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Original article

Ten-year prognostic impact of target versus non-target vessel failure after STEMI. Insight from the EXAMINATION-EXTEND trial

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ABSTRACT

Introduction and objectives: After ST-segment myocardial infarction (STEMI), the impact of different adverse events on prognosis remains unknown. We aimed to assess very long-term predictors of patient-oriented composite endpoints (POCE) and investigate whether the occurrence of target vessel failure (TVF) vs a non-TVF event as the first event could potentially influence subsequent outcomes.

Methods: The EXAMINATION-EXTEND trial randomized STEMI patients to receive either an everolimus-eluting stent or a bare-metal stent. The follow-up period was 10 years. Predictors of POCE (a composite of all-cause death, any myocardial infarction, or any revascularization) were evaluated in the overall study population. The patients were stratified based on the type of first event (TVF-first vs non–TVF-first) and were compared in terms of subsequent POCE. TVF was defined as a composite of cardiac death, TV myocardial infarction, or TV revascularization.

Results: Out of the 1498 enrolled patients, 529 (35.3%) experienced a POCE during the 10-year follow-up. Independent predictors of POCE were age, diabetes mellitus, previous myocardial infarction, peripheral arterial disease, and multivessel coronary disease. The first event was a TVF in 296 patients and was a non-TVF in 233 patients. No significant differences were observed between TVF-first and non–TVF-first patients in terms of subsequent POCE (21.7% vs 39.3%, time ratio 1.79; 95%CI, 0.87-3.67; $P = .12$) or its individual components.

Conclusions: At the 10-year follow-up, approximately one-third of STEMI patients had experienced at least 1 POCE. Independent predictors of these events were age, diabetes, and more extensive atherosclerotic disease. The occurrence of a TVF or a non-TVF as the first event did not seem to influence subsequent outcomes. Trial registration number: NCT04462315.

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Impacto pronóstico a diez años del fallo del vaso diana tras un IAMCEST. Perspectivas del ensayo EXAMINATION-EXTEND

Palabras clave:
Infarto de miocardio con elevación del segmento ST
Intervención coronaria percutánea
Fallo del vaso diana

RESUMEN

Introducción y objetivos: Se desconoce el impacto pronóstico de los diferentes tipos de eventos adversos tras el infarto agudo de miocardio con elevación del segmento ST (IAMCEST). El objetivo de este trabajo es evaluar los predictores a largo plazo del objetivo combinado orientado al paciente (POCE) y si tener un fallo del vaso diana (FVD) como primer evento puede influir en los resultados.

Métodos: El ensayo EXAMINATION-EXTEND aleatorizó a pacientes con IAMCEST a tratamiento con *stents* liberadores de everolimus o a *stents* convencionales, con un seguimiento de hasta 10 años. En la población del estudio, se evaluaron los predictores de POCE (combinado de mortalidad por cualquier causa, infarto de miocardio y cualquier revascularización). Se clasificó a los pacientes según el tipo de primer evento (FVD primero o FDV no primero) y comparado en términos de POCE posterior. El FVD se definió como el compuesto de muerte cardiaca, IAMCEST del vaso diana y revascularización del vaso diana.

Resultados: De los 1.498 pacientes del estudio, 529 (35,3%) tuvieron POCE durante el seguimiento a los 10 años. Los predictores independientes de POCE fueron la edad, la diabetes mellitus, el infarto de miocardio previo, la enfermedad arterial periférica y la enfermedad coronaria multivaso. El primer evento fue un FVD o no FVD en 296 y 233 casos respectivamente. No hubo diferencias estadísticamente significativas entre quienes tuvieron primero un FVD y los que tuvieron un evento no FVD en cuanto a POCE (el 21,7 frente al 39,3%; razón de tiempo, 1,79; IC95%, 0,87-3,67; p = 0,12) o sus componentes individuales.

Conclusiones: En el seguimiento a 10 años, alrededor de un tercio de los pacientes con IAMCEST tuvo al menos 1 evento de POCE, cuyos predictores independientes fueron la edad, la diabetes mellitus y una mayor extensión de la enfermedad ateroesclerótica. Un FVD como primer evento, en comparación con un evento no FVD, no parece tener impacto en los resultados posteriores.

Abbreviations

POCE: patient-oriented composite endpoint
STEMI: ST-segment elevation myocardial infarction
TVF: target vessel failure
TVR: target vessel revascularization

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) patients are at high risk for subsequent cardiovascular events.[1] Their outcomes may vary significantly, with some experiencing event-free periods lasting years while others have recurrent events. Due to improvements in procedural aspects and continuous advancements in pharmacotherapy, the proportion of STEMI patients with event-free follow-up has increased over the years. However, data on very long-term follow-up are scarce or focus on mortality rates.[2–5] Additionally, little is known about the impact of different types of adverse events on subsequent outcomes. Previous data from the HORIZON-AMI trial showed that target vessel revascularization (TVR) was associated with an increased risk of subsequent myocardial infarction,[6] while reinfarctions increased the risk of death.[7] Nevertheless, it remains unknown whether the time of occurrence of such events and their association with the culprit vessel can determine the nature of future outcomes.

We aimed to assess the very long-term predictors of a patient-oriented composite endpoint (POCE) and determine whether having a target vessel failure (TVF) vs a non-TVF as the first event would influence subsequent outcomes in the STEMI population from the EXAMINATION-EXTEND trial.

