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ST-elevation myocardial infarction in young (<50 years old) patients. Clinical characteristics and long-term follow-up

Luís Manuel Costa e Silva

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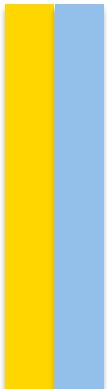

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**

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ST-elevation myocardial infarction in young (<50 years old) patients. Clinical characteristics and long-term follow-up

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Abstract

Background

The burden associated with the occurrence of a ST-segment Elevation Acute Myocardial Infarction (STEMI) in a young person is quite substantial, being these patients faced with the possibility of having a Major Adverse Cardio Cerebrovascular Event (MACCE) post STEMI at a younger age. Data regarding the clinical outcomes after the first STEMI and eventual predictors of a MACCE in this group of people is quite limited.

Aim

Our aim was to assess the clinical features and predictors of a MACCE at 2-year follow-up of a consecutive series of young STEMI patients (<50 years old) who underwent Primary Percutaneous coronary Intervention (PCI) from January 1, 2008, and June 31, 2018.

Results

From 1207 STEMI patients, two-hundred (16,6%) were <50 years old and comprised our studied sample.

Smoking (near 90% were active smokers) and dyslipidaemia were the most prevalent risk factors and 11.3% had a family history of Acute Myocardial Infarction (AMI) in a first degree relative. The median total ischemic time was 3.3hours. From PCI to follow-up, 23 (11.5%) developed a MACCE. Nine (4.5%) needed a Target Lesion Revascularization (TLR), four (1.5%) developed a new AMI and three (2%) a stroke. Ten (5%) patients died, seven due to heart failure, one after a new AMI, one after a TLR and another after a stroke. Most deaths (75%) occurred during index hospitalization. At 2-year follow-up, the only found independent predictor of a MACCE was a higher Killip-Kimball class during hospitalization (Hazard Ratio [HR], 15.2; 95% Confidence Interval [CI], 2.90–79.9; P = 0.001).

Conclusion

In younger STEMI-patients, acute heart failure complicating STEMI was independently related to worst outcomes. Smoking cessation and treatment of dyslipidemia may reduce the burden of premature coronary artery disease.

Keywords

Myocardial infarction, ST-elevation myocardial infarction, risk factors, survivorship.

Abbreviation index

ACEi: Angiotensin-Converting Enzyme inhibitor
AMI: Acute Myocardial Infarction
ARA: Angiotensin Receptor Antagonist
BBs: Beta-Blocker
Ca2+: Calcium
CAD: Coronary Artery Disease
CI: Confidence Interval
CK: Creatine-Kinase
CVD: Cardiovascular Disease
DALYs: Disability Adjusted Life Years
HR: Hazard Ratio
IHD: Ischemic Heart Disease
IQR: Interquartile Range
LVEF: Left Ventricle Ejection Fraction
MACCE: Major Adverse Cardio Cerebrovascular Event
OAD: Oral Antidiabetic
PAD: Peripheral Arterial Disease
PCI: Primary Percutaneous coronary Intervention
PIA: Pre-Infarct Angina
SPSS: Statistical Package for Social Sciences
STEMI: ST-segment Elevation Acute Myocardial Infarction
TLR: Target Lesion Revascularization
WHO: World Health Organization

Index

Introduction

Acute Myocardial Infarction (AMI) is one of the leading causes of death worldwide[1 2 3 4]. According to the World Health Organization (WHO), the leading cause of death in 2019 was Ischemic Heart Disease (IHD), accounting for about 16% of all deaths[5]. Despite being a more prevalent disease in the elderly, the number of Disability Adjusted Life Years (DALYs) and the associated burden of premature death raise a greater clinical interest in the study of AMI in young patients[1 3]. Furthermore, its prevalence in this group of patients is not negligible, and it is estimated that it may correspond to 10% of all AMIs[6 7 8].

