Relation of Timing of Percutaneous Coronary Intervention on Outcomes in Patients With Non-ST Segment Elevation Myocardial Infarction

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International guidelines suggest revascularization within 24 hours in non-ST segment elevation myocardial infarction (NSTEMI). Within a large population cohort study, we aimed to explore clinical practice regarding timing targets for percutaneous coronary intervention (PCI) in NSTEMI. The Victorian Cardiac Outcomes Registry was established in 2013 as a state-wide clinical quality registry, pooling data from public and private PCI capable centers. Data were collected on 11,852 PCIs performed for NSTEMI from 2014 to 2018. Patients were divided into 3 groups by time of symptom onset to PCI (<24 hours; 24 to 72 hours; >72 hours). We performed multivariable logistic regression analysis conditional on several baseline covariates in investigating the impact of timing of PCI in NSTEMI on clinical outcomes. Patients who underwent PCI within 24 hours represented 18.4% (n = 2,178); 24 to 72 hours 45.8% (n = 5,434); >72 hours 35.8% (n = 4,240). Patients waiting longer for PCI were older (62.6 ± 12.2 vs 64.8 ± 12.6 vs 67.0 ± 12.7, p <0.001), more likely to be female (23.1% vs 24.2% vs 26.4%, p = 0.007), and have diabetes (18.6% vs 21.1% vs 27.1%, p <0.001). Multivariate logistic regression found that as compared with PCI <24 hours, PCI 24 to 72 hours and PCI >72 hours of symptom onset were associated with a decreased risk of 30-day mortality (odds ratio 0.55; 95% confidence interval 0.35 to 0.86, p = 0.008 and odds ratio 0.64; 95% confidence interval 0.35 to 1.01, p = 0.053, respectively). There was no significant difference in 30-day mortality between groups following exclusion of patients presenting with cardiogenic shock or out of hospital cardiac arrest requiring intubation. In conclusion, many registry patients undergo PCI outside the 24-hour window following NSTEMI. This delay is at odds with current guideline recommendations but does not appear to be associated with an increased mortality risk.
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ST-elevation myocardial infarction (STEMI) is most often associated with acute coronary occlusion, benefiting from expedited reperfusion therapy, in most cases with percutaneous coronary intervention (PCI) to improve clinical outcomes.[1] By contrast, timing of PCI in non-ST elevation myocardial infarction (NSTEMI) is more variable and intervention within 90 minutes is not routinely undertaken,[2] with multiple randomized trials conducted comparing early and delayed invasive strategies.[3−6] Results of these trials have been conflicting, with no clear mortality benefit favoring early intervention found in large meta analyses.[7, 8] Current guidelines on the management of non-ST segment elevation acute coronary syndromes (NSTEACS) categorize timing of intervention as immediate invasive (<2 hours), early invasive (<24 hours), invasive (<72 hours), with intervention recommended within 24 hours for NSTEMI, patient risk factors considered.[2] In clinical practice at PCI centers in Australia, time from symptom onset to PCI often varies in patients with NSTEMI. Unstable patients with ongoing ischemic symptoms are typically triaged for more urgent PCI. Nevertheless, stable patients with complicating co-morbidities may wait over weekends for PCI during staffed hours, or until other co-morbid conditions have settled. The present study aims to utilize data from the Victorian Cardiac Outcomes Registry (VCOR) to report on the timing of

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PCI in NSTEMI, and its potential impact on clinical outcomes in a contemporary population of Australian patients.

Methods

VCOR was established in 2013 as a state-wide clinical quality registry in Victoria, Australia, with all 32 public and private PCI capable centers contributing from 2017. VCOR is managed by Monash University and is represented by a steering committee constituted by specialists from contributing centers. The full VCOR methodology is described elsewhere.[9] VCOR is ethics approved and operates with an opt-off consent process. Following VCOR research and local institutional ethics committee approvals (project no. 509/19), we analyzed data from all adult patients who underwent PCI for NSTEMI between January 1, 2014 and December 31, 2018.

NSTEMI was defined by elevation in at least one of the biomarkers for myocardial necrosis (troponin T or I, CK-MD, total CK) along with stent thrombosis (ST) segment depression or T wave abnormalities on electrocardiogram, or ischemic symptoms (i.e., chest discomfort, nausea, vomiting, persistent dyspnea, fatigue, presyncope, and syncope). Patients who underwent PCI for NSTEMI were grouped based on time from symptom onset to PCI procedure start time as follows: "<24" = PCI <24 hours; "24 to 72" = PCI 24 to 72 hours; ">72" = PCI >72 hours. Patients who underwent PCI for NSTEMI >7 days ago were excluded.

