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

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Submitted in fulfilment of the requirements for the Degree of Master of Pharmacy

University of Tasmania
School of Pharmacy
May 2013
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.

To the best of my knowledge and belief, this thesis contains no material previously published or written by any other person except where due reference is made in the text of the thesis.

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18th May 2013
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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government’s Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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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18th May 2013
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## Abbreviations

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

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
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>TSI</td>
<td>Torres Strait Islands</td>
</tr>
<tr>
<td>UA</td>
<td>unstable angina</td>
</tr>
<tr>
<td>VASP</td>
<td>vasodilator-stimulated phosphoprotein</td>
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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.