Regarding the risk factors for AMI, young patients are generally male, smokers, overweight and with a family history (possibly premature) of acute events or other Cardiovascular Diseases (CVDs), but without a personal history of angina, AMI, or congestive heart failure[1 4 8 9]. Therefore, a high degree of suspicion is critical for the diagnosis. Despite being more prevalent in males, the female gender may be more prone to cardiovascular events, although evidence in this field is scarce[10]. Other risk factors also commonly seen in young people that may contribute to premature development of coronary atherosclerosis are diabetes, familial hypercholesterolemia, hyperhomocysteinemia or emotional stress[7 11]. However, for many risk factors listed above (namely a family history of CVDs), an association with a higher probability of AMI that does not consider traditional risk factors has not yet been demonstrated[4].

The short and long-term post-AMI prognosis in young people is generally favourable[12]. However, as smoking is the strongest independent predictor of a Major Adverse Cardio Cerebrovascular Events (MACCE) in young people and given its high prevalence in this group of patients, a potential worse prognosis is highly probable[13]. Furthermore, some argue that younger patients may respond not so good to dual antiplatelet therapy, whereas a suboptimal use of Beta-Blockers (BBs) and Angiotensin-Converting Enzyme inhibitors (ACEis) may also contribute to a worse prognosis[2 12].

Given the lack of data in this patient population, we sought to assess the clinical features which were related to MACCE in a 2-year follow-up period starting from admittance, in a series of young patients with a ST-segment Elevation Acute Myocardial Infarction (STEMI), who underwent Primary Percutaneous coronary Intervention (PCI) in a tertiary care centre[12].

Methods

Studied population and definitions

We conducted a retrospective study including adults with a diagnosis of STEMI treated with PCI, between January 1, 2008, and June 31, 2018. Considering our focus on young STEMI patients and given the range of age cut-offs used in different surveys, we included in our studied population STEMI patients aged less than 50 years old[4 6 8 12].

All STEMI patients entered an anonymized prospective database which included demographic, clinical, and procedural characteristics. Data were obtained by medical chart review. According to the 4th Universal Definition of Myocardial Infarction, STEMI was defined as typical chest discomfort or other ischemic symptoms, associated with new ST-segment elevations in two contiguous leads or new bundle branch blocks with ischemic repolarization patterns. The ST-elevation cutpoints (measured at the J-point) were considered as follows: in leads V2–V3 ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years; ≥1.5 mm in women regardless of age, and ≥1 mm in all the other leads[14]. In addition, to be included in this study, all patients were required to have a culprit lesion identified and to have undergone PCI. Patients' treatment strategy followed per current guidelines[15].

Clinical and demographic characteristics are detailed in Table I. Pre-Infarct Angina (PIA) was diagnosed if a patient had arm, jaw, or chest pain in the preceding eight days before the diagnosis of STEMI. Total ischemic time and door-to-balloon time were the time elapsed from symptom onset (the time when chest pain became more intense and sustained) and presentation to the hospital or the passage of the coronary guidewire, respectively. Peripheral arterial disease (PAD) was considered if the patient had peripheral claudication and established aorto-iliac or peripheral disease. Left Ventricle Ejection Fraction (LVEF) was calculated by trans-thoracic echocardiography and patients were divided as follows: good to mildly reduced LVEF, if LVEF ≥45%, moderate to severe dysfunction if LVEF <45%.

Clinical follow-up was performed by record-linkage using electronic medical records to check for the occurrence of a MACCE. In our research, we've only considered for MACCE count the first event occurred of the following: death (any cause), cerebrovascular accident (brain imaging was mandatory), new myocardial infarction in any vessel, or Target Lesion Revascularization (TLR — new intervention on target lesion due to angina or ischemia), during the first 2 years after the index STEMI. The study was approved by the hospital ethics committee [2021-321(266-DEFI/274-CE)], and the informed consent for the studied cohort was waived due to the retrospective nature of the analysis.