Patient demographic data, including baseline, procedural and medication characteristics were compared across groups. Within procedural characteristics, lesion complexity was defined as A, B1, B2, or C according to American College of Cardiology/American Heart Association classification guidelines.[10] Clinical outcomes collected in hospital and at 30 days included all-cause mortality, new myocardial infarction (MI), repeat PCI, any target vessel revascularization or target lesion

Table 1
Baseline clinical characteristics

Variable	All patients (n = 11,852)	Hours			p value
		<24 (n = 2,178)	24-72 (n = 5,434)	>72 (n = 4,240)	
Age (years)	65.2 ± 12.6	62.6 ± 12.2	64.8 ± 12.6	67.0 ± 12.7	0.033
Women	2938 (24.8%)	503 (23.1%)	1317 (24.2%)	1118 (26.4%)	0.007
Symptom to procedure time (hours)	53.7 ± 38.4	14.3 ± 6.4	44.3 ± 13.7	106.0 ± 28.3	N/A
Year of PCI					0.051
2014	1967 (16.6%)	335 (15.4%)	906 (16.7%)	726 (17.1%)	
2015	2191 (18.5%)	371 (17.0%)	1004 (18.5%)	816 (19.2%)	
2016	2401 (20.3%)	430 (19.7%)	1104 (20.3%)	867 (20.4%)	
2017	2539 (21.4%)	508 (23.3%)	1138 (20.9%)	893 (21.1%)	
2018	2754 (23.2%)	534 (24.5%)	1282 (23.6%)	938 (22.1%)	
Time of PCI					<0.001
Weekday in hours	10488 (88.2%)	1763 (80.9%)	4822 (88.7%)	3863 (91.1%)	
Weekday out of hours	762 (6.4%)	186 (8.5%)	306 (5.6%)	270 (6.4%)	
Weekend	534 (4.5%)	197 (9.0%)	255 (4.7%)	82 (1.9%)	
Public holiday	108 (0.9%)	32 (1.5%)	51 (0.9%)	25 (0.6%)	
Private hospital	3017 (25.5%)	462 (21.2%)	1386 (25.5%)	1169 (27.6%)	<0.001
Length of stay (days)	4.4 ± 11.3	3.6 ± 4.3	3.6 ± 4.0	5.8 ± 18.0	<0.001
BMI (kg/m^2)	28.9 ± 5.6	28.8 ± 5.4	28.9 ± 5.5	29.0 ± 5.9	0.001
Diabetes mellitus	2701 (22.8%)	406 (18.6%)	1147 (21.1%)	3092 (27.1%)	<0.001
Peripheral vascular disease	507 (4.3%)	64 (2.9%)	216 (4.0%)	227 (5.4%)	<0.001
Cerebrovascular disease	463 (3.9%)	56 (2.6%)	181 (3.3%)	226 (5.3%)	<0.001
Previous PCI	2475 (20.9%)	403 (18.5%)	1073 (19.7%)	999 (23.6%)	<0.001
Previous CABG	863 (7.3%)	111 (5.1%)	348 (6.4%)	404 (9.5%)	<0.001
LVEF (%)					<0.001
>50	6940 (66.5%)	1174 (60.1%)	3301 (69.5%)	2465 (66.0%)	
45-50	2082 (20.0%)	469 (23.6%)	904 (19.0%)	718 (19.2%)	
35-44	968 (9.3%)	227 (11.6%)	388 (8.2%)	353 (9.5%)	
<35	443 (4.2%)	92 (4.7%)	154 (3.2%)	197 (5.3%)	
eGFR ($ml/min/1.73\ m^2$)					<0.001
>60	9145 (78.8%)	1752 (83.5%)	4331 (81.5%)	3062 (73.1%)	
45-60	1240 (10.7%)	186 (8.9%)	548 (10.3%)	506 (12.1%)	
30-44	789 (6.8%)	102 (4.9%)	302 (5.7%)	385 (9.2%)	
<30	424 (3.7%)	58 (2.8%)	130 (2.4%)	236 (5.6%)	
Cardiogenic shock or OHCA	130 (1.1%)	65 (3.0%)	43 (0.8%)	22 (0.5%)	<0.001

Values are expressed as mean ± standard deviation or n (%).

BMI = body mass index; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fracture; OHCA = out of hospital cardiac arrest; PCI = percutaneous coronary intervention.

Table 2
Procedural characteristics

Variable	All patients (n = 11,852)	Hours			p value
		<24 (n = 2,178)	24-72 (n = 5,434)	>72 (n = 4,240)	
Access					<0.001
Brachial/radial	7124 (60.1%)	1407 (64.6%)	3432 (63.2%)	2285 (53.9%)	
Femoral	4728 (39.9%)	771 (35.4%)	2002 (36.8%)	1995 (46.1%)	
Coronary artery narrowed					<0.001
Right	3392 (28.6%)	574 (26.4%)	1539 (28.3%)	1279 (30.2%)	
Left anterior descending	4460 (37.6%)	900 (41.3%)	2074 (38.2%)	1486 (35.0%)	
Left circumflex	3491 (29.5%)	634 (29.1%)	1623 (29.9%)	1234 (29.1%)	
Left main	209 (1.8%)	31 (1.4%)	81 (1.5%)	97 (2.3%)	
Graft	300 (2.5%)	39 (1.8%)	117 (2.2%)	144 (3.4%)	
Lesion complexity					0.016
A or B1	5236 (44.2%)	941 (43.2%)	2478 (45.6%)	1817 (42.9%)	
B2 or C	6616 (55.8%)	1237 (56.8%)	2956 (54.4%)	2423 (57.1%)	

