One-Year Outcomes of Patients With Established Coronary Artery Disease Presenting With Acute Coronary Syndromes

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The risk of major adverse cardiovascular events (MACE) remains high in patients with established coronary artery disease (CAD). The aim of this study was to assess the prognostic significance of established CAD in patients who present with acute coronary syndromes (ACS) using a large established multicenter registry. Consecutive patients from the Melbourne Interventional Group registry who presented with ACS and underwent percutaneous coronary intervention from 2005 to 2015 were included. Patients with a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery were included in the established CAD cohort. The primary end points were 12-month mortality and 12-month MACE. Of the 12,878 ACS patients included in our study, 3,542 (28%) patients had established CAD. Over the 10-year study period, the proportion of patients presenting with established CAD decreased (30.7% to 25.2%; p-for-overall-trend <0.001). Non-ST elevation myocardial infarction was the most prominent presentation in the established CAD cohort (45.1%) whereas ST-elevation myocardial infarction was the most prominent in the de novo CAD cohort (51%; $p < 0.001$). The patients in the established CAD cohort were older, had more co-morbidities and were more likely to present with high-risk features such as atrial fibrillation, left main disease, multivessel CAD and left ventricular dysfunction (all $p < 0.001$). Regarding revascularization in ST-elevation myocardial infarction presentations, symptom-to-door time was shorter, whereas door-to-balloon-time was longer in those with established CAD ($p < 0.001$). On multivariate analysis, established CAD was an independent risk factor for 12-month MACE (odds ratio 1.40, 95% confidence intervals 1.23 to 1.58, $p < 0.001$), but not for 12-month mortality (odds ratio 1.08, 95% confidence intervals 0.77 to 1.52, $p = 0.66$). In conclusion, patients with a history of myocardial infarction or previous revascularization have a higher rate of MACE at 12 months. Despite this they do not appear to suffer from higher mortality. **(Am J Cardiol 2019;123:1387−1392)**

Coronary artery disease (CAD) is a leading cause of death across the globe.[1] There has been an overall decline in age-adjusted mortality over recent decades attributable to the emergence of guideline directed medical therapy and coronary revascularisation.[2] Despite this, the risk of major adverse cardiovascular events (MACE) remains high in patients with established CAD.[3−5] As a result, patients with established CAD represent nearly half of presentations with coronary events, despite only accounting for 6% of the total population.[6] As survival post myocardial infarction (MI) improves, the population of patients with established CAD will increase and management should be aimed at the prevention of recurrent cardiac events. The prognostic significance of established CAD in patients who present with acute coronary syndromes (ACS) has not been fully explored in contemporary literature. In this observational cohort study, we aimed to assess the mortality and morbidity hazard at 12 months associated with established CAD in patients who present with ACS and are treated with percutaneous coronary intervention (PCI).

Methods

This observational cohort study included consecutive patients from the Melbourne Interventional Group (MIG) registry who presented with ACS and underwent PCI from 2005 to 2015. The MIG registry is a multicenter PCI registry comprising 6 Australian public tertiary hospitals which

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has been previously described in detail.[7] Briefly, demographic, clinical, procedural, and in-hospital outcome data are prospectively recorded. In hospital outcomes were recorded at the time of either death or discharge, with 30-day and 12-month follow-up recorded by way of a combination of reviewing medical records and/or a telephone interview, using a standardized questionnaire.[8] Follow-up rates at 30 days and 12 months were 99.6% and 97.1%, respectively. An audit of several verifiable fields from 5% of randomly selected procedures at each institution is undertaken periodically. In the most recent audit, 27 fields were assessed with data accuracy of 98%.[9] This compares favorably with audits from other large registries.[10] The ethics committee in each participating hospital has approved the MIG registry, including the use of "opt-out" consent. If a patient informs a staff member that they do not wish to participate, the patient's data are not collected.

