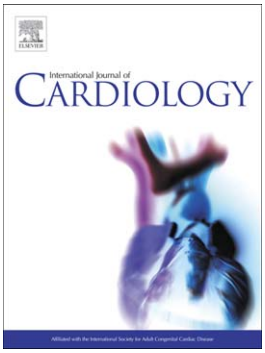
Accepted Manuscript



The Underutilisation of Dual Antiplatelet Therapy in Acute Coronary Syndrome

Malcolm Anastasius, Jerrett K. Lau, Karice Hyun, Mario D'Souza, Anushka Patel, Jamie Rankin, Darren Walters, Craig Juergens, Bernadette Aliprandi-Costa, Andrew T. Yan, Shaun G. Goodman, Derek Chew, David Brieger

PII: S0167-5273(17)30303-0
DOI: doi:10.1016/j.ijcard.2017.04.077
Reference: IJCA 24921

To appear in: *International Journal of Cardiology*

Received date: 20 January 2017
Revised date: 1 April 2017
Accepted date: 21 April 2017

Please cite this article as: Anastasius Malcolm, Lau Jerrett K., Hyun Karice, D'Souza Mario, Patel Anushka, Rankin Jamie, Walters Darren, Juergens Craig, Aliprandi-Costa Bernadette, Yan Andrew T., Goodman Shaun G., Chew Derek, Brieger David, The Underutilisation of Dual Antiplatelet Therapy in Acute Coronary Syndrome, *International Journal of Cardiology* (2017), doi:10.1016/j.ijcard.2017.04.077

TITLE PAGE

TITLE: The Underutilisation of Dual Antiplatelet Therapy in Acute Coronary Syndrome

Authors, affiliations, address for correspondence

Malcolm Anastasius MBBS MMed FRACP[a], Jerrett K. Lau MBBS FRACP[a], Karice Hyun MAppStat[b], Mario D'Souza PhD MSc[c], Anushka Patel MBBS PhD FRACP[b], Jamie Rankin MBBS FRACP[d], Darren Walters MBBS MPhil FRACP[e], Craig Juergens MBBS D MedSc FRACP[f], Bernadette Aliprandi-Costa BHSc[g], Andrew T. Yan MD[h], Shaun G. Goodman MD MSc[h], Derek Chew MBBS MPH FRACP[i], David Brieger MBBS MMed PhD FRACP[a*]

[a]Department of Cardiology, Concord Repatriation General Hospital, University of Sydney, Sydney, Australia. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[b]The George Institute for Global Health, Sydney Medical School, University of Sydney, Sydney, Australia. This author contributed in the formulation of the concept and critical analysis of this manuscript.

[c]School of Public Health, University of Sydney, Sydney, Australia;
Clinical Research Centre, Sydney Local Health District, Sydney, Australia. This author contributed in the formulation of the concept and critical analysis of this manuscript.

[d]Department of Cardiology, Fiona Stanley Hospital, Perth, Australia. This author contributed in the formulation of the concept and critical analysis of this manuscript.

[e]Department of Cardiology, Prince Charles Hospital, University of Queensland, Brisbane, Australia. This author contributed in the formulation of the concept and critical analysis of this manuscript.

[f]Department of Cardiology, Liverpool Hospital, University of New South Wales, Sydney, Australia. This author contributed in the formulation of the concept and critical analysis of this manuscript.

[g]Sydney Medical School, The University of Sydney, Sydney, Australia. This author contributed in the formulation of the concept and critical analysis of this manuscript.

[h]Division of Cardiology, St. Michaels Hospital, University of Toronto, Toronto, Canada. This author contributed in the formulation of the concept and critical analysis of this manuscript.

[i]Department of Cardiology, Flinders University, Adelaide, Australia. This author contributed in the formulation of the concept and critical analysis of this manuscript.

*Corresponding author at: Department of Cardiology, Concord Repatriation General Hospital, 1A Hospital Road, Concord, NSW 2139, Australia. Tel.: +(612) 9767 6296; fax: +(612) 9767 6994.

Email: dbrieger@uni.sydney.edu.au

Word Count: 2690

The Underutilisation of Dual Antiplatelet Therapy in Acute Coronary Syndrome

ABSTRACT

Background: Despite guideline recommendation of dual antiplatelet therapy (DAPT) in treating ACS, DAPT is underutilized. Our objective was to determine independent predictors of DAPT non-prescription in ACS and describe pattern of DAPT prescription over time.

Methods: Patients presenting to 41 Australian hospitals with an ACS diagnosis between 2009 and 2016 were stratified according to discharge prescription with DAPT and single antiplatelet therapy (SAPT) or no antiplatelet therapy. Multiple stepwise logistic regression, accounting for within hospital clustering, was used to determine the independent predictors of DAPT non-prescription, defined as discharge with SAPT alone or no antiplatelet agent.

