The outcomes of clopidogrel therapy in patients with ACS in Southern Tasmania

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School of Pharmacy

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Declaration of Originality

This thesis contains no material that has been accepted for the award of any degree or diploma in any other tertiary institution.

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All research procedures reported in the thesis were approved by the Tasmania Health and Medical Human Research Ethics Committee or the Tasmanian Social Sciences Human Research Ethics Committee.

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Abbreviations

ACC/ACG/AHA	American College of Cardiology/American College of Gastroenterologists/American Heart Association
ACCF/AHA	American College of Cardiology Foundation and the American Heart Association
ACEI	angiotensin converting enzyme inhibitor
ACS	acute coronary syndromes
ADP	adenosine 5'-diphosphate
AF	atrial fibrillation
AR-DRG	Australian Refined Diagnosis Related Group
ARB	angiotensin II receptor blocker
ASA	acetylsalicylic acid
BMI	body mass index
BMS	bare metal stents
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel inhibitor
CHF	congestive heart failure
CI	contra indications
CK	creatine kinase
CSANZ	Cardiac Society of Australia and New Zealand
CV	cardiovascular
CYP450	cytochrome P450
DAT	dual antiplatelet therapy
DES	drug eluting stents
DHI	Diversity Health Institute
DMACS	Discharge Management of Acute Coronary Syndromes
DMR	digital medical record
ECG	electrocardiogram
EF	ejection fraction
FDA	Food and Drug Administration

GI	gastrointestinal
GORD	gastro-oesophageal reflux disease
GP	glycoprotein
GTN	glyceryl trinitrate
HTPR	high on-treatment platelet reactivity
IPA	inhibition of platelet aggregation
LLA	lipid lowering agent
LMWH	low molecular weight heparin
LTPR	low on-treatment platelet reactivity
MAQ	Medication Adherence Questionnaire
MARS	Medication Adherence Report Scale
MI	myocardial infarction
NHF	National Heart Foundation
NSAID	non-steroidal anti-inflammatory drug
NSTEACS	non-ST-elevation acute coronary syndromes
NSTEMI	non–ST-segment elevation myocardial infarction
OR	odds ratio
PBS	Pharmaceutical Benefits Scheme
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PON1	paraoxonase 1
PPI	proton pump inhibitor
PTCA	percutaneous transluminal coronary angioplasty
PVD	peripheral vascular disease
RF	risk factor
RHH	Royal Hobart Hospital
SD	standard deviation
SNP	single-nucleotide polymorphism
SPSS	Statistical Package for the Social Sciences
SSRI	selective serotonin re-uptake inhibitor
STEMI	ST-segment elevation myocardial infarction
TGA	Therapeutic Goods Administration

TIA	transient ischaemic attack
TSI	Torres Strait Islands
UA	unstable angina
VASP	vasodilator-stimulated phosphoprotein

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Abstract

Background: Clopidogrel has become an essential component in the management of acute coronary syndromes (ACS); however there is a significant variability in patient outcomes in relation to rethrombosis and major bleeding. Australian data regarding the use and outcomes of clopidogrel therapy are limited.

Objectives: Our study aimed to evaluate the rates of hospital readmission due to recurrent ACS or bleeding among patients with a first episode of ACS admitted to the Royal Hobart Hospital (RHH) and discharged taking clopidogrel, and to investigate the influence of a variety of factors including drug interactions, adherence and persistence with clopidogrel therapy, and cytochrome P450 genotype on the risk of readmission.

Method: In a retrospective observational study, patients discharged between 1 July 2007 and 31 December 2009 were identified and followed for 18 months for readmissions due to recurrent ACS or bleeding. Patients were then surveyed regarding their attitudes to, and experiences of, clopidogrel therapy; community pharmacy dispensing records were used to assess adherence and persistence; and cytochrome P450 2C19 genotypes were determined. Adherence was defined as the degree in which patients take medications as prescribed, while persistence referred to whether the patient stayed on therapy for the duration planned. Statistical analysis was then used to determine the relative influence of each potential contributing factor on the risk of readmission due to recurrent ACS and bleeding.

Results: Thirty-three of the 297 patients identified (11.1%) were readmitted to the RHH for recurrent ACS and nine (3.0%) for bleeding. None of the factors investigated significantly influenced the likelihood of readmission for ACS. Patients taking antiplatelet agents plus other medications that increase the risk of bleeding had a higher risk of a bleeding-related readmission ($p < 0.05$). Though the proportion of patients who were persistent with clopidogrel therapy was high (73%), the rate of early discontinuation of the therapy was concerning (27%). The proportion of patients who were adherent was also low (55%). Patients with CYP450 2C19*17 (19 out of 50 patients) demonstrated an increased risk of bleeding compared to the non-carriers (16% vs 0%, $p= 0.022$).

Conclusions: Compared to previous studies, our study cohort demonstrated a slightly higher readmission rate due to ACS but a lower rate of bleeding. Concerns remain regarding the concomitant use of drugs that increase the risk of bleeding, as well as the use of gastroprotective agents in patients with a high risk of haemorrhage. The level of adherence and persistence with clopidogrel therapy was also concerning. Larger studies are required to determine the relationship between CYP450 2C19 status and the risk of major bleeding.

Chapter 1 – Introduction

1.1 Clopidogrel

Clopidogrel, as an antiplatelet agent, has been used to prevent thrombotic events with various manifestations including coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD)[1 2]. It is estimated that more than 40 million patients worldwide receive clopidogrel, with global selling reported to be more than 9 billion USD per year [3 4 5]. In Australia, the utilisation of this drug has risen considerably since it was first introduced onto the Pharmaceutical Benefits Scheme (PBS) in 2000[6]. In 2010, almost $191 million government expenditure had been spent for clopidogrel, making this medication the third most expensive medicine by cost to the government[7]. In term of its efficacy compared to the established antiplatelet drugs, clopidogrel is superior to aspirin in patients with atherosclerotic vascular disease in reducing adverse cardiovascular outcomes[8 9]. Despite its efficacy as a modern-day antiplatelet therapy, a substantial number of patients are still experiencing a recurrent cardiovascular (CV) event during the first year of treatment with clopidogrel[10 11]. The drug has been linked with several limitations, including a delayed onset of action, irreversibility of its antiplatelet effect and a wide inter-patient variability in response[1 12 13]. It is believed that a number of mechanisms may contribute to the variable response to clopidogrel, although not all of these have been fully elucidated.

1.1.1 Pharmacology

Clopidogrel is an inactive prodrug which requires metabolic activation into its active thiol metabolite in order to exert its antiplatelet action (Fig. 1)[14-16]. Prior to its metabolism, clopidogrel undergoes active enteric absorption modulated by the intestinal efflux transporter P-glycoprotein (which is coded for on the ABCB1 gene)[14 17]. Almost 85% of the administered dose of clopidogrel is converted to an inactive metabolite, the carboxylic acid derivative, by ubiquitous plasma esterases[1 15 18-20]. Thus, only the remaining 15% of the dose is then bioactivated through the two sequential cytochrome-dependent oxidative steps[1 14]. The metabolism process involves a series of different hepatic cytochrome P450

(CYP450) isoenzymes, including CYP2C1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5[21-24]. The first step of clopidogrel activation leads to the formation of 2-oxo-clopidogrel, which is then metabolised to the active thiol metabolite[14 15 20]. This active form of clopidogrel then selectively and irreversibly blocks the adenosine 5'-diphosphate (ADP) receptor P2RY12 on platelets[16 25-27], which causes the inactivation of the glycoprotein (GP) IIb/IIIa receptor. The inactivation of this fibrinogen receptor then results in the antiaggregant effects of clopidogrel. The maximal inhibition of platelet aggregation (IPA) caused by clopidogrel ranges from 40%-60%[28 29]. A recent study suggested that paraoxonase 1 (PON1) may also be involved in clopidogrel activation[30]. Nonetheless, data regarding the exact mechanism involving PON1 are still lacking.

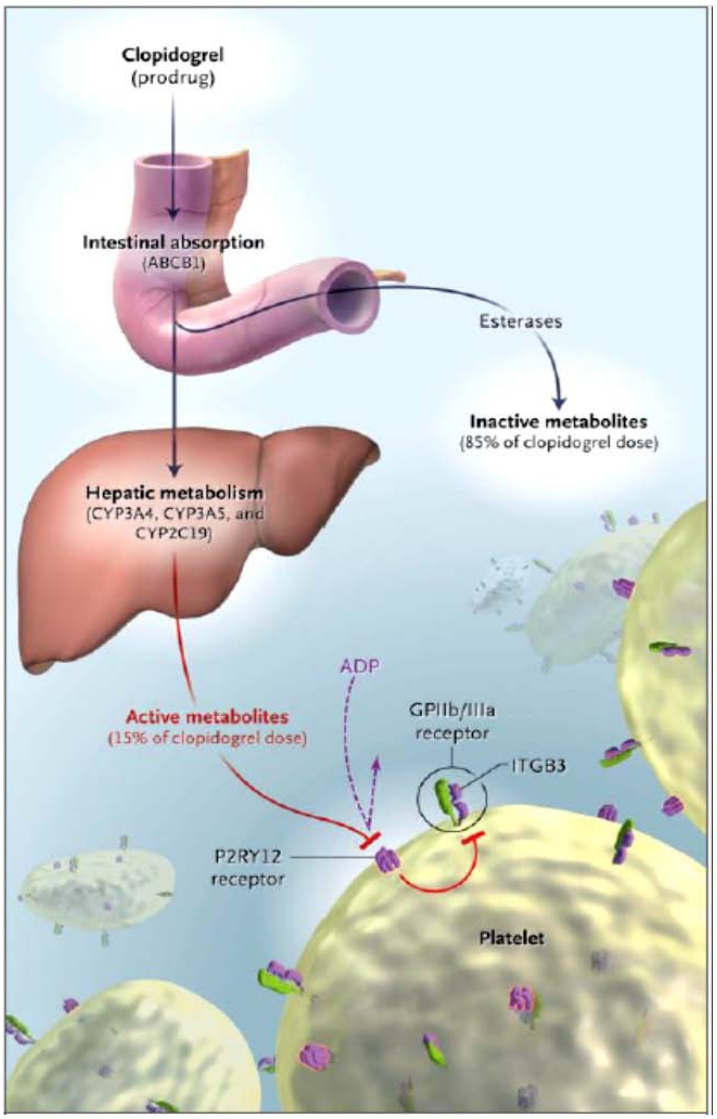


Figure 1.1 Clopidogrel bioactivation pathways (taken from Simon et al., 2009)[24]

1.1.2 Dosage and duration of treatment

Ex vivo studies show that clopidogrel produces its antiaggregating activity within 2 hours of a 75mg dose being administered[31] and achieves a steady state level after 3-7 days of daily administration of this dose[28]. Even after reaching steady state, however, interindividual variations in levels of IPA still occur[32-34]. Due to its metabolic activation that causes the slow onset of action of clopidogrel, a loading dose is required to reduce the time needed for to produce its activity. The regulatory bodies (e.g. US Food and Drug Administration (FDA), Australian Therapeutic Goods Administration (TGA)) approved the 300mg loading dose of clopidogrel and the maintenance dose of 75mg per day. Nonetheless, research regarding the optimal loading dose of clopidogrel is still ongoing[35-37]. Several studies have reported that a 600mg loading dose of clopidogrel produces a more effective and rapid antiplatelet effect compared to a 300mg dose[38]. Studies have also reported that the administration of the 600mg loading dose among patients undergoing percutaneous coronary intervention (PCI) was associated with better clinical outcomes[39-41]. Following these findings, a bigger trial, the CURRENT/OASIS-7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes) trial, was designed in order to evaluate the optimal dosing regimens for clopidogrel among acute coronary syndromes (ACS) patients with PCI[1 42 43]. The trial results suggested that the use of a double dose of clopidogrel (a 600mg loading dose on day 1 followed by 150mg once daily for 7 days, then 75mg daily) produced a better outcome in patients who underwent PCI compared to the standard dose (300mg followed by 75mg)[43]. However, the results of this trial can only be applied to patients with certain conditions (e.g patients undergoing percutaneous coronary intervention)[42]. To date, there is still no large clinical trial conducted aiming to directly compare clopidogrel loading doses of 600mg and 300mg. Hence, the debate regarding the safety of administering the double dose of clopidogrel (a 600mg loading dose) still remains[36]. Also, the criteria of patients who need a higher clopidogrel loading dose have not yet been specified[36 42 44-46].

In addition, the duration for the optimal treatment with clopidogrel remains uncertain. The duration highly depends on the differences in patients' conditions (e.g. type of stent implanted, the risk of bleedings, type of ACS)[46 47]. Table 1.1 shows the duration of clopidogrel treatment based on several clinical trials.

Table 1.1 Duration of clopidogrel treatment based on several clinical trials

Clinical trials	Patients' characteristics	Duration of clopidogrel treatment (average)
CURE[48]	NSTEACS patients	6 months
COMMIT[49]	STEMI patients	12 months
CHARISMA[50]	Patients with high atherothrombotic risk	24 months
PCI-CURE[51]	NSTEACS patients undergoing PCI	12 months
CREDO[52]	Patients undergoing PCI	12 months

1.1.3 Adverse outcomes

The most important adverse events occurring during the treatment of patients with clopidogrel is bleeding, which has been reported in both clinical trial studies[49 51 53 54] and real world studies[55 56]. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study found that about 3.7% of patients in their study had major bleeding (primarily gastrointestinal (GI) bleeding) with dual aspirin and clopidogrel treatment compared to 2.7% with placebo with aspirin[46 51 54]. Minor bleeding, such as epistaxis, haematuria and bruising, were also frequently reported in the clopidogrel group[46 51]. Lower rates of major bleeding were found in the ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), the CLopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (0.6%, 1.3% and 1.7% , respectively)[49 50 53 54]. Nonetheless, reports from clinical trials suggest that the benefit in using clopidogrel might outweigh the risk of major bleeding. In comparison with the risk of bleeding caused by aspirin, the result from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial showed that there was no statistical difference in the overall incidence of bleeding events in two treatment groups (9.27% for clopidogrel *vs* 9.28% for aspirin; $p = 0.98$)[9 57]. The results even showed a lower rate of any reported GI haemorrhage in the clopidogrel group than in the aspirin group (1.99% vs 2.66%; $p < 0.002$)[57 58].

However, fears regarding the concomitant use of clopidogrel with other antithrombotic agents have long been raised, with reports suggesting that the concurrent use of the medications may escalate the risk of haemorrhage[55 59 60]. The latest reports have also

expressed concerns about the increased risk of bleeding in patients who concurrently take selective serotonin re-uptake inhibitors (SSRIs) with clopidogrel[61].

1.2 Clopidogrel in the Management of ACS

Coronary artery disease is the most common cause of death worldwide[62 63], including in Australia[64 65]. The acute obstruction of a coronary artery typically results in ACS[66]. It was estimated that in 2009, there were about 80,000 hospitalisations for ACS in Australia[67]. ACS is associated with significant costs to the health care system, individuals, and society in general[67]. The common underlying cause of ACS is plaque disruption because of either atherosclerotic plaque rupture or endothelial erosion, leading to partial or complete occlusion of the coronary artery[66 68]. The clinical presentations of the disease range from ST-segment elevation myocardial infarction (STEMI), to non–ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA)[69-72]. In patients with STEMI or NSTEMI (classified as MI), the ischaemia causes myocardial damage which results in the release of a biomarker of myocardial necrosis into the circulation[73]. The electrocardiogram (ECG) results and the myocardial biomarker assist clinicians to distinguish STEMI and NSTEMI from UA. The biomarkers could be troponin T or I, or creatine kinase (CK)[73]. Furthermore, ECG tests will assist clinicians to detect the presence of ST-segment-elevation, thus diagnosing patients with STEMI. Patients are diagnosed with UA if the biomarker is not detected hours after the initial onset of ischemic chest pain[73]. NSTEMI and UA are often classified into a group called non-ST-elevation acute coronary syndromes (NSTEACS).

Patients who survive their initial episode of ACS are at high risk of having subsequent atherothrombotic events[74], the clinical consequences of which might include death, MI and stroke[48]. The activation and aggregation of platelets play an important role in the initiation and proliferation of this process[2 74 75]. Accordingly, effective antiplatelet therapy has become an essential component in the management of ACS, including those undergoing PCI with stent implantation[48 76].

Based on its mechanism of action, the most effective way in producing the antiaggregant activity is by inhibiting the closing pathway that ultimately leads to platelet activation[31].

Clopidogrel, as mentioned previously, acts in this manner and it has also has been proven to significantly improve the outcomes of patients with ACS[16 77].

Clopidogrel is commonly prescribed together with aspirin and the therapy is known as dual antiplatelet therapy (DAT). This combination has been shown to produce greater efficacy than aspirin alone in treating patients with ACS[31]. Furthermore, several trials have shown that DAT can significantly improve the outcomes of patients with ACS whether they are undergoing a PCI or not[53 77].

1.2.1 Clinical trials

Clopidogrel's approval was based on the clinical trial called CAPRIE[9], which was designed to assess the clinical efficacy and safety of clopidogrel compared to aspirin. The trial was performed among patients at risk of ischaemic events and the results were first published in 1998 not long after clopidogrel was approved[78]. Patients, who were followed for 1 to 3 years, were randomised to clopidogrel 75mg once a day or aspirin 325mg once a day. The study reported that clopidogrel was superior to aspirin by 8.7% (p=0.043) in reducing the incidence of ischaemic stroke, MI or vascular death[9].

Before clopidogrel became an option for treating patients with ACS, the use of aspirin in ACS patients had been widely accepted. Nonetheless, treatment with aspirin was reported to still result in a significant risk of death from cardiovascular events, recurrent infarction and ischaemia in ACS patients, either in the short or long term. Another group of antiplatelet medications that used to be a mainstay of ACS treatment, GP IIb/IIIa inhibitors, also did not show an improvement in treating patients with ACS. Long-term treatment with GP IIb/IIIa inhibitors was linked with increased mortality, no change in the incidence of MI and increased bleeding complications[79 80].

The use of clopidogrel for ACS patients received approval in 2002[81 82] after the results of the CURE trial were published. The study was a randomised trial assessing the benefit of adding clopidogrel to NSTEACS patients treated with aspirin. The study patients randomly received either clopidogrel with aspirin or placebo with aspirin for the duration of 3 to 12 months. Adverse events (e.g. ischaemic stroke, MI or vascular death) occurred in patients treated with clopidogrel and aspirin at a lower rate than in patients treated with placebo and aspirin (relative risk [RR] = 0.80, 95% confidence interval [CI] = 0.72-0.90); p<0.001).

Additionally, the results also showed that the use of clopidogrel and aspirin for 9 to 12 months in NSTEMI patients was able to minimise the relative risk of death from cardiovascular causes, non-fatal MI or stroke by 20% ($p < 0.001$).

Adding the list of clopidogrel indications in ACS patients, the CLARITY-TIMI 28 and COMMIT trials provided evidence for the combination use of clopidogrel and aspirin in patients with STEMI[31 53]. The CLARITY-TIMI 28 study was done in patients presenting within 12 hours after their onset of STEMI and who were planned to have PCI. The patients were randomised to therapy of a 300mg clopidogrel loading dose followed by 75mg per day, or placebo. All patients were treated with aspirin, heparin, and fibrinolytics and then underwent angioplasty. The results showed that the concomitant use of clopidogrel and aspirin yielded a beneficial effect in reducing further risk of thrombotic events (improving patient outcome) in the patients by 36% (odds ratio[OR] = 0.64, 95% CI = 0.53-0.76, $p < 0.001$). Despite also receiving thrombolytic therapy, the investigators did not find an increase in major bleeding among patients treated with DAT.

The use of DAT following PCI was also evaluated in the Clopidogrel for the Reduction of Events During Observation (CREDO) and PCI CURE trials. The CREDO trial, the largest clinical trial in this setting, compared the use of clopidogrel at a daily dose of 75mg for a long term (12 months) and short term (28 days) after stenting. Both groups of patients were also receiving aspirin during the study. At the study endpoint, it was found that patients receiving clopidogrel for long-term had a significantly reduced in risk of adverse ischaemic events compared with the group receiving clopidogrel for the short term (95% CI 3.9-44.4; $p = 0.02$).

The results from different clinical trials regarding the use of clopidogrel in ACS patients or patients undergoing PCI are summarised in Table 1.2.

Table 1.2 The results from different clinical trials regarding the use of clopidogrel in ACS patients or patients undergoing PCI

Clinical trial	Patients' characteristics	Study primary endpoint	Results	
			Clopidogrel group	Placebo/control group
CURE[77] (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events)	UA or NSTEMI patients	Death from CV causes, nonfatal MI, stroke or refractory ischaemia at 3 to 12 months	9.3%	11.4%
COMMIT[49] (Clopidogrel and Metoprolol in Myocardial Infarction Trial)	STEMI patients	Death from any cause, reinfarction or stroke at the first discharge from hospital or at day 28	9.2%	10.1%
CLARITY-TIMI[53] (Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction)	STEMI patients planned to have coronary angiography	Incidence of CV death, MI or occluded artery at 30 days	15.0%	21.7%
CREDO[52] (Clopidogrel for the Reduction of Events During Observation)	Patients planned to undergo elective PCI	Death, MI or stroke at 12 months after PCI	8.5%	11.5%
PCI-CURE[51] (Percutaneous Coronary Intervention - Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events	UA or NSTEMI patients undergoing PCI	CV death, MI or urgent target-vessel revascularisation (TVR) at 30 days after PCI	4.5%	6.4%

1.2.2 Guidelines

In Australia, the National Heart Foundation (NHF) of Australia and the Cardiac Society of Australia and New Zealand (CSANZ) published national guidelines for the management of ACS in 2006[83]. The guidelines, which were updated in 2007 and 2011, provided recommendations based on the clinical practice evidence that have been shown to improve the outcomes of patients with ACS.

According to the guidelines, patients diagnosed with ACS at hospital admission need to be treated immediately with oxygen therapy, aspirin, glyceryl trinitrate (GTN) and intravenous analgesics, whether or not a PCI is planned.

Furthermore, those diagnosed with STEMI are recommended to undergo early reperfusion therapy (PCI or fibrinolysis) within the first hours of hospital presentation and further started on DAT, unless it is contraindicated. PCI, which is described in section 1.2.3, is the preferred reperfusion therapy. However, if such therapy is not available, fibrinolysis should be delivered promptly. As an adjuvant to reperfusion therapy, the guidelines also recommended the use of antiplatelet agent(s) and anticoagulants (e.g. heparin) in STEMI patients.

The guidelines also recommended a PCI to be performed in patients with high risk NSTEACS, since evidence shows that this procedure will likely improve patients' outcome. As early medical management, NSTEACS patients are recommended to receive aspirin, clopidogrel, heparin or enoxaparin, intravenous GP IIb/IIIa inhibitors and a β-blocker.

Multiple medications are essential in managing patients with ACS, as each type of medication in the discharge regimen aims to reduce a different risk factor associated with cardiovascular disease. At discharge, the national guidelines emphasise all patients with ACS must receive long-term therapy with antiplatelet(s), a β-blocker, an angiotensin converting enzymes inhibitor (ACEI), an HMG-CoA reductase inhibitors (statin) and sublingual GTN, for the symptomatic treatment of future angina. It is stated in the guidelines that ACS patients, particularly those implanted with a stent, should receive clopidogrel for up to 12 months. However, it is added that the duration of time that patients need to take clopidogrel should be based on the type of stent implanted and the conditions of implantation.

Furthermore, all ACS patients are recommended to be referred to a cardiac rehabilitation program and receive lifestyle advice. Lifestyle advice includes information regarding diet and alcohol intake, encouragement for smoking cessation and regular physical activity, and a weight management plan for those noted to be obese.

1.2.3 Percutaneous Coronary Intervention

As mentioned previously, PCI is the preferred reperfusion therapy in managing patients with STEMI and those with high risk NSTEACS. The term PCI is also known as coronary angioplasty or percutaneous transluminal coronary angioplasty (PTCA)[84]. PCI procedures might result in patients having stent or not[84]. During the procedure, a balloon with or without a stent is inserted into a coronary artery[84]. This will enlarge the narrowed area of the artery by pushing aside the blockage caused by plaque[84]. At the end of the procedure, the balloon is removed[84]. For patients who require the implantation of a stent, there are two types of stents commonly used, bare metal stents (BMS) and drug eluting stents (DES). BMS, made from nickel-titanium alloy, provide structural support to help prevent the artery from re-narrowing (restenosis)[85]. DES, on the other hand, are bare metal stents coated with a certain drug, which also have the support advantages as BMS does[86]. The drug released continuously from DES is reported to benefit the patient by inhibiting the incidence of restenosis due to tissue growth[84 86]. The issues of restenosis are reported to occur less frequently among patients with DES than those with BMS[85-88].

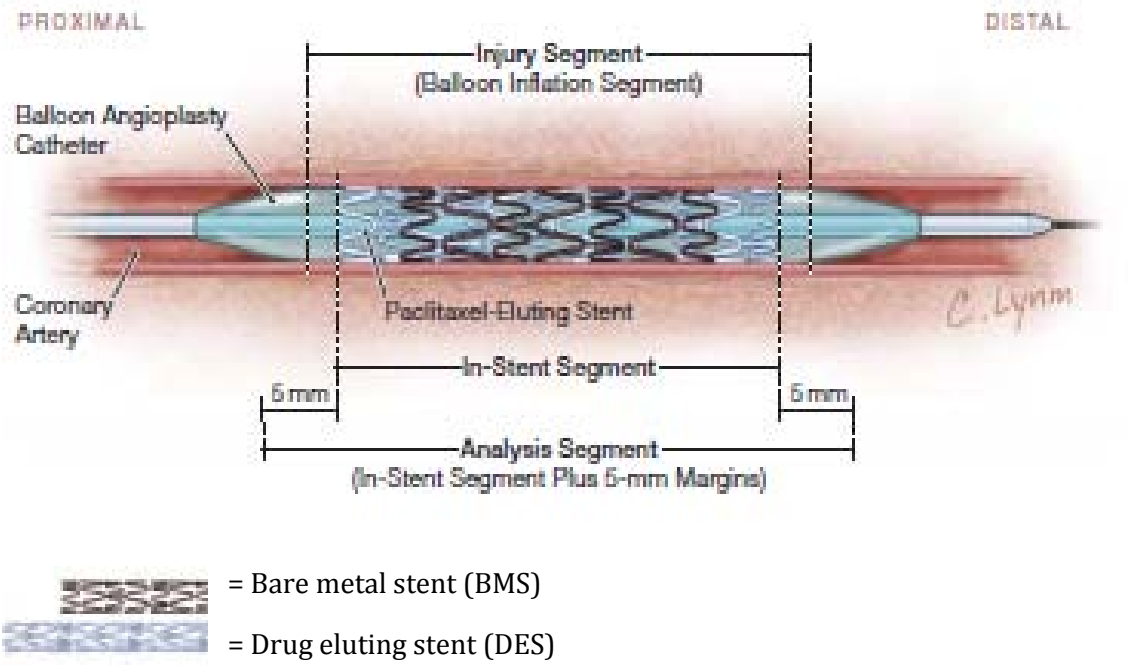


Figure 1.2 Bare metal stent vs. drug eluting stent (taken from Stone et al., 2006)[89]

The major limitation of performing coronary stenting is the risk of stent thrombosis (blood clot), which may lead to the complete blockage of the coronary artery[90-92]. Stent thrombosis may occur soon after stent is implanted (within 30 days), or later[84 92]. The reasons this occurs may be associated with malposition of the stent at the time the procedure is performed, the type of stent implanted, patients' resistance to antiplatelet therapy or, for late stent thrombosis, it may be due to discontinuation of aspirin or clopidogrel[93-96].

1.3 Variability in clopidogrel responsiveness

Despite a number of large clinical trials that have shown the effectiveness of clopidogrel as an anti-thrombotic agent (discussed more in section 1.2.1)[51 97 98], there is still a reasonable incidence of patients having CV events during clopidogrel treatment[99-101]. As stated earlier

in section 1.1, one of the limitations with clopidogrel treatment is the large interindividual variability in response[13 16 99]. Some early studies used the term of "clopidogrel resistance" in describing the individual variations in response to clopidogrel[1 13 31 76 99 102]. This concept was defined as the failure of the drug to achieve its pharmacological activity in blocking platelet activity, confirmed by laboratory measurements of platelet function[1 103 104]. The first study to report the incidence of clopidogrel resistance was done by Jaremo et al. in 2002[105]. The study was performed under laboratory circumstances, assessing patients' platelet activity by measuring ADP-evoked platelet fibrinogen binding using a flow cytometry technique. The results from the study suggested that some patients had a weak antiplatelet activity while others showed strong platelet inhibition after treatment with a 300mg clopidogrel loading dose and 75mg maintenance dose. Platelet reactivity among the study patients varied from 1%-58% before clopidogrel treatment and from 0%-29% after treatment. However, the study was limited by the small number of patients (n=18). Since then, larger studies trying to replicate the findings of the Jaremo et al. study have started to emerge[76 106]. The study performed by Serebruany et al. in 544 patients with various conditions – ranging from healthy people to those with stents, heart failure or stroke – confirmed the interindividual variability with clopidogrel treatment. The study, which measured participants' platelet function using flow cytometry and light-transmittance aggregometry, showed that the residual ADP-induced aggregation after clopidogrel treatment range from 3% to 84%. However, due to insufficient data regarding the standard laboratory method and the use of different assays for platelet activity testing, the term of resistance is not commonly used nowadays[3 101]. In this study, the terms "variable responsiveness" or "response variability" are used, indicating interindividual differences in response to clopidogrel based on patients' clinical outcomes.

Data regarding the variable response to clopidogrel have been well-established [99 107], yet, the mechanisms behind this interindividual heterogeneity have not been fully elucidated. It is proposed, however, to be caused by multifactorial mechanisms[1 3 12 101]. Reports indicate that factors contributing to variability in the clopidogrel response relate to metabolic, genetic, cellular and clinical factors[3 18 101 104] (Figure 1.2). In the ex vivo study conducted by Shuldiner et al., it was suggested that approximately 22% of the variation in clopidogrel response is related to age, body mass index (BMI), lipid levels, and genetics[108].

The results also suggested that genetic polymorphism might account for about 12% of the variability[108].

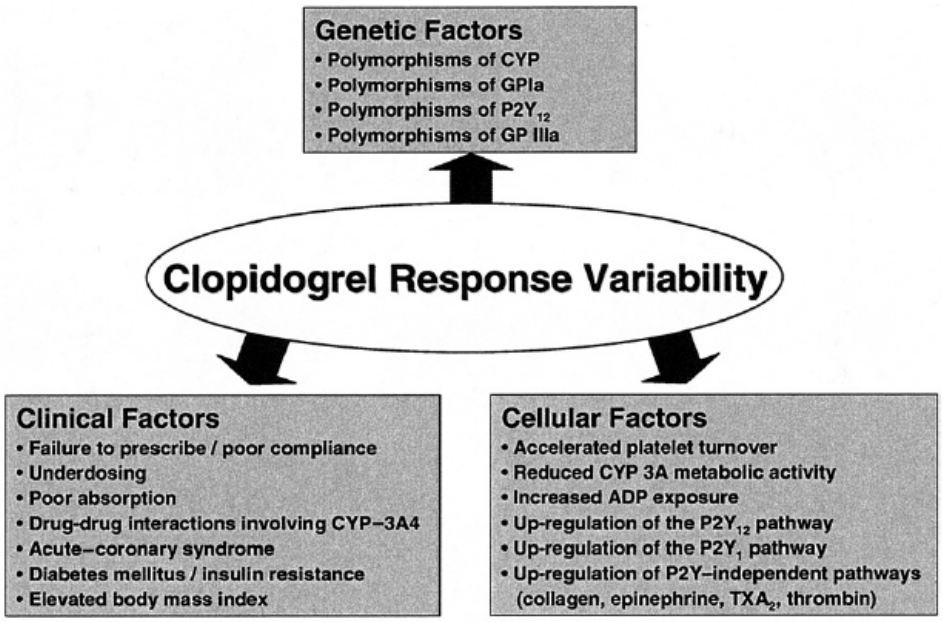


Figure 1.3 Clopidogrel response variability (taken from Angiolillo et al., 2009)[1]

Several factors associated with the variability in clopidogrel response, namely platelet function and patients' underlying comorbidities, drug interactions, genetic polymorphisms and adherence, are discussed below.

1.3.1 Platelet function and underlying diseases

Platelets are suggested to play the key role in ischaemic complications, particularly in those undergoing stent implantation[109-111]. Therefore, an effective anti-platelet represents a foundation therapy in preventing such events. Platelet function testing is one of the parameters used to indicate the responsiveness to, and clinical effectiveness of, antiplatelet drugs[112 113]. The standard platelet reactivity method is assessment by light transmittance aggregometry[112]. This method measures ADP-stimulated platelet aggregation in whole blood or platelet-rich plasma[113]. Another technique that is also commonly used is based on the measurement of phosphorylation of vasodilator-stimulated phosphoprotein (VASP) in whole blood[113]. The newest test, the Verify Now

P2Y12 assay, is similar to VASP[101 113]. The new analysis techniques are assumed to be more accurate in predicting clopidogrel responsiveness in patients[101]. The earlier studies assessing the variable response to clopidogrel were based on assessing platelet activity in the ex vivo setting[13]. During the early investigations, there was more focus on describing the phenomenon than on assessing the factors that contribute to the variability and the implications of the variability on the clinical outcome. From various platelet function tests, it was reported that a significant number of patients treated with clopidogrel are unable to reach an optimal level of platelet reactivity inhibition[3 100]. This was identified even in patients receiving a high loading dose of clopidogrel[3 100]. A recent paper by Camilleri et al. highlighted the critical role of patients' baseline platelet activity in causing the variability among patients treated with clopidogrel, suggesting the term 'high on-treatment platelet reactivity' (HTPR) in defining the variability[100]. Several studies have shown that patients' high platelet reactivity after treatment with clopidogrel following stent implantation is one predictor of an increased risk of thrombotic events at short- and long-term follow-up [110 112 114]. In addition, Migliorini et al. performed a study which looked at the impact of HTPR following clopidogrel treatment and the clinical outcome[112]. The study reported that patients in the HTPR group continued to have an increased rate of cardiac mortality or stent thrombosis during the observation time compared with patients with low on-treatment platelet reactivity (LTPR)[112]. Other studies, including a recent meta-analysis, have confirmed this finding[99 109]. Despite the potential importance of platelet function in determining the outcome of clopidogrel therapy, platelet tests are currently not commonly recommended or performed.