All patients who presented with ACS and underwent PCI were included. Those with a history of previous MI, previous PCI, or previous coronary artery bypass graft surgery (CABG) were defined as having established CAD. Those with no history of MI, previous PCI, or previous CABG were defined as de novo CAD. ACS was defined as a presentation of unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI). UA was defined as ischemic chest pain and/or electrocardiographic (ECG) changes suggestive of myocardial ischemia without a rise in cardiac enzymes. NSTEMI was defined as a rise in cardiac enzymes in addition to features defining UA. STEMI was defined as ECG evidence of either ST segment elevation or new/presumed new left bundle branch block that had not resolved within 20 minutes. The ST-elevation is defined as new or presumed new, continued ST segment elevation at the J-point in 2 contiguous ECG leads (≥0.2 mV in men or ≥0.15 mV in women in leads V2 to V3, and/or ≥0.1 mV in other leads). In addition, cardiac biomarkers must exceed the upper limits of normal at the relevant institution and a clinical presentation which is consistent with or suggestive of cardiac ischemia is required. ACS rehospitalization was defined as a readmission to hospital with either UA, NSTEMI, or STEMI.

All patients included had 12-month follow-up. Patients treated with PCI for a non-ACS indication were excluded.

The primary end points for this study were 12-month mortality and 12-month MACE. MACE was defined as the composite of mortality, MI, stroke, and target vessel revascularization. Secondary end points included the individual components of MACE at 12-month, as well as 12-month ACS rehospitalization.

Categorical data have been expressed as numbers/percentages and continuous variables as mean ± standard deviation. Categorical variables were compared using Fisher's exact or chi-square tests as appropriate. Continuous variables were compared using Student's *t* test or Kruskal-Wallis equality-of-populations rank test as appropriate.

Multivariate logistic regression was used to assess for independent predictors of 12-month mortality and MACE. Univariate variables with $p < 0.10$ were included in our model to obtain adjusted odds ratios (OR) and 95% confidence intervals (CI). The variables considered were age category, gender, eGFR, hypertension, diabetes, hypercholesterolemia, family history of coronary disease, previous MI, previous PCI, previous CABG, heart failure, peripheral vascular disease, cerebrovascular disease, left ventricular ejection fraction, multivessel CAD, chronic lung disease, cardiogenic shock, glycoprotein IIb/IIIa use, drug-eluting stent use, long stent (>20 mm), small diameter (<2.5 mm), and treated lesion location (ostial, bifurcation, left main, LAD, circumflex, right coronary artery, and bypass graft). The data analysis was carried out using Stata 14.1 (StataCorp LP, College Station, Texas). A p value of <0.05 was considered to be statistically significant.

Results

Of the 12,878 ACS patients included in our study, 3,542 (28%) patients had established CAD and 9,336 (72%) patients had de novo CAD. Over the 10-year study period, the proportion of patients presenting with established CAD decreased (30.7% to 25.2%) with a corresponding increase in the proportion of patients with de novo CAD (69.3% to 74.8%; p-for-overall-trend <0.001; Figure 1).

NSTEMI was the most prominent presentation in the established CAD cohort (45.1%), followed by STEMI (29.6%) and UA (25.3%). STEMI was most prominent in the de novo CAD cohort (51%), followed by NSTEMI (39.9%) and UA (9.1%; p <0.001; Table 1).

Presenting and baseline characteristics are shown (Table 1). The patients in the established CAD cohort were older, had more co-morbidities, and were more likely to present with high-risk features such as renal dysfunction, atrial fibrillation, left main disease, multivessel CAD, and left ventricular dysfunction (p value for all <0.001). Those with de novo CAD were more likely to present with an out of hospital cardiac arrest ($p < 0.001$) and to have single vessel disease ($p < 0.001$). Rates of cardiogenic shock on presentation were similar between the 2 groups (4.2% vs 4.5%, p value 0.38). Regarding revascularization in STEMI presentations, symptom-to-door time was shorter (90 vs 115 minutes, p value <0.001) but door-to-balloon-time (DTBT) was longer (89 vs 77 minutes, p value <0.001) in those with established CAD (p value for all <0.001).

Angiographic and procedural characteristics are shown in Table 1. Patients with established CAD were less likely to receive glycoprotein IIb/IIIa inhibitors and were more likely to receive drug-eluting stents. This group also had a higher rate of periprocedural MI ($p = 0.002$) and a longer length of stay ($p < 0.001$).

Secondary prevention pharmacotherapy for patients who were alive at 12 months is shown in Table 2. Those with established CAD were prescribed less aspirin and statins but were more likely be on spironolactone, ezetimibe, or a fibrate. Additionally, this group was more likely to be anticoagulated with either Warfarin or a novel oral anticoagulant (p value for all <0.005).