Values are expressed as mean ± standard deviation or n (%).

revascularization, emergency coronary artery bypass graft (CABG), ST, major bleeding, and new stroke. Rehospitalization was collected at 30 days. A composite endpoint of major adverse cardiovascular events (MACE) comprised of all-cause mortality, MI, target vessel revascularization, or ST. Within clinical outcomes, major bleeding was defined according to the Bleeding Academic Research Consortium (BARC) classification, BARC 3 (overt hemorrhage with hemoglobin drop of >3 g/dl, intracranial bleeding, cardiac tamponade, or transfusion requirement), or BARC 5 (probable or definite fatal hemorrhage).[11] ST was defined according to the Academic Research Consortium definitions of definite or probable.[12]

Univariate comparison of baseline, procedural, medication characteristics, and clinical outcomes across each group was undertaken. Continuous variables are expressed as mean and standard deviation, and categorical variables are expressed as number and percentage. The chi-square, *t* test, or Mann-Whitney *U* test were used as appropriate to compare categorical and continuous variables. Differences between groups were considered statistically significant if the 2-tailed p value was <0.05. Multivariate logistic regression was performed to estimate the odds ratio (OR) of all-cause mortality and MACE at 30 days across each group. Separate analyses were run following exclusion of patients that presented with cardiogenic shock or out of hospital cardiac arrest (OHCA) requiring intubation. We adjusted for baseline covariates including age, gender, timing of PCI, private hospital, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, previous PCI, previous CABG, left ventricular ejection fraction, renal function, medications administered within 24 hours of PCI (oral anticoagulation, glycoprotein IIb/IIIa inhibitor, thienopyridine, ticagrelor, aspirin, and antithrombin).

Results

Of the 11,852 consecutive patients who underwent PCI for NSTEMI between January 2014 and December 2018, 2,178 (18.4%) underwent PCI <24 hours from symptom onset, 5,434 (45.8%) underwent PCI 24 to 72 hours from symptom onset, and 4,240 (35.8%) underwent PCI >72 hours from symptom onset. Patients waiting longer for PCI were older, more likely to be female, and more commonly had co-morbidities such as diabetes mellitus, peripheral vascular disease, cerebrovascular disease, poor renal function, and a history of previous PCI or CABG (Table 1). A greater number of patients proceeding to PCI <24 hours from symptom onset had presented with cardiogenic shock or OHCA requiring intubation (Table 1).

Radial access was most common route of access in patients who underwent PCI within 24 hours (Table 2). PCI to lesions located in the left anterior descending artery were more common in patients who underwent PCI within 24 hours (Table 2). By contrast, PCI to the right coronary artery was more commonly seen in patients waiting longer than 72 hours for PCI (Table 2). Ticagrelor appeared to be favored over thienopyridine use in those who underwent PCI within 24 hours of symptom onset (Table 3). Medications on discharge from hospital were largely comparable between groups, with the exception again of ticagrelor which was again more often favored over alternative P2Y12 inhibitors (Table 3).

In-hospital mortality was twice as common in those who underwent PCI within 24 hours as compared with those who underwent PCI 24 to 72 hours or >72 hours later (1.9% vs 0.7% vs 0.9%; p <0.001) (Table 4). Post procedural outcomes, including MI, emergency PCI or CABG, stroke, and major bleeding were comparable between groups when measured in-hospital or at 30 days (Table 4).

Following adjustment for several significant covariates, multivariate binary regression found that, as compared with PCI in less than 24 hours, PCI 24 to 72 hours and PCI >72 hours from symptom onset were associated with a decreased risk of mortality (OR 0.55; 95% confidence interval [CI] 0.35 to 0.86, p = 0.008 and OR 0.64; 95% CI 0.41 to 1.01, p = 0.053, respectively) (Table 5, Figure 1). As compared with PCI in less than

Table 3
Medication characteristics

Variable	All patients (n = 11,852)	Hours <24 (n = 2,178)	Hours 24-72 (n = 5,434)	Hours >72 (n = 4,240)	p value
24 hours prior to PCI					
Oral anticoagulation	664 (5.6%)	68 (3.1%)	256 (4.7%)	340 (8.0%)	<0.001
Aspirin	10804 (91.4%)	2016 (92.9%)	4949 (91.3%)	3839 (90.8%)	0.014
Thienopyridine	3413 (28.8%)	515 (23.6%)	1501 (27.6%)	1397 (32.9%)	<0.001
Ticagrelor	6084 (51.3%)	1293 (59.4%)	2889 (53.2%)	1902 (44.9%)	<0.001
Glycoprotein IIb/IIIa inhibitor	848 (7.2%)	253 (11.6%)	375 (6.9%)	220 (5.2%)	<0.001
Antithrombin	10527 (90.6%)	1985 (91.9%)	4828 (90.5%)	3714 (90.1%)	0.078
No antiplatelet	420 (3.5%)	52 (2.4%)	191 (3.5%)	177 (4.2%)	0.001
On discharge from Hospital					
Oral anticoagulation	856 (7.3%)	89 (4.2%)	362 (6.7%)	405 (9.6%)	<0.001
Aspirin	11486 (97.9%)	2105 (98.5%)	5280 (97.9%)	4101 (97.6%)	0.131
Thienopyridine	4157 (35.4%)	559 (26.2%)	1838 (34.1%)	1760 (41.9%)	<0.001
Ticagrelor	7424 (63.3%)	1549 (72.5%)	3502 (64.9%)	2373 (56.5%)	<0.001
Beta blocker	8958 (76.4%)	1683 (78.8%)	4023 (74.6%)	3252 (77.4%)	0.002
ACEi/ARB	8759 (74.7%)	1672 (78.3%)	4059 (75.3%)	3028 (72.1%)	<0.001
Statin	11084 (94.5%)	2049 (95.9%)	5105 (94.6%)	3930 (93.6%)	0.001
Other lipid lowering therapy	817 (7.0%)	114 (6.7%)	343 (6.4%)	330 (7.9%)	0.043

Values are expressed as n (%).
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; PCI = percutaneous coronary intervention.

Table 4
Outcomes in hospital and at 30 days

Variable	All patients (n = 11,852)	Hours <24 (n = 2,178)	Hours 24-72 (n = 5,434)	Hours >72 (n = 4,240)	p value
In-hospital					
Mortality	112 (1.0%)	42 (1.9%)	40 (0.7%)	40 (0.9%)	<0.001
Myocardial infarction	76 (0.6%)	17 (0.8%)	30 (0.6%)	29 (0.7%)	0.481
Repeat percutaneous coronary intervention	478 (4.0%)	107 (4.9%)	204 (3.8%)	167 (3.9%)	0.063
Target vessel revascularization	78 (0.7%)	11 (0.5%)	33 (0.6%)	34 (0.8%)	0.311
Target lesion revascularization	60 (0.5%)	6 (0.3%)	28 (0.5%)	26 (0.6%)	0.195
Coronary artery bypass graft	76 (0.6%)	14 (0.6%)	31 (0.6%)	31 (0.7%)	0.617
Stent thrombosis	13 (0.1%)	3 (0.1%)	5 (0.1%)	5 (0.1%)	0.845
Major bleed	93 (0.8%)	16 (0.7%)	38 (0.7%)	39 (0.9%)	0.455
Stroke	25 (0.2%)	6 (0.3%)	13 (0.2%)	6 (0.1%)	0.447
30 day					
Mortality	117 (1.5%)	50 (2.3%)	59 (1.1%)	68 (1.6%)	<0.001
Myocardial infarction	157 (1.3%)	29 (1.3%)	64 (1.2%)	64 (1.5%)	0.367
Target vessel revascularization	77 (0.6%)	14 (0.6%)	44 (0.8%)	19 (0.4%)	0.090
Target lesion revascularization	46 (0.4%)	9 (0.4%)	26 (0.5%)	11 (0.3%)	0.223
Coronary artery bypass graft	29 (0.2%)	4 (0.2%)	12 (0.2%)	13 (0.3%)	0.570
Stent thrombosis	43 (0.4%)	8 (0.4%)	21 (0.4%)	14 (0.3%)	0.900
Major bleed	139 (1.2%)	26 (1.2%)	55 (1.0%)	58 (1.4%)	0.271
Stroke	39 (0.3%)	8 (0.4%)	20 (0.4%)	11 (0.3%)	0.614
Re-hospitalization	1573 (13.4%)	268 (12.5%)	722 (13.4%)	583 (13.9%)	0.337

Values are expressed as n (%).

24 hours, PCI 24 to 72 hours or >72 hours following symptom onset was not associated with increased risk of MACE (OR 0.86; 95% CI 0.65 to 1.13, p = 0.27 and OR 0.89; 95% CI 0.67 to 1.20, p = 0.45 respectively) (Table 5, Figure 2). Other multivariate predictors of all-cause mortality included age (OR 1.05; 95% CI 1.03 to 1.07, p <0.001), diabetes mellitus (OR 1.55; 95% CI 1.08 to 2.21, p = 0.02), and severe left ventricular systolic dysfunction (OR 11.14; 95% CI 7.02 to 17.70, p <0.001) (Table 5).

Table 5
Multivariate analysis for mortality and MACE

Variable	Mortality		MACE	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Age	1.05	1.03-1.07	1.03	1.02-1.04
Women	0.80	0.55-1.19	0.99	0.79-1.26
Timing (by group)				
Group 1 (<24 hours)	1.00	REF	1.00	REF
Group 2 (24-72 hours)	0.55	0.35-0.86	0.86	0.65-1.13
Group 3 (>72 hours)	0.64	0.41-1.01	0.89	0.67-1.20
Timing (by day)				
Weekday in hours	1.00	REF	1.00	REF
Weekday out of hours	2.10	1.17-3.75	1.24	0.82-1.86
Weekend	2.91	1.69-5.01	1.76	1.19-2.60
Public holiday	1.08	0.22-5.35	1.04	0.36-2.96
Private hospital	0.70	0.45-1.08	0.89	0.69-1.15
Diabetes mellitus	1.55	1.08-2.21	1.33	1.06-1.67
Peripheral vascular disease	1.36	0.78-2.35	1.47	1.01-2.15
Cerebrovascular disease	1.39	0.75-2.57	1.41	0.93-2.12
Previous PCI	1.21	0.82-1.77	1.36	1.07-1.72
Previous CABG	1.11	0.67-1.82	0.96	0.67-1.37
LVEF (%)				
>50	1.00	REF	1.00	REF
45-50	1.77	1.08-2.90	1.12	0.84-1.48
35-44	4.16	2.60-6.66	2.40	1.81-3.18
<35	11.14	7.02-17.70	4.05	2.92-5.61
Chronic anticoagulant therapy	0.71	0.38-1.33	0.89	0.60-1.34
Aspirin	0.68	0.40-1.14	0.88	0.63-1.25
Thienopyridine	0.72	0.46-1.13	0.79	0.59-1.06
Ticagrelor	0.82	0.53-1.28	0.94	0.72-1.23
Glycoprotein IIb/IIIa inhibitor	0.88	0.45-1.71	1.40	0.98-1.99
Antithrombin	1.03	0.55-1.96	1.26	0.84-1.89

Adjusted for age, gender, timing of PCI, private hospital, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, previous PCI, previous CABG, LVEF, renal function, medications administered within 24 hours of PCI (oral anticoagulation, glycoprotein IIb/IIIa inhibitor, thienopyridine, ticagrelor, aspirin, and antithrombin).

CABG = coronary artery bypass graft; CI = confidence interval; LVEF = left ventricular ejection fracture; MACE = major adverse cardiovascular event; OR = odds ratio; PCI = percutaneous coronary intervention.

An additional analysis was conducted on 11,722 patients, with the exclusion of 130 patients who underwent PCI for NSTEMI but had presented with cardiogenic shock or OHCA requiring intubation. Exclusion of these high-risk patients highlighted no significant adjusted difference between early or delayed PCI (Figure 3).

Discussion

This study of a large contemporary cohort of patients who underwent PCI for NSTEMI demonstrated that only 18.4% of patients underwent PCI within the guideline recommended 24-hour window, with 35.8% patients who underwent PCI outside 72 hours. Patients who underwent earlier revascularization had fewer high-risk characteristics overall, apart from those that presented with cardiogenic shock or OHCA requiring intubation. A higher rate of mortality was observed in patients who underwent PCI <24 hours from symptom onset, as compared with PCI 24 to 72 hours and >72 hours from symptom onset. This finding persisted following adjustment for covariates, however, was attenuated in subsequent analyses excluding patients presenting with cardiogenic shock or OHCA requiring intubation. This suggests that cardiogenic shock and OHCA accounted for most of the early harm observed in the PCI <24 hours group. As expected in contemporary practice, unstable, very high-risk patients are generally more likely to be treated early and are therefore primarily represented in this group. In keeping with previous data, patients presenting with NSTEMI were demonstrated to be a complex population with a number of co-morbidities.[13] Irrespective of timing of PCI, age, diabetes mellitus, and left ventricular systolic dysfunction were all found to be independent predictors of mortality and MACE following PCI for NSTEMI. The results of this study suggest that, despite a large number of patients falling outside the guideline recommended 24-hour window, delayed PCI in select, stable NSTEMI patients does not carry an increased risk of mortality and that, in a complex patient group, a considered approach to PCI timing may be reasonable.

The primary results of this study are in keeping with previous randomized controlled trials and subsequent meta-analyses. The Timing of Intervention in Acute Coronary Syndromes trial randomized 3,031 patients with NSTEACS to early intervention (≤24 hours) or delayed intervention (≥36 hours) found a lack of significant difference in mortality and MI at 6 months.[14] However, patients included in the Timing of Intervention in Acute Coronary Syndromes trial scoring higher than 140 on the Global Registry of Acute Coronary Events scale were demonstrated to benefit from

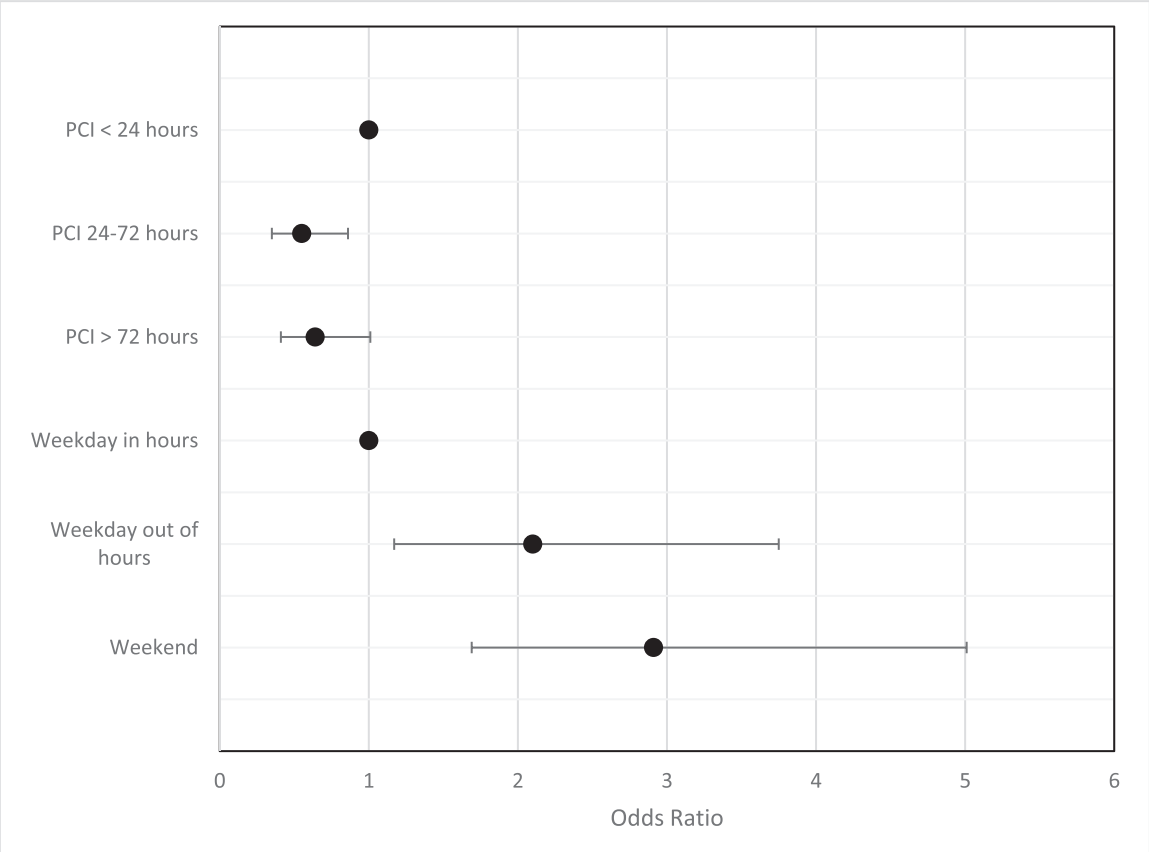

Figure 1. Multivariate analysis for all-cause mortality. Adjusted for age, gender, timing of PCI, private hospital, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, previous PCI, previous CABG, LVEF, renal function, medications administered within 24 hours of PCI (oral anticoagulation, glycoprotein IIb/IIIa inhibitor, thienopyridine, ticagrelor, aspirin, and antithrombin). PCI = percutaneous coronary intervention. PCI 24-72 and >72 hours generated as compared with baseline PCI < 24; weekday out of hours and weekend as compared with baseline weekday in hours.

early intervention over a composite of mortality, MI and stroke.[14] The early or late intervention in high-risk non-ST elevation acute coronary syndrome (ELISA-3) study found that, after randomizing 542 patients hospitalized with non-ST elevation acute coronary syndrome to immediate (<12 hours) or delayed (>48 hours) revascularization, immediate intervention was not superior to delayed in terms of the combined primary endpoint of death, reinfarction and/or recurrent ischemia at 30 days.[3] The OPTIMA trial randomized 142 patients with NSTEMI to immediate or delayed (24 to 48 hours) intervention following establishment of a PCI amenable lesion at angiography.[15] This trial demonstrated that the 30-day composite endpoint of death, MI and unplanned revascularization was more common in the immediate PCI group, predominantly due to new MI (relative risk 1.5; 95% CI 1.09 to 2.15, p = 0.004).[15] By contrast, the Immediate Versus Delayed Invasive Intervention for Non-STEMI patients (RIDDLE-NSTEMI) study demonstrated that an immediate invasive strategy (<2 hours) was associated with lower rates of mortality and new MI as compared with the delayed invasive strategy (2 to 72 hours) in 323 total patients.[4] Meta-analysis of 6,397 patients across 10 randomized controlled trials found no benefit with early intervention on mortality (OR 0.85; 95% CI 0.67 to 1.09, p = 0.20, I2 = 0%) or MI (OR 0.88; 95% CI 0.53 to 1.45, p = 0.62, I2 = 77.5%).[7]

