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A. Viveiros Monteiro · R. Ramos · A. Fiarresga · L. de Sousa · D. Cacela · L. Patrício · L. Bernardes · C. Soares · R. Cruz Ferreira

Cardiology Department, Hospital of Santa Marta, Lisbon, Portugal

Timing and long-term prognosis of recurrent MI after primary angioplasty

Stent thrombosis vs. non-stent-related reinfarction

Primary percutaneous coronary intervention (PCI) with routine stenting of the culprit lesion and adjuvant double or triple antithrombotic therapy has significantly improved the immediate and short-term outcomes of ST-segment elevation myocardial infarction (STEMI) [1–4]. Although stent implantation was shown to reduce the incidence of reocclusion of the related artery and the need for repeat revascularization, it did not eliminate the risk of in-stent restenosis with recurrent myocardial infarction (MI) after PCI [5, 6]. Stent thrombosis (ST) has also remained a rare but serious cause of recurrent MI, usually followed by a short-term negative impact on mortality and repeat revascularization [7]. In general, ST seems to be associated with worse clinical outcome than MI resultant from *native* coronary thrombosis [7]. However, in the specific population of patients recovering from a STEMI, it is not clear whether the negative outcome associated with ST is different from that of nonstent-related recurrent MI (NSRMI) [9, 10].

The main goal of this study was to evaluate the long-term incidence and impact of recurrent MI after PCI for STEMI by comparing long-term outcomes of ST relative to NSRMI.

Methods

Patient selection, data collection, and clinical follow-up

This is a retrospective analysis from a prospective ongoing single-center acute MI registry. The sole patient inclusion criterion was PCI for STEMI with stent implantation between 2001 and 2007. This study period was selected to permit long-term follow-up. From the 1124 eligible STEMI patients, those who did not receive a stent ($n = 87$) and those lost to follow-up in the first month after the index hospitalization ($n = 12$), mainly nonresidents and foreign citizens, were excluded from further analysis (■ Fig. 1). Thus, the study population consisted of 1,025 patients. Clinical, angiographic, and baseline procedural data using standardized definitions were collected and prospectively entered in a dedicated database. Follow-up data were obtained by a structured telephone interview at 1, 12, 36, and 60 months. Also, every hospital readmission was checked by an adjudication team through chart review for occurrence of MI, ST, stroke, coronary revascularization, bleeding, heart failure, arrhythmias, or death. Mortality data were also obtained through the national death index database and the Portuguese National Patient Registry®. The local ethics institutional review board approved the study and informed consent was given by all subjects.

Definitions and study outcomes

PCI for STEMI was defined as any PCI attempt in a STEMI setting in the first 12 h after presentation, or 24 h for those with ongoing symptoms or 36 h in cases of cardiogenic shock [11]. Cases of rescue PCI after failed thrombolysis were also included. Procedure success was defined as final Thrombolysis in Myocardial Infarction (TIMI) flow III and lesion residual stenosis < 30 % by visual estimation after stent implantation.

Recurrent MI was defined as any MI occurring after the index PCI for STEMI. These events were diagnosed through standard clinical follow-up by clinicians not necessarily involved in the study. An independent research team validated all events. Using established criteria for MI definition [12], recurrent MIs were adjudicated whenever a suggestive clinical, ECG, or imaging finding was reported and there was: (1) at least 20 % increase of the cTn value from baseline level for events occurring in the same index STEMI hospitalization or (2) any elevation of cTn value, for events occurring after index STEMI hospitalization. ST was defined according to the Academic Research Consortium criteria [13] as definite (angiographic or pathological confirmation of thrombus, with or without vessel occlusion, associated with the presence of an acute coronary syndrome) or probable (unexplained death within 30 days of stent implantation or recurrent MI in the stented culprit territory