12-month outcomes are shown in Table 3. The primary end points of 12-month mortality and 12-month MACE were significantly higher in the established CAD cohort when compared with the de novo CAD cohort (7.9% vs 5.4%, $p < 0.001$ and 20.2% vs 12.8%, $p < 0.001$, respectively).

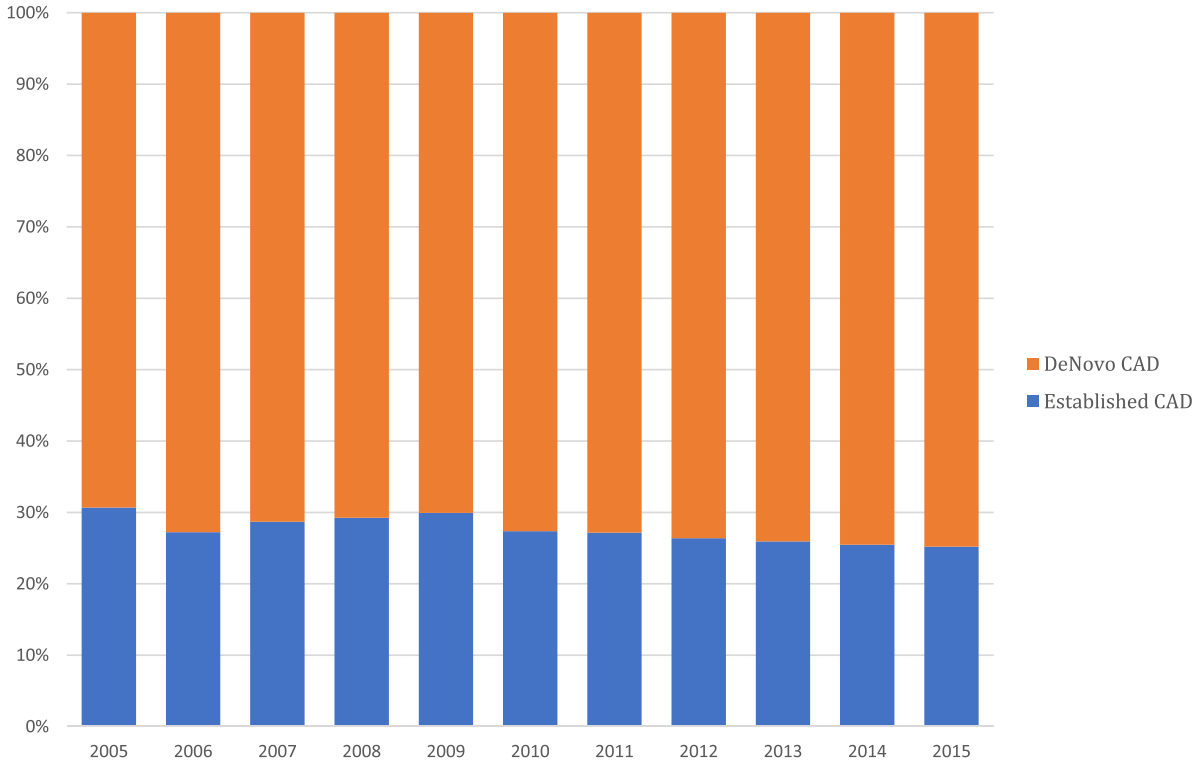

Figure 1. Proportion of patients with established CAD versus De Novo CAD presenting with ACS each year.

Secondary end points were also more prevalent in patients with established CAD (p value for all <0.005).

Tables 4 and 5 show independent predictors of 12-month mortality and 12-month MACE. Established CAD was an independent risk factor for 12-month MACE (OR 1.40, 95% CI 1.23 to 1.58, $p < 0.001$), but not for 12-month mortality (OR 1.08, 95% CI 0.77 to 1.52, $p = 0.66$).

Discussion

From this observational cohort study of patients with ACS who are treated with PCI, 4 conclusions merit attention. Firstly, NSTEMI is more prevalent in patients with established CAD. Secondly, patients in the established CAD cohort were older, had more co-morbidities, and were more likely to present with high-risk features. Thirdly, in patients presenting with STEMI the DTBT is longer in the established CAD cohort despite faster symptom-to-door time. Lastly, established CAD was an independent risk factor for 12-month MACE, but not for 12-month mortality.