Results: 8939 patients survived to discharge with an ACS diagnosis. Of these, 6294 (70.4%) patients were discharged on DAPT, 2154 (24.1%) on SAPT and 491 (5.5%) on no antiplatelet agent. Independent predictors of DAPT non-prescription in the overall cohort were: in-hospital CABG (OR 0.09, 95%CI 0.05-0.14), discharge with warfarin (0.10 (0.07-0.14)), in hospital major bleeding (0.48 (0.34-0.67), diagnosis of unstable angina (0.35, (0.27-0.45)), non-ST-elevation myocardial infarction (0.67 (0.57-0.78)) [both vs. ST-segment elevation myocardial infarction], in hospital atrial arrhythmia (0.72 (0.60-0.86)), history of hypertension (0.83 (0.73-0.94)) and GRACE high risk (0.83 (0.71-0.98)). There was an increase in prescription of DAPT and a shift towards ticagrelor over clopidogrel for ACS from

2013 to 2016 ($p<0.0001$), but no overall change in the frequency of DAPT prescription over the entire study period.

Conclusion: This study revealed high-risk ACS subgroups who do not receive optimal DAPT. Strategies are necessary to bridge the treatment gap in ACS antiplatelet management.

Keywords: Dual antiplatelet therapy, Acute Coronary Syndrome

The Underutilisation of Dual Antiplatelet Therapy in Acute Coronary Syndromes

INTRODUCTION

The benefit of dual antiplatelet therapy (DAPT) in patients presenting with ACS is both clinically important and unequivocal [1] . This is true for both ST-segment elevation acute coronary syndrome (STEACS) [2, 3] and non-ST elevation acute coronary syndrome (NSTEACS) [1]. However, there are treatment gaps in the management of patients with an ACS, with studies during the 2000's reporting anywhere from 30% to 50% of ACS patients being discharged on single antiplatelet therapy [4, 5].

Since that time, newer, more potent alternatives to clopidogrel have been shown to further improve outcomes across the spectrum of ACS [6, 7]. Yet as recently as 2012, a comprehensive Australian and New Zealand audit encompassing over 90% of hospitals across both countries showed that only 63% of ACS patients received a second antiplatelet agent at hospital discharge[8]. In all reported studies, one consistent observation was the difference between prescription of a second antiplatelet for patients following PCI (percutaneous coronary intervention), where rates were higher than for those undergoing CABG or medical management, despite a consistent accumulation of evidence supporting the use of these second agents in each of these contexts [9-11]

There remains a significant risk of events following an ACS, with mortality in the 12-18 months following an ACS reported to be 12.6%, and the composite rate of myocardial infarction, stroke or cardiovascular death to be 18.3% [12, 13]. Therefore, there is a

continued need to improve clinical outcomes in patients with an ACS by bridging the gap in antiplatelet therapy prescription at hospital discharge [14]. Indeed, modelling studies have suggested that up to 10.9% of deaths by 6 months may be prevented through implementation of adenosine diphosphate (ADP) receptor antagonist therapy following an ACS[14].

The aims were: first, to better understand the Australian practice of DAPT prescription at hospital discharge following acute coronary syndrome; second, to determine the independent predictors of DAPT non-prescription; and third, to evaluate the impact of the availability of newer ADP receptor antagonists on the pattern of prescription of DAPT over time.

METHODS

Study population

This study reports individual patient data from the Australian CONCORDANCE (Cooperative National Registry of Acute Coronary Care, Guideline Adherence and Clinical Events), an ongoing prospective registry, which has recruited patients from 41 hospitals since 2009. Methods for this study have been published [15] and are summarised briefly below.

To be included in CONCORDANCE patients were at least 18 years of age, and presented with symptoms suggestive of coronary ischaemia together with either ECG changes, elevation of serum cardiac biomarkers of myocardial necrosis or documented coronary artery disease.

ACS events precipitated by non-cardiovascular co-morbidities such as anaemia or trauma (including Type 2 myocardial infarction) were excluded. The first 10–20 consecutive eligible patients were recruited from each site per month. Trained coordinators using standardised case report forms collected data. Demographic characteristics, medical history, presenting symptoms, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardised definitions for all patient-related variables and clinical diagnoses were used. This analysis included patients enrolled between 2009 and 2016 with a discharge diagnosis of confirmed ACS.

Outcome measures

The principal objective of the study was to determine the predictors of DAPT non-prescription at discharge following admission for an ACS. DAPT was defined as discharge prescription with a combination of aspirin plus one of clopidogrel, prasugrel or ticagrelor. Single antiplatelet therapy (SAPT) was prescription at discharge with one of these agents alone. DAPT non-prescription at ACS discharge was defined as prescription of SAPT alone or no antiplatelet agent.

