoea, it did cause significantly greater rates of ticagrelor discontinuation. This demonstrates that the safety and tolerability of ticagrelor is similar to clopidogrel in a real world ACS population.

In hospital MACE

While this study was not designed to specifically look at ischaemic events, we observed that patients treated with ticagrelor experienced significantly lower combined in hospital MACE rates than patients treated with clopidogrel (4.5% vs 10.0%, p=0.019). This was primarily driven by a numerically lower rates of MI (4.1% vs 8.1%, p=0.064), which was predominantly comprised of periprocedural MI (91.2%). It should be noted that the clopidogrel group were older, and had higher risk (GRACE scores) that may have contributed to these observed differences. Our in-hospital MACE rate was relatively high. In the GRAPE ACS PCI registry in hospital MACE, defined as death, MI, definite or probable stent thrombosis, urgent revascularization or stroke, occurred in 2.4% of patients [144]. The majority of our events were periprocedural and these were defined according to the criteria in the 3rd Universal Definition of Myocardial Infarction [10]. Our routine measurement of high sensitivity troponin following each angiogram may have contributed to a higher detection rate of these events than described in other registries.

MACE between hospital discharge and 30 day follow up

This study was not powered to examine ischaemic events between hospital discharge and the 30 day follow up, which were infrequent with a similar incidence in patients treated with ticagrelor and clopidogrel (1.1% vs 0.8%, respectively, p=0.788). Our observed MACE rates were substantially lower than reported in the PLATO trial where MACE, defined as death from vascular causes, MI or stroke, occurred in 4.8% of ticagrelor patients and 5.4% clopidogrel patients within 30 days (p=0.045) [91]. However, we examined MACE incidence separately during hospital admission and between hospital discharge and 30 day follow up, as ticagrelor or clopidogrel therapy was discontinued in 100 patients. Our results

are more consistent with the GRAPE ACS PCI registry where MACE occurred in 4.1% of patients, 1.7% between hospital discharge and 30 day follow up [144]. This is consistent with time dependent risk of ischaemic events. In the ACUITY trial in ACS patients, MI had a dramatic early risk of death, with hazard ratios of 17.6 within two days, 8.2 within a week, before dropping to 2.9 within 30 days [65].

4.4.1 Limitations

Our study did not capture outcomes of every patient prescribed DAPT. We only enrolled patients presenting to or referred to Wellington Hospital for invasive management who had been adequately pre-treated with DAPT. This means that we have missed the outcomes of some of the highest risk patients (STEMIs undergoing primary PCI). We have also missed patients undertaking angiography at secondary centers not referred for intervention, who are likely to have had relatively lower risk.

Due to the numerous bleeding definitions in use, classifying bleeding can be problematic. We have used the TIMI and BARC so we can compare our results to the wider literature, but there are also numerous trial-specific definitions which can make direct comparisons difficult. Furthermore, classifying bleeding post discharge is complicated by patient self-reporting and different thresholds for what individuals consider serious enough to seek medical attention. As follow up was via telephone, we were unable to investigate dyspnoea further than asking whether it was new and hence were unable to establish the aetiology.

4.4.2 Conclusion

We have demonstrated in a real world cohort of ACS patients that bleeding rates on ticagrelor and clopidogrel within 30 days of study enrolment were low and were not significantly different. At 30 day follow up, significantly more patients treated with ticagrelor reported dyspnoea, however discontinuation of the drug due to dyspnoea was infrequent. Ticagrelor and clopidogrel therapy is primarily discontinued due to patient management strategies rather than adverse events associated with therapy. These results may alleviate concerns about substantially increased bleeding, dyspnoea and non-compliance rates in ticagrelor patients in the real world, outside a clinical trial population. These findings suggest the safety and tolerability of ticagrelor in a real world ACS population is similar to that of clopidogrel.

