ORIGINAL RESEARCH

Impact of Diabetes on 10-Year Outcomes Following ST-Segment–Elevation Myocardial Infarction: Insights From the EXAMINATION-EXTEND Trial

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BACKGROUND: Long-term outcomes of ST-segment–elevation myocardial infarction in patients with diabetes have been barely investigated. The objective of this analysis from the EXAMINATION-EXTEND (10-Years Follow-Up of the EXAMINATION trial) trial was to compare 10-year outcomes of patients with ST-segment–elevation myocardial infarction with and without diabetes.

METHODS AND RESULTS: Of the study population, 258 patients had diabetes and 1240 did not. The primary end point was patient-oriented composite end point of all-cause death, any myocardial infarction, or any revascularization. Secondary end points were the individual components of the primary combined end point, cardiac death, target vessel myocardial infarction, target lesion revascularization, and stent thrombosis. All end points were adjusted for potential confounders. At 10 years, patients with diabetes showed a higher incidence of patient-oriented composite end point compared with those without (46.5% versus 33.0%; adjusted hazard ratio [HR], 1.31 [95% CI, 1.05–1.61]; *P*=0.016) mainly driven by a higher incidence of any revascularization (24.4% versus 16.6%; adjusted HR, 1.61 [95% CI, 1.19–2.17]; *P*=0.002). Specifically, patients with diabetes had a higher incidence of any revascularization during the first 5 years of follow-up (20.2% versus 12.8%; adjusted HR, 1.57 [95% CI, 1.13–2.19]; *P*=0.007) compared with those without diabetes. No statistically significant differences were found with respect to the other end points.

CONCLUSIONS: Patients with ST-segment–elevation myocardial infarction who had diabetes had worse clinical outcome at 10 years compared with those without diabetes, mainly driven by a higher incidence of any revascularizations in the first 5 years.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04462315.

Key Words: diabetes ■ drug-eluting stent ■ percutaneous coronary intervention ■ ST-segment–elevation myocardial infarction

CLINICAL PERSPECTIVE

What Is New?

- Role of diabetes in influencing outcomes in patients with ST-segment–elevation myocardial infarction beyond 5 years is unknown.
- Our analysis is the first 10-year follow-up in patients with ST-segment–elevation myocardial infarction who have diabetes.
- Diabetes plays a continuous active role in determining outcomes in patients with ST-segment–elevation myocardial infarction up to 10 years, with a higher incidence of any revascularizations in the first 5 years of follow-up.

What Are the Clinical Implications?

- Patients with diabetes have a higher risk of stent-related events and adverse cardiovascular events after percutaneous coronary intervention, especially in a thrombotic clinical situation such as ST-segment–elevation myocardial infarction.
- Future studies should be focused on either dedicated stents on population with diabetes or specific long-term pharmacological treatments.

Nonstandard Abbreviations and Acronyms

POCE   patient-oriented combined end point
TVR   target vessel revascularization

Diabetes is a critical global health problem representing an important, independent risk factor conferring a 2-fold excess risk of coronary heart disease, ischemic stroke, and vascular death.[1] Patients with diabetes constitute about 30% to 40% of all patients undergoing percutaneous coronary intervention (PCI), and they are burdened with worse clinical and angiographic outcomes compared with patients without diabetes.[2–4] Furthermore, diabetes is often associated with unfavorable coronary anatomy because of a greater atherosclerosis burden and blood thrombogenicity, resulting in a higher risk of stent-related events and adverse cardiovascular events after PCI, especially in a thrombotic clinical situation such as ST-segment–elevation myocardial infarction (STEMI).[5–7]

Outcomes of patients with STEMI who have diabetes and are undergoing PCI have been improved by the use of a drug-eluting stent.[8,9] However, it is known that outcomes may be influenced by the type of stent implanted up to 5 years of follow-up, but thereafter it is rather dependent on patient-related factors.[10] The role of diabetes in influencing outcomes beyond 5 year is unknown.