Statistical analysis

ACS patients discharged alive on DAPT, SAPT or no antiplatelet therapy were included in this analysis. Analyses were performed in the ACS population as a whole, as well as the subgroups of patients who were medically managed. We also examined the pattern of

antiplatelet prescription according to year of admission. Baseline patient demographics were compared between patients discharged with DAPT and SAPT/no antiplatelet agent following admission with ACS using the Rao-Scott chi-square test for categorical variables and univariable regression model for continuous variables, accounting for clustering of patients within hospitals. The frequency of DAPT prescription at discharge was determined for all patients and then also for those managed medically without PCI or CABG. Univariable unadjusted predictors were used in building a multivariable model to identify the independent predictors for non-prescription of DAPT at discharge. The covariates were added to the logistic regression model using stepwise selection. Missing values were present in <5% of the data. A 2-tailed alpha-level of 0.05 was considered the threshold for statistical significance for all tests. To account for within-hospital clustering, the regression models were built using a logistic generalized estimating equations method with exchangeable working correlation matrix, because patients at the same hospital are more likely to be similar and have similar responses relative to patients at other hospitals. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for the statistical analysis.

RESULTS

Baseline characteristics

This study included 8939 patients who survived to discharge with a final diagnosis of ACS. Of these, 6294 (70.4%) patients were discharged with DAPT, and 2645 (29.6%) were discharged with SAPT or no antiplatelet agent. Of those receiving SAPT, the majority were given aspirin (89.5%), followed by clopidogrel (9.8%), then ticagrelor (0.6%) or prasugrel (0.1%) alone.

Those prescribed SAPT/no antiplatelet agent compared with those prescribed DAPT at discharge were older (p<0.0001) and of high GRACE risk (p<0.0001) with greater prevalence of comorbidities (Table 1).

Table 1: Baseline characteristics for the overall cohort of patients admitted with ACS and survived to discharge.

Variable	Statistic/Level	DAPT n=6294 n (%)	Other* n=2645 n (%)	Overall n=8939 n (%)	P-value
Age (years)	**Mean**	63.3	67.3	64.5	<0.0001
	SD	13.28	13.22	13.39	.
Sex	**Female**	1642 (26)	938 (35)	2580 (29)	<0.0001
	Male	4652 (74)	1707 (65)	6539 (71)	.
GRACE risk score**	**Median (q1, q3)**	102.6 (82.9, 124.0)	107.0 (84.6, 131.3)	103.9 (83.3, 125.9)	<0.0001
GRACE risk score categories	**Low**	3485 (57)	1304 (51)	4789 (56)	<0.0001
	Intermediate	1849 (30)	805 (32)	2654 (31)	.
	High	739 (12)	441 (17)	1180 (14)	.
Previous myocardial infarction		1783 (28)	812 (31)	2595 (29)	0.003
Previous angiographic coronary artery disease		2088 (33)	1008 (38)	3096 (35)	0.0003
Previous Coronary Intervention		1399 (22)	464 (18)	1863 (21)	<0.0001
Previous CABG		641 (10)	368 (14)	1009 (11)	<0.0001
Prior diagnosis of CAD		1293 (21)	733 (28)	2026 (23)	<0.0001
Family history of CAD		2239 (36)	828 (31)	3067 (34)	0.0008
Diabetes Mellitus		1614 (26)	818 (31)	2432 (27)	<0.0001
Hypertension		3719 (59)	1825 (69)	5544 (62)	<0.0001
Dyslipidaemia		3475 (55)	1586 (60)	5061 (57)	0.0002
Congestive heart failure		363 (6)	300 (11)	663 (7)	<0.0001
Previous mechanical valve replacement		39 (1)	59 (2)	98 (1)	<0.0001

Variable	Statistic/Level	DAPT n=6294 n (%)	Other* n=2645 n (%)	Overall n=8939 n (%)	P-value
Chronic Renal Failure		441 (7)	299 (11)	740 (8)	<0.0001
Previous stroke or transient ischemic attack		376 (6)	251 (9)	627 (7)	<0.0001
Peripheral arterial disease		336 (5)	208 (8)	544 (6)	<0.0001
Smoking history	**Never**	2145 (34)	1011 (38)	3156 (35)	<0.0001
	Ex-smoker	2108 (34)	1075 (41)	3183 (36)	.
	Current smoker	2020 (32)	554 (21)	2574 (29)	.
Previous major bleed		108 (2)	75 (3)	183 (2)	0.0006

Data presented using non-missing data. *Other: discharge with SAPT or no antiplatelet at discharge, **GRACE score predicting risk of death and myocardial infarction in the six months after ACS presentation [16]. CABG: coronary artery bypass grafting surgery, CAD: coronary artery disease, DAPT: dual antiplatelet therapy, GRACE: Global registry of acute coronary events, SAPT: single antiplatelet therapy, SD: standard deviation.

There was a difference in the rate of prescription of DAPT according to ACS diagnosis, whereby patients with STEMI were most likely and those with UA least likely to be prescribed DAPT (Table 2). Furthermore, there was a gradient of prescription of DAPT associated with the presence and mode of revascularisation; patients undergoing PCI were most likely, those medically managed were intermediate, and those undergoing CABG least likely to be discharged on DAPT. In patients undergoing CABG, those prescribed SAPT or no antiplatelet compared to those prescribed DAPT were more likely to have a history of hypertension or to have been discharged with warfarin; to have a previous history of bleeding or to have in hospital major bleeding (table 4-6, supplementary data).