METHODS

Study population

The EXAMINATION-EXTEND trial, a multicenter, prospective, controlled trial, randomly assigned 1498 STEMI patients to receive either an everolimus-eluting stent or a bare-metal stent. The inclusion and exclusion criteria, as well as the clinical outcomes at the 5-year follow-up, have been previously reported.[8] The EXAMINATION-EXTEND trial was subsequently reinitiated as an EXAMINATION study (NCT04462315) to focus on 10-year outcomes. This follow-up study maintained the same methodology and event adjudication as the original trial. A complete clinical follow-up was obtained for 1427 patients (95.3%). Detailed information on the study and the 10-year follow-up results have been previously reported.[9–11]

This study is a post-hoc analysis conducted to evaluate the 10-year predictors of POCE in the overall population of the trial. Additionally, patients were stratified based on the type of first event, either TVF-first or non–TVF-first, and subsequently compared in terms of subsequent POCE (figure 1). In this analysis, TVF was defined as a composite outcome consisting of cardiac death, target vessel myocardial infarction, and target vessel revascularization (TVR).[12] Non-target vessel failure (non-TVF) encompassed noncardiac death, nontarget vessel myocardial infarction, and nontarget vessel revascularization.

Endpoints

The primary endpoint of this study was defined as a POCE consisting of all-cause death, any myocardial infarction, or any

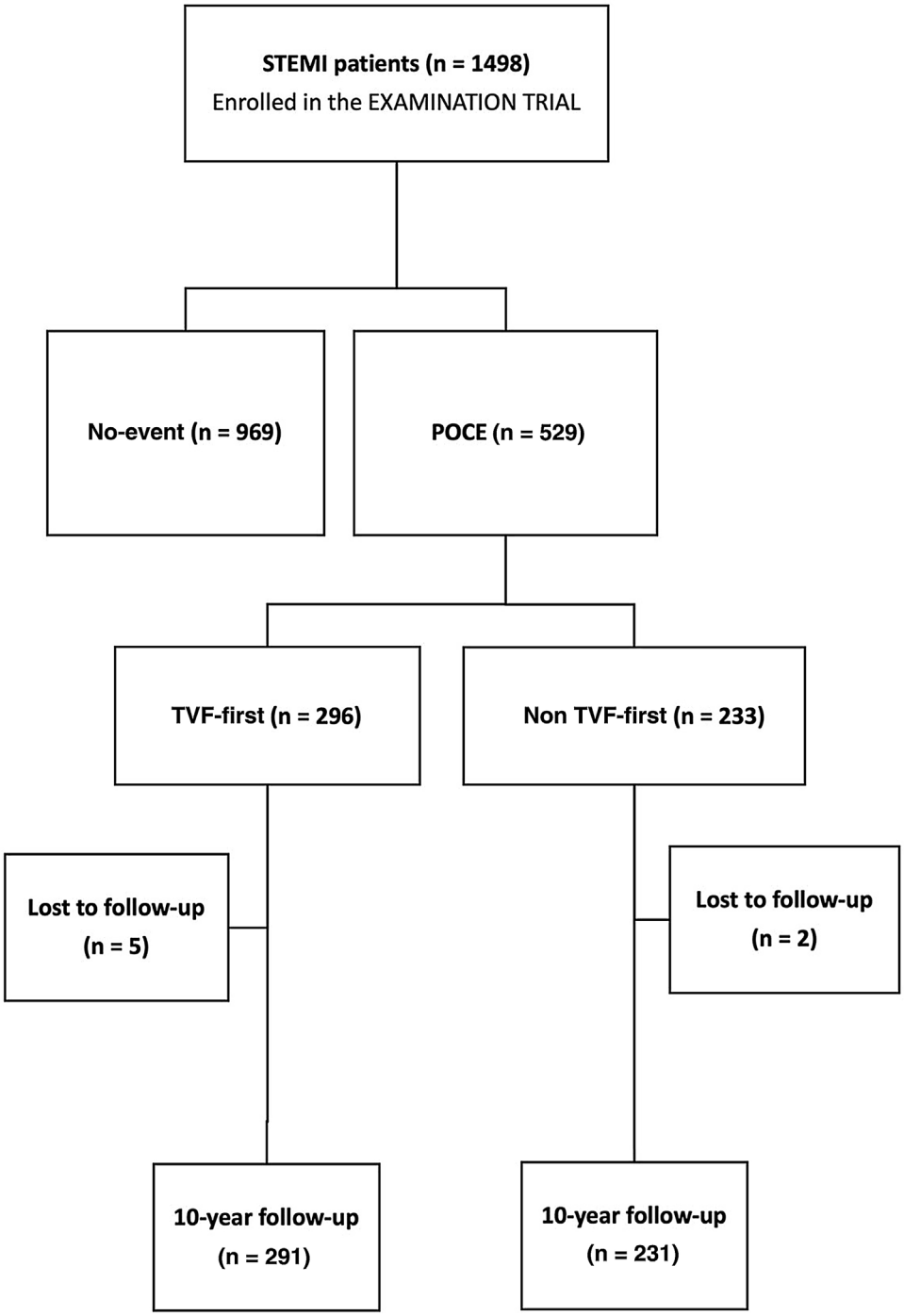

Figure 1. Flow chart of the EXAMINATION trial, which enrolled 1498 patients. Patients were stratified first according to the occurrence of any POCE during the 10-year follow-up. Then, the 529 patients who experienced at least 1 event where further stratified according to the type of first event into 2 groups, TVF-first vs non–TVF-first, with comparison of subsequent outcomes up to 10 years. Loses to follow-up in the TVF-first and non–TVF-first groups were 1.7% and 0.9%, respectively. POCE, patient-oriented composite endpoint; STEMI, ST elevation myocardial infarction; TVF, target vessel failure.