Timing to PCI in this study cohort was in contrast to current guideline recommendations. European Guidelines describe a series of risk criteria, guiding the timing of invasive strategy in NSTEACS.[2] Very high-risk criteria include hemodynamic instability or cardiogenic shock, refractory chest pain, life-threatening arrhythmia (or arrest), mechanical complications of MI, acute heart failure and recurrent dynamic ST-T wave changes. Patients with at least one very high-risk criterion are recommended for an immediate invasive strategy (<2 hours), though patients with NSTEACS meeting very high-risk criteria have generally been excluded from previous randomized trials.[2] It is recommended that patients with confirmed NSTEMI (but without very high-risk criterion) undergo PCI within 24 hours. Over 80% of patients included in this study fell outside that window. We found that any perceived benefit with delayed PCI was likely driven by the high rate of short-term mortality in patients presenting with cardiogenic shock and with OHCA requiring intubation, demonstrated by attenuation of this association in the cohort in which very high-risk patients had been excluded. Our results suggest that, while timing within 24 hours may be ideal, if resources are short and logistics preclude PCI within this timeframe, mortality and MACE may not be substantially affected if PCI is delayed beyond 24 hours in this group of patients after exclusion of those with very high-risk factors.

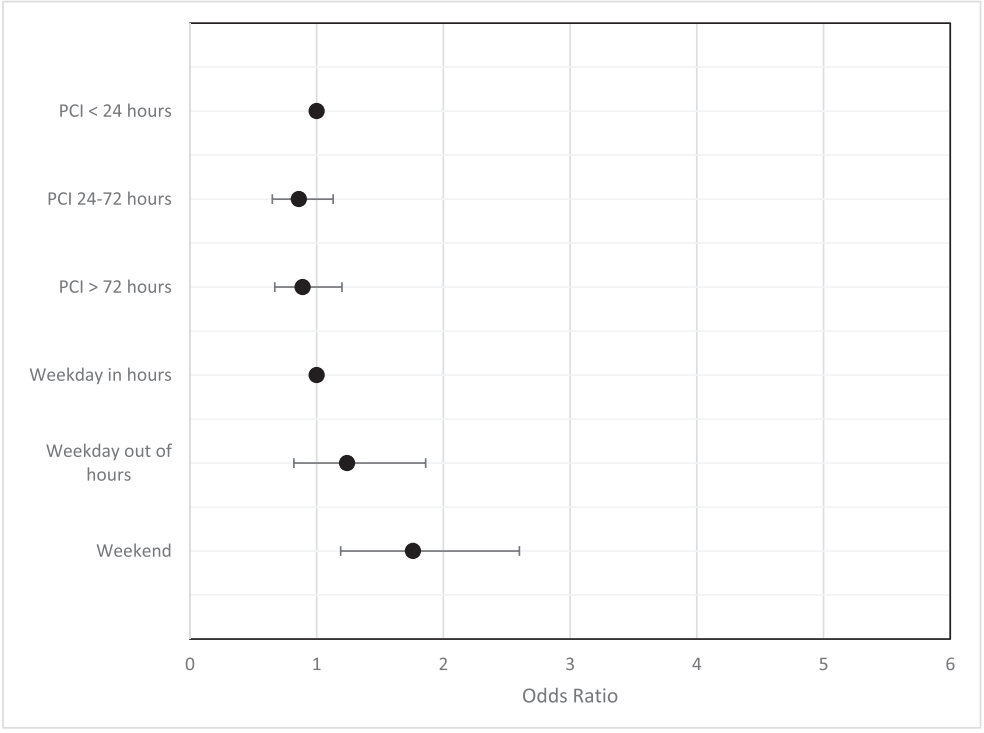

Figure 2. Multivariate analysis for MACE. Adjusted for age, gender, timing of PCI, private hospital, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, previous PCI, previous CABG, LVEF, renal function, medications administered within 24 hours of PCI (oral anticoagulation, glycoprotein IIb/IIIa inhibitor, thienopyridine, ticagrelor, aspirin, and antithrombin). PCI = percutaneous coronary intervention. PCI 24-72 and >72 hours generated as compared with baseline PCI < 24; weekday out of hours and weekend as compared with baseline weekday in hours.