It was noteworthy that more than 40% of the medically managed cohort were discharged on SAPT or no therapy (Figure 1a-b, supplementary data).

Table 2 ACS diagnosis, in hospital revascularisation strategy and events

Diagnosis/Procedures/ Complications/ Discharge medication	Level	DAPT n=6294 [%]	Other* n=2645 [%]	Overall n=8939 n (%)	P-value
Diagnosis	**STEMI**	2349 (37)	360 (14)	2709 (31)	<0.0001
	NSTEMI	3000 (49)	1435 (54)	4435 (50)	
	UA	945 (15)	850 (32)	1795 (20)	
Percutaneous coronary intervention		4144 (66)	146 (6)	4290 (48)	<0.0001
Fibrinolysis**		776 (33)	141 (39)	917 (34)	<0.0001
Coronary artery bypass grafting		103 (2)	671 (25)	774 (9)	<0.0001
Cardiogenic Shock		86 (1)	39(1)	125 (1)	0.6
Congestive Failure		354 (6)	296 (11)	650 (7)	<0.0001
Renal Failure		210 (3)	176 (7)	386 (4)	<0.0001
Cardiac Arrest		128 (2)	37 (1)	165 (2)	0.005
AV-Block		67 (1)	40 (2)	107 (1)	0.08
Atrial arrhythmia		382 (6)	470 (18)	852 (10)	<0.0001
Sustained VT		90 (1)	46 (2)	136 (2)	0.2
Stroke		20 (0.4)	21 (1)	41 (0.4)	0.0009
Major Bleeding		367 (6)	324 (12)	691 (8)	<0.0001

Data presented using non-missing data. *Other: discharge with SAPT or no antiplatelet at discharge, **Values expressed as a percentage of patients admitted with STEMI.
NSTEMI: non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction, UA: unstable angina.

Referral to cardiac rehabilitation and discharge medication

Patients prescribed DAPT were more likely to have been referred for cardiac rehabilitation and to be discharged on other evidence based medications including angiotensin-converting enzyme inhibitors, statins and beta-blockers. ((Table 1, supplementary data). Warfarin was prescribed more frequently for patients on SAPT or no antiplatelet.

Independent predictors of DAPT non-prescription

The independent predictors of DAPT non- prescription at discharge in the full cohort were: in-hospital CABG, discharge with warfarin, in hospital major bleeding, diagnosis of unstable angina or non-ST-elevation myocardial infarction [both vs. ST-segment elevation myocardial infarction], in hospital atrial arrhythmia, history of hypertension and GRACE high risk (0.83 (0.71-0.98)). Factors predicting a greater likelihood of DAPT prescription were prior MI, in hospital PCI (percutaneous coronary intervention), previous coronary intervention and discharge with ACEI (angiotensin-converting enzyme inhibitor), beta-blocker or statin. [Figure 1(a)].

Medically managed patients

Amongst those admitted with an ACS, 3922 (43.9%) patients were medically managed. Of these, 2063 (52.6%) were prescribed DAPT and 1859 (47.4%) SAPT or no antiplatelet at discharge. Those prescribed SAPT or no antiplatelet compared with those prescribed DAPT at discharge were older ($p<0.0001$), of high GRACE risk ($p=0.0006$), had a history of congestive heart failure ($p=0.04$), previously undergone mechanical valve replacement ($p<0.0001$) and experienced greater in hospital congestive cardiac failure, atrial arrhythmia and major bleeding (table 2-3, supplementary data)

Independent predictors of DAPT non-prescription in the medically managed cohort

The independent predictors of DAPT non-prescription at discharge amongst those medically managed included: discharge with warfarin, in hospital major bleeding, NSTEMI, unstable angina (both vs STEMI) and in hospital atrial arrhythmia. History of hypertension neared significance as an independent predictor of DAPT non-prescription [Figure 1(b)].

Antiplatelet prescription according to year of admission with ACS

Overall there was no discernible trend ($p=0.2$) in the percentage of patients with DAPT and SAPT prescription between 2009 and 2016 [Figure 2(a)]. However, when the analysis was restricted to the years from 2013, there was evidence for an increasing trend in DAPT prescription (69.4% in 2013 to 78.4% in 2016, $p<0.0001$, test for trend). There was an absolute 12.9% increase in ticagrelor prescription over this time period ($p<0.0001$), and a modest 7.0% decrease in clopidogrel prescription. Prasugrel prescription for ACS remained low throughout the study period, with prescription rates not exceeding 5% (since availability of the drug in 2011).

In the cohort of medically managed patients, there was a gradual decrease in DAPT prescription and increase in SAPT prescription between 2010 and 2013; this trend was reversed from 2013 to 2016 [Figure 2(b)]. There was an absolute 11.5% increase in ticagrelor prescription ($p<0.0001$), accompanied by a small 2.6% decline in clopidogrel prescription.