ACS comprises a spectrum of clinical manifestations ranging from UA to NSTEMI and STEMI. Although the underlying pathophysiological substrate is similar, the different clinical manifestations across the spectrum of ACS vary.[11–13] It has been previously reported that, in patients presenting with ACS, NSTEMI was associated with a higher risk of long-term mortality than STEMI. This is likely a result of more co-morbidities and a higher burden of atherosclerotic disease.[12,13] Consistent with Chan et al, in our cohort, patients with established CAD had a greater burden of atherosclerosis with higher rates of multivessel disease and left main disease as well as more medical co-morbidities.[12] Consequently, they were more likely to present with NSTEMI. Those with de novo CAD had less burden of atherosclerosis and as such had greater rates of single vessel disease and presentation with STEMI. Interestingly, they were more likely to be current smokers who have been associated with endothelial dysfunction and thrombogenicity rather than atherosclerosis.[14]

The determinants of disease progression and the prognostic significance of established CAD in patients presenting with recurrent ACS remains poorly understood. In a large-scale national Swedish registry study 1 in 5 patients discharged with MI had a subsequent cardiovascular event. The risk of this was independently associated with age, medical co-morbidities, and the use of revascularization for the index event.[15] This is consistent with our results as patients with known CAD who represented with ACS were older and had more medical co-morbidities. Furthermore, these patients presented with more high-risk features such as renal dysfunction, atrial fibrillation, left main disease, multivessel CAD, and left ventricular dysfunction. The importance of this is reflected in the work of Park et al who demonstrated that patients presenting with ACS with underlying advanced CAD have worse outcomes than those with disease limited to the infarct-related artery.[16]

Rapid mechanical reperfusion is an established treatment for patients presenting with STEMI. This is supported by international guidelines and is founded on the principal that reducing ischemic time will decrease myocardial necrosis and limit infarct size.[17,18] In our study, the established CAD group had a greater DTBT despite shorter symptom-to door time. It is plausible that the delay in revascularization is a result of more complex coronary

Table 1
Baseline, presentation, and angiographic characteristics

Variable	Coronary artery disease: Established n = 3,542	Coronary artery disease: De novo n = 9,336	p value
Baseline			
Age (years, mean + SD)	67.5 + 12.0	63.1 + 12.5	<0.001
Age >75 years	1145 (32%)	1967 (21%)	<0.001
Men	2734 (77%)	6928 (74%)	0.001
Body mass index	28.2 + 5.3	28.2 + 5.3	0.32
Current smoker	710 (20%)	3056 (33%)	<0.001
Hypertension	2827 (80%)	5139 (55%)	<0.001
Hypercholesterolemia	2956 (84%)	5164 (55%)	<0.001
Diabetes mellitus	1148 (32%)	1664 (18%)	<0.001
Family history of CAD	1307 (39%)	3600 (40%)	0.32
Previous MI	2710 (77%)		
Previous PCI	2342 (66%)		
Previous CABG	779 (22%)		
Congestive heart failure	268 (8%)	146 (2%)	<0.001
Peripheral vascular disease	402 (11%)	290 (3%)	<0.001
Stroke	333 (9%)	396 (4%)	<0.001
Chronic lung disease	476 (13%)	895 (10%)	<0.001
Rheumatoid arthritis	83 (3%)	165 (2%)	0.02
Oral anticoagulation	37 (6%)	51 (3%)	<0.001
eGFR ≥60 ml/min/1.73 m^2	2423 (69%)	7239 (80%)	
eGFR 30−<60 ml/min/1.73 m^2	887 (25%)	1642 (18%)	
eGFR <30 ml/min/1.73 m^2	185 (5%)	196 (2%)	<0.001
Ejection fraction >45%	2053 (68%)	6413 (75%)	
Ejection fraction 30−45%	834 (28%)	1979 (23%)	
Ejection fraction <30%	128 (4%)	138 (2%)	<0.001
Presentation			
Unstable angina pectoris	896 (25%)	849 (9%)	
NSTEMI	1599 (45%)	3725 (40%)	
STEMI	1047 (30%)	4762 (51%)	<0.001
Cardiogenic shock	149 (4%)	426 (5%)	0.38
Out of hospital cardiac arrest	81 (2%)	391 (4%)	<0.001
Mechanical support required	10 (2%)	34 (2%)	0.71
Single vessel disease	820 (23%)	4843 (52%)	
Multivessel CAD	2714 (77%)	4455 (48%)	<0.001
Left main disease	175 (12%)	127 (5%)	<0.001
DTBT (STEMI) (minutes) (Median IQR)	89 (57, 135)	77 (49, 114)	<0.001
Symptom-door time (STEMI) (minutes) (Median IQR)	90 (60,163)	115 (70,220)	<0.001
DTBT <90 min	391 (51%)	2336 (61%)	<0.001
On Inotropes	74 (4%)	274 (5%)	0.03
Atrial fibrillation	200 (7%)	372 (5%)	<0.001
Angiographic characteristics			
Radial approach	617 (17%)	1907 (20%)	<0.001
Femoral approach	2903 (82%)	7404 (79%)	<0.001
Thrombolytics	134 (4%)	673 (7%)	<0.001
Glycoprotein IIb/IIIa inhibitors	1049 (30%)	4200 (45%)	<0.001
De novo coronary lesion	3451 (81%)	10903 (100%)	
Instent restenosis	776 (18%)	0 (0%)	<0.001
Stent length (mm)	19.7 + 9.6	19.8 + 8.8	0.004
Balloon angioplasty only	368 (10%)	385 (4%)	
Bare metal stent only	1312 (37%)	4698 (50%)	
Drug eluting stent only	1793 (50%)	4092 (44%)	
Both bare and drug eluting stents	65 (2%)	144 (2%)	<0.001
Number of stents inserted.	1.2 + 0.7	1.2 + 0.6	<0.001