Patients' medical conditions are also important in predicting their response to clopidogrel[102], since the outcomes of therapy may be affected by their underlying disease or other risk factors (e.g. BMI, smoking).

A study conducted by Geisler et al., which investigated the clinical factors that affect patients' platelet aggregation, suggested several clinical variables were associated with a high residual platelet aggregation. The variables include an advanced age (> 65 years), ACS, diabetes mellitus, renal failure, and reduced left ventricular function[115]. The study also detailed a scoring tool to predict platelet reactivity after stent placement; the Residual Platelet Aggregation after Deployment of Intracoronary Stent (PREDICT) score. The

investigators offered this score as a tool to assist identifying atherothrombotic risk and individualising antiplatelet therapy.

From its pathophysiology, patients with diabetes have an increased tendency for atherosclerosis and higher platelet reactivity, the latter of which results in premature CAD[116-118]. The addition of clopidogrel to aspirin improves the outcome of ischaemic events in diabetic patients[118]. However, compared with non-diabetic patients, several studies have shown that patients with diabetes still experience enhanced platelet reactivity and reduced in vitro responsiveness after the treatment with an antiplatelet, either in the short or long term[116 118-121]. Thus, it is predicted to exacerbate patients' outcome[116 118-122]. It has been suggested, moreover, that patients with diabetes have higher platelet aggregation at baseline, therefore predisposing to a poor response to clopidogrel therapy in comparison with non-diabetic patients[102]. Other studies, which did not take into account platelet function, have also found that ACS patients who have diabetes mellitus are at higher risk of developing other cardiac events such recurrent ischaemic event, congestive heart failure (CHF) and arrhythmias after their initial ACS episode[114 118 119 121].

Obesity may also contribute to a poor response to clopidogrel. Several studies have reported that the administration of clopidogrel did not result in optimum platelet inhibition in overweight patients (body mass index (BMI) ≥ 25 kg/m^2) in comparison with patients with normal weight[123 124].

The data regarding the effect of cigarette smoking on platelet inhibition after clopidogrel treatment have been inconsistent. Early ex vivo studies suggested that smoking is associated with increased platelet inhibition and lower aggregation in response to clopidogrel[125]. The mechanism behind this proposed theory is presumably by inducing CYP450 isoenzymes which are involved in the transformation of clopidogrel into its active metabolite[125]. A post hoc study that was conducted based on these findings showed that clopidogrel was significantly more effective at reducing the rate of cardiovascular death and MI among those who smoked 10 cigarettes/ day compared with those who did not[126]. However, recent studies disproved this theory by reporting that smoking does not affect platelet reactivity in patients treated with clopidogrel[127 128]. Presently, there is no definite conclusion regarding the impact of smoking on platelet activation or its clinical implication.

Regardless of its impact on platelet activity, cigarette smoking has been long known as one of the most important risk factor for coronary disease[129]. The toxins in cigarette have been proposed to be responsible in causing the development of atherosclerotic plaque (a progressive hardening of the arteries) in the arterial walls[129 130]. Atherosclerosis will subsequently impair blood flow and, make the artery less elastic and more vulnerable to rupture[129]. Cigarette smoking is also the most modifiable risk factor contributing to the cardiovascular disease[131 132].

1.3.2 Drug interactions

Among the many proposed theories for the variability in clopidogrel response are interactions when it is co-administered with other medications. Clopidogrel is more susceptible to drug interactions because it is a prodrug, thus any medication that undergoes metabolism via the same pathways will potentially affect its conversion into the active metabolite[113]. The interaction may then lead to poor clopidogrel responsiveness. As mentioned above, clopidogrel is activated by CYPP450 isoenzymes. Therefore, among drugs that are suspected to have an interaction with clopidogrel are drugs that also undergo CYP450 hepatic metabolism (Figure 1.4)[104 133].

In this section, however, only the drugs that commonly administered together with clopidogrel will be discussed further.

Among the drugs that have received attention for a possible interaction with clopidogrel are proton pump inhibitors (PPIs). PPIs share common metabolic pathways with clopidogrel in the liver via CYP2C19[134 135]. PPIs are often administered concomitantly with clopidogrel, or when patients are taking DAT[134 136], for the prophylaxis of GI bleeding[104 137]. This strategy is supported by several consensus guidelines[113 138]. Several studies have proposed that the interaction of these two drugs might be due to the competitive inhibition of CYP2C19 by PPIs which leads to the reduced conversion to the active metabolite of clopidogrel[136 137].

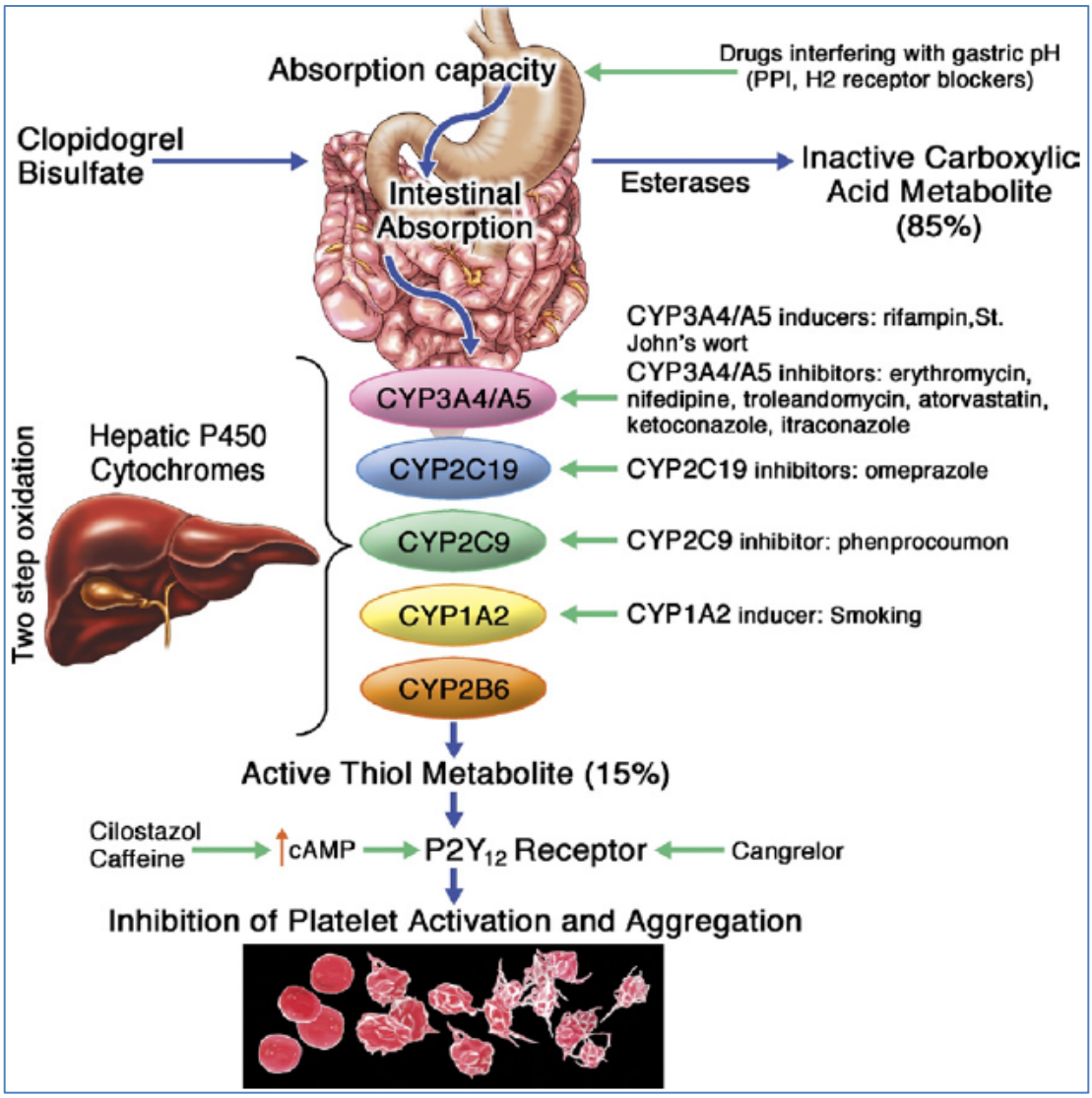


Figure 1.4 Clopidogrel – multiple pharmacodynamic drug interactions (taken from Bates et al., 2011)[133]

The American College of Cardiology/American College of Gastroenterologists/American Heart Association (ACCF/ACG/AHA) published a clinical expert consensus document in 2008 regarding the use of PPIs to minimise the risk of GI bleeding due to the use of antiplatelets and NSAIDs[138]. The guidelines recommended the use of PPIs for the therapy and prophylaxis of aspirin (ASA) related GI injury, particularly in patients who also take clopidogrel[104]. Patients with a history of GI bleeding who required DAT were also among those who were recommended to receive concomitant therapy with a PPI (Figure 1.5).[104]

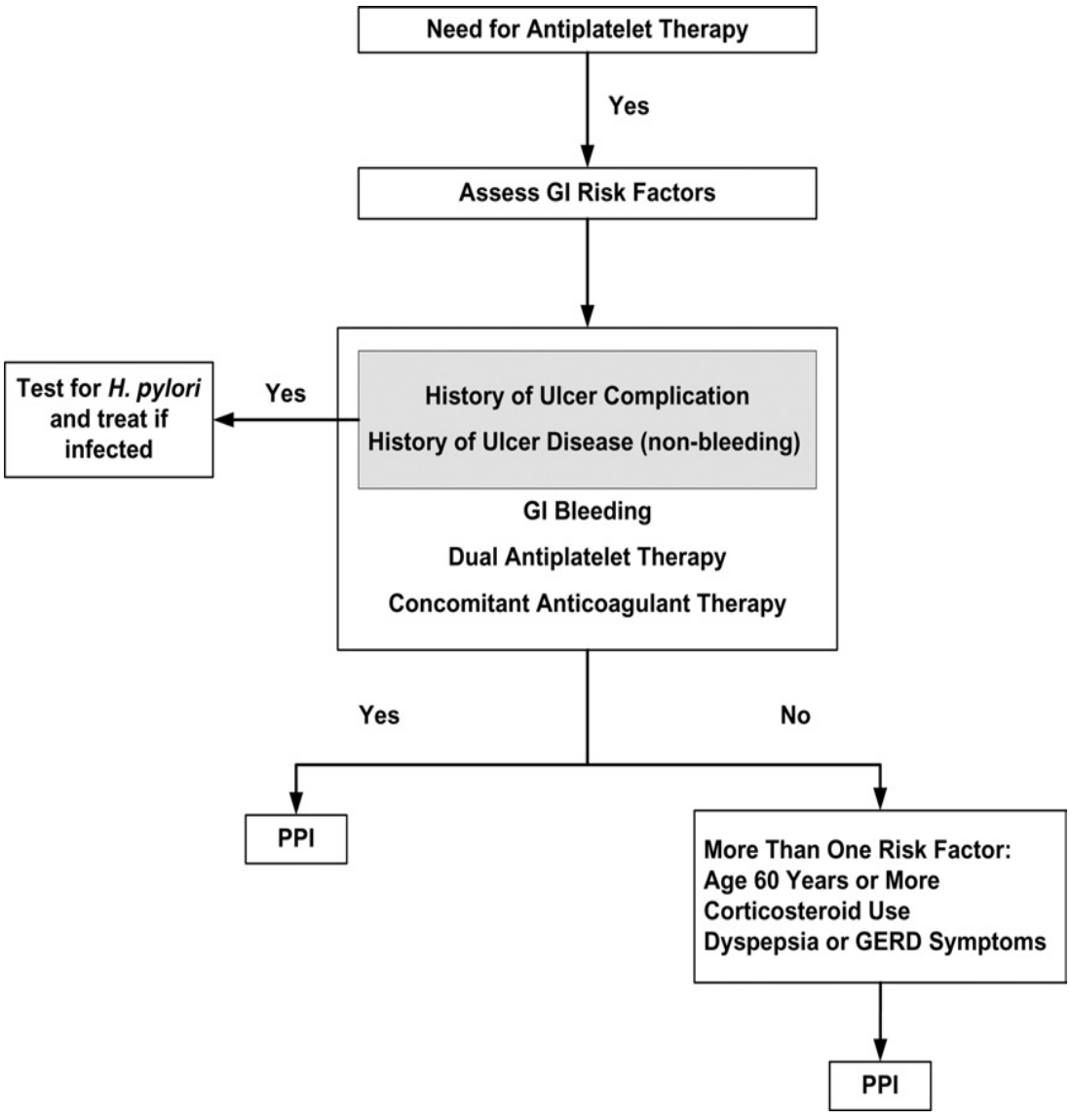


Figure 1.5 ACCF/ACG/AHA 2008 recommendation for PPI prescription[138]

Since the guidelines were published, observational studies started to emerge proposing the possible interaction between clopidogrel and PPIs which might increase the risk of adverse cardiac events among the patients. Recently, the numbers of studies reporting the higher risk of adverse outcomes due to the concurrent use of clopidogrel and PPIs have started to grow[134 139 140]. Ho et al. reported that rehospitalisation among patients with ACS is higher among patients who received clopidogrel and a PPI, compared with patients who only received clopidogrel[134]. On the other hand, findings from the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis In Myocardial Infarction 38) trial reported that there was no increased cardiovascular risk associated with concomitant use of clopidogrel and PPIs[141].

Despite the inconsistent results from these observational studies, the FDA released a safety alert in November 2009 recommending avoiding the use of omeprazole and esomeprazole with clopidogrel[142]. However, due to insufficient data, the FDA made no specific recommendations concerning other PPIs. Current findings have suggested that the drug interaction between clopidogrel and PPIs may be more important in those who carry normal CYP2C19 alleles than those with CYP2C19 loss-of-function alleles[143 144].

The most recent randomised clinical trial conducted by Bhatt et al. found that there was no increased risk of MI, stroke or CV death among patients receiving the combination of clopidogrel and omeprazole[145]. Up until now, there has been no definitive conclusion able to be drawn regarding the clopidogrel-PPI interaction as well as the interpretation of the interaction in clinical practice. Moreover, questions are still raised whether the possible interaction is applicable for every PPI or whether it is limited to certain PPI as data regarding the other PPIs, particularly pantoprazole, are less clear. The latest ACCF/ACG/AHA 2010 Expert Consensus Document acknowledged the possibility of interaction between clopidogrel and PPI[113]. However, the use of PPIs is still recommended in order to prevent the risk of GI bleeding, particularly in patients with a GI bleeding history and other additional risk factors (e.g., advanced age, concomitant use of warfarin, steroids, NSAIDs or *Helicobacter pylori* infection).

The other drugs that have been suspected to interact with clopidogrel are statins and calcium channel blockers (CCBs)[146-148]. The concern underlying these interactions is that these drugs are metabolised by CYP3A4, which is another isoenzyme involved in the activation of clopidogrel[133 147-149]. Despite the pharmacodynamic studies that have

reported evidence for this interaction, further studies did not show that it carried clinical consequences[133 150 151]. Current evidence suggests that statins can be safely used together with clopidogrel and evidence regarding interactions with CCBs is limited[152].

1.3.3 Genetics

Evidence has recently emerged reporting that variations in the metabolic processes involved in the activation of clopidogrel are one of the reasons for variability in clopidogrel response[24 153]. Besides playing a role in drug–drug interactions, the process is also prone to the interference of genetic polymorphisms[16]. As mentioned earlier, genetic polymorphisms have been considered to be a major contributor to the variability of the biologic antiplatelet activity of clopidogrel compared to other suspected factors[108]. The genes encoding the enzymes involved in the activation of clopidogrel are polymorphic[153], which can cause decreased or increased availability of the active form of clopidogrel[22 153].

Among the CYP450 subtype enzymes that are involved in clopidogrel metabolism (e.g. CYP3A4/5, CYP2C19, CYP2B6, and CYP1A2), studies have most commonly focussed on CYP2C19. The effects of other subtypes are less well established, with the current findings showing that CYP3A4, CYP3A5 and CYP2B6 have no association with the heterogeneity in clopidogrel responsiveness[101 154 155]. The polymorphism of CYP2C19, instead, can lead to substantial phenotypic variation in its activity and hence affect conversion of the inactive prodrug to its active metabolite[23 108 156]. Therefore, it is suggested that it may be a strong biological candidate to explain the variable response to clopidogrel[22 113 156].

The CYP2C19 gene is vastly polymorphic, with more than 25 variant alleles already identified[21]. The most common alleles reported to influence the outcome of clopidogrel are CYP2C19*1, CYP2C19*2, CYP2C19*3 and CYP2C19*17[21]. Depending on the allele present, laboratory demonstrations of the enzymatic activity of CYP2C19 can be normal, reduced, or increased[14 24 157]. The CYP2C19*1 allele, the normal or 'wild type' copy, is considered as an allele that has a normal function and has full enzymatic activity, while CYP2C19*2 and CYP2C19*3 are considered as loss-of-function alleles[25 157]. The presence of these alleles varies by ethnicity. In Caucasians, African Americans, and Asians, the proportion of patients who carry at least one copy of CYP2C19*2 is 15%-30%, 33%-40%, and 40-50%,

respectively, while the proportion for CYP2C19*3 is <1%, <1%, and 7%, respectively[22 24 108 157].

Individuals who are heterozygous for loss-of function alleles (e.g., CYP2C19*1/*2, CYP2C19*1/*3) are referred as "intermediate metabolisers," and those who are homozygous (e.g., CYP2C19*2/*2, CYP2C19*2/*3) are "poor metabolisers"[21 113]. In the intermediate metabolisers, platelet responsiveness to clopidogrel lies somewhere between the responsiveness in individuals who are normal metabolisers and that in those who are poor metabolisers[21]. It is proposed that the intermediate metabolisers have 26% to 31% lower exposure to the active metabolite of clopidogrel, and those who are poor metabolisers have 46% to 55% lower exposure compared with those with no CYP2C19 polymorphisms[22].

Hulot et al. were among the first to report an association between CYP2C19*2 genotype and reduced inhibition of ADP-stimulated platelet aggregation in response to clopidogrel[25]. Further investigations found that both CYP2C19*2 and CYP2C19*3 alleles are associated with this effect, which is presumably caused by the reduced formation of clopidogrel's active metabolite [22 25 108 113].

In relation to clinical response, substantial evidence shows that the possession of the CYP2C19*2 allele contributes to an increased risk of cardiovascular events in patients receiving clopidogrel, including an increased occurrence of stent thrombosis[22-25 108 158]. Additionally, Simon et al. reported that the presence of two variant alleles of CYP2C19 (*2, *3, *4 or *5) was linked to an increase in cardiovascular events among patients who underwent PCI by a factor of 3.6 compared to those with the CYP2C19*1 allele[24]. A study among patients taking clopidogrel along with aspirin following MI showed that those carrying the CYP2C19*2 genotype were more likely to experience a second cardiovascular event[108 158].

A conflicting finding was reported by Pare et al., who stated that the effect of clopidogrel compared with placebo in reducing the risk of adverse events (e.g. death, MI) was similar between carriers of loss-of-function alleles and non-carriers[159]. Therefore, the study suggested that the use of clopidogrel should not be excluded in patients with loss-of-function allele carrier status whose ACS condition is being managed conservatively.

The role of CYP2C19*17 has recently been understood, in that it is assumed to increase CYP2C19 activity[21-23] [153], CYP2C19*17 (e.g. CYP2C19*1/*17, CYP2C19*2/*17, CYP2C19*3/*17, CYP2C19*17/*17) is therefore considered as a gain-of-function allele[159]. The variant of CYP2C19*17 is present in nearly 40% of Caucasians, Blacks, and Asians[22]. In terms of metaboliser phenotype, those who are carriers of CYP2C19*1/*17 or CYP2C19*17/*17 are categorised as "rapid" or "ultra-metabolisers", while the phenotype of CYP2C19*2/*17 or CYP2C19*3/*17 are unknown[21]. This variant results in higher production of the active metabolite, and improves clopidogrel-induced platelet inhibition but may possibly increase the risk of bleeding complications[21 22 124 159 160]. However, the association of this allele with the risk of bleeding is still questionable and studies demonstrate conflicting results[24 108], with the evidence for improved clinical outcomes still insufficient[5 21 24 108].

Other CYP2C19 variant alleles (CYP2C19*4 - CYP2C19*8) are reported to be present in less than 1% of any ethnic population[21], and insufficient studies have been performed on these alleles to make any conclusions.

Regardless of the contradictory data, the FDA launched a boxed warning regarding the possible impact of genetic polymorphisms of CYP2C19 on the clinical outcome of clopidogrel in March 2010, particularly in poor metabolisers[161]. The warning implied that the benefit of individualising antiplatelet therapy based on genotype testing would result in improved patient outcomes.

Shortly after the warning issued by the FDA, the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) published their consensus document[157]. They highlighted that genotyping might not solve the issue of variable responses to clopidogrel, as the genetic polymorphisms only contribute to about 12% of the variability. However, the report did not rule out the possible impact of individual genetic polymorphisms on clopidogrel's clinical outcome, adding that genotyping may be considered to determine if a patient is a poor metaboliser in those who are at moderate or high risk for poor outcomes.

Still, recent reports regarding the impact of CYP2C19 as well as the importance of performing genotype testing are conflicting[5 21 157 162]. Up to this date, no randomised

controlled trial study regarding the impact of CYP2C19 allele carrier status on clopidogrel efficacy has been published.

Current evidence suggests that other polymorphisms may influence the response to clopidogrel. These include the adenosine 5′-triphosphate-binding cassette gene, ABCB1, which may partly contribute to the variability in clopidogrel responsiveness by affecting the oral bioavailability of clopidogrel[101]. The ADP receptors P2RY12 and GP IIb/IIIa have also been mentioned as playing a role in causing the biologic variability of clopidogrel[24]. Yet, the studies regarding whether allelic variants of P2RY12 are associated with varying antiaggregant activity of clopidogrel and their clinical significance are still conflicting[163-165]. Recently, another enzyme called paraoxonase-1 (PON1) was shown be crucial for the activation of clopidogrel[30 101 166]. However, the data are still limited and the potential therapeutic implications of PON1 polymorphisms require further investigation.

1.3.4 Adherence and persistence

Among the numerous factors proposed as possible reasons for the individual response variability to clopidogrel, non-adherence must also be considered. Poor adherence with any type of medication has been associated with increased health care expenditure, deterioration of disease, and death[167-172]. A study performed among patients with CHF by Miura et al. found that patients who were non-adherent to their medication had a 1.95 times higher risk of CV death than patients who regularly took their medication[170]. Moreover, those who stopped their β-blocker regimen were 5 times more likely to have a subsequent CHD event than those who persist with the therapy[170]. [169 170].

Different methods have been used to determine patients' adherence, from surveys using questionnaires or telephone calls, direct interviews, to counting of tablets[96]. Previously called "compliance", the term "adherence" is now more accepted by the health care providers[167]. The term "compliance" suggests that patients are considered to be more passive following what doctors suggest, without showing the same interest in wanting to take the medicine[167]. However, both of these terms are still not fully accepted and might not perfectly represent patients' medication-taking behaviour[167]. In this study, the term "adherence" is defined as "the extent to which patients take medications in accordance with the regimen prescribed by their health care providers with respect to timing, dosage, and frequency of medication taking"[167 168 173]. Apart from adherence, another term that is important regarding patients' behaviour in taking their medication is "persistence". Persistence refers to "continuing to take the medication for the prescribed length of time"[174].

In regards to clopidogrel therapy, patients' good adherence and persistence are among the essential factors for the drug to exert its optimum activity and protect patients from the deterioration of their disease[175]. As mentioned before, guidelines recommend the use of clopidogrel following a stent placement after ACS for at least 12 months in order to improve patients' outcome. Spertus et al. reported in the results from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) study that almost 14% patients treated with a thienopyridine after the placement of DES stopped taking the medication within 30 days of being stented[175]. Furthermore, the study also

found that stopping thienopyridine therapy prematurely was strongly associated with subsequent mortality[175].

Serebruany et al., in their paper published in 2010, proposed that patient adherence might be the leading contributor to variable clopidogrel responses[176]. Their study assessed patients' adherence by detecting the plasma level of the inactive carboxyl metabolite of clopidogrel. Patients were considered as non-adherent if their plasma concentration of the metabolite was less than 5000ng/mL after at least 1 month of therapy with clopidogrel. The results showed that 22% of patients were non-adherent. Furthermore, it was also found that many of those who were non-adherent also had a low level of platelet inhibition.

From the discussion above, it is clear that a wide range of factors have been proposed to impact on the variability of response to clopidogrel. None of these, however, have been identified unequivocally to be clinically significant in the treatment of patients with clopidogrel or found to be the main contributor to the response variability.

1.4 Aims and Objectives

Even though the studies regarding the variable responsiveness to clopidogrel have been conducted rigorously on an international scale, the local data on the outcomes of clopidogrel therapy are still extremely limited. Given how frequently clopidogrel is used to treat patients with ACS and the lack of local data regarding the use of the medication, this study aimed to assess the therapeutic outcomes of patients treated with clopidogrel after presentation with a first episode of ACS at the Royal Hobart Hospital (RHH). The primary outcomes observed were any readmission to the RHH due to recurrent ACS or bleeding.

As the determinants of the clinical outcomes of clopidogrel are multifactorial, a variety of issues relating to the patients and their management were evaluated, namely:

- In-patient management, as well as the planned management at the time of discharge;
- Adherence and persistence while taking clopidogrel;
- Cytochrome P450 genotypes;
- The concomitant use of other medications that can increase risk of bleeding; and
- The use of gastro protective therapy.

The hypotheses to be tested included:

- That patients with poor adherence and persistence with clopidogrel therapy would demonstrate an increased risk of readmission due to recurrent ACS;
- That patients with a reduced ability to metabolise clopidogrel to its active metabolite, due to interacting drugs or reduced cytochrome P450 enzymatic activity, would demonstrate an increased risk of readmission due to recurrent ACS; and
- That patients taking multiple antithrombotic agents would demonstrate an increased risk of hospital readmission due to bleeding.

Clopidogrel has become an essential component in the management of ACS. It was hoped that this study would provide useful local data on the prevalence of treatment failure and major bleeding with clopidogrel, and the relative impact of various factors that may contribute to these adverse outcomes. It was believed that the information obtained from this study would potentially permit a better systematic approach to clinical practice in an attempt to reduce the occurrence of treatment failure with clopidogrel. This study was also intended to collect data on how patients took their medication following hospital discharge, providing valuable information regarding patients' adherence and persistence in the "real world" setting.

Chapter 2 – Methods

2.1 Overview

This study was a two-phase, retrospective observational study designed to assess the management and outcome of patients discharged from the RHH with a diagnosis of ACS and who had been treated with clopidogrel. The first phase of this study focused on collecting patients' baseline data from the medical records at RHH. This was followed by phase two, which involved direct contact with the patients and further data collection regarding patients' adherence and persistence with therapy, as well as their genotype profiling.

2.2 Study Population and Outcome

Subjects included in this study were patients who underwent a first admission for ACS at the RHH and were prescribed clopidogrel at the time of discharge. The study also included patients with ACS transferred into RHH from other hospitals.

The study was focused on observing two main outcomes, which were patients' hospital readmissions due to recurrent ACS or stenosis and readmissions due to bleeding. Only patients whose records stated that their reason for admission was ACS (either STEMI, NSTEMI, UA or unspecified ACS) or a stent stenosis at hospital readmission were then considered as having recurrent ACS or stenosis. Bleeding was defined as any bleed (either major or minor bleeding) that led to patients being admitted to the hospital. These outcomes were observed within 18 months after the patients' initial discharge from the hospital. Data were obtained from patients' digital medical record (DMR) at the RHH and were also confirmed by the patients by contacting them with a letter. The researcher also obtained information regarding whether the patients died outside the hospital and the reason for their death, from the Tasmanian Registry of Births, Deaths, and Marriages, Department of Justice. Patients who were recorded as deceased due to recurrent ACS or heart attack during the 18 months post discharge were considered as having recurrent ACS resulting in death. For completeness, these patients were then classified together with

those who had a hospital readmission due to recurrent ACS or stenosis during the follow-up period.

2.3 Phase One

Phase one of this study aimed to identify patients meeting the study criteria who were discharged from the RHH between 1 July 2007 and 31 December 2009. It was initially calculated that the minimum sample size required to be able to demonstrate a statistically significant difference between the two groups based on adherence and persistence would be 300. This calculation was based on previous studies of adherence and CYP2C19 status in ACS populations[158 177]. Originally, it was predicted that the review of medical records from the time period 1 July 2007 to 31 July 2009 would produce adequate subject numbers. The time frame for the study was however later extended (1 July 2007 to 31 December 2009) due to an insufficient number of patients within the original study period.

2.3.1 Patients' identification

The initial identification of potential patients was done by the Medical Records Department at the RHH using the Australian Refined Diagnosis Related Group (AR-DRG) codes relating to ACS. The AR-DRG codes that were used and the definition of each code are displayed in Table 2.1.

Table 2.1 AR-DRG codes[178]

AR-DRG Codes	Description
F70A	Major Arrhythmia and Cardiac Arrest With Catastrophic or Severe Complications/Comorbidities
F70B	Major Arrhythmia and Cardiac Arrest Without Catastrophic or Severe Complications/ Comorbidities
F71A	Non-Major Arrhythmia and Conduction Disorders With Catastrophic or Severe Complications/Comorbidities
F71B	Non-Major Arrhythmia and Conduction Disorders Without Catastrophic or Severe Complications/Comorbidities
F72A	Unstable Angina With Catastrophic or Severe Complications/Comorbidities
F72B	Unstable Angina Without Catastrophic or Severe Complications/Comorbidities
F10Z	Percutaneous coronary intervention and Acute Myocardial Infarction
F41A	Circulatory Disorder + Acute Myocardial Infarction + Invasive Investigative Procedure + Catastrophic/ Severe Complications/Comorbidities

F41B	Circulatory Disorder + Acute Myocardial Infarction + Invasive Investigative Procedure - Catastrophic/Severe Complications/Comorbidities
F60A	Circulatory Disorder + Acute Myocardial Infarction - Invasive Investigative Procedure + Catastrophic/Severe Complications/Comorbidities
F60B	Circulatory Disorder + Acute Myocardial Infarction - Invasive Investigative Procedure - Catastrophic/Severe Complications/Comorbidities
F66A	Coronary atherosclerosis + Complications/Comorbidities
F66B	Coronary atherosclerosis - Complications/Comorbidities
F74Z	Chest pain

Initial screening of the identified patients' medical records revealed that the AR-DRG codes were too broad and many patients failed to meet the study inclusion criteria. Discharge diagnosis codes were therefore used to narrow the search. Based on the experience of the initial screening process, subsequently only the medical records of those patients with discharge diagnosis codes of I200, I210, I211, I212, I213 and I214 were further screened for inclusion in the study (details of these codes are shown in Table 2.2.).

Table 2.2 Discharge diagnosis codes used in study

Diagnosis code	Description
I200	Unstable angina
I210	Acute transmural myocardial infarction of anterior wall
I211	Acute transmural myocardial infarction of inferior wall
I212	Acute transmural myocardial infarction of other sites
I213	Acute transmural myocardial infarction of unspecified site
I214	Acute subendocardial myocardial infarction

Study inclusion and exclusion criteria are presented in Table 2.3. Patients with a home address recorded outside of Tasmania were excluded as any subsequent readmissions were likely to occur at other hospitals and as such data on these would not be available. For those who had more than one ACS admission during the observation period, analysis was done on the first admission. Patients who died during the follow-up phase were included in the study data collection, but those who died during the first ACS presentation were excluded.

Table 2.3 Study inclusion and exclusion criteria

Inclusion Criteria	
	Male or female aged over 18
	Patients with a first ACS admission
	Prescribed clopidogrel at discharge
Exclusion Criteria	
	Patients with a history of ACS or a stent
	Patients already on clopidogrel at the time of admission
	Patients discharged to a private/other hospital
	Patients deceased during ACS presentation
	Patients with a home address outside of Tasmania
	Patients recorded having memory loss or dementia
	Patients unable to speak and/or read English

2.3.2 Data collection

2.3.2.1 Baseline

The baseline data were collected from the DMRs of the identified patients. Each patient's DMR was thoroughly reviewed and any relevant notes in the record were documented. Generally, the useful data were generated from the patient hospital admission and discharge summary, medical progress notes, drug therapy charts, clinical pathway notes, emergency department records, outpatient records, and diagnostic results regarding any relevant biochemical tests, as well as doctors' correspondence.

The baseline data were collected using a standard data collection form (Appendix I), which included the following variables[112 114 179-181].

1) Demographic characteristics, including age, gender, postcode and race (age was recorded from their first ACS presentation).

2) Patients' height and weight, also BMI if recorded. BMI, if not stated, was calculated based on the patients' weight and height.

3) Cardiovascular risk factors and previous medical history[112 114 179-181]; included in the cardiovascular risk factors were age 65 years or older, smoking, recorded obesity, other related cardiovascular conditions and a family history of coronary artery disease (CAD).

Patients who smoked cigarettes and/or pipes until the time of hospital presentation were classified as current smokers, while those who reported that they had stopped smoking were described as ex-smokers. Both of these groups were included as having the 'smoking' risk factor. However, ex-smokers were considered as non-smokers for the purpose of data analysis.