Statistical analysis

Categorical variables are expressed as absolute values and percentages, comparison was performed by Pearson chi-square. Continuous data are expressed as the median and Interquartile Range (IQR) and were compared using the Mann-Whitney test or the Independent-Samples t test, as suitable. Normality of distribution was assessed from visual inspection of histograms and the Shapiro-Wilk test.

MACCE rates were plotted as Kaplan-Meier curves. To identify the independent predictors of MACCE during the follow-up period we ran a stepwise multivariable logistic regression that included variables with a P <0.25 in the univariable analysis. Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS version 27.0) and a two-tailed P <0.05 was considered significant for all tests.

Results

During the studied period, 1207 STEMI-patients underwent PCI at our centre. Two-hundred and three patients were <50 years old. Because three had a spontaneous coronary dissection, they were excluded from our analysis. Therefore, our sample comprised two-hundred STEMI patients (16.6% out of all STEMI-patients who underwent PCI).

The median age of our sample was 45 years-old and 83.0% of them were men. 48.5% of our patients had three or more risk factors for AMI, being smoking and dyslipidaemia the most prevalent risk factors (87.5% were active smokers and 49.5% had dyslipidaemia). 11.3% had a family history of AMI in a first degree relative. The median duration of symptoms was 3.3hours, and the anterior descendent artery was the culprit vessel in 47.5% of the entire cohort.

Of the 200 STEMI patients, 23 (11.5%) developed a MACCE (Table II – depicts the first MACCE). As shown in Figure 1, nine patients (4.5%) needed a TLR, four (1.5%) developed a new AMI and three (2%) a stroke. Ten patients died (cumulative mortality at follow-up = 5%), seven due to heart failure, one after a new AMI, one after a TLR and another after a stroke (Table III). Most deaths occurred in men (75%, Figure 2) and during hospitalization (75%, Figures 3 and 4). Patients who developed a MACCE had more comorbidities: Diabetes Mellitus (30.4% vs 5.1%), PAD (17.4% vs 3.4%) and were more likely to be medicated before STEMI [i.e., with BBs (17.4% vs 3.4%), Angiotensin Receptor Antagonists (ARAs)/ACEis (26.1% vs 9.6%), or with Oral Antidiabetics (OADs)/insulin (13.0% vs 1.7%)]. They also had lower systolic blood pressure on admission (103mmHg vs 117mmHg), as well as a higher (≥3) Killip-Kimball class during the hospital stay (52.2% vs 2.3%) and a higher (>4) TIMI score for STEMI on arrival (47.8% vs 6.2%). The median

Creatine-Kinase (CK) mass and the median peak CK were also higher (271.1U/L vs 163.3U/L and 2542U/L vs 1874U/L, respectively). (Table I) There were no other significant differences between groups.

Predictors of MACCE

Twelve variables were eligible for multivariable analysis, as shown in Table IV, and the only independent predictor of MACCE was a higher Killip-Kimball class. In our analysis, patients who had developed a Killip-Kimball class ≥3 during the hospital stay were approximately 15 times more likely to develop a MACCE in a 2-year period (Hazard Ratio [HR], 15.2; 95% Confidence Interval [CI], 2.90–79.9; P = 0.001).

Discussion

In several cohorts, young patients with STEMI are generally male, smokers, overweight and with a family history of CVDs[1 4 8 9]. In our cohort, it was interesting to find that only 11.3% of first-degree relatives had CAD. This comes as surprising since some series identified this association as a major risk factor for premature CAD[16]. Alike in other series, smoking was very prevalent and dyslipidaemia was found in nearly half of the population, as well as an anterior infarction. However, statin pre-treatment was present in only 10%[17]. This may highlight the opportunity to review which patients deserve the most from primary prevention with statins. Total ischemic time was slightly more than 3 hours, which is not too large, and it was lower than a previous report from our institution[18]. This may reflect that younger patients are more aware of STEMI symptoms as compared to the overall unselected population.

Our study revealed that, from admission to a 2-year follow-up, 11.5% of our cohort had an event, which is suggestively lower than reported in another retrospective survey, even more if it's taken into consideration its shorter period of follow-up (combined MACCE rates at 1 year of 18.4%[19]). On the other hand, in the same comparison, mortality rates were higher in our study (5% vs 3.2%). However, comparisons should be cautious since follow-up studies in this group of patients are generally reduced and these values may also fluctuate significantly with different age cut-offs.

Our analysis led us to notice the weight depicted by male gender in developing a MACCE. They comprised 83.0% of STEMI patients and 73.9% of MACCE after the index STEMI. Mortality rates were also higher among men (as shown in Figure 2), even though several studies portray the female gender (including young women) as a vulnerable population and with higher mortality following AMI, mainly before hospital discharge[6 7 10]. Still, we must consider a major limitation in our survey: the low event rate.

As observed in Figures 3 and 4, mortality occurred mainly in the short-term after STEMI despite evidence that suggests a drop in survival in much latter stages[1]. As showed not only by our study, but also by a series from our institution, mortality was mostly related to incident heart failure (notwithstanding its prevalence only corresponding to 8% of the entire cohort), emphasizing its importance of being the main cause of death after STEMI in the long run[20]. Although a moderate to severe reduced LVEF on discharge was not an independent variable for 2-year MACCE, this may become apparent in the long term for those patients who survived the acute phase. Moreover, in a multivariate equation where Killip-Kimball class is included, other meaningful variables may turn to be not so relevant. Finally, due to the small event rate in relation to the variables candidate to the multivariate analysis, these results should be interpreted with caution due to model overfitting.

Still in the topic related to MACCE predictors, even though it was shown that people with a MACCE were more likely diabetic and/or with PAD, they had a lower blood pressure profile and were more likely to present themselves in cardiogenic shock, the only found independent predictor of a MACCE was a higher Killip-Kimball class during hospitalization. Despite being able to spoil other variable results in the multivariate equation (like the blood pressure profile), this could also be explained by an overlap of risk factors between groups, which means that, even though some risk factors are more associated with patients more predisposed to have a MACCE, they behave more like risk factors for developing an index STEMI than to develop a MACCE. In other words, diabetes and peripheral artery disease may be a proxy for a larger coronary plaque burden, rendering these STEMI-patients to a worse prognosis[21].

Limitations

The major limitation of our study is the relatively small observational sample, which may undermine covariate adjustment and limit its conclusions and generalization. Also, the 50-year-old cut-off used for the definition of young STEMI is debatable, given the wide range of age cut-offs used, limiting comparisons with other published works. Only taking into consideration patients who underwent PCI is as well a limitation, when we know there are some STEMI-patients who do not go to the hospital or may not be able to reach it (for instance, may have died before admission). Another limitation is the lack of information collected regarding some non-traditional cardiovascular risk factors usually only seen in young patients, like familial hypercholesterolemia, hyperhomocysteinemia or connective tissue disorders[7 11]. Lastly, being a single-centre cohort study, generalization should be cautious.

Conclusion

Our study found that young STEMI patients still have an adverse event rate of 11.5%, and a cumulative mortality of 5%. Acute heart failure complicating STEMI was independently related to worst outcomes. Alike in other series, a large proportion of young STEMI-patients presents with anterior infarction. It cannot be overemphasized that all measures to further decrease total ischemic time and to adopt preventive measures like smoke eviction and dyslipidemia treatment are of paramount importance to improve prognosis. Further analyses are required to determine whether more risk factors associated with MACCE can predict their development in young STEMI patients.