We aim to analyze 10-year outcomes of patients with STEMI according to diabetes.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients and Study Design

This is a post hoc analysis study from the all-comer, multicenter, controlled and randomized EXAMINATION-EXTEND trial (10-Years Follow-Up of the EXAMINATION trial).[10] The EXAMINATION (Clinical Evaluation of the Xience-V Stent in Acute Myocardial Infarction) trial (NCT00828087) compared clinical outcomes of everolimus-eluting stent (Xience; Abbott Vascular, Santa Clara, CA) and Multilink Vision bare metal stent (Abbott Vascular) in 1504 patients with STEMI (randomized 1:1). It was an all-comers, multicenter, prospective, randomized, 2-arm, single-blind, controlled trial with broad inclusion criteria and few exclusion criteria, to ensure an all-comers population with STEMI representative of routine clinical practice. The primary end point was a patient-oriented composite end point of all-cause death, any myocardial infarction, and any revascularization at 1 year, whereas the secondary end point was a device-oriented combined end point of cardiac death, target vessel myocardial infarction, and ischemia-driven target vessel revascularization at 1 year. All end points were examined at 1 year and yearly up to 5 years.[11] The EXAMINATION trial completed follow-up at 5 years and was reinitiated as the EXAMINATION-EXTEND study to evaluate patient- and device-oriented composite end points at 10 years.

The EXAMINATION-EXTEND study is registered at ClinicalTrial.gov (NCT04462315) as an investigator-driven extension of follow-up of the EXAMINATION trial. Ethical approval for this study was granted at the institutions of the principal investigators (Hospital Clinic and Hospital Bellvitge, Barcelona, Spain). All patients provided written informed consent. The results of the EXAMINATION-EXTEND trial have been previously reported.[10] Data for this substudy were treated in the same way as in the main trial, without any specifics.

Study End Points

The primary end point of this study was patient-oriented combined end point (POCE) of all-cause death, any recurrent myocardial infarction (MI), and any revascularization at 10 years. Secondary end points included individual components of the primary end

point, cardiac death, target vessel MI and target lesion revascularization, and stent thrombosis. End points were defined according to the Academic Research Consortium definitions.[12]

All adverse events were reviewed, adjudicated, and classified by a Clinical Event Committee (Barcicore Lab, Barcelona, Spain).

All the end points have been stratified according to the presence of diabetes. Patients with diabetes were defined as those patients who were treated with insulin or hypoglycemic agents at the time of the primary PCI procedure.

Statistical Analysis

Continuous variables are presented as mean and SD (or medians and interquartile ranges, whenever appropriate), and categorical variables were expressed as absolute and relative frequency. Variables were compared using standardized difference, defined as difference in means or proportions divided by SE. For time-to-event variables, survival curves were constructed using Kaplan-Meier estimates, and hazard ratios (HRs) (95% CIs) are displayed using Cox regression model adjusted for clinical confounders that were considered of clinical significance (age, sex, previous smoker, arterial hypertension, hyperlipidemia, and body mass index). Landmark analyses were done from 0 to 5 years and from 5 to 10 years of follow-up to assess the effect of time on the occurrence of events.

Test for interaction was performed between diabetes status and type of stent used at the index event for each end point. To identify 10-year POCE predictors, 10-year mortality predictors, and 10-year revascularization predictors in the diabetes and nondiabetes subgroups, a Cox regression for 10-year POCE predictors and 10-year mortality and a competitive risk analysis for 10-year revascularization were performed, selecting candidate predictors based on directed acyclic graphs. The following candidate predictors were considered: age, sex, body mass index, smoking history, arterial hypertension, hyperlipidemia, family cardiovascular history, cardiovascular history (previous myocardial infarction, PCI, coronary artery bypass graft, or stroke), clinical condition (primary PCI [<12 hours], rescue PCI, PCI after successful thrombolysis, and late comer [>12 and <48 hours]), clinical status on admission (Killip), infarct-related artery, multivessel disease, cardiogenic shock, congestive heart failure, ejection fraction, and procedural characteristics.

Two-tailed $P<0.05$ was considered as significant. The SAS v.9.4 software was used for all analyses.