Patients were described as obese if either they were recorded as having a BMI≥ 30 or there was a record at their first ACS admission in the DMR stating that the patient was obese.

For the purposes of this study, those who were noted in the DMR as having a left ventricular ejection fraction (EF) less than 40% were classified as having reduced left-ventricular function while the others were considered as having normal left-ventricular function.

All cardiovascular-related medical conditions (e.g., hypertension, atrial fibrillation (AF), CHF) as well as other related conditions that can worsen the patients' condition (e.g., diabetes, kidney failure) were included as risk factors.

Patients' risk factors for bleeding were recorded, with the risk factors being defined as age≥ 65 years [136], previous GI ulcer or bleeding, history of gastro-oesophageal reflux disease (GORD)[182], any previous bleeding history and on discharge taking three medications that can increase risk of bleeding. The medications which were included as medications that can increase the risk of bleeding among this cohort, who were all treated with clopidogrel, were ASA, warfarin, low molecular weight heparin (LMWH), NSAIDs, oral corticosteroids and SSRIs[60 61 113].

Data on medications on admission were also collected from patients' medical records, including all vitamins and other supplements (e.g. cholecalciferol, calcium carbonate) taken regularly by patients. For further data analysis, these medications were then classified based on their pharmacological mechanism of action (e.g., angiotensin converting enzymes inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers, lipid lowering agents (LLAs)). Medications that were recorded as being taken as needed were excluded from the list of medications on admission.

4) Laboratory results, including cholesterol, creatine kinase (CK) and troponin.

In-patient care, including clinical interventions and medication management,

Details regarding both approaches to reperfusion therapy, namely PCI and fibrinolysis, were obtained from patients' medical records.

Besides the detailed data regarding clopidogrel (e.g. loading dose, maintenance dose), other medical therapy or adjuvant therapy recommended for patients with ACS, namely other antiplatelets agents (e.g., ASA, glycoprotein IIb/IIIa inhibitors), anticoagulants (heparin or enoxaparin), ACEIs/ARBs, β-blockers, LLAs and nitrates, were also recorded during in-patient stays.

5) Discharge and ACS management plan

The principal diagnosis stated on patients' discharge summary was used to confirm the patients' type of ACS. If the diagnosis on the discharge summary did not specify what type of ACS that patients had, the data from the doctors' correspondence was then used. In some cases where both of these sources of data were not specific, the classification of ACS was then made based on patients' CK and troponin values. STEMI patients were those who were recorded with the elevation of both troponin and CK values and who underwent emergent reperfusion treatment (e.g. primary PCI or thrombolysis)[183]. Patients with the elevated cardiac markers who did not receive the emergent reperfusion therapy were classified as NSTEMI patients[183].

Medications prescribed on discharge were also recorded to allow the assessment of compliance with the Guidelines for the Management of ACS 2006[83]. There are four groups of medications recommended for long-term management of patients after ACS [83]. These medications include antithrombotic agents, statins, ACEIs/ARBs, and β-blockers. However, patients recorded with contraindications (Appendix II) to the medications were considered as not being appropriate to receive the medications. The duration of patients' planned therapy with clopidogrel was also recorded.

Other management recommended for patients post ACS, including lifestyle advice and referral to cardiac rehabilitation, were recorded[83]. Compliance to the guideline regarding these factors was then investigated.

2.3.2.2 Follow-up period

Patients' DMRs were reviewed for 18 months after their initial ACS admission to observe their outcomes over that period. This data was recorded in the same form as for the baseline data (Appendix I).

The information collected regarding the patients' outcomes included:

1) Patients' readmissions,

   Any readmission recorded within 18 months after the patients' first ACS episode were recorded. However, only the readmissions due to recurrent ACS or bleeding were included in the data analysis. Recurrent ACS readmission was based on the principal diagnosis stated in the patients' medical records. Patients readmitted due to restenosis were also included in this group.

2) Whether the patient was still taking clopidogrel on readmission and, if not, when and why it was ceased,

3) Other medications at readmission, and

4) Outcomes of the readmission.

2.4 Phase Two

In the first phase of study, no contact with the patients was made. Direct contact with the identified patients was undertaken in the second phase of this study and aimed to further assess the patients' outcomes after their first episode of ACS and treatment with clopidogrel, as well as to evaluate certain factors that might affect their outcome of therapy with clopidogrel.

2.4.1 Patient recruitment

The identified patients were reviewed and those who were not recorded as deceased during the 18-month follow-up were contacted by mail and invited to participate in phase two of the study.

The patients were sent a pre-packaged envelope that contained:

1) A letter explaining the purpose of the study (Appendix III)
2) The study questionnaire (described below)(Appendix IV)
3) A consent form (Appendix V), and
4) A pre-paid return envelope.

Unless the patients were willing to consent to genotype testing, no further contact with the patients was made following this initial contact. Patients who completed the questionnaire received a $25 gift voucher as reimbursement for their time.

As this study consisted of three different parts, the response rates are based on patients' responses to each part of the study. Only those who completed the questionnaire and/or gave consent to the study request were considered as responding.

2.4.2 Data Collection

In the phase two, there were three different aspects of data collection that patients could choose to take part in: completing a questionnaire, consenting to give an access to community pharmacy dispensing records and performing cytochrome P450 (CYP450) genotype testing. Patients could choose to participate in one, two or all three parts of the study.

2.4.2.1 Questionnaire

In order to confirm whether the patients had another readmission due to recurrent ACS or bleeding, as well as to explore their experience and behaviour while taking clopidogrel, patients was asked to complete a study questionnaire. The questionnaire was also developed to explore patients' opinions about taking clopidogrel. Throughout the questionnaire, the generic name – clopidogrel – was used; however brand names available in Australia were also mentioned in the first part of questionnaire. The questions in the survey consisted of two parts. The first part contained questions about clopidogrel use and patients' experiences during clopidogrel use, which included whether they had any readmission to another hospital apart from RHH due to recurrent ACS or bleeding. Also

assessed was patients' attendance at cardiac rehabilitation services after their ACS presentation.

Part two of the questionnaire was intended to assess participants' adherence while taking clopidogrel. The validated Medication Adherence Report Scale (MARS) was used as a tool to assess the participants' adherence. This questionnaire is one of the simplest tools in identifying medication non-adherence and has a greater validity compared to other tools (e.g Medication Adherence Questionnaire (MAQ)). It uses a five-item scale to ask about the frequency of non-adherent behaviour[184 185]. MARS has been used in numerous studies in different settings and different countries to assess self-reported medication adherence in clinical practice[185]. However, this validated scale was initially designed for psychiatric populations; therefore, this might limit its generalizability.

2.4.2.2 Community pharmacy dispensing records

Patients' adherence and persistence were assessed by requesting that patients give consent for the researchers to access their dispensing records from their regular community pharmacy for the study period. Adherence was defined as whether a patient took clopidogrel according to schedule, while persistence referred to whether a patient stayed on therapy for the time from initiation to intended discontinuation of therapy[174].

The pharmacies identified by consenting participants as their regular community pharmacies were contacted by mail and requested to provide the participants' complete dispensing records for the specified 18-month period (Appendix VI). These data were then used to assess participants' adherence and persistence to clopidogrel as well as to observe patients' concomitant drug use within the 18-month follow up period.

Each dispensing date for clopidogrel was recorded along with how many tablets were supplied on the day of dispensing; then both of these data were summed. Patients' adherence was assessed by comparing the total number of daily doses of clopidogrel supplied to patients with the total date range of the dispensings. Clopidogrel is usually prescribed as 75mg (one tablet) daily[28]; therefore the dispensing of 30 tablets of clopidogrel was assumed to be sufficient for 30 days at this dosing regimen. Patients were classified as adherent if their percentage adherence was 80% or more[186]. For instance, if the sum of tablets taken by a patient during the observation time was 492 tablets and the

range of the patient dispensing record was 540 days, the patient's percentage adherence would be (492/540) x 100% = 91.1%, thus the patient would be considered as adherent.

In order to assess patients' persistence with clopidogrel, the duration of time that patients had clopidogrel dispensed was compared to the planned duration at discharge; both durations were calculated in months and a percentage was calculated (i.e. treatment duration/planned duration x 100). Those whose percentage persistence was 80% or more were categorised as persistent. Therefore, if patient took the medication for 10 months, while the initial plan was for 12 months' therapy, the patient was still considered as persistent ((10months/12months) x 100% = 83.3%).

Further assessment of the dispensing records was performed regarding the use of other medications that could increase the risk of bleeding[60] (e.g. warfarin, ASA, NSAIDs, oral corticosteroids, SSRIs) and the use of gastro protective drugs[187-189] (H2 receptor antagonists and PPIs).

2.4.2.3 CYP2C19 genotype testing

Patients were asked to provide a saliva sample so that their genotype profile could be tested and related to their therapy outcomes. Consenting participants were mailed a pack containing two buccal swabs with instructions and a research test request form (Appendix VII and Appendix VIII). Samples were returned directly to the Diversity Health Institute (DHI) Research Laboratory (more information about the laboratory can be obtained from the DHI website: http://www.dhi.gov.au/). The DHI holds NATA accreditation (No. 17073) for Research and Development and operates in a secure environment, both physically and for electronic data storage. The DHI laboratory performed the genotype testing by extracting DNA from the buccal samples using the manufacturer's protocol for the QIAGEN EZ1 robot system. The genotyping performed was on three single-nucleotide polymorphisms (SNPs) of CYP2C19 alleles (*2, *3 and *17). The method involved the restriction digestion of amplified polymerase chain reaction (PCR) products using specific enzymes, or tetra-primer allele-specific amplification PCR where applicable. PCR and digestion products were analysed on the lab-on-a-chip Agilent Bio analyser capillary electrophoresis system according to the manufacturer's instructions. Specific polymorphisms were identified by the presence or absence of specific peaks on chromatograms[190].

The patients' genotype profiles were then sent to the researcher for further analysis. Patients were classified into categories of metaboliser phenotypes with the use of established common-consensus star allele nomenclature. The definition of each metaboliser type used in this study was following the classifications found in Pare et al.[159]. Nevertheless, due to the lack of patients involved in our study, those who carried one (i.e., *1/*2 or *1/*3) or two loss-of-function alleles (i.e., *2/*2, *2/*3 or *3/*3) were both categorised as "poor metabolisers". Patients without a *2, *3, or *17 allele (i.e., *1/*1) were classified as "extensive metabolisers," and carriers of a single *17 allele (i.e., *1/*17) and *17 homozygotes were classified as "rapid metabolisers". Patients with one *17 allele and one loss-of-function allele (i.e., *2/*17 or *3/*17) were classified as having an "unknown" phenotype.

2.5 Data Analysis

Patients' data recorded in the data collection forms were transformed into numerical codes and entered into a spread sheet using Microsoft® Office Excel 2010. The data were then transferred into an IBM Statistical Package for the Social Sciences (SPSS) for Windows 19.0 (SPSS Inc., Chicago, IL) database for all of the statistical analyses. All data coding and entries were double-checked against the original data collection sheets.

Data regarding patients' baseline demographics, clinical characteristics on admission, care pattern and discharge characteristics were presented using descriptive statistics.

Median values (range) were used to describe non-parametric continuous data, and mean values (standard deviation (SD)) were used for parametric data. Frequencies and percentages were reported for categorical data. The Mann-Whitney U Test was used to compare the differences between two independent groups if the data were non-parametric (e.g. median age in male group compared to female group). To allow the comparison of more than two independent groups of non-parametric data, the Kruskal-Wallis H Test was used. Chi-squared testing was used to explore the possibility of a relationship between two categorical variables. A p value of <0.05 was accepted as significant for all statistical analyses.

2.6 Ethics Approval

The study was approved by the Human Research Ethics Committee (Tasmania); Ethics References No. H11540 and No. H11606 (Appendix IX).

Chapter 3 – Results

3.1 Patient Identification

During the observation period (1 July 2007 to 31 December 2009), 3174 patient admissions to the RHH were reviewed. Of these admissions, more than half were non-ACS admissions (e.g. AF, ventricular tachycardia, CHF) and thus were excluded from further screening.

Overall, 1712 medical records were screened based on patients' discharge diagnosis codes, and 297 eligible patients were identified. Details of screening and eligibility criteria are presented in Figure 3.1.

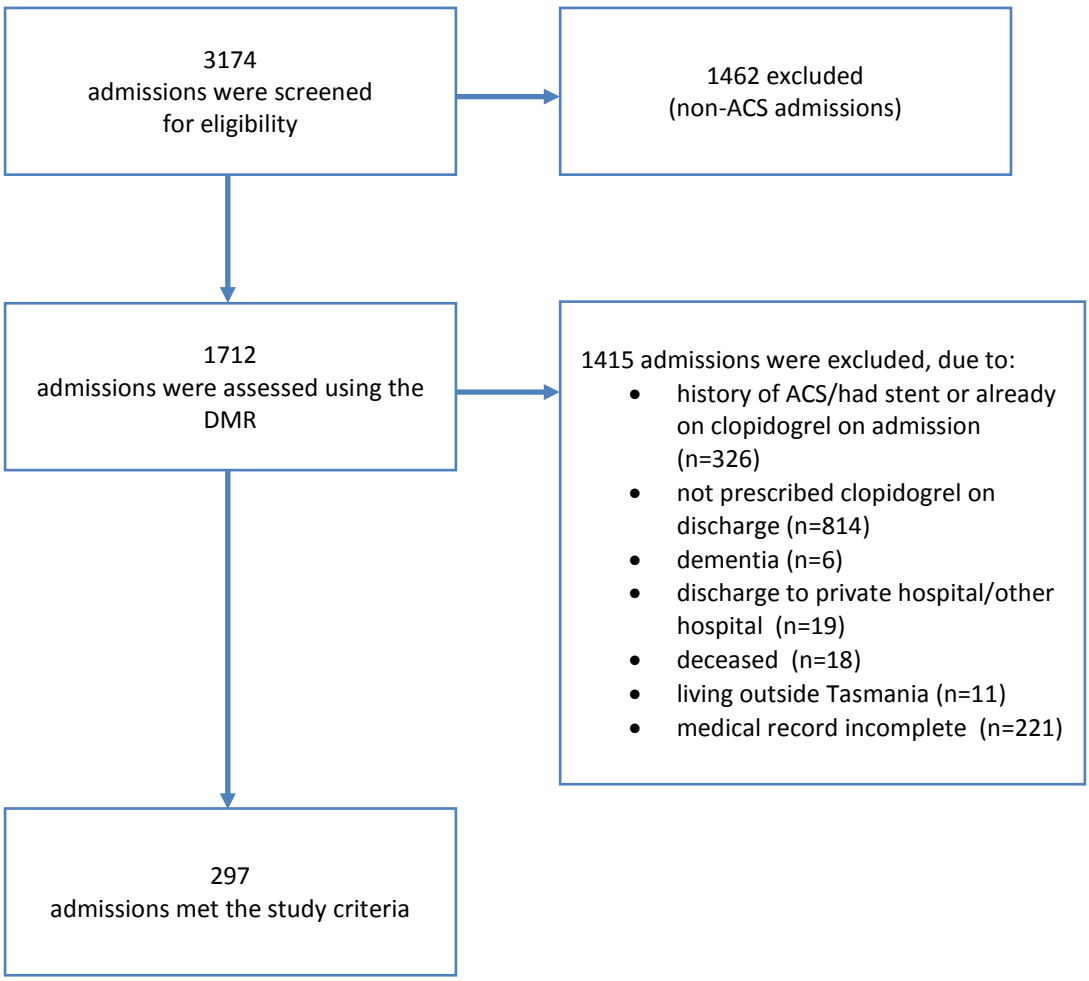


Figure 3.1 Patient screening and identification

3.2 Patient Demographics

The participants' demographics are shown in Table 3.1. The majority of participants identified were non-Aboriginal/non Torres Strait Islands (TSI) patients, with males accounting for three-quarters of the cohort. The median age of the patients in this cohort was 61 years and the women were significantly older than the men (Mann-Whitney U=6539, z=-2.6 p<0.01). The majority of patients (88.6%) were southern Tasmania residents, with the remainder having an address in northern Tasmania.

Table 3.1 Patients demographics (n=297)

Variable	Number (n)	Proportion (%)
Gender		
Male	224	75.4
Median age in years (Range)		
Male	60 (29-87)	
Female	65 (28-88)	
Residence		
Southern Tasmania	263	88.6
Race		
Non Aboriginal/TSI	276	92.9

The distribution of age among the study participants is displayed in Figure 3.2. The figure shows that the peak age for patients with their first ACS presentation was in their early 60s. However, the peak for male patients was later than for the females (66 years and 61 years, respectively).

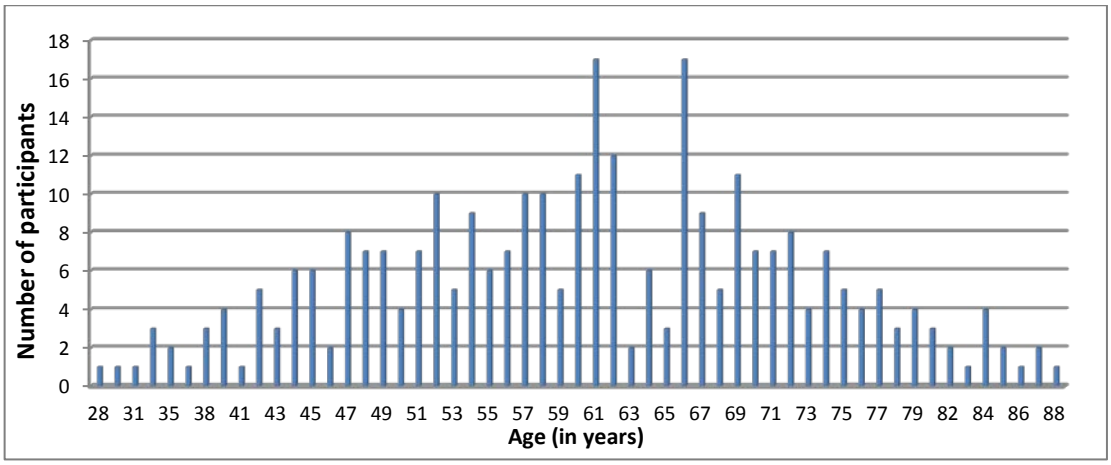


Figure 3.2 Age distribution among participants

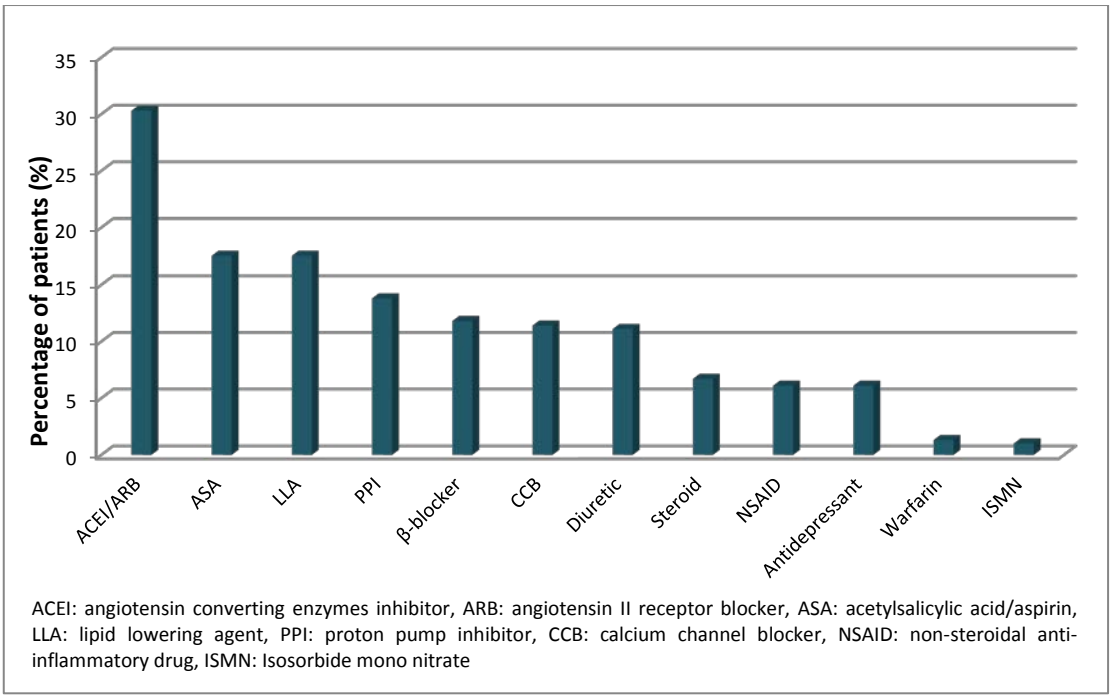
Of the patients included in this study, 144 patients (48.5%) were diagnosed with STEMI, 117 (39.4%) with NSTEMI, 29 (9.8%) with UA and 7 patients (2.4%) with unspecified ACS. As there was a small number of patients recorded with unspecified ACS, these patients were combined with the UA patients for the purposes of analysis.

3.3 Medical Characteristics on Admission

3.3.1 Medication on admission

One-third of the patients' records (33%) had no details of medications on admission, with nearly 25% of these patients being recorded as taking nil medications. No information was available about the medications on admission for about 8% of the total patients identified. The median number of regular medications on admission was 1 (range: 0-13).

Among the 199 patients who were recorded as taking medication(s) on admission, more than half were taking at least two medications regularly. Of the 90 participants who were already taking ACEIs or ARBs, nearly all (98.8%) were also recorded as suffering from hypertension. Given that all of ACS admissions for this study were first events, the 52 patients (17.5%) who were already taking aspirin 100mg at admission had presumably been prescribed the drug for the primary or secondary prevention of CAD or transient ischaemic attack (TIA). Interestingly, of the 152 patients who were not recorded as taking any cardiovascular drugs on admission, almost 80% had at least two cardiovascular risk factors. Almost half of these patients (46.7%) had hypertension, while 25.7% and 21.1% of those patients had dyslipidaemia and were recorded as obese in the medical notes, respectively. Figure 3.3 shows details of the patients' medications on admission.



ACEI: angiotensin converting enzymes inhibitor, ARB: angiotensin II receptor blocker, ASA: acetylsalicylic acid/aspirin, LLA: lipid lowering agent, PPI: proton pump inhibitor, CCB: calcium channel blocker, NSAID: non-steroidal anti-inflammatory drug, ISMN: Isosorbide mono nitrate

Figure 3.3 Patients' medications on admission

3.3.1 Risk factors

Cigarette smoking was the most frequent cardiovascular risk factor among the patients, with the majority of patients (73%) having a history of smoking. Another common risk factor observed in this study population was hypertension, which was present in 153 patients (52.7%). Of these patients, almost two-fifths (39.9%) were recorded as already taking either a CCB, β-blocker, ACEI or ARB on admission. However, about one-quarter (24.8%) of those recorded as having hypertension were not on any medication, including a medication for hypertension. Among 52 patients who were recorded as taking a statin or other LLA, the majority (84.6%) were noted as having dyslipidaemia. Family history, as one of the non-modifiable risk factors of CAD, was recorded for 140 patients (47.1%) in this cohort. The proportions of patients with each contributing risk factor recorded on admission are presented in Figure 3.4

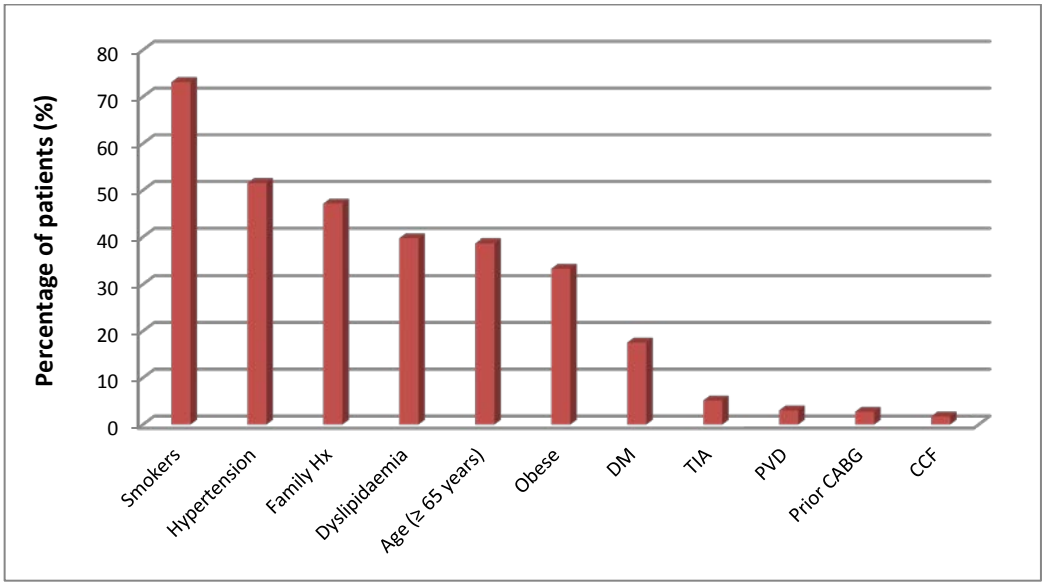


Figure 3.4 Patients presenting with cardiovascular risk factors

Figure 3.5 displays the data on patients' smoking habits and alcohol intake. Of the 218 patients who were recorded as having a history of smoking on admission, half of those were still smoking leading up to their admission. Data regarding patients' alcohol intake were incomplete, with the drinking status of more than half of the patients not recorded. Among those whose alcohol intake was recorded, most were noted to have moderate alcohol intake (e.g. having 2 standard drinks at the weekend).

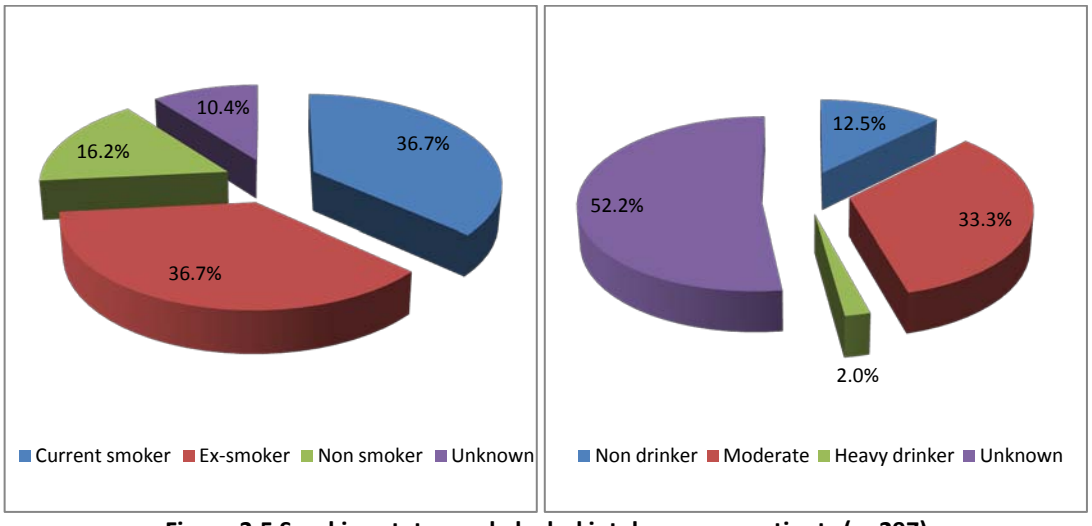


Figure 3.5 Smoking status and alcohol intake among patients (n=297)

The number of risk factors that patients had at the time of their first ACS presentation was summed to produce the data in Table 3.2. Almost two-third of patients (57.3%) had at least three cardiac risk factors on admission (median: 3), with only a small number of patients (2.0%) having no risk factors at all.

Table 3.2 Cardiovascular risk factors

Number of Risk Factors	Participants' risk factors*	
	Number	Percentage
None	6	2.0
1	49	16.5
2	72	24.2
3	91	30.6
4	46	15.5
5	26	8.8
6 or more	7	2.4

* Risk factors included current smoking status, age (65 years or older), hypertension, family history of CV disease, dyslipidaemia, obesity, diabetes mellitus, stroke, peripheral vascular disease, congestive heart failure and prior coronary artery bypass grafting (CABG).

3.4 In-patient Characteristics

The median in-patient stay for the study cohort was 3 days (range: 1-63 days), with no difference in the median length of stay of patients diagnosed with UA, NSTEMI and STEMI (Kruskal-Wallis Test; H= 0.6, df=2, p= 0.738).

While in hospital, a small numbers of patients had complications such as cardiac arrest (4.0%), minor and major bleeding (3.7%), three vessel disease (2.0%), arrhythmia (1.7%) and venous thrombosis (1.0%).

3.4.1 In-patient medications

3.4.1.1 Clopidogrel

Details of the patients' in-patient clopidogrel therapy are seen in Table 3.3. The majority of the patients (56.9%) received a 300mg loading dose, while about one-third (29.9%) were treated with a 600mg loading dose. Data on a clopidogrel loading dose were not available for 37 patients, 14 of whom were transferred from northern Tasmanian hospitals. All patients received a 75mg daily maintenance dose.

Table 3.3 In-patient treatment with clopidogrel

Variable	Number	Percentage
Clopidogrel loading doses		
600mg	89	29.9
300mg	169	56.9
150mg	2	0.7
Unknown	37	12.5
Clopidogrel maintenance doses		
75mg daily	297	100

3.4.1.2 Other medications

Figure 3.6 shows that the utilisation of each group of medications was similar across the different types of ACS patients. However, there was a significant difference in the use of ACEIs/ARBs across the patient groups, with the proportion being 86.8%, 71.6% and 58.3% for STEMI, NSTEMI and UA patients, respectively (χ^2= 17.0, df=2, p<0.001). Among the different ACS patients groups, almost all (98.3%) were on DAT and most (87.9%) received anticoagulants while hospitalised. Approximately half of the patients (56.2%) were treated with all four guideline-recommended drugs (antiplatelet, ACEI/ARB, β-blocker and LLA; adjusted for contraindications) during their in-patient period, with β-blockers being the least prescribed medication among all the four medication classes (75.8%).

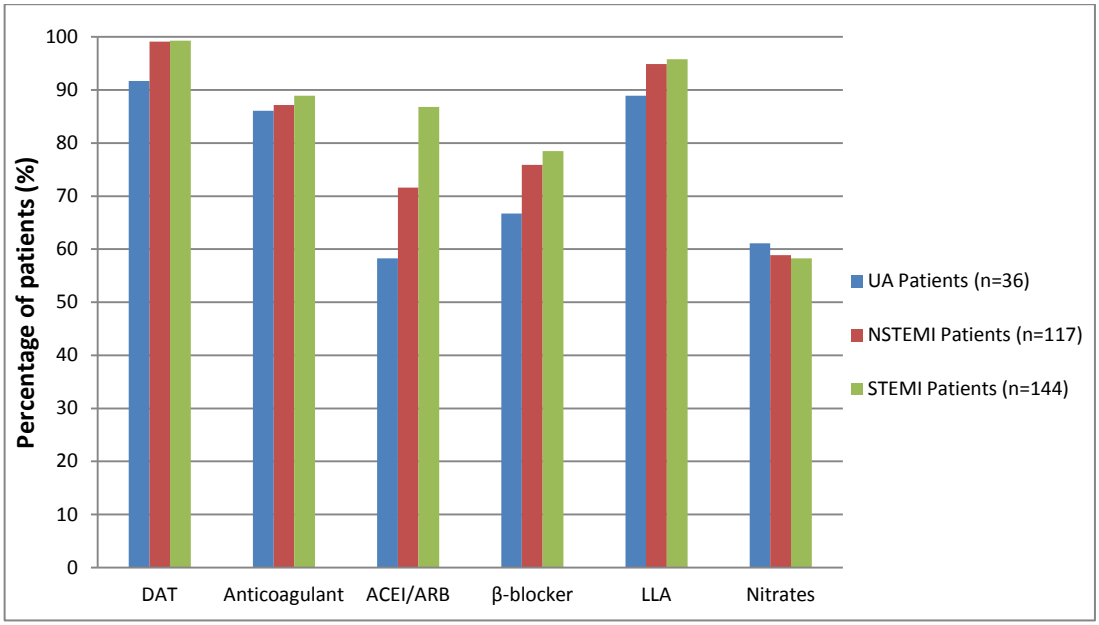


Figure 3.6 Patients' medication therapy during the in-patient period

3.4.2 Reperfusion therapy

During their admission, the majority of patients (79.8%) received reperfusion therapy, with 228 patients (76.8%) had an intracoronary stent. The majority of those stented (81.9%) were implanted with a BMS, with 14.5% being treated with a DES. Of the total study population, only one patient received both a BMS and DES, while the data for seven patients were unclear on whether they were stented or not. Among those who were not stented during their first ACS admission (69 patients), 10 were readmitted for an elective PCI. Of the 18 patients treated with a fibrinolytic agent, half were patients transferred from northern Tasmania.

