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ORIGINAL ARTICLE

Evidence-practice gaps in $P2Y_{12}$ inhibitor use after hospitalisation for acute myocardial infarction: findings from a new population-level data linkage in Australia

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Key words
acute myocardial infarction, medication adherence, dual antiplatelet therapy, hospital variation, $P2Y_{12}$ inhibitor.

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Abstract

Background: $P2Y_{12}$ inhibitor therapy is recommended for 12 months in patients hospitalised for acute myocardial infarction (AMI) unless the bleeding risk is high.
Aims: To describe real-world use of $P2Y_{12}$ inhibitor therapy following AMI hospitalisation.
Methods: We used population-level linked hospital data to identify all patients discharged from a public hospital with a primary diagnosis of AMI between July 2011 and June 2013 in New South Wales and Victoria, Australia. We used dispensing claims to examine dispensing of a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) within 30 days of discharge and multilevel models to identify predictors of post-discharge dispensing and persistence of therapy to 1 year.
Results: We identified 31 848 patients hospitalised for AMI, of whom 56.8% were dispensed a $P2Y_{12}$ inhibitor within 30 days of discharge. The proportion of patients with post-discharge dispensing varied between hospitals (interquartile range: 25.0–56.5%), and significant between-hospital variation remained after adjusting for patient characteristics. Patient factors associated with the lowest likelihood of post-discharge dispensing were: having undergone coronary artery bypass grafting (odds ratio (OR): 0.17; 95% confidence intervals (CI): 0.15–0.20); having oral anticoagulants dispensed 180 days before or 30 days after discharge (OR: 0.39, 95% CI: 0.35–0.44); major bleeding (OR: 0.68, 95% CI: 0.61–0.76); or being aged ≥85 years (OR: 0.68, 95% CI: 0.62–0.75). A total of 26.8% of patients who were dispensed a $P2Y_{12}$ inhibitor post-discharge discontinued therapy within 1 year.
Conclusion: Post-hospitalisation use of $P2Y_{12}$ inhibitor therapy in AMI patients is low and varies substantially by hospital of discharge. Our findings suggest strategies addressing both health system (hospital and physician) and patient factors are needed to close this evidence-practice gap.

Introduction

The evidence supporting treating patients who have experienced an acute myocardial infarction (AMI) with dual antiplatelet therapy is unequivocal, greatly reducing the risk of recurrent cardiovascular events, such as subsequent myocardial infarction (MI), stroke and stent thrombosis.[1–6] Class I clinical guidelines recommend dual antiplatelet therapy with a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, prasugrel) and aspirin for 12 months following hospital discharge,[7] unless contraindicated such as by the excess risk of major

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bleeding.[5] Current Australian guidelines recommend clopidogrel or ticagrelor as first-line treatment for all patients with acute coronary syndrome (ACS), regardless of coronary revascularisation; prasugrel is indicated only for patients receiving a percutaneous coronary intervention (PCI).[3,4,7]

Despite the evidence, prescribing of $P2Y_{12}$ inhibitor therapy is consistently underutilised, with approximately 63–70% of ACS patients in Australia and New Zealand being prescribed $P2Y_{12}$ inhibitors at hospital discharge,[8,9] with slightly higher proportions in Europe (68–76%)[10–13] and in the USA (79–81%).[14,15] However, few studies have investigated use of $P2Y_{12}$ inhibitors in the community setting, generally finding a lower proportion of patients having dispensed the medicines following hospital discharge (52–73%).[16,17] Primary adherence among AMI patients to prescribed medicines is known to be low,[18] with approximately half of patients prescribed antiplatelet therapy filling their prescription within 30 days of discharge.[19] As such, it is possible that the evidence-practice gap in use of $P2Y_{12}$ inhibitor therapy in the community setting is underestimated, with lower use in Australia than the current evidence might suggest.

We investigated the real-world use of $P2Y_{12}$ inhibitors in AMI patients following hospital discharge, using a novel population-level linkage of Australian hospital and pharmaceutical data for residents of Australia's two most populous states: New South Wales (NSW) and Victoria. Our aims were: to describe dispensing of a $P2Y_{12}$ inhibitor within 30 days of discharge, quantify variation between hospitals in post-discharge dispensing, identify patient and hospital predictors of post-discharge dispensing and identify predictors of discontinuation of therapy within 1 year.

Methods

Setting

Australia has a universal healthcare system entitling all citizens and permanent residents to a range of subsidised healthcare services, publicly funded through a combination of federal, state and local level governments.[20,21] The hospital sector includes a mixture of public and private hospital facilities,[21] with public primarily funded and managed by the states and territories, and private hospitals primarily funded through health insurance funds and patient out-of-pocket payments.

Subsidised access to prescription medicines is funded by the Australian Government through the Pharmaceutical Benefits Scheme (PBS), which reimburses community pharmacies and private hospitals for dispensing of PBS-listed medicines.[22] A subsidised PBS claim occurs when the price of the medicine is above a PBS co-payment threshold (e.g. $34.20 in 2011), with lower thresholds (e.g. $5.60 in 2011) for concessional beneficiaries (patients eligible for government entitlements, such as people ≥65 years and low-income earners).

Data sources

This analysis used linked admitted patient, mortality, pharmaceutical dispensing and Medicare claims data from the National Data Linkage Demonstration Project (NDLDP).[23] The NDLDP contains population-level linked data from July 2010 to June 2015 for residents of NSW and Victoria, Australia's two most populous states comprising over half the nation's population.