RESULTS

Baseline and Procedural Characteristics

Of 1498 patients recruited, 258 (17.2%) had diabetes and 1240 (82.8%) did not. Among patients with diabetes, 45 (17.2%) were treated with insulin. Complete
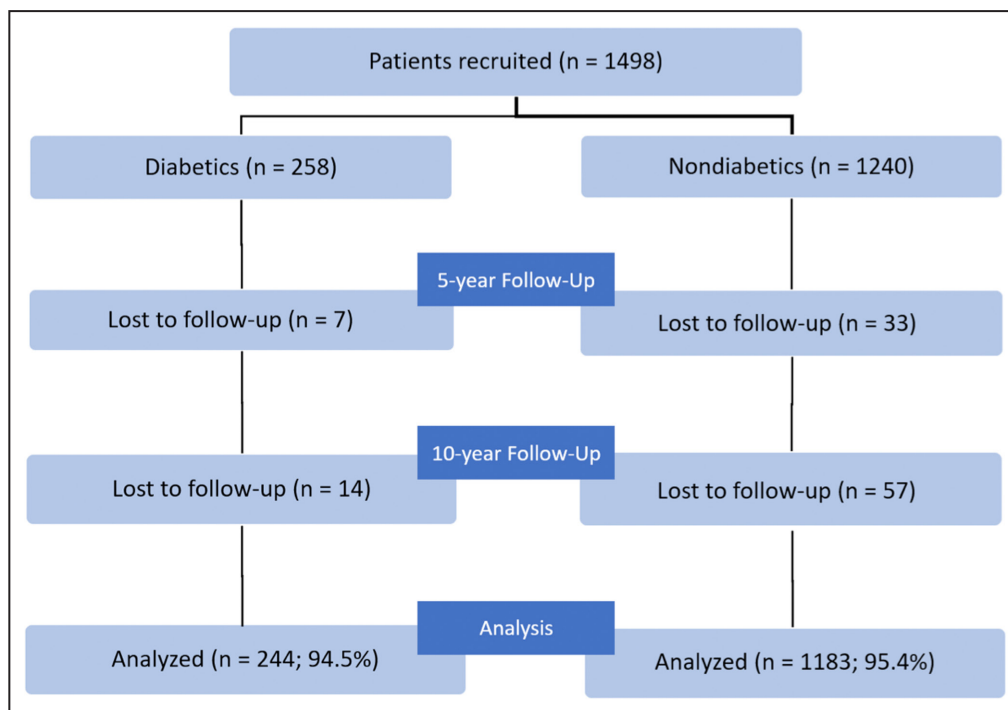

Figure 1. Flowchart of the study up to 10-year follow-up.
A total of 1498 patients were initially recruited. At 10 years, clinical follow-up was obtained in 95.2% of the patients.

Table 1. Baseline Characteristics

	Patients with diabetes (n=258)	Patients without diabetes (n=1240)	Standardized differences[†]
Baseline characteristics			
Age, mean (SD), y	65.8 (11.7)	60.2 (12.3)	0.47
Male sex, n (%)	212 (82.2)	1032 (83.2)	0.03
Body mass index, mean (SD), kg/m^2	28.1 (4.1)	27.2 (3.8)	0.23
Coronary risk factors, n (%)			
(Previous) smoker	155 (60.1)	927 (74.8)	−0.32
Arterial hypertension	175 (67.8)	550 (44.4)	0.49
Hyperlipidemia	135 (52.3)	520 (41.9)	0.21
Family history, n (%)	30 (11.6)	223 (18.0)	0.19
Cardiovascular history, n (%)			
Previous MI	17 (6.6)	63 (5.1)	0.06
Previous PCI	14 (5.4)	47 (3.8)	0.08
Previous CABG	1 (0.4)	9 (0.7)	−0.05
Previous stroke	9 (3.5)	22 (1.8)	0.11
Clinical condition, n (%)			0.12
Primary PCI (<12 h)	213 (82.6)	1055 (85.1)	
Rescue PCI	24 (9.3)	74 (6.0)	
PCI after successful thrombolysis	4 (1.6)	30 (2.4)	
Late comer (>12 h and <48 h)	17 (6.6)	80 (6.5)	
Clinical status on admission, n (%)			0.17
Killip I	220 (85.3)	1117 (90.1)	
Killip II	29 (11.2)	86 (6.9)	
Killip III	4 (1.6)	19 (1.5)	
Killip IV	5 (1.9)	13 (1.0)	
Infarct-related artery, n (%)			0.02
Left anterior descending artery	110 (42.6)	518 (41.8)	
Left circumflex	36 (14.0)	173 (14.0)	
Right coronary artery	110 (42.6)	541 (43.6)	
Left main	1 (0.4)	2 (0.2)	
Saphenous vein graft	1 (0.4)	6 (0.5)	
Multivessel disease, n (%)	37 (14.3)	151 (12.2)	0.340
Cardiogenic shock, n (%)	3 (1.2)	15 (1.2)	0.950
Congestive heart failure, n (%)	1 (0.4)	1 (0.1)	0.219
Ejection fraction at discharge, mean (SD), %	49.2 (10.7)	51.4 (10.4)	0.019