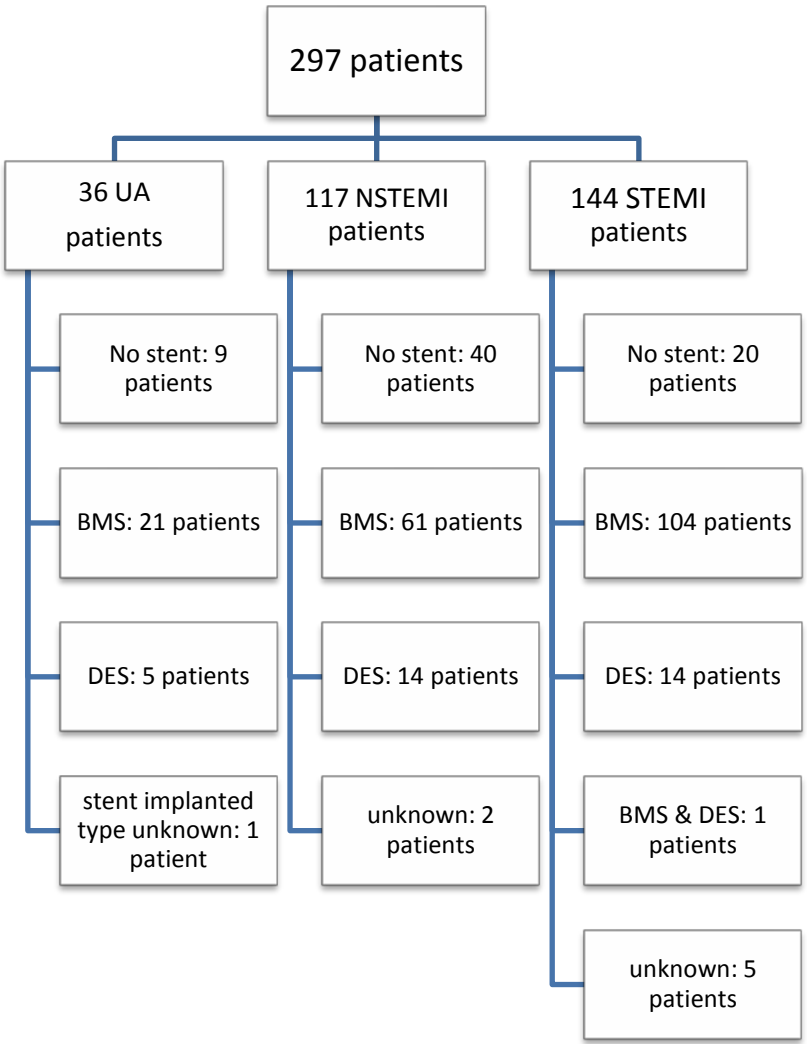


Figure 3.7 Proportion of patients undergoing PCI

3.4.3 Laboratory data

Recorded laboratory values are presented in Table 3.4. About 70% of patients had their total cholesterol levels measured while they were in-patients. Unsurprisingly, those who were taking a statin or other LLA had a lower average cholesterol level in comparison to those not taking these medications; 4.6mmol/L and 5.4mmol/L, respectively (Mann-Whitney U=1872.5, z=-3.1 p=0.002). Ejection fraction (EF) was recorded for 127 patients. From the available data, only about 5% had reduced left ventricular function.

Table 3.4 Laboratory result

Variable	Value	
Left Ventricular Function (n, %)		
Less than 40%	n = 18	(5.5%)
40% or above	n = 109	(40.1%)
Not recorded	n = 170	(54.4%)
Median total cholesterol (mmol/L) (range)		
Patients taking LLA at admission	4.57 (3.17 – 7.44)	(Mann-Whitney; U=1872, z=-3.1, p=0.002).
Patients not taking LLA at admission	5.41 (1.26 – 45.00)	
Median CK (IU/L) (range)		
STEMI patients	1337.50 (13.00 – 5938.00)	(Kruskal-Wallis Test; H= 69.3, df=2, p= 0.000)
NSTEMI patients	316.50 (35.00 – 3913.00)	
UA patients	131.00 (29.00 – 986.00)	
Median Troponin (µg/L) (range)		
STEMI patients	37.03 (0.10 – 361.14)	(Kruskal-Wallis Test; H= 102.1, df=2, p= 0.000)
NSTEMI patient	2.25 (0.03 – 75.00)	
UA patients	0.04 (0.01 - 65.53)	

3.5 Discharge Characteristics

3.5.1 Discharge medications

Within the study cohort, almost all patients (98.3%) were taking DAT (clopidogrel and aspirin) at hospital discharge. Other guideline-recommended medications for long term management of ACS, namely statins (or other LLAs), ACEI/ARBs and β-blockers were prescribed for 95.6%, 75.8% and 72.4% of patients, respectively. Warfarin was prescribed for some patients in this study cohort (5.7%), as were other drugs that can increase risk of bleeding e.g. oral corticosteroids and NSAIDs (5.4% and 2.0%, respectively). Gastroprotective agent use on discharge was not very common, with only 83 patients (27.9%) prescribed a PPI and eight patients (2.7%) received an H2 receptor antagonist. The details of patients' discharge medications can be seen in Figure 3.8.

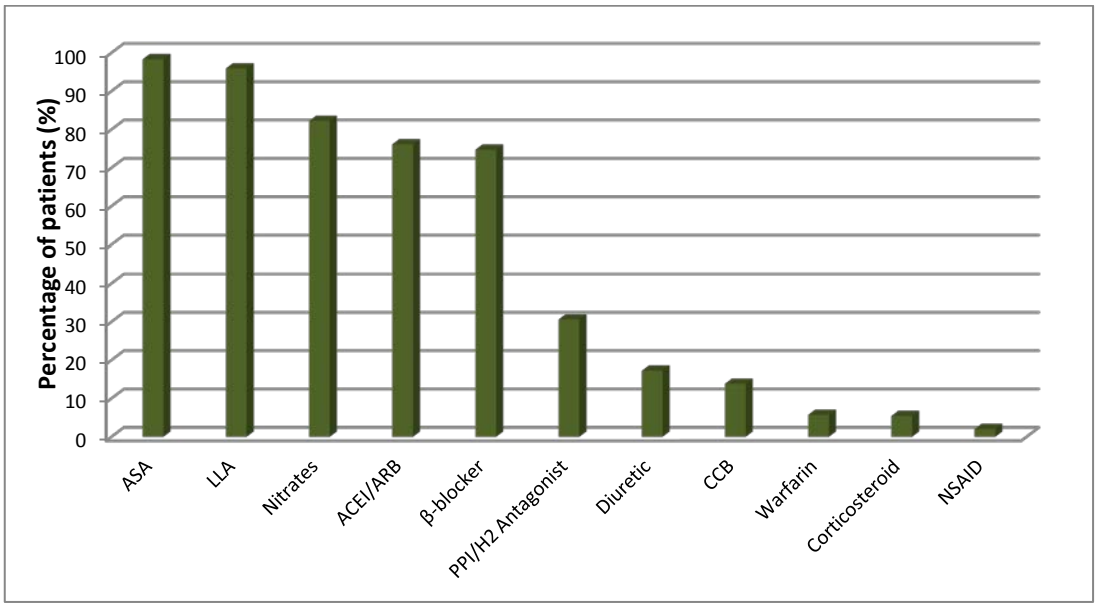


Figure 3.8 Patients' medication at discharge

Overall, across the different diagnoses, 55.9% of patients were prescribed all four recommended medications at the time of discharge. There was a significant difference in terms of rates of prescribing of the four guideline-recommended medications across the three different groups of patients (χ^2=22.5, df=4, p< 0.001). Patients experiencing NSTEACS (i.e. either a NSTEMI or UA) were less likely to be prescribed the four medications compared to patients in the STEMI group (46.4% vs 66.0%; χ^2=11.5, df=1, p<

0.001). Figure 3.9 displays the proportion of patients in the three different patient groups and the proportions prescribed two or less, three, or all four medications.

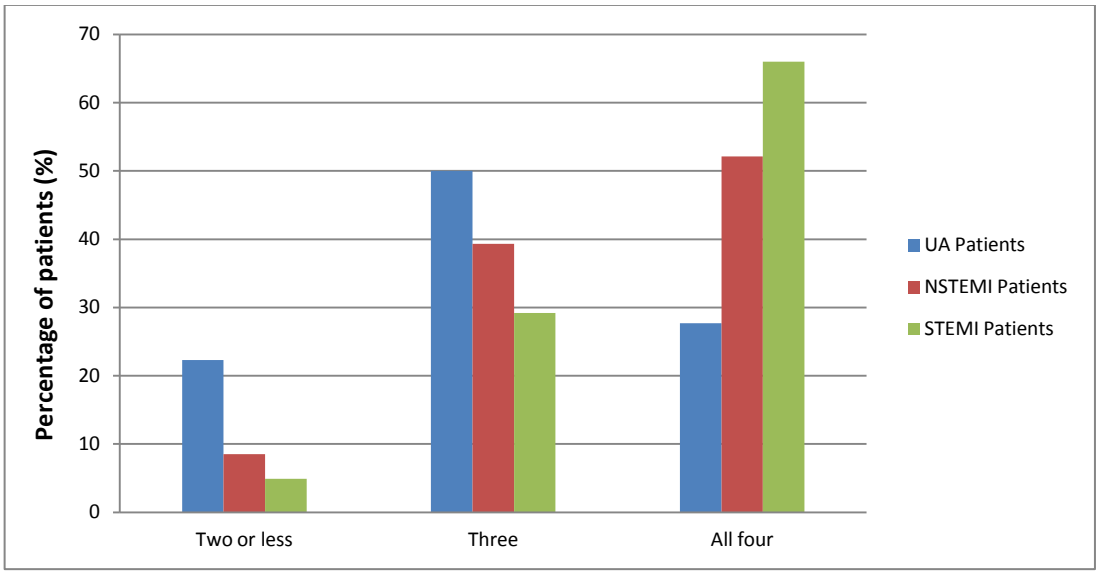


Figure 3.9 Guideline-recommended ACS medications prescribed among patients

Comparing the patients' medications recorded at the time of admission and discharge (shown in Figure 3.10. below), there was an increase in the number of medications received by patients after treatment for ACS. The median numbers of medication at admission and discharge were 1 and 6, respectively ($z=-14.5$; $p< 0.001$).

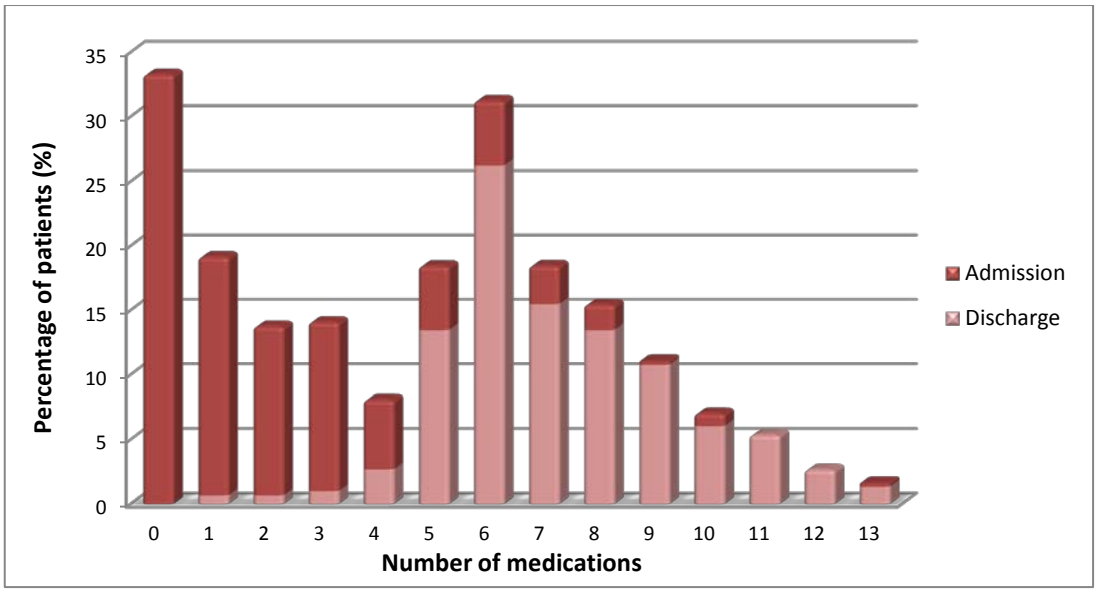


Figure 3.10 Numbers of medications at admission and discharge

As expected, the number of cardiovascular medications prescribed to the patients at the time of their discharge was increased compared to the recorded cardiovascular drugs at admission. Also not surprisingly, the greatest increases were particularly for the four medications recommended for patients post-ACS. An increase was also seen in the number of patients discharged taking a PPI, although the rates at both time points were low; 13.8% and 27.9% at admission and at discharge, respectively. NSAIDs were the only group of drugs that was prescribed less frequently at the time of discharge, with their use declining from 6.1% to 2.0% of patients.

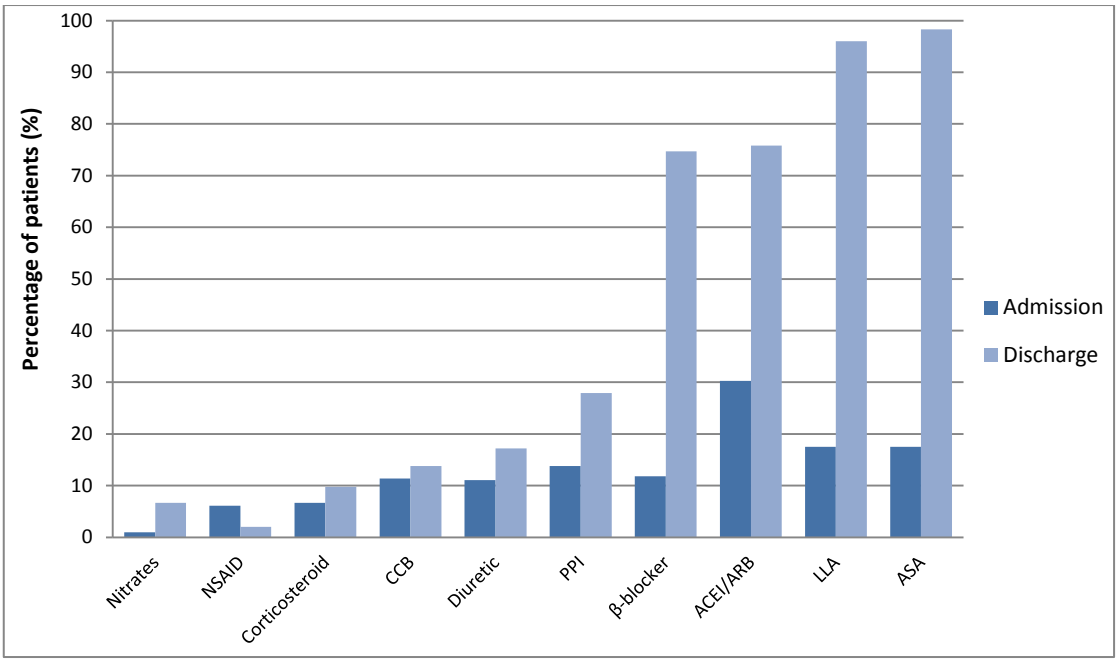


Figure 3.11 Proportions of patients taking different medication groups at admission and discharge

3.5.2 Clopidogrel therapy plan

No records were available concerning the planned duration of clopidogrel therapy for one-quarter of the patients (74 out of 297 patients). For those with recorded plans, the intended durations of clopidogrel therapy ranged from one month to indefinitely. Patients who underwent stent placement, either a BMS or DES or both, were more likely to be intended to take clopidogrel for 12 months than patients without any stent (93.0% vs 3.0%; χ^2=138.9, df=1, p< 0.001). Figure 3.12 shows the various planned durations of clopidogrel therapy among different groups of patients.

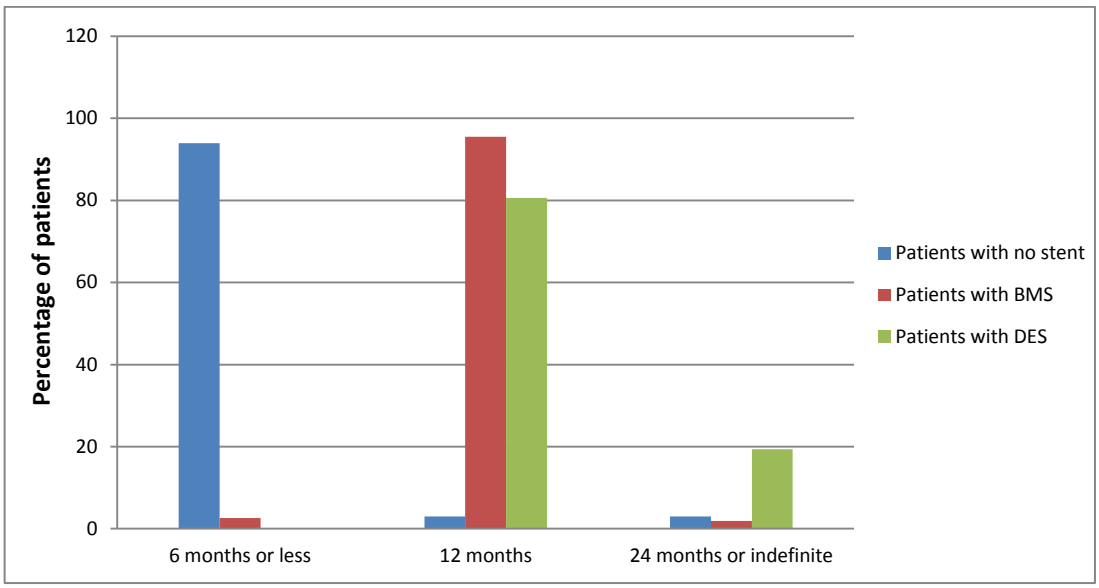


Figure 3.12 Clopidogrel therapy plan among study participant (n=223)

3.5.3 PPI utilisation

Despite almost all (98.3%) patients in this study being discharged with DAT, only 30.6% were also prescribed gastroprotection at the time of discharge. The majority (83 out of 91) were taking a PPI. Of those, 23 were taking pantoprazole, with the reminder prescribed other PPIs. None of the patients in this study were prescribed antacids at discharge. In addition, only about a third (23 out of 64 patients) of those prescribed medications that increase the risk of GI bleeding (e.g. DAT plus warfarin, NSAID, etc.) also received a gastroprotective agent at discharge.

Of the patients who did not receive a PPI at discharge, 111 patients (51.9%) had at least one risk factor for bleeding; either the patients were 65 years or older, had a recorded history of GI bleeding/GORD or they were taking medications that can increase the risk of bleeding.

Overall, patients with an additional risk of bleeding were more likely to receive a PPI at discharge than patients without risk factors (39.5% vs 8.9%; χ^2=32.3, df=1, p= p< 0.001). Table 3.5 presents the number of patients with the risk factors for bleeding and the proportion among them who received a PPI.

Table 3.5 Patients' bleeding risk factors and the number of patients prescribed a PPI

Risk factors of bleeding	Patients with risk factors (n (% of total patients))	Patients with risk factors prescribed a PPI (n(%))
Patients ≥ 65 years	115 (38.7%)	40 (34.8%)
History of GI ulcer/bleeding/GORD	71 (23.9%)	50 (70.4%)
Discharged on DAT/clopidogrel alone + any other medications*	64 (21.5%)	23 (35.9%)
Patients with ≥ 1 risk factors for bleeding	185 (62.3%)	73 (39.4%)
Total cohort	**297**	**PPI prescribing = 83 (27.9%)**

*anticoagulant, NSAIDs, steroids, SSRIs

Figure 3.13 displays the pattern of PPI prescribing among the study patients by quarter during the observation period. The figure shows that there was an increase in PPI prescribing from mid-2007 to late-2008, which was then followed by a gradual drop until early-2009. During 2009, PPI prescribing displayed an unpredictable trend.

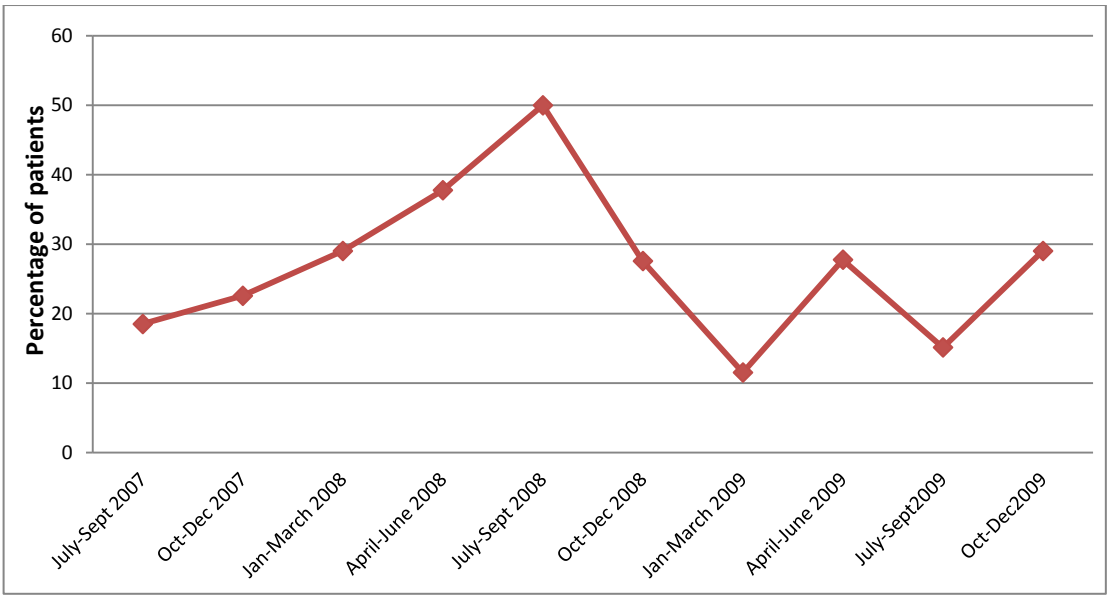


Figure 3.13 PPI prescribing during the study period

3.5.4 Cardiac rehabilitation and lifestyle plan

Only 148 patients' (49.8%) records contained information regarding referral to cardiac rehabilitation and 133 (44.8%) patients were reported as having received lifestyle modification advice during their in-patient stay. However, the data obtained from the RHH cardiac rehabilitation service showed that another 57 patients from the study cohort were also referred to cardiac rehabilitation. Also, another eight patients stated in the survey that they were referred to the cardiac rehabilitation. Therefore, data for these 213 patients were observed regarding their attendance at cardiac rehabilitation. It was found that among these patients only 20.6% were reported as attending at least 5 sessions of the 6 planned sessions, while the remaining patients were reported as declining or not attending (60.6%) or failing to complete (18.8%) their planned cardiac rehabilitation sessions. Among those who recorded as being referred to cardiac rehabilitation, patients' age or risk factors did not seem to influence healthcare providers' tendency to promote the service.

3.6 Follow-up Period; 18 Months Post-ACS

3.6.1 Patients' outcomes

During the 18 month follow-up period after their first ACS episode, 108 patients (36.4%) were readmitted to hospital for any reason. Sixteen patients (14.8%) came to the hospital complaining of chest pain which then diagnosed as angina pectoris or CAD. Five patients (4.6%) were readmitted for a planned CABG and three (2.7%) were readmitted due to cardiac failure. One third of patients (34.6%) had two or more readmissions within the observation period. Among 16 patients recorded in the DMR as having died during the follow-up period, the majority (15 patients) did so due to their other conditions (e.g. multiple organ failure, cancer), while one patient died in hospital following the recurrent ACS. Another three patients were confirmed as deceased in response to the study letters. Data from the Tasmanian Registry of Births, Deaths and Marriages further indicated that two other patients in the study cohort had died due to a heart attack and cardiac arrest outside hospital; however these deaths were both after the 18-month follow-up period.

3.6.1.1 Recurrent ACS or stenosis

Thirty-three patients (11.1%) had a readmission to the RHH due to recurrent ACS or stenosis; one died in hospital after being readmitted (as above). This cohort consisted of more males than females (84.8% vs 15.2%); the proportion of males being readmitted appeared to be slightly higher than that of the total population (84.8% vs 75.8%). Chi-squared testing showed that there was no significant association between gender and the likelihood of patients having a readmission due to recurrent ACS (p=0.182).

The majority of patients in the readmitted group (84.8%) were recorded as still taking clopidogrel at the time of readmission. Ten patients (30.3%) were taking a PPI. The numbers of cardiovascular risk factors among this group were variable, ranging from two to six. This group of patients also included patients who were previously diagnosed with UA (12.1%), NSTEMI (51.5%) and STEMI (36.4%) on their first ACS presentation. More details of patients readmitted due to recurrent ACS are displayed in Table 3.6.

Table 3.6 Patients' readmissions 18-month post ACS

Variable	Readmission due to ACS or restenosis		
	Number	Percentage	
Number of Readmissions	33		
Clopidogrel use at readmission			
Still taking clopidogrel	28	84.8	
No longer taking clopidogrel as planned	3	9.1	
Not recorded	2	6.1	
Smoking status at readmission			
Stopped smoking	2	6.1	χ^2= 1.9, df=1, p= 0.389
Still smoking	7	21.2	
Unknown	24	72.7	

Table 3.7 shows the relationships between the presence of each cardiovascular risk factor and the likelihood of patients being readmitted due to recurrent ACS. Also presented in the table are the relationships with factors such as patients' type of ACS, medications prescribed upon discharge as well as the type of stent implanted. None of these factors investigated demonstrated a significant association with the likelihood of patients being readmitted for recurrent ACS. As displayed in the table, the only factor that demonstrated a significant relationship was whether the patients were referred to the cardiac rehabilitation service or not ($p < 0.05$). Nonetheless, statistical testing showed that there was no association between patients' cardiac rehabilitation attendance or completion and the likelihood that patients had a readmission for recurrent ACS or stenosis (χ^2= 0.9, df=1, p= 0.339; χ^2= 2.3, df=1, p= 0.133, respectively).

Table 3.7 Patients' risk factors, ACS management, and the likelihood of having an ACS readmission

Variable		Readmission due to recurrent ACS or stenosis		p Value
		No (264)	Yes (33)	
Age	≥ 65 (115)	100 (87.0%)	15 (13.0%)	0.400
	< 65 (182)	164 (90.1%)	18 (9.9%)	
Gender	Male (224)	196 (87.5%)	28 (12.5%)	0.182
	Female (73)	68 (93.2%)	5 (6.8%)	
Smoking at first ACS presentation	Yes (109)	96 (88.1%)	13 (11.9%)	0.733
	No (188)	168 (89.4%)	20 (10.6%)	
History of smoking	Yes (219)	192 (87.7%)	27 (12.3%)	0.263
	No (78)	72 (92.3%)	6 (7.7%)	
Obesity	Yes (99)	92 (92.9%)	7 (7.1%)	0.117
	No (198)	172 (86.9%)	26 (13.1%)	
Dyslipidaemia	Yes (118)	106 (89.8%)	12 (10.2%)	0.675
	No (179)	158 (88.3%)	21 (11.7%)	
HTN	Yes (153)	134 (87.6%)	19 (12.4%)	0.460
	No (144)	130 (90.3%)	14 (9.7%)	
DM	Yes (52)	48 (92.3%)	4 (7.7%)	0.388
	No (245)	216 (88.2%)	29 (11.8%)	
Family history of CAD	Yes (140)	127 (90.7%)	13 (9.3%)	0.345
	No (157)	137 (87.3%)	20 (12.7%)	
Number of cardiovascular risk factors	3 or less (223)	198 (88.8%)	25 (11.2%	0.924
	4 or more (74)	66 (89.2%)	8 (10.8%)	
Discharge diagnosis	NSTEACS (153)	132 (86.3%)	21 (13.7%)	0.139
	STEMI (144)	132 (91.7%)	12 (8.3%)	
Number of ACS guideline medications	3 or less (131)	117 (89.3%)	14 (10.7%)	0.836
	All 4 (166)	147 (88.6%)	19 (11.4%)	
ASA	Yes (259)	259 (88.7%)	33 (11.3%)	0.476
	No (4)	4 (100%)	0 (0%)	
β-blocker	Yes (222)	197 (88.7%)	25 (11.3%)	0.915
	No (74)	66 (89.2%)	8 (10.8%)	
ACEI	Yes (225)	200 (88.9%)	25 (11.1%)	0.971
	No (71)	63 (88.7%)	8 (11.3%)	
Statin	Yes (285)	254 (89.1%)	31 (10.9%)	0.532
	No (12)	10 (83.3%)	2 (16.7%)	
Use of PPI (excluding pantoprazole)	Yes (60)	55 (91.7%)	5 (8.3%)	0.443
	No (237)	209 (88.2%)	28 (11.8%)	
Stent implanted	Yes (228)	206 (90.4%)	22 (9.6%)	0.145
	No (69)	58 (84.1%)	11 (15.9%)	
Cardiac rehabilitation referral	Yes (213)	195 (91.5%)	18 (8.5%)	**0.020**
	No (84)	69 (82.1%)	15 (17.9%)	

3.6.1.2 Readmission due to bleeding

Overall, there were nine patients (3.0%) who were readmitted because of bleeding. However, some of these bleeding readmissions were recorded as secondary to other causes, namely alleged assault (1 patient) and bleeding due to injection of enoxaparin (1 patient). Of the patients readmitted for bleeding, all were recorded as still taking DAT (clopidogrel and aspirin) at the time of readmission, with five of them (55.5%) also taking other drugs that could increase the risk of bleeding (warfarin (n=1), enoxaparin (n=1), both warfarin and enoxaparin (n=1), oral steroid (n=1), SSRI (n=1)). Despite their bleeding episodes, seven out of nine patients in this group were still prescribed clopidogrel at discharge. Table 3.8 presents the details of patients who were readmitted due to bleeding.

Patients who were taking antiplatelets together with other medications that increase the risk of bleeding (anticoagulants, NSAIDs, oral corticosteroids or SSRIs) were more likely to experience a bleeding readmission (7.8% vs 1.7%, χ^2= 6.349, df=1, p= 0.012). However, there was no significant association between readmission due to bleeding and failing to be prescribed a PPI (χ^2= 3.514, df=1, p=0.061). The results actually show that, there was a higher proportion of patients being readmitted due to bleeding in the group who were prescribed with a PPI compared to the group without a PPI (6.1% vs 1.9%, respectively). Nonetheless, it is worth noting that the bleeding assessed in the study included all type of readmissions due to bleeding and was not limited to GI bleeding only. Others factors such patients' age and a history of bleeding did not show a relationship with the risk of a bleeding readmission. Details of patients' bleeding risk factors and the likelihood of having a bleeding readmission are presented in Table 3.9.

Table 3.10 displays the details regarding seven patients who had bleeding while taking clopidogrel that did not lead to hospital readmission; instead this was reported during their outpatient visits or readmissions due to other causes.

Table 3.8 Characteristics of patients experiencing bleeding readmissions (n=9)

Gender	Age	Time of readmission after first ACS presentation	Bleeding details	Smoking on readmission	Concomitant drugs increasing bleeding risk at readmission				PPI at readmission		Still taking clopidogrel after this readmission	Other risk factors for bleeding
					DAT	Warfarin/ Enoxaparin	NSAID/ steroid	SSRI	Admission	Discharge		
M*	67	1 day	GI bleeding, malaena, haematoma	No	Yes	Yes	No	No	No	Yes	Yes	None
M	70	3 month	Upper GI bleeding, malaena	No	Yes	No	No	No	Yes	Yes	Yes	No
		5 month	GI bleeding	No	Yes	No	No	No	No	Yes	Yes	
M	47	3 days	Anterior chest wall haematoma (due to alleged assault)	No	Yes	No	No	Yes	No	No	Yes	None
M	36	9 month	Epistaxis	Yes	Yes	Yes	No	No	Yes	NR	NR	None
M	55	11 days	Bladder haemorrhage	Yes	Yes	No	No	No	Yes	No	Yes	Bladder biopsy
F	66	5 days	Bleeding at enoxaparin injection site	No	Yes	Yes	No	No	No	No	Yes	None
M**	43	5 month	Epistaxis, PR bleeding, haematochezia	Yes	Yes	No	No	No	Yes	NR	NR (self-discharged)	Barrett's oesophagus
F	64	1 month	Malaena	No	Yes	No	Yes	No	Yes	Yes	Yes	Cirrhotic liver disease
		6 month	GI bleeding	No	Yes	No	No	No	No	Yes	No	
M	57	19 days	Epistaxis	Yes	Yes	No	NR	NR	NR	NR	Yes	None

*Readmission due to recurrent ACS as well as bleeding, **Principal diagnosis at this readmission was Barrett's oesophagus, but also noted having nose bleeding, haematochezia and some episodes of rectal bleeding, NR = Not recorded

Table 3.9 Comparison between patients' bleeding risk factors and readmission due to bleeding

Risk factors		Readmission due to bleeding		p Value
		No (288)	Yes (9)	
Patients prescribed a PPI	Yes (83)	78 (93.9%)	5 (6.1%)	0.061
	No (214)	210 (98.1%)	4 (1.9%)	
Prescribed medications that increase risk of bleeding	Clopidogrel + aspirin or clopidogrel alone (233)	229 (98.3%)	4 (1.7%)	**0.005**
	(Clopidogrel + aspirin or clopidogrel alone) + any other meds* (64)	59 (92.2%)	5 (7.8%)	
Patients' age	≥ 65 (115)	112 (97.4%)	3 (2.6%)	0.736
	< 65 (182)	176 (96.7%)	6 (3.3%)	
Recorded with history of GI ulcer/bleeding/GORD	Yes (71)	68 (95.8%)	3 (4.2%)	0.501
	No (226)	220 (97.3%)	6 (2.7%)	
Patients with ≥ 1 risk factors for bleeding**	Yes (185)	177 (95.7%)	8 (4.3%)	0.095
	No (112)	111 (99.1%)	1 (0.9%)	

*Any other medications included: anticoagulants, NSAIDs, oral steroids and SSRIs

** Risk factors including having medications that increased risk of bleeding, advanced age, and history of GI ulcer/bleeding/GORD

Table 3.10 Characteristics of patients experiencing bleeding during treatment with clopidogrel (recorded during outpatient visits) (n=7)

Gender	Age	Time noted with bleeding after first ACS presentation	Bleeding details	Smoking history	Concomitant drug use recorded at follow up			Risk factors for bleeding
					Dual antiplatelet	Drug that increases risk of bleed	PPI	
M	52	2 months	Rectal bleeding	Smoker	Yes	None	No	None
M	60	8 months	Blood stained sputum	Non-smoker	Yes	Warfarin	No	Other disease: pneumonia
M	35	8 months	Taste of blood in mouth	Smoker	Yes	TRACER drug	No	None
F	52	18 months	Post-menopausal vaginal bleeding	Smoker	Unknown	Unknown	Unknown	Atrophic endometrium
M	51	2 months	Haematoma	Smoker	Yes	None	Yes	None
M	82	15 months	Active bleeding	Non-smoker	Yes	None	Yes	None
M	52	3 months	Epistaxis	Smoker	Yes	None	No	None

3.6.2 Smoking status post-ACS

On their first ACS admission, 109 patients (36.7%) were recorded as being current smokers. Following discharge, the smoking status for 71 patients (65.1%) was able to be observed from their outpatient notes or readmission records. Of those who were smokers on the first admission, 42 patients were recorded as still smoking following their first ACS episode.