A. Viveiros Monteiro and R. Ramos contributed equally to this work.

Fig. 1 ▲ Study flow chart. First, occurrence of recurrent MI is determined. Then, long-term prognosis (MACCE) of patients with ST, NSRMI, or no recurrent MI after PCI for STEMI is assessed. Recurrent MI is classified according to time of occurrence after PCI for STEMI as: early = 0–30, late = 31–364, or very late ≥ 365 days. MACE were determined at 60 months after recurrent MI (for patients with ST or NSRMI) or at 60 months after index PCI for STEMI (for patients with no recurrent MI). MACCE major adverse cardiac and cerebrovascular events, MI myocardial infarction, PCI percutaneous coronary intervention, STEMI ST-segment elevation MI, NSRMI nonstent-related recurrent MI, ST stent thrombosis

except when there was no visible stent thrombus and an alternative culprit lesion could be identified by angiographic or pathological examination). NSRMI was defined as any MI occurring after the index PCI for STEMI not fulfilling criteria for definite or probable ST.

The first objective of the study was to determine the incidence of recurrent MI (ST or NSRMI) in the first 60 months after PCI for STEMI. Patients were then divided into three groups according to recurrence of MI. Group A: ST; group B: NSRMI; and group C: no reinfarction. The second purpose was to compare the

outcomes of patients with ST, NSRMI, or no reinfarction. Occurrence of subsequent major adverse cardiac and cerebrovascular events (MACCE) – all-cause death, reinfarction, cerebrovascular accident, and target vessel revascularization (TVR) – were recorded for each group and only those events occurring in the subsequent period after ST or NSRMI were considered. Therefore, for follow-up purposes, time 0 was reset on the date of first recurrent MI for groups A and B. For group C time 0 remained the date of index STEMI (■ Fig. 1). All deaths were defined as cardiac unless unequivocally

proved to be noncardiac. In order to determine the impact of the timing of recurrent MI on prognosis, time elapsed after the index MI was used to classify recurrent MI as early (0–30 days), late (31–360 days), or very late (>360 days).

Statistical analysis

The SPSS version 21 software (SPSS Inc., Chicago, Ill.) was used for computations. Data are expressed as means $\pm$ standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Data distribution

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Timing and long-term prognosis of recurrent MI after primary angioplasty. Stent thrombosis vs. non-stent-related reinfarction**Abstract**

Background. In patients recovering from an ST-segment elevation myocardial infarction (STEMI), it is not clear whether the negative impact of stent thrombosis (ST) is different from a non-stent-related recurrent myocardial infarction (NSRMI). This study sought to assess the long-term incidence and prognostic impact of recurrent myocardial infarction (MI) after percutaneous coronary intervention (PCI) for STEMI by comparing outcomes of ST versus NSRMI.

Patients and methods. From 2001 to 2007, 1025 patients undergoing PCI for STEMI were prospectively followed up. Patients with ST, with NSRMI, and those free from recurrent MI were compared regarding mortality and major

adverse cardiac and cerebrovascular events (MACCE).

Results. Recurrent MI decreased from 37 events per 1000 person/months in the first month to 3.3 events per 1000 person/months after the first year. The cumulative 5-year incidence of ST and NSRMI was 5.27 % and 13.2 %, respectively. MACCE at 60 months after recurrence were not significantly different for patients with reinfarction but were significantly higher than for patients free from any recurrent MI (both log-rank $p < 0.001$). However, the cumulative all-cause death rate did not differ between the three groups (27.8 vs. 26.7 vs. 23.0 %). Compared with ST occurring in the first 30 days after

PCI for STEMI, early NSRMI was associated with a significantly reduced risk for all-cause death (HR, 0.21; 95 % CI, 0.33–3.30) but this association did not persist for recurrent MIs occurring in the late (HR, 1.05; 95 % CI, 0.33–3.30) or very late follow-up periods.

Conclusion. Although ST was associated with a significant increase in adverse events in the early recovery period, in the long term, MACCE and all-cause mortality rates were comparable to those for NSRMI.

Keywords

Myocardial infarction · ST-segment elevation · Primary percutaneous coronary intervention · Stent thrombosis

Timing und Langzeitprognose bei rekurrerendem Myokardinfarkt nach primärer Angioplastik. Stentthrombose vs. nicht stentbedingtem Reinfarkt**Zusammenfassung**

Hintergrund. Bei Patienten, die sich von einem ST-Streckenerhebungsinfarkt (STEMI) erholen, ist es nicht klar, ob sich die negativen Auswirkungen der Stentthrombose (ST) von einem nicht stentbedingten rekurrerenden Myokardinfarkt (NSRMI) unterscheiden. Diese Studie untersuchte die Langzeitinzidenz und die prognostischen Auswirkungen eines rekurrerenden Myokardinfarkts (MI) nach perkutaner koronarer Intervention (PCI) wegen STEMI, indem die ST- mit den NSRMI-Outcomes verglichen wurden.

