RESEARCH ARTICLE

In-hospital management and intermediate term outcomes in stable patients with ST segment elevation myocardial infarction presenting between 12-48 hours of symptom onset versus 2-7 days after the onset of chest pain; a single center study

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Abstract

Objective: To evaluate hospital management, revascularisation and intermediate-term major adverse cardiac events amongst ST elevation myocardial infarction patients and to compare them in early and late presentations.

Methods: The retrospective study was conducted at Tabba Heart Institute, Karachi, and comprised data from July 2013 to December 2016. ST elevation myocardial infarction patients presenting between 12-48 hours of symptom onset were designated as early-late, while those presenting 2-7 days after the onset of symptoms were designated as late-late. Data included related to patients admitted consecutively with >12hrs of chest pain without immediate reperfusion. Major adverse cardiac events were composite of death, re- myocardial infarction, need for revascularisation or heart failure. SPSS 19 was used for data analysis.

Results: Out of 234, patients, 110(47%) were early-late and 124(53%) were late-late. Overall mean age was 58.5±12.2years, and 188(80.3%) subjects were men. Anterior all myocardial infarction was in 134(57.3%) cases. Non-invasive assessment for ischaemia/viability was performed in 96(41%) cases and angiography in 196(83.8%). Early-late were revascularised more frequently 53(48.2%) than late-late 49(39.5%) (p>0.05). Median follow-up was 23 months (interquartile range: 13-34 months). Major adverse cardiac events occurred in 45(19.6%) patients but there was no significant difference between early-late and late-late patients (p>0.05).

Conclusion: Revascularisation was found to have favourable impact on intermediate-term adverse cardiac events.

Keywords: STEMI, ST segment elevation myocardial infarction, Myocardial revascularisation.

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Introduction

Acute ST segment elevation myocardial infarction (STEMI) is the most time-sensitive presentation of coronary heart disease (CHD) and multiple randomised trials show life-saving benefits of immediate reperfusion therapy in the form of fibrinolysis or percutaneous coronary intervention (PCI).[1,2] Immediate reperfusion therapy results in reduction of infarct size and mortality, with maximum benefit when done within 3 hours of symptom onset and with some mortality reduction up to 12 hours of symptom onset.[3] In the recent European guidelines this time window for PCI is now extended to 48 hours.[2]

In registries from North America and Europe, 18-40% STEMI patients present later than 12 hours of symptom onset[4,5] whereas the Treatment and outcomes of acute coronary syndromes in India (CREATE) registry from India showed this to be 30.8%.[6] The benefit of reperfusion in this patient population is less clear as nearly 80% of myocardium at risk gets permanently damaged by 3 hours of vessel occlusion.[7] However, there is individual variability in the timing and extent of myocardial necrosis due to the intermittent nature of acute coronary occlusion, spontaneous reperfusion or presence of pre-existing collaterals. The two largest trials of late PCI in STEMI, Occluded Artery Trial (OAT) and Beyond 12 hours Reperfusion Alternative Evaluation (BRAVE 2) show conflicting results. The OAT trial, that included mostly occluded vessels with PCI done more than 48-72 hours

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after STEMI onset, showed no benefit,[8] while the BRAVE 2 trial, that included majority re-canalised and collateralised culprit vessel with PCI done within12-48 hours of STEMI onset, showed benefit.[9] A pooled meta-analysis in late STEMI patients, including both acute and sub-acute (7-30 days post- myocardial infarction [MI]) patients, suggested benefit of revascularisation at median time of 12 days post-MI.[10]

In STEMI patients presenting late who are unstable with on-going chest pain, haemodynamic or electrical instability, current treatment guidelines recommend reperfusion with PCI.[2] For patients who are pain-free and stable 12-48 hours after STEMI onset, current European guidelines give a class I recommendation for PCI while the US guidelines still keep it as a class II recommendation, suggesting benefit in some patients with need for individual patient assessment.[1,2] In patients not deemed candidates for immediate PCI, use of non-invasive ischaemia and viability (NIV) assessment plays a role in identifying patients who will still benefit from revascularisation.[11]

Thus, for patients who present late with STEMI and are stable, trial data and guidelines give a mixed recommendation regarding revascularisation approach. The current study was planned to assess the early management strategies of stable patients admitted with STEMI more than 12 hours after symptom onset and without an immediate indication for reperfusion. It was planned to evaluate the use of invasive and non-invasive assessment, use of revascularisation, hospital mortality and intermediate-term major adverse cardiac events (MACE).

Methods

The retrospective observational study with prospective follow-up was conducted at Tabba Heart Institute, Karachi, and comprised data of adult patients of both genders admitted with STEMI between July 2013 and December 2016. Data of patients who had presented after 12 hours of chest pain onset and without having received immediate reperfusion was assessed for eligibility using consecutive sampling technique. The patients having other indications for urgent / emergent invasive management, such as ongoing chest pain, heart failure or haemodynamic and electrical instability, were excluded. Late presenters beyond 7 days post-MI and patients who did not continue treatment at our institute were also excluded. Patients presenting between 12-48 hours of symptom onset were designated as early-late, while those presenting 2-7 days after the onset of symptoms were designated as late-late.

The initial data was obtained from the institutional database maintained according to the standard National Cardiovascular Data Registry (NCDR)'s Acute Coronary Treatment and Intervention Outcomes Network (ACTION)-based acute coronary syndrome (ACS) registry, while data on coronary angiography (CAG) and PCI was obtained from the catheterisation laboratory (CathPCI) registry. The registry collects data on patient's clinical presentation, NIV tests, treatments, and outcomes. There is a comprehensive data quality programme and data collected is exported in a standard format. The complete definitions of all variables were defined by a committee of the American College of Cardiology (ACC).[12] The study questionnaire was designed in line with the registry questions that included data on all STEMI patients, their characteristics, clinical presentation such as Killip class (to predict risk of 30-day mortality), treatments, and outcomes. Follow-up status was established prospectively from file review and outpatient follow-up visits of the patients, In case of missing information, patients were contacted by data collectors via telephone calls. Prior to data extraction from the institutional database, approval was obtained from the institutional ethics review committee.

Data on hospital management, including decision regarding left ventricle (LV) functional assessment using transthoracic echo, NIV stress testing (Tc99 rest nitroglycerin or stress / rest nitroglycerin, low dose or maximum dose Dobutamine echo) and plan for CAG and revascularisation were recorded. Frequency of revascularisation within four weeks of index event was counted as part of initial management. In-hospital mortality was also recorded.

MACE at follow-up was defined as a composite of all-cause death, re-MI (positive cardiac biomarkers with / without CAG), need for revascularisation or heart failure. Individual components were reported separately as well.

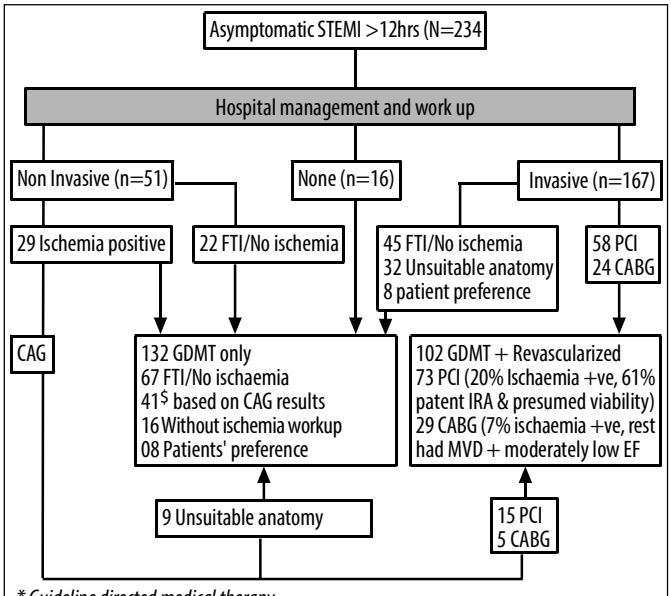
SPSS 19 was used for statistical analysis. Means and standard deviations were calculated for continuous variables and frequencies and percentages for categorical variables. In-hospital management and outcomes were reported as frequencies and percentages and compared using chi square test. Univariate analysis was performed

to measure significant association between independent variables using chi square and, if needed, logistic regression analysis. Predictors of MACE were evaluated using Cox regression modelling with stepwise technique (entry p-value of 0.25; exit 0.10). Hazard ratios (HR) with 95% confidence intervals (CIs) were reported. P<0.05 was considered significant.

Results

Of the 583 STEMI cases evaluated, 234(40.1%) met the inclusion criteria. Of them, 110 (47%) presented early-late and 124 (53%) late-late. Overall mean age was 58.5±12.2 years, and 188(80.3%) were men. Anterior wall MI was 134(57.3%). Median ejection fraction (EF) was 35% (interquartile range [IQR]: 32-45%). Overall, 16(6.9%) patients did not undergo any risk stratification either because of 10 increased age or due to concomitant severe medical conditions. NIV for ischaemia / viability before or after CAG was performed in 96(41%) and diagnostic CAG (before or after NIV) was performed in 196(83.8%). Commonest indication for CAG, in 168 (71.7) % was moderate or severe LV systolic dysfunction (LVEF <40% on echocardiogram) whereas in 27(13.8%) patients it was based on physician's preference, and the rest had NIV risk stratification (Figure 1). When comparing between early-late and late-late presenters, most parameters were equally distributed except single vessel disease (SVD) in early-late group (58[61.1%] vs. 47[46.5%]) and multi-vessel coronary disease in late-late group (46.5 vs. 30%). Also, more patients had hypertension (HTN) (79[63.7%] in late-late, 57[51.8%] in early-late) and increased NIV stress testing (57[46%} in late-late, 39[39.9%] in early-late) though the difference was not statistically significant (p>0.05) (Table 1).

Overall, 132 (56.4%) were continued on guideline-directed medical therapy (GDMT) only. Mean time to revascularisation was 3±1.1 days. More patients in early-



** Guideline directed medical therapy.*
$ Non obstructive or branch vessel disease in 10, occluded infarct related artery in 8 and23 diffuse/ distal disease not amenable for revascularization.

Figure-1: Flow chart of hospital management and use of invasive coronary angiography (CAG) and non-invasive (NIV) ischaemia evaluation in reperfusion eligible ST elevation myocardial infarction (STEMI) patients.

Table-2: Discharge medication in early-late vs. late-late presentation.

Variables	Total (n=230)	Early-late (n=109)	Late-late (n=121)
Aspirin	216 (93.9)	103 (94.5)	113 (93.4)
Thienopyridines	185 (80.4)	92 (84.4)	93 (76.9)
Statins	221 (96.1)	105 (96.3)	116 (95.9)
Beta blockers	217 (94.3)	102 (93.6)	115 (95.0)
ACE-Inhibitors/ ARBs*	179 (77.8)	82 (75.2)	97 (80.2)
Aldosterone antagonists	43 (18.7)	26 (23.9)	17 (14.0)
GDMT combination$	167(72.6)	77 (70.6)	90 (74.4)

*ACE-Inhibitors/ ARB: Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker, $GDMT combination: Guideline directed medical therapy comprising at least one anti-platelet along with statin, beta blocker and ACE-I/ ARB.

Table-1: Baseline characteristics.

Variables	Total (n=234)	Early-late (n=110) 47%	Late-late (n=124) 53%	Sig.
Time to arrival, median (days)	2 (1-4)	1 (1-2)	4 (3-5)	
Age (years)	58.5 ± 12.2	58.1 ± 11.9	58.8 ± 12.5	0.6
Males	188 (80.3)	85 (77.3)	103 (83.1)	0.3
Diabetes mellitus	106 (45.3)	47 (42.7)	59 (47.6)	0.4
Hypertension	136(58.1)	57 (51.8)	79 (63.7)	0.06
Dyslipidaemia	42 (17.9)	16 (14.5)	26 (21.0)	0.2
Family history of premature CAD	43 (18.4)	21 (19.1)	22 (17.7)	0.8
Smoking	68 (29.1)	30 (27.3)	38 (30.6)	0.5
Anterior wall MI	134 (57.3)	63 (57.3)	71 (57.3)	0.9
Systolic BP <100mmHg	14 (6.2)	8 (7.5)	6 (5.0)	0.4
Heart rate >100 bpm	54 (23.8)	26 (24.3)	28 (23.3)	0.8
Prior history of CAD	19 (8.1)	9 (8.2)	10 (8.1)	0.9
Cardiac arrest at presentation	13 (2.8)	8 (3.0)	5 (2.5)	0.2
Killip I at presentation	195 (83.3)	95 (86.4)	100 (80.6)	0.2
NIV stress testing	96 (41.0)	39 (39.9)	57 (46.0)	0.07
LVEF % (n=464)	38.2 ± 9.3	38.0 ± 9.5	38.3 ± 9.9	0.8
Diagnostic angiogram	196 (83.8)	95 (86.4)	101 (80.8)	0.3
Angiogram findings (n=196)				
Non obstructive CAD	10 (5.1)	4 (4.2)	6 (5.9)	0.01
Left main trunk	5 (2.6)	4 (4.2)	1 (1.0)	
2/3VCAD including Prox LAD	42 (21.4)	11 (11.6)	31 (30.7)	
2/3VCAD excluding Prox LAD	34 (17.3)	18 (18.9)	16 (15.8)	
1VCAD including Prox LAD	105 (53,6)	58 (61,1)	47 (46,5)	
In-hospital death	4 (1.7)	1 (0.9)	3 (2.4)	0.5

CAD: Coronary artery disease , MI: Myocardial infarction,
NIV: Non-invasive ischemia and viability, LVEF: Left ventricular ejection fraction,
LAD: Left anterior descending artery

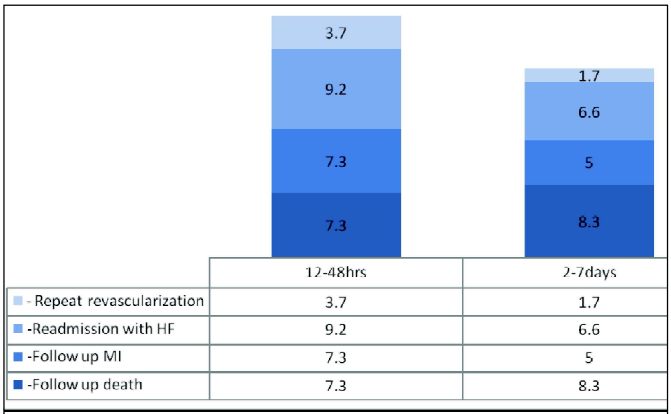


Figure-2: Frequency distribution of major adverse cardiac events (MACE) components at follow-up according to time of presentation.

late group underwent revascularization (53[48.2%] vs. 49[39.5%]) (p>0.05). PCI was significantly more common in early-late group [46 (41.8%)] compared to late-late [27(21.8%)] whereas coronary artery bypass grafting (CABG) was preferred mode of revascularisation in late-late group [22(17.7%)] compared to early-late [7(6.4%)]. Most PCIs; 60(82.2%), were performed during index hospitalisation, while more than 11(38%) CABGs were performed as outpatients within four weeks of discharge. Patent infarct related artery (IRA) was present in 45 (61.6%) of all PCIs).

Dual antiplatelet therapy (DAPT) was utilised in 178(77.4%) subjects at discharge and (227(97.1%) patients were discharged on at least one anti-platelet (Table 2). Median length of stay was 4 days (IQR: 3-5 days). There were 4(1.7%) hospital deaths in total; all were cardiac. There was no statistically significant association between hospital mortality and early-late or late-late presentation (p>0.05).

Out of 230 patients discharged alive, follow-up was completed for all patients. Median follow-up duration was 23 months (IQR: 13-34 months). Of them, 18(7.7%) died during follow-up period with 16(90%) cardiac deaths. MACE occurred in 45(19.6%) patients (Figure 2). The early-late versus late-late presentation remained non-significant with and without adjustment for key predictors using Cox regression analysis (p>0.05). EF less than 40%, presence of multi-vessel disease, age >50 years at the time of index event, presence of diabetes mellitus (DM), HTN, Killip III or IV on presentation, GDMT prescribed on discharge, revascularisation within 4 weeks of index event and admission within 12-48 hours or beyond were included in the Cox regression modelling. Absence of revascularisation was the only significant predictor for MACE on adjusted regression analysis (adjusted HR: 2.5, 95% CI: 1.2-5.2, p<0.02). Multi-vessel disease showed a marginal trend towards increased MACE (adjusted HR: 1.9, 95% CI: 0.92-3.9, p0.08) while prescription of GDMT combination (at least one anti-platelet along with statin, beta blocker and angiotensin converting enzyme inhibitor-1 / angiotensin receptor blocker [ACE-I / ARB]) had a non-significant protective association with MACE (adjusted HR: 0.5, 95% CI: 0.23-1.1, p=0.09).

Discussion

Among other things, the study found that of the STEMI patients who presented >12 hours after symptom onset, 40% were asymptomatic. Most of the clinical and demographic parameters were equally distributed in early-late and late-late presenters. CAG remained the most common mode of risk stratification (>80%) despite asymptomatic status, and revascularisation was utilised in less than half regardless of the time to presentation. Hospital mortality was low in both early and late presenters. Those who were not revascularised were at 2.5 time higher risk of MACE at two-year follow-up, while early-late or late-late presentation had no impact on follow-up outcomes.

Although the findings suggest that revascularisation >12hrs of symptom onset in asymptomatic STEMI confers benefit in terms of reduced MACE, the results from prior research are varied. Benefits of revascularisation in late STEMI are mainly linked to myocardial viability and / or presence of significant disease in other coronary vessels where revascularisation tend to improve LV remodelling and EF. Even in the setting of acute STEMI, some amount of blood flow might still be present in the infarcted area. Reasons could be presence of collateral blood flow, residual ante grade flow in IRA and stuttering or intermittent occlusion of the IRA. Presence of patent IRA is considered an angiographic marker of myocardial viability.[13] OAT trial in late STEMI where most of the patients had occluded IRA, failed to show benefit of PCI.[14] Conversely, BRAVE 2 trial, the only randomised trial, enrolled early-late STEMI with half of the patients having patent IRA and a quarter had flow through collateral circulation, thus implying myocardial viability. The trial results suggest benefit of late revascularisation in asymptomatic STEMI in terms of infarct size[9] and 4-year all-cause mortality. However, the trial was underpowered

for clinical outcomes.[15,16] In our trial, around 60% of PCI patients had patent IRA and half of the CABG patients had Thrombolysis in Myocardial Infarction (TIMI) flow >0 in IRA, suggesting myocardial viability that may have resulted in favourable outcomes with revascularisation.

Importance of viability and ischemia assessment is vital in risk stratification of stable post-MI patients and is related to improved outcome after revascularisation.[17,18] The Swiss Interventional Study on Silent Ischaemia Type II (SWISS II) trial, based on hypothesis of favourable outcome of revascularisation in silent ischaemia, enrolled 192 patients with recent MI within 3 months if NIV was suggestive of silent ischaemia. The trial results showed 10-year mortality benefit in revascularisation arm.[11] In the current study, 41% patients had revascularisation decisions based on NIV ischaemia / viability testing and almost all of the tested negative patients received GDMT only. Over-representation of benefits of revascularisation in the study might have been due to the presence of ischaemia on NIV testing and patent IRA presumed as a marker of viable myocardium in the revascularised arm, leading to superior cardiovascular outcomes in revascularised arm, and, conversely, worse outcomes in non-revascularised group due to the presence of completed infarct with non-viable myocardium and unfavourable LV remodelling. However, as no definite viability testing, such as cardiac magnetic resonance imaging (MRI), was utilised for viability assessment in the current study, the selection of patients for revascularisation based on presumed viability and improved intermediate-term outcomes in revascularised arm attributable to the presence of viability should be interpreted with caution.

Role of T wave inversion can also be considered in late STEMI. It has been suggested that T inversions are associated with patent IRA, thus implying myocardial viability and likely favourable effect of revascularisation.[9] It is proposed that these electrocardiogram (ECG) changes should be utilised in early risk stratification of late STEMI patient to directly refer them for invasive CAG and revascularisation.

The current study could not demonstrate intermediate-term (23 months) advantages of revascularisation performed within 48 hours versus during 2-7 days post-MI. In addition, overall long-term mortality was 8% in the study population which is much lower than overall STEMI mortality estimated to be around 20% at 3-year post-index event.[20] This may suggest that stable late presenting patients were a relatively lower-risk population. The burden of such patients is also variable as in some geographical areas with advanced healthcare delivery system, proportion of patients with STEMI presenting late is low (<10%).[21] In other areas with less advanced healthcare systems, such as South Asia, this proportion is around one-third of patients[6] and hence their appropriate and cost-effective management becomes more relevant. Therefore, although European guidelines for STEMI have been updated in favour of mechanical reperfusion as late as 48 hours after symptom onset based on results of BRAVE 2 trials,[9] this may not be necessarily applicable to other regions of the world. To apply these in a resource-poor setup of less-developed countries requires appropriately designed trials including patients from these regions.

There is a need for GDMT, and multi-vessel disease have previously been proved as important predictors of long-term MACE, but the current study failed to reach statistical significance in an adjusted analysis likely due to small sample size.[22,23]

The Major limitation of the current study is that it is based on the registry of a single centre. However, the study is the first to report finding in late STEMI case from this geographical area. The data is thoroughly validated and the follow-up is complete.

Conclusion

A significant proportion of late STEMI patients had no impending indication for mechanical reperfusion. There is need to distinguish those who can potentially benefit from revascularisation. Use of clinical judgment, identifying salvageable myocardium using surrogates of patent IRA or non-invasive viability assessment or identification of high-risk multi-vessel disease should be emphasised to achieve optimal outcomes in individual patients.

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