Table 3.11 Patients' smoking status post-ACS discharge (n=109)

Smoking status*	Number	Percentage
Still smoking	42	38.5
Stopped smoking	29	26.6
Unknown	38	34.9

* Time frames of the smoking status observations differ

3.7 Phase Two Data Collection

A total of 281 patients were mailed a study letter, as 16 patients were known to be deceased based on data collected during phase one of the study. Five letters (1.8%) were returned due to the incorrect address. There were 10 notifications received from the patients or the patients' families that stated that the patients were deceased, no longer at that address, or not able to participate due to other reasons. Thus, the overall response rate was 26.7%. Figure 9 shows a schematic diagram of the patients' recruitment for all parts of the phase two study.

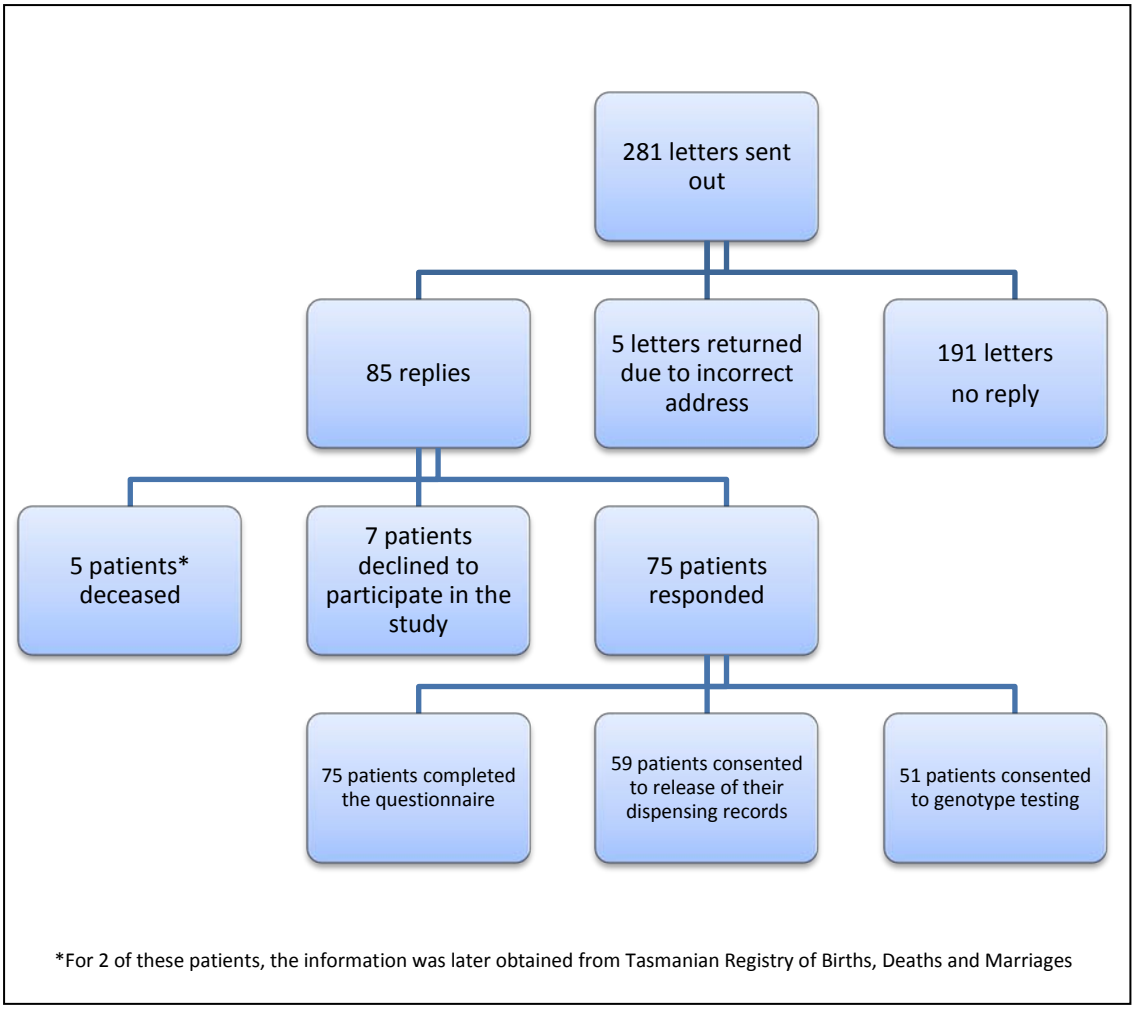


Figure 3.14 Patient recruitment and responses for each part of the phase two study

3.7.1 Questionnaire

Seventy-five patients returned completed questionnaires, giving a response rate of 26.7%. The respondents' demographics compared with those of the entire study cohort are presented in Table 3.12 below.

Table 3.12 Comparison of respondents' characteristics with those of the study cohort

Variable	Respondent (n=75) n (%)	Total Population (n=297) n (%)
Gender		
Male	51 (68.0)	224 (75.4)
Median age (years) (range)	61 (34—88)	61 (28—88)
Type of ACS		
Unstable angina	9 (12.0)	36 (12.1)
NSTEMI	24 (32.0)	117 (39.4)
STEMI	42 (56.0)	144 (48.5)
Reported readmission		
Recurrent ACS	12 (16.0)	
Bleeding	1 (1.3)	
Number of medications		
Median (Range)	7 (0 – 16)	
Cardiac rehabilitation referral	45 (60.0%)	
Finished all the sessions	25 (33.3%)	
Did not complete the sessions	8 (10.6%)	
Did not attend at all	12 (16.0%)	

This subgroup, which will henceforth be referred as respondents, consisted of more men than women (68% vs 32%), a similar trend to that seen within the total population. Approximately half of the respondents (54.6%) reported still taking clopidogrel. Of those who had stopped taking the drug (45.3%), almost all stated that their discontinuation was due to their doctor's instructions (82.4%). The remaining stated that they stopped taking the drug because their doctor changed it to another medication, decided not to take it anymore, or because the price of the medication was too expensive. Twelve respondents (16.0%) reported having an ACS readmission to another hospital apart from the RHH. However, most of these admissions were not relevant to the study outcome e.g. the readmission time was beyond the study observation period or the readmission was only precautionary. Fifteen respondents (20.0%) stated that they had a bleeding problem while

they were taking clopidogrel, the majority of which were bruises and nose bleeding. The only patient who reported having a bleeding readmission had been admitted to the RHH so their details had been obtained from the DMR; two other respondents who had a bleeding readmission in their DMR did not report this on the questionnaire. Following their episode of ACS, 19 patients (25.3%) in this cohort stated that they were still smoking, and up to 30 cigarettes in a day. Almost half of respondents reported drinking alcohol (49.3%), though most were only drinking one standard drink in a week. About two-thirds of the respondents (60%) said that they had been referred to attend cardiac rehabilitation, but only half reported completing all of the sessions. Eighty per cent were still taking at least three medications recommended for patients post ACS.

Seventy-two patients returned a completed MARS questionnaire (96.0%), among these patients 73.6% of them having the maximum MARS score of 25.

3.7.2 Community pharmacy dispensing records

Fifty-nine patients (19.9%) consented to the release of their dispensing records by their regular community pharmacy/pharmacies. Dispensing records for 56 patients (18.9%) were able to be obtained, including two patients who had records at two pharmacies. Eight patients (14.3%) had no records of having clopidogrel dispensed within the observation period, even though one of them was a patient whose dispensing records were able to be obtained from his two regular community pharmacies. For these eight patients, six were planned to take clopidogrel for 12 months or more. Furthermore, even though there were no records of clopidogrel dispensing for these patients, three reported still taking clopidogrel in the questionnaire and five had a score of 25 for the MARS questionnaire.

Table 3.13 presents the respondents' persistence and adherence rates during the 18 month observation period. The data show that there was a high proportion of the respondents who were persistent with therapy (73.3%). Even though the median rate of adherence was high (88.9%), only half of the patients were adherent according to the study definition (55.4%). For the majority of respondents, the initial plan was that they were to take clopidogrel for 12 months (73.2%). Among this sub-group, as for the respondents overall, the number of persistent patients were high (78.0%) but those who were adherent was lower (58.5%).

From the respondents' dispensing records, the concomitant use of medications that can increase the risk of bleeding and the use of gastroprotective agents was observed. From 48 respondents who had clopidogrel dispensing records, 15 were taking antiplatelets as well as other medications that can increase the risk of bleeding, but only five were also prescribed a PPI or H2 antagonist.

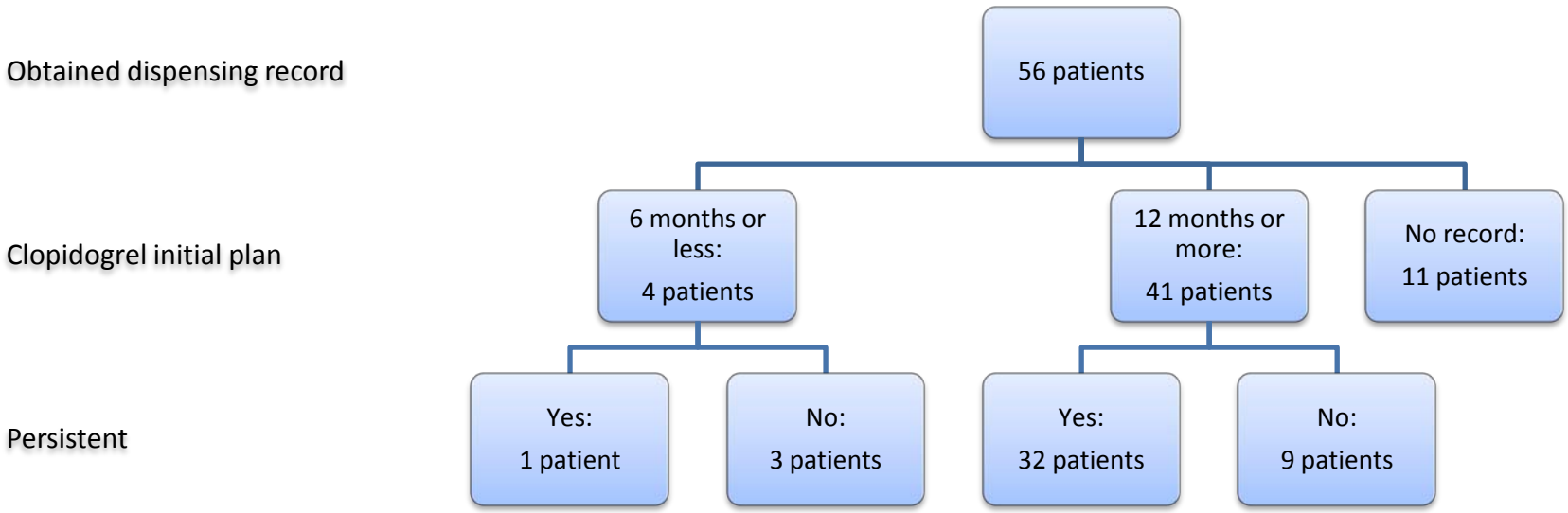


Figure 3.15 Patients' initial plan and the actual therapy with clopidogrel

Table 3.13 Adherence and persistence

Intended duration	n	Median actual duration (range)	Number of persistent patients (%)	Median adherence (range)	Number of adherent patients (%)
6 months or less	4	1.0 months (0 – 18.2)	1 (25.0)	51.2% (0 – 103.7)	2(50.0)
12 or indefinite	41	14.2 months (0 – 18.2)	32 (78.0)	91.1% (0 – 117.1)	24 (58.5)
unknown	11	17.2 months (0 – 18.1)	N/A	78.2% (0 – 108.0)	5 (45.5)
Total	**56**	**N/A**	**33 (73.3)**	**88.9% (0 – 117.1)**	**31 (55.4)**

Table 3.14 and 3.15 15 show that none of the factors investigated (age, gender, the number of medications patients took and cardiac risk factors) influenced patients' adherence or persistence.

Table 3.14 The effect of patient factors on adherence

Variable		Adherent		p Value
		No (25)	Yes (31)	
Age	< 65 years old (32)	14 (43.8%)	18 (56.3%)	0.877
	≥ 65 years old (24)	11 (45.8%)	13 (54.2%)	
Gender	Male (39)	17 (43.6%)	22 (56.4%)	0.810
	Female (17)	8 (47.1%)	9 (52.9%)	
Number of medications on discharge	Less than 6 (23)	10 (43.5%)	13 (56.5%)	0.884
	6 or more (33)	15 (45.5%)	18 (54.5%)	
Number of cardiac risk factors	Less than 3 (24)	9 (37.5%)	15 (62.5%)	0.352
	3 or more (32)	16 (50.0%)	16 (50.0%)	

Table 3.15 The effect of patient factors on persistence

Variable		Persistent		p Value
		No (12)	Yes (33)	
Age	< 65 years old (28)	7 (25.0%)	21 (75.0%)	0.746
	≥ 65 years old (17)	5 (29.4%)	12 (70.6%)	
Gender	Male (30)	8 (26.7%)	22 (73.3%)	1.000
	Female (15)	4 (26.7%)	11 (73.3%)	
Number of medications on discharge	Less than 6 (22)	6 (27.3%)	16 (72.7%)	0.928
	6 or more (23)	6 (26.1%)	17 (73.9%)	
Number of cardiac risk factors	Less than 3 (21)	4 (19.0%)	17 (81.0%)	0.280
	3 or more (24)	8 (33.3%)	16 (66.7%)	

Although there were numerical trends, there was no statistically significant between non-adherence and being readmitted due to recurrent ACS, as well as being adherent or persistent and the risk of having a bleeding readmission. These trends, and more on the relationship between patients' adherence or persistence and the likelihood of having a readmission, are presented in Table 3.16 below

Table 3.16 Relationship between patients' adherence or persistence and their outcome

Variable		Readmission		p Value
		Readmission due to recurrent ACS		
		Yes (6)	**No (50)**	
Adherent	Yes (31)	3 (9.7%)	28 (90.3%)	0.780
	No (25)	3 (12.0%)	22 (88.0%)	
Persistent	Yes (33)	4 (12.1%)	29 (87.9%)	0.721
	No (12)	1 (8.3%)	11 (91.7%)	
		Readmission due to bleeding		
		Yes (3)	**No (53)**	
Adherent	Yes (31)	2 (6.5%)	29 (93.5%)	0.685
	No (25)	1 (4.0%)	24 (96.0%)	
Persistent	Yes (33)	2 (6.1%)	31 (93.9%)	0.383
	No (12)	0 (0.0%)	12 (100.0%)	

3.7.3 Genotype testing

Of 51 patients (17.1%) who consented to genotype testing and were sent a test pack, only one failed to send their sample to the DHI Laboratory.

Table 3.17 shows patients' genotype status classified based on the functional allele carrier status, while Table 3.18 shows the genotype status of patients based on their metaboliser phenotype.

Table 3.17 CYP2C19 results classified according to patients' functional allele carrier status (n=50)

Allele carrier	Normal function	Loss-of-function allele	
		CYP2C19*1/*2	**CYP2C19*2/*2**
CYP2C19*2	34 (68.0%)	11 (22.0%)	5 (10.0%)
		CYP2C19*1/*3	**CYP2C19*3/*3**
CYP2C19*3	50 (100%)	-	-
	Normal function	**Gain-of-function allele**	
		CYP2C19*1/*17	**CYP2C19*17/*17**
CYP2C19*17	31 (62.0%)	14 (28.0%)	5 (10.0%)

Table 3.18 CYP2C19 results classified according to patients' metaboliser phenotype (n=50)

Phenotype status	Number	Percentage
Extensive metabolisers	21	42.0
Poor metabolisers	10	20.0
Rapid metabolisers	13	26.0
Unknown	6	12.0

In attempt to relate patients' genotype profile with their outcome, both types of classifications were used (Table 3.19 and Table 3.20). Six patients who agreed to participate in genotype testing had readmissions due to recurrent ACS or restenosis. Among those patients, four possessed the wild type allele, and only one possessed a loss-of-function allele (and was therefore a poor metaboliser), while the other had a CYP2C19*17 allele. There was no relationship between either possession of a loss-of-function allele or being a poor metaboliser and the risk of readmission due to ACS or stenosis.

Table 3.19 Patients' genotype status and their likelihood of readmission

Allele carrier status		Readmission		p Value
		Readmission due to recurrent ACS		
		Yes (6)	**No (44)**	
Loss-of-function allele	Yes (16)	1 (6.3%)	15 (93.7%)	χ^2= 0.7, df=1, p= 0.391
	No (34)	5 (14.7%)	29 (85.3%)	
		Readmission due to bleeding		
		Yes (3)	**No (47)**	
Gain-of-function allele	Yes (19)	3 (15.8%)	16 (84.2%)	χ^2= 5.2, df=1, p= **0. 022**
	No (31)	0 (0%)	31 (100%)	

Conversely, a correlation was shown between both possession of a gain-of-function allele and being a rapid metaboliser and the risk of a bleeding readmission. Among patients who had a bleeding readmission, only three consented to genotype testing. Interestingly, all of these three patients possessed a gain-of-function allele; one was carrier of a single *17 allele (CYP2C19*1/*17) and the other was a *17 homozygote (CYP2C19*17/*17). The other patient who had a bleeding readmission possessed the *17 allele and one loss-of-function allele (CYP2C19*2/*17). There was a significant difference in outcomes between those with and without a gain-of-function allele in terms of readmissions due to bleeding (p= 0. 022).

Table 3.20 Patients phenotype status and their likelihood having a readmission

Phenotype		Readmission		p Value
		Readmission due to bleeding		
		Yes (2)	**No (42)**	
Rapid metabolisers	Yes (13)	2 (15.4%)	11 (84.6%)	χ^2= 4.9, df=1, p= **0.025**
	No* (31)	0 (0.0%)	31 (100.0%)	
		Readmission due to recurrent ACS		
		Yes (6)	**No (38)**	
Poor metabolisers	Yes (10)	1 (10.0%)	9 (90.0%)	χ^2= 0.1, df=1, p= 0. 703
	No** (34)	5 (14.7%)	29 (85.3%)	

*Patients who were extensive metabolisers and poor metabolisers

** Patients who were extensive metabolisers and rapid metabolisers

Comparing the readmission rates between patients who were extensive or poor metabolisers and rapid metabolisers, those who were rapid metabolisers were more likely

to be readmitted due to bleeding compared to those who were not a rapid metabolisers (p = 0.025) (Table 3.20). Patients whose phenotypes were unknown were excluded from this analysis.

Chapter 4 – Discussion

This study was designed to assess the outcomes of clopidogrel therapy among ACS patients in Southern Tasmania. Within the 18-month follow-up period, 11% of patients were readmitted due to recurrent ACS and stenosis, while the rate of readmission due to bleeding was 3%. Previous studies have demonstrated variable rates of recurrent ACS or death and bleeding after treatment with clopidogrel using different follow-up periods[112 114 179-181 191]. In order to be able to compare our results to those of other studies, it is important to firstly compare the characteristics of the patients in the various studies. In addition, due to the focus of our study being patients with a first episode of ACS, it was also necessary to evaluate how the patients were managed during their hospital admission as this was likely to impact significantly on their subsequent outcomes.

4.1 Population Characteristics

The incidence of ischaemic heart disease is higher among men than women[192 193]. As expected, and similar to previous studies[112 114 180 181], the ratio of males to females in our population was three to one. Our results are also consistent with the finding by Ostini et al. that usage of clopidogrel was higher in males than in females[194].

The overall age of patients in this study was slightly younger (median: 61 years) than that of other study cohorts[112 114 179-181 191]. This was expected given the patients in our study were those with a first episode of ACS. Female patients admitted to the RHH with their first ACS episode were significantly older than their male counterparts. This result also matches the established data[192 193 195 196]. The incidence of any ischaemic heart disease has been known to increase sharply with age, but previous data have also documented that females are less prone to develop ischaemic heart disease at any given age[193 196 197].

A large proportion of the study patients had exposure to at least one of the major risk factors for atherosclerosis – which subsequently can lead to ACS – including dyslipidaemia, hypertension, cigarette use and diabetes[198].

Although these risk factors occurred commonly in the other studies[114 179-181], the overall prevalence of the risk factors in our study was slightly lower. For instance, patients with diabetes, which is generally found in about 20-35% of ACS patients[116], accounted for less than 20% of the patients in this study. The only risk factor that appeared at a higher rate in the present study compared to other studies was smoking[199 200]. Smoking is a well-recognised risk factor for CAD according to many epidemiologic studies[201-204] and within our cohort the exposure to smoking was the most common risk factor observed, present in 73% of the patients (about 37% were recorded as a current smokers). This proportion is relatively high compared to the national smoking rate. A survey conducted in 2004 by the Australian Institute of Health and Welfare revealed that about 4 million adults, or approximately 19% of the total adult population, were current smokers [205]. In regards to the presence of medical conditions, hypertension was the most prevalent risk factor seen in the study (53% of patients), followed by dyslipidaemia (40% of patients). This demonstrates how important the diagnosis of these two conditions is and for the patients to be receiving effective treatment to lower blood pressure or cholesterol. Despite the high frequency of cardiovascular risk factors, 38 patients (13%) were not taking any primary prevention medications. This suggests that the use of evidence-based preventive therapy in patients presenting with ACS is suboptimal. Yusuf et al. recently reported that a similar trend occurring around the world[206]. Among the possible reasons proposed for this finding, those that may be relevant to the patients in this study are that risk factor identification is not routinely conducted and non-adherence on the part of the patients.

Having another form of cardiac disease increases the risk of an ACS[198]. In our study the proportion of patients with other cardiac diseases was low, particularly in comparison to that in the larger cohorts of patients in previous studies[112 179 180]. This might be related to the inclusion criteria of this study, which limited patients to those with a first ACS episode.

Comparing the proportion of each type of ACS (STEMI, NSTEMI and UA) in our cohort, it seems that the patients in our study were more likely to have more severe types of ACS (STEMI or NSTEMI) compared to other studies. This was owing to the fact that our study criteria limited patients to those with ACS and taking clopidogrel. It has been shown elsewhere that, despite guidelines, only those with a greater risk of recurrent thrombosis were prescribed this medication, with or without aspirin[70 83]. This is further supported by

the researcher's observation that most of the patients with UA identified in the screening process were subsequently excluded from the study because they were not receiving clopidogrel at discharge.

Overall, the patients in our study cohort seemed to display a lower rate of risk factors compared with other similar studies, possibly related to the patient selection process.

4.2 Patients' ACS Management

Patients' length of hospital stay can be a parameter of a successful treatment[207]. In this study, although patients were diagnosed with different types of ACS, each group shared a similar average hospital stay of three days. Although there is no international guideline that can be used to justify whether the length of stay in the present study was good or not, the results seems to show no complication from in-patient management in most of the patients.

Knowing how patients were treated during their in-patient stay will be helpful in determining the likelihood of their ACS outcome. According to the guidelines[83], patients diagnosed with STEMI are recommended to have a PCI or receive fibrinolysis therapy (reperfusion therapy) soon after hospital presentation and those with high risk of NSTEACS are recommended to undergo early PCI. Our results show that most patients in our study received this treatment.

In our study, the prescribing rates for each of the four recommended medications at discharge indicated non-compliance with the guidelines in that they did not achieve 100% but they closely matched the data in the Australian DMACS study[208]. Of particular note, the results showed a high prescribing rate for statins, but lower rates for ACEIs/ARBs and β-blockers. Most notably, the rate of β-blocker prescription in our study was lower than the previous Australian data regarding the use of the drug in ACS patients from 2006-2007 (when β-blocker use was 83%)[199].

Table 4.1 displays the rates of the guideline-recommended medication prescribing in our study compared to other studies.

Table 4.1 Comparison of guideline-recommended medication use

Guideline-recommended medications prescribed at discharge	Percentage use		
	Present study	Aliprandi-Costa et al.[199]	Wai et al. (DMACS)[208]
Anti-platelet agent(s)	98*	93	97
Statin	96	86	92
ACEI/ARB	76	73	78
β-blocker	75	83	75

*The percentage of DAT use, 100% received at least 1 antiplatelet (clopidogrel)

In similarity with the findings reported by Chew et al., our study also showed that patients with the more severe classification of ACS (STEMI) were more likely to receive all four recommended medications compare to other groups. The majority of our study patients had a stent placed (77%), regardless of the type of ACS they had. According to the guidelines, patients who undergo stent placement should continue taking clopidogrel for up to 12 months[83]. Among those who were stented and had a recorded plan for their clopidogrel therapy, the majority (82%) were to take clopidogrel for 12 months or longer. Most of the remaining patients did not have a clearly recorded clopidogrel therapy plan.

Numerous studies have reported that attending cardiac rehabilitation after ACS or PCI is associated with reduced mortality and morbidity rates[209-212]. Patients' participation in a cardiac rehabilitation program is reported to produce a similar benefit as treatment with statins, aspirin, and β-blockers[212 213]. The program facilitates patients' recovery and improves their quality of life following their cardiac events[214]. In recent years, there has been a rapid growth in the number of available programs throughout Australia[215]. Clinical practice guidelines in Australia[83] recommend healthcare professionals to vigorously refer their patients to cardiac rehabilitation. A strong recommendation to a rehabilitation program given by healthcare professionals has been reported to increase the likelihood of patients' attendance[212 216-219]. Despite this finding, only about 70% of the patient cohort was referred to cardiac rehabilitation in our study. Factors such as age, patients' risk factors and condition have been proposed to affect patients' likelihood to be invited to join rehabilitation programs[209 217 220]. However, our study showed that these factors did not seem to influence patients' referral to cardiac rehabilitation. Importantly, there was evidence of incomplete documentation of referral to cardiac rehabilitation, with several patients having been found to have attended rehabilitation sessions despite no

documentation of their referral being found in their DMR. Although these individual patients were not disadvantaged as a referral obviously occurred at some point despite the lack of documentation, this does not negate the systemic issue - the risk of patients 'falling through the gaps' and failing to be appropriately referred if the assumption is made by health care professionals that someone else has accepted responsibility for the task.

A second significant issue was that our results showed that partial or full attendance at the rehabilitation program was low, particularly compared to national data. In Australia, a survey found that cardiac rehabilitation attendance is high compared to other developed countries (30%-60% vs 28%-40%)[221]. Despite the reported benefits of the rehabilitation programs, data from other studies also show that many patients do not attend at all or drop out early after attending only one or two sessions[215 221]. The higher number of cardiac rehabilitation sessions attendance is associated with the better long-term outcomes. The result from the present study found only 20% of patients who invited to the rehabilitation program completed the all sessions. This might be due to several reasons, such as long travelling distances and time conflicts, or it might have been due to the lack of interest among patients. Additionally, patients who have suffered cardiac problem often show a marked reduction in their self-confidence and alterations to their self-image[222]. Patients also tend to have misconceptions and have little knowledge about the rehabilitation [223]. It again suggests that health professionals need to be more proactive in encouraging cardiac rehabilitation attendance; review of the literature shows that strong physician recommendation may increase patients' attendance to cardiac rehabilitation[223].

Based on these findings, the overall in-patient and immediate post-discharge management in this study appeared to follow the guideline recommendations. Nonetheless, the prescribing rates of ACEIs/ARBs and β-blockers were low compared to some contemporary Australian data[199]. The primary objective of this study was not to investigate the reasons for the underuse of these medications, but there was a possibility that patients did not receive the medications due to the presence of CIs, which may not have been recorded in their DMR. Hence, there is again room for improvement regarding documentation in medical records. This again highlights the need for improved interprofessional communication processes to ensure all health professionals are aware of

the reasons medications are prescribed, or not. Another possibility regarding the low use of β-blockers might due to individual prescriber non-belief in the evidence underlying the guidelines itself[224]. This trend has been shown in a European study regarding physicians' acceptance of guideline recommendation, in which more than 10% physicians involved in the study stated that they did not agree with the content of the surveyed guidelines[225]. On a positive note, our findings support that the other aspects of ACS management of RHH patients (apart from the prescribing of clopidogrel) was of a sufficiently high standard that our clinical outcomes data could be confidently compared with those of large-scale international studies.

4.3 Therapy Outcomes

4.3.1 Readmission due to recurrent ACS

During the 18-month follow-up period, the rate of hospital readmission due to ACS or restenosis in this study was 11%. Few studies had a follow-up period similar to our study; hence it was difficult to make a direct comparison to previous findings. Table 4.2 displays some clinical trials that have similar characteristics to our study and their results. Even though the rate of the readmission in our study appears to be broadly in line with the previous studies[112 114 179-181], it is perhaps higher than what would have been expected. Several factors need to be taken into account when considering this finding, including the outcome observed, the patients' risk factors and the different clinical settings used in the various studies. In most of the other studies, the outcomes were broader, including ischaemic stroke, unplanned revascularisation and stent thrombosis. Also, the patients in our cohort appeared to have a lower rate of overall risk factors (e.g. a younger median age, first episode of ACS) compared to the clinical trials. The clinical trial investigators were also able to follow up the patients' outcomes directly. In our study, since we limited the patient selection criteria to those with ACS, we only observed the outcomes of hospital readmission due to ACS or restenosis. Although data regarding death rates were able to be obtained from another source, the data regarding hospital readmissions was mainly dependent on the records from one major public hospital, RHH. This was because not all of the patients contacted in the second phase of the study to confirm their outcomes of therapy with clopidogrel responded. Therefore, we were not able to ascertain for all patients if they had had a readmission to another hospital (e.g. a private hospital). In the clinical trials, however, the researchers were able to have direct contact with the study participants by conducting a scheduled examination[112 114] or via telephone contact[180]. Based on these considerations, the observed rate of readmission in our study might be an underestimate of the true rate.

The reason for the higher than expected rate of ischaemic events is uncertain, as inpatient management appeared to be of a high standard. This suggests that there could be some problems with post-discharge management. In the present study, the post discharge

management assessed included patients' attendance at rehabilitation programs and how the patients took their medications (discussed later in section 4.4.1), but data on other aspects such as patients' lifestyle were not investigated. Some trends, however, particularly the high ongoing smoking rate, seem to suggest that this might be a concern. A report has suggested that changes to a patient's diet, exercise and smoking habits should be prioritised as high as adherence to a drug regimen following an ACS event[226]. If the true rate of patients having recurrent ACS events was actually higher than expected, one possible hypothesis to explain this might be that it is related to patients' poor lifestyle choices and/or their medication-taking behaviour post-discharge. A future study assessing patients' lifestyles post-discharge is needed to confirm this hypothesis, and therefore the need for additional attention in promoting healthy choices to this patient group.

Table 4.2 Comparison of patient characteristic and adverse outcomes between the present study and other studies

Study	Patient characteristics	Clinical outcome observed	Percentage of outcome*	Observation period
Present study	First episode of ACS treated with clopidogrel	Readmission due to recurrent ACS or restenosis	11.1%	18 months
Migliorini et al.[112]	CAD patients who underwent PCI and later taking DAT	Cardiac mortality, stent thrombosis	13.9%	24 months
Bliden et al.[179]	Patients undergoing PCI taking clopidogrel	Death, myocardial infarction, stent thrombosis, stroke, or ischaemia	12%	12 months
Breet et al.[180]	Patients with CAD undergoing PCI taking clopidogrel	Death, reinfarction, stent thrombosis and ischaemic stroke	8.9%	12 months
Marcucci et al.[114]	Patients with ACS undergoing PCI taking DAT	Cardiovascular death, reinfarction, revascularisation	6.4%	12 months
Zeymer et al.[181]	ACS patients treated with ASA or DAT	Death, reinfarction, and stroke	6.4%	12 months

***The percentage refers to the rate of outcome observed**

A number of reports have been published evaluating variability in the response to clopidogrel therapy and assessing the factors that might affect its antiplatelet activity[1 12 13 96]. The initial aim of the study was to observe the influence of a variety of factors on the

outcomes of clopidogrel therapy in the real world setting. Even though the majority of patients (28 out of 33 patients) who were readmitted were still taking clopidogrel at the time of readmission, we were not able to link whether the readmission was associated with clopidogrel treatment. The main obstacle for this was the limited number of patients, which led to an inability to perform multivariate analyses.

Several factors suggested in the literature to contribute to the likelihood of patients with ACS having a subsequent readmission were assessed. For instance, previous reports have proposed that women have a higher risk of readmission after ACS than men[227]. The present study, however, showed that there were a greater proportion of males having a readmission. Nonetheless, there was no statistically significant association demonstrated between gender and the likelihood of patients having an ACS readmission. Due to the data collection relying solely on hospital records, we were not able to obtain all information regarding patients' smoking status. Studies have suggested that smoking cessation may offer a better benefit in decreasing the subsequent morbidity and mortality in patients with previous ACS than any pharmacologic treatment[228 229]. Of concern, among patients who had recurrent ACS and for whom information was available, most (7 out of 9) were recorded as still smoking following their first ACS episode and at the time of their second event.

Furthermore, observing patients overall (those with and without recurrent ACS) who were recorded as a smoker at their first ACS presentation, 39% (46 out of 109) were found to still be smoking sometime after their ACS episode. This finding is disturbing and more effort needs to be made in order to encourage patients to help themselves to cease smoking. A study on the interaction between physicians and their smoker patients showed that many physicians still had not asked their patient about their smoking status (which perhaps partly explains the high rate of 'unknown' results in our study) and only a small number of smokers had been advised by their physician to quit[230]. Another study regarding the involvement of pharmacists in assisting patients to quit smoking also indicated a low intervention rate[231]. Thus, healthcare practitioners need to be more active in offering counselling interventions at discharge or post-discharge.

Despite the results showing that patients with STEMI were more likely to be treated as recommended by the guidelines (e.g. more likely to receive all four guideline medications

at discharge), the statistical tests did not show any difference between ACS type in the discharge diagnosis, or any individual medical therapies, and the risk of having a subsequent readmission. Hypertension is another risk factor that increases the likelihood of patients having a readmission for MI[195]. Yet, this also was not apparent in our study. Overall, the statistical analysis failed to show any difference between those having risk factors being readmitted due to recurrent ACS or restenosis and those with no risk factors. The only factor that seemed to have an association with patients being readmitted was whether the patient was referred to cardiac rehabilitation or not ($p = 0.020$). Nonetheless, there was no relationship between patients' actual cardiac rehabilitation attendance or completion and the likelihood of patients having a recurrent ACS or stenosis. Cardiac rehabilitation is an important component of the current multidisciplinary approach to the management of patients with various presentations of ACS[209]. Following our finding that there were low numbers of patients referred to rehabilitation program with fewer then attended the program, strategies are needed to increase the awareness among the health care providers to be more involved in promoting the cardiac rehabilitation program to the patients. Cardiac rehabilitation might also be one of the answers to help smoker patients with their attempts at smoking cessation.

4.3.2 Readmission due to bleeding

The percentage of patients readmitted to hospital due to bleeding in this cohort was 3%. This is comparable to, though slightly lower than the results from the clinical trial done by Breet et al.[180] (5%), and also those of the retrospective observational study done by Ng et al. (4%)[56]. It needs to be noted, however, that the observation period was again different to these studies (shown in Table 4.3). As it was performed in clinical trial circumstances, Breet et al. excluded those with a high risk of bleeding (e.g. patients taking other drugs known to increase platelet activity, patients with a low platelet count), while our results showed that about 40% of the patients in our cohort had at least one risk factor of bleeding (age≥ 65 years, treated with medications that increase the risk of bleeding, history of GI ulcer/GORD). It is also important to distinguish the definition of bleeding used in our study and the other studies. In our study, the bleeding adverse outcome was defined as any bleeding that resulted in hospital readmission, thus such bleeding reported during an outpatient visit was not included. Our study was therefore designed to capture

primarily major bleeding. Nevertheless, it seems to be reasonable to say that the incidence of bleeding in our study was low for a 'real world' study. Table 4.3 shows the comparison between our study and the other studies done previously.

Several studies have clearly found that the combination of clopidogrel plus aspirin is more effective in ACS than aspirin therapy alone[31 232]. However, the combination therapy is also associated with an increased risk of bleeding[53 77 233]. In a report based on the CHARISMA trial, Berger et al. reported that the most common types of bleeding seen in patients treated with clopidogrel and aspirin were GI bleeds, followed by intracranial bleeding and bleeding related to a surgical procedure[234]. This was also confirmed by several other reports[46 51 54]. The well-anticipated risk of GI bleeding was also seen in our population, with among 9 patients being readmitted due to bleeding, 4 of them were GI related bleeds. However, it should be noted that from the details of bleeding recorded, some of the patients had a bleeding event that was not solely an adverse outcome of clopidogrel therapy (e.g. chest wall haematoma due to an alleged assault).

The most important finding of this aspect of the study was that a higher risk of bleeding was apparent in patients who were not taking clopidogrel alone, but in combination with other medications that increased their bleeding risk. This suggests that these are the patients who require most intervention, monitoring and routine review of their ongoing need for clopidogrel, as well as other medications that increase the risk of bleeding.

Table 4.3 Comparison of bleeding rates between the present study and other studies

Study	Study type	Patients characteristics and bleeding risk factors	Outcome observed	Observation period	Percentage of outcome*
Present study	Observational retrospective study	age 65 years or over prescribed with DAT/ clopidogrel only + other medications** history of having GI bleeding/ulcer or GORD	Readmission due to any bleeding	18 months	3.0%
Breet et al.[180]	Clinical trial	stented patients treated with DAT none were using concomitant medications known to affect platelet function (except ASA) patients with platelet function disorder were excluded	Major and minor bleeding	12 months	5.1%
Berger et al.[234]	CHARISMA trial review	none had high risk of bleeding (e.g., severe hepatic insufficiency, current peptic ulceration) none had previous severe bleeding (e.g., GI bleeding) none were receiving dipyridamole or warfarin	Major and minor bleeding (as defined by GUSTO)	28 months	3.1%
Ray et al.[235]	Retrospective cohort study	patients with ACS or plan for revascularisation treated with clopidogrel not treated with PPI	Hospitalisation for GI bleeding	12 months	1.2%
Ng et al.[56]	Observational retrospective study	patients prescribed DAT for any indications during 2001-2006 patients with concomitant use of antithrombotic agents were excluded	Upper GI bleeding	At any point the bleeding occurred before March 2007	4.0%

NR: Not reported

***The percentage refers to the rate of outcome observed**

****Other medications include anticoagulants, NSAIDs, oral steroids and SSRIss**

4.4 Factors Potentially Influencing the Outcomes of Clopidogrel Therapy

As discussed earlier, several factors have been proposed to influence the outcomes of therapy with clopidogrel. In this study, the data regarding some of these factors (e.g. adherence, genotype status) were collected with the initial aim of relating them with the patient outcomes.

4.4.1 Adherence and Persistence

Despite the many theories that have emerged regarding factors that might lead to variability in the outcomes of clopidogrel therapy, the basic issue that needs to be ascertained is whether the medication has been taken by the patient. Therefore, when assessing the variable outcomes of clopidogrel, adherence and persistence with therapy are two important issues that need to be examined, particularly for studies outside of the closely monitored trial setting.

Unfortunately, only 20% of the patients in our study consented to the release of their dispensing records by their regular community pharmacy or pharmacies. Therefore, we could not observe the overall adherence and persistence for the entire patient group during their treatment with clopidogrel and relate it to their outcome. Some overall trends were apparent, however (Table 3.16). Although not statistically significant, the results show that the rate of readmission due to bleeding tended to be greater in both groups of adherent patients and persistent patients. This is intuitive, in that people who take the medication regularly and for a longer period of time (i.e. those who are adherent and persistent), have a greater exposure to the drug. As stated earlier in the first chapter, one of the limitations of treatment with clopidogrel is the irreversibility of its inhibitory effect on platelets, which may lead to bleeding events. Therefore, for such medication like this, beside encouraging patients to follow the prescription regimen, clinicians also need to be aware of the adverse events that might occur and need to keep monitoring the patients for the presence of additional factors that increase patients' risk of bleeding (e.g. concomitant drug use).

On the other hand, non-adherence and non-persistence to prescribed medication treatments have been acknowledged to be the most common medical problem encountered[168]. The clinical outcomes of treatment are not only the results of how patients take their medication, but also how long they stay taking the medication. In regards to clopidogrel treatment, the early discontinuation of the medication is reported commonly among patients after having stent implantation[236]. In the PCI-CURE study, it was found that 9.7% of patients stopped taking clopidogrel during the 9 months follow-up after their PCI procedure[51]. In the Prospective Registry Evaluating Myocardial Infarction: Event Recovery (PREMIER) registry, there were 16% of patients who did not take clopidogrel 30 days following their stent implantation[175].

In our study, the results at the time of discharge (see 3.5.2) showed that the planned duration of clopidogrel therapy varied among study patients, ranging from only 1 month to indefinite, with some of the patients not having the therapy plan recorded. Comparing the actual therapy plan and the initial plan, our results found that the proportion of patients who continued to take the drug for the planned period (persistent patients) was 73%. Although the proportion was high, the fact that there was almost 30% of patients who discontinued the drug within their planned duration of treatment is worrying as early discontinuation of clopidogrel is associated with ischaemic events and potentially devastating stent thrombosis[175 237].

Of particular note, among patients who were planned to take clopidogrel for 12 months or longer, there were 6 patients (15%) recorded as not filling a single clopidogrel prescription during the 18 month observation period following their ACS hospital discharge. All of these patients were stented, with the majority being diagnosed with STEMI. The tendency for patients to stop taking clopidogrel following their PCI has also been reported previously in other studies [51 175 237-239]. One of the main concerns of not taking an antiplatelet agent after stent implantation is the risk of stent thrombosis, which may lead to subsequent MI or death[236 240]. This concern has been proved by Ho et al., whose study results showed that ACS patients who stopped taking clopidogrel after the initial 90 days of therapy were more likely to have a subsequent AMI or increased risk of mortality compared to patients who discontinued the treatment later[237].

Some of the respondents for whom no dispensing prescribing records for clopidogrel were found stated on the questionnaire that they were still taking clopidogrel. However, the question was referring to their clopidogrel therapy at the time they filled the questionnaire, not necessarily in their 18 months post-discharge for when the dispensing data were reviewed. Considering the patients' conditions (e.g., had stent, MI) it is unlikely that their doctor had discontinued their clopidogrel therapy. Also, given that these patients were willing to give access to their dispensing records and therefore were perhaps more engaged with their health care, it was expected that they would also have had good adherence and persistence. While there is some possibility that these patients had their prescription filled in other pharmacies and neglected to inform the researcher of this fact, this finding is worth further exploration.

One of the limitations of assessing patients' persistence in this study was that the data used on the therapy plan was only that obtained from the patients' DMR at time of discharge. Therefore, we were not able to detect if there was any change in the patients' therapy plan, and whether the patients were later instructed to take clopidogrel for longer or shorter than the initial duration plan. For medications such as clopidogrel, where there usually a definite duration of treatment, it is recommended that future research attempts to gather information from patients' health providers to determine whether there was a subsequent change in their patient's treatment plan. It was not feasible for a retrospective study like the present study to ask the patients regarding any changes in their therapy plans, due to the possible inaccuracy and bias of patients' memories.

It is also recognised that adherence with chronic medications, especially those without obvious effects for the patient, is often low[167 174]. Conversely, the median adherence rate in this study was actually high (89%). However, it is important to note that the adherence results varied from 0 to more than 100%, since the amount of medication filled for patients might exceed the sum of the days over which each prescription was filled. Therefore, the median adherence value might have been influenced by the high adherence rates of some patients (e.g. 18 patients had an adherence rate of more than 100%). Further analysis assessing the proportion of patients who were adherent indicated that a low proportion of patients were actually adherent according to our definition (55%).

Numerous studies have tried to define independent factors (e.g., gender, age, medical conditions) that might contribute to patients' adherence or persistence with therapy. However, the results are still not consistent regarding the definite factors that actually link to poor or good adherence. Our study also failed to show relationships between several factors such as gender, age, the number of medications patients took and patients' adherence or persistence (Table 3.14 and Table 3.15).

In our attempt to obtain data regarding adherence to therapy with clopidogrel, we requested patients to provide us with all of their regular pharmacy names. There is still the chance that patients might have been filled their clopidogrel prescription in a different pharmacy. To minimise this possibility, another way of obtaining patients' dispensing records can be from Medicare Australia data. Clopidogrel is among the PBS subsidised medicines for the indications of treatment or secondary prevention of ACS and treatment after stent implantation. Thus, if patients filled the prescription for clopidogrel, the PBS record will be able to track the detail of each prescription dispensed. The timeframe of this work, however, did not allow for obtaining data from Medicare.

In our study we did not ask the patients regarding the factors that might be the obstacle for them on being adherent or persistent. However, in a previous study done by Muntner et al. in patients treated with clopidogrel after PCI, factors such as cost issues, physician and pharmacy access, and patient-provider communication were suggested as contributing factors to poor adherence or persistence[236]. It has also been reported that patients who did not receive instructions regarding the use or the benefits of clopidogrel at discharge are more likely not to take medication following their hospital discharge[236]. Successfully determining the key factors of poor adherence and persistence may assist with interventions to increase patients' adherence and persistence with the medication[236]. Future studies with larger samples and comprehensive follow-up (e.g. direct contact with patients, assessing their prescriptions via PBS records) are needed to better inform local interventions.

4.4.2 Genotype Testing

While the proportion of the overall study cohort who consented to genotype testing was low (17%), statistical analysis yielded an interesting finding in that patients who were rapid metabolisers showed an increased likelihood of being readmitted due to bleeding. It is important to note that the sample size of our study might result in questions regarding the validity of the statistical test. Nonetheless, the results from this study are still useful as a preliminary analysis and a basis for a future larger study.

In our study, the genotype testing performed was only to detect the presence of the CYP2C19*2, CYP2C19*3 and CYP2C19*17 alleles. According to the literature[22 108 113 157], about 15%-30% of Caucasians are carriers of at least one copy of CYP2C19*2, while 40% are carriers of CYP2C19*17. Our study results were closely in line with the data from literature. Among the genotyped respondents (who were all Caucasians), 32% of them had either a single *2 allele or were *2 homozygotes and 38% possessed at least one CYP2C19*17 allele.

Based on the genotype results, the classification of patients was made according to their functional allele carrier status (e.g. normal function, loss-of-function, gain-of-function) and metaboliser phenotype. Phenotype classifications divided patients into those who were extensive (normal) metabolisers, poor metabolisers and rapid metabolisers. Both of these classifications were referring to the classification made by Pare et al.[159], with little change in defining the poor metaboliser phenotype. In this present study, those who had 2 loss-of-function alleles or 1 copy of a loss-of function allele were classified as poor metabolisers. The established publications, however, commonly consider those who are heterozygous for loss-of-function alleles as intermediate metabolisers, and those who are homozygous as poor metabolisers. This classification was not able to be applied in this study, due to the low patient numbers.

Previous reports regarding the association between carriage of a loss-of function allele and clopidogrel clinical outcome have been indeterminate. Several studies have proposed that carriers of a loss-of-function allele have a risk of a recurrent cardiovascular events or death of up to two times that of non-carriers[22 24 108 156]. Others have reported no relationship between carriage of a loss-of-function allele and risk of cardiovascular

events[159]. Our data appears to confirm this theory. Our results showed that there was no difference between the poor outcome of recurrent ACS and stenosis between the carriers of CYP2C19*2 (poor metabolisers) and those who were not, although the patient numbers were small.

The CYP2C19*17 gain of function allele, on the other hand, has recently been studied and has been suggested to improve clopidogrel-induced platelet inhibition[22 23 153], which might confer an increased bleeding risk[23]. Our data showed an association between patients who are rapid metabolisers (carriers of CYP2C19*1/*17 or CYP2C19*17/*17) and a higher risk of bleeding readmission.

In contrast to this finding, a recent meta-analysis study reported that there was no strong evidence supporting the clinical significance of CYP2C19 polymorphism[5]. The study summarised that the data available did not show the substantial impact of CYP2C19 on the clinical efficacy of clopidogrel. Hence, the study proposed that it is unnecessary to personalise treatment with clopidogrel until there is more reliable evidence regarding the effect of CYP2C19. Nonetheless, given the large interindividual variability in response to clopidogrel resulting from both clinical and genetic factors, to date there is still no definite answer on whether genotyping is worth doing in everyday practice. Despite the recommendation made by the FDA, performing routine genetic testing is not preferred by most clinicians. Beside the high additional price that patients need to pay, clinicians are still doubtful as to whether such testing is clinically useful and would be sufficient to explain interindividual variation in treatment with clopidogrel[241].

To the best of our knowledge, these data are the first genotype data on southern Tasmanian patients and their relationship to adverse clinical outcomes. This study failed to confirm the findings of previous studies that have suggested patients who are poor metabolisers have a greater possibility of stent thrombosis. The data did, however, seem to strengthen the theory that patients who are rapid metabolisers have a greater risk of bleeding.

4.4.3 PPI utilisation

At discharge, most patients in this study were treated with DAT. Most of those who were taking DAT were planned to take it for 12 months, and then take aspirin alone for an

unspecified period. It has been reported that the benefit from using DAT comes at the cost of increasing GI complications, such as ulceration that can lead to GI haemorrhage, with the rate being greater among patients taking DAT compared to those taking aspirin alone[51 113 138 242]. Clopidogrel itself actually does not cause ulcers to the GI mucosa[138 243]. However, its antiplatelet activity is assumed to impair the healing of asymptomatic GI lesions that already exist or have been promoted by another risk factor (e.g., the use of NSAIDs)[138 235 244]. The GI tract is the most common site of spontaneous haemorrhage[54 101]. The prevalence of GI bleeding is reportedly to be higher among people with a history of previous bleeding[113 245]. Our results showed that among those who recorded having a history of GI ulcer/GORD, the majority (70%) were then discharged with a PPI. However, the prescribing rate among those with other risk factors - older patients and those who were treated with other medications that could increase the risk of bleeding, was low (35% and 36%, respectively).

In addition, the more risk factors that patients possess (e.g. advanced age, concomitant use of anticoagulants, NSAIDs, oral steroids) is reported to elevate the risk of patients having another event of GI bleeding [235]. Although our data supported this trend, it failed to definitively prove this relationship (Table 3.9). This might have been due to the limited sample size of our study, as well as the low rate of overall bleeding, in which the rate of GI bleeding was even lower (3 out of 9 bleeding readmissions). The absence of a relationship between PPI use and hospital readmission (Table 3.9) was logical given that PPIs only protect against upper GI bleeding and only 3 of the patients experienced a readmission due to upper GI bleeding. It may also have been that the patients who bled were recognised by their prescribers as being at high bleeding risk, and therefore prescribed a prophylactic PPI, that certainly would not be able to protect them from other causes of bleeding. The rate of GI bleeding observed in our study appeared to be similar to previous findings, which also indicated that the incidence of bleeding in clinical practice is low[235].

According to some definitions[113 138], patients in our study were already in high risk of bleeding simply because they were taking antiplatelet therapy and, in most cases, DAT. This then was compounded by other risk factors such as age, history of GI bleeding and the concomitant use of other medications. Overall, among patients who were having a risk factor of taking DAT, 40% of them also had an additional risk factor of bleeding. Despite

this, only 83 patients (28%) were prescribed a PPI. An Australian study by Luinstra et al. found that the rate of PPI prescribing among patients discharged with DAT to be 35%[182]. Another international retrospective study by Ray et al. also reported the similar rate of PPI prescribing (37%) in patients who received clopidogrel[235]. Compared to both of these studies, the proportion of patients discharged on a PPI in our study seems to be slightly lower. This is of particular concern as the risk of bleeding among this cohort was higher than in the study by Luinstra et al. Although the results show that there was a tendency for patients with more risk factors to receive a PPI, more than half of patients with additional risk factors were still not prescribed a PPI.

The ACCF/ACG/AHA consensus statement, published in 2008, recommended that patients treated with DAT and having other risk factors should be prescribed a PPI, in order to minimise the risk of having GI bleeding (Figure 4.1)[138]. The early recommendation was to use a PPI for patients on DAT treatment, but after the evidence started to accumulate regarding the possible clopidogrel-PPI interaction, the FDA addressed the concerns in the updated guideline which was published in 2010[113]. The updated guideline acknowledged the possibility of the interaction between clopidogrel and PPIs, particularly omeprazole. However, no definite recommendation was made, as the evidence whether the data are clinically meaningful is still lacking. Furthermore, reemphasising the previous guideline recommendation, the updated guideline also stated that patients with significant risk factors of bleeding (e.g., ACS patients and history of GI bleeding) might be indicated to receive PPI.

Considering that the present study used data for patients discharged from hospital from late 2007 until late 2009, it is not appropriate to comment on the quality of PPI prescribing based on the ACCF/ACG/AHA 2010 guideline.

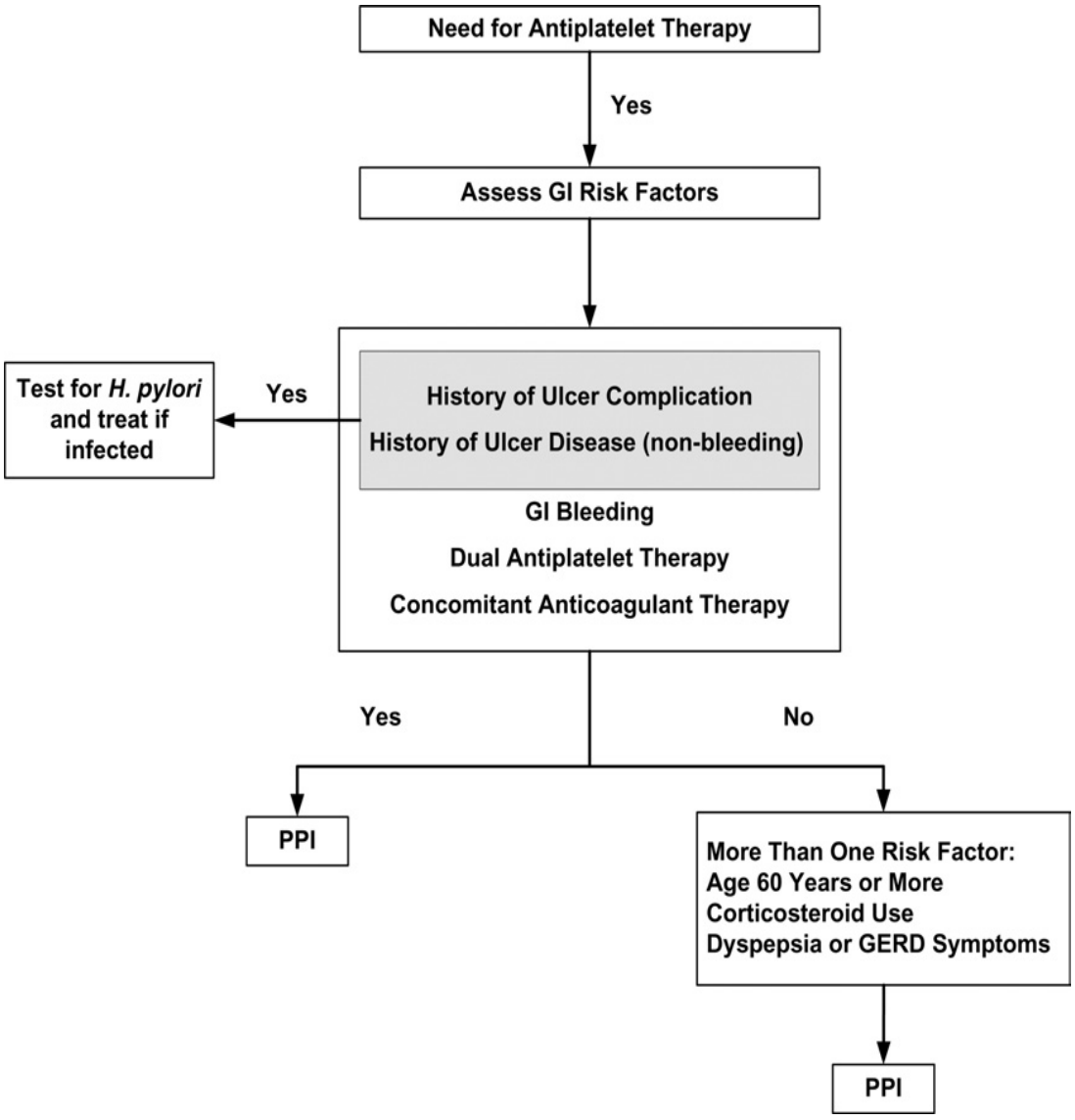


Figure 4.1 ACCF/ACG/AHA 2008 recommendation for PPI prescription[138]

From our data, we observed that the uncertainty regarding the ideal treatment strategies for preventing GI bleeding among patients taking antiplatelet therapy seemed to affect the tendency of clinicians using the combination of clopidogrel and a PPI (discussed more below). Until more evidence is available which leads to guidelines that give more definitive recommendations, there is a concern that patients with risk factors for bleeding will still not receive optimal gastroprotection. The present study cannot give any recommendations regarding the association of PPIs with the adverse events of clopidogrel,

nor rule out the possibility of an interaction. Even up to this date, there is no guideline giving a definite recommendation on the co-administration of clopidogrel and a PPI. If the risk of interaction is of concern, the ACCF/ACG/AHA 2010 guideline states that there is a possibility of using timing of dosing as a solution[113]. From a pharmacokinetic study, it is reported that clopidogrel, after achieving its steady state, will exert its antiplatelet effect within 2 hours after the dose is administered. Therefore, for patients with a high risk of bleeding, given that PPI has been proven to prevent GI bleeding in patients treated with DAT, adjusting the time of clopidogrel and PPI administration might be worth consideration.

Despite the fact that the use of PPIs for patients treated with ASA has been well accepted, concerns still emerge if a PPI is prescribed for patients taking ASA together with clopidogrel. In the last 3 years, conflicting studies have appeared concerning the possible interaction between PPIs and clopidogrel. The first experimental study regarding this matter was conducted by Gilard et al. and published in early 2008[246]. This study reported that omeprazole (a PPI) underwent metabolism via the same P450 pathway as clopidogrel, blocking the metabolism of clopidogrel into its active compound, therefore reducing its activity as an antiplatelet agent[246]. Further data resulting from observational retrospective studies[134 135] advised of the possibility of an interaction between clopidogrel and PPIs that might affect clopidogrel clinical activity. However, the evidence on whether these data are clinically significant is still relatively inconclusive.

Although data from experimental studies have clearly shown the possible interaction, there is still no definite conclusion on whether all PPIs will increase the adverse outcome of patients treated with clopidogrel, or whether it applies to certain PPIs only.

How this issue has developed and has affected the trend of PPI prescribing seems to concur with the result in our study (Figure 3.13). From the figure, it is apparent that the rate of PPI prescription reached its peak in mid-2008 then gradually declined, until it reached the lowest point in early 2009. During 2007 to mid-2008, the possible adverse effects of PPIs on the antiplatelet activity of clopidogrel were less well-known, with few peer-reviewed papers published. Based on a PubMed search, until July 2008 the literature was more focussed on the benefit of using PPIs to avoid upper GI bleeding due to DAT. This might explain why the use of PPIs remained high during those periods.

After the experimental study done by Gilard et al. was published in January 2008, which was then followed by the observational studies published in late 2008, awareness of the possible interaction may have grown among prescribers. These concerns may have been gradually implemented into clinical practice and affected the tendency of prescribers to prescribe PPIs on discharge. As seen in Figure 3.13, during this period a fall in the rate of PPI prescribing occurred.

Based on our results, the controversy regarding cardiovascular adverse events arising from a potential drug interaction with concomitant use of clopidogrel and PPIs seemed to influence the prescribing tendency. Thus, it is not possible to decisively comment on the quality of prescribing due to the uncertainty in the literature. Nonetheless, since the uncertainty regarding this issue is still continuing up to this date, it is important for the clinicians to focus on potential harm from GI ulcers/bleeding in making the decision on prescribing a PPI to patients taking clopidogrel.

4.5 Implications for the Future Use of Clopidogrel

Regardless of the fact that patients' baseline risk factors in this study seemed to be low, having an episode of ACS, and especially having a stent implanted (as most of our patients did), increases the risk of having a subsequent atherothrombotic event. Thus, it is important for patients to be effectively treated with antiplatelet(s) in order to reduce the likelihood of this adverse event. This requires good adherence to, and persistence with, therapy, so it was concerning that there was high proportion of patients in our cohort being non-adherent, and also some showing non-persistence. Promoting and then monitoring persistence and adherence in patients with ACS, and identifying and addressing the causes of non-persistence and non-adherence, remain essential roles for all of the healthcare professionals involved in the care of these patients.

Treatment with antiplatelet agents, however, is a delicate balance between the risk of adverse atherothrombotic events and bleeding. In this study, as in previous work, the risk of bleeding was associated with concurrent use of other medications such as anticoagulants, NSAIDs, and steroids; patients' genotype profile (being a rapid metaboliser); and also adherence and persistence. In order to avoid the unwanted effects of the medication, patients need to be informed about the risk of bleeding,, and educated regarding the factors that increase the risk. They also need to keep in touch with their doctors, updating them about their condition and not take the decision to stop taking the medication abruptly if they experience any events of minor bleeding (e.g., bruises, epistaxis).

Despite the low rate of bleeding found in the present study, it is important to note that patients with multiple risk factors for bleeding were still not receiving the optimum treatment for avoiding major haemorrhagic events – that is, prescription of gastroprotective agents was suboptimal. Recent findings show that there is no clear evidence of increased CV risk among patients administered clopidogrel and a PPI together[137 143 145]. There is still no definite recommendation regarding the co-administration of clopidogrel and PPIs. This study, therefore, re-emphasised the recommendations based on the ACCF/ACG/AHA 2010 consensus guideline. Rather than placing more emphasis on the clopidogrel-PPI interaction, which still has no significant clinical evidence to support it, clinicians need to be encouraged to prescribe a PPI for

patients with multiple risk factors for bleeding. The concerns of adverse outcomes related to the drug interaction were also not borne out in our present observational study. It is plausible that the interaction between clopidogrel and PPIs is too weak to translate into cardiovascular risk. Even though our data are statistically underpowered, they still deliver supportive evidence indicating that PPIs can be used safely in patients taking clopidogrel. If clinicians still do not want to take the risk of the possible interaction, at least they can consider prescribing a PPI for which reports suggest the interaction with clopidogrel is less likely (i.e. pantoprazole)[133 247].

Due to the limited sample size of our study, it was not possible for our data to clarify the impact of CYP2C19 polymorphism on the clinical response to clopidogrel, or to support either way the conflicting opinions on performing genotype testing. While our study appeared to support the recent theory that there is no association between CYP2C19*2 status and an increased risk of CV events, the CYP2C19*17 allele seemed to impact on patients' risk of bleeding. Further prospective randomised control trials investigating the role of CYP2C19 polymorphisms in clopidogrel response are necessary in order to provide more robust evidence and definitively address the confusion regarding this matter.

At present, new antiplatelet agents, such as prasugrel and ticagrelor are available in Australia. These drugs have been promoted to be able to overcome the limitations of clopidogrel (e.g. a slow onset of action, incomplete platelet inhibition, and an irreversible antiplatelet effect). Clinical trials have also shown better clinical outcomes from use of these new agents compared to clopidogrel[248-250]. Compared to clopidogrel, genetic variations are less important in treatment with prasugrel[251], while ticagrelor is fully independent of genetic variations, since it does not require metabolic activation[16]. These new agents may be alternatives for patients who are showing – or are at risk of – poor outcomes with clopidogrel or for patients whose physicians are concerned that they may be experiencing drug interactions. Still, a risk-benefit evaluation should be conducted when administering these agents to ACS patients as they also have their limitations. Prasugrel has been reported to increase the risk of bleeding events compared to clopidogrel, especially in certain patient populations[252], while the reversible antiplatelet activity of ticagrelor may also become an issue (e.g. patients' adherence might be affected by twice daily dosing)[253].

4.6 Study Limitations

4.6.1 Data collection

There are several limitations to this observational study. Given that this study was done using an observational retrospective methodology, most of the limitations were linked to the data collection itself. Firstly, since the main data were collected retrospectively based on the patients' DMRs, important data were sometimes missing due to the suboptimal recording in the DMR (e.g., patients' clopidogrel duration plan, cardiac rehabilitation referral).

The phase two data collection of this study was also limited by the information regarding patients' home addresses. Each patient's address was initially recorded from their DMR at RHH. However, there was a possibility that patients who did not have a recent visit or admission to the RHH might have had a different address to what was stated in the DMR. This was shown by the number of letters returned due to an incorrect address. Another concern that might have caused patients to be reluctant to take part in the study was if they were uncomfortable that the University had obtained details from the RHH DMR. This issue, however, was explained to them in the initial study letter.

Even for those who decided to participate in this study, it proved impossible to obtain all of their further data. From 75 patients who responded to the study letter, only 59 of them gave consent to the researchers to access their dispensing records. This was further complicated by the fact that no reply was received from some of the pharmacies in response to the request for their patient's dispensing records, despite a reminder letter being sent to non-responders.

In assessing adherence and persistence, the researchers could only rely on the information given by the respondents regarding their regular community pharmacies. Based on the fact that, for some patients, no record of clopidogrel dispensing could be found, there is a concern that some respondents may have had their prescriptions filled elsewhere, so their dispensing records were therefore incomplete. The questionnairre exploring patients' adherence also did not asses patients' health belief and experiences.

4.6.2 Assessing patients' outcome and factors contributing to the poor outcome

Although the study methodology assumed that patients experiencing significant events would represent to the RHH, patients might have been readmitted to another hospital (e.g. a private hospital). Hence, the rate of adverse outcomes reported in this study might have been lower from the true rate. The inclusion of a question in the patient survey aimed to at least partly address this issue, but this was only completed by a limited number of participants and the information provided was of questionable accuracy. Although several studies have suggested the important role of platelet function in predicting patients' outcome when treated with clopidogrel, our study was not able to assess this factor. Due to the limited sample size identified and the low response rate we were not able to achieve our initial aim of investigating the factors that might influence the variability of clopidogrel response using multivariate analyses and assessing which of the factors have a major role. Despite several apparent trends being shown from the data analysis, further investigations with a larger sample size might be necessary to produce more robust data and confirm our findings.

4.7 Conclusions

Despite the limitations of this study, the findings successfully updated our knowledge of the management and outcomes of patients with high-risk ACS in southern Tasmania, and provided the first data on the pharmacogenetic profile of this patient group. Among the reassuring findings is that the patients received a treatment regimen that complied largely with the Australian guidelines, allowing comparison of their outcomes with those of international cohorts. During an 18 month follow-up period, the rate of hospital readmission due to recurrent ACS was a little higher than expected, but the rate of bleeding was relatively low. Some important areas of improvement regarding patients' post discharge management were highlighted, including the need for greater support for smoking cessation and better documented cardiac rehabilitation referral. Perhaps of most concern was that, despite the fact that there was an overall good rate of persistence, there was a trend towards early clopidogrel discontinuation. There were also only a small number of patients who could be classified as adherent. Close attention to these aspects of management will be likely to improve the patients' outcomes even further.