Patienten und Methoden. Von 2001 bis 2007 wurden 1025 Patienten, die sich einer PCI wegen STEMI unterzogen, prospektiv untersucht. Patienten mit ST oder NSRMI sowie Patienten ohne rekurrerenden MI wurden bezüglich Mortalität und schweren

unerwünschten kardialen Ereignissen („major adverse cardiac and cerebrovascular events“, MACCE) verglichen.

Ergebnisse. Rekurrerende MI verringerten sich nach einem Jahr von 37 Ereignissen pro 1000 Personen/Monat im ersten Monat auf 3,3 Ereignisse pro 1000 Personen/Monat. Die kumulative 5-Jahres-Inzidenz von ST und NSRMI lag bei 5,27 % bzw. 13,2 %. Die MACE unterschieden sich 60 Monate nach dem Wiederauftreten nicht signifikant von Patienten mit einem Reinfarkt, sie waren jedoch signifikant höher als bei Patienten ohne rekurrerenden MI (beide Log-Rank $p < 0,001$). Jedoch gab es bei der kumulativen Gesamtmortalitätsrate keinen Unterschied zwischen den drei Gruppen (27,8 vs. 26,7 vs. 23,0 %). Verglichen mit einer ST, die in

den ersten 30 Tagen nach PCI wegen STEMI auftrat, waren NSRMI mit einem signifikant geringeren Risiko für die Gesamtmortalität assoziiert (HR 0,21; 95 % KI 0,33–3,30). Diese Assoziation hielt allerdings bei rekurrerenden MIs im späteren (HR 1,05; 95 % KI 0,33–3,30) oder sehr späten Follow-up-Zeitraum nicht an.

Schlussfolgerung. Obwohl ST in der frühen Erholungsphase mit einem signifikanten Anstieg unerwünschter Ereignisse assoziiert waren, waren die Langzeit-MACE und Gesamtmortalitätsraten mit denen für NSRMI vergleichbar.

Schlüsselwörter

Myokardinfarkt · ST-Streckenerhebung · Perkutane koronare Intervention, primär · Stentthrombose

was tested for normality using the Kolmogorov–Smirnov or Shapiro–Wilk test as appropriate. It was possible to assume, by Little’s missing completely at random (MCAR) test, that data presented are not MCAR. To understand if the missing data could be ignored in the analysis, an imputation of missing values was performed by creating 10 datasets with multiple linear regression. No significant differences were found when comparing

imputed and nonimputed data (excluding subjects with missing data). Thus the missing values were ignored. Moreover, the most important variables to study had less than 5 % missing values. Cumulative incidence and incidence rates of ST and NSRMI were determined. Incidence rates are presented in events per 1,000 person/months of follow-up. Pairwise comparisons (group A vs. B, A vs. C, and B vs. C) of baseline characteristics

and outcomes were performed using the chi-square test or Fisher’s exact test, when appropriate, for categorical variables and Student’s *t* test or the Mann–Whitney test for continuous variables. Prognostic follow-up data are presented as cumulative events at 60 months after ST or NSRMI or 60 months after index PCI for patients with no recurrent MI. Also, the Kaplan–Meier (KM) method was used to construct survival curves for all-cause