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Table I. Baseline characteristics of STEMI patients

	All patients (n=200)	***MACCE (n=23, 11.5%)***	***No MACCE (n=177, 88.5%)***	***P-value***
Median age (IQR), years	45 (42-47)	47 (43-49)	45 (42-47)	0.054
Men, n (%)	166 (83.0)	17 (73.9)	149 (84.2)	0.348
Medical history, n (%)				
AMI	11 (5.5)	3 (13.0)	8 (4.5)	0.230
PIA	53 (26.5)	5 (21.7)	48 (27.1)	0.765
Family history of CVD	45 (22.6)	1 (4.3)	44 (25.0)	0.050
1st grade family history of AMI	20 (11.3)	1 (4.3)	19 (12.3)	0.438
<50years	12 (6.8)	1 (4.3)	11 (7.1)	0.958
PAD	10 (5.0)	4 (17.4)	6 (3.4)	0.017
Smoking habits	175 (87.5)	20 (87.0)	155 (87.6)	1.000
Diabetes mellitus	16 (8.0)	7 (30.4)	9 (5.1)	<0.001
Hypertension	60 (30.0)	8 (34.8)	52 (29.4)	0.772
Obesity	31 (15.5)	1 (4.3)	30 (16.9)	0.206
Dyslipidaemia	99 (49.5)	10 (43.5)	89 (50.3)	0.695
Nº of risk factors, n (%)				0.788
1	43 (21.5)	6 (26.1)	37 (20.9)	
2	51 (25.5)	4 (17.4)	47 (26.6)	
≥3	97 (48.5)	12 (52.2)	85 (48.0)	
Medication before STEMI, n (%)				
BB	10 (5.0)	4 (17.4)	6 (3.4)	0.017
ACEi/ARA	23 (11.5)	6 (26.1)	17 (9.6)	0.047
Ca^{2+} Channel-Blocker	8 (4.0)	2 (8.7)	6 (3.4)	0.512
Statin	21 (10.5)	5 (21.7)	16 (9.0)	0.132
Nitrate	4 (2.0)	0 (0.0)	4 (2.3)	1.000
Antiplatelet agents	9 (4.5)	3 (13.0)	6 (3.4)	0.117
OADs/insulin	6 (3.0)	3 (13.0)	3 (1.7)	0.019
At admission				
Median total ischemic time (IQR), hours	3.3 (2.2-6.0)	3.5 (2.0-5.8)	3.2 (2.2-6.0)	0.960
Median door-to-balloon time (IQR), hours	1.0 (0.7-1.9)	1.0 (0.8-2.5)	1.0 (0.7-1.8)	0.413
Median creatinine clearance (IQR), mL/min	115.5 (96.0-139.6)	113.0 (85.7-126.7)	117.0 (97.7-141.0)	0.094
Median hemoglobin (IQR), g/dL	14.7 (13.8-15.7)	14.7 (13.3-15.1)	14.7 (13.8-15.7)	0.240
Median Systolic pressure (IQR), mmHg	115 (105-130)	103 (88-130)	117 (105-130)	0.033
Killip-Kimball class ≥3, n (%)	16 (8.0)	12 (52.2)	4 (2.3)	<0.001
GRACE score >170, n (%)	89 (46.1)	14 (66.7)	75 (43.6)	0.077
TIMI score >4, n (%)	22 (11.0)	11 (47.8)	11 (6.2)	<0.001
Anterior descendent artery as culprit, n (%)	95 (47.5)	13 (56.5)	82 (46.3)	0.485
During hospitalization (IQR)				
Median nº of days	5 (4-7)	6 (3-11)	5 (4-7)	0.539
Median peak troponin, nanog/mL	4.1 (2.5-7.6)	7.5 (4.2-10.7)	4.0 (2.4-7.4)	0.054
Median CK mass, U/L	181.0 (63.0-302.0)	271.1 (171.2-427.5)	163.3 (58.8-300.0)	0.021
Median peak CK, U/L	1896 (1135-3604)	2542 (1716-5543)	1874 (1120-3292)	0.033
Median peak creatinine[a], mg/dL	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.721
Median hemoglobin minimum, g/dL	13.6 (12.5-14.3)	13.0 (11.9-13.9)	13.6 (12.5-14.4)	0.093
At discharge, n (%)				
BB	174 (91.1)	13 (86.7)	161 (91.5)	0.876
ACEi	119 (62.3)	10 (66.7)	109 (61.9)	0.932
Statin	187 (97.9)	14 (93.3)	173 (98.3)	0.727
LVEF <45%	107 (56.6)	12 (80.0)	95 (54.6)	0.102
Right Ventricle affection	47 (24.7)	2 (11.1)	45 (26.2)	0.262