DISCUSSION

This study describes patterns of DAPT use in a real world cohort of Australian ACS patients over a 7-year period. A gap in DAPT use was identified with an overall prevalence of 70.4% at discharge. The independent predictors of DAPT non-prescription at ACS discharge were: in-hospital CABG, discharge with warfarin, in hospital major bleeding, diagnosis of unstable angina or non-ST-elevation myocardial infarction [both vs. ST-segment elevation myocardial infarction], in hospital atrial arrhythmia, history of hypertension and GRACE high risk. Despite no overall changes in patterns of DAPT prescription in the overall study period, in more recent years from 2013 to 2016 there was an increasing trend in DAPT prescription, paralleled by a significant absolute increase in ticagrelor use.

Although the 30% failure rate of DAPT prescription in ACS patients is contrary to the strong evidence base [1, 6, 7], these data are consistent with other representative local and international studies. In the CRUSADE registry, use of clopidogrel was 73% during 2004 and 2005[5]. The third EUROHEART survey conducted during 2007 reported discharge clopidogrel prescription of 76.4%. More recently, the Australian and New Zealand SNAPSHOT ACS study representing >90% of hospitals across Australia and all hospitals in New Zealand, reported discharge prescription of a second antiplatelet drug in 63% of ACS patients[17].

Patients undergoing PCI were most likely to receive DAPT, an observation consistently reported in other observational studies[5, 8], and reflects the accepted view of DAPT following coronary stenting for the vast majority of PCI patients.

Patients undergoing CABG were more likely to be prescribed SAPT or no antiplatelet agent, with a failure to initiate a second antiplatelet reflecting failure to apply secondary prevention therapies to this population in general [18, 19]. This perhaps occurs due to the usual discontinuation of an ADP receptor antagonist prior to surgery and concern of bleeding on the part of surgical teams. A post-hoc analysis of the CURE trial supported the use of a second antiplatelet in the CABG, although most of the differential in events occurred in the pre-operative phase[9]. A substudy of patients who underwent CABG in the PLATO study, identified a significant reduction in cardiovascular death and total mortality with ticagrelor use as compared with clopidogrel administration, without any difference in CABG related major bleeding[10]. A most recent comprehensive review of the data including both randomised and observational data by the ACC/AHA writing group focussed on duration of DAPT therapy, endorsed therapy with DAPT in patients at hospital discharge following CABG[20].

The non-prescription of DAPT was strongly associated with certain comorbidities. The failure to prescribe DAPT in those with hypertension may be related to concerns of bleeding complications, particularly intracranial bleeding, or may have reflected unmeasured or unreported comorbidities in this cohort. SAPT or no antiplatelet prescription was more likely in those with a history of previous bleeding, presumably due to concern of future bleeding with antiplatelet therapy. However aspirin alone reduces the risk of death or myocardial infarction by up to 50%[21], whilst increasing the risk of major bleeding by only 1-3%[1, 22].

Over 43% of our patients were not revascularised following their ACS presentation (medically managed cohort). Barely half of these patients were discharged on DAPT despite their higher GRACE risk score when compared to revascularised patients, closely matching the 54% reported in CRUSADE 2004-2005 [5]. A recent Italian registry study showed that at the time of discharge, DAPT was prescribed in 58.8% of medically managed patients [23]. Although the use of DAPT was pioneered in patients receiving coronary stents[24, 25], the medically managed ACS population experience comparable relative risk reduction to those receiving stents, which translates to an even greater absolute benefit because of their higher absolute risk[1]. Indeed this observation of greater absolute benefit with provision of therapies with greater antiplatelet potency among the medically managed patients is reinforced in the PLATO trial [7].

In Australia, government funding of clopidogrel for all ACS patients was not available until early 2009[26] . It was not surprising then, that earlier ACS registries in this country have shown use of this drug in the medically managed cohort to be low (15-30%)[27]. However, even with government funding now available, the increase in uptake has been limited. Our findings suggest that DAPT non-prescription in this group is driven by concerns around atrial arrhythmia (presumably because of the potential for concomitant anticoagulant therapy), a history of major bleeding and discharge on warfarin. However, these factors alone were relatively infrequent (individually <15% of this population) and do not explain the continued resistance to provision of a second antiplatelet to these high-risk patients. The under-treatment of medically managed ACS patients with guideline recommended antiplatelet therapy is associated with poorer prognosis [28, 29].

We observed little variation in the provision of DAPT during the first few years of the study, despite several large, well designed randomised trials early in this period strengthening the evidence base in the ACS population, and providing justification for the newer, more potent ADP receptor antagonist drugs, prasugrel and ticagrelor [6, 7].