Fig. 2 ▲ Incidence rate of recurrent MI after PCI for STEMI. In the first month of follow-up there were cases of 17 ST (definite ST = 8; probable ST = 7) and 18 of NSRMI. For the remaining part of the first year there were 15 cases of ST and 42 of NSRMI, representing 1.57 and 4.47 events per 1,000 person/months, respectively. After the first year there were 22 cases of ST and 75 of NSRMI, 0.65 and 2.38 events per 1,000 person/months, respectively. *NSRMI* nonstent-related myocardial infarction, *PCI* percutaneous coronary intervention, *ST* stent thrombosis, *STEMI* ST-segment elevation myocardial infarction

mortality, cardiovascular mortality, and MACCE with additional landmark analysis at 1 and 12 months. For this analysis time 0 was considered to be the date of first recurrent MI for groups A and B and the date of index STEMI for group C. Censoring for each outcome was present when patients were dead, alive but no longer at risk for that particular outcome, lost to follow-up, or when the defined study period ended. In order to determine the impact of timing of recurrent MI on prognosis, time elapsed after the index MI was stratified in intervals of 0–30 days, 31–360 days, and beyond 360 days. Cox proportional hazards models were used to calculate the unadjusted and adjusted hazard ratios and 95 % confidence intervals for all-cause mortality, cardiac death, and MACCE. Median times on the survival analyses were obtained using non-parametric censored data. A sensitivity analysis was performed to assess the impact on the findings if cases of probable ST were classified as NSRMI.

Results

Incidence and timing of stent thrombosis or reinfarction

Overall, 189 patients (18.4 %) had at least one episode of recurrent MI during the

follow-up period. The cumulative incidence of ST was 5.27 % (28 definite and 26 probable ST) and 13.2 % for NSRMI (135 patients). In the first month after PCI for STEMI, there were 35 recurrent MIs (36.7 per 1,000 person/months). In the subsequent months during the first year, there was a sharp decrease in the incidence rate of recurrent MI (6.25 per 1,000 person/months) driven by a decline in both ST and NSRMI. Thereafter, frequency of recurrent MI continued to decrease but at a slower rate. It is noteworthy that while ST accounted for almost half of the incidence of recurrent MIs in the first month, by the end of follow-up ST represented only 20 % of the incidence rate of recurrent MIs (0.65 ST cases from a total of 3.3 recurrent MI per 1,000 person/months; **Fig. 2**).

Baseline clinical and angiographic characteristics

Clinical and angiographic characteristics of patients who ultimately had ST, NSRMI, or no recurrent MI were fairly balanced at baseline (time of PCI for STEMI; **Table 1**). Despite having a similar number of diseased vessels or treated lesions in the index procedure, patients with ST were significantly more likely to have long lesions and receive more

stents than patients with no recurrent MI. However, these differences were not significant between patients with ST and NSRMI. Immediate procedural success was high and similar among the groups (over 93 %). There were also no differences in the rate of no-reflow phenomenon or achievement of complete revascularization.

Clinical outcomes: follow-up

In the hospitalization period relative to index PCI for STEMI, mortality was 5.9 % (61 patients), with two cases of nonfatal acute ST and no case of NSRMI occurred. Long-term survival free from MACCE, all-cause mortality, and cardiac mortality presented through KM curves are shown in **Fig. 3**. Cumulative MACCE in patients with ST was not significantly different from those with NSRMI (**Table 2**). However, patients free from any recurrent MI had significantly lower cumulative MACCE than those with ST or NSRMI at the end of follow-up (28.8 %, both $p < 0.001$) and at both landmark time points (all log-rank $p < 0.05$; **Fig. 3a,b**).

The landmark analysis showed that patients surviving the first month after ST were still at increased risk for cardiac or all-cause mortality relative to the other two groups in the subsequent months (log-rank $p < 0.001$), but this risk did not persist beyond 1 year nor did it translate into long-term all-cause mortality (cumulative incidence of all cause-mortality 27.8 vs. 26.7 vs. 23.0 %; **Fig. 3c-f**).

Timing of recurrent MI had a different prognostic impact depending on the type of MI (**Table 3**). Early NSRMI was associated with a lower all-cause mortality risk than early ST (adjusted HR = 0.22, $p = 0.02$) and at a longer time-to-death interval, 83 months (95 % CI, 70.97–95.33) vs. 39 months (95 % CI, 17.96–60.12), log-rank ($p = 0.005$).

In a sensitivity analysis, however, if probable STs were reclassified as NSRMI this difference would no longer remain statistically significant (HR = 0.55, 95 % CI, 0.12–2.49; supplemental material). For the late period there was no excess risk associated with the type of recurrent MI (adjusted HR 1.05, $p = 0.93$). Very late ST was a rather benign event resulting in

	ST (Group A = 54)	NSRMI (Group B = 135)	No rein- farction (Group C = 833)	p	p (A vs. B)	p (A vs. C)	p (B vs. C)
<i>Demographic characteristics</i>							
Age, mean ± SD	58.88 ± 10.41	61.32 ± 12.10	62.24 ± 12.51	0.126	0.528	0.151	0.804
Male gender (%)	44 (81.5)	101 (74.8)	635 (76.2)	0.615	0.327	0.375	0.727
Diabetes mellitus (%)	7 (13.0)	25 (18.5)	159 (19.1)	0.531	0.358	0.260	0.865
Hypertension (%)	29 (54.3)	65 (48.5)	453 (54.4)	0.631	0.602	0.934	0.300
Smoking (%)	30 (55.3)	47 (34.8)	352 (42.3)	0.093	0.445	0.058	0.123
Dyslipidemia (%)	26 (48.9)	53 (39.4)	353 (42.4)	0.589	0.940	0.360	0.090
Family history (%)	3 (5.0)	6 (4.8)	57 (6.8)	0.944	0.516	1.000	0.188
CKD (%)	1 (2.2)	2 (1.7)	12 (1.5)	0.940	1.000	0.520	0.700
Prior myocardial infarction (%)	1 (2.2)	11 (7.8)	18 (2.2)	0.577	0.285	1.000	0.064
<i>Angiographic and procedural characteristics</i>							
Vessels with lesions (n)	1.54 ± 0.67	1.70 ± 0.77	1.62 ± 0.75	0.327	0.421	0.804	0.558
Treated vessels (n)	1.15 ± 0.36	1.14 ± 0.35	1.10 ± 0.31	0.201	0.998	0.584	0.362
Treated lesions (n)	1.15 ± 0.53	1.19 ± 0.64	1.10 ± 0.49	0.144	0.958	0.847	0.167
Long lesion (%)	31 (58.3)	64 (47.7)	345 (41.4)	0.043	0.220	0.022	0.216
Angiographic thrombi (%)	30 (54.9)	78 (58.0)	505 (60.6)	0.654	0.710	0.424	0.593
Left main trunk (%)	1 (1.9)	0 (0.0)	6 (0.7)	0.370	0.283	0.360	1.000
Left anterior descending (%)	31 (56.6)	77 (56.7)	396 (47.5)	0.076	0.989	0.197	0.047
Abciximab therapy (%)	50 (92.6)	116 (85.9)	724 (87.0)	0.442	0.205	0.228	0.741
Implanted stents (n)	1.69 ± 0.93	1.51 ± 0.80	1.36 ± 0.65	< 0.001	0.450	0.039	0.103
Drug-eluting stent (%)	24 (45.1)	62 (46.2)	365 (43.8)	0.807	0.743	0.551	0.743
Total stented length (mm)	20.40 ± 6.67	19.27 ± 6.51	19.25 ± 6.08	0.425	0.597	0.473	1.000
CKD chronic kidney disease							

a notable late catch-up phenomenon in the global survival curves. For the 22 patients having very late ST, only one cardiac death occurred. By contrast, a steady and progressive survival decline was observed among patients with NSRMI as well as in those free from recurrent MI throughout the follow-up.

Discussion

Recurrent MI after STEMI is not infrequent [14, 16, 17]. ST is associated with a dismal prognosis, but currently there is no evidence of the extent to which out-

comes are different from other types of recurrent MI after STEMI. To our knowledge, this is the first report comparing long-term clinical outcomes of ST versus NSRMI after PCI for STEMI.

Chechi et al. compared outcomes of primary PCI for de novo lesions versus primary PCI for ST [8]. They found that in-hospital mortality was higher for ST patients. However, at baseline, only 11 % of the patients with de novo lesions had prior MI, which was much lower than the 68 % frequency found in patients with ST. Thus, after adjustment for baseline risk, the 6-month survival and MACCE rates

did not differ significantly. It has been suggested that long-term prognosis of recurrent MI after PCI for STEMI is probably more dependent on timing than on the type of MI itself. In the *Valsartan in Acute Myocardial Infarction Trial* (VALIANT), early recurrent MI was associated with the highest mortality rate [15]. This observation was consistent with the findings reported by Kikkert et al. [5] in a contemporary cohort of 1,700 primary PCI-treated patients. In their analysis, a J-shaped curve of mortality was observed with the highest rates in the first day after recurrent MI followed by a recrudescence after 365 days. Recently published data [9] on long-term outcomes after ST show a significantly lower mortality rate for very late ST (14.7 %) than for early ST (29.3 %) or late ST (41.6 %). Our results corroborate these findings. We found that cumulative mortality for early ST (58.8 %) was significantly higher than for late or very late ST (26.7 and 4.54 %, respectively). Furthermore, in early ST, death occurred at a significantly shorter interval than for early NSRMI.

Mechanisms behind these observations are not entirely clear although pathophysiologic explanations have been put forward. Some studies have suggested that, as opposed to early ST, very late ST is not related to lesion complexity (a prognostic marker) in index PCI but rather to neoatherosclerosis [13, 18]. It is also possible that in a STEMI context, where some degree of myocardial necrosis is invariably present, late ST and very late ST may not have the same impact as recurrent NSRMI has in a remote territory. Other factors hypothetically implicated in these observations, but not readily evident from our results, could be differences in management in favor of patients with late ST and very late ST in comparison with NSRMI owing to a higher perceived risk for ST.

The long-term cause of death in patients with STEMI remains uncharted. Epidemiological studies [31] with comprehensive national-based long-term follow-up have found that noncardiac causes are responsible for the majority of later deaths in STEMI patients. This is in line with our results, where we found that despite worse cardiovascular

Fig. 3 ◀ Kaplan–Meier estimates of survival free from major adverse cardiac and cerebrovascular events (MACCE; **a**), all-cause mortality (**c**), and cardiac mortality (**e**) in patients with stent thrombosis (*Group A*), non-stent-related myocardial infarction (*Group B*), and no reinfarction (*Group C*). Landmark analysis at 1 and 12 months for each endpoint (**b**, **d**, **f**). Log-rank *p* values presented represent groups A vs. B vs. C.

outcomes, patients with recurrent MI had a similar overall mortality to patients with no recurrent MI.

Effective management strategies for recurrent MI are currently lacking. Secondary prevention studies testing en-

hanced anticoagulation regimens or systemic anti-inflammatory therapies have shown improvement in cardiovascular outcomes but at the expense of significant adverse events [31–33]. Therefore, more sophisticated patient

or timing selection tools are needed to identify those who can benefit most from these innovative therapies and also to guide further research.

Table 2 Cumulative outcomes at 60 months after recurrent MI (groups A and B) or 60 months after index PCI for STEMI (group C)

	ST (n = 54)	NSRMI (n = 135)	No rein- farction (n = 833)	<i>p</i> All	<i>p</i> (A vs. B) ^a	<i>p</i> (A vs. C) ^a	<i>p</i> (B vs. C) ^a
Death (%)	15 (27.8)	36 (26.7)	192 (23.0)	0.496	0.876	0.417	0.347
Cardiac death (%)	14 (25.9)	33 (24.4)	117 (13.9)	0.001	0.831	0.016	0.347
Reinfarction (%)	15 (27.8)	28 (20.7)	0 (0.00)	<0.001	0.822	<0.001	<0.001
Stroke (%)	0 (0.00)	4 (2.9)	33 (3.9)	0.284	0.579	0.161	0.433
MACCE (%)	28 (51.9)	60 (44.4)	241 (28.8)	<0.001	0.356	<0.001	<0.001

NSRMI nonstent-related myocardial infarction, PCI percutaneous coronary intervention, ST stent thrombosis

^aBonferroni correction

Table 3 Risk of adverse events for NSRMI according to timing of occurrence after PCI for STEMI (ST set as reference group)