CABG indicates coronary artery bypass graft; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

[†]Standardized difference = difference in means or proportions divided by standard error.

10-year follow-up was obtained in 244 (94.5%) patients with and 1183 (95.4%) without diabetes (Figure 1).

Baseline characteristics according to the presence of diabetes are presented in Table 1. Diabetes was significantly associated with advanced age, higher body mass index, higher rate of hyperlipemia, and reduced left ventricular ejection fraction at discharge. Conversely, patients without diabetes were more often previous smokers and with familiar history of cardiovascular disease. Procedural characteristics of the primary PCI are shown in Table 2.

Clinical Outcomes of Patients With STEMI With Versus Without Diabetes

At 10 years, patients with diabetes exhibited a higher incidence of POCE (Figure 2A) compared with those without (46.5% versus 33.0%; adjusted HR, 1.31 [95% CI, 1.05–1.61]; P=0.016), mainly driven by a higher incidence of any revascularization (24.4% versus 16.6%; adjusted HR, 1.61 [95% CI, 1.19–2.17]; P=0.002) (Figure 2D). No statistically significant differences were found with respect to all-cause death (29.5%

Table 2. Procedural Characteristics of Primary PCI

	Patients with diabetes (n=258)	Patients without diabetes (n=1240)	Standardized differences†
Procedural characteristics			
TIMI flow before PCI ≤1, n (%)	157 (60.9)	845 (68.1)	0.17
Anticoagulation regimen, n (%)			
Unfractionated heparin	202 (78.3)	987 (79.6)	−0.03
Low-molecular-weight heparin	24 (9.3)	109 (8.8)	0.02
Bivalirudin	24 (9.3)	81 (6.5)	0.10
Antiplatelet regimen, n (%)			
Aspirin before PCI	243 (94.2)	1145 (92.3)	0.07
Clopidogrel before PCI	244 (94.6)	1174 (94.7)	−0.00
IIb/IIIa inhibitor, n (%)	115 (44.6)	670 (54.0)	−0.19
Manual thrombectomy, n (%)	155 (60.1)	821 (66.2)	−0.13
Type of stent, n (%)			0.07
EES/DES	137 (53.1)	614 (46.5)	
Multilink vision/BMS	121 (46.9)	626 (50.5)	
Direct stenting, n (%)	128 (49.6)	757 (61.1)	−0.23
Predilation, n (%)	126 (48.8%)	458 (36.9%)	0.24
Postdilatation, n (%)	38 (14.7)	183 (14.8)	−0.00
Overlapping stent, n (%)	77 (29.8)	327 (26.4)	0.08
No. of stents, mean (SD)	1.4 (0.7)	1.4 (0.6)	0.08
Total stent length, median (IQR), mm	23 (18–35)	23 (18–35)	0.05
Stent diameter, median (IQR), mm	3 (3–3.5)	3 (3–3.5)	−0.05
TIMI flow after PCI ≥2, n (%)	252 (97.7)	1203 (96.9)	0.17

BMS indicates bare metal stent; DES, drug-eluting stent; EES, everolimus-eluting stent; IQR, interquartile range; PCI, percutaneous coronary intervention; and TIMI, thrombolysis in myocardial infarