ORIGINAL RESEARCH

Impact of Multivessel Coronary Artery Disease on Long Term Prognosis in Patients with ST-segment Elevation Myocardial Infarction

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ABSTRACT

Background: A significant proportion of patients with ST-segment elevation myocardial infarction (STEMI) have multivessel coronary artery disease (MVD), and they are at high risk for recurrent cardiac events. The **aim** of the present study was to analyze the impact of MVD on long-term cardiovascular mortality in STEMI patients treated with primary percutaneous coronary intervention (pPCI). **Method:** This study included 3,115 consecutive STEMI patients hospitalized in the Coronary Care Unit of the Clinical Centre of Serbia, between November 2005 and January 2012. Patients were divided in two groups: MVD and no MVD. MVD disease was defined as stenosis greater than 50% by visual assessment in more than one major coronary artery. Primary PCI was limited to the infarct-related artery (IRA). Cardiovascular mortality was defined as any death from cardiovascular reason (myocardial reinfarction, low-output heart failure, and sudden death). Patients presenting with cardiogenic shock were excluded. Patients were followed-up for 6 years after enrollment. **Results:** Among 3,115 analyzed patients, 1,352 (43.4%) patients had no MVD and 1,763 (56.6%) had MVD; among patients with MVD, 926 (52.6%) had two-vessel disease and 837 (47.4%) had three-vessel disease. Compared with patients with single-vessel disease, patients with MVD were older, had longer pain duration, and presented more often with heart failure; they were more likely to have previous coronary artery disease, diabetes, hypertension, and chronic kidney disease; post-procedural flow TIMI <3 was more frequently observed in patients with MVD than in patients with no MVD (5.9% vs. 3.1%, p <0.001). Patients with MVD had lower left ventricular ejection fraction than patients with single-vessel disease: 45% (interquartile range [IQR] 40¬–55%) vs. 50% (IQR 43–55%), p <0.001. Revascularization of non-IRA lesions was performed at index hospitalization in 1,075 (61%) patients, and in 602 (34.1%) patients revascularization was performed in the first few months after pPCI (median 1.5 months, IQR 1–2.5 months); coronary artery bypass grafting was performed in 291 (18.4%) patients and PCI (with stent implantation) in 1,368 (81.6%) patients. Six-year cardiovascular mortality was significantly higher in patients with MVD than in patients with single-vessel disease (10.4% vs. 4.6%, p <0.001). In multivariate Cox regression analysis, MVD remained an independent

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predictor for 6-year cardiovascular mortality (HR 1.55, 95% CI 1.11–2.06, p = 0.041). **Conclusion:** In STEMI patients treated with pPCI, the presence of MVD remained an independent predictor for higher long-term cardiovascular mortality despite early revascularization of the remaining stenosis in non-IRA.

INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is the reperfusion of choice for the treatment of patients with ST-segment elevation myocardial infarction (STEMI). Primary PCI improves survival compared with thrombolysis, mainly due to the large percentage of restoration of TIMI 3 flow through the infarct-related artery (IRA).[1–4] Concomitant atherosclerosis in coronary vessels other than the IRA is observed in a significant number of STEMI patients.[1,2,4–9] According to the current guidelines, the standard therapeutic approach in STEMI patients with multi-vessel coronary artery disease (MVD) is represented by pPCI of the IRA in acute settings, followed by the subsequent revascularization of other lesions during the same hospitalization or, rarely, within the first month following discharge.[8,10] A small number of patients are treated conservatively (medically), unless recurrent ischemia occurs.[3] Many studies so far have shown worse outcomes for STEMI patients with MVD compared to STEMI patients with single-vessel coronary artery disease (SVD) in short- and medium-term follow-up, regardless of the reperfusion strategy.[1,3,4–6] In STEMI subjects with MVD who undergo interventional therapies with angioplasty, a worse reperfusion rate is also observed when compared with patients with SVD.[2,4,6] The mechanism through which MVD adversely affects the outcome of patients with STEMI is multifactorial and relatively poorly characterized.[1,6] To our best knowledge, the longer term impact of MVD on patient outcomes for STEMI treated with contemporary pPCI has not been extensively investigated so far.

The aim of the present study is to analyze the impact of MVD on long-term cardiovascular mortality in STEMI patients treated with pPCI.

METHODS

The present study used data from the prospective Clinical Centre of Serbia STEMI Registry, for a subgroup of 3,115 consecutive patients who were hospitalized between November 2005 and January 2012. The purpose of the prospective Clinical Centre of Serbia STEMI Registry has been published elsewhere.[11] In brief, the objective of the registry is to gather complete and representative data on the management and short- and long-term outcomes of patients with STEMI who have undergone primary PCI at the Centre. All consecutive patients with STEMI, aged >18 years, who had been admitted to the Coronary Care Unit after undergoing pPCI at the Centre, were included in the Registry. For this study, patients with cardiogenic shock at admission were excluded.

The study protocol was approved by the local research ethics committee. The research was performed in accordance with the code of ethics of the World Medical Association's Declaration of Helsinki. All patients signed a written informed consent before being enrolled in the study.

Coronary angiography was performed via the femoral approach. Aspirin, 300 mg, and clopidogrel, 600 mg, were administered to all eligible patients before pPCI. Selected patients, with visible intracoronary thrombi, were also given the glycoprotein (GP) IIb/IIIa receptor inhibitor tirofiban during pPCI. Flow grades were assessed according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Primary PCI was limited to the culprit lesion (IRA) in acute settings. After pPCI, patients were treated according to current guidelines.

The extent of coronary artery disease (CAD) was graded as no MVD and MVD (bi-vascular of three-vascular atherosclerotic involvement). MVD was considered in case of a vascular stenosis of more than 50%, as assessed by visual analysis of the coronary angiography, in more than a single coronary artery. The indication for revascularization (PCI or aorto-coronary bypass grafting, CABG) of additional lesions was decided by the clinician assigned to the case, in collaboration with the interventional cardiology physician. Reperfusion therapy for associated atherosclerotic lesions was achieved during the index hospitalization period, or during the second follow-up.

Demographic, baseline clinical, angiographic, and procedural data were collected and analyzed. Baseline renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at admission (before pPCI). The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Echo-

cardiographic examination was performed within the first 3 days following pPCI. Left ventricular ejection fraction (LVEF) was assessed according to the biplane Simpson method, in classical two- and four-chamber apical projections.

Patients were followed-up for 6 years after enrollment. Follow-up data were obtained by scheduled telephone interviews and out-patient visits. Cardiovascular death included any death due to cardiac cause (myocardial reinfarction, low-output heart failure, fatal arrhythmia) and sudden death.

STATISTICAL ANALYSIS

Continuous variables were expressed as the median (med), with the interquartile range (IQR) between the 25th and 75th quartiles, whereas categorical variables were expressed as frequency and percentage. Analysis for normality of data (continuous variables) was performed using the Kolmogorov-Smirnov test. Baseline differences between groups were analyzed using the Mann-Whitney test for continuous variables and the Pearson χ^2 test for categorical variables. The Kaplan-Meier method was used for constructing probability curves for 6-year cardiovascular mortality, whereas the difference between the groups was tested with the Log Rank test. Multiple logistic regression analysis was used for identifying predictors

TABLE 1. Baseline characteristics and therapy at discharge of the analyzed patients according to presence of MVD

Characteristics	No MVD N = 1,352	MVD N = 1,763	p value
Age, years med (IQR)	56 (49–75)	62 (55–72)	<0.001
Male, n (%)	974 (72)	1,264 (71.6)	0.409
Previous MI, n (%)	80 (5.9)	247 (14)	<0.001
Previous CABG, n (%)	17 (1.2)	30 (1.7)	0.116
Previous PCI, n (%)	20 (1.5)	30 (1.7)	0.235
Diabetes, n (%)	197 (14.6)	413 (23.4)	<0.001
Hypertension, n (%)	814 (60.2)	1,276 (72.4)	<0.001
HLP, n (%)	804 (59.5)	1,086 (61.6)	0.229
Smoking, n (%)	807 (59.7)	852 (48.4)	<0.001
Pain duration, hours med (IQR)	2 (1.5–4)	3 (2–5)	<0.001
HF at admission, n (%)	117 (8.7)	274 (15.5)	<0.001
Systolic BP (mmHg) at admission, med (IQR)	135 (120–150)	140 (120–150)	0.081
HR at admission, med (IQR)	78 (70–80)	80 (70–90)	0.320
Anterior infarction, n (%)	566 (41.8)	691 (39.2)	0.409
Preprocedural flow TIMI 0, n (%)	928 (68.7)	1,297 (73.5)	0.309
Postprocedural flow TIMI <3, n (%)	42 (3.1)	104 (5.9)	<0.001
IIb/IIIa inhibitors, n (%)	495 (36.6)	665 (37.6)	0.750
LVEF %, med (IQR)	50 (43–55)	45 (40–50)	<0.001
CKmax, med (IQR)	1,868 (921–3,568)	1,892 (967–3,460)	0.268
Troponin I (μg/L), med (IQR)	30.77 (8.05–79)	31.26 (9.71–94.76)	0.169
eGFR <60 mL/min/m^2	143 (10.6)	346 (19.6)	<0.001
In-hospital death, n (%)	30 (2.2)	101 (5.8)	<0.001
Therapy at discharge[*]			
Beta blockers, n (%)	1,164 (86.1)	1,415 (80.3)	0.757
ACE inhibitors, n (%)	1,074 (79.4)	1,330 (75.4)	0.230
Statins, n (%)	1,155 (85.4)	1,399 (79.4)	0.636
Diuretics, n (%)	165 (12.2)	313 (17.8)	<0.001
Nitrates, n (%)	125 (9.2)	335 (19)	<0.001
Antiarrhythmics, n (%)	42 (3.1)	40 (2.3)	0.229
Ca antagonist, n (%)	45 (3.4)	60 (3.4)	0.649

[*]all patients had aspirin and clopidogrel at discharge; MVD – multivessel disease; MI – myocardial infarction; CABG – aortocoronary bypass grafting; HLP – hyperlipidemia; HF – heart failure; BP – arterial blood pressure; HR – heart rate; CK – creatinine kinase; eGFR – estimated glomerular filtration rate; LVEF – left ventricular ejection fraction; ACE – angiotensin converting enzyme
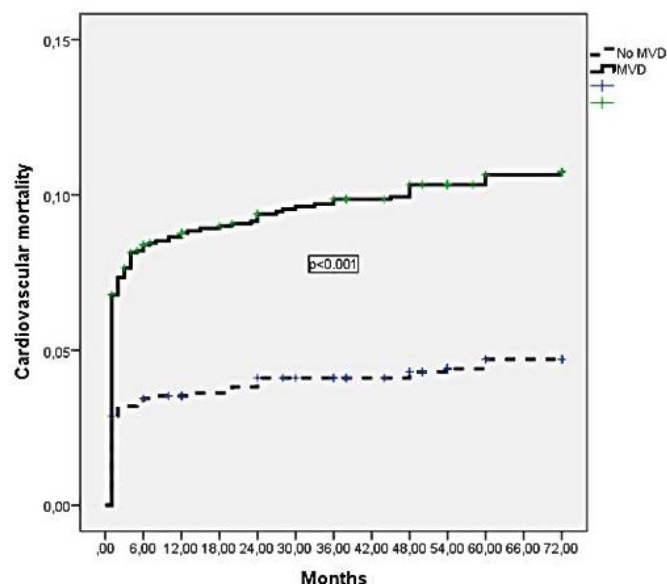
FIGURE 1. Kaplan-Meier curves estimating probability for six-year cardiovascular mortality in patients with MVD and no MVD

for cardiovascular mortality. Multivariate Cox regression analysis (backward method, with p <0.10 for entrance into the model) was used for identifying independent risk factors for the occurrence of 6-year cardiovascular mortality. SPSS statistical software, version 19.0, was applied (SPSS Inc, Chicago, IL).

RESULTS

The average age of all analyzed patients was 59 (52–69) years. From the total of 3,115 analyzed patients, 2,238 (71.8%) were men and 877 (28.2%) were women; 1,352 (43.4%) patients had no MVD and 1,763 (56.6%) had MVD. Among patients with MVD, 926 (52.6%) had two-vessel

disease and 837 (47.4%) had three-vessel disease. Compared with patients with no MVD, patients with MVD were older, had longer pain duration (before the first medical contact), and presented more often with heart failure (Killip class II and III); they were more likely to have diabetes, hypertension, renal dysfunction, and post-procedural flow TIMI <3 through the IRA. EF was lower in patients with MVD compared to patients without MVD. Demographic, clinical, laboratory echocardiographic, angiographic, procedural characteristics of analyzed patients and discharge therapy according to the presence of MVD are presented in Table 1.

In 1,075 (61%) patients, revascularization of the remaining stenosis was performed at index hospitalization (median 10.5 days, IQR 7.4–13.5 days), in 602 (34.1%) patients, revascularization was performed during the second visit (median 1.5 months, IQR 1–2.5 months), while 86 (4.9%) patients were treated medically. Among patients in whom revascularization was performed, CABG was performed in 308 (18.4%) patients and PCI (with stent implantation) in 1,368 (81.6%) patients.

Cardiovascular mortality at 6 years was significantly higher in patients with MVD than in patients with no MVD (10.4% vs. 4.6%, p <0.001), as presented in Figure 1.

After adjustment for variables defined in univariate analysis as predictors of cardiovascular mortality, MVD remained an independent predictor of cardiovascular mortality during the 6-year follow-up.

DISCUSSIONS

The results of the present study confirmed that STEMI patients with MVD had higher long-term mortality compared to STEMI patients with no MVD. After multivariate

TABLE 2. Association between MVD and 6-year cardiovascular mortality (univariate analysis and multivariate Cox regression analysis)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Postprocedural flow TIMI <3	9.63 (6.15–14.23)	<0.001	4.23 (2.35–4.78)	<0.001
Killip II and III at admission	9.35 (6.85–12.76)	<0.001	3.23 (3.31–5.36)	<0.001
RD	5.15 (3.79–6.99)	<0.001	1.75 (1.29–2.49)	0.024
MVD	2.42 (1.74–3.36)	<0.001	1.55 (1.11–2.06)	0.041
Diabetes	2.13 (1.52–2.89)	<0.001		
Anterior infarction	2.18 (1.18–2.92)	<0.001		
Previous MI	1.99 (1.35–2.93)	<0.001		
Age	1.07 (1.06–1.08)	<0.001	1.03 (1.02–1.04)	<0.001
EF	0.86 (0.84–0.88)	<0.001	0.90 (0.70–0.99)	<0.001

MI – myocardial infarction; EF – ejection fraction; RD – renal dysfunction; MVD – multivessel disease

adjustment, MVD remained an independent predictor for long-term mortality (up to six years) in analyzed patients. The percentage of patients with MVD in our study (56.6%) was similar to the previously published studies and registry analyses in which the percentage of patients with MVD range from 50% to 65%.[1–5] The clinical characteristics of our patients with MVD are also in consistence with data found in the literature.[1,2,5] Patients with MVD are generally an older and sicker cohort (e.g., presenting more frequently diabetes, renal dysfunction, previous coronary disease etc.).[1–4] This finding can partially explain their worse outcome compared to patients with no MVD. However, we found an independent association between MVD and long-term cardiovascular mortality. We also found a poorer success rate of reperfusion (post-procedural TIMI flow) in patients with MVD, and this is also in consistence with previously published data.[3,4,6] Our patients with MVD had lower EF than patients without MVD, which could strongly influence survival, but the enzymatic infarct size did not differ between groups. This may suggest that patients with STEMI and MVD had left ventricular dysfunction before the index event as a consequence of their coronary artery disease.[2]

Mortality rates and the independent prognostic impact of MVD on long-term mortality in our study are in consistence with data found in the literature. In a study by Lekston *et al.*, MVD was an independent predictor of 5-year mortality in STEMI patients, predominantly treated with pPCI (around 30% of patients were treated with thrombolysis, with subsequent early PCI) in this study.[2] This finding is in consistence with our results and also confirms that the presence of MVD adversely affects long-term prognosis in STEMI patients, regardless of reperfusion strategy. In a study by Park *et al.* it was found that the presence of MVD was significantly associated with an increased risk for 30-day and 1-year mortality in patients treated with pPCI.[5] Similar results are reported in studies by De Luca *et al.* and Sorajja *et al.*[4,12] However, there are no data about the prognostic impact of MVD after 1 year in these studies. In a study by de Waha *et al.*, it was reported that the presence of MVD in patients with STEMI treated with contemporary pPCI is independently associated with the occurrence of composite endpoint major adverse cardiac events (MACE) (comprising reinfarction, all-cause death, and newly developed heart failure) at the one-year follow-up. These results could be explained by an important correlation between MVD and increased rates of reinfarction, while the presence of MVD did not predict the all-cause mortality rates of newly developed heart failure.[1]

In more than 60% of our patients with MVD, revascularization of the remaining stenosis was performed during the index hospitalization. It is well known that preventive PCI to treat non-IRA stenosis early after pPCI reduces the risk of cardiac death, non-fatal reinfarction, or refractory angina by up to 65%.[13] Despite this, a higher risk for increasing cardiovascular death rates are probably influenced by several factors, and not just by the presence of other significant coronary stenoses.[1] MVD can be understood as a marker of more advanced CAD and diffuse atherosclerosis, slow flow in critically narrowed non-IRA, and the presence of stunned and hibernating myocardium. That is why the early revascularization of the remaining stenosis, as suggested by current guidelines, is very important.[1–4,10,13] In acute coronary syndromes, plaque instability may not be limited to the culprit lesion, but may rather involve large areas of the coronary tree because of systemic endothelial dysfunction and higher platelet activity.[3,4,8] Thus, patients with MVD should benefit of a closer monitoring and follow-up strategy, both during hospitalization and after discharge. This approach should include early and more intense therapeutic measures for classic atherosclerosis risk factors, as well as recurrent ischemia testing, for a longer period of time than just during the first weeks and months after the acute event.[1]

STUDY LIMITATIONS

This is an observational, prospective, single-center study; however, it included consecutive patients, limiting possible selection bias. The decision whether to revascularize the non-culprit lesions and the timing of revascularization were decided by the interventional cardiologist, who was not part of the study protocol. MVD assessment was performed only by analyzing the invasive coronary angiography, without evaluating the functional significance of the coronary lesions, which could have provided additional information (e.g., fractional flow reserve). Nevertheless, most clinical trials on STEMI in MVD patients are based on angiographic judgment only. Primary PCI was predominantly performed using bare metal stents. Patients were treated with clopidogrel; there were no patients treated with more recently developed antithrombotic drugs (since ticagrelor was not available for routine administration to patients at the time of their entry into the Registry), and this could have influenced the prognosis of the patients, i.e. reduce the occurrence of cardiovascular deaths. We excluded patients presenting with cardiogenic shock; by definition, these patients fall into the highest risk category, and their treatment differs from the overall pPCI population.[10]

Also, the protocol of the study stipulated that patients with cardiogenic shock at admission should have separate risk stratification and a different treatment strategy.11 In this study we did not analyze whether the relationship between MVD and mortality would be different in case of other treatment strategies.

CONCLUSIONS

In STEMI patients treated with pPCI, the presence of MVD is an independent predictor for higher long-term cardio-vascular mortality, despite early revascularization of the remaining stenosis in non-IRA.

CONFLICT OF INTEREST

Nothing to disclose.

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