None of the patient-related factors investigated showed an association with the likelihood of patients being readmitted due to recurrent ACS or restenosis; however, several factors were associated with the risk of a readmission due to bleeding. From our study, it is shown that patients taking multiple antithrombotic agents were more likely to have hospital readmission due to bleeding. Ensuring that the durations of use of antiplatelet agents are regularly reviewed and targeting the appropriate prescribing of gastroprotective agents, especially in patients taking multiple medications that increase the risk of bleeding, may help in balancing the thrombotic and bleeding risks in this group.

Finally, our study findings suggested that there are significant rates of possession of loss-of-function and gain-of-function CYP2C19 alleles in the southern Tasmanian ACS population. Given that there appeared to be an association between possessing the gain-of-function genotype and bleeding risk, the issue of genotype testing in the real world ACS population warrants further investigation. Such information is crucial to the development of a better systematic approach to the clinical use of clopidogrel in the management of ACS now and into the future.

Chapter 5 –References

1. Angiolillo D. Variability in responsiveness to oral antiplatelet therapy. *Journal of the American College of Cardiology* 2009;103(3S):27-34.
2. Geiger J, Brich J, Hönig-Liedl P, Eigenthaler M, Schanzenbächer P, Herbert J, et al. Specific impairment of human platelet P2Yac ADP receptor–mediated signaling by the antiplatelet drug clopidogrel. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1999;19(8):2007-2011.
3. Yukhanyan L, Freynhofer MK, Siller-Matula J, Schrör K, Huber K. Genetic variability in response to clopidogrel therapy and its clinical implications. *Thrombosis and Haemostasis* 2011;97(2):212-217.
4. Pena A, Collet JP, Hulot JS, Silvain J, Barthelemy O, Beygui F, et al. Can we override clopidogrel resistance? *Circulation* 2009;119(21):2854.
5. Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *British Medical Journal* 2011;343:d4588.
6. Department of Health and Ageing. Pharmaceutical Benefits Scheme (PBS) Publications. Expenditure and prescriptions: Twelve months to 30 June 2009; 2009 [cited 2010 2011 Oct 22]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/696CBFCEB2FFD713CA257679000EABCA/$File/Expenditure%20and%20Prescirption%202009.pdf.
7. Department of Health and Ageing. Pharmaceutical Benefits Scheme (PBS) Publications. Expenditure and prescriptions: Twelve months to 30 June 2010; 2010 [cited 2010 2011 Oct 22]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/4A3477B8447EC695CA25788600037450/$File/Expenditure%20and%20prescriptions%2012%20months%20to%2030%20June%202010.pdf.
8. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. *Drugs* 2000;60(2):347-377.
9. Creager MA. Results of the CAPRIE trial: efficacy and safety of clopidogrel. *Vascular Medicine* 1998;3(3):257.

10. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109(25):3171-3175.
11. O'Donoghue M, Wiviott SD. Clopidogrel response variability and future therapies. *Circulation* 2006;114(22):e600-e606.
12. Angiolillo D, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass T, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *Journal of the American College of Cardiology* 2007;49(14):1505.
13. Serebruany V, Steinhubl S, Berger P, Malinin A, Bhatt D, Topol E. Variability in platelet responsiveness to clopidogrel among 544 individuals. *Journal of the American College of Cardiology* 2005;45(2):246-51.
14. Brandt J, Close S, Iturria S, Payne C, Farid N, Ernest I, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *Journal of Thrombosis and Haemostasis* 2007;5(12):2429-2436.
15. Savi P, Pereillo J, Uzabiaga M, Combalbert J, Picard C, Maffrand J, et al. Identification and biological activity of the active metabolite of clopidogrel. *Thrombosis and Haemostasis - Stuttgart* 2000;84(5):891-896.
16. Schömig A. Ticagrelor—Is there need for a new player in the antiplatelet-therapy field? *New England Journal of Medicine* 2009;361(11):1108-1111.
17. Taubert DBN, Grimberg GLA, Jung NGT, Kastrati ASA, Schomig E. Impact of P-glycoprotein on clopidogrel absorption. *Clinical Pharmacology and Therapeutics* 2006;80(5):486-501.
18. McLachlan AJ, Campbell TJ. Variability in response to clopidogrel. *Circulation* 2009;119:2854-7.
19. Caplain H, Donat F, Gaud C, Necciari J. Pharmacokinetics of Clopidogrel. 1999;25(Suppl 2):25-28.
20. Taubert D, Kastrati A, Harlfinger S, Gorchakova O, Lazar A, von Beckerath N, et al. Pharmacokinetics of clopidogrel after administration of a high loading dose. *Thrombosis and Haemostasis* 2004;92(2):311.

21. Scott S, Sangkuhl K, Gardner E, Stein C, Hulot J, Johnson J, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. *Clinical Pharmacology & Therapeutics* 2011;90(2):328-332.
22. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *New England Journal of Medicine* 2009;360(4):354-362.
23. Sibbing D, Koch W, Gebhard D, Schuster T, Braun S, Stegherr J, et al. Cytochrome 2C19* 17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation* 2010;121(4):512-518.
24. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *New England Journal of Medicine* 2009;360(4):363-375.
25. Hulot JS, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood* 2006;108(7):2244.
26. Hollopeter G, Jantzen HM, Vincent D, Li G, England L, Ramakrishnan V, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature* 2001;409(6817):202-207.
27. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999;100(15):1667.
28. Product information. Plavix® (clopidogrel bisulfate tablets). US prescribing information New York (NY): Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership.; 2006.
29. Savcic M, Hauert J, Bachmann F, Wyld P, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. *Seminars in Thrombosis and Hemostasis* 1999;25(Suppl 2):15-19.
30. Bouman HJ, Schömig E, van Werkum JW, Velder J, Hackeng CM, Hirschhäuser C, et al. Paraoxonase-1 is a major determinant of clopidogrel efficacy. *Nature Medicine* 2010;17(1):110-116.
31. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. *Drugs* 2007;67(4):613-646.

32. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey Jr DE, Ettinger SM, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;57:1920-1959.

33. James S, Åkerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, et al. Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *American Heart Journal* 2009;157(4):599-605.

34. Wallentin L, Varenhorst C, James S, Erlinge D, Braun OÖ, Jakubowski JA, et al. Prasugrel achieves greater and faster P2Y12receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. *European Heart Journal* 2008;29(1):21.

35. Patti G, Bárczi G, Orlic D, Mangiacapra F, Colonna G, Pasceri V, et al. Outcome Comparison of 600- and 300-mg Loading Doses of Clopidogrel in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction: Results From the ARMYDA-6 MI (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Myocardial Infarction) Randomized Study. *Journal of the American College of Cardiology* 2011;58(15):1592-1599.

36. Fernandez A, Aboodi MS, Milewski K, Delgado JA, Rodríguez A, Granada JF. Comparison of Adverse Cardiovascular Events and Bleeding Complications of Loading Dose of Clopidogrel 300 mg Versus 600 mg in Stable Patients Undergoing Elective Percutaneous Intervention (from the CADICE Study). *The American Journal of Cardiology* 2011;107(1):6-9.

37. Mangiacapra F, Muller O, Ntalianis A, Trana C, Heyndrickx GR, Bartunek J, et al. Comparison of 600 Versus 300-mg clopidogrel loading dose in patients with ST-Segment Elevation Myocardial Infarction undergoing primary coronary angioplasty. *The American Journal of Cardiology* 2010;106(9):1208-1211.

38. Yong G, Rankin J, Ferguson L, Thom J, French J, Brieger D, et al. Randomized trial comparing 600-with 300-mg loading dose of clopidogrel in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: results of the Platelet Responsiveness to Aspirin and Clopidogrel and Troponin

Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial. *American Heart Journal* 2009;157(1):60. e1-60. e9.

39. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2005;111(16):2099.
40. Fefer P, Hod H, Hammerman H, Segev A, Beinart R, Boyko V, et al. Usefulness of pretreatment with high-dose clopidogrel in patients undergoing primary angioplasty for ST-elevation myocardial infarction. *The American Journal of Cardiology* 2009;104(4):514-518.
41. Lotrionte M, Biondi-Zoccai GGL, Agostoni P, Abbate A, Angiolillo DJ, Valgimigli M, et al. Meta-analysis appraising high clopidogrel loading in patients undergoing Percutaneous Coronary Intervention. *The American Journal of Cardiology* 2007;100(8):1199-1206.
42. Fuster V. Fine-tuning therapy for Acute Coronary Syndromes. *New England Journal of Medicine* 2010;363(10):976-977.
43. Mehta SR, Tanguay J-F, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *The Lancet* 2010;376(9748):1233-1243.
44. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, et al. Standard-vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention. *The Journal of the American Medical Association* 2011;305(11):1097.
45. Siller-Matula JM, Huber K, Christ G, Schrör K, Kubica J, Herkner H, et al. Impact of clopidogrel loading dose on clinical outcome in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Heart* 2011;97(2):98-105.
46. Chua D, Ignaszewski A. Clopidogrel in Acute Coronary Syndromes. *British Medical Journal* 2009;338:998-1002.

47. Jackowski L, Stocks N, Rowett D. Reducing the risk of adverse thrombotic events-The role of aspirin and clopidogrel. *Australian Family Physician* 2008;37(9):721.

48. Mehta S, Yusuf S. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *European Heart Journal* 2000;21(24):2033.

49. Chen Z, Jiang L, Chen Y, Xie J, Pan H, Peto R, et al. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366(9497):1607-1621.

50. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. A global view of atherothrombosis: baseline characteristics in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *American Heart Journal* 2005;150(3):401. e1-401. e7.

51. Mehta S, Yusuf S, Peters R, Bertrand M, Lewis B, Natarajan M, et al. Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358(9281):527-533.

52. Steinhubl S, Berger P, Mann III J, Fry E, De Lago A, Wilmer C, et al. Clopidogrel for the reduction of events during observation (CREDO) investigators: early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *The Journal of the American Medical Association* 2002;288(19):2411-2420.

53. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *New England Journal of Medicine* 2005;352(12):1179-1189.

54. Eikelboom JW, Hirsh J. Bleeding and management of bleeding. *European Heart Journal* 2006;8(suppl G):G38.

55. Sørensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jørgensen C, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a

retrospective analysis of nationwide registry data. *The Lancet* 2009;374(9706):1967-1974.

56. Ng FH, Lam KF, Wong SY, Chang CM, Lau YK, Yuen WC, et al. Upper Gastrointestinal Bleeding in Patients with Aspirin and Clopidogrel Co-Therapy. *Digestion* 2008;77(3-4):173-177.
57. Harker LA, Boissel JP, Pilgrim AJ, Gent M. Comparative Safety and Tolerability of Clopidogrel and Aspirin: Results from CAPRIE. *Drug Safety* 1999;21(4):325-335.
58. Myers RI. The variability of platelet response to aspirin and clopidogrel: revisiting the Caprie, Cure, Credo, and Match trials. *Proceedings (Baylor University. Medical Center)* 2005;18(4):331-336.
59. Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. *British Medical Journal* 2006;333(7571):726.
60. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Archives of Internal Medicine* 2010;170(16):1433.
61. Labos C, Dasgupta K, Nedjar H, Turecki G, Rahme E. Risk of bleeding associated with combined use of selective serotonin reuptake inhibitors and antiplatelet therapy following acute myocardial infarction. *Canadian Medical Association Journal* 2011;183(16):1835-1843.
62. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117(4):e25.
63. Thom T, Haase N, Rosamond W, Howard V, Rumsfeld J, Manolio T, et al. American heart association statistics committee and stroke statistics subcommittee. *Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation* 2006;113(6):e85-e151.
64. Australian Bureau of Statistics. Cause of Death, 2009. Canberra, 2011. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/mediareleasesbytitle/63AFD409CBAA7592CA25757C00272CF2?OpenDocument.
65. Australian Institute of Health and Welfare. Chronic diseases mortality. 2006. Available from: http://www.aihw.gov.au/chronic-diseases-mortality/.

66. Epstein FH, Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *New England Journal of Medicine* 1992;326(4):242-250.
67. Access Economics Pty Limited. The economic costs of heart attack and chest pain (Acute Coronary Syndrome); June 2009. Available from: http://www.bakeridi.edu.au/Assets/Files/FullReport%20-%20the%20economic%20costs%20of%20heart%20attack%20and%20chest%20pain%20(emilable.pdf.
68. Fuster V, O'Rourke RA, Poole-Wilson P, Walsh RA. *Acute coronary syndromes*. New York: McGraw-Hill, 2008.
69. Grech ED, Ramsdale DR. Acute coronary syndrome: unstable angina and non-ST segment elevation myocardial infarction. *British Medical Journal* 2003;326(7401):1259.
70. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr DE, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Journal of the American College of Cardiology* 2007;50(7):e1.
71. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Journal of the American College of Cardiology* 2004;44(3):671.
72. Pollack Jr CV, Braunwald E. 2007 update to the ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation

myocardial infarction: implications for emergency department practice. *Annals of Emergency Medicine* 2008;51(5):591-606.

73. Acute coronary syndromes: diagnosis and management, part I; 2009. Mayo Clinic.
74. Zimarino M, De Caterina R. Long-term treatment strategies for atherothrombotic disease: do platelets define the course? *European Heart Journal* 2008;10(suppl I):I8.
75. Massberg S, Schultz C, Gawaz M. Role of platelets in the pathophysiology of acute coronary syndrome. *Thieme Medical Publishers* 2003;3:147-162.
76. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;107(23):2908.
77. Yusuf S, Zhao F, Mehta S, Chrolavicius S, Tognoni G, Fox K. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. The CURE study. *The New England Journal of Medicine* 2001;345-502(7):494.
78. US Food and Drug Administration. Drug Approval Package - Plavix/Clopidogrel bisulfate. 1998. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020839_plavix_toc.cfm.
79. Zambahari R, Kwok O. Clinical use of clopidogrel in acute coronary syndrome. *International Journal of Clinical Practice* 2007;61(3):473-481.
80. Chew DP, Bhatt DL, Sapp S, Topol EJ. Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: a meta-analysis of phase III multicenter randomized trials. *Circulation* 2001;103(2):201.
81. Wood S. FDA approves clopidogrel for acute coronary syndromes. Maryland: Heartwire, 2002. Available from: http://www.theheart.org/article/276081.do.
82. Center Watch. Drug Name: Plavix (clopidogrel bisulfate). 2002. Available from: http://www.centerwatch.com/drug-information/fda-approvals/drug-details.aspx?DrugID=764.
83. Aroney CN, Aylward P, Kelly AM, Chew DPB, Cline E. Natioanal Heart Foundation of Australia - Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006: Medical Journal of Australia, 2006:s1-s30.
84. Grech ED. Percutaneous coronary intervention. II: The procedure. *British Medical Journal* 2003;326(7399):1137-1140.

85. Bokhoor P, Lee M. Benefits of drug eluting stents versus bare metal stents in ST-elevation myocardial infarction: a contemporary review. *Minerva Cardioangiologica* 2010.

86. Maisel WH, Laskey WK. Drug-eluting stents. *Circulation* 2007;115(17):e426-e427.

87. Jensen LO, Maeng M, Kaltoft A, Thayssen P, Hansen HHT, Bottcher M, et al. Stent Thrombosis, Myocardial Infarction, and Death After Drug-Eluting and Bare-Metal Stent Coronary Interventions. *Journal of the American College of Cardiology* 2007;50(5):463-470.

88. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbæk H, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *New England Journal of Medicine* 2007;356(10):1030-1039.

89. Stone GW, Ellis SG, O'Shaughnessy CD, Martin SL, Satler L, McGarry T, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents. *The Journal of the American Medical Association* 2006;295(11):1253.

90. Mauri L, Hsieh W, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *New England Journal of Medicine* 2007;356(10):1020-1029.

91. Mak KH, Belli G, Ellis SG, Moliterno DJ. Subacute stent thrombosis: evolving issues and current concepts. *Journal of the American College of Cardiology* 1996;27(2):494-503.

92. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007;115(18):2426-2434.

93. Wenaweser P, Dörffler-Melly J, Imboden K, Windecker S, Togni M, Meier B, et al. Stent Thrombosis Is Associated With an Impaired Response to Antiplatelet Therapy. *Journal of the American College of Cardiology* 2005;45(11):1748-1752.

94. Uren N, Schwarzacher S, Metz J, Lee D, Honda Y, Yeung A, et al. Predictors and outcomes of stent thrombosis. An intravascular ultrasound registry. *European Heart Journal* 2002;23(2):124.

95. Cuisset T, Frere C, Quilici J, Barbou F, Morange PE, Hovasse T, et al. High post-treatment platelet reactivity identified low-responders to dual antiplatelet therapy at increased risk of recurrent cardiovascular events after stenting for acute coronary syndrome. *Journal of Thrombosis and Haemostasis* 2006;4(3):542-549.

96. Ferguson A, Dokainish H, Lakkis N. Aspirin and clopidogrel response variability: review of the published literature. *Texas Heart Institute Journal* 2008;35(3):313.

97. Diener PHC, Bogousslavsky PJ, Brass PLM, Cimminiello PC, Csiba PL, Kaste PM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *The Lancet* 2004;364(9431):331-337.

98. Catalano M. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348(9038):1329-1339.

99. Aradi D, Komócsi A, Vorobcsuk A, Rideg O, Tokés-Füzesi M, Magyarlaki T, et al. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: Systematic review and meta-analysis. *American Heart Journal* 2010;160(3):543-551.

100. Camilleri E, Jacquin L, Paganelli F, Bonello L. Personalized Antiplatelet Therapy: Review of the Latest Clinical Evidence. *Current Cardiology Reports* 2011;13(4):296-302.

101. Ma TKW, Lam Y-Y, Tan VP, Yan BP. Variability in response to clopidogrel: how important are pharmacogenetics and drug interactions? *British Journal of Clinical Pharmacology* 2011;72(4):697-706.

102. Musallam KM, Charafeddine K, Bitar A, Khoury M, Assaad S, Beresian J, et al. Resistance to aspirin and clopidogrel therapy. *International Journal of Laboratory Hematology* 2011;33(1):1-18.

103. Gurbel PA, Tantry US. Clopidogrel resistance? *Thrombosis Research* 2007;120(3):311-321.

104. Norgard NB, Mathews KD, Wall GC. Drug-drug interaction between clopidogrel and the proton pump inhibitors. *The Annals of Pharmacotherapy* 2009;43(7):1266.

105. Järemo P, Lindahl T, Fransson S, Richter A. Individual variations of platelet inhibition after loading doses of clopidogrel. *Journal of Internal Medicine* 2002;252(3):233-238.

106. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *Journal of the American College of Cardiology* 2005;45(8):1157-1164.

107. Geisler T, Langer H, Wydymus M, Göhring K, Zürn C, Bigalke B, et al. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *European Heart Journal* 2006;27(20):2420.

108. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *The Journal of the American Medical Association* 2009;302(8):849.
109. Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim H-S, et al. Impact of Platelet Reactivity on Clinical Outcomes After Percutaneous Coronary Intervention: A Collaborative Meta-Analysis of Individual Participant Data. *Journal of the American College of Cardiology* 2011;58(19):1945-1954.
110. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, et al. High Residual Platelet Reactivity After Clopidogrel Loading and Long-term Cardiovascular Events Among Patients With Acute Coronary Syndromes Undergoing PCI. *The Journal of the American Medical Association* 2011;306(11):1215-1223.
111. Wiviott SD. Clopidogrel response variability, resistance, or roth? *The American Journal of Cardiology* 2006;98(10, Supplement 1):S18-S24.
112. Migliorini A, Valenti R, Marcucci R, Parodi G, Giuliani G, Buonamici P, et al. High residual platelet reactivity after clopidogrel loading and long-term clinical outcome after drug-eluting stenting for unprotected left main coronary disease. *Circulation* 2009;120(22):2214-2221.
113. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Circulation* 2010;56(24):1-16.
114. Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay. *Circulation* 2009;119(2):237-242.
115. Geisler T, Grass D, Bigalke B, Stellos K, Drosch T, Dietz K, et al. The residual platelet aggregation after deployment of intracoronary stent (PREDICT) score. *Journal of Thrombosis and Haemostasis* 2008;6(1):54-61.
116. Sarker DK, Haque K, Siddique MA, Ahmed MK, Rahman F, Mahmood M, et al. In-Hospital Outcome Of Acute Coronary Syndrome In Patients With Diabetes Mellitus. *University Heart Journal* 2009;5(1):24-27.

117. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis. *The Journal of the American Medical Association* 2002;287(19):2570.

118. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramírez C, Sabaté M, Jimenez-Quevedo P, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes* 2005;54(8):2430.

119. Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D, et al. Implications of diabetes in patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Archives of Internal Medicine* 2004;164(13):1457.

120. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non–Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000;102(9):1014-1019.

121. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, et al. Diabetes and mortality following acute coronary syndromes. *The Journal of the American Medical Association* 2007;298(7):765.

122. Angiolillo DJ, Shoemaker SB, Desai B, Yuan H, Charlton RK, Bernardo E, et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. *Circulation* 2007;115(6):708.

123. Angiolillo DJ, Fernández-Ortiz A, Bernardo E, Barrera Ramirez C, Sabaté M, Fernandez C, et al. Platelet Aggregation According to Body Mass Index in Patients Undergoing Coronary Stenting: Should Clopidogrel Loading-Dose Be Weight-Adjusted? *Journal of Invasive Cardiology* 2004;16(4):169-174.

124. Sibbing D, von Beckerath O, Schömig A, Kastrati A, von Beckerath N. Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. *The American Journal of Cardiology* 2007;100(2):203-205.

125. Bliden KP, DiChiara J, Lawal L, Singla A, Antonino MJ, Baker BA, et al. The association of cigarette smoking with enhanced platelet inhibition by clopidogrel. *Journal of the American College of Cardiology* 2008;52(7):531-533.

126. Desai NR, Mega JL, Jiang S, Cannon CP, Sabatine MS. Interaction between cigarette smoking and clinical benefit of clopidogrel. *Journal of the American College of Cardiology* 2009;53(15):1273-1278.

127. Hochholzer W, Trenk D, Mega JL, Morath T, Stratz C, Valina CM, et al. Impact of smoking on antiplatelet effect of clopidogrel and prasugrel after loading dose and on maintenance therapy. *American Heart Journal* 2011;162(3):518-526. e5.
128. Cho JH, Jeong YH, Ahn YJ, Kang MK, Koh JS, Kim IS, et al. The impact of smoking on post-clopidogrel platelet reactivity in patients with acute myocardial infarction. *Korean Circulation Journal* 2010;40(3):119.
129. Scollo MM, Winstanley MH, Woodward S, Walker N [editors]. Tobacco in Australia: facts and issues. Melbourne: Cancer Council Victoria; 2008. Available from: www.TobaccoInAustralia.org.au.
130. Oates JA, Wood AJJ, Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. *New England Journal of Medicine* 1988;319(20):1318-1330.
131. The National Health and Medical Research Council. National Vascular Disease Prevention Alliance. Guidelines for the assessment of absolute cardiovascular disease risk. 2009. Available from: http://www.diabetesaustralia.com.au/PageFiles/9156/A_AR_Guidelines_FINAL%20FOR%20WEB.pdf.
132. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. *Circulation* 1997;96(9):3243-3247.
133. Bates ER, Lau WC, Angiolillo DJ. Clopidogrel–Drug Interactions. *Journal of the American College of Cardiology* 2011;57(11):1251-1263.
134. Ho P, Maddox T, Wang L, Fihn S, Jesse R, Peterson E, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *The Journal of the American Medical Association* 2009;301(9):937.
135. Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *Canadian Medical Association Journal* 2009;180(7):713.
136. Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009:2322-2329.

137. O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *The Lancet* 2009;374(9694):989-997.

138. Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FKL, Furberg CD, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology* 2008;52(18):1502.

139. Gupta E, Bansal D, Sotos J, Olden K. Risk of Adverse Clinical Outcomes with Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Percutaneous Coronary Intervention. *Digestive Diseases and Sciences* 2010;55(7):1964-1968.

140. Stockl KM, Le L, Zakharyan A, Harada ASM, Solow BK, Addiego JE, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Archives of Internal Medicine* 2010;170(8):704.

141. Wiviott S, Montalescot G, Braunwald E, Murphy S, Gibson C, McCabe C, et al. TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009;373(9665):723-731.

142. Public Health Advisory: Updated safety information about a drug interaction between Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm190825.htm.

143. O'Donoghue ML. CYP2C19 Genotype and Proton Pump Inhibitors in Clopidogrel-Treated Patients. *Circulation* 2011;123(5):468-470.

144. Simon T, Steg PG, Gilard M, Blanchard D, Bonello L, Hanssen M, et al. Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Registry. *Circulation* 2011;123:474-482.

145. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease. *New England Journal of Medicine* 2010;363(20):1909-1917.
146. Piorkowski M, Weikert U, Schwimmbeck PL, Martus P, Schultheiss HP, Rauch U. ADP induced platelet degranulation in healthy individuals is reduced by clopidogrel after pretreatment with atorvastatin. *Thrombosis and Haemostasis-Stuttgart* 2004;92:614-620.
147. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation. *Circulation* 2003;107(1):32-37.
148. Siller-Matula JM, Lang I, Christ G, Jilma B. Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. *Journal of the American College of Cardiology* 2008;52(19):1557-1563.
149. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation* 2002;107(1):32-37.
150. Olesen JB, Gislason GH, Charlot MG, Fosbol EL, Andersson C, Weeke P, et al. Calcium-Channel Blockers Do Not Alter the Clinical Efficacy of Clopidogrel After Myocardial Infarction: A Nationwide Cohort Study. *Journal of the American College of Cardiology* 2011;57(4):409-417.
151. Serrano Júnior CV, Soeiro AM, Araújo LF, Jabot B, Rached F, Orii NM, et al. Lack of clopidogrel-statin interaction in patients undergoing coronary stent implantation. *Arquivos Brasileiros de Cardiologia* 2010;95(3):321-327.
152. Wood S. Esomeprazole, but not rosuvastatin, affects clopidogrel post-PCI: SPICE. Vancouver: Heartwire, 2011 [cited 2011 13 November]; Available from: http://www.theheart.org/article/1301049.do.
153. Tiroch KA, Sibbing D, Koch W, Roosen-Runge T, Mehilli J, Schömig A, et al. Protective effect of the CYP2C19* 17 polymorphism with increased activation of clopidogrel on cardiovascular events. *American Heart Journal* 2010;160(3):506-512.
154. Smith SMG, Judge HM, Peters G, Armstrong M, Fontana P, Gaussem P, et al. Common sequence variations in the P2Y12 and CYP3A5 genes do not explain the variability in the inhibitory effects of clopidogrel therapy. *Platelets* 2006;17(4):250-258.

155. Fontana P, HULOT JS, De Moerloose P, Gaussem P. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. *Journal of Thrombosis and Haemostasis* 2007;5(10):2153-2155.

156. Mega J, Simon T, Collet J, Anderson J, Antman E, Bliden K, et al. Reduced-Function CYP2C19 Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI: A Meta-analysis. *The Journal of the American Medical Association* 2010;304(16):1821.

157. Holmes Jr DR, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA" boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Journal of the American College of Cardiology* 2010;56(4):321.

158. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *The Lancet* 2009;373(9660):309-317.

159. Paré G, Mehta SR, Yusuf S, Anand SS, Connolly SJ, Hirsh J, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *New England Journal of Medicine* 2010;363(18):1704-1714.

160. Frere C, Cuisset T, Gaborit B, Alessi M, Hulot J. The CYP2C19* 17 allele is associated with better platelet response to clopidogrel in patients admitted for non ST acute coronary syndrome. *Journal of Thrombosis and Haemostasis* 2009;7(8):1409-1411.

161. FDA Drug Safety Communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm.

162. Hulot JS, Collet JP, Silvain J, Pena A, Bellemain-Appaix A, Barthélémy O, et al. Cardiovascular Risk in Clopidogrel-Treated Patients According to Cytochrome P450 2C19* 2 Loss-of-Function Allele or Proton Pump Inhibitor Coadministration:: A Systematic Meta-Analysis. *Journal of the American College of Cardiology* 2010;56(2):134-143.

163. Rudež G, Bouman HJ, van Werkum JW, Leebeek FWG, Kruit A, Ruven HJT, et al. Common Variation in the Platelet Receptor P2RY12 Gene Is Associated With Residual

On-Clopidogrel Platelet Reactivity in Patients Undergoing Elective Percutaneous Coronary Interventions. *Circulation: Cardiovascular Genetics* 2009;2(5):515.

164. Lee S-J, Jung I-S, Jung E-J, Choi J-Y, Yeo C-W, Cho D-Y, et al. Identification of P2Y12 single-nucleotide polymorphisms and their influences on the variation in ADP-induced platelet aggregation. *Thrombosis Research* 2011;127(3):220-227.
165. Giusti B, Gori AM, Marcucci R, Saracini C, Sestini I, Paniccia R, et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10+ 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenetics and Genomics* 2007;17(12):1057.
166. Simon T, Steg P, Becquemont L, Verstuyft C, Kotti S, Schiele F, et al. Effect of Paraoxonase-1 Polymorphism on Clinical Outcomes in Patients Treated With Clopidogrel After an Acute Myocardial Infarction. *Clinical Pharmacology & Therapeutics* 2011;90(4):561-567.
167. Osterberg L, Blaschke T. Adherence to medication. *New England Journal of Medicine* 2005;353(5):487-497.
168. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. *Medscape General Medicine* 2007;9(3):58.
169. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. *Advances in Therapy* 2005;22(4):313-356.
170. Miura T, Kojima R, Mizutani M, Shiga Y, Takatsu F, Suzuki Y. Effect of digoxin noncompliance on hospitalization and mortality in patients with heart failure in long-term therapy: a prospective cohort study. *European Journal of Clinical Pharmacology* 2001;57(1):77-83.
171. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *The Journal of the American Medical Association* 2007;297(2):177.
172. LaFleur J, Oderda GM. Methods to measure patient compliance with medication regimens. *Journal of Pain and Palliative Care Pharmacotherapy* 2004;18(3):81-87.
173. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. *Value in Health* 2008;11(1):44-47.

174. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and Drug Safety* 2006;15(8):565-574.

175. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement. *Circulation* 2006;113(24):2803-2809.

176. Serebruany V, Cherala G, Williams C, Kuliczkowski W, Atar D. Association of platelet responsiveness with clopidogrel metabolism: Role of compliance in the assessment of "resistance". *Journal of the American College of Cardiology* 2010;55(10 Supplement 1):A113. E1055.

177. Kronish IM, Rieckmann N, Shimbo D, Burg M, Davidson KW. Aspirin adherence, aspirin dosage, and C-reactive protein in the first 3 months after Acute Coronary Syndrome. *The American Journal of Cardiology* 2010;106(8):1090-1094.

178. Department of Health and Ageing. AR-DRG Version 6.0 Classification. 2009 [cited 2011 June 25]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/2A68FBBD47DC69D0CA25753E00032FC2/$File/DRG%20long%20descriptions.pdf.

179. Bliden KP, DiChiara J, Tantry US, Bassi AK, Chaganti SK, Gurbel PA. Increased Risk in Patients With High Platelet Aggregation Receiving Chronic Clopidogrel Therapy Undergoing Percutaneous Coronary Intervention: Is the Current Antiplatelet Therapy Adequate? *Journal of the American College of Cardiology* 2007;49(6):657-666.

180. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJT, Bal ET, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *The Journal of the American Medical Association* 2010;303(8):754.

181. Zeymer U, Gitt AK, Jünger C, Heer T, Wienbergen H, Koeth O, et al. Effect of clopidogrel on 1-year mortality in hospital survivors of acute ST-segment elevation myocardial infarction in clinical practice. *European Heart Journal* 2006;27(22):2661.

182. Luinstra M, Naunton M, Peterson G, Bereznicki L. PPI use in patients commenced on clopidogrel: a retrospective cross sectional evaluation. *Journal of Clinical Pharmacy and Therapeutics* 2010;35(2):213-217.

183. Montalescot G, Dallongeville J, Van Belle E, Rouanet S, Baulac C, Degrandsart A, et al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial

infarction as defined by the ESC/ACC definition (the OPERA registry). *European Heart Journal* 2007;28(12):1409.

184. Lavsa SM, Holzworth A, Ansani NT. Selection of a validated scale for measuring medication adherence. *Journal of the American Pharmacists Association* 2011;51(1):90-94.
185. Mahler C, Hermann K, Horne R, Ludt S, Haefeli WE, Szecsenyi J, et al. Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany. *Journal of Evaluation in Clinical Practice* 2010;16(3):574-579.
186. Zhu B, Zhao Z, McCollam P, Anderson J, Bae JP, Fu H, et al. Factors associated with clopidogrel use, adherence, and persistence in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Current Medical Research & Opinion* 2011(0):633-641.
187. Ng F, Wong S, Chang C, Chen W, Kng C, Lanas A, et al. High incidence of clopidogrel associated gastrointestinal bleeding in patients with previous peptic ulcer disease. *Alimentary Pharmacology & Therapeutics* 2003;18(4):443-449.
188. Ng FH, Chan P, Kwanching CP, Loo CK, Cheung TK, Wong SY, et al. Management and outcome of peptic ulcers or erosions in patients receiving a combination of aspirin plus clopidogrel. *Journal of Gastroenterology* 2008;43(9):679-686.
189. Yeomans ND, Tulassay Z, Juhász L, Rácz I, Howard JM, van Rensburg CJ, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. *New England Journal of Medicine* 1998;338(11):719-726.
190. Piatkov I, Jones T, Rochester C. Cytochrome P450 loss-of-function polymorphism genotyping on the Agilent Bioanalyzer and clinical application. *Pharmacogenomics* 2009;10(12):1987-1994.
191. Angiolillo DJ, Bernardo E, Sabaté M, Jimenez-Quevedo P, Costa MA, Palazuelos J, et al. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. *Journal of the American College of Cardiology* 2007;50(16):1541-1547.
192. 2004-2005 National Health Survey: Summary of Results. *Australian Bureau Statistics* 2006;4364.0:92.
193. Rosengren A, Wallentin L, Gitt AK, Behar S, Battler A, Hasdai D. Sex, age, and clinical presentation of acute coronary syndromes. *European heart journal* 2004;25(8):663.