revascularization. Secondary endpoints included the individual components of the POCE, as well as cardiac death, target vessel myocardial infarction, target lesion or TVR, and stent thrombosis (definite/probable). All events were adjudicted by an independent clinical events committee, specifically the Barcicore Lab in Spain, based on the definitions provided by the Academic Research Consortium.[13]

Statistical analysis

Quantitative variables are expressed as either mean and standard deviation or median and interquartile range, depending on their distribution. Statistical comparisons between groups were performed using either the Student t-test or the Mann–Whitney U test, as appropriate. Categorical variables are

expressed as numbers and percentages and were compared using either the chi-square test or Fisher exact test, as appropriate. To assess the independent correlates of the first occurrence of POCE and the independent predictors of TVF/non-TVF-first events, a Cox regression model was used. All variables that achieved a P value of < .10 in the univariate analysis were included in the Cox model.

Long-term outcomes were compared between patients according to the nature of their first event (TVF-first vs non–TVF-first). The follow-up time for TVF-first and non–TVF-first patients began from the date of their first event occurrence. Any subsequent recurrent event of each type during the remaining follow-up period was included in the analysis, as required for time-to-event analysis. The Kaplan-Meier method was used to estimate event rates. The cumulative incidence of the primary and secondary endpoints was calculated, taking into account any death as a competing risk.[14] Since the proportional hazard assumption for the primary endpoint, tested with Schoenfeld residuals, was not met ($P < .05$), both the accelerated time failure model and the difference in restricted mean survival time[15] were used as the primary analyses to compare the effect of TVF-first or non–TVF-first on subsequent outcomes. The accelerated time failure model provided a Time Ratio, which describes the estimated delay until an event occurs in one group compared with the other. The restricted mean survival time represents the mean time free from an outcome event throughout the follow-up. Additionally, a landmark analysis was conducted to better describe the change in the risk of the primary and secondary endpoints over time. In this exploratory analysis, hazard ratios were estimated between the 2 groups within 2 intervals: 0 to 5 years and 5 to 10 years, during which proportional hazards were preserved. The hazard ratio, time ratio, and difference in

Table 1
Baseline clinical and procedural characteristics of patients with and without a 10-year POCE

Clinical and procedural characteristics	No event (n = 969)	POCE (n = 529)	*P*
Age, y	58.6 ± 11.2	65.9 ± 13.1	< .001
Male sex	818 (84.4)	426 (80.5)	.055
Previous smoker	726 (75.0)	356 (67.3)	.001
Diabetes mellitus	138 (14.3)	120 (22.7)	< .001
Hypertension	433 (44.7)	292 (55.2)	< .001
Hyperlipidemia	435 (44.9)	220 (41.6)	.21
Family history	63 (6.5)	41 (7.8)	.01
Previous myocardial infarction	36 (3.7)	44 (8.3)	< .001
Previous PCI	30 (3.1)	31 (5.9)	.01
Previous CABG	3 (0.3)	7 (1.3)	.21
Previous stroke	14 (1.5)	17 (3.2)	.02
Peripheral artery disease	20 (2.1)	35 (6.6)	< .001
TIMI flow before PCI			.13
0	575 (59.6)	303 (57.8)	
1	84 (8.7)	31 (5.9)	
2	122 (12.6)	77 (14.7)	
3	184 (19.1)	113 (21.6)	
Multivessel disease	101 (10.4)	87 (16.5)	.001
LAD as infarct-related artery	186 (19.2)	104 (19.7)	.80
Manual thrombectomy	645 (66.6)	331 (62.6)	.12
Type of stent			.02
BMS	461 (47.6)	286 (54.1)	
EES	508 (52.4)	243 (45.9)	
Direct stenting	611 (63.9)	274 (53.5)	< .001
Postdilatation	137 (14.1)	84 (15.9)	.36
≥ 2 stents	273 (28.2)	188 (36.1)	.002
Overlapping stent	239 (87.6)	165 (87.8)	.94
Total stent length, mm	23 [15; 18-33]	28 [20; 18-38]	< .001
Maximum stent diameter, mm	3.21 ± 0.45	3.19 ± 0.47	.35
TIMI flow after PCI			.23
0	15 (1.6)	11 (2.1)	
1	5 (0.5)	7 (1.3)	
2	35 (3.6)	24 (4.6)	
3	911 (94.3)	485 (92.0)	

BMS, bare-metal stent; CABG, coronary artery bypass graft; EES, everolimus-eluting stent; IQR, interquartile range; LAD, left anterior descending; PCI, percutaneous coronary intervention; TVF, target vessel failure.
Data are presented as No. (%), mean ± standard deviation of median [interquartile range].

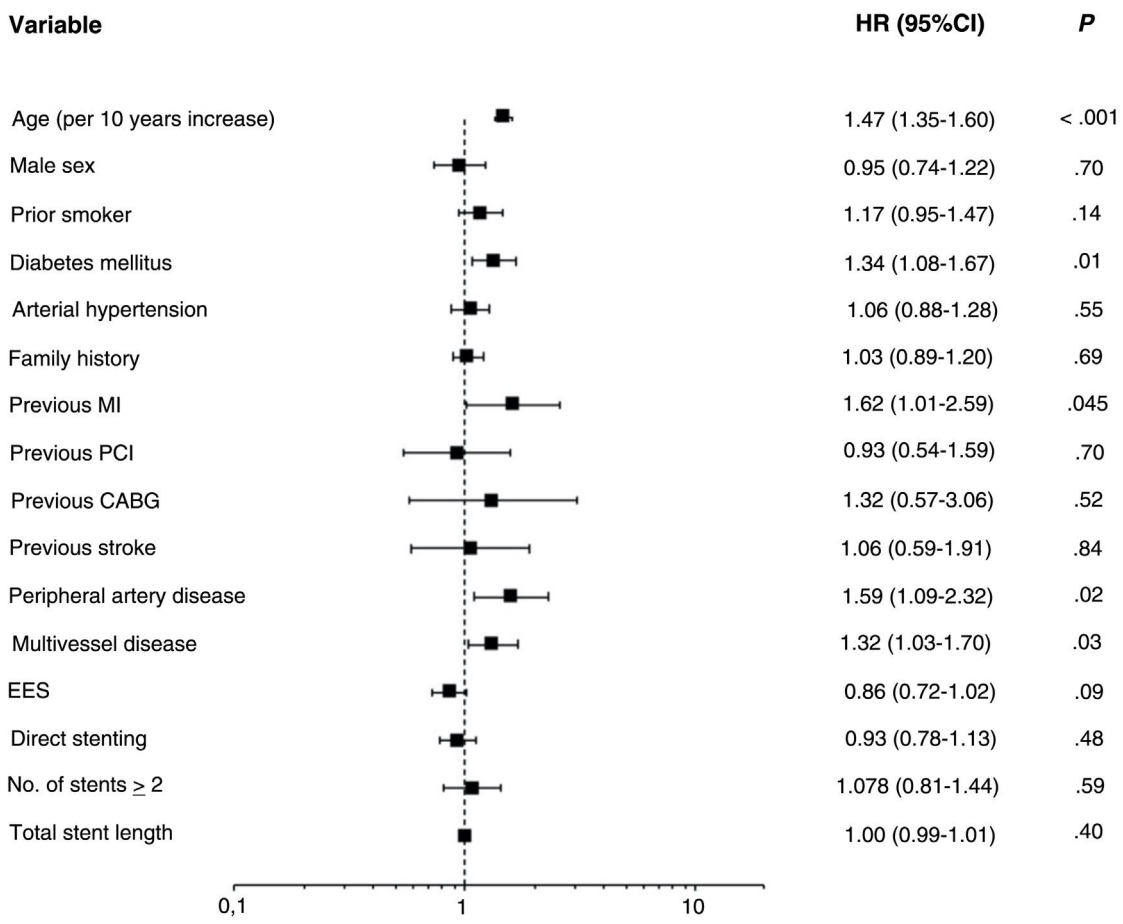

Figure 2. Forest plot presenting the results of a multivariate analysis of factors associated with the risk of POCE in the overall population. The analysis was performed with a Cox regression model including all variables obtaining a *P* value of < .10 in the univariate analysis. independent predictors of 10-year POCE were age, diabetes mellitus, previous myocardial infarction, peripheral artery disease, and multivessel disease. CABG, coronary artery bypass graft; 95%CI, 95% confidence interval; EES, everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

restricted mean survival time are reported with associated 95% confidence intervals and *P* values. Statistical significance was considered for a 2-tailed *P* value < .05. Statistical analyses were performed using STATA, Version 14.1 (StataCorp LLC, United States.

Table 2
Type of events qualifying TVF-first and non–TVF-first groups

Events	No. (%)
TVF-first	296 (56.0)
Cardiac death	145 (49.0)
TV myocardial infarction	42 (14.2)
TV revascularization	141 (47.6)
Non–TVF-first	233 (44.0)
Noncardiac death	116 (49.8)
Non-TV myocardial infarction	22 (9.4)
Non-TV revascularization	110 (47.2)

POCE, patient-oriented composite endpoint; TV target vessel; TVF, target vessel failure.
Data are presented as No. (%).

RESULTS

Overall patient population

Out of the 1498 STEMI patients enrolled in the EXAMINATION-EXTEND study, 969 (64.7%) had an event-free 10-year follow-up, while 529 (35.3%) experienced a POCE. The clinical and procedural characteristics of these 2 groups are shown in table 1. Compared with patients with an event-free follow-up, those who experienced a POCE were older and had a higher prevalence of smoking, diabetes mellitus, hypertension, a family history of coronary artery disease, as well as a history of previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, stroke, and peripheral artery disease. In terms of procedural data, patients with POCE had an increased prevalence of multivessel disease, and more frequently received bare-metal stents and direct stenting, with longer stent length and a higher number of stents.

Incidence and predictors of POCE in the overall population

On multivariate analysis, the only independent predictors of POCE occurrence were age (hazard ratio [HR] 1.48, 95%CI: 1.34-1.63; *P* < .001), diabetes mellitus (HR 1.34, 95%CI, 1.08-1.66;

Table 3
Baseline clinical and procedural characteristics of TVF-first and non–TVF-first patients

Clinical and procedural characteristics	TVF-first (n = 296)	non–TVF-first (n = 233)	*P*
Age, y	65.6 ± 13.3	66.3 ± 12.8	.57
Male sex	241 (81.4)	185 (79.4)	.56
Previous smoker	192 (64.9)	164 (70.4)	.18
Diabetes mellitus	63(21.3)	57 (24.5)	.39
Hypertension	167 (56.4)	125 (53.7)	.53
Hyperlipidemia	127 (42.9)	93 (39.9)	.49
Family history	36 (14.2)	33 (14.2)	.12
Cardiovascular history			
Previous myocardial infarction	26 (8.8)	18 (7.7)	.66
Previous PCI	20 (6.8)	11 (4.7)	.32
Previous CABG	3 (1.0)	4 (1.7)	.48
Previous stroke	11 (3.7)	6 (2.6)	.46
Peripheral artery disease	19 (6.4)	16 (6.9)	.84
TIMI flow before PCI			.36
0	166 (59.3)	137 (56.7)	
1	17 (5.8)	14 (6.1)	
2	39 (13.3)	38 (16.5)	
3	71 (24.2)	42 (18.2)	
Multivessel disease	49 (16.6)	38 (16.3)	.94
LAD as infarct-related artery	61 (20.8)	43 (18.5)	.51
Manual thrombectomy	171 (57.8)	160 (68.7)	.01
Type of stent			.72
BMS	158 (53.4)	128 (54.9)	
EES	138 (46.6)	105 (45.1)	
Direct stenting	152 (53.3)	122 (53.7)	.93
Postdilatation	50 (16.9)	34 (14.6)	.47
≥ 2 stents	115 (39.5)	73 (31.7)	.07
Overlapping stent	100 (87.0)	65 (89.0)	.67
Total stent length, mm	28 [20; 18-38]	23 [17; 18-35]	.13
Maximum stent diameter, mm	3.20 ± 0.47	3.12 ± 0.43	.04
TIMI flow after PCI			.054
0	8 (2.7)	3 (1.3)	
1	7 (2.3)	0 (0.0)	
2	15 (5.1)	9 (3.9)	
3	264 (89.8)	221 (94.9)	

BMS, bare-metal stent; CABG, coronary artery bypass graft; EES, everolimus-eluting stent; IQR, interquartile range; LAD, left anterior descending; PCI, percutaneous coronary intervention; TVF, target vessel failure.
The data are presented as No. (%), mean ± standard deviation, or median [interquartile range].

P = .01), previous myocardial infarction (HR 1.66; 95%CI: 1.04-2.63, *P* = .03), peripheral artery disease (HR 1.58, 95%CI: 1.08-2.31; *P* = .02), and multivessel disease (HR 1.33; 95%CI; 1.04-1.70; *P* = .02) (figure 2).

Outcomes according to the type of first event

Among the 529 patients with POCE, the first event was a TVF in 296 and a non-TVF in 233 patients. The component of the TVF event was cardiac death in 49%, target vessel myocardial infarction in 14.2%, and TVR in 47.6%. In non-TVF, the component was noncardiac death in 44.1%, nontarget vessel myocardial infarction in 9.4%, and non-TVR in 47.2% (table 2). The median [interquartile range] time was 718 [70-1961] days to TVF-first and and 1518 [213-2495] days to non–TVF-first. Baseline and procedural characteristics between TVF-first and non–TVF-first groups differed only in manual thrombectomy use (*P* = .01), and the maximum diameter of the stent implanted in the culprit lesion (*P* = .04) (table 3), while no independent predictors were found in the multivariate analysis.

Fifty out of 296 patients in the TVF-first group and forty-nine out of 233 patients in the non–TVF-first group had a subsequent POCE during their remaining follow-up. According to the accelerated failure estimation model, there was no significant difference in the time to primary endpoint between TVF-first vs non–TVF-first (time ratio 1.79, 95%CI, 0.87-3.67; *P* = .12) (figure 3). The restricted mean survival time was 2852 days for the TVF-first group and 2731 days for the non–TVF-first group (difference, 121 days, 95%CI, − 64 to 307; *P* = .20). Furthermore, as shown in table 4, the time to occurrence of any secondary outcome did not statistically differ between TVF-first and non–TVF-first patients.

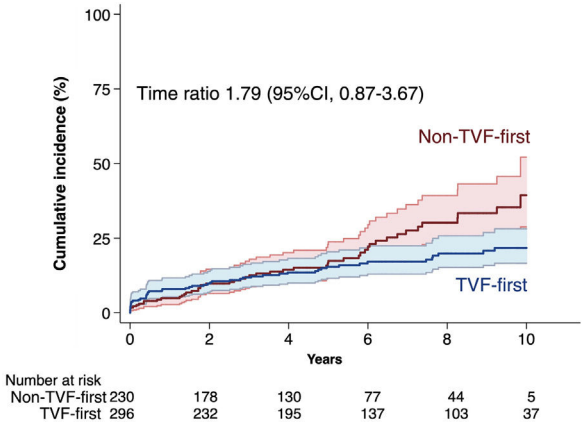

Figure 3. Kaplan-Meier estimated cumulative incidence with 95% confidence intervals of subsequent POCE according to the type of first event: TVF-first vs non-TVF-first. Because of the nonproportionality of the hazards, the effect of TVF-first or non–TVF-first on subsequent POCE was evaluated with an accelerated time failure model providing a time ratio value that describes the estimated delay until the occurrence of an event one group compared with the other. CI, confidence interval; POCE, patient-oriented composite endpoint; TVF, target vessel failure.

The risk of the primary endpoint varied over time, with no difference in the event rate between the 2 groups (TVF-first vs non-TVF-first) during the first 5 years of follow-up (HR, 0.93; 95%CI, 0.59-1.48; $P = .77$), while the TVF-first group was characterized by a lower risk of POCE (HR 0.28; 95%CI, 0.12-0.62; $P = .002$) from 5 to 10 years (figure 4). The reduced risk of POCE during the late follow-up of TVF-first patients was mainly driven by a lower rate of late mortality (table 5).

DISCUSSION

Our study reveals the following main findings: *a)* Approximately one-third of primary percutaneous coronary intervention STEMI patients experienced at least 1 POCE event during the 10-year follow-up. These patients were characterized by a worse risk profile, including older age, a higher prevalence of diabetes, and more extensive atherosclerotic disease. The remaining patients remained event-free for 10 years. *b)* The type of the first event (TVF or non-TVF) was not associated with a different risk of subsequent POCE (figure 5). *c)* However, non-TVF-first patients exhibited an increased risk of very late POCE (5-10 years), mainly driven by a higher mortality rate.

Predictors of very long-term outcome in STEMI patients

STEMI patients represent a widely investigated population, with several studies reporting the incidence and predictors of adverse events during short- or mid-term follow-up.[4,16–19] However, there is a scarcity of data on very long-term outcomes in these patients and most studies have focused only on mortality.[5] In our post-hoc analysis of the EXAMINATION-EXTEND trial, we provide unique results by evaluating predictors of POCE over a 10-year follow-up. Our findings reveal that only one-third of STEMI patients experienced a POCE event after 10 years, while the remaining patients remained event-free during this period. Coughlan et al.[20] reported results on the 10-year occurrence of POCE in patients treated with DES for acute coronary syndrome, including unstable angina and non–ST-segment elevation myocardial infarction patients. In their analysis, more than 60% of patients had a POCE at 10 years. The discrepancy between these findings and our own can be attributed, at least in part, to the differences in clinical presentation and consequently in the patients' baseline risk profile, with our STEMI population being younger and with a lower proportion of comorbidities.

Table 4
Subsequent outcomes in TVF-first vs non–TVF-first patients

	TVF-first (n = 296)	Non–TVF-first (n = 233)	Accelerated failure time		RMST	
Outcomes	No. (%)*	No. (%)*	*Time ratio (95%CI)*	*P*	*Difference in RMST, d (95%CI)*	*P*
POCE	50 (21.7)	49 (39.3)	1.79 (0.87 to 3.67)	.12	122 (−64 to 307)	.20
All-cause death	24 (21.5)	27 (36.8)	1.34 (0.84 to 2.15)	.31	24 (−167 to 214)	.81
Cardiac death	11 (8.7)	11 (15.6)	1.35 (0.46 to 3.97)	.58	−50 (−111 to 12)	.11
MI	15 (6.7)	15 (9.4)	1.72 (0.57 to 5.15)	.33	29 (−51 to 109)	.48
TVMI	6 (2.4)	6 (3.9)	1.87 (0.22 to 16.17)	.57	1 (−37 to 39)	.96
Any revascularization	27 (9.7)	26 (13.8)	2.16 (0.46 to 10.02)	.33	4 (−51 to 60)	.88
TVR	18 (6.5)	16 (9.0)	1.70 (0.24 to 12.16)	.60	−14 (−47 to 20)	.43
TLR	15 (5.4)	11 (5.6)	0.94 (0.07 to 12.51)	.96	−9 (−40 to 22)	.56
Definitive or probable ST	7 (2.9)	9 (13.3)	2.58 (0.52 to 12.80)	.25	12 (−18 to 43)	.43

95%CI, 95% confidence interval; HR, hazard ratio; MI, myocardial infarction; POCE, patient-oriented composite endpoint; ST, stent thrombosis; TVF, target vessel failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction TVR, target vessel revascularization.
* Cumulative incidence estimated with the Kaplan-Meier method.

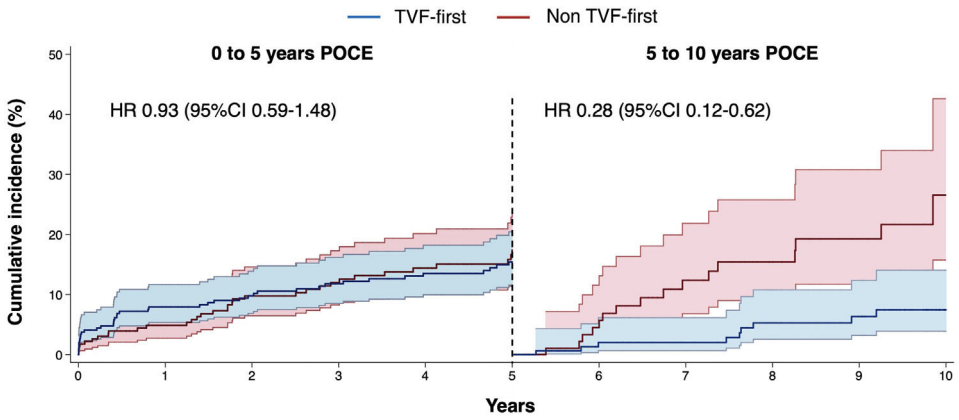

Figure 4. Landmark analysis showing the cumulative incidence of POCE within 2 intervals. Cumulative incidence curves with 95% confidence intervals (95%CI) estimated with the Kaplan-Meier method within 2 intervals: the first 5 years and from 5 to 10 years of follow-up. Hazard ratios (HR) with 95%CI were determined by Cox regression. POCE, patient-oriented composite endpoint; TVF, target vessel failure.