[a] Independent-Samples T test

Abbreviations: ACEi, Angiotensin-Converting Enzyme inhibitor; AMI, Acute Myocardial Infarction; ARA, Angiotensin Receptor Antagonist; BB, Beta-Blocker; Ca^{2+}, Calcium; CK, Creatine-Kinase; CVD, Cardiovascular Disease; IQR, Interquartile Range; LVEF, Left Ventricle Ejection Fraction; MACCE, Major Adverse Cardio Cerebrovascular Event; OAD, Oral Antidiabetic; PAD, Peripheral Arterial Disease; PIA, Pre-Infarct Angina; STEMI, ST-segment Elevation Acute Myocardial Infarction

Table II. Number and type of MACCE

	N
New AMI	3
TLR	9
Stroke	4
Death	7
Total MACCE	23

Abbreviations: TLR, Target Lesion Revascularization – others see *Table I*
First event censored at follow-up

Table III. Cause of death

	N
New AMI	1
TLR	1
Stroke	1
Heart failure	7
Total Deaths	10

Abbreviations: see *Table I and II*
Total mortality at follow-up

Table V. MACCE predictors at 2-year follow-up

	Univariable		*Multivariable (without interaction)*	
	HR (95% CI)	*P-value*	*HR (95% CI)*	*P-value*
Age, years	1.09 (0.98-1.21)	0.109		
Men vs women	0.57 (0.22-1.44)	0.231	2.42 (0.52-11.2)	0.258
Medical history (Yes vs. No)				
AMI	2.68 (0.80-9.02)	0.112	0.39 (0.03-4.45)	0.448
PIA	0.79 (0.30-2.14)	0.647		
Family history of CVD	0.14 (0.02-1.05)	0.056	0.23 (0.03-1.97)	0.179
PAD	4.72 (1.60-13.90)	0.005	2.71 (0.34-21.9)	0.350
Smoking habits	0.95 (0.28-3.19)	0.930		
Diabetes mellitus	6.25 (2.56-15.22)	<0.001	1.50 (0.32-7.05)	0.605
Hypertension	1.25 (0.53-2.95)	0.609		
Obesity	0.24 (0.03-1.80)	0.166		
Dyslipidaemia	0.74 (0.33-1.69)	0.479		
At admission				
Total ischemic time, hours	0.99 (0.93-1.06)	0.809		
Door-to-balloon time, hours	0.99 (0.88-1.13)	0.918		
Creatinine clearance, mL/min	0.99 (0.98-1.00)	0.106	0.99 (0.97-1.01)	0.226
Hemoglobin, g/dL	0.83 (0.67-1.04)	0.101	0.90 (0.57-1.43)	0.655
Systolic pressure, mmHg	0.97 (0.95-0.99)	0.006	1.01 (0.99-1.04)	0.351
Killip-Kimball class (≥3 vs. <3)	23.1 (10.0-53.1)	<0.001	15.2 (2.90-79.9)	0.001
TIMI score (>4 vs. ≤4)	11.2 (4.89-25.5)	<0.001	2.25 (0.34-14.9)	0.402
Anterior descendent artery as culprit	1.54 (0.67-3.50)	0.308		
During hospitalization				
*Peak CK, U/L*10^3*	1.25 (1.07-1.46)	0.005	1.10 (0.86-1.41)	0.440
Hemoglobin minimum, g/dL	0.76 (0.61-0.96)	0.019	0.89 (0.56-1.41)	0.614
At discharge, n (%)				
LVEF <45%	3.24 (0.92-11.49)	0.068		