	Stent thrombosis (%)	NSRMI (%)	Unad- justed HR	95 % CI	<i>p</i>	Adjusted HR	95 % CI	<i>p</i>
MACCE								
Early	11/17 (64.7)	6/18 (33.3)	0.25	0.09–0.72	0.01	0.36	0.12–1.04	0.06
Late	8/15 (53.3)	27/42 (64.3)	1.48	0.67–3.26	0.33	0.99	0.41–2.39	0.99
Very late	10/22 (45.5)	29/75 (38.7)	1.19	0.58–2.45	0.64	0.83	0.37–1.84	0.65
All-cause death								
Early	10/17 (58.8)	3/18 (16.7)	0.19	0.05–0.71	0.01	0.22	0.06–0.81	0.02
Late	4/15 (26.7)	18/42 (42.9)	1.98	0.67–5.86	0.21	1.05	0.33–3.30	0.93
Very late	1/22 (4.5)	15/75 (20.0)	7.29	0.95–54.8	0.06	^a	^a	^a
Cardiac death								
Early	10/17 (58.8)	2/18 (11.1)	0.15	0.03–0.69	0.01	0.17	0.04–0.79	0.02
Late	4/15 (26.7)	18/42 (42.9)	1.97	0.67–5.83	0.22	1.02	0.32–3.24	0.97
Very late	0/22 (0.0)	13/75 (17.3)	^a	^a	^a	^a	^a	^a

HR Hazard ratios were calculated using Cox proportional hazard models. HRs were adjusted using a Cox proportional hazard model for baseline differences (age and number of stents). MACCE major adverse cardiac and cerebrovascular events, NSRMI nonstent-related myocardial infarction, PCI percutaneous coronary intervention, ST stent thrombosis, STEMI ST-segment elevation myocardial

^aModels did not converge (only one death occurred in the very late ST group)

Limitations

This study has some limitations. First, as a single-center study, there is a question about whether these results can be extrapolated. Long-term data from real-world reports describe results similar to those we have found (5-year mortality rates between 15 and 25 % and recurrent MI as high as 23 %) [25–30]. The long-

term prevalence of ST published in the literature varies and depends on aspects such as the definition and type of ST, the study era, the antiplatelet therapy strategy used, and the proportion of acute patients. In this study, where first-generation drug-eluting stents were used in almost half the population, the long-term cumulative rate of definite or probable ST (5.27 %) was fairly equivalent to what is

usually described in the same circumstances (4–8 %) [19–24]. Second, this is an exploratory analysis from a prospective MI registry. The registry was not specifically designed to answer the research question presented, and thus the results can only be considered as hypothesis-generating. Third, almost half of the cases classified according to the ARC criteria were considered probable ST, and therefore without confirmation by angiography or autopsy this could have led to an overestimation of the true incidence of ST. We could not determine the exact causes of extra-hospital deaths. Fourth, we did not include data related to adherence or compliance to medications, particularly regarding antiplatelet therapy. Thus, despite a similar baseline anti-platelet regimen, we cannot exclude the possibility that subsequent medical management could be different among the groups. Fifth, assessment of the extent of myocardial injury by quantification of cardiac biomarkers, left ventricular ejection fraction or, more importantly, scar quantification was not systematically evaluated in all patients at standardized time points and therefore was not analyzed.

Finally, comparisons between patient subgroups may not have had adequate statistical power to detect significant differences owing to the limited number of patients with ST.

Conclusion

At long term after PCI for STEMI more than one third of patients had recurrent MI or death. NSRMI was 2.5 times more frequent than ST. Overall, rates of all-cause and cardiac mortality were equivalent after ST or NSRMI. However, timing of recurrent MI had a different impact on prognosis depending on the type of recurrent MI: a higher mortality for ST occurring in the first 30 days, but thereafter differences in mortality were not significant. In patients free from recurrent MI, cardiovascular events were lower than in patients with recurrent MI but all-cause mortality was comparable.

Corresponding address

A. Viveiros Monteiro, MD

Cardiology Department, Hospital of Santa Marta
Rua de Santa Marta, 1169-1024 Lisbon,
Portugal
andreviveirosmonteiro@gmail.com

Compliance with ethical guidelines

Conflict of interest. A. Viveiros Monteiro, R. Ramos, A. Fiarresga, L. de Sousa, D. Cacula, L. Patrício, L. Bernardes, C. Soares, and R. Cruz Ferreira state that there are no conflicts of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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