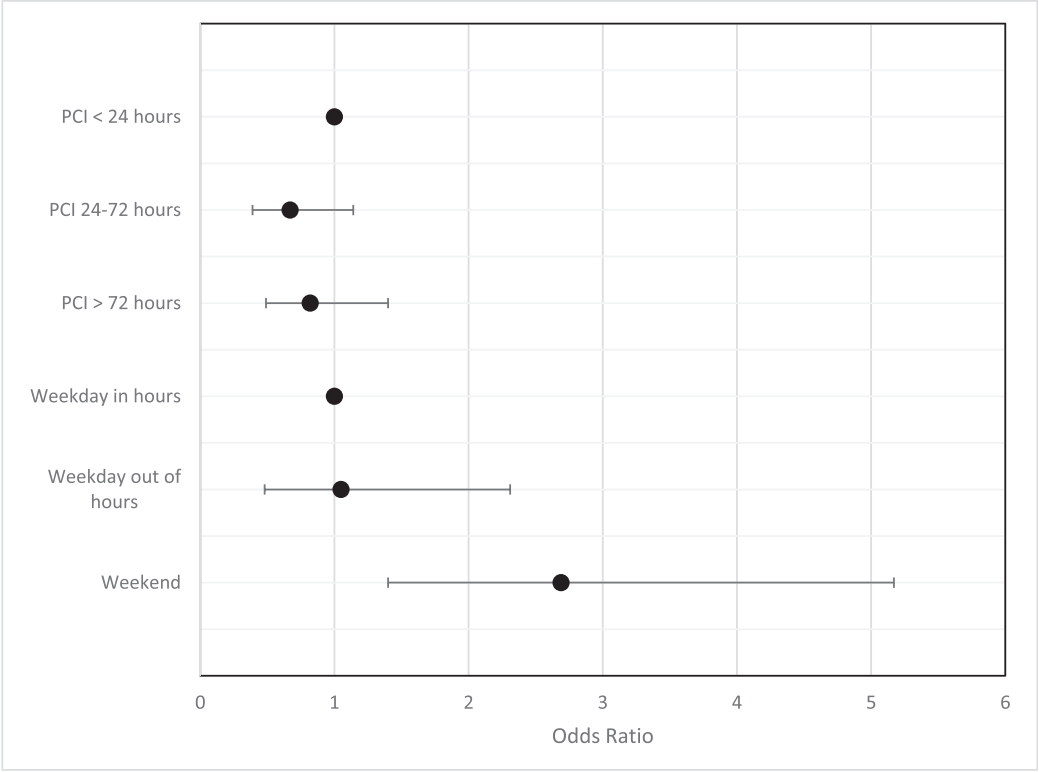

Figure 3. Multivariate analysis for mortality, cardiogenic shock, and OHCA requiring intubation excluded (n = 11,722 patients included). Adjusted for age, gender, timing of PCI, private hospital, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, previous PCI, previous CABG, LVEF, renal function, medications administered within 24 hours of PCI (oral anticoagulation, glycoprotein IIb/IIIa inhibitor, thienopyridine, ticagrelor, aspirin, and antithrombin). PCI = percutaneous coronary intervention. PCI 24-72 and >72 hours generated as compared with baseline PCI < 24; weekday out of hours and weekend as compared with baseline weekday in hours.

This study provides a modern-day analysis of patients stratified by timing to PCI in Victoria and offers a large cohort comparison to international data, however, it is not without limitations. The major limitation of this study is its retrospective, observational design and thus susceptibility to bias that occurs in all large-scale quality registries. Although major confounders including age, gender and select co-morbidities including diabetes, cerebrovascular disease, and peripheral vascular disease were adjusted for in multivariate logistic regression, variables known to contribute to cardiovascular risk such as smoking status[16] and chronic obstructive pulmonary disease[17] were not. Cardiac biomarkers, such as troponin I, creatinine kinase and brain natriuretic peptide were also not evaluated. Further, as VCOR does not collect data on recurrent dynamic ST-T wave changes or refractory arrhythmia, other very high-risk category patients may not have been excluded from secondary analyses with those that presented with cardiogenic shock or OHCA requiring intubation which may have driven the reported outcome rate up in the <24 hours group. As this was also true for select intermediate-risk factors, analysis with guideline-based risk stratification (i.e., Global Registry of Acute Coronary Events or Thrombolysis in Myocardial Infarction [TIMI] scores) was not possible.

In conclusion, over 80% of patients presenting with NSTEMI included in this registry underwent PCI outside the guideline recommended 24-hour time frame. Nevertheless, the results of this study suggest that in a large cohort of patients presenting with NSTEMI, delaying PCI beyond 24 was not associated with an increased risk short-term mortality or MACE.

Authors' Contributions

Riley J. Batchelor: Conceptualization, Methodology Investigation, Writing − Original Draft, Visualization

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Nathan Wong: Writing − Review & Editing

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Nicholas Cox: Validation, Data curation, Writing − Review & Editing

Danny Liew: Validation, Data curation, Writing − Review & Editing

Dion Stub: Conceptualization, Data curation, Validation, Writing − Review & Editing, Supervision

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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