Patients experiencing a POCE were characterized by an unfavorable cardiovascular risk profile, including advanced age, diabetes mellitus, previous myocardial infarction, peripheral artery disease, and multivessel coronary disease. Some of these factors, such as age, diabetes mellitus, and multivessel disease, have been widely recognized as predictors of short-term outcomes after STEMI and are included in most of the existing prognostic risk scores.[21–25] Our study confirms that these characteristics continue to correlate with the occurrence of adverse events over long-term follow-up. Therefore, their presence should prompt patients and physicians to adopt a more vigilant approach to secondary prevention, even a decade after the index event.

If we take an alternative perspective on our results, it is noteworthy that a high proportion of patients (969 out of 1498, 64.7%) experienced no events during the 10-year period after STEMI. This result is reassuring and suggests that the outcome may be even more favorable in contemporary practice due to advancements procedural aspects and medical treatment over the last decade: since the enrolment of patients in the EXAMINATION trial (from December 31, 2008 to May 15, 2010) numerous important recommendations have been established and implemented in routine clinical practice. These recommendations include the adoption of radial access as the standard approach, use of second-generation DES over bare-metal stents, and the use

Table 5
Outcomes in the landmark analysis

Outcomes	TVF-first (n = 296)	non–TVF-first (n = 233)	HR (95%CI)	*P*
Outcomes at 5 y	n*	n*		
POCE	41 (15.4)	33 (17.4)	0.93 (0.59-1.48)	.77
All-caused death	15 (11.2)	9 (8.9)	1.36 (0.59-3.10)	.49
Cardiac death	9 (6.8)	3 (2.9)	2.41 (0.65-8.92)	.19
Myocardial infarction	12 (4.5)	11 (5.6)	0.70 (0.34-1.44)	.34
TV myocardial infarction	5 (1.8)	4 (2.0)	0.96 (0.26-3.56)	.95
Any revascularization	27 (9.7)	24 (11.7)	0.86 (0.50-1.49)	.59
TV revascularization	18 (6.5)	14 (7.0)	0.99 (0.49-1.98)	.97
TL revascularization	15 (5.4)	10 (4.8)	1.15 (0.52-2.57)	.73
ST	6 (2.4)	5 (2.4)	0.88 (0.27-2.90)	.84
Outcomes from 5-10 y				
POCE	9 (7.5)	16 (26.6)	0.28 (0.12-0.62)	.002
All-caused death	9 (11.6)	18 (30.6)	0.38 (0.17-0.84)	.02
Cardiac death	2 (2.0)	8 (13.2)	0.70 (0.52-0.96)	.03
Myocardial infarction	3 (2.3)	4 (4.0)	0.43 (0.10-1.95)	.28
TV myocardial infarction	1 (0.6)	2 (2.0)	0.31 (0.03-3.37)	.33
Any revascularization	0	2 (2.3)	-	-
TV revascularization	0	2 (2.1)	-	-
TL revascularization	0	1 (0.9)	-	-
ST	1 (0.5)	4 (11.2)	0.12 (0.01-1.11)	.06

95%CI, 95% confidence interval; HR, hazard ratio; POCE, patient-oriented composite endpoint; ST, stent thrombosis; TL, target lesion; TV, target vessel; TVF, target vessel failure.
Data are expressed as No. (%).
* Cumulative incidence estimated with the Kaplan-Meier method.

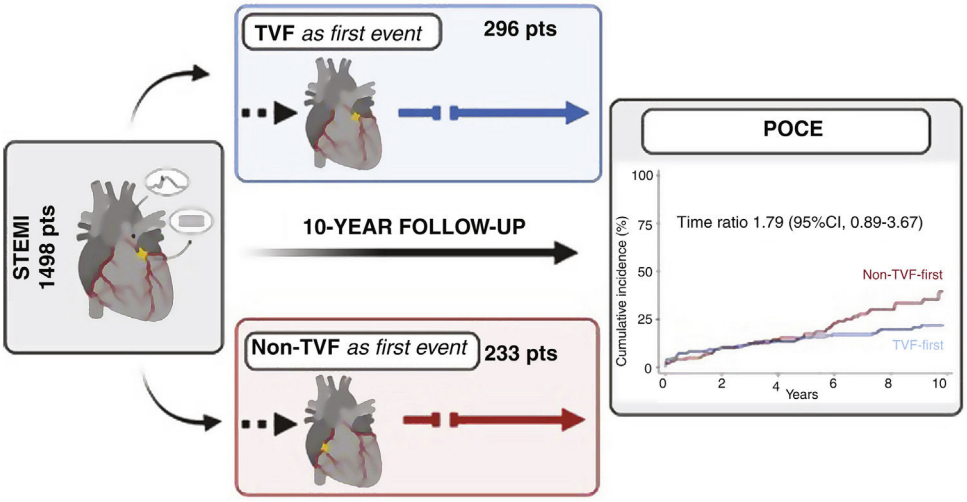

Figure 5. Central illustration. Impact on very long-term outcomes of TVF vs non-TVF as the first event after STEMI. CI, confidence interval; POCE, patient-oriented composite endpoint; STEMI, ST-segment elevation myocardial infarction; TVF, target vessel failure.

of potent $P2Y_{12}$-inhibitors fur dual antiplatelet therapy when not contraindicated.[26]

Nature of the first event in determining subsequent outcome

In our analysis, TVF was the first event during follow-up in most patients (56% vs 44%), with a median time to occurrence of 718 [70-1961] days, compared with 1518 [213-2495] days for non-TVF events. These results confirm the previously reported trend of early occurrence of TV vs non-TV-related adverse events,[27,28] due to the time frame of the healing process following stent implantation. In contrast, non-TV-related events may be partially attributed to disease progression that involves the entire coronary tree. As a result, these events tend to occur with a more uniform distribution over the years, becoming the most prevalent events during long-term follow-up.

We also investigated whether a TV-related event occurring as the first event would have a significantly different impact on the risk of subsequent outcomes. We hypothesized that patients who experienced an event in the culprit vessel as their first event would be at higher risk of subsequent events than patients experiencing a non-TV-related event. However, our findings indicate that the type of first event does not influence the occurrence of subsequent POCE.

Previous limited data have suggested that early reinfarctions may be associated with an increased risk of subsequent mortality. However, the data were drawn from studies conducted in the thrombolysis era or during the early adoption of primary percutaneous coronary intervention.[29–32] Two more recent sub-analyses of the HORIZON-AMI trial demonstrated that reinfarction was associated with subsequent cardiac and all-cause mortality,[7] while target vessel revascularization increased the risk of subsequent myocardial infarctions without a significant impact on mortality.[6]

The additional value provided by our analysis is that the risk of recurrent adverse events is not influenced by the type of first event, whether TV or non-TV-related). Therefore, both who experiencing a TVF and those experiencing a non-TVF after STEMI should be followed up with careful secondary prevention.

Of note, the cumulative incidence curves of POCE for TVF-first and non–TVF-first events crossed and diverged during the later follow-up period, suggesting a change in hazards over time. By examining this trend with a landmark analysis, we observed a higher risk of late (5 to 10 years) POCE in the non–TVF-first group, primarily driven by a higher rate of late deaths. A non-TVF event may indicate the progression of atherosclerotic disease throughout the coronary tree, which could identify a population at even higher risk.

Furthermore, it is important to consider that risk factors, comorbidities and drug treatments can change over a 10-year follow-up period. Similarly, the patients' risk profile, which was initially stratified at the time of enrolment, can evolve over time. These factors may partly explain the delayed shift in hazards between patients with TVF-first and non–TVF-first events. This finding should be considered only as hypothesis-generating and require confirmation by further studies with the same length of follow-up.

Limitations

This study has several limitations. First, this was a post-hoc analysis and therefore its conclusions can only be considered as hypothesis-generating. Second, the need to use nonproportional hazard models to compare outcomes led to a loss of statistical power. Finally, several clinical and procedural characteristics (eg, Syntax scores, medical treatment during follow-up, etc), as well as other key clinical endpoints, such as stroke, bleeding, vascular complications, and hospitalization for heart failure, were not available for the analysis.

CONCLUSIONS

Our post-hoc analysis found that STEMI patients who experienced an adverse event during the 10-year follow-up were characterized by a worse cardiovascular risk profile, but outcomes did not seem to be associated with whether the first event was related to the target vessel of the primary percutaneous coronary intervention or not.

WHAT IS KNOWN ABOUT THE TOPIC?

- Data on very long-term outcomes in STEMI patients are limited.
- It is currently unclear whether the type of first event, and particularly its correlation with the target vessel of the primary percutaneous coronary intervention, influences subsequent outcomes in these patients.

WHAT DOES THIS STUDY ADD?

- Approximately one-third of STEMI patients experienced a POCE during the 10-year follow-up.
- These patients were characterized by a worse cardiovascular risk profile.
- Careful secondary prevention is needed regardless of the type of first adverse event occurring during follow-up.
- This analysis showed that outcomes did not seem to be influenced by whether the first adverse event was related to the target vessel or not.

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AUTHORS' CONTRIBUTION

S. Brugaletta and F.M. Verardi participated in study conception and design. J. Gomez-Lara, V. Jiménez-Diaz, M. Jiménez, P. Jiménez-Quevedo, R. Diletti, P. Bordes, G. Campo, A. Silvestro, J. Maristany, X. Flores, A. De Miguel-Castro, A. Iñiguez, A. Ielasi, M. Tespili, M. Lenzen, N. Gonzalo, M. Tebaldi, S. Biscaglia, P. Vidal-Cales, L. Ortega-Paz, R. Romaguera, J.A. Gomez-Hospital, P.W. Serruys, M. Sabaté and S. Brugaletta contributed to data acquisition. F.M. Verardi performed the analysis and interpretation of data, aided by S. Brugaletta, K. Bujak and P. Tolomeo. F.M. Verardi and S. Brugaletta drafted the manuscript. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

CONFLICTS OF INTEREST

S. Brugaletta is a consultant for Boston Scientific and iVascular. M. Sabaté has receiving consulting and speaker fees from Abbott Vascular and iVascular. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

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