CABG = coronary artery bypass grafts; CAD = coronary artery disease; DTBT = door-to-balloon-time; eGFR = estimated glomerular filtration rate; IQR = Interquartile range; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

Table 2
Pharmacotherapy at 12 months

Variable	Coronary artery disease: Established n = 3,542	Coronary artery disease: De novo n = 9,336	p value
Aspirin	2827 (94%)	7805 (96%)	<0.001
Clopidogrel/Prasugrel/ Ticagrelor	2381 (76%)	6184 (74%)	0.009
Statin	2760 (92%)	7619 (94%)	0.001
Beta-blocker	2254 (76%)	6045 (75%)	0.40
ACEi/ARB	2379 (80%)	6537 (81%)	0.16
Warfarin	221 (7%)	342 (4%)	0.001
NOAC	22 (2%)	38 (1%)	0.05
Spironolactone	123 (4%)	159 (2%)	<0.001
Eplerenone	53 (2%)	130 (2%)	0.49
Ezetimibe	302 (11%)	311 (4%)	<0.001
Fibrate	79 (3%)	102 (1%)	<0.001

ACEi = angiotensin converting enzyme inhibitor; ARB = aldosterone receptor blocker; NOAC = novel oral anticoagulant.

Table 3
Outcomes at 12-months

Variable	Established CAD n = 3,542	De novo CAD n = 9,336	p value
Primary end points			
12-month mortality	281 (8%)	507 (5%)	<0.001
12-month MACE	716 (20%)	1195 (13%)	<0.001
Secondary end points			
12-month MI	299 (8%)	308 (3%)	<0.001
12-month stroke	53 (2%)	77 (1%)	0.001
12-month TVR	307 (9%)	513 (6%)	<0.001
12-month ACS rehospitalization	581 (17%)	946 (11%)	<0.001

ACS = acute coronary syndrome; MACE = major adverse cardiovascular events; MI = myocardial infarction, TVR = target vessel revascularization.

disease. Additionally, the older age and greater burden of medical comorbidities requires more thorough preintervention assessment and screening.[19] Despite the longer DTBT, the long-term prognostic significance of this may be

Table 4
Multivariate logistic regression OR and 95% CI for predictors of 12-month mortality

	Odds ratio	95% CI	p value
Established CAD	1.08	0.77−1.52	0.66
Age	1.05	1.04−1.06	<0.001
Cardiac arrest	4.60	3.13−6.74	<0.001
Diabetes	1.80	1.29−2.51	0.001
eGFR 30−59	1.91	1.41−2.60	<0.001
eGFR <30	6.77	3.86−11.87	<0.001
EF 30−45%	2.57	1.91−3.47	<0.001
EF <30%	7.87	4.61−13.42	<0.001
CLD	1.75	1.17−2.60	0.006
DTBT <90 min	0.70	0.53−0.93	0.01

CLD = chronic liver disease; DTBT = door-to-balloon-time; EF = ejection fraction; eGFR = estimated glomerular filtration rate.

Table 5.
Multivariate logistic regression OR and 95% CI for predictors of 12-month MACE

	Odds ratio	95% CI	p value
Established CAD	1.40	1.23−1.58	<0.001
Age	1.01	1.01−1.02	<0.001
Cardiogenic shock	3.84	3.07−4.81	<0.001
Cardiac arrest	1.94	1.49−2.52	<0.001
Diabetes	1.49	1.31−1.70	<0.001
DES	0.60	0.54−0.68	<0.001
eGFR 30−59	1.37	1.20−1.87	<0.001
eGFR <30	3.28	2.52−4.26	<0.001
EF 30−45%	1.66	1.46−1.87	<0.001
EF <30%	3.11	2.33−4.14	<0.001
CLD	1.21	1.02−1.43	0.03

CAD = coronary artery disease; CLD = chronic liver disease; DES = drug-eluting stent; eGFR = estimated glomerular filtration rate; EF = ejection fraction.

overstated.[20] Of public health interest, those with established CAD had a shorter symptom-to-door time. Although the reason for this is unclear, those with a history of CAD may be more aware of the importance of cardiac symptoms leading to earlier presentation.

There has been a decline in mortality in patients with established CAD over the past decade.[3,6] There are a number of explanations for this, including decreasing severity of disease, increasing rates of revascularization with drug-eluting stents and utilization of optimal medical therapy (OMT).[21,22] OMT is defined as the use of all guideline-directed medications (at least 1 antiplatelet drug, β blocker, ACEi/ARB, and statin). Multiple large-scale trials have demonstrated a higher mortality and MACE when OMT is underutilized.[2,23−25] We observed that patients with established CAD were prescribed less secondary prevention pharmacotherapy as evidenced by lower rates of statin and aspirin use. Although the exact cause for this is uncertain, older patients with more co-morbidities may be less likely to tolerate statins.[26] Furthermore, those with established CAD were more likely to present with atrial fibrillation and require long-term anticoagulation. Therefore, the lower use of aspirin in this cohort could be explained by avoidance of triple therapy. As we have learnt from recent trials, anticoagulation combined with only a single antiplatelet agent is associated with less bleeding hazard without compromising efficacy.[27−29]

In our study, we found established CAD was an independent predictor of MACE but it was not a predictor for 12-month mortality. Our result is consistent with the progressive nature of atherosclerosis as those with established CAD experienced more cardiovascular events, including both MI and ACS rehospitalizations. It is reassuring that these patients do not have higher mortality once baseline differences are accounted for. This is likely due to the fact our patients all received at least culprit-vessel revascularization acutely and high levels of guideline-directed OMT in the short- and medium-term. This homogeneity in treatment may also account for the lower MACE rate we have shown when compared with large registries.[15] Furthermore, previous studies have shown improved outcomes with revascularization in ACS and OMT.[12]

This study has a number of inherent limitations due to its observational design. Firstly, there are likely unmeasured factors we have not accounted for in our analysis and thus the associations we have reported are hypothesis generating rather than conclusive. Secondly, the generalizability of our study is limited to only those patients with ACS who were treated with PCI. Thirdly, although we capture utilization of secondary prevention therapies we do not know whether patients are achieving optimal control of blood pressure, cholesterol, and diabetic. We do not capture reasons why patients were not on OMT nor are we able to ascertain if patients not on statin therapy were tried on multiple agents and/or lower doses. Furthermore, this study included a significant proportion of patients on Clopidogrel, as Ticagrelor, with its associated mortality benefit, was not available in Australia before 2013.[30] Lastly, our follow-up was limited to only 12 months and it is possible those with established CAD could have a worse prognosis when followed for a longer period of time.

In conclusion, patients with a history of myocardial infarction or previous revascularization, whether surgical or percutaneous, have a higher rate of major cardiovascular events at 12 months. Despite this they do not appear to suffer from higher mortality.

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