Comparison of Short-term Clinical Outcomes of Proximal versus Non-Proximal Lesion Location in Patients Treated with Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction – the PROXIMITI study

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Abstract

Objectives: The objective of this study was to investigate the association of proximal and non-proximal location of culprit coronary lesions with clinical outcomes of patients presenting with ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI).

Background: Proximal culprit lesion location in patients presenting with STEMI is associated with increased mortality when compared to distal culprit lesions in the thrombolytic era. The impact of lesion location on clinical outcomes in the era of PCI remains unclear.

Methods: We analyzed 3,283 patients with STEMI who enrolled in the Victorian Cardiac Outcomes Registry. We compared outcomes in those with proximal lesion location versus patients with non-proximal location.

Results: Of 3,283 participants, 1,376 (41.9%) had a proximal lesion location. Patients with proximal lesion location presented with greater rates of cardiogenic shock and out-of-hospital cardiac arrest, and left ventricular systolic dysfunction, all $p < 0.01$. Procedural success rates were similar (96% vs. 95%, $p = 0.08$). Patients with proximal lesion location had higher rates of in-hospital and 30-day mortality, major adverse cardiac events (MACE; mortality, myocardial infarction, stent thrombosis and unplanned revascularization) and major adverse cardiac and cerebrovascular events (MACCE; MACE and stroke) compared to the non-proximal group, all $p < 0.001$. However, on multivariable regression analysis, proximal lesion location was not independently associated with MACE during in-hospital stay or at 30-days (OR 1.32, 95% CI 0.95-1.83, $p = 0.09$ and OR 1.23, 95% CI 0.92-1.65, $p = 0.15$) respectively.

Conclusions: Patients with proximal lesion location had greater hemodynamic instability and higher-risk features; however, proximal lesions *per se* were not

independently associated with worse clinical outcomes compared to non-proximal lesions.

Key Words

Percutaneous Coronary Intervention

Acute myocardial infarction/STEMI

Angiography, Coronary

Abbreviation list

STEMI - ST-Elevation Myocardial Infarction

PCI - Percutaneous Coronary Intervention

CABG - Coronary Artery Bypass Graft

ST - Stent Thrombosis

MACE - Major Adverse Cardiac Events

MACCE - Major Adverse Cardiac and Cerebrovascular Events

Introduction

ST-elevation myocardial infarction (STEMI) is a major cause of death and morbidity worldwide ¹. In patients presenting with STEMI, the primary objective is to restore coronary blood flow in the infarct-related artery by thrombolytic therapy or primary percutaneous coronary intervention (PCI) in a timely fashion. In such patients, well-described prognostic factors include infarct size, infarct location and residual left ventricular ejection fraction (LVEF) ². Proximal culprit lesions have been shown to be associated with increased short-term mortality when compared to distal culprit lesions in patients treated with thrombolytic therapy ^{3,4} as well as worse left ventricular systolic function ⁵. Primary PCI is now the revascularization method of choice due to superior rates of successful reperfusion and lower rates of stroke, re-infarction and mortality compared to thrombolysis ⁶. Published studies have shown that culprit lesion location correlates with the amount of myocardium at-risk ⁷. There is a paucity of data evaluating the association of anatomical location of the lesion with short-term outcomes in patients presenting with STEMI treated with primary PCI and contemporary adjunctive pharmacotherapy. Whether lesion location may be used as another predictor of clinical outcomes in addition to the currently established independent predictors of adverse outcomes such as infarct size and LVEF in patients presenting with STEMI remains to be determined. The objective of this study was to investigate the association of proximal and non-proximal location of coronary lesions with in-hospital and 30-day outcomes in patients presenting with STEMI undergoing primary PCI.

Methods

We retrospectively analyzed data from patients who presented with STEMI and treated by primary PCI to a single lesion, who were prospectively enrolled in the Victorian Cardiac Outcomes Registry (VCOR) between January 2013 and December 2015. VCOR⁸ is a state-wide population-based clinical registry established to improve the quality of care in cardiovascular disease in Victoria, Australia. It is coordinated by Monash University in conjunction with the Victorian Cardiac Clinical Network and Department of Health and Human Services involving 23 participating public and private hospitals. In the PCI module, the registry is approved by the ethics committee at each participating hospital. The registry records PCI-related clinical, demographic and procedural data including complications and outcomes with a 30-day follow-up period. All patients undergoing PCI at each hospital are included in the registry unless the patient “opts out”. We analysed all patients enrolled in VCOR consecutively from all the participating Victorian Hospitals/Centers to minimize selection bias. Patients who received fibrinolysis or those who were treated with conservative medical therapy were excluded from the analysis.

The anatomical coronary lesion classification used for this study was based on the SYNTAX trial definition of lesion location⁹. A proximal left anterior descending (LAD) artery segment was defined as proximal to and including the first major septal branch. Proximal right coronary artery (RCA) segment extended from the ostium to one half the distance to the acute margin of the heart. Proximal left circumflex (LCx) artery included the main stem of circumflex from its origin of left main to and including the origin of the first obtuse marginal branch. Non-proximal lesions were, therefore, defined as all other lesion locations other than a proximal lesion location. Lesions

located in the left main coronary artery or grafts from previous coronary artery bypass graft (CABG) surgery were excluded from the analysis. Patients who underwent multi-vessel PCI were also excluded from the analysis.

In-hospital complications were recorded during the in-hospital stay and prior to discharge or death. New renal impairment was defined as an absolute rise of serum creatinine of $\geq 44.2 \mu\text{mol/L}$ or $\geq 25\%$ up to 5 days after the index PCI when compared to baseline creatinine. Cardiogenic shock was defined as a sustained (>30 minutes) episode of systolic blood pressure <90 mm Hg (or vasopressors required to maintain blood pressure >90 mm Hg) and evidence of elevated left ventricular filling pressure (e.g. pulmonary congestion) as well as evidence of end-organ hypoperfusion (e.g. urine output < 30 mL/hour; or altered mental status, etc.). Myocardial infarction (MI) was defined as new elevation of cardiac biomarkers $\geq 20\%$ above the pre-procedure level with at least one of the following (1) evolutionary ST-segment elevation distinct from the index event; (2) development of new Q-waves in 2 or more contiguous leads; (3) ischemic symptoms lasting ≥ 20 minutes; (4) angiographic evidence of flow limiting complications; (5) imaging evidence of new regional wall motion abnormalities. Stent thrombosis (ST) included definite and possible but not probable stent thrombosis. Major bleeding was defined as category 3a and above according to the Bleeding Academic Research Consortium definition¹⁰. Stroke was defined by persistent loss of neurological function caused by an ischemic or hemorrhagic event during or after the PCI.

The 30-day follow-up outcomes were recorded post discharge from the PCI admission. Clinical events were verified from patients, medical records and/or contact

with their primary care physician. Events recorded in the 30-day follow-up included the primary cause of death, new heart failure, new MI, new ST, new bleeding event, new stroke and its type, rehospitalization (including cardiac, PCI, CABG and planned rehospitalization), target vessel revascularization (TVR), target lesion revascularization (TLR), target vessel CABG and medications at 30-days. Major adverse cardiac events (MACE) were defined as a composite of mortality, MI, ST and unplanned revascularization. Major adverse cardiac and cerebrovascular events (MACCE) included MACE variables with the addition of stroke.

Continuous variables are presented as medians and interquartile ranges or mean $\pm$ standard deviation (as appropriate), categorical variables are presented as frequencies and percentages. Differences between proximal and non-proximal lesion groups were evaluated using non-parametric tests – sign rank test for continuous variables and Fisher's exact test for categorical variables. The independent effect of proximal lesion location on each of the clinical outcomes was evaluated using separate logistic regressions. Variables included in the multivariable analysis were selected based on their clinical significance and/or their unequal distribution between the two groups. The variables included were proximal lesion location, the infarct-related artery, cardiogenic shock, out-of-hospital cardiac arrest (OHCA), new renal impairment, left ventricular dysfunction, mechanical circulatory support, drug-eluting stent (DES) type, two or more stents inserted, successful lesion revascularization, preloading with aspirin/ticagrelor/thienopyridine, female gender, age, door-to-balloon time (DTBT), type B2/C lesion, adjunctive device use, glycoprotein IIb/IIIa use, previous PCI/CABG, chronic oral anti-coagulant use, cerebrovascular disease (CVD), peripheral vascular disease (PVD) and diabetes requiring treatment. Continuous variables were

transformed to form a linear relationship with the log odds of the clinical outcome (age as a linear and quadratic term, door to balloon time as its natural logarithm). To assess the impact of proximal lesion location on clinical outcomes without the contributory effects of well-recognized high-risk variables, namely cardiogenic shock, OHCA and mechanical ventilation support, we assessed the incidence of MACE in a subset of hemodynamically stable STEMI patients who did not have cardiogenic shock, OHCA or required mechanical ventilator support. Two-tailed p-values below 0.05 were considered statistically significant. All analyses were performed using StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

Results

Of 3,283 participants, 1,376 (41.9%) had a proximal and 1,907 (58.1%) had a non-proximal lesion location. Baseline characteristics of the two groups are presented in Table 1. Compared to the non-proximal lesion group, more patients with proximal lesion location presented with cardiogenic shock and OHCA and had higher rates of pre-procedural cardiac arrest, pre-procedural intubation and left ventricular systolic dysfunction, all $p < 0.01$. There were no significant differences in rates of cardiovascular risk factors between proximal and non-proximal groups, however, the proximal lesion group had a higher baseline creatinine, $p = 0.01$. While there were lower rates of aspirin preloading in the proximal lesion group compared to the non-proximal cohort, higher rates of thienopyridine/ticagrelor preloading were observed in the proximal lesion group, all $p < 0.05$.

Medications prescribed at discharge are shown in Table 2. Medication use at discharge was similar apart from a higher prescription of oral anticoagulants in the proximal group (8.8% vs. 6.2%, $p=0.01$).

The proximal lesion group had higher rates of femoral access ($p=0.05$) and mechanical circulatory support device use ($p=0.001$) compared to the non-proximal group. There was no significant difference in the DTBT between the two groups, however, the proximal group had a shorter symptom-to-door time, $p=0.01$, resulting in a corresponding shorter symptom-to-balloon/device time (STBT), $p=0.02$. There was greater use of glycoprotein IIb/IIIa inhibitor and thrombus aspiration devices in the proximal lesion group, both $p<0.001$. Procedural revascularization success rates between the two groups were similar (96% vs. 95%, $p=0.08$). However, there were more stents inserted in the proximal group, $p=0.001$, with no difference in the type of stents or total stent length implanted. Procedural characteristics are presented in Table 3.

Patients with proximal lesion location had significantly higher rates of in-hospital and 30-day mortality, MACE and MACCE compared to the non-proximal group, all $p<0.001$ (Table 4). In-hospital complications were also more prevalent in the proximal group, particularly new renal impairment (5.9% vs. 3.7%, $p=0.004$), post-procedural cardiogenic shock (8.4% vs. 3.8%, $p<0.001$), recurrent MI (1.7% vs. 0.8%, $p=0.02$). At 30-days, there were higher rates of new heart failure in the proximal group (3.6% vs. 2.1%, $p=0.003$).

On multivariable regression analysis, proximal lesion location was, however, not independently associated with MACE during in-hospital stay or at 30 days (OR 1.32, 95% CI 0.95-1.83, $p=0.09$ and OR 1.23, 95% CI 0.92-1.65, $p=0.15$) respectively. Cardiogenic shock, new renal failure, OHCA, mechanical circulatory support requirement and left ventricular systolic dysfunction had the strongest consecutive independent association with in-hospital and 30-day MACE; see Table 5 and Figure 1 for independent predictors of MACE. Multivariable analysis revealed that PCI to LAD infarct-related coronary artery was not a predictor of 30-day MACE (OR 0.91, 95% CI 0.62-1.32, $p=0.60$). A subgroup analysis of hemodynamically stable STEMI patients was undertaken excluding 649 patients with cardiogenic shock, OHCA and mechanical ventilation requirement. Similarly, this subgroup analysis demonstrated the lack of association between proximal lesion location and in-hospital or 30-day MACE (OR 1.53, 95% CI 0.89-2.61, $p=0.12$ and OR 1.27, 0.84-1.19, $p=0.26$) respectively. The unadjusted MACE rates are displayed in Figure 2.

Discussion

Classical, well-described variables affecting myocardial salvage after STEMI include infarct location¹¹ and the timeliness of reperfusion¹². Patients with proximal coronary lesions potentially have larger myocardial area-at-risk when compared to non-proximal lesions particularly in the LAD territory,¹³ and may result in larger infarct size¹⁴. In this study, we aimed to elucidate the significance of coronary lesion site in patients with STEMI treated by primary PCI and contemporary adjunctive medical therapy. The major finding of our study is that proximal lesion location was not independently associated with worse in-hospital or short-term clinical outcomes despite a greater prevalence of patients in the proximal lesion group presenting with

higher rates of hemodynamic compromise, i.e. cardiogenic shock and OHCA, as well as requiring procedural mechanical circulatory and airway support. Both DTBT and procedural success rates were similar between the proximal and non-proximal cohorts, however, the proximal group had significantly shorter STBT, which is an important determinant of infarction size,¹⁵ and might have attenuated the impact of proximal lesion location on short-term clinical outcomes. While in-hospital and 30-day MACE and MACCE rates were significantly higher in the proximal group, proximal lesion location, *per se*, was not independently associated with in-hospital and 30-day MACE following multivariable adjustment suggesting that lesion location might have a lesser impact on clinical outcomes in the contemporary era of rapid mechanical revascularization and adjunctive pharmacotherapy.

Previously published studies investigating the impact of proximal lesion location in STEMI patients on clinical outcomes reported different results to those of our study findings. Karha and colleagues³ investigated 2,488 patients enrolled in four fibrinolysis trials comparing proximal lesion location with mid or distal lesions. In that study, an independent inverse association of the planimetered distance from the LAD ostium to the culprit lesion site was observed with adverse outcomes after fibrinolytic administration. In contrast, our study excluded participants treated with fibrinolysis and our study cohort was much more contemporary and well treated with guideline-recommended secondary prevention therapies. In the balloon angioplasty era, Harjai and colleagues¹⁷ compared short and intermediate-term clinical outcomes of proximal versus non-proximal culprit lesions in 3,535 patients pooled from the Primary Angioplasty in Myocardial Infarction (PAMI) database. After adjustment for other variables, proximal lesion location was independently associated with in-hospital

mortality and MACE but not 1-year mortality or MACE. Given these findings, the authors suggested that culprit lesion location should be used as an angiographic prognostication tool in addition to other established predictors. Compared to our study, Harjai *et al* excluded patients with cardiogenic shock and renal failure, both of which were included in our analysis. Moreover, the majority of patients included in the study by Harjai *et al* were treated by balloon angioplasty and <40% were treated by stenting. In another study by Elsmann *et al* ¹⁸, the authors investigated a total of 1,468 consecutive patients with STEMI treated by primary PCI at a single centre. This study reported worse short and long-term clinical outcomes in patients with reperfused proximal LAD culprit lesions compared to distal LAD lesions. However, such an association was lacking for lesions located in the proximal RCA or LCx. The interventions implemented in this study were primarily balloon angioplasty with limited medical therapy when compared to the contemporary adjunctive pharmacotherapies. For example, stents were used in only 42% of the population studied and a second antiplatelet agent (ticlopidine or clopidogrel) was prescribed only if a stent was used, and dual antiplatelet therapy was given for a limited duration of 4 weeks.

Contrary to previously published studies comparing proximal versus non-proximal culprit lesion location, our study cohort was treated by primary PCI and received contemporary adjunctive medical therapy. Therefore, our study results could be, in part, explained by the high rates of contemporary guideline-directed medical therapy coupled with timely reperfusion delivered to both of the proximal and non-proximal groups. Approximately 90% of patients in both proximal and non-proximal lesion location groups in our study received a second anti-platelet agent. Similarly, the use of beta blockers and ACE-I/ARB was approximately 80% with no significant

difference in the proximal and the non-proximal groups. Statins were also prescribed in about 90% in both groups. In the study by Elsman *et al* ¹⁸, only those treated with a stent received a second antiplatelet agent in addition to aspirin. The rates of other adjunctive therapies such as beta-blockers, statins and ACE-/ARB were not reported. Harjai and colleagues ¹⁷ in their *post hoc* analysis of PAMI trial patients, found that the rates of beta blocker use (about 50%-80% when reported) and ACE-I use (about 54%-68% when reported) were low, and lower than in our study population. Also the proportion of patients who received a second antiplatelet agent, ticlopidine, was not reported. The mortality and morbidity benefits conferred by contemporary pharmacological therapies are well established in patients with STEMI such as the prescription of high intensity statins ¹⁹⁻²¹, beta blockers at discharge ²², ACE-I/ARB for left ventricular dysfunction ^{23,24}. The use of such therapies is a key performance measure for the contemporary evidence-based management of STEMI ²⁵. Thus, the results of our study are different to earlier studies and the difference in outcome association might be attributable to optimal medical therapy in STEMI patients treated with PCI, thereby mitigating the negative prognostic impact of other variables such as that of proximal lesion location ^{22,26-29}.

The proximal lesion group included patients presenting with higher rates of cardiogenic shock (12.4% vs. 5.7%) and OHCA (11.8% vs. 7.9%) with more culprit lesions located in the LAD (51.3% vs. 36.2%) compared to the non-proximal group, which likely accounted for the greater incidences of hemodynamic and airway support requirements during the procedure. These high-risk patient and procedural characteristics could also explain the higher short-term mortality rates compared to the non-proximal group. While there was a lack of independent association of proximal

lesion location with short-term MACE (including within the hemodynamically stable subgroup analysis), proximal lesion location should still be regarded a high-risk feature not only because of higher rates of 30-day MACE and mortality but also significantly higher rates of left ventricular dysfunction during in-hospital stay and higher rates of new heart failure diagnosis at 30-day follow-up compared to the non-proximal group. Patients presenting with larger infarcts or with larger area of myocardium at risk have greater potential for adverse pathological myocardial remodelling as evident from studies utilizing cardiac magnetic resonance reporting that final infarction size and the amount of myocardium salvaged to be predictors of adverse remodelling ^{11,16}.

Our study had certain limitations including the retrospective design and observational nature and is, therefore, subject to unmeasured confounders that could impact on clinical outcomes despite multivariable adjustments. The VCOR does not capture a history of previous myocardial infarction, the extent of coronary artery disease or the extent of residual disease following revascularisation nor the completeness of revascularisation. Quantitative assessment of coronary flow grades or collateral supply to culprit vessel was also not available. The follow-up duration of 30 days in our study was short and longer-term follow-up would be needed to detect significant differences in clinical outcomes (such as MACE, mortality, TVR and TLR) between the proximal versus non-proximal groups. Lastly, our study sample size was small and may be underpowered to detect the effect of lesion location on clinical outcomes given the higher rates of adverse in-hospital and 30-day clinical outcomes among patients with proximal lesion location.

In conclusion, our study demonstrated that patients presenting with STEMI secondary to a proximal lesion location undergoing primary PCI were more likely to present with hemodynamic instability, and had higher-risk features. However, proximal lesion location *per se* was not independently associated with worse short-term clinical outcomes compared to a non-proximal lesion. The lack of independent association underscores the importance of timely mechanical reperfusion and the application of contemporary guideline-recommended adjunctive medical therapies. Larger prospective studies are needed to assess the importance of proximal lesion location in the contemporary era.

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Figure 1 Independent predictors of 30-day MACE on multivariable logistic regression.

Figure 2

A Unadjusted in-hospital and 30-day MACE in all patients (n=3,283).

B Unadjusted in-hospital and 30-day MACE in the hemodynamically stable subgroup (n=2,634)

Table 1. Baseline clinical and demographic characteristics of patients with STEMI treated by single lesion primary PCI.

	Proximal lesion (n=1376)	Non-proximal lesion (n=1907)	P value
Age (years), mean $\pm$ SD	61.6 $\pm$ 12.8	61.9 $\pm$ 12.5	0.49
Body mass index (kg/m ²), mean $\pm$ SD	28.0 $\pm$ 5.1	28.1 $\pm$ 5.2	0.46
Women, n (%)	274 (19.9)	394 (20.7)	0.62
Pre-hospital notification, n (%)	655 (47.6)	916 (48.0)	0.83
Cardiogenic shock, n (%)	171 (12.4)	108 (5.7)	<0.001
OHCA, n (%)	162 (11.8)	151 (7.9)	<0.001
In-hospital pre-procedure cardiac arrest, n (%)	100 (7.3)	90 (4.7)	0.002
Pre-procedure intubation, n (%)	90 (6.5)	79 (4.1)	0.002
Left ventricular dysfunction#, n (%)	437 (31.8)	348 (18.2)	<0.001
Diabetes requiring treatment, n (%)	209 (15.2)	325 (17.0)	0.16
PVD, n (%)	36 (2.6)	45 (2.4)	0.65
CVD, n (%)	40 (2.9)	63 (3.3)	0.54
Chronic oral anti- coagulant therapy, n (%)	33 (2.4)	43 (2.3)	0.81

Previous CABG, n (%)	26 (1.9)	28 (1.5)	0.40
Previous PCI, n (%)	157 (11.4)	241 (12.6)	0.30
Pre-procedure creatinine (μmol/L), median (IQR)	87.0 (74.0 - 105.0)	85.0 (72.0 - 100.0)	0.01
Estimated GFR (mL/min/1.73m ²), median (IQR)	86.7 (65.4 - 109.9)	88.2 (67.7 - 115.0)	0.08
Dialysis therapy, n (%)	7 (0.5)	17 (0.9)	0.22
Functioning renal transplant, n (%)	2 (0.1)	6 (0.3)	0.48
Acute renal replacement therapy, n (%)	1 (0.1)	0 (0.0)	0.42
Aspirin preloading, n (%)	1242 (90.3)	1761 (92.3)	0.04
Thienopyridine preloading, n (%)	488 (35.5)	605 (31.7)	0.02
Ticagrelor preloading, n (%)	639 (46.4)	816 (42.8)	0.03

CABG, coronary artery bypass graft; CVD, cerebral vascular disease; GFR, glomerular filtration rate; OHCA, Out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Left ventricular dysfunction defined as ejection fraction <45%.

Table 2. Medications at discharge from hospital

	Proximal lesion (n=1376)	Non-proximal lesion (n=1907)	P value
Aspirin, n (%)	1236 (89.8)	1774 (93.0)	0.97
Thienopyridine, n (%)	493 (35.8)	644 (33.8)	0.20
Ticagrelor, n (%)	748 (54.4)	1118 (58.6)	0.58
Beta blockers, n (%)	1102 (80.1)	1563 (82.0)	0.13
ACE-I/ARB*, n (%)	1075 (78.1)	1527 (80.1)	0.31
Statin, n (%)	1213 (88.2)	1754 (92.0)	0.73
Other dyslipidemia medications, n (%)	34 (2.5)	75 (3.9)	0.11
Oral anti-coagulation, n (%)	121 (8.8)	118 (6.2)	0.01

*ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker.

Table 3. Procedural characteristics.

	Proximal lesion (n=1376)	Non-proximal lesion (n=1907)	p value
Door-to-balloon/device time (mins), median (IQR)	64.0 (43.0 - 93.0)	64.0 (41.0 - 97.0)	0.71
Symptom-to-door time (mins), median (IQR)	104.0 (72.0 - 184.0)	115.0 (74.0 - 217.8)	0.01
Symptom-to-balloon/device	180.0 (134.0 - 265.0)	193.0 (139.0 - 308.0)	0.02

time (mins), median (IQR)			
Percutaneous entry site, n (%)			<i>0.05</i>
Brachial	2 (0.1)	1 (0.1)	
Femoral	879 (63.9)	1151 (60.4)	
Radial	495 (36.0)	755 (39.6)	
Glycoprotein IIb/IIIa inhibitor, n (%)	707 (51.4)	813 (42.6)	<0.001
Thrombus aspiration device, n (%)	431 (31.3)	432 (22.7)	<0.001
Procedural intubation, n (%)	58 (4.2)	57 (3.0)	<i>0.06</i>
Mechanical circulatory support, n (%)	69 (5.0)	53 (2.8)	0.001
Lesion location, n (%)			<0.001
LAD	706 (51.3)	691 (36.2)	
RCA	461 (33.5)	906 (47.5)	
LCx	209 (15.2)	310 (16.3)	
Type B2/C lesion*, n (%)	897 (65.2)	1203 (63.1)	<i>0.22</i>
In-stent restenosis, n (%)	61 (4.4)	88 (4.6)	<i>0.86</i>
Stent thrombosis, n (%)	45 (3.3)	71 (3.7)	<i>0.32</i>
Successful lesion revascularization, n (%)	1321 (96.0)	1805 (94.7)	<i>0.08</i>
Number of stents inserted, n			0.001

(%)			
One	1084 (78.8)	1491 (78.2)	
None	84 (6.1)	177 (9.3)	
Two or more	208 (15.1)	239 (12.5)	
Type of inserted stent, n			0.65
(%)			
DES only	854 (62.1)	1117 (58.6)	
BMS only	432 (31.4)	603 (31.6)	
Total length of all stents			
implanted (mm) , median	20.0 (16.0 - 28.0)	20.0 (16.0 - 28.0)	0.12
(IQR)			

DES, drug eluting stent; BMS, bare metal stent; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery.

*Type B2/C lesion is based on the American College of Cardiology/American Heart Association classification of coronary lesions.

Table 4. In-hospital and 30-day outcomes

	Proximal lesion (n=1376)	Non-proximal lesion (n=1907)	P value
In-hospital outcomes			
Length of stay (days) , mean			
± SD	5.7 ± 11.4	4.8 ± 4.7	<0.006
New renal impairment, n (%)	81 (5.9)	71 (3.7)	0.004
New requirement for	17 (1.2)	15 (0.8)	0.21

dialysis, n (%)			
Cardiogenic shock, n (%)	115 (8.4)	72 (3.8)	<0.001
Recurrent MI, n (%)	24 (1.7)	16 (0.8)	0.024
PCI, n (%)	60 (4.4)	84 (4.4)	1.0
Planned PCI, n (%)	47 (3.4)	62 (3.3)	0.56
TVR (PCI), n (%)	17 (1.2)	19 (1.0)	0.44
TLR, n (%)	14 (1.0)	13 (0.7)	0.28
CABG, n (%)	30 (2.2)	41 (2.1)	1.0
Planned CABG, n (%)	7 (0.5)	19 (1.0)	0.08
TVR (CABG), n (%)	22 (1.6)	20 (1.0)	0.051
Stent thrombosis, n (%)	11 (0.8)	17 (0.9)	0.84
Major bleeding, n (%)	32 (2.3)	33 (1.7)	0.25
Stroke, n (%)	12 (0.9)	11 (0.6)	0.39
Mortality, n (%)	110 (8.0)	85 (4.5)	<0.001
MACE, n (%)	145 (10.5)	124 (6.5)	<0.001
MACCE, n (%)	153 (11.1)	131 (6.9)	<0.001
30-day outcomes			
New heart failure, n (%)	50 (3.6)	41 (2.1)	0.003
New MI, n (%)	4 (0.3)	13 (0.7)	0.06
Stent thrombosis, n (%)	2 (0.1)	7 (0.4)	0.32
Major bleeding, n (%)	8 (0.6)	5 (0.3)	0.16
New stroke, n (%)	2 (0.1)	1 (0.1)	0.06
Rehospitalization, n (%)	163 (11.8)	248 (13.0)	0.33
Cardiac readmission, n	92 (6.7)	180 (9.4)	0.005

(%)

Mortality, n (%)	123 (8.9)	95 (5.0)	<0.001
MACE, n (%)	169 (12.3)	157 (8.2)	<0.001
MACCE, n (%)	178 (12.9)	164 (8.6)	<0.001

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TVR, target vessel revascularization; TLR, target lesion revascularization.

Table 5. Multivariable predictors of in-hospital and 30-day MACE

	In-hospital MACE	P-value	30-day MACE	P-value
	OR (95% CI)		OR (95% CI)	
Cardiogenic shock	5.39 (3.61 – 8.04)	<0.001	3.79 (2.54 - 5.66)	<0.001
New renal impairment	3.74 (2.47 – 5.65)	<0.001	2.69 (1.72 - 4.21)	<0.001
OHCA	3.74 (2.47 – 5.65)	<0.001	2.24 (1.49 - 3.37)	<0.001
Mechanical circulatory support	2.67 (1.56 – 4.57)	<0.001	1.94 (1.14 - 3.30)	0.015
Left ventricular systolic dysfunction	2.19 (1.50 – 3.19)	<0.001	1.76 (1.26 - 2.47)	0.001
Proximal lesion location	1.32 (0.95 – 1.83)	0.09	1.23 (0.92 – 1.65)	0.15
DES stent type	0.63 (0.46 – 0.88)	0.006	0.63 (0.47 - 0.85)	0.002
Two or more of stents inserted	0.56 (0.30 – 1.07)	0.08	0.55 (0.31 - 0.97)	0.04
Successful lesion revascularization	0.23 (0.12 – 0.44)	<0.001	0.35 (0.19 - 0.63)	<0.001
Ticagrelor preloading	0.5 (0.33 – 0.77)	0.001	0.62 (0.42 - 0.91)	0.014

Thienopyridine preloading	0.6 (0.38 – 0.93)	0.02	0.57 (0.38 - 0.86)	0.007
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MACE were defined as a composite of mortality, MI, ST and unplanned revascularization

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Figure 1 Independent predictors of 30-day MACE on multivariable logistic regression.

280x198mm (150 x 150 DPI)

Author

Figure 2
A Unadjusted in-hospital and 30-day MACE in all patients (n=3,283).

143x105mm (96 x 96 DPI)

Author

B Unadjusted in-hospital and 30-day MACE in the hemodynamically stable subgroup (n=2,634)

143x105mm (96 x 96 DPI)

Author |

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31st March 2018

To: Dr. Steven R. Bailey
Editor in Chief
Catheterization and Cardiovascular Interventions Journal

Re: Comparison of Short-term Clinical Outcomes of Proximal versus Non-Proximal Lesion Location in Patients Treated with Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction – the PROXIMITI study

Dear Dr. Bailey,

Thank you for the opportunity to resubmit our revised manuscript for consideration as an Original Research article in the Catheterization and Cardiovascular Interventions Journal.

We have carefully reviewed your editorial comments and the reviewer's comments and queries and have provided below a point-by-point response/rebuttal (in *Italics*). We have edited our revised manuscript with tracked changes so that they can be clearly tracked.

We believe that our manuscript has been enhanced with the incorporation of reviewer suggestions and comments and hope that it is now suitable for publication in your journal.

We confirm that all authors have read and approved the manuscript as written. We confirm that all conflicts of interest and disclosures have been declared. We are able to edit our manuscript further if found acceptable. We look forward to your review of our revised manuscript.

Kind regards,

A/Prof William Chan
Corresponding author

Reviewers' comments

Reviewer #1 major comments:

1. The key message of the study is that clinical outcome following primary PCI is regardless of proximal lesion location; accordingly, even the clinical benefit related to primary PCI may be regardless of proximal lesion location. This should be more extensively addressed in the Discussion.

We thank Reviewer 1 for their comments. As per our analysis and discussion, proximal lesion location per se was not an independent predictor of short-term clinical outcomes when considered among other significant clinical variables such as cardiogenic shock, new renal failure, out-of-hospital cardiac arrest etc.... We have outlined our explanation for this finding in the Discussion as well as limitations of our study, which could have impacted on our analysis.

We are not certain which other points the Reviewer would like underscored in our revised manuscript. We would certainly make these changes or add further if deemed necessary for publication.

2. The authors indicate that patients undergoing multivessel PCI were excluded; however, no mention on the prevalence of multivessel coronary disease and of completeness of revascularization in the two groups is provided. In particular, residual significant coronary disease after primary PCI and completeness of revascularization should be also added in the multivariable analysis

Thank you for this comment. We included patients undergoing single vessel percutaneous coronary intervention (PCI) only and excluded patients requiring multivessel PCI within the same catheterization lab visit to avoid the confounding effects of different lesion location and different coronary vessel PCI on outcomes.

We did report on further in-hospital modes of revascularizations such as further PCI, planned PCI, coronary artery bypass graft (CABG), planned CABG, target vessel revascularization (TVR) and target lesion revascularization (TLR) in Table 4. However, the Victorian Cardiac Outcomes Registry (VCOR) does not capture the completeness of revascularisation, the extent of coronary artery disease being treated with PCI nor the extent of residual coronary artery disease post revascularisation and this has now been acknowledged in the limitations paragraph of the Discussion section (page 14, line 12). The following sentences have now been added

"The VCOR does not capture a history of previous myocardial infarction, the extent of coronary artery disease or the extent of residual disease following revascularisation nor the completeness of revascularisation. Quantitative assessment of coronary flow grades or collateral supply to culprit vessel was also not available".

3. The authors should specify the prevalence of rescue PCI and adjust the data also for this variable

Thank you for this comment. Our study population included only patients presenting with ST-elevation myocardial infarction (STEMI) treated with primary PCI and excluded those who received fibrinolysis. This has been further clarified in the Methods section (page 5, line 14) with the following sentence

"Patients who received fibrinolysis or those who were treated with medical therapy only were excluded from the analysis".

4. A sample size calculation should be provided

Thank you for this comment. Our study was a hypothesis-generating retrospective observational cohort study. In designing this study, we included all patients presenting with STEMI enrolled in the VCOR from January 2013 to December 2015. We did not perform sample size calculation based on the primary outcome of 30-day major adverse cardiac events (MACE) as this was a retrospective study. However, we did acknowledge the relatively

small sample size in the *Limitations* section (page 14, line 20). The small sample size is certainly an important consideration for any negative study given that the sample size could have been underpowered to detect a significant difference in the primary outcome.

- 5. The authors should specify in the Methods how they limited the possibility of selection bias and of treatment bias in the conduction of their study.**

As with any registry data, there is an inherent risk in selection and treatment bias as highlighted by this Reviewer. We minimised the effect of selection and treatment bias by including and analysing all consecutive patients enrolled in the VCOR registry from all participating Victorian Hospitals/Centres. Additionally, we only included patients who underwent primary PCI as a treatment strategy, and we did not include those who were treated (or selected for treatment) with medical therapy. This has been clarified further in the *Methods* section (page 5, line 13) with the following sentences

"We analysed all patients enrolled in VCOR consecutively from all the participating Victorian Hospitals/Centres to minimize selection bias. Patients who received fibrinolysis or those who were treated with conservative medical therapy were excluded from the analysis".

- 6. Indeed, current definition of stroke is "an abrupt onset of a focal neurological deficit lasting >24 hours or causing death within 24 hours of symptom onset" (rather than a persistent neurological deficit, as defined in the study) (Sacco RL, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089).**

We thank this Reviewer for highlighting to us the current definition of stroke, which differs to the one used in our study. This difference in stroke definition reflects the time of conception of the VCOR registry in 2011 which predated the current definition. However, the definition of stroke used in our study is in accord with another published registry study examining stroke as a complication of PCI (Werner et al., *Incidence and Clinical Impact of Stroke Complicating Percutaneous Coronary Intervention Results of the Euro Heart Survey Percutaneous Coronary Interventions Registry*, *Circ Cardiovasc Interv*. 2013;6:362-369).

- 7. Follow-up duration is short to identify differences between the two groups for TVR and TLR. This should be specifically indicated in the text.**

Thank you for this comment. We agree that the 30-day follow-up would likely be too short to detect meaningful differences between the 2 groups with respect to TVR and TLR. We have already mentioned the short 30-day duration of follow-up as a limitation but have now further specified this with regards to TLR, and TVR (page 14, line 19) with the following sentence

"The follow-up duration of 30 days in our study was short and longer-term follow-up would be needed to detect significant differences in clinical outcomes (such as MACE, mortality, TVR and TLR) between the proximal versus non-proximal groups".

- 8. In my opinion, the variables entered in the multivariable analysis are not complete. Indeed, other features with relevant clinical significance should be included, although most of them were not significantly different in the two groups, in particular, post-PCI renal deterioration, stent diameter, type of DAPT (ASA + clopidogrel versus ASA+ ticagrelor), use of statins, beta-blockers and ACE-inhibitors/sartans. Indeed, the use of ticagrelor, statins, beta-blockers and ACE-inhibitors/sartans was less prevalent in patients with proximal lesion location.**

Thank you for this comment. Variables that were included in the multivariable analysis were selected based on their clinical significance and/or their unequal distribution between the two groups (Tables 1 and 2). The variables in the multivariable analysis (please see *Methods* section) included proximal lesion location, the infarct-related artery, cardiogenic shock, out-of-hospital cardiac arrest (OHCA), new renal impairment, left ventricular dysfunction, mechanical circulatory support, drug-eluting stent (DES) type, two or more stents inserted, successful

lesion revascularization, preloading with aspirin/ticagrelor/thienopyridine, female gender, age, door-to-balloon time, type B2/C lesion complexity, adjunctive device use, glycoprotein IIb/IIIa use, previous PCI/CABG, oral anti-coagulant use, cerebrovascular disease, peripheral vascular disease and diabetes requiring treatment.

New renal impairment post PCI was included in the multivariable analysis and was found to be a strong predictor of 30-day MACE (Table 5). Stent diameter was not collected in VCOR. However, coronary lesion complexity and the type of stent used (drug-eluting vs. bare metal stent) were included in the multivariable analysis. The use of aspirin, thienopyridine, and ticagrelor was also included in the analysis (Table 5). There were no significant differences in the use of other medications (e.g. ACE-inhibitors, beta blockers) between the two groups and, therefore, was not included in the analysis. In contrast, oral anticoagulant use was significantly different between the two groups and was, therefore, included in the multivariable analysis.

Reviewer #2: You have provided a well-written manuscript that retrospectively studies the clinical impact of culprit lesion location (proximal vs. non-proximal) in STEMI cohort after primary PCI.

- Please specify how many study participants have a history of prior myocardial infarction (MI). Consider excluding patients with prior MI - as re-infarction in non-vital myocardium would relate to a different outcome.

We thank Reviewer 2 for their comments and agree that re-infarction in areas affected by prior infarction would likely lead to different outcome compared to index infarction.

There are limitations to the data set of any registry. The VCOR registry does not collect the field of 'previous MI' so we are unable to report on rates of previous MI between the 2 groups. However, our data reported no significant difference between the 2 groups with regards to previous PCI and previous CABG rates. This is now acknowledged in the Limitations section (page 14, line 12). The following sentences have been added

"The VCOR does not capture a history of previous myocardial infarction, the extent of coronary artery disease or the extent of residual disease following revascularisation nor the completeness of revascularisation. Quantitative assessment of coronary flow grades or collateral supply to culprit vessel was also not available".

- Abstract/objectives: the word "primary" mentioned twice.

Thank you for this comment. This has been changed in the Abstract/Objectives section.

- Abstract/Methods: please specify that this is a STEMI cohort

Thank you for this comment. This has been specified in the Abstract/Methods section.

- High rate of BMS implantation (approx. 30%), which is not "contemporary"

Thank you for this comment. The reported rate of bare metal stent (BMS) use of approximately 30% was the average rate of BMS use over the study duration of three years (between 2013 and 2015). A recent Australian study by our group reported declining rates of BMS use over the years with 46% used in 2013 down to only 19% in 2016 (Biswas et al, Australian Trends in Procedural Characteristics and Outcomes in Patients Undergoing Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction. American Journal of Cardiology, Volume 121, Issue 3, 279 – 288).

While the rate of BMS use was relatively high (~30%) for STEMI, reflecting data collected during the earlier years of the study period, we do not believe this would have impacted on the primary clinical outcome between the 2 groups.

- There is a relevant difference between culprit vessels in both groups which could influence the study results and therefore weaken study's proposition.

Thank you for this comment. We agree that differences in the rates of LAD, and non-LAD IRA between the 2 groups could influence clinical outcomes as LAD infarcts are generally larger and portend poorer prognosis. The rates of LAD IRA was higher in the proximal lesion group compared to the non-proximal group (51.3% vs. 36.2%, $p < 0.001$).

In our multivariable analysis for the primary outcome, we attempted to account for the impact of the IRA by including it as a variable as stated in the Methods section. Following adjustment, IRA was not a predictor of the primary outcome (LAD OR 0.91, 95% CI 0.62-1.32, $p = 0.604$). The following sentence has been added to the Results section (page 10, line 7) "Multivariable analysis revealed that PCI to LAD infarct-related coronary artery was not a predictor of 30-day MACE (OR 0.91, 95% CI 0.62-1.32, $p = 0.60$)".

- Many study limitations that are fairly and thoroughly mentioned

Thank you for this comment.

- Tables are too long

Thank you for this comment. We have, at this stage, not altered the contents of the Tables because we believe in presenting data on all captured fields, which will provide granularity to the reader regarding the VCOR registry. We are, of course, able to edit the Tables if this was felt necessary for publication.

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Financial support

The Victorian Cardiac Outcomes Registry (VCOR) was originally co-funded by the Victorian Department of Health in 2011 and a one-off grant from Medibank Private. It is currently funded by the Department of Health and Human Services, Victoria with in-kind funding from Monash University.

Abstract

Objectives: The objective of this study was to investigate the association of proximal and non-proximal location of culprit coronary lesions with clinical outcomes of patients presenting with ST-elevation myocardial infarction (STEMI) treated by ~~primary~~-primary percutaneous coronary intervention (PCI).

Background: Proximal culprit lesion location in patients presenting with STEMI is associated with increased mortality when compared to distal culprit lesions in the thrombolytic era. The impact of lesion location on clinical outcomes in the era of PCI remains unclear.

Methods: We analyzed 3,283 patients with STEMI who enrolled in the Victorian Cardiac Outcomes Registry. We compared outcomes in those with proximal lesion location versus patients with non-proximal location.

Results: Of 3,283 participants, 1,376 (41.9%) had a proximal lesion location. Patients with proximal lesion location presented with greater rates of cardiogenic shock and out-of-hospital cardiac arrest, and left ventricular systolic dysfunction, all $p < 0.01$. Procedural success rates were similar (96% vs. 95%, $p = 0.08$). Patients with proximal lesion location had higher rates of in-hospital and 30-day mortality, major adverse cardiac events (MACE; mortality, myocardial infarction, stent thrombosis and unplanned revascularization) and major adverse cardiac and cerebrovascular events (MACCE; MACE and stroke) compared to the non-proximal group, all $p < 0.001$. However, on multivariable regression analysis, proximal lesion location was not independently associated with MACE during in-hospital stay or at 30-days (OR 1.32, 95% CI 0.95-1.83, $p = 0.09$ and OR 1.23, 95% CI 0.92-1.65, $p = 0.15$) respectively.

Conclusions: Patients with proximal lesion location had greater hemodynamic instability and higher-risk features; however, proximal lesions *per se* were not

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independently associated with worse clinical outcomes compared to non-proximal lesions.

Key Words

Percutaneous Coronary Intervention

Acute myocardial infarction/STEMI

Angiography, Coronary

Abbreviation list

STEMI - ST-Elevation Myocardial Infarction

PCI - Percutaneous Coronary Intervention

CABG - Coronary Artery Bypass Graft

ST - Stent Thrombosis

MACE - Major Adverse Cardiac Events

MACCE - Major Adverse Cardiac and Cerebrovascular Events

Introduction

ST-elevation myocardial infarction (STEMI) is a major cause of death and morbidity worldwide ¹. In patients presenting with STEMI, the primary objective is to restore coronary blood flow in the infarct-related artery by thrombolytic therapy or primary percutaneous coronary intervention (PCI) in a timely fashion. In such patients, well-described prognostic factors include infarct size, infarct location and residual left ventricular ejection fraction (LVEF) ². Proximal culprit lesions have been shown to be associated with increased short-term mortality when compared to distal culprit lesions in patients treated with thrombolytic therapy ^{3,4} as well as worse left ventricular systolic function ⁵. Primary PCI is now the revascularization method of choice due to superior rates of successful reperfusion and lower rates of stroke, re-infarction and mortality compared to thrombolysis ⁶. Published studies have shown that culprit lesion location correlates with the amount of myocardium at-risk ⁷. There is a paucity of data evaluating the association of anatomical location of the lesion with short-term outcomes in patients presenting with STEMI treated with primary PCI and contemporary adjunctive pharmacotherapy. Whether lesion location may be used as another predictor of clinical outcomes in addition to the currently established independent predictors of adverse outcomes such as infarct size and LVEF in patients presenting with STEMI remains to be determined. The objective of this study was to investigate the association of proximal and non-proximal location of coronary lesions with in-hospital and 30-day outcomes in patients presenting with STEMI undergoing primary PCI.

Methods

We retrospectively analyzed data from patients who presented with STEMI and treated by primary PCI to a single lesion, who were prospectively enrolled in the Victorian Cardiac Outcomes Registry (VCOR) between January 2013 and December 2015. VCOR⁸ is a state-wide population-based clinical registry established to improve the quality of care in cardiovascular disease in Victoria, Australia. It is coordinated by Monash University in conjunction with the Victorian Cardiac Clinical Network and Department of Health and Human Services involving 23 participating public and private hospitals. In the PCI module, the registry is approved by the ethics committee at each participating hospital. The registry records PCI-related clinical, demographic and procedural data including complications and outcomes with a 30-day follow-up period.

All patients undergoing PCI at each hospital are included in the registry unless the patient “opts out”. We analysed all patients enrolled in VCOR consecutively from all the participating Victorian Hospitals/Centers to minimize selection bias. Patients who received fibrinolysis or those who were treated with conservative medical therapy were excluded from the analysis.

The anatomical coronary lesion classification used for this study was based on the SYNTAX trial definition of lesion location⁹. A proximal left anterior descending (LAD) artery segment was defined as proximal to and including the first major septal branch. Proximal right coronary artery (RCA) segment extended from the ostium to one half the distance to the acute margin of the heart. Proximal left circumflex (LCx) artery included the main stem of circumflex from its origin of left main to and including the origin of the first obtuse marginal branch. Non-proximal lesions were, therefore, defined as all other lesion locations other than a proximal lesion location. Lesions

located in the left main coronary artery or grafts from previous coronary artery bypass graft (CABG) surgery were excluded from the analysis. Patients who underwent multi-vessel PCI were also excluded from the analysis.

In-hospital complications were recorded during the in-hospital stay and prior to discharge or death. New renal impairment was defined as an absolute rise of serum creatinine of $\geq 44.2 \mu\text{mol/L}$ or $\geq 25\%$ up to 5 days after the index PCI when compared to baseline creatinine. Cardiogenic shock was defined as a sustained (>30 minutes) episode of systolic blood pressure <90 mm Hg (or vasopressors required to maintain blood pressure >90 mm Hg) and evidence of elevated left ventricular filling pressure (e.g. pulmonary congestion) as well as evidence of end-organ hypoperfusion (e.g. urine output < 30 mL/hour; or altered mental status, etc.). Myocardial infarction (MI) was defined as new elevation of cardiac biomarkers $\geq 20\%$ above the pre-procedure level with at least one of the following (1) evolutionary ST-segment elevation distinct from the index event; (2) development of new Q-waves in 2 or more contiguous leads; (3) ischemic symptoms lasting ≥ 20 minutes; (4) angiographic evidence of flow limiting complications; (5) imaging evidence of new regional wall motion abnormalities. Stent thrombosis (ST) included definite and possible but not probable stent thrombosis. Major bleeding was defined as category 3a and above according to the Bleeding Academic Research Consortium definition¹⁰. Stroke was defined by persistent loss of neurological function caused by an ischemic or hemorrhagic event during or after the PCI.

The 30-day follow-up outcomes were recorded post discharge from the PCI admission. Clinical events were verified from patients, medical records and/or contact

with their primary care physician. Events recorded in the 30-day follow-up included the primary cause of death, new heart failure, new MI, new ST, new bleeding event, new stroke and its type, rehospitalization (including cardiac, PCI, CABG and planned rehospitalization), target vessel revascularization (TVR), target lesion revascularization (TLR), target vessel CABG and medications at 30-days. Major adverse cardiac events (MACE) were defined as a composite of mortality, MI, ST and unplanned revascularization. Major adverse cardiac and cerebrovascular events (MACCE) included MACE variables with the addition of stroke.

Continuous variables are presented as medians and interquartile ranges or mean $\pm$ standard deviation (as appropriate), categorical variables are presented as frequencies and percentages. Differences between proximal and non-proximal lesion groups were evaluated using non-parametric tests – sign rank test for continuous variables and Fisher's exact test for categorical variables. The independent effect of proximal lesion location on each of the clinical outcomes was evaluated using separate logistic regressions. Variables included in the multivariable analysis were selected based on their clinical significance and/or their unequal distribution between the two groups. The variables included were proximal lesion location, the infarct-related artery, cardiogenic shock, out-of-hospital cardiac arrest (OHCA), new renal impairment, left ventricular dysfunction, mechanical circulatory support, drug-eluting stent (DES) type, two or more stents inserted, successful lesion revascularization, preloading with aspirin/ticagrelor/thienopyridine, female gender, age, door-to-balloon time (DTBT), type B2/C lesion, adjunctive device use, glycoprotein IIb/IIIa use, previous PCI/CABG, chronic oral anti-coagulant use, cerebrovascular disease (CVD), peripheral vascular disease (PVD) and diabetes requiring treatment. Continuous variables were

transformed to form a linear relationship with the log odds of the clinical outcome (age as a linear and quadratic term, door to balloon time as its natural logarithm). To assess the impact of proximal lesion location on clinical outcomes without the contributory effects of well-recognized high-risk variables, namely cardiogenic shock, OHCA and mechanical ventilation support, we assessed the incidence of MACE in a subset of hemodynamically stable STEMI patients who did not have cardiogenic shock, OHCA or required mechanical ventilator support. Two-tailed p-values below 0.05 were considered statistically significant. All analyses were performed using StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

Results

Of 3,283 participants, 1,376 (41.9%) had a proximal and 1,907 (58.1%) had a non-proximal lesion location. Baseline characteristics of the two groups are presented in Table 1. Compared to the non-proximal lesion group, more patients with proximal lesion location presented with cardiogenic shock and OHCA and had higher rates of pre-procedural cardiac arrest, pre-procedural intubation and left ventricular systolic dysfunction, all $p < 0.01$. There were no significant differences in rates of cardiovascular risk factors between proximal and non-proximal groups, however, the proximal lesion group had a higher baseline creatinine, $p = 0.01$. While there were lower rates of aspirin preloading in the proximal lesion group compared to the non-proximal cohort, higher rates of thienopyridine/ticagrelor preloading were observed in the proximal lesion group, all $p < 0.05$.

Medications prescribed at discharge are shown in Table 2. Medication use at discharge was similar apart from a higher prescription of oral anticoagulants in the proximal group (8.8% vs. 6.2%, $p=0.01$).

The proximal lesion group had higher rates of femoral access ($p=0.05$) and mechanical circulatory support device use ($p=0.001$) compared to the non-proximal group. There was no significant difference in the DTBT between the two groups, however, the proximal group had a shorter symptom-to-door time, $p=0.01$, resulting in a corresponding shorter symptom-to-balloon/device time (STBT), $p=0.02$. There was greater use of glycoprotein IIb/IIIa inhibitor and thrombus aspiration devices in the proximal lesion group, both $p<0.001$. Procedural revascularization success rates between the two groups were similar (96% vs. 95%, $p=0.08$). However, there were more stents inserted in the proximal group, $p=0.001$, with no difference in the type of stents or total stent length implanted. Procedural characteristics are presented in Table 3.

Patients with proximal lesion location had significantly higher rates of in-hospital and 30-day mortality, MACE and MACCE compared to the non-proximal group, all $p<0.001$ (Table 4). In-hospital complications were also more prevalent in the proximal group, particularly new renal impairment (5.9% vs. 3.7%, $p=0.004$), post-procedural cardiogenic shock (8.4% vs. 3.8%, $p<0.001$), recurrent MI (1.7% vs. 0.8%, $p=0.02$). At 30-days, there were higher rates of new heart failure in the proximal group (3.6% vs. 2.1%, $p=0.003$).

On multivariable regression analysis, proximal lesion location was, however, not independently associated with MACE during in-hospital stay or at 30 days (OR 1.32, 95% CI 0.95-1.83, $p=0.09$ and OR 1.23, 95% CI 0.92-1.65, $p=0.15$) respectively. Cardiogenic shock, new renal failure, OHCA, mechanical circulatory support requirement and left ventricular systolic dysfunction had the strongest consecutive independent association with in-hospital and 30-day MACE; see Table 5 and Figure 1 for independent predictors of MACE. Multivariable analysis revealed that PCI to LAD infarct-related coronary artery was not a predictor of 30-day MACE (OR 0.91, 95% CI 0.62-1.32, $p=0.60$). A subgroup analysis of hemodynamically stable STEMI patients was undertaken excluding 649 patients with cardiogenic shock, OHCA and mechanical ventilation requirement. Similarly, this subgroup analysis demonstrated the lack of association between proximal lesion location and in-hospital or 30-day MACE (OR 1.53, 95% CI 0.89-2.61, $p=0.12$ and OR 1.27, 0.84-1.19, $p=0.26$) respectively. The unadjusted MACE rates are displayed in Figure 2.

Discussion

Classical, well-described variables affecting myocardial salvage after STEMI include infarct location¹¹ and the timeliness of reperfusion¹². Patients with proximal coronary lesions potentially have larger myocardial area-at-risk when compared to non-proximal lesions particularly in the LAD territory,¹³ and may result in larger infarct size¹⁴. In this study, we aimed to elucidate the significance of coronary lesion site in patients with STEMI treated by primary PCI and contemporary adjunctive medical therapy. The major finding of our study is that proximal lesion location was not independently associated with worse in-hospital or short-term clinical outcomes despite a greater prevalence of patients in the proximal lesion group presenting with

higher rates of hemodynamic compromise, i.e. cardiogenic shock and OHCA, as well as requiring procedural mechanical circulatory and airway support. Both DTBT and procedural success rates were similar between the proximal and non-proximal cohorts, however, the proximal group had significantly shorter STBT, which is an important determinant of infarction size,¹⁵ and might have attenuated the impact of proximal lesion location on short-term clinical outcomes. While in-hospital and 30-day MACE and MACCE rates were significantly higher in the proximal group, proximal lesion location, *per se*, was not independently associated with in-hospital and 30-day MACE following multivariable adjustment suggesting that lesion location might have a lesser impact on clinical outcomes in the contemporary era of rapid mechanical revascularization and adjunctive pharmacotherapy.

Previously published studies investigating the impact of proximal lesion location in STEMI patients on clinical outcomes reported different results to those of our study findings. Karha and colleagues³ investigated 2,488 patients enrolled in four fibrinolysis trials comparing proximal lesion location with mid or distal lesions. In that study, an independent inverse association of the planimetered distance from the LAD ostium to the culprit lesion site was observed with adverse outcomes after fibrinolytic administration. In contrast, our study excluded participants treated with fibrinolysis and our study cohort was much more contemporary and well treated with guideline-recommended secondary prevention therapies. In the balloon angioplasty era, Harjai and colleagues¹⁷ compared short and intermediate-term clinical outcomes of proximal versus non-proximal culprit lesions in 3,535 patients pooled from the Primary Angioplasty in Myocardial Infarction (PAMI) database. After adjustment for other variables, proximal lesion location was independently associated with in-hospital

mortality and MACE but not 1-year mortality or MACE. Given these findings, the authors suggested that culprit lesion location should be used as an angiographic prognostication tool in addition to other established predictors. Compared to our study, Harjai *et al* excluded patients with cardiogenic shock and renal failure, both of which were included in our analysis. Moreover, the majority of patients included in the study by Harjai *et al* were treated by balloon angioplasty and <40% were treated by stenting. In another study by Elsmann *et al*¹⁸, the authors investigated a total of 1,468 consecutive patients with STEMI treated by primary PCI at a single centre. This study reported worse short and long-term clinical outcomes in patients with reperfused proximal LAD culprit lesions compared to distal LAD lesions. However, such an association was lacking for lesions located in the proximal RCA or LCx. The interventions implemented in this study were primarily balloon angioplasty with limited medical therapy when compared to the contemporary adjunctive pharmacotherapies. For example, stents were used in only 42% of the population studied and a second antiplatelet agent (ticlopidine or clopidogrel) was prescribed only if a stent was used, and dual antiplatelet therapy was given for a limited duration of 4 weeks.

Contrary to previously published studies comparing proximal versus non-proximal culprit lesion location, our study cohort was treated by primary PCI and received contemporary adjunctive medical therapy. Therefore, our study results could be, in part, explained by the high rates of contemporary guideline-directed medical therapy coupled with timely reperfusion delivered to both of the proximal and non-proximal groups. Approximately 90% of patients in both proximal and non-proximal lesion location groups in our study received a second anti-platelet agent. Similarly, the use of beta blockers and ACE-I/ARB was approximately 80% with no significant

difference in the proximal and the non-proximal groups. Statins were also prescribed in about 90% in both groups. In the study by Elsmann *et al*¹⁸, only those treated with a stent received a second antiplatelet agent in addition to aspirin. The rates of other adjunctive therapies such as beta-blockers, statins and ACE-/ARB were not reported. Harjai and colleagues¹⁷ in their *post hoc* analysis of PAMI trial patients, found that the rates of beta blocker use (about 50%-80% when reported) and ACE-I use (about 54%-68% when reported) were low, and lower than in our study population. Also the proportion of patients who received a second antiplatelet agent, ticlopidine, was not reported. The mortality and morbidity benefits conferred by contemporary pharmacological therapies are well established in patients with STEMI such as the prescription of high intensity statins¹⁹⁻²¹, beta blockers at discharge²², ACE-I/ARB for left ventricular dysfunction^{23,24}. The use of such therapies is a key performance measure for the contemporary evidence-based management of STEMI²⁵. Thus, the results of our study are different to earlier studies and the difference in outcome association might be attributable to optimal medical therapy in STEMI patients treated with PCI, thereby mitigating the negative prognostic impact of other variables such as that of proximal lesion location^{22,26-29}.

The proximal lesion group included patients presenting with higher rates of cardiogenic shock (12.4% vs. 5.7%) and OHCA (11.8% vs. 7.9%) with more culprit lesions located in the LAD (51.3% vs. 36.2%) compared to the non-proximal group, which likely accounted for the greater incidences of hemodynamic and airway support requirements during the procedure. These high-risk patient and procedural characteristics could also explain the higher short-term mortality rates compared to the non-proximal group. While there was a lack of independent association of proximal

lesion location with short-term MACE (including within the hemodynamically stable subgroup analysis), proximal lesion location should still be regarded a high-risk feature not only because of higher rates of 30-day MACE and mortality but also significantly higher rates of left ventricular dysfunction during in-hospital stay and higher rates of new heart failure diagnosis at 30-day follow-up compared to the non-proximal group. Patients presenting with larger infarcts or with larger area of myocardium at risk have greater potential for adverse pathological myocardial remodelling as evident from studies utilizing cardiac magnetic resonance reporting that final infarction size and the amount of myocardium salvaged to be predictors of adverse remodelling ^{11,16}.

Our study had certain limitations including the retrospective design and observational nature and is, therefore, subject to unmeasured confounders that could impact on clinical outcomes despite multivariable adjustments. The VCOR does not capture a history of previous myocardial infarction, the extent of coronary artery disease or the extent of residual disease following revascularisation nor the completeness of revascularisation. Quantitative assessment of coronary flow grades or collateral supply to culprit vessel was also not available. Our data collection did not include quantitative assessment of coronary flow grades or collateral supply to culprit vessels prior to and following PCI, which could potentially have affected outcomes. The follow-up duration of 30 days in our study was short and longer-term follow-up ~~might~~ would be needed to detect significant differences in clinical outcomes (such as MACE, mortality, TVR and TLR) between the proximal versus non-proximal groups. Lastly, our study sample size was small and may be underpowered to detect the effect of lesion location on clinical outcomes given the higher rates of adverse in-hospital and 30-day clinical outcomes among patients with proximal lesion location.

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In conclusion, our study demonstrated that patients presenting with STEMI secondary to a proximal lesion location undergoing primary PCI were more likely to present with hemodynamic instability, and had higher-risk features. However, proximal lesion location *per se* was not independently associated with worse short-term clinical outcomes compared to a non-proximal lesion. The lack of independent association underscores the importance of timely mechanical reperfusion and the application of contemporary guideline-recommended adjunctive medical therapies. Larger prospective studies are needed to assess the importance of proximal lesion location in the contemporary era.

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Figure 1 Independent predictors of 30-day MACE on multivariable logistic regression.

Figure 2

A Unadjusted in-hospital and 30-day MACE in all patients (n=3,283).

B Unadjusted in-hospital and 30-day MACE in the hemodynamically stable subgroup (n=2,634)

Comparison of Short-term Clinical Outcomes of Proximal versus Non-Proximal Lesion Location in Patients Treated with Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction – the PROXIMITI study

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Short Title: Proximal vs. Non-Proximal Lesions in STEMI

Key Words: Percutaneous Coronary Intervention, Acute myocardial infarction/STEMI, Angiography, Coronary

Word Count 5,790

Abstract

Objectives: The objective of this study was to investigate the association of proximal and non-proximal location of culprit coronary lesions with clinical outcomes of patients presenting with ST-elevation myocardial infarction (STEMI) treated by primary ~~primary~~ percutaneous coronary intervention (PCI).

Background: Proximal culprit lesion location in patients presenting with STEMI is associated with increased mortality when compared to distal culprit lesions in the thrombolytic era. The impact of lesion location on clinical outcomes in the era of PCI remains unclear.

Methods: We analyzed 3,283 patients with STEMI who enrolled in the Victorian Cardiac Outcomes Registry. We compared outcomes in those with proximal lesion location versus patients with non-proximal location.

Results: Of 3,283 participants, 1,376 (41.9%) had a proximal lesion location. Patients with proximal lesion location presented with greater rates of cardiogenic shock and out-of-hospital cardiac arrest, and left ventricular systolic dysfunction, all $p < 0.01$. Procedural success rates were similar (96% vs. 95%, $p = 0.08$). Patients with proximal lesion location had higher rates of in-hospital and 30-day mortality, major adverse cardiac events (MACE; mortality, myocardial infarction, stent thrombosis and unplanned revascularization) and major adverse cardiac and cerebrovascular events (MACCE; MACE and stroke) compared to the non-proximal group, all $p < 0.001$. However, on multivariable regression analysis, proximal lesion location was not independently associated with MACE during in-hospital stay or at 30-days (OR 1.32, 95% CI 0.95-1.83, $p = 0.09$ and OR 1.23, 95% CI 0.92-1.65, $p = 0.15$) respectively.

Conclusions: Patients with proximal lesion location had greater hemodynamic instability and higher-risk features; however, proximal lesions *per se* were not independently associated with worse clinical outcomes compared to non-proximal lesions.

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independently associated with worse clinical outcomes compared to non-proximal lesions.

Key Words

Percutaneous Coronary Intervention

Acute myocardial infarction/STEMI

Angiography, Coronary

Abbreviation list

STEMI - ST-Elevation Myocardial Infarction

PCI - Percutaneous Coronary Intervention

CABG - Coronary Artery Bypass Graft

ST - Stent Thrombosis

MACE - Major Adverse Cardiac Events

MACCE - Major Adverse Cardiac and Cerebrovascular Events

Introduction

ST-elevation myocardial infarction (STEMI) is a major cause of death and morbidity worldwide ¹. In patients presenting with STEMI, the primary objective is to restore coronary blood flow in the infarct-related artery by thrombolytic therapy or primary percutaneous coronary intervention (PCI) in a timely fashion. In such patients, well-described prognostic factors include infarct size, infarct location and residual left ventricular ejection fraction (LVEF) ². Proximal culprit lesions have been shown to be associated with increased short-term mortality when compared to distal culprit lesions in patients treated with thrombolytic therapy ^{3,4} as well as worse left ventricular systolic function ⁵. Primary PCI is now the revascularization method of choice due to superior rates of successful reperfusion and lower rates of stroke, re-infarction and mortality compared to thrombolysis ⁶. Published studies have shown that culprit lesion location correlates with the amount of myocardium at-risk ⁷. There is a paucity of data evaluating the association of anatomical location of the lesion with short-term outcomes in patients presenting with STEMI treated with primary PCI and contemporary adjunctive pharmacotherapy. Whether lesion location may be used as another predictor of clinical outcomes in addition to the currently established independent predictors of adverse outcomes such as infarct size and LVEF in patients presenting with STEMI remains to be determined. The objective of this study was to investigate the association of proximal and non-proximal location of coronary lesions with in-hospital and 30-day outcomes in patients presenting with STEMI undergoing primary PCI.

Methods

We retrospectively analyzed data from patients who presented with STEMI and treated by primary PCI to a single lesion, who were prospectively enrolled in the Victorian Cardiac Outcomes Registry (VCOR) between January 2013 and December 2015. VCOR⁸ is a state-wide population-based clinical registry established to improve the quality of care in cardiovascular disease in Victoria, Australia. It is coordinated by Monash University in conjunction with the Victorian Cardiac Clinical Network and Department of Health and Human Services involving 23 participating public and private hospitals. In the PCI module, the registry is approved by the ethics committee at each participating hospital. The registry records PCI-related clinical, demographic and procedural data including complications and outcomes with a 30-day follow-up period. All patients undergoing PCI at each hospital are included in the registry unless the patient “opts out”. We analysed all patients enrolled in VCOR consecutively from all the participating Victorian Hospitals/Centers to minimize selection bias. Patients who received fibrinolysis or those who were treated with conservative medical therapy were excluded from the analysis.

The anatomical coronary lesion classification used for this study was based on the SYNTAX trial definition of lesion location⁹. A proximal left anterior descending (LAD) artery segment was defined as proximal to and including the first major septal branch. Proximal right coronary artery (RCA) segment extended from the ostium to one half the distance to the acute margin of the heart. Proximal left circumflex (LCx) artery included the main stem of circumflex from its origin of left main to and including the origin of the first obtuse marginal branch. Non-proximal lesions were, therefore, defined as all other lesion locations other than a proximal lesion location. Lesions

located in the left main coronary artery or grafts from previous coronary artery bypass graft (CABG) surgery were excluded from the analysis. Patients who underwent multi-vessel PCI were also excluded from the analysis.

In-hospital complications were recorded during the in-hospital stay and prior to discharge or death. New renal impairment was defined as an absolute rise of serum creatinine of $\geq 44.2 \mu\text{mol/L}$ or $\geq 25\%$ up to 5 days after the index PCI when compared to baseline creatinine. Cardiogenic shock was defined as a sustained (>30 minutes) episode of systolic blood pressure <90 mm Hg (or vasopressors required to maintain blood pressure >90 mm Hg) and evidence of elevated left ventricular filling pressure (e.g. pulmonary congestion) as well as evidence of end-organ hypoperfusion (e.g. urine output < 30 mL/hour; or altered mental status, etc.). Myocardial infarction (MI) was defined as new elevation of cardiac biomarkers $\geq 20\%$ above the pre-procedure level with at least one of the following (1) evolutionary ST-segment elevation distinct from the index event; (2) development of new Q-waves in 2 or more contiguous leads; (3) ischemic symptoms lasting ≥ 20 minutes; (4) angiographic evidence of flow limiting complications; (5) imaging evidence of new regional wall motion abnormalities. Stent thrombosis (ST) included definite and possible but not probable stent thrombosis. Major bleeding was defined as category 3a and above according to the Bleeding Academic Research Consortium definition¹⁰. Stroke was defined by persistent loss of neurological function caused by an ischemic or hemorrhagic event during or after the PCI.

The 30-day follow-up outcomes were recorded post discharge from the PCI admission. Clinical events were verified from patients, medical records and/or contact

with their primary care physician. Events recorded in the 30-day follow-up included the primary cause of death, new heart failure, new MI, new ST, new bleeding event, new stroke and its type, rehospitalization (including cardiac, PCI, CABG and planned rehospitalization), target vessel revascularization (TVR), target lesion revascularization (TLR), target vessel CABG and medications at 30-days. Major adverse cardiac events (MACE) were defined as a composite of mortality, MI, ST and unplanned revascularization. Major adverse cardiac and cerebrovascular events (MACCE) included MACE variables with the addition of stroke.

Continuous variables are presented as medians and interquartile ranges or mean $\pm$ standard deviation (as appropriate), categorical variables are presented as frequencies and percentages. Differences between proximal and non-proximal lesion groups were evaluated using non-parametric tests – sign rank test for continuous variables and Fisher's exact test for categorical variables. The independent effect of proximal lesion location on each of the clinical outcomes was evaluated using separate logistic regressions. Variables included in the multivariable analysis were selected based on their clinical significance and/or their unequal distribution between the two groups. The variables included were proximal lesion location, the infarct-related artery, cardiogenic shock, out-of-hospital cardiac arrest (OHCA), new renal impairment, left ventricular dysfunction, mechanical circulatory support, drug-eluting stent (DES) type, two or more stents inserted, successful lesion revascularization, preloading with aspirin/ticagrelor/thienopyridine, female gender, age, door-to-balloon time (DTBT), type B2/C lesion, adjunctive device use, glycoprotein IIb/IIIa use, previous PCI/CABG, chronic oral anti-coagulant use, cerebrovascular disease (CVD), peripheral vascular disease (PVD) and diabetes requiring treatment. Continuous variables were

transformed to form a linear relationship with the log odds of the clinical outcome (age as a linear and quadratic term, door to balloon time as its natural logarithm). To assess the impact of proximal lesion location on clinical outcomes without the contributory effects of well-recognized high-risk variables, namely cardiogenic shock, OHCA and mechanical ventilation support, we assessed the incidence of MACE in a subset of hemodynamically stable STEMI patients who did not have cardiogenic shock, OHCA or required mechanical ventilator support. Two-tailed p-values below 0.05 were considered statistically significant. All analyses were performed using StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

Results

Of 3,283 participants, 1,376 (41.9%) had a proximal and 1,907 (58.1%) had a non-proximal lesion location. Baseline characteristics of the two groups are presented in Table 1. Compared to the non-proximal lesion group, more patients with proximal lesion location presented with cardiogenic shock and OHCA and had higher rates of pre-procedural cardiac arrest, pre-procedural intubation and left ventricular systolic dysfunction, all $p < 0.01$. There were no significant differences in rates of cardiovascular risk factors between proximal and non-proximal groups, however, the proximal lesion group had a higher baseline creatinine, $p = 0.01$. While there were lower rates of aspirin preloading in the proximal lesion group compared to the non-proximal cohort, higher rates of thienopyridine/ticagrelor preloading were observed in the proximal lesion group, all $p < 0.05$.

Medications prescribed at discharge are shown in Table 2. Medication use at discharge was similar apart from a higher prescription of oral anticoagulants in the proximal group (8.8% vs. 6.2%, $p=0.01$).

The proximal lesion group had higher rates of femoral access ($p=0.05$) and mechanical circulatory support device use ($p=0.001$) compared to the non-proximal group. There was no significant difference in the DTBT between the two groups, however, the proximal group had a shorter symptom-to-door time, $p=0.01$, resulting in a corresponding shorter symptom-to-balloon/device time (STBT), $p=0.02$. There was greater use of glycoprotein IIb/IIIa inhibitor and thrombus aspiration devices in the proximal lesion group, both $p<0.001$. Procedural revascularization success rates between the two groups were similar (96% vs. 95%, $p=0.08$). However, there were more stents inserted in the proximal group, $p=0.001$, with no difference in the type of stents or total stent length implanted. Procedural characteristics are presented in Table 3.

Patients with proximal lesion location had significantly higher rates of in-hospital and 30-day mortality, MACE and MACCE compared to the non-proximal group, all $p<0.001$ (Table 4). In-hospital complications were also more prevalent in the proximal group, particularly new renal impairment (5.9% vs. 3.7%, $p=0.004$), post-procedural cardiogenic shock (8.4% vs. 3.8%, $p<0.001$), recurrent MI (1.7% vs. 0.8%, $p=0.02$). At 30-days, there were higher rates of new heart failure in the proximal group (3.6% vs. 2.1%, $p=0.003$).

On multivariable regression analysis, proximal lesion location was, however, not independently associated with MACE during in-hospital stay or at 30 days (OR 1.32, 95% CI 0.95-1.83, $p=0.09$ and OR 1.23, 95% CI 0.92-1.65, $p=0.15$) respectively. Cardiogenic shock, new renal failure, OHCA, mechanical circulatory support requirement and left ventricular systolic dysfunction had the strongest consecutive independent association with in-hospital and 30-day MACE; see Table 5 and Figure 1 for independent predictors of MACE. Multivariable analysis revealed that PCI to LAD infarct-related coronary artery was not a predictor of 30-day MACE (OR 0.91, 95% CI 0.62-1.32, $p=0.60$). A subgroup analysis of hemodynamically stable STEMI patients was undertaken excluding 649 patients with cardiogenic shock, OHCA and mechanical ventilation requirement. Similarly, this subgroup analysis demonstrated the lack of association between proximal lesion location and in-hospital or 30-day MACE (OR 1.53, 95% CI 0.89-2.61, $p=0.12$ and OR 1.27, 0.84-1.19, $p=0.26$) respectively. The unadjusted MACE rates are displayed in Figure 2.

Discussion

Classical, well-described variables affecting myocardial salvage after STEMI include infarct location¹¹ and the timeliness of reperfusion¹². Patients with proximal coronary lesions potentially have larger myocardial area-at-risk when compared to non-proximal lesions particularly in the LAD territory,¹³ and may result in larger infarct size¹⁴. In this study, we aimed to elucidate the significance of coronary lesion site in patients with STEMI treated by primary PCI and contemporary adjunctive medical therapy. The major finding of our study is that proximal lesion location was not independently associated with worse in-hospital or short-term clinical outcomes despite a greater prevalence of patients in the proximal lesion group presenting with

higher rates of hemodynamic compromise, i.e. cardiogenic shock and OHCA, as well as requiring procedural mechanical circulatory and airway support. Both DTBT and procedural success rates were similar between the proximal and non-proximal cohorts, however, the proximal group had significantly shorter STBT, which is an important determinant of infarction size,¹⁵ and might have attenuated the impact of proximal lesion location on short-term clinical outcomes. While in-hospital and 30-day MACE and MACCE rates were significantly higher in the proximal group, proximal lesion location, *per se*, was not independently associated with in-hospital and 30-day MACE following multivariable adjustment suggesting that lesion location might have a lesser impact on clinical outcomes in the contemporary era of rapid mechanical revascularization and adjunctive pharmacotherapy.

Previously published studies investigating the impact of proximal lesion location in STEMI patients on clinical outcomes reported different results to those of our study findings. Karha and colleagues³ investigated 2,488 patients enrolled in four fibrinolysis trials comparing proximal lesion location with mid or distal lesions. In that study, an independent inverse association of the planimetered distance from the LAD ostium to the culprit lesion site was observed with adverse outcomes after fibrinolytic administration. In contrast, our study excluded participants treated with fibrinolysis and our study cohort was much more contemporary and well treated with guideline-recommended secondary prevention therapies. In the balloon angioplasty era, Harjai and colleagues¹⁷ compared short and intermediate-term clinical outcomes of proximal versus non-proximal culprit lesions in 3,535 patients pooled from the Primary Angioplasty in Myocardial Infarction (PAMI) database. After adjustment for other variables, proximal lesion location was independently associated with in-hospital

mortality and MACE but not 1-year mortality or MACE. Given these findings, the authors suggested that culprit lesion location should be used as an angiographic prognostication tool in addition to other established predictors. Compared to our study, Harjai *et al* excluded patients with cardiogenic shock and renal failure, both of which were included in our analysis. Moreover, the majority of patients included in the study by Harjai *et al* were treated by balloon angioplasty and <40% were treated by stenting. In another study by Elsmann *et al* ¹⁸, the authors investigated a total of 1,468 consecutive patients with STEMI treated by primary PCI at a single centre. This study reported worse short and long-term clinical outcomes in patients with reperfused proximal LAD culprit lesions compared to distal LAD lesions. However, such an association was lacking for lesions located in the proximal RCA or LCx. The interventions implemented in this study were primarily balloon angioplasty with limited medical therapy when compared to the contemporary adjunctive pharmacotherapies. For example, stents were used in only 42% of the population studied and a second antiplatelet agent (ticlopidine or clopidogrel) was prescribed only if a stent was used, and dual antiplatelet therapy was given for a limited duration of 4 weeks.

Contrary to previously published studies comparing proximal versus non-proximal culprit lesion location, our study cohort was treated by primary PCI and received contemporary adjunctive medical therapy. Therefore, our study results could be, in part, explained by the high rates of contemporary guideline-directed medical therapy coupled with timely reperfusion delivered to both of the proximal and non-proximal groups. Approximately 90% of patients in both proximal and non-proximal lesion location groups in our study received a second anti-platelet agent. Similarly, the use of beta blockers and ACE-I/ARB was approximately 80% with no significant

difference in the proximal and the non-proximal groups. Statins were also prescribed in about 90% in both groups. In the study by Elsman *et al*¹⁸, only those treated with a stent received a second antiplatelet agent in addition to aspirin. The rates of other adjunctive therapies such as beta-blockers, statins and ACE-/ARB were not reported. Harjai and colleagues¹⁷ in their *post hoc* analysis of PAMI trial patients, found that the rates of beta blocker use (about 50%-80% when reported) and ACE-I use (about 54%-68% when reported) were low, and lower than in our study population. Also the proportion of patients who received a second antiplatelet agent, ticlopidine, was not reported. The mortality and morbidity benefits conferred by contemporary pharmacological therapies are well established in patients with STEMI such as the prescription of high intensity statins¹⁹⁻²¹, beta blockers at discharge²², ACE-I/ARB for left ventricular dysfunction^{23,24}. The use of such therapies is a key performance measure for the contemporary evidence-based management of STEMI²⁵. Thus, the results of our study are different to earlier studies and the difference in outcome association might be attributable to optimal medical therapy in STEMI patients treated with PCI, thereby mitigating the negative prognostic impact of other variables such as that of proximal lesion location^{22,26-29}.

The proximal lesion group included patients presenting with higher rates of cardiogenic shock (12.4% vs. 5.7%) and OHCA (11.8% vs. 7.9%) with more culprit lesions located in the LAD (51.3% vs. 36.2%) compared to the non-proximal group, which likely accounted for the greater incidences of hemodynamic and airway support requirements during the procedure. These high-risk patient and procedural characteristics could also explain the higher short-term mortality rates compared to the non-proximal group. While there was a lack of independent association of proximal

lesion location with short-term MACE (including within the hemodynamically stable subgroup analysis), proximal lesion location should still be regarded a high-risk feature not only because of higher rates of 30-day MACE and mortality but also significantly higher rates of left ventricular dysfunction during in-hospital stay and higher rates of new heart failure diagnosis at 30-day follow-up compared to the non-proximal group. Patients presenting with larger infarcts or with larger area of myocardium at risk have greater potential for adverse pathological myocardial remodelling as evident from studies utilizing cardiac magnetic resonance reporting that final infarction size and the amount of myocardium salvaged to be predictors of adverse remodelling ^{11,16}.

Our study had certain limitations including the retrospective design and observational nature and is, therefore, subject to unmeasured confounders that could impact on clinical outcomes despite multivariable adjustments. The VCOR does not capture a history of previous myocardial infarction, the extent of coronary artery disease or the extent of residual disease following revascularisation nor the completeness of revascularisation. Quantitative assessment of coronary flow grades or collateral supply to culprit vessel was also not available. The follow-up duration of 30 days in our study was short and longer-term follow-up would be needed to detect significant differences in clinical outcomes (such as MACE, mortality, TVR and TLR) between the proximal versus non-proximal groups. Lastly, our study sample size was small and may be underpowered to detect the effect of lesion location on clinical outcomes given the higher rates of adverse in-hospital and 30-day clinical outcomes among patients with proximal lesion location.

In conclusion, our study demonstrated that patients presenting with STEMI secondary to a proximal lesion location undergoing primary PCI were more likely to present with hemodynamic instability, and had higher-risk features. However, proximal lesion location *per se* was not independently associated with worse short-term clinical outcomes compared to a non-proximal lesion. The lack of independent association underscores the importance of timely mechanical reperfusion and the application of contemporary guideline-recommended adjunctive medical therapies. Larger prospective studies are needed to assess the importance of proximal lesion location in the contemporary era.

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Figure 1 Independent predictors of 30-day MACE on multivariable logistic regression.

Figure 2

A Unadjusted in-hospital and 30-day MACE in all patients (n=3,283).

B Unadjusted in-hospital and 30-day MACE in the hemodynamically stable subgroup (n=2,634)

Comparison of Short-term Clinical Outcomes of Proximal versus Non-Proximal Lesion Location in Patients Treated with Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction – the PROXIMITI study

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Short Title: Proximal vs. Non-Proximal Lesions in STEMI

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Abstract

Objectives: The objective of this study was to investigate the association of proximal and non-proximal location of culprit coronary lesions with clinical outcomes of patients presenting with ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI).

Background: Proximal culprit lesion location in patients presenting with STEMI is associated with increased mortality when compared to distal culprit lesions in the thrombolytic era. The impact of lesion location on clinical outcomes in the era of PCI remains unclear.

Methods: We analyzed 3,283 patients with STEMI who enrolled in the Victorian Cardiac Outcomes Registry. We compared outcomes in those with proximal lesion location versus patients with non-proximal location.

Results: Of 3,283 participants, 1,376 (41.9%) had a proximal lesion location. Patients with proximal lesion location presented with greater rates of cardiogenic shock and out-of-hospital cardiac arrest, and left ventricular systolic dysfunction, all $p < 0.01$. Procedural success rates were similar (96% vs. 95%, $p = 0.08$). Patients with proximal lesion location had higher rates of in-hospital and 30-day mortality, major adverse cardiac events (MACE; mortality, myocardial infarction, stent thrombosis and unplanned revascularization) and major adverse cardiac and cerebrovascular events (MACCE; MACE and stroke) compared to the non-proximal group, all $p < 0.001$. However, on multivariable regression analysis, proximal lesion location was not independently associated with MACE during in-hospital stay or at 30-days (OR 1.32, 95% CI 0.95-1.83, $p = 0.09$ and OR 1.23, 95% CI 0.92-1.65, $p = 0.15$) respectively.

Conclusions: Patients with proximal lesion location had greater hemodynamic instability and higher-risk features; however, proximal lesions *per se* were not independently associated with worse clinical outcomes compared to non-proximal lesions.

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