Admitted patient data were from the National Hospital Morbidity Database, containing records for all separations (discharges, transfers and deaths) in public hospitals. Fact of death was from the National Death Index. Pharmaceutical data were from the PBS, containing claims for subsidised dispensing of PBS-listed medicines.[22] Medicare data were from the Medicare Benefits Scheme (MBS) containing claims for MBS subsidised clinical, diagnostic and procedural services provided out-of-hospital as well as in-hospital services to private (but not public) patients within public and private hospitals.[24]

Ethical approval for linkage of the NDLDP was given by the Australian Institute of Health and Welfare (AIHW) Human Research Ethics Committee, in which a waiver of informed consent was granted. Data linkage of the NDLDP was undertaken by the AIHW.[25] Oversight of the NDLDP, including approval of project outputs, is by a Steering Committee comprising representatives from Australian Government Department of Health, AIHW, NSW Ministry of Health and Department of Health and Human Services Victoria.

Study population

We included all patients discharged from a NSW or Victorian public hospital between July 2011 and June 2013, with a primary diagnosis of AMI (ICD-10-AM code I21.x),[26] who were 18 years or older and alive at discharge. We followed up patients from the last recorded admission in a public hospital ('index admission'). Changes to the type of care within a hospital (e.g. from acute to subacute care) and transfers between hospitals were treated as a single hospital admission.

We excluded patients if they were not a resident of NSW or Victoria, had a Department of Veteran's Affairs funding status on admission, or if they had inconsistent data indicating potential linkage errors.

Medicines of interest

$P2Y_{12}$ inhibitors of interest were clopidogrel, prasugrel or ticagrelor (Supporting Information Table S1). While dual antiplatelet therapy of a $P2Y_{12}$ inhibitor with aspirin is best-practice treatment for patients with AMI, the availability of aspirin as an over-the-counter medicine means it is under-ascertained in the PBS data. Given monotherapy with clopidogrel is only recommended if aspirin is contraindicated or not tolerated,[7] and recent Australian findings show that as most patients with ACS on a $P2Y_{12}$ inhibitor are as dual therapy with aspirin,[8] we have assumed dispensing of a $P2Y_{12}$ inhibitor to be reflective of dual therapy. The cost of all $P2Y_{12}$ inhibitors was above the PBS co-payment threshold during the period of analysis and so captured in the PBS data; some forms of clopidogrel dropped below the co-payment threshold in August 2013 (Table S1).

Baseline characteristics

We assessed patient demographic and clinical characteristics at the time of discharge, including age, sex, year, type of MI, as ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI),[27] as well as revascularisation. We also identified hospitalisation for AMI or revascularisation in the year prior to admission. We identified patient morbidities from hospital diagnosis codes in the year prior to admission and/or during the index admission (history of major bleeding, atrial fibrillation (AF), ischaemic stroke, heart failure, diabetes and chronic kidney disease). We identified patients with prior exposure to a $P2Y_{12}$ inhibitor at baseline if there was at least one dispensing record in the 180 days prior to admission. We also identified patients with baseline exposure to other medicines, including angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), beta-blockers, statins and oral anticoagulants (OAC) if there was at least one dispensing record for the medicine in the 180 days prior to admission or 30 days following discharge, to capture medicine exposure more proximal to the AMI event. Codes for identifying patient characteristics are included in Table S2.

We categorised hospital of discharge by state and hospital type: 'principal referral' (very high-volume public facilities with a broad range of specialised service units, 24-h emergency department and intensive care unit); 'large public acute' (large-volume facilities with fewer specialised services, but still likely contain a coronary care unit); and all 'other public' facilities, including small- and medium-volume facilities and hospitals in regional and remote areas. Hospital type was determined according to peer group classification, which groups similar facilities based on shared characteristics[28] (Table S3).

Outcomes of interest and statistical analysis

Dispensing of $P2Y_{12}$ inhibitor within 30 days of discharge

We identified dispensing of a $P2Y_{12}$ inhibitor within 30 days of discharge (including the day of discharge), according to patient characteristics and hospital of discharge.

We explored predictors of dispensing of $P2Y_{12}$ inhibitors within 30 days of discharge using multilevel logistic regression, with patients nested within their hospital of discharge. Patient-level factors include year, demographics, morbidities and exposure to other medicines. Hospital-level factors include state and type of hospital of discharge. We quantified residual between-hospital variation, after adjusting for patient and hospital factors using a median odds ratio (MOR). The MOR can be interpreted as the median increase in odds of post-discharge dispensing if you were to compare all possible pairwise combinations of hospitals, that is, if a patient were to change from their hospital to one where a higher proportion of patients had a post-discharge dispensing.[29]

Persistence of $P2Y_{12}$ inhibitor therapy

Among patients who were dispensed a $P2Y_{12}$ inhibitor within 30 days, we determined persistence (i.e. continued use of $P2Y_{12}$ inhibitor without a break in therapy) to 1 year from first dispensing. We assumed each dispensing lasted for 30 days; the validity of this assumption was confirmed by examining the median time between dispensing within individuals (range 28–30 days between drugs). We considered patients to have a break in therapy if they had a period ≥60 days without exposure to a $P2Y_{12}$ inhibitor, even if they restarted within the year.