Chapter 5- Summary and future directions

5.1 Summary

5.1.1 Introduction

The PLATO trial demonstrated that ticagrelor significantly reduced the rate of death from vascular causes, MI and stroke in comparison to clopidogrel [91]. Ticagrelor's superior efficacy in the PLATO trial was in part attributed to ticagrelor's greater platelet inhibitory effect [92]. On the basis of the benefit shown in the PLATO trial, PHARMAC funded ticagrelor for use in patients with ACS in July 2013. Furthermore, national and international guidelines recommend using ticagrelor in moderate to high risk NSTEMI patients [16, 123, 132] and STEMI patients 24 hours post thrombolysis [110, 111].

The PLATO trial demonstrated ticagrelor's superior efficacy over clopidogrel was not at the expense of an increase in overall bleeding rates. However, there was a significant increase in non-CABG related bleeding events in ticagrelor patients [100]. Ticagrelor patients also reported significantly more dyspnoea than clopidogrel patients [102] and significantly greater proportion of ticagrelor patients discontinued the study drug due to adverse effects [91]. Increased incidence of adverse effects with ticagrelor coupled with a twice daily dosing regimen [137] led to concerns of the impact on patient compliance with ticagrelor therapy.

This thesis aimed to examine platelet reactivity, antiplatelet use, safety and tolerability of ticagrelor in comparison to clopidogrel. In Chapter 2, we examined the absolute values of residual platelet reactivity in patients treated with ticagrelor or clopidogrel and the extent to which ticagrelor reduced the incidence of HOTPR. In addition, we investigated whether clinical variables linked to HOTPR differed between ticagrelor and clopidogrel. In Chapter 3, we investigated clinical factors influencing prescription of clopidogrel over ticagrelor and whether this was driven by clinical risk. In Chapter 4, we examined adverse effects of antiplatelet therapy, bleeding and dyspnoea, and whether they contributed to therapy discontinuation within 30 days.

5.1.2 Chapter 2- Platelet reactivity

We have demonstrated that ticagrelor exerts more potent platelet inhibition than clopidogrel (30.3 AU vs 43.7 AU, p<0.0001). Ticagrelor's greater platelet inhibitory effect translates into a reduced proportion of patients with HOTPR compared to clopidogrel treated patients (15.9% vs 37.7%, p<0.0001). The incidence of HOTPR in clopidogrel is similar to that observed in a previous cohort of clopidogrel patients published by our research group [61]. Our rates of ticagrelor HOTPR are higher than previously published using MEA, but our larger ACS patient population comprising both STEMIs and NSTEMIs, and the timing of the platelet reactivity measure, differ [105-107]. As we measured residual platelet reactivity, we were unable to determine whether this HOTPR was due to a suboptimal magnitude of ticagrelor's antiplatelet effect.

We identified clopidogrel dosing regimen, renal insufficiency, STEMI and platelet count as drivers of HOTPR in patients treated with clopidogrel. BMI was higher in clopidogrel patients with HOTPR and a greater proportion of diabetic patients than non-diabetic patients had HOTPR, but neither of these relationships were statistically significant. All of these factors have been previously associated with HOTPR in clopidogrel patients [49, 116].

None of the factors associated with HOTPR in clopidogrel treated patients were statistically related to HOTPR in ticagrelor treated patients. A prior MI was the only factor that was statistically associated with HOTPR in our cohort. However, absolute values of platelet reactivity did not differ significantly between those with and without a prior MI, so the significance of this relationship is unclear. Further studies are required to investigate whether this is a consistent relationship. The only factor associated with ticagrelor HOTPR in the literature is STEMI in the setting of primary PCI [105, 109]. As we excluded STEMIs receiving primary PCI due to insufficient time between antiplatelet loading and platelet function testing, we did not observe this. The lower incidence and factors associated with HOTPR with ticagrelor treatment results in a more predictable antiplatelet effect than clopidogrel.

5.1.3 Chapter 3- Antiplatelet prescription

Patients treated with clopidogrel prior to angiography were older, more likely to have had a prior MI, present with STEMI, and had higher GRACE and CRUSADE risk scores. Increasing age and history of MI contributed to the higher GRACE scores onserved in clopidogrel patients. Decreasing creatinine clearance was a surrogate for age in the CRUSADE score. As the GRACE and CRUSADE risk scores share risk factors, they correlated modestly well in our patients. An implication of this is that it is difficult to identify a group of patients with high mortality/ ischaemic risk (GRACE score) who do not also have a high bleeding risk (CRUSADE score). Patients presenting with STEMI were also more frequently treated with clopidogrel prior to angiography.

This pattern of prescription conflicts with published national and international guidelines that recommend prescribing ticagrelor to moderate to high risk NSTEMI patients [16, 123] and to STEMI patients 24 hours post thrombolysis [110, 111]. Furthermore, antiplatelet switching was not common, occurring in 4.5% of patients, 91.7% of these being switched to ticagrelor.

Prescription of antiplatelet agent was in part determined by the hospital patients initially presented to. The proportion of patients prescribed ticagrelor ranged from 65.3% in Wellington, a tertiary center, to 7.8% in Wanganui, a secondary provincial hospital. The patient populations presenting to the different hospitals were not significantly different, except for the proportion of STEMIs. In the three secondary hospitals staffed by cardiologists, Hutt, Palmerston North and Hawkes Bay, increasing age, GRACE and CRUSADE risk scores and presenting with STEMI were still associated with clopidogrel prescription. We have also demonstrated slow adoption of ticagrelor between July 2013 and June 2015. There has only been a detectable increase from January 2015 and only from April 2015 have more than half the ACS patients been treated with ticagrelor.

Prescription of clopidogrel to patients with both high GRACE and CRUSADE risk scores suggests clinical factors associated with an elevated bleeding risk are

influencing clinician choice of antiplatelet agent more strongly than clinical factors associated with ischaemic risk. The slow uptake of ticagrelor use, coupled with the prescription of ticagrelor being, in part, determined by the hospital patients initially present to, and low rates of antiplatelet switching, suggests system inertia in adopting new therapeutic agents.

5.1.4 Chapter 4- Clinical outcomes

The incidence of total TIMI bleeding during hospital admission was similar between patients treated with ticagrelor and clopidogrel (1.4% vs 1.3, respectively). Whilst numerically greater, the rate of in hospital total BARC classified bleeding was not significantly different between the ticagrelor and clopidogrel groups (4.5% vs 2.3%, p=0.146). However, the incidence of BARC type 2 bleeding was significantly greater in patients treated with ticagrelor compared to clopidogrel (4.1% vs 1.3%, p=0.041). Increased BARC 2 bleeding without TIMI major or BARC type 3 bleeding events suggests that many documented bleeding events were fairly minor in nature. Exclusion of patients administered GP IIb/IIIa antagonists within 7 days of enrolment and angiography performed via a radial route may have contributed to our low documented bleeding incidence [100, 145]. Prescription of ticagrelor selectively in the real world to ACS patients with lower CRUSADE bleeding risk scores may also contribute [147]. The rates of total TIMI bleeding between hospital discharge and 30 day follow up in the ticagrelor and clopidogrel groups were 2.2% and 1.3% respectively and were not significantly different (p=0.458). Nor was the rate of BARC bleeding, occurring in 3.3% of ticagrelor patients and 2.5% of clopidogrel patients (p=0.638).

Dyspnoea following hospital discharge was common and was reported in significantly more patients treated with ticagrelor than clopidogrel (43.3% vs 27.0%, p=0.001). Significantly more ticagrelor patients (41.9%) compared to clopidogrel patients (21.6%, p<0.0001) reported that their dyspnoea was new or worse since hospital admission. As the majority of dyspnoea observed was not new or worse since patients hospital admission, it is important not to attribute all

dyspnoea in patients treated with ticagrelor to the drug. This was reflected in the low rate of ticagrelor discontinuation due to dyspnoea (1.7%).

Discontinuation of ticagrelor and clopidogrel therapy during hospital admission was common (22.6% and 16.2%, respectively, p=0.062), but was primarily due to patient management strategies, not adverse effects. Significantly more patients were switched from clopidogrel to ticagrelor (7.1% vs 3.2%, p=0.049), with adverse effects responsible for 0.9% of ticagrelor patients being switched to cloidogrel. It is reasonable to suggest the remaining patients were switched due to management strategy. Discontinuation of ticagrelor or clopidogrel between hospital discharge and 30 day follow up was not significantly different (4.9% vs 3.3%, p=0.409). Three ticagrelor patients were switched to clopidogrel due to dyspnoea and one due to tinnitus. There was no discontinuation due to bleeding or non-compliance.