194. Ostini R, Hegney D, Mackson J, Williamson M, Tett S. Why is the use of clopidogrel increasing rapidly in Australia? An exploration of geographical location, age, sex and cardiac stenting rates as possible influences on clopidogrel use. *Pharmacoepidemiology and Drug Safety* 2008;17(11):1077-1090.
195. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics—2010 update. *Circulation* 2010;121(7):e46-e215.
196. Rosengren A, Wallentin L, Simoons M, Gitt AK, Behar S, Battler A, et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. *European Heart Journal* 2006;27(7):789.
197. Heer T, Gitt AK, Juenger C, Schiele R, Wienbergen H, Towae F, et al. Gender differences in acute non-ST-segment elevation myocardial infarction. *The American journal of cardiology* 2006;98(2):160-166.
198. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, Lopez-Sendon J, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes. Observations from the Global Registry of Acute Coronary Events (GRACE). *Circulation* 2004;109:494-499.
199. Aliprandi-Costa B, Ranasinghe I, Chow V, Kapila S, Juergens C, Devlin G, et al. Management and outcomes of patients with acute coronary syndromes in Australia and New Zealand, 2000–2007. *The Medical Journal of Australia* 2011;195(3):116.
200. Chew D, Amerena J, Coverdale S, Rankin J, Astley C, Brieger D. Current management of acute coronary syndromes in Australia: observations from the acute coronary syndromes prospective audit. *Internal Medicine Journal* 2007;37(11):741-748.
201. Black H. Smoking and cardiovascular disease. *Hypertension: Pathophysiology, Diagnosis and Management*:2621-2647.
202. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *New England Journal of Medicine* 1987;317(21):1303-1309.
203. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GDO, Fowkes FGR. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease; Edinburgh Artery Study. *European heart journal* 1999;20(5):344.

204. Jonas MA, Oates J, Ockene J, Hennekens C. Statement on smoking and cardiovascular disease for health care professionals. American Heart Association. *Circulation* 1992;86(5):1664.

205. Scollo MM WM, Woodward S, Walker N [editors]. . Tobacco in Australia: facts and issues. Melbourne.: Cancer Council Victoria, 2008.

206. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *The Lancet* 2011;378(9798):1231-1243.

207. McNamara K, Peterson G, Friesen W. Changes in the management of acute myocardial infarction in Southern Tasmania. *Journal of Clinical Pharmacy and Therapeutics* 2000;25(2):111-118.

208. Wai A, Pulver LK, Oliver K, Thompson A. Current discharge management of acute coronary syndromes: Baseline results from a national quality improvement initiative. *Internal Medicine Journal* 2011:doi: 10.1111/j.1445-5994.2010.02308.

209. Cupples ME, Tully MA, Dempster M, Corrigan M, McCall DO, Downey B. Cardiac rehabilitation uptake following myocardial infarction: cross-sectional study in primary care. *The British Journal of General Practice* 2010;60(575):431.

210. Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of Cardiac Rehabilitation on Mortality and Cardiovascular Events after Percutaneous Coronary Intervention in the Community. *Circulation* 2011;123(21):2344.

211. Suaya JA, Stason WB, Ades PA, Normand S-LT, Shepard DS. Cardiac Rehabilitation and Survival in Older Coronary Patients. *Journal of the American College of Cardiology* 2009;54(1):25-33.

212. Grace SL, Russell KL, Reid RD, Oh P, Anand S, Rush J, et al. Effect of cardiac rehabilitation referral strategies on utilization rates: a prospective, controlled study. *Archives of Internal Medicine* 2011;171(3):235.

213. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *The American Journal of Medicine* 2004;116(10):682-692.

214. Bethell H, Lewin R, Dalal H. Cardiac rehabilitation in the United Kingdom. *Heart* 2009;95(4):271-275.

215. Department of Health and Ageing, Heart Research Centre. Patterns of attendance at cardiac rehabilitation. 2009. Available from: http://www.heartresearchcentre.org/about-our-research/past-projects/patterns-of-attendance-at-cardiac-rehabilitation/.

216. Johnson NA, Inder KJ, Nagle AL, Wiggers JH. Attendance at outpatient cardiac rehabilitation: is it enhanced by specialist nurse referral? *Australian Journal of Advanced Nursing* 2010;27(4):31.

217. Jackson L, Leclerc J, Erskine Y, Linden W. Getting the most out of cardiac rehabilitation: a review of referral and adherence predictors. *Heart* 2005;91(1):10.

218. Grace SL, Gravely-Witte S, Brual J, Monette G, Suskin N, Higginson L, et al. Contribution of patient and physician factors to cardiac rehabilitation enrollment: a prospective multilevel study. *European Journal of Cardiovascular Prevention & Rehabilitation* 2008;15(5):548.

219. Shanks LC, Moore SM, Zeller RA. Predictors of cardiac rehabilitation initiation. *Rehabilitation Nursing* 2007;32(4):152.

220. Cortés O, Arthur HM. Determinants of referral to cardiac rehabilitation programs in patients with coronary artery disease: a systematic review. *American Heart Journal* 2006;151(2):249-256.

221. Hughes S. Cardiac rehabilitation: What works, what doesn't, and why. London: Heartwire, 2011. Available from: http://www.theheart.org/article/1257713.do.

222. Clark AM, Barbour RS, White M, MacIntyre PD. Promoting participation in cardiac rehabilitation: patient choices and experiences. *Journal of Advanced Nursing* 2004;47(1):5-14.

223. Cooper AF, Jackson G, Weinman J, Horne R. Factors associated with cardiac rehabilitation attendance: a systematic review of the literature. *Clinical Rehabilitation* 2002;16(5):541-552.

224. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-AC, et al. Why don't physicians follow clinical practice guidelines? *JAMA: The Journal of the American Medical Association* 1999;282(15):1458-1465.

225. Hobbs FDR, Erhardt L. Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. *Family Practice* 2002;19(6):596-604.

226. Chow CK, Jolly S, Rao-Melacini P, Fox KAA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation* 2010:750-58.

227. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 2009;95(1):20.

228. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease. *The Journal of the American Medical Association* 2003;290(1):86.

229. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Archives of Internal Medicine* 2000;160(7):939.

230. Stead L, Bergson G, Lancaster T. Physician advice for smoking cessation. *Cochrane Database System Review* 2008;2(4):1-58.

231. Bock BC, Hudmon KS, Christian J, Graham AL, Bock FR. A tailored intervention to support pharmacy-based counseling for smoking cessation. *Nicotine & Tobacco Research* 2010;12(3):217.

232. Yusuf S, Zhao F, Mehta S. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators [Errata in. *N Engl J Med* 2001;345:1716.

233. Steinhubl S, Berger P, Mann III J, Fry E, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *The Journal of the American Medical Association* 2002;288(19):2411.

234. Berger PB, Bhatt DL, Fuster V, Steg PG, Fox KAA, Shao M, et al. Bleeding Complications With Dual Antiplatelet Therapy Among Patients With Stable Vascular Disease or Risk Factors for Vascular Disease. *Circulation*, 2010:2575-2583.

235. Ray WA, Murray KT, Griffin MR, Chung CP, Smalley WE, Hall K, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors. *Annals of Internal Medicine* 2010;152(6):337.

236. Muntner P, Mann DM, Woodward M, Choi JW, Stoler RC, Shimbo D, et al. Predictors of low clopidogrel adherence following Percutaneous Coronary Intervention. *The American Journal of Cardiology* 2011;108:822– 827.

237. Ho PM, Peterson ED, Wang L, Magid DJ, Fihn SD, Larsen GC, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *The Journal of the American Medical Association* 2008;299(5):532.

238. Pallares MJ, Powers ER, Zwerner PL, Fowler A, Reeves R, Nappi JM. Barriers to clopidogrel adherence following placement of drug-eluting stents. *The Annals of Pharmacotherapy* 2009;43(2):259.

239. Melloni C, Alexander KP, Ou FS, Allen LaPointe NM, Roe MT, Newby LK, et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. *The American Journal of Cardiology* 2009;104(2):175-181.

240. Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS, et al. Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation* 2004;109(16):1930.

241. Anderson CD, Biffi A, Greenberg SM, Rosand J. Personalized Approaches to Clopidogrel Therapy: Are We There Yet? *Stroke* 2010;41(12):2997.

242. Moukarbel GV, Signorovitch JE, Pfeffer MA, McMurray JJV, White HD, Maggioni AP, et al. Gastrointestinal bleeding in high risk survivors of myocardial infarction: the VALIANT Trial. *European Heart Journal* 2009;30(18):2226.

243. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *The American Journal of Medicine* 2006;119(8):624-638.

244. Cryer B. Reducing the risks of gastrointestinal bleeding with antiplatelet therapies. *New England Journal of Medicine* 2005;352(3):287-289.

245. Hernandez-Diaz S, Rodriguez LAG. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Archives of Internal Medicine* 2000;160(14):2093.

246. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, et al. Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated With Aspirin:: The Randomized, Double-Blind OCLA (Omeprazole CLopidogrel Aspirin) Study. *Journal of the American College of Cardiology* 2008;51(3):256-260.

247. Neubauer H, Engelhardt A, Krüger JC, Lask S, Börgel J, Mügge A, et al. Pantoprazole does not influence the antiplatelet effect of clopidogrel-a whole blood aggregometry study after coronary stenting. *Journal of Cardiovascular Pharmacology* 2010;56(1):91.

248. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *The Lancet* 2010;375(9711):283-293.

249. Kleiman NS. PLATO Study of Ticagrelor Versus Clopidogrel in Patients With High-Risk Acute Coronary Syndromes. *Current Cardiology Reports* 2010;12(4):283-285.

250. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *The Lancet* 2009;373(9665):723-731.

251. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *New England Journal of Medicine* 2007;357(20):2001-2015.

252. Unger EF. Weighing benefits and risks—the FDA's review of prasugrel. *New England Journal of Medicine* 2009;361(10):942-945.

253. Storey RF, Bliden KP, Ecob R, Karunakaran A, Butler K, Wei C, et al. Earlier recovery of platelet function after discontinuation of treatment with ticagrelor compared with clopidogrel in patients with high antiplatelet responses. *Journal of Thrombosis and Haemostasis* 2011;9(9):1730-1737.

Chapter 6 – Appendices

Appendix I - Data Collection Form

FACTORS INFLUENCING THE OUTCOMES OF CLOPIDOGREL THERAPY IN PATIENTS WITH ACS - PROJECT

Patient Data Collection Form

1. PATIENT DEMOGRAPHICS

Patient Study Number: _____

1.1 Gender: Male / Female 1.2 Postcode: _____ 1.3 Date of birth: / / _____

1.4 Is this patient:

1. White / Caucasian/European
2. Asian
3. Not stated

2. ADMISSION HISTORY

2.1 Admission date: / / to / /			
2.2 Were any of the following documented in the patient's admission notes:			
	Obesity		Previous CABG
	Dyslipidaemia		Congestive cardiac failure (CCF or CHF)
	Hypertension		Bleeding (details)*
	Diabetes		Peripheral vascular disease
	Previous stroke or TIA		Liver Disease
	Family history of CAD		Renal Impairment
	*details bleeding:		

2.3 Smoking status:							
	Never		Current (cig/day)		Former		Unknown
2.4 Alcohol intake:							
	Non-drinker		Moderate		Heavy drinker		Unknown
2.5 Medications at admission:							

3. CHARACTERISTIC OF IN-HOSPITAL CARE OF PATIENT

Heart Rate on admission	beats/min	Blood pressure on admission	
BMI (if recorded)		Systolic	mmHg
Height	cm	Diastolic	mmHg
Weight	kg	Lipids	
Creatinine Kinase (CK)		Total Cholesterol	mg/dL
Troponin (cTnI)		LDL-C	mg/dL
Left ventricular function	%	HDL-C	mg/dL
		Triglycerides	mg/dL

4. IN-HOSPITAL CARE (during this admission)

4.1 Percutaneous coronary intervention (PCI):							
	Yes				No		
If Yes, Stent type:							
	BMS		DES		Both		Unknown
4.2 Cardiac surgery:							
	Yes				No		
	Note						
4.3 Medication:							
	Clopidogrel				Aspirin		
	Other:						
4.4 Loading dose of clopidogrel:							
	600 mg		300 mg		Other:		
4.5 Maintenance dose of clopidogrel:							
	150 mg		75 mg		Other:		

5. DISCHARGE

5.1 Discharge Diagnosis:							
	Unstable Angina		Non-STEMI		STEMI		Unspecified ACS
5.2 Medications at Discharge:							
	Clopidogrel Dose:				Aspirin		Dose:
	Other:						
5.3 Planned therapy with clopidogrel: (if documented) _____ **months**							
5.4 Patient was given lifestyle advice:							
	Yes				No		
5.5 Patient was planned to receive cardiac rehabilitation services:							
	Yes				No		
5.6 Patient was discharged to:							
	Home		Hostel		Nursing home		Other/Rehab. Hospital
	Note:						

6. READMISSION ( )

6.1 Readmission date: / / to / /							
6.2 Readmission due to:							
	Recurrent ACS*		Bleeding**		Other:		
*If readmission due to recurrent ACS, type of ACS:							
	Unstable Angina		Non-STEMI		STEMI		Unspecified ACS
**If readmission due to bleeding, bleeding details:							
6.3 Smoking status:							
	Never		Current (cigs/day)		Former		Unknown
6.4 Was patient still taking clopidogrel at readmission?							
	Yes				No		
If No, when clopidogrel ceased (if recorded): Reason for clopidogrel cessation (if recorded):							
6.5 Medications at Readmission:							
	Clopidogrel Dose:				Aspirin		Dose:
	Other:						
6.6 Percutaneous coronary intervention (PCI):							
	Yes				No		
If Yes, Stent type							
	BMS		DES		Both		Unknown
6.7 Cardiac surgery:							
	Yes		No		Note:		
6.14 Patient outcome after readmission:							
	Died						
	Discharged to:						
	Home		Hostel		Nursing home		Rehab. hospital
	Other:						
6.5 Medications at Readmission discharge:							
Note for patient readmission:							

Appendix II - Reasons for Contraindication with the Medications

Guideline-Recommended Medications	Reason for Contraindication
Aspirin	• Allergic reaction to aspirin or other NSAID • Active peptic ulcer disease or GI bleeding • Haemophilia or other bleeding disorder
β-blocker	• β-blocker allergy • Bradycardia (heart rate <60bpm) • Reversible airway disease (asthma) • Shock (cardiogenic & hypovolaemic) • Severe hypotension • Uncontrolled heart failure • Sinus sick syndrome • Second or third degree heart block on ECG on arrival or during hospital stay and does not have a pacemaker • Systolic pressure <100mmHg
ACEI/ARB	• Allergy or intolerance to ACE-inhibitors or ARAs • Severe renal dysfunction • Pregnancy • Systolic blood pressure <100mmHg • Renal artery stenosis • Hyperkalaemia (plasma K+ concentration > 5.0 mmol/L)
Statin/LLA	• Allergic to stains or myopathy with lipid lowering agents • Major surgery within a few days • Women planning to conceive or who are using inadequate contraception

Appendix III – Study Letter for Participants

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UNIT FOR MEDICATION OUTCOMES RESEARCH AND EDUCATION
Innovative research. Inspired results.

Factors influencing the outcomes of clopidogrel therapy in patients with acute coronary syndromes: Participant Information Sheet

You are invited to participate in a research study, conducted by the Tasmanian School of Pharmacy. You were selected as a possible participant in this research because you were treated for a heart attack or unstable angina at the Royal Hobart Hospital between July 2007 and December 2009 and discharged from hospital taking a medication called clopidogrel.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. 'What is the background of this study?'

Heart disease is very common in Australia, and heart attacks or unstable angina (conditions collectively known as 'acute coronary syndromes') are a frequent cause of people being admitted to hospital. A large number of procedures and medications are used in hospital to treat people suffering from acute coronary syndromes; however they do not appear to work equally well for everybody. The reasons for this are not entirely clear.

Clopidogrel (brand names include Plavix® and Iscover®) is a very useful anti-clotting medication for people suffering heart attacks or unstable angina. It has been noticed, however, that some people do not experience the full anti-clotting effect of clopidogrel and some are more prone to its major side effect, which is bleeding.

2. 'What is the purpose of this study?'

The purpose of this study is to investigate what happens to people after they leave hospital after a heart attack or episode of unstable angina, especially whether they later need to be readmitted to hospital with another heart attack, a further episode of unstable angina or a bleeding problem.

The major focus of this study is how well clopidogrel works in people after a heart attack or episode of unstable angina. The factors that will be investigated in this study are:

1. what happens when people take other medications that may interfere with the effectiveness of clopidogrel;
2. how people choose to take clopidogrel; and
3. people's genetic ability to 'activate' clopidogrel to its active form in the liver.

This project will form a part of Azizah Vonna's Masters of Pharmacy thesis.

3. 'What does this study involve?'

This study consists of three different parts. **You may choose to participate in one, two, or all three parts of the study.** If you agree to participate in this study, you can indicate which part or parts of the study that you want to be involved in using the attached Participant Consent Form.

The three ways that you can participate in this study are:

1 **Completing the enclosed questionnaire regarding your experiences with clopidogrel and your opinions about taking clopidogrel and returning it in the reply paid envelope provided.** The questionnaire will take about 10 minutes to complete. If you return the questionnaire, we would like to offer you a $25 Coles Myer gift voucher to thank you for your willingness to be involved in our research and to compensate you for your time.

2 **Providing the researchers with permission to contact your regular community pharmacy and ask for the records of the medicines that you had dispensed in the 18 months after you were discharged from hospital.** This will allow us to determine what other medications you were taking that may have interfered with your clopidogrel therapy, and how long you took clopidogrel for, and how often during this period you took it. You can write the name and the address of your usual community pharmacy on the Participant Consent Form provided and return it in the reply paid envelope.

3 **Providing a saliva sample using a swab of the inside of your cheek and returning it to us by mail.** This will provide us with a small amount of your genetic material which will be used to determine the influence of your genetics on the activity of specific enzymes within your liver and therefore your body's ability to activate clopidogrel.

If you consent to participate in this part of the study, the researchers will contact you again to arrange the test which will be posted to you to complete at home. Your genetic material will be destroyed after the analysis. All the information gathered for this study (including genetic material) will only be used by the investigators for research into genetic differences as outlined in this Information Sheet. Genetic material will not be retained for any other unspecified genetic testing.

4. 'What are the risks associated with these procedures?'

There are no additional risks involved in participating in this study. The genetic testing that will be performed is only to assess the influence of liver enzyme activity on

clopidogrel activation; this can be done simply by swabbing of the inside of your cheek. The risks of harm or discomfort from this study are very low.

5. 'What are the benefits of this study?'
Your participation may contribute to a better understanding of people's different responses to clopidogrel therapy. This may lead to future improvements in anti-clotting therapy for patients like you, with the aim of reducing the risks of heart attacks, unstable angina and bleeding episodes for these patients.

6. 'What happens if I don't want to take part in the study?'
Participation is entirely voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect your future care.

7. 'How will my confidentiality be protected?'
All information will be treated in a confidential manner and all data, including your genetic information, will be coded against a unique identifying number so your personal information will be protected. Your name and any other personal information will not be used in reports or publications resulting from this study. All of the information collected as part of this research will be kept in secure storage in the School of Pharmacy and will be destroyed after a period of 5 years in line with University regulations.

8. 'What should I do if I want to discuss this study further before I decide?'
When you have read this information, if you have any queries regarding this study or your participation in this study, please do not hesitate to contact one of the study investigators listed below:

Azizah Vonna
Telephone: (03) 6226 8535; Email: vazizah@utas.edu.au

Leanne Stafford (PhD candidate)
Telephone: (03) 6226 1024; Email: Leanne.Stafford@utas.edu.au

Dr Luke Bereznicki (Senior Lecturer and Senior Research Fellow)
Telephone: (03) 6226 2195; Email: Luke.Bereznicki@utas.edu.au

Professor Gregory Peterson (Professor of Pharmacy and Head of School)
Telephone: (03) 6226 2197; Email: G.Peterson@utas.edu.au

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H11606.

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix IV – Questionnaire

Tasmanian School of Pharmacy
Private Bag 26
HOBART TASMANIA 7001
Telephone (03) 6226 2190
Fax (03) 6226 7627

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Factors Influencing the Outcomes of Clopidogrel Therapy in Patients with Acute Coronary Syndromes: Questionnaire

Thank you for choosing to participate in this survey. The survey will take about 10 minutes to complete. It contains questions related to your experiences with clopidogrel and opinions about taking clopidogrel.

Please tick the relevant boxes and feel free to add comments on the lines provided. We realise that it may be some time since you started taking clopidogrel and you might not remember all the details. Please just answer the questions as accurately as you can. We are interested in your thoughts and experiences – there are no right or wrong answers.

Part A: Clopidogrel Therapy Details

Our data indicate that have been treated with clopidogrel (brand names include Plavix® and Iscover®, or CoPlavix® or Duocover® in combination with aspirin) in recent years.

1. Sometimes people take clopidogrel for a short time (e.g. 6-12 months), and sometimes people are asked to take it for an extended period (e.g. longer than 12 months).

   Are you still taking clopidogrel?

   ☐ Yes – *please go to Question 2*

   ☐ No

2. Approximately when did you stop treatment with clopidogrel?

☐ I stopped taking clopidogrel in _____ (Month)/ _____(Year)

OR if you can't remember the exact time, please indicate approximately how many months ago you stopped taking clopidogrel

_____ months ago

☐ Unsure

3. Why did you stop taking clopidogrel at this time? (Please choose the ONE response that most closely reflects your experience with clopidogrel)

☐ My doctor told me that it was no longer required

☐ My doctor stopped it because I was having problems with bleeding

☐ My doctor changed it to another medication

☐ The medicine was too expensive

☐ I didn't realise I needed to keep taking it

☐ Other reason

☐ I decided not to take it any more

☐ Unsure

Please provide any further details about why you have stopped taking clopidogrel here:

_____

_____

_____

_____

4. Have you experienced any bleeding problems while taking clopidogrel?

☐ Yes

☐ No– *please go to Question 3*

☐ Unsure

a. Did these problems result in you being admitted to hospital?

- ☐ Yes
- ☐ No
- ☐ Unsure

Please provide further details of your bleeding problems below (if known):

_____

_____

5. Since your first hospital admission due to a heart attack or unstable angina, have you experienced any readmissions to a hospital apart from the Royal Hobart Hospital due to another heart attack or episode of unstable angina?

- ☐ Yes
- ☐ No
- ☐ Unsure

Please provide further details below (if known):

_____

_____

_____

6. Did you take a daily dose of aspirin while you were taking clopidogrel?

- ☐ Yes, my doctor wrote me a prescription for it which I had dispensed at my community pharmacy
- ☐ Yes, I bought it over-the-counter at my pharmacy or supermarket
- ☐ No
- ☐ Unsure

7. Do you smoke cigarettes or another form of tobacco?

   ☐ Yes

   If you answered "Yes", approximately how many cigarettes would you smoke on a normal day? _____

   ☐ No

8. Do you drink alcohol?

   ☐ Yes

   If you answered "Yes", approximately how many standard drinks would you drink in a normal week? _____

   ☐ No

9. It is recommended in certain situations that people attend cardiac rehabilitation after a heart attack or unstable angina but not everyone is able to attend. Do you remember being referred to cardiac rehabilitation after your first admission to the Royal Hobart Hospital due to a heart attack or unstable angina?

   ☐ Yes

   ☐ No

   ☐ Unsure

   If you answered "Yes", did you attend the rehabilitation program?

   ☐ Yes – attended all sessions

   ☐ Yes – attended some sessions

   ☐ No – why not? (For example, you found that you were too busy, you returned to work, etc.)

   _____

   _____

   _____

   _____

Please list all the current medications that you are taking (please include eye drops, inhalers, herbal and vitamin supplements and medicines that you buy in a pharmacy or supermarket).

Medicine name	Dose or strength	How often do you take it?

Part B: MARS Questionnaire

Many people find a way of using clopidogrel which suits them. This may differ from the instructions on the label or from what their doctor has said. Below are some ways in which people have said they use their clopidogrel. ***For each statement, please tick the box which best applies to you in relation to your clopidogrel therapy, or if you've stopped taking clopidogrel, please tick the box which best applied to you while you were taking clopidogrel.***

		Never	Rarely	Sometimes	Often	Very often
1	**I alter the dose**	☐	☐	☐	☐	☐
		Never	Rarely	Sometimes	Often	Very often
2	**I forget to take it**	☐	☐	☐	☐	☐
		Never	Rarely	Sometimes	Often	Very often
3	**I stop taking it for a while**	☐	☐	☐	☐	☐
		Never	Rarely	Sometimes	Often	Very often
4	**I decide to miss out a dose**	☐	☐	☐	☐	☐
		Never	Rarely	Sometimes	Often	Very often
5	**I take less than instructed**	☐	☐	☐	☐	☐

Thank you for your time and honesty.

Please place your completed survey in the envelope provided and place it in the mail.

Appendix V – Consent Form

Tasmanian School of Pharmacy
Private Bag 26
HOBART TASMANIA 7001
Telephone (03) 6226 2190
Fax (03) 6226 7627

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Factors influencing the outcomes of clopidogrel therapy in patients with acute coronary syndromes: Participant Consent Form

1. I have read and understood the 'Information Sheet' for this study.

2. *Please indicate which part or parts of the study that you want to be involved in by ticking the boxes below.*

I would like to participate in this study by:

☐ completing the questionnaire attached,

☐ providing the researchers with the name of my regular community pharmacy and permission to access the records of the medicines I've had dispensed to me for the 18 months after I was discharged from hospital taking clopidogrel,

Name of pharmacy: _____

Pharmacy address: _____

_____

_____

☐ providing a saliva sample using a swab of the inside of my cheek to allow the researchers to determine the influence of my genetics on the activity of my liver enzymes responsible for activating clopidogrel.

3. I have been informed that the results of the study may not be of any direct benefit to my medical management.

4. If I agreed to providing a saliva sample in Part 2, I agree to allow my sample to be used for genetic determination as described above, and the sample will not be used for purposes other than those agreed to in this consent form. I understand that the genetic material collected will be destroyed after the genetic analysis.

5. If I agreed to providing a saliva sample in Part 2, the result of my genetic test, and the fact that I had a test, will not be revealed to any other person or organisation without my written consent except under court order.

6. I agree to participate in this investigation and understand that I may withdraw at any time without prejudice.

7. I agree that research data gathered for the study may be published provided that I cannot be identified.

8. Any questions I have asked have been answered to my satisfaction.

Name of participant: _____

Signature: _____

Date: _____

Statement by Investigator

☐ I have explained the project & the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation

Name of Investigator _____

Signature of Investigator _____

Appendix VI – Study Letter for Pharmacists

Tasmanian School of Pharmacy
Private Bag 26
HOBART TASMANIA 7001
Telephone (03) 6226 2190
Fax (03) 6226 7627

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2 June 2011

Dear Pharmacist,

Re: "Factors influencing the outcomes of clopidogrel therapy in patients with acute coronary syndromes" study.

The Tasmanian School of Pharmacy is currently undertaking a research project that aims to collect information on how patients use their medications after they leave hospital following an admission for acute coronary syndrome (ACS). In particular, we are focusing on assessing patients' adherence in taking clopidogrel, and their experiences while taking the drug. This project forms Azizah Vonna's Masters degree.

As you would know, clopidogrel is a very useful antiplatelet medication for people with coronary artery disease. It is recognised, however, that some people do not experience the full antithrombotic effect of clopidogrel and some are more prone to its major adverse effect, which is bleeding.

The purpose of this study is to investigate what happens to patients following their ACS-related hospital admission, especially whether they later need to be readmitted to hospital due to recurrent ACS or a bleeding problem.

The factors that will be investigated in this study include:

- what happens when people take other medications that may interfere with the effectiveness of clopidogrel; and
- how people choose to take clopidogrel.

We are writing to you to request your involvement in our project. Briefly, we have identified a group of patients who have consented to take part in our study. These patients have consented to the release of their dispensing history for the time following their ACS-related hospital admission to allow us to review their adherence and persistence to clopidogrel during this time.

The patients listed below indicated that your pharmacy is their regular pharmacy and have provided their consent (see the attached consent form) for their dispensing history to be released to the project team. Please provide their complete dispensing record for the specified period of time using the postage-paid envelope provided. This information will

provide details of how long the patients took clopidogrel and the use of any potentially interacting drugs.

An honorarium of $10 per patient is being offered for your assistance with this project.

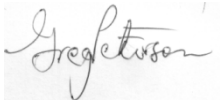
This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H11606.

If possible, we would be very grateful if you could send us the patients' dispensing record by Friday, 17 June.

Thank you for your assistance. Please do not hesitate to contact us if you have any questions.

Yours sincerely,

Ms Azizah Vonna
MPharm candidate



Professor Gregory Peterson
Professor of Pharmacy and Head of School

Dr Luke Bereznicki
Senior Research Fellow, Senior Lecturer in Pharmacy Practice

Miss Leanne Stafford
PhD candidate

TASMANIAN SCHOOL OF PHARMACY
Telephone: (03) 6226 8535
Email: vazizah@utas.edu.au

Appendix VII – Study Letter for Patients Consent for Genotyping

Tasmanian School of Pharmacy
Private Bag 26
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Telephone (03) 6226 2190
Fax (03) 6226 7627

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Dear MR/MRS

We would like to thank you for agreeing to participate in this part of our study, **"Factors influencing the outcomes of clopidogrel therapy in patients with acute coronary syndromes"**.

You will find enclosed a request form and TWO swabs which you can use to provide us with a sample of your saliva from the inside of your cheeks. Please follow the sampling procedure below to ensure the best possible results.

The swabs need to be posted back to our research partner, Diversity Health Institute, AS SOON AS POSSIBLE after you have performed your test.

1. The presence of food particles in the mouth can sometimes interfere with the test. **Please perform the test when your mouth is free of food – for example, between meals and not too soon after eating.**
2. **Check your details in the "Patient Details" section of the "Research Test Request" form.** If any of the information is incorrect, please correct it on the form.
3. **Write the date and time** that you perform the test in the highlighted box in the top right hand corner ("Date and Time Collected").
4. **Open the packaging of one of the buccal swabs and carefully remove the swab.** Do not touch the tip.
5. **Open your mouth and scrape the collection tip firmly against the inside of one cheek 5 or 6 times.**

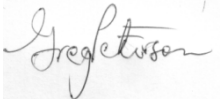
6. **Carefully put the swab back into the labelled collection tube.**
7. **Repeat the procedure with the second swab using the other cheek.**
8. **Please place the "Research Test Request" form and both swabs in the paid postage envelope provided and <u>post immediately</u>**. This can be posted in any usual post box.

Please do not hesitate to contact us if you have any questions. We will be happy to talk you through the process.

If possible, we would be very grateful if you could return the swabs by Wednesday, 06 July.

Yours sincerely,

Ms Azizah Vonna
MPharm candidate



Professor Gregory Peterson
Professor of Pharmacy and Head of School

Dr Luke Bereznicki
Senior Research Fellow, Senior Lecturer in Pharmacy Practice

Miss Leanne Stafford
PhD candidate

TASMANIAN SCHOOL OF PHARMACY
Telephone: (03) 6226 8535
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Appendix VIII – Request Form for Genotype Profile

Diversity Health Institute

SYDNEY WEST AREA HEALTH SERVICE | NSW HEALTH

Research Test Request

DHI Laboratory, Level 2 ICPMR,
Westmead Hospital, Westmead, 2145, NSW

NATA

Phone: (02) 9845 8755
Fax: (02) 9845 6334

Patient Information

Last Name	First Name	Middle Initial	Date and Time Collected

Date of Birth	Sex	Project / File number
/ /	Male ☐ Female ☐	

Address

Postcode

Requester

Name	Signature

Postal address for results

Email address

Preferred delivery:
- ☐ Post
- ☐ Fax
- ☐ Email

Test Requested

Indicate the required test :

- ☐ CYP 2D6
- ☐ CYP 2C9
- ☐ CYP 2C19
- ☐ Combination (all three CYP)
- ☐ PPAR
- ☐ HLA-B*1502
- ☐ IL6
- ☐ GST M1
- ☐ GST P1
- ☐ GST T1
- ☐ Combination (all three GST)
- ☐ MTRR
- ☐ VKORC1

or:

Indicate the drug(s) of interest on the form overleaf
or
Specify drug not listed in the table to be considered for cytochrome P450 related drug interactions only:

.....

Specimen Collection for research genetic testing

Suitable specimens are whole blood with EDTA, ACD or heparin preservative, and buccal swabs collected with flocked nylon swabs in dry transport tube (supplied by the laboratory).

Blood:

Whole blood samples with EDTA, ACD or heparin can be used and may be either fresh or frozen.
Minimum volume 0.5 mL.
Follow standard procedures for venipuncture.
Transport at 4°C or -20°C.

Buccal swabs:

Follow the sampling procedure to ensure the optimum DNA recovery and to avoid sample contamination.

- Open the buccal swab packaging and carefully remove the swab. Do not touch the tip.
- Scrape the collection tip firmly against the inside of the cheek 5-6 times.
- Carefully put the tip into labelled collection tube.
- Repeat the sampling procedure with another swab using the other cheek.

After collection swabs can be kept at room temperature if posted immediately. If storage is necessary, freeze the tubes at -20°C.

For lab use only:

Date/time received:	Case No.:	Received by:

Specimen: ☐ Blood ☐ Buccal swab ☐ Other (specify) .....

 03/10 DHILF-109 Page 1 of 2

Appendix IX – Ethics Approval