However from 2013, we did observe an increase in the use of DAPT, which paralleled increased prescription of ticagrelor, only partly offset by a reduction in the prescription of clopidogrel, with little use of prasugrel. Reasons for this failure to adopt prasugrel potentially include the study design of TRITON-TIMI 38 [6] not being reflective of Australian practice, contraindication in patient subgroups (absolute with age >75 and relative for those with weight <60kg and history of stroke/TIA) due to increased risk of bleeding, and a apparent lack of benefit in medically managed ACS patients compared to clopidogrel [30].

The lag in uptake of ticagrelor is less easy to understand. This drug was approved and its use reimbursed by the Australian PBS (pharmaceutical benefits scheme) in February 2012. In a Greek ACS registry collecting data from Jan 2012 to Jan 2013, rates of discharge on clopidogrel and ticagrelor were comparable[31] in an ACS population undergoing PCI, suggesting Australian practice to be out of step with data from European cohorts. In fact, the use of ticagrelor relative to clopidogrel use in Australia since 2012, more closely resembles reported practice in the US where limited uptake has been attributed to concerns regarding lack of benefit in the subgroup of US patients enrolled in the PLATO trial[32],

together with a Department of Justice investigation into the conduct of the study which did not report until 2014[33].

There are limitations of our study. A comparison of long-term outcomes of ACS patients based upon DAPT prescription at discharge has not been presented. However the cardioprotective effect of DAPT prescription at ACS hospital discharge is indisputable [34]. In addition, variations in continued use of antiplatelet drugs in the short and long-term after discharge have not been reflected in this study. Being an observational study, there might be unmeasured biases that influenced physicians' choice of therapies, including antiplatelet agents for ACS. Furthermore we did not collect specific reasons for failure to prescribe DAPT.

CONCLUSION

Our study illustrates the under-treatment with ideal antiplatelet therapy in high-risk ACS patient populations, and the independent predictors for non-prescription of DAPT at discharge following an ACS have been described in Australian practice. Additional strategies are required to bridge the treatment gap in antiplatelet management of ACS patients.

ACKNOWLEDGEMENTS:

The authors would like to thank all the investigators and study coordinators who have and continue to contribute to the CONCORDANCE registry.

Funding Sources: CONCORDANCE has been supported by grants from Astra Zeneca, Sanofi-Aventis, The Merck Sharp and Dohme/Schering Plough Joint Venture, Eli Lilly, Boehringer Ingelheim, the National Heart Foundation of Australia, and the National Health and Medical Research Council (NHMRC) post-graduate scholarship funding programme. Funding bodies played no role in the design, analysis or preparation of this manuscript.

REFERENCES

1. Yusuf S, Zhao F, Mehta S, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. The New England Journal of Medicine. 2001;345:494-502.

2. Chen Z, Jiang L, Chen Y, Xie J, Pan H, Peto R, et al. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. The Lancet. 2005;366:1607-21.

3. Sabatine M, Cannon C, CLARITY-TIMI 28 Investigators ea. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with STsegment elevation. The New England Journal of Medicine. 2005;352:1179-89.

4. Tricoci P, Roe M, Mulgund J, et al. Clopidogrel to treat patients with non-ST segment elevation acute coronary syndromes after hospital discharge. Archives of Internal Medicine. 2006;166:806-11.

5. Mehta R, Roe M, Chen A, Lytle B, Pollack C, Brindis R, et al. Recent Trends in the Care of Patients With Non–ST-Segment Elevation Acute Coronary Syndromes. Insights From the CRUSADE Initiative. Archives of Internal Medicine. 2006;166:2027-34.

6. Wiviott S, Braunwald E, McCabe C, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. The New England Journal of Medicine. 2007;357:2001-15.

7. Wallentin L, Becker R, Budaj A, et al. PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. The New England Journal of Medicine. 2009;361:1045-57.

8. Redfern J, Hyun K, Chew D, Astley C, Chow C, Aliprandi-Costa B, et al. Prescription of secondary prevention medications, lifestyle advice, and referral to rehabilitation among acute coronary syndrome inpatients: results from a large prospective audit in Australia and New Zealand. Heart. 2014;100:1281-8.

9. Fox K, Mehta S, Peters R, Zhao F, Lakkis N, Gersh B, et al. Benefits and Risks of the Combination of Clopidogrel and Aspirin in Patients Undergoing Surgical Revascularization for Non–ST-Elevation Acute Coronary Syndrome. The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004;110:1202-8.

10. Held C, Asenblad N, Bassand J, Becker R, Cannon C, Claeys M, et al. Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery. Results From the PLATO (Platelet Inhibition and Patient Outcomes) Trial. Journal of the American College of Cardiology. 2011;57:672-84.

11. Lindholm D, Varenhorst C, Cannon C, Harrington R, Himmelmann A, Maya J, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. European Heart Journal. 2014;35:2083-93.

12. Brieger D, Chew D, Redfern J, Ellis C, Briffa T, Aliprandi-Costa B, et al. Survival after an acute coronary syndrome: 18-month outcomes from the Australian and New Zealand SNAPSHOT ACS study. Medical Journal of Australia. 2015;203:368.e1-9.

13. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. European Heart Journal. 2015;36:1163-70.

14. Chew D, Anderson F, Avezum A, Eagle K, FitzGerald G, Gore J, et al. Six-month survival benefits associated with clinical guideline recommendations in acute coronary syndromes. Heart. 2010;96:1201-6.

15. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, et al. The Design and Rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). Heart, Lung, Circulation. 2013;22:533-41.

16. Fox K, Dabbous O, Goldberg R, Pieper K, Eagle K, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). British Medical Journal. 2006;333:1091-4.

17. Chew D, French J, Briffa T, Hammett C, Ellis C, Ranasinghe I, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. Medical Journal of Australia. 2013;199(3):185-91.

18. Rao R, Goodman S, Yan R, Spencer F, Fox K, DeYoung J, et al. Temporal trends and patterns of early clopidogrel use across the spectrum of acute coronary syndromes. American Heart Journal. 2009;157:642-50.

19. Krimly A, Yan R, Yan A, DeYoung J, Gallo R, Steg G, et al. Use of Clopidogrel Post-Coronary Artery Bypass Surgery in Canadian Patients With Acute Coronary Syndromes. Canadian Journal of Cardiology. 2011;27:711-5.

20. Levine G, Bates E, Bittl J, Brindis R, Fihn S, Fleisher L, et al. Focused Update Writing Group, 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. Journal of the American College of Cardiology. 2016.

21. Lewis HJ, Davis J, Archibald D, Steinke W, Smitherman T, Doherty JI, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. The New England Journal of Medicine. 1983;309:396-403.

22. Bhatt D, Fox K, Hacke W, Berger P, Black H, Boden W, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. The New England Journal of Medicine. 2006;354:1706-17.

23. De Luca L, Leonardi S, Smecca I, Formigli D, Lucci D, Gonzini L, et al. Contemporary antithrombotic strategies in patients with acute coronary syndromes managed without revascularization: insights from the

EYESHOT study. European Heart Journal - Cardiovascular Pharmacotherapy. 2015;1:168-78.

24. Fischman D, Leon M, Baim D, Schatz R, Savage M, Penn I, et al. A Randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. The New England Journal of Medicine. 1994;331:496-501.

25. Bertrand M, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, et al. Randomized Multicenter Comparison of Conventional Anticoagulation Versus Antiplatelet Therapy in Unplanned and Elective Coronary Stenting. The Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) Study. Circulation. 1998;98:1597-603.

26. Pharmaceutical Benefits Advisory Committee. March 2008 PBAC outcomes - positive recommendations.

27. 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. Medical Journal of Australia. 2011;195:116-21.

28. Amsterdam E, Peterson E, Ou F, Newby L, Pollack C, Gibler W, et al. Comparative trends in guidelines adherence among patients with non-ST-segment elevation acute coronary syndromes treated with invasive versus conservative management strategies: results from the CRUSADE quality improvement initiative. American Heart Journal. 2009;158:748-54.

29. Roe M, White J, Kaul P, Tricoci P, Lokhnygina Y, Miller C, et al. Regional patterns of use of a medical management strategy for patients with non-ST-segment elevation acute coronary syndromes: insights from the EARLY-ACS Trial. Circulation Cardiovascular Quality Outcomes. 2012;5:205-13.

30. Roe M, Armstrong P, Fox K, White H, Prabhakaran D, Goodman S, et al. Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization. The New England Journal of Medicine. 2012;367:1297-309.

31. Alexopoulos D, Goudevenos J, Xanthopoulou I, Deftereos S, Sitafidis G, Kanakakis I, et al. Implementation of contemporary oral antiplatelet treatment guidelines in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A report from the GReek AntiPlatelet rEgistry (GRAPE). International Journal of Cardiology. 2013;168:5329-35.

32. Mahaffey K, Wojdyla D, Carroll K, Becker R, Storey R, Angiolillo D, et al. Ticagrelor Compared With Clopidogrel by Geographic Region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Circulation. 2011;124:544-54.

33. AstraZeneca. United States Department of Justice closes investigation into PLATO clinical trial for Brilinta [press release]. August 19, 2014.

34. Varenhorst C, Jensevik K, Jernberg T, Sundstrom A, Hasvold P, Held C, et al. Duration of dual antiplatelet treatment with clopidogrel and aspirin in patients with acute coronary syndrome. European Heart Journal. 2014;35:969-78.

FIGURE LEGENDS

Figure 1

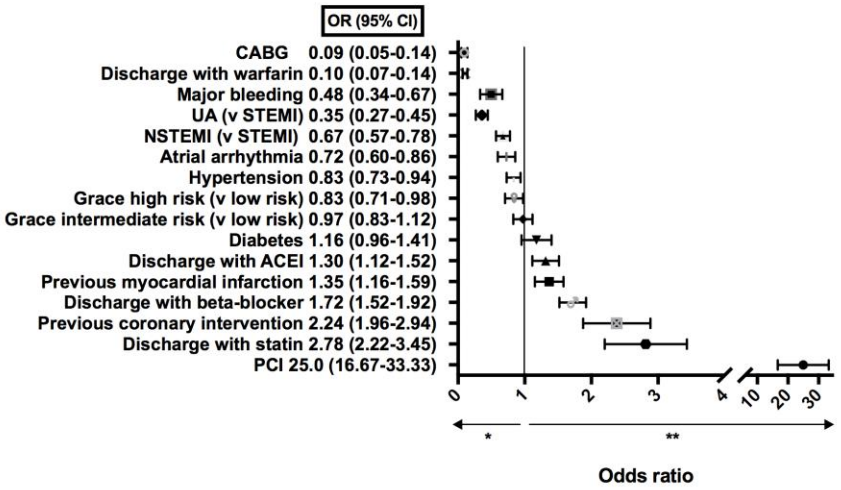
(a) Adjusted multivariable regression model built using logistic generalized estimating equations to identify predictors of DAPT non-prescription in those admitted with an ACS. Point estimates (OR, odds ratio) are indicated by points, and the 95% confidence interval (CI) are shown as bars. **(b)** Adjusted multivariable regression model built using logistic generalized estimating equations to identify predictors of DAPT non-prescription in those with ACS and medically managed. Point estimates (OR, odds ratio) are indicated by points, and the 95% confidence interval (CI) are shown as bars. *****Reduced likelihood of DAPT prescription, ******Increased likelihood of DAPT prescription. ACEI: Angiotensin-converting enzyme inhibitor, PCI: Percutaneous coronary intervention

Figure 2

(a) Percentage of patients prescribed with DAPT (dual antiplatelet therapy) or SAPT (single antiplatelet therapy) at time of discharge according to year of admission, and trend of second antiplatelet (clopidogrel, ticagrlor, prasugrel) discharge prescription over time. **(b)** Percentage of patients with DAPT (dual antiplatelet therapy) or SAPT (single antiplatelet therapy) prescription at time of discharge, in those medically managed, according to year of admission, and trend of second antiplatelet (clopidogrel, ticagrlor, prasugrel) discharge prescription over time.

Figure 1

(a)



(b)

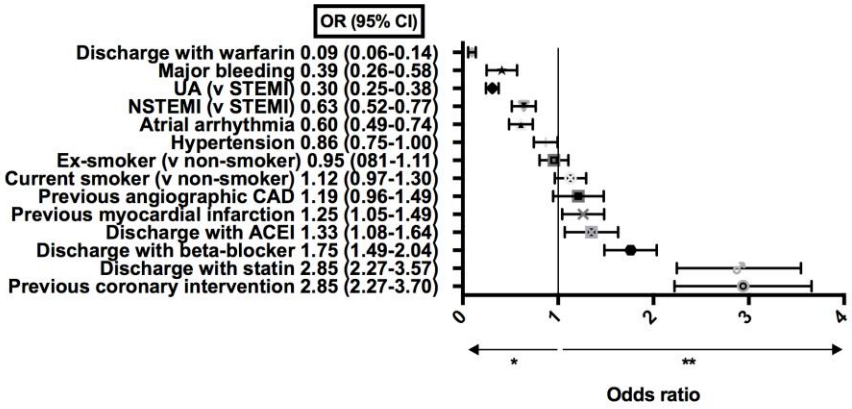
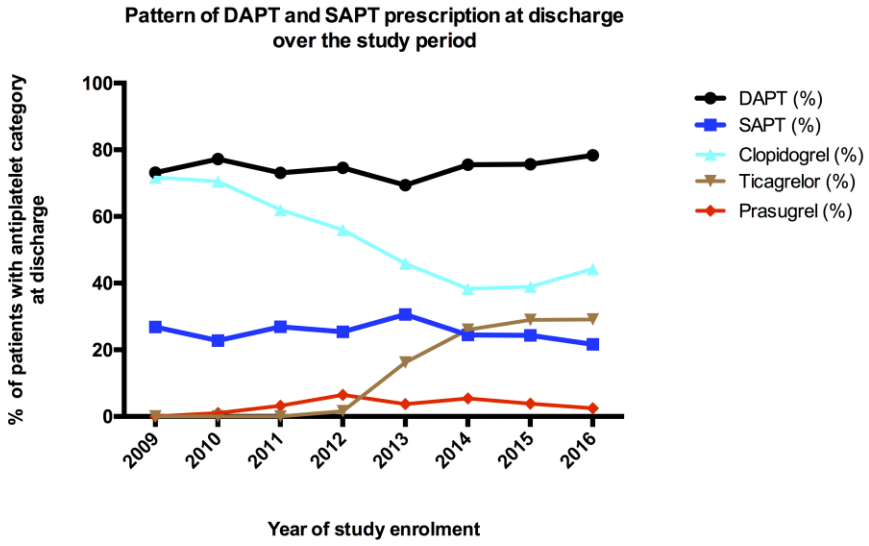


Figure 2

(a)



(b)