While this study was not specifically designed to examine ischaemic events, we observed patients treated with ticagrelor experienced significantly lower MACE than patients treated with clopidogrel during hospital admission (4.5% vs 10.0%, p=0.019). This was primarily driven by numerically lower rates of MI (4.1% vs 8.1%, p=0.064), predominantely comprised of periprocedural MI (91.2%). The higher GRACE scores of the clopidogrel group and our routine measurement of high sensitivity troponin following each angiogram may have contributed to a higher detection rate than described in other ACS PCI registries [144]. MACE between hospital discharge and 30 day follow up were infrequent, with a similar incidence in patients treated with ticagrelor and clopidogrel (1.1% vs 0.8%, p=0.788), which was consistent with other ACS PCI registries [144].

Bleeding rates on ticagrelor and clopidogrel within 30 days of study enrolment were low and not significantly different. While ticagrelor use was associated with significantly more reported dyspnoea, discontinuation of the drug due to dyspnoea was infrequent. Ticagrelor and clopidogrel therapy is primarily discontinued due to patient management strategies rather than adverse effects associated with therapy. Bleeding, dyspnoea and twice daily dosing did not result

in patients treated with ticagrelor being non-compliant with therapy. These findings suggest the safety and tolerability of ticagrelor in a real world ACS population is similar to that of clopidogrel.

5.2 Implications

Greater platelet inhibition, a surrogate marker of antiplatelet efficacy, and reduced MACE without a significant increase in bleeding during hospital admission demonstrates ticagrelor's benefit over clopidogrel. Yet ticagrelor was only prescribed to 41.7% of patients over the two year study period. Given ticagrelor's ischaemic benefit without adverse effects that result in therapy discontinuation, we believe ticagrelor is being underused. Furthermore, there is a treatment paradox, where patients that are older, with a history of MI, present with STEMI, have higher GRACE and CRUSADE risk scores and who are essentially higher risk, are less likely to be prescribed the superior antiplatelet agent at time of angiography. This treatment practice conflicts with national and international guidelines of how to treat moderate to high risk patients [16, 110, 111, 123]. This may be due to system inertia in adopting new therapeutics or concerns about bleeding, dyspnoea and non-compliance in patients prescribed ticagrelor. We have demonstrated that bleeding in ticagrelor patients is fairly minor in nature and while there is an increased incidence in reported dyspnoea, it rarely causes therapy discontinuation. Furthermore, all patients treated with ticagrelor are compliant with their therapy.

5.3 Future directions

As the prescription of antiplatelet agent appears to be heavily influenced by the hospital patients present to, it is important to examine the factors contributing to this geographic treatment disparity. This could be explored by surveying the clinician's prescribing antiplatelet agents at both Wellington and referring hospitals. Questions could include patient scenarios of moderate to high risk NSTEMI patients and STEMI patients post thrombolysis, what antiplatelet the

clinicians' prescribe and their rational for their decision. Additional questions could examine clinicians' sources of information, for example treatment guidelines, clinical trials, observational studies, conferences, colleagues and/or pharmaceutical representatives. Alternatively a checklist could be implemented that identifies moderate to high risk patients, the antiplatelet agent prescribed and rationale for prescription. Checklists have been demonstrated to improve patient clinical outcomes in both New Zealand and international hospitals [112]. Suboptimal adherence to cardiovascular disease prevention guidelines has been associated with patient risk level assignment by clinicians [152]. Hence, educational interventions focused on improving clinician assessment of patient risk, coupled with clinical evidence for ticagrelor use, may reduce geographic disparities in care.