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio – others see *Table I*

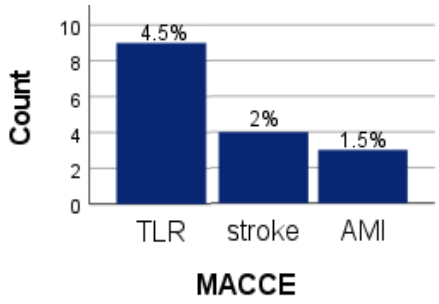

Figure 1. Type of MACCE

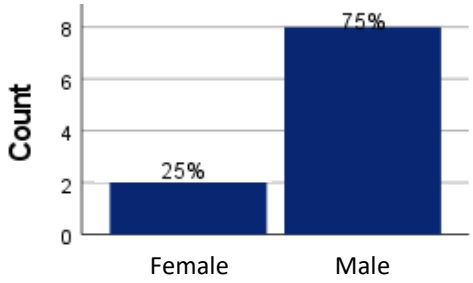

Figure 2. Mortality by gender

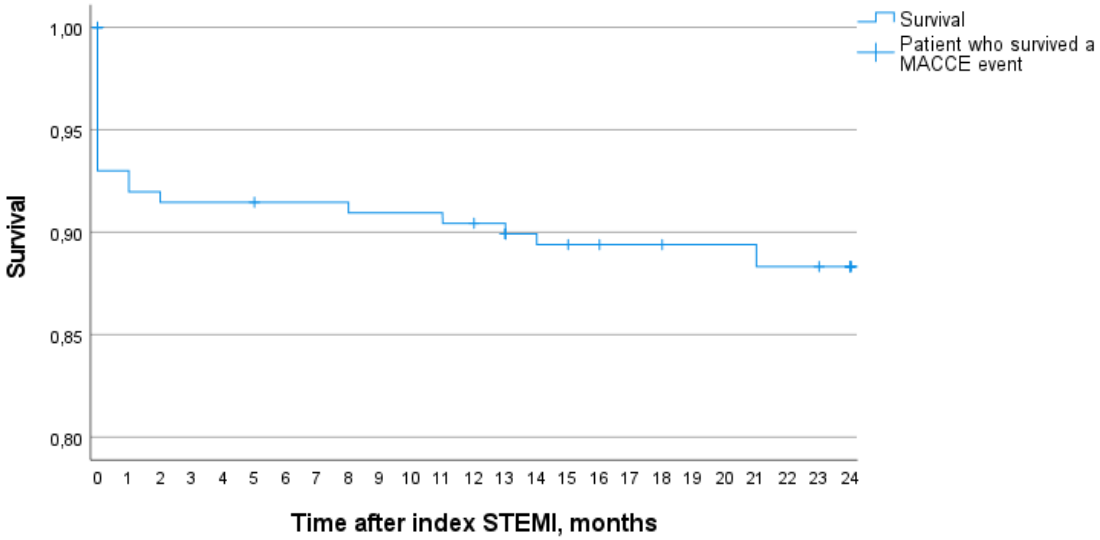

Figure 3. Kaplan-Meier MACCE-free survival curve for a young STEMI patient

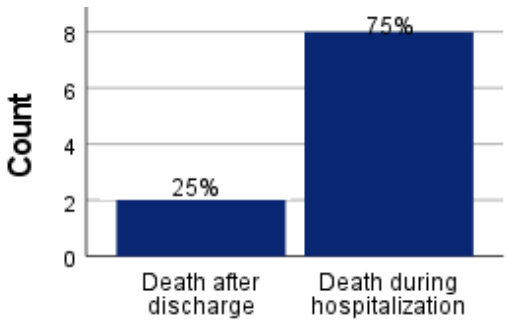

Figure 4. Time of death