As the cost of some forms of clopidogrel dropped below the PBS co-payment threshold in August 2013 (Table S1), we restricted the persistence analysis to patients with their index admission between July 2011 and June 2012, to allow for complete capture or medicines dispensed.

We explored predictors of time to first break in therapy within 1 year using multilevel Cox proportional hazards models, with follow-up time censored at first break in therapy, death or end of follow up (whichever came first). These models were adjusted for patient- and hospital-level factors, with patients nested within their hospital of discharge. We quantified residual between-

hospital variation using a median hazard ratio[30] and time to discontinuation using Kaplan–Meier curves.

All analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, NC, USA), and figures produced in StataSE 14.2 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics

We identified 36 242 patients discharged from a NSW or Victorian public hospital between July 2011 and June 2013 with a primary diagnosis of AMI; we excluded 4394, leaving 31 848 patients for analysis (Fig. 1), discharged from 292 hospitals. The median age was 68 years (interquartile range (IQR): 57–79%), with 40.1% of patients aged <65 years (Table 1). Among these patients, 65.9% were male, 28.8% were admitted for a STEMI and 38.4% underwent PCI during their admission. A small proportion of patients had a prior admission for AMI (11.6%), a prior PCI or CABG (4.6%), or had a dispensing record for a $P2Y_{12}$ inhibitor in the 180 days prior to admission (12.0%). The majority (84.8%) of patients were discharged from large hospitals with specialised cardiac or coronary care units (principal referral, large public acute). Almost all (96.5%) patients were from hospitals in major city or inner regional areas (data not shown).

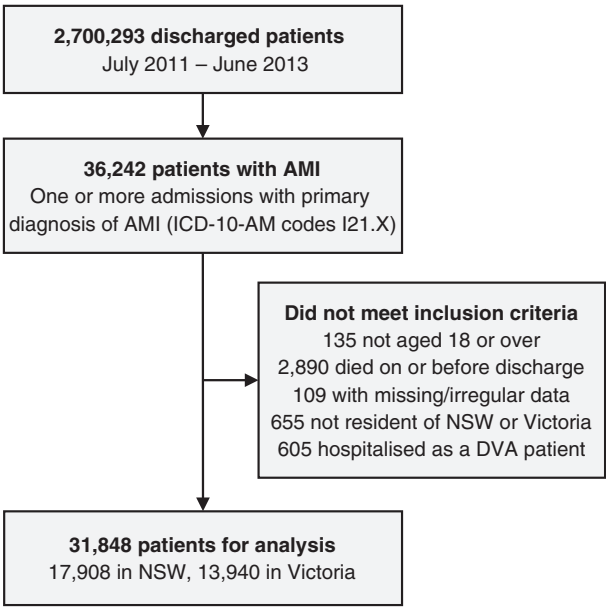

Figure 1 Selection of patient cohort from patients discharged with acute myocardial infarction.

Table 1 Patient demographic and clinical characteristics

	No. patients	% of *n*
Study cohort (*n*)	31 848	100.0
Age on discharge (years)		
18–64	12 978	40.8
65–74	7465	23.4
75–84	7255	22.8
≥85	4150	13.0
Sex		
Female	10 857	34.1
Male	20 991	65.9
Revascularisation		
PCI only	12 231	38.4
CABG (with/without PCI)	2419	7.6
No revascularisation	17 198	54.0
Type of MI		
STEMI	9183	28.8
NSTEMI	21 874	68.7
Unspecified	791	2.5
Patient morbidities†		
Prior AMI	3704	11.6
Prior PCI or CABG	1456	4.6
Major bleeding	2533	8.0
Atrial fibrillation	5054	15.9
Ischaemic stroke	484	1.5
Heart failure	5135	16.1
Diabetes	6463	20.3
Chronic kidney disease	4091	12.9
Medicine exposure (180 days prior, 30 days after admission)‡		
Prior $P2Y_{12}$ inhibitors	3821	12.0
ACE inhibitors/ARB	16 125	50.6
Beta-blockers	14 567	45.7
Statins	24 682	77.5
Oral anticoagulants	2740	8.6
Time of index admission		
2011 (July–December only)	8272	26.0
2012	15 983	50.2
2013 (January–June only)	7593	23.8
Hospital type		
Principal referral	14 915	46.8
Large public acute	12 098	38.0
Other public	4835	15.2
State		
New South Wales	17 908	56.2
Victoria	13 940	43.8

†Any hospital diagnosis in year prior to admission and/or index admission. For prior AMI and prior PCI or CABG, any diagnosis or procedure in the year prior to index admission.

‡Any dispensing in the 180 days prior to admission or 30 days following discharge; For prior $P2Y_{12}$ inhibitors, within 180 days prior to admission only.

ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

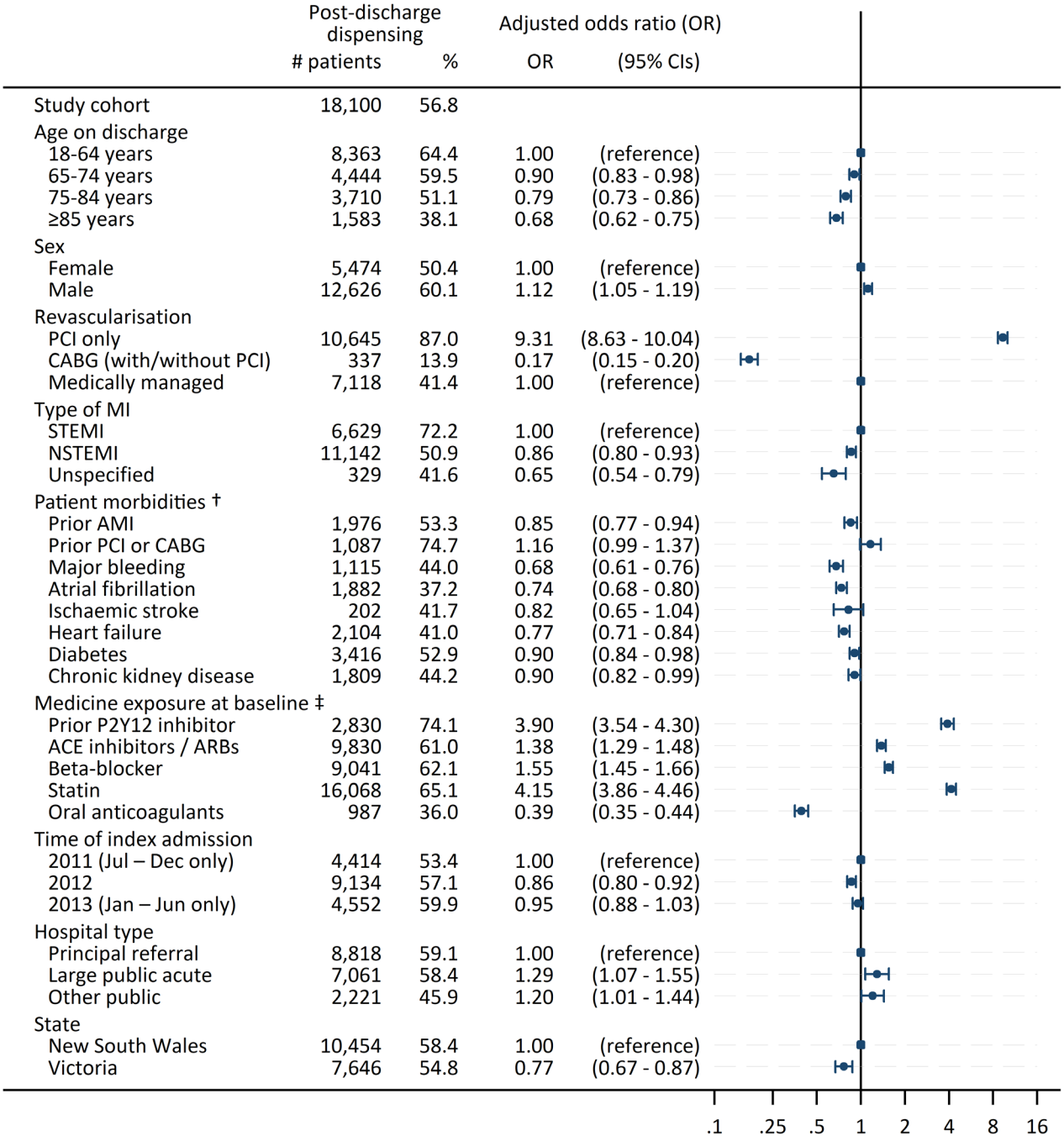

Figure 2 Dispensing of P2Y$_{12}$ inhibitor within 30 days of discharge among patients with AMI. †Any hospital diagnosis in year prior to admission and/or index admission. For prior acute myocardial infarction (AMI) and prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), any diagnosis or procedure in the year prior to index admission. Referent category is no prior diagnosis/procedure for each condition. ‡Any dispensing between 180 days prior to admission and 30 days following discharge; For prior P2Y$_{12}$ inhibitors, within 180 days prior to admission only. Referent category is no prior dispensing for each medicine. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CI, confidence intervals; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; STEMI, ST-elevation myocardial infarction.

Post-discharge dispensing of P2Y$_{12}$ inhibitors

In total, 56.8% of patients were dispensed a P2Y$_{12}$ inhibitor within 30 days of discharge (Fig. 2). This proportion of patients was highest in patients who had received a PCI (87.0%), had a prior PCI or CABG (74.7%), were under 65 years of age (64.4%) or male (60.1%). Post-

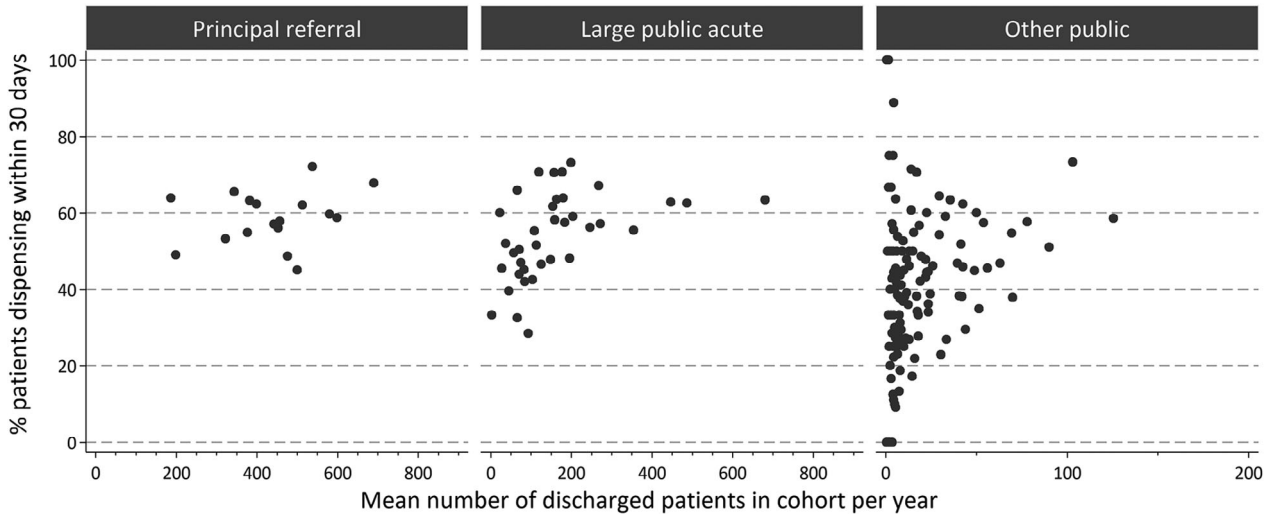

Figure 3 Proportion of acute myocardial infarction patients at each hospital who dispensed a $P2Y_{12}$ inhibitor within 30 days of discharge, stratified by hospital type and sorted by volume of patients within the study period.

discharge dispensing was lowest in patients who received a CABG during their admission (13.9%); had a diagnosis of AF (37.2%), ischaemic stroke (41.7%), heart failure (41.0%), major bleeding (44.0%) and chronic kidney disease (44.2%) or had baseline exposure to OAC in the 180 days prior to or 30 days following index admission (36.0%). Patients discharged from principal referral or large public acute hospitals had higher post-discharge dispensing (59.1% and 58.4%) than patients discharged from other facilities (45.9%).

The proportion of patients with post-discharge dispensing varied between hospitals *(n* = 292; Fig. 3), with a median 43% of discharged patients dispensed a $P2Y_{12}$ inhibitor within 30 days of discharge (IQR: 25–56.5%). We found a higher proportion of post-discharge dispensing, and less variation between hospitals, among principal referral hospitals (median: 58.8%; IQR: 54.8–63.2%; range: 45.1–72.1%) and large public acute facilities (median: 55.4%; IQR: 46.6–62.8%; range: 28.5–73.1%) than among the other public hospitals (median: 38%; IQR: 21.9–50%; range 0–100%). The vast majority (95%) of the latter facilities had fewer than 50 patients discharged for AMI each year.

Predictors of post-discharge dispensing

The strongest predictor of dispensing a $P2Y_{12}$ inhibitor within 30 days of discharge (Fig. 2) was receipt of PCI (odds ratio (OR): 9.31; 95% confidence intervals (CI): 8.63–10.0), pre-hospital use of $P2Y_{12}$ inhibitors (OR: 3.90; 95% CI: 3.54–4.30), as well as medicine exposure (in the 180 days prior to or 30 days following index admission) to statins (OR: 4.15; 95% CI: 3.86–4.46), beta-blockers (OR: 1.55; 95% CI: 1.45–1.66) or ACE inhibitors/angiotensin II receptor blockers (ARB) (OR: 1.38; 95% CI: 1.29–1.48). Patients with the lowest odds of post-discharge dispensing were those who received a CABG (OR: 0.17; 95% CI: 0.15–0.20) or had exposure to OAC at baseline (OR: 0.39; 95% CI: 0.35–0.44). We observed significant between-hospital variation in post-discharge dispensing (σ^2 = 0.088; standard error = 0.018) in these models adjusted for patient characteristics, such that similar patients discharged from any two different hospitals would have a median 33% difference in their odds of dispensing a $P2Y_{12}$ inhibitor post-discharge (MOR: 1.33).

Persistence of $P2Y_{12}$ inhibitor therapy over 1 year

Of the 8801 patients discharged between July 2011 and June 2012 who were dispensed a $P2Y_{12}$ inhibitor therapy within 30 days of discharge, 8282 were still alive 1 year after dispensing. Almost three-quarters (72.6%) of these patients remained on therapy without a break. Of the patients who died during the 1-year follow up, most (82.7%) were on treatment until death.

Significant predictors of discontinuation included receipt of CABG in the index admission (hazard ratio (HR): 1.66; 95% CI:1.29–2.12), ischaemic stroke (HR: 1.51; 95% CI: 1.09–2.11) and baseline exposure to OAC in the 180 days prior to or 30 days following index admission (HR: 1.49; 95% CI: 1.24–1.78; Figs 4,S2, Table S4). Patients less likely to discontinue therapy

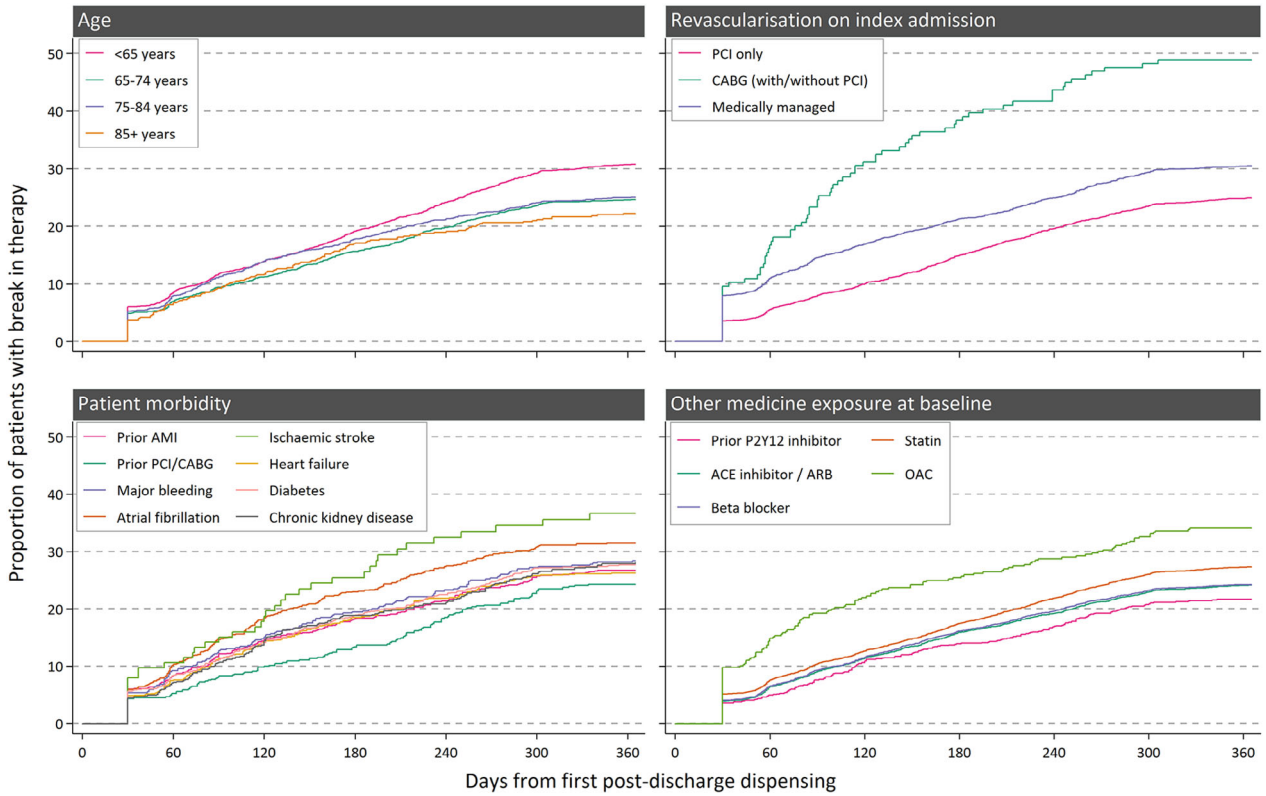

Figure 4 Time from first dispensing of P2Y$_{12}$ inhibitor (within 30 days of discharge among patients with acute myocardial infarction (AMI)) to first break in therapy (60 days from prior dispensing), stratified by age, revascularisation, patient morbidities and history of medicine exposure. CABG, coronary artery bypass grafting; OAC, oral anticoagulants; PCI, percutaneous coronary intervention.

were those who received a PCI (HR: 0.66; 95% CI: 0.60–0.73) or had pre-hospitalisation dispensing of P2Y$_{12}$ inhibitors (HR: 0.67; 95% CI: 0.57–0.78).

Discussion

We found substantive evidence practice gaps in the use of P2Y$_{12}$ inhibitor therapy among patients discharged with AMI, with a little over half being dispensed a P2Y$_{12}$ inhibitor within 30 days of discharge, and over one-quarter of these patients discontinuing therapy within 1 year. While the strongest clinical predictors of post-discharge dispensing and persistence of therapy were consistent with indications from clinical guidelines (receipt of PCI, younger age, risk of bleeding), significant between-hospital variation in post-discharge dispensing persisted after adjusting for these clinical characteristics – suggesting that both patient and health-system factors play an important role in contributing to this evidence-practice gap.

Our findings show real-world use of P2Y$_{12}$ inhibitor therapy following MI is lower than previously reported in Australia, with the proportion of patients dispensing the medicine post-discharge (56.8%) substantially lower than the proportion reported to receive a prescription in the Australian CONCORDANCE registry (74.9%),[8] even among patients receiving a PCI (87.0 vs 96.6%). While CONCORDANCE recruited patients from larger and select hospitals, not one of the principal referral or large public acute hospitals had post-discharge dispensing comparable to the level of prescription reported in CONCORDANCE. This discrepancy likely reflects poor primary adherence in patients with AMI.[18,19] We also observed variation in post-discharge dispensing within all types of hospital facilities. While this variation is adjusted for patient clinical characteristics, it likely reflects both variation in hospital prescription practices and patient adherence following discharge. These results highlight the important role of hospitals in instigating follow-up therapy, for example through effective implementation of evidence-guided care, or enhanced care transitions pathways, such as early outpatient follow-up consultations.[31]

Predictors of post-discharge dispensing were largely consistent with prior studies,[8,16,17,32] including higher use among patients who received a PCI (reflective of the

risk of stent thrombosis[33]), males, younger age and prior use of beta-blockers or statins. The post-discharge dispensing among patients with prior dispensing of $P2Y_{12}$ inhibitor may indicate patients' existing treatments. The post-discharge dispensing among patients who received a CABG, with a history of major bleeding, AF or use of OAC, was also consistent with prior studies, reflecting possible contraindications due to risk of bleeding.[16] The low post-discharge dispensing among patients with a history of stroke or heart failure has been less consistently reported,[16,32] but high-risk cardiac patients have been found paradoxically to be less likely to receive a range of evidence-based therapy.[34–38] The second Euro Heart Survey on ACS patients found the most common reason for non-prescription of antiplatelet therapy was a perceived lack of indication,[10] and patients with cardiac comorbidities are often excluded from clinical trials. Further real-world evidence among this population may help encourage adherence to current guidelines for treatment.

The recommended duration of $P2Y_{12}$ inhibitor treatment following MI is 12 months, and the proportion of patients who discontinued therapy in the present study (26.8%) was similar to those in other observational studies,[13,16] but higher than observed in clinical trials of these therapies (e.g. 17.2%),[4] where they were closer to discontinuation observed at 30 (22–24%)[39] and 36 months (21–32%).[40] Consistent with prior evidence, we found a lower proportion of patients who discontinued therapy among patients who received a PCI[16,17,32] and a higher proportion among patients who received a CABG or had a history of AF, stroke or OAC use, reflecting risks of stent thrombosis and bleeding complications respectively. Other factors influencing discontinuation of therapy are less well understood. The lower proportion of patients discontinuing therapy among those with a prior dispensing of $P2Y_{12}$ inhibitor, or use of ACE inhibitors/ARBs and beta-blockers, may indicate patients' propensity for engagement with preventive care.

Strengths and limitations

The present study used linked administrative data, the limitations of which are well known.[22] Our dataset did not include information from private hospitals, which in Australia account for 15% of overnight acute separations for AMI;[21] however, our estimates of post-discharge dispensing for patients transferred from public to private facilities remain valid as medicines dispensed within the private setting are captured in the PBS data. The data also did not include dispensing records for medicines priced under the PBS co-payment threshold,[22] limiting capture of clopidogrel in later years, thus restricting the period of analysis.

The key strength of our study is the population-level coverage, with linked admission and pharmaceutical dispensing data for over half the Australian population. The availability of such data in Australia is unprecedented, with our study cohort comprising more than twice the number of patients with AMI than the largest comparable Australian study.[8] Continued development of this population-level data asset, and inclusion of more contemporary data, can overcome these limitations and provide an invaluable asset for evaluation of real-world medicine use.

Conclusion

We found $P2Y_{12}$ inhibitor therapy is underutilised in patients discharged with AMI in Australia, with only a little over half of patients receiving guideline-concordant care. This is lower than previously reported prescription at hospital discharge, suggesting a need to improve the real-world utilisation of this best-practice care. Significant between-hospital remained after adjusting for patient-level factors, indicating both health system (hospital and physician) and patient factors play an important role in closing this evidence-practice gap.

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References

1 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK *et al*. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502.

2 Wilson SJ, Newby DE, Dawson D, Irving J, Berry C. Duration of dual antiplatelet therapy in acute coronary syndrome. *Heart* 2017; **103**: 573–80.

3 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S *et al*. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001–15.

4 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**: 1045–57.

5 Udell JA, Bonaca MP, Collet J-P, Lincoff AM, Kereiakes DJ, Costa F *et al*. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J* 2016; **37**: 390–9.

6 Squizzato A, Bellesini M, Takeda A, Middeldorp S, Donadini MP. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular events. *Cochrane Database Syst Rev* 2017; CD005158.

7 Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA *et al*. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *Med J Aust* 2016; **205**: 128–33.

8 Anastasius M, Lau JK, Hyun K, D'Souza M, Patel A, Rankin J *et al*. The underutilisation of dual antiplatelet therapy in acute coronary syndrome. *Int J Cardiol* 2017; **240**: 30–6.

9 Redfern J, Hyun K, Chew DP, 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.

10 Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G *et al*. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J* 2006; **27**: 2285–93.

11 Schiele F, Puymirat E, Bonello L, Dentan G, Meneveau N, Collet JP *et al*. Impact of prolonged dual antiplatelet therapy after acute myocardial infarction on 5-year mortality in the FAST-MI 2005 registry. *Int J Cardiol* 2015; **187**: 354–60.

12 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. *Eur Heart J* 2015; **36**: 1163–70.

13 Bueno H, Pocock S, Danchin N, Annemans L, Gregson J, Medina J *et al*. International patterns of dual antiplatelet therapy duration after acute coronary syndromes. *Heart* 2017; **103**: 132–8.

14 Roe MT, Messenger JC, Weintraub WS, Cannon CP, Fonarow GC, Dai D *et al*. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol* 2010; **56**: 254–63.

15 Mehta RH, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Brindis RG *et al*. Recent trends in the care of patients with non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE initiative. *Arch Intern Med* 2006; **166**: 2027–34.

16 Prami T, Khanfir H, Deleskog A, Hasvold P, Kytö V, Reissell E *et al*. Clinical factors associated with initiation of and persistence with ADP receptor-inhibiting oral antiplatelet treatment after acute coronary syndrome: a nationwide cohort study from Finland. *BMJ Open* 2016; **6**: e012604.

17 Green A, Pottegard A, Broe A, Diness TG, Emneus M, Hasvold P *et al*. Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction: a Danish nationwide population-based cohort study. *BMJ Open* 2016; **6**: e010880.

18 Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M *et al*. Full coverage for preventive medications after myocardial infarction. *N Engl J Med* 2011; **365**: 2088–97.

19 Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation* 2008; **117**: 1028–36.

20 Mossialos EDA; Osborn, R.; Sarnak, D. International profiles of health care systems: Australia, Canada, China, Denmark, England, France, Germany, India, Israel, Italy, Japan, the Netherlands, New Zealand, Norway, Singapore, Sweden, Switzerland, Taiwan, and the United States: The Commonwealth Fund; 2017.

21 Australian Institute of Health and Welfare. *Admitted Patient Care 2016–17: Australian Hospital Statistics*. Health Services Series. Canberra: Australian Institute of Health and Welfare; 2018.

22 Mellish L, Karanges EA, Litchfield MJ, Schaffer AL, Blanch B, Daniels BJ *et al*. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Res Notes* 2015; **8**: 634.

23 Australian Institute of Health and Welfare. *Transition between Hospital and Community Care for Patients with Coronary Heart Disease: New South Wales and Victoria, 2012–2015*. Vol Cat. No. CDK 9. Canberra: Australian Institute of Health and Welfare; 2018.

24 Australian Government Department of Health. *Medicare Benefits Schedule Book*. Canberra: Australian Government; 2017.

25 National Health Information and Performance Principal Committee. *National Data Linkage Demonstration Project, Governance and Technical Papers*. Canberra: Australian Institute of Health and Welfare; 2017.

26 Australian Institute of Health and Welfare. *Australian Atlas of Healthcare Variation: Number of Acute Myocardial Infarction Hospitalisations with Percutaneous Coronary Interventions and/or Coronary Artery Bypass Graft per 100,000 People, 35-84Years, 2014–15*. Canberra: Australian Institute of Health and Welfare; 2017. Available from URL: https://meteor.aihw.gov.au/content/index.phtml/itemId/640170

27 Nedkoff L, Lopez D, Goldacre M, Sanfilippo F, Hobbs M, Wright FL.

Identification of myocardial infarction type from electronic hospital data in England and Australia: a comparative data linkage study. *BMJ Open* 2017; **7**: e019217.
28 Australian Institute of Health and Welfare. Australian hospital peer groups. In: *Health Services Series*. Canberra: Australian Institute of Health and Welfare; 2015.
29 Austin PC, Merlo J. Intermediate and advanced topics in multilevel logistic regression analysis. *Stat Med* 2017; **36**: 3257–77.
30 Austin PC, Wagner P, Merlo J. The median hazard ratio: a useful measure of variance and general contextual effects in multilevel survival analysis. *Stat Med* 2017; **36**: 928–38.
31 Faridi KF, Peterson ED, McCoy LA, Thomas L, Enriquez J, Wang TY. Timing of first postdischarge follow-up and medication adherence after acute myocardial infarction. *JAMA Cardiol* 2016; **1**: 147–55.
32 Sorensen R, Gislason GH, Fosbol EL, Rasmussen S, Køber L, Madsen JK *et al*. Initiation and persistence with clopidogrel treatment after acute myocardial infarction: a nationwide study. *Br J Clin Pharmacol* 2008; **66**: 875–84.
33 Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G *et al*. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; **293**: 2126–30.
34 Shore S, Jones PG, Maddox TM, Bradley SM, Stolker JM, Arnold SV *et al*. Longitudinal persistence with secondary prevention therapies relative to patient risk after myocardial infarction. *Heart* 2015; **101**: 800–7.
35 Roe MT, Peterson ED, Newby LK, Chen AY, Pollack CV Jr, Brindis RG *et al*. The influence of risk status on guideline adherence for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2006; **151**: 1205–13.
36 Ranasinghe I, Naoum C, Aliprandi-Costa B, Sindone AP, Steg PG, Elliott J *et al*. Management and outcomes following an acute coronary event in patients with chronic heart failure 1999-2007. *Eur J Heart Fail* 2012; **14**: 464–72.
37 Zhang H, Goodman SG, Yan RT, Steg PG, Kornder JM, Gyenes GT *et al*. In-hospital management and outcomes of acute coronary syndromes in relation to prior history of heart failure. *Eur Heart J Acute Cardiovasc Care* 2016; **5**: 214–22.
38 Joynt KE, Huynh L, Amerena JV, Brieger DB, Coverdale SG, Rankin JM *et al*. Impact of acute and chronic risk factors on use of evidence-based treatments in patients in Australia with acute coronary syndromes. *Heart* 2009; **95**: 1442–8.
39 Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG *et al*. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012; **367**: 1297–309.
40 Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC *et al*. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015; **372**: 1791–800.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Medicines of interest and PBS restrictions.
Table S2. Codes for identifying patient clinical characteristics.
Table S3. Summary of hospital type categorisation, based on hospital peer groups (source: Australian Institute of Health and Welfare 2015. Australian hospital peer groups. Health services series no. 66. Cat no HSE 170. Canberra: AIHW).
Table S4. Hazard ratios for break in $P2Y_{12}$ inhibitor therapy, among patients discharged for AMI with a dispensing of a $P2Y_{12}$ inhibitor within 30 days of discharge.
Figure S1. Time to first break in $P2Y_{12}$ inhibitor therapy, by further patient characteristics.