As national and international guidelines recommend DAPT to be prescribed for up to a year following an ACS [16, 110, 111, 123], it is important to examine clinical outcomes of patients treated with ticagrelor and clopidogrel in longer term follow up. Between one month and one year post MI, the risk of death is higher from a major bleeding event than from a recurrent MI (2.4 vs 1.4, respectively) [65]. This is reflected in the higher rate of non-CABG related bleeding documented in the PLATO trial only becoming statistically significant following 30 days of treatment [100]. In contrast, much of the excess dyspnoea associated with ticagrelor treatment in the PLATO trial occurred early in the first month of treatment [102]. Adherence to prescribed medication is higher among patients with acute conditions, in comparison to chronic diseases. Consistent adherence to medication in patients with chronic conditions drops dramatically after the first six months of therapy [153]. Patient follow up at one year post MI would also be more robust in capturing MACE, with the difference between the event rates in the ticagrelor and clopidogrel groups of the PLATO trial increasing over the one year trial period [91]. Patient follow up at one year is therefore warranted to examine whether bleeding and dyspnoea after 30 day follow up is an issue leading to therapy discontinuation or patient non-compliance with treatment in a real world population.

Ticagrelor has never been studied as adjunctive antiplatelet therapy to fibrinolytic therapy in a clinical trial. While administration of a potent antiplatelet agent such as ticagrelor in conjunction with fibrinolytic therapy may increase bleeding risk, it could also counterbalance the prothrombotic milieu of greater platelet activation induced by fibrinolyisis [6]. A delay in the onset of ticagrelor's antiplatelet action and subsequent HOTPR has been demonstrated in STEMI patients receiving primary PCI [105, 109]. HOTPR is also common in STEMI patients receiving thrombolytic therapy. In a small cohort of STEMI patients, treatment with ticagrelor early, post thrombolysis, was more effective in providing rapid, consistent and potent platelet inhibition and seemed to be well tolerated [154]. Off label ticagrelor administration in conjunction with thrombolysis has appeared to be safe in 44 patients [155]. Hence, a direct comparison between ticagrelor and clopidogrel in conjunction with fibrinolyic therapy in a large clinical trial is warranted. As we have demonstrated low rates of antiplatelet switching, if ticagrelor is able to be safely used alongside thrombolysis, this may increase the proportion of patients treated with ticagrelor.

5.4 Limitations

Our observational study carries limitations inherent in this type of study. The prescription of antiplatelet agent was at the discretion of the attending physicians. This meant our ticagrelor and clopidogrel patient groups differed both in size and composition of factors influencing clinical risk. Furthermore, the number of patients enrolled in our study was not large enough to be able to correct for the differences between the groups.

Patient follow up was conducted at 30 days post study enrolment. Prescription of DAPT is commonly for a year post ACS due to heightened clinical risk within this period. Hence, patient follow up one year post study enrolment is warranted. Due to the time restrictions of a Master's thesis, it was not possible in this study.

5.5 Conclusion

Ticagrelor exerts greater platelet inhibition than clopidogrel and reduces the proportion of patients with HOTPR. A prior MI is the only factor statistically associated with ticagrelor HOTPR. As the absolute values of platelet reactivity did not differ significantly by HOTPR, the significance of this relationship is unclear.

Patients treated with clopidogrel prior to angiography were significantly older, more likely to present with STEMI and had higher GRACE and CRUSADE risk scores. Prescription of antiplatelet agent was in part determined by the hospital patients initially presented to, despite similar patient populations presenting to each hospital. The adoption of ticagrelor into clinical practice has been slow, demonstrating system inertia in adopting new therapeutic agents.

Bleeding rates on ticagrelor and clopidogrel within 30 days of study enrolment were low and not significantly different. While ticagrelor use was associated with significantly higher rates of reported dyspnoea, discontinuation of the drug due to dyspnoea was infrequent. Ticagrelor and clopidogrel therapy is primarily discontinued due to patient management strategies rather than adverse effects associated with therapy. Bleeding, dyspnoea and twice daily dosing did not result in patients treated with ticagrelor being non-compliant with their therapy. These findings suggest the safety and tolerability of ticagrelor in a real world ACS population is similar to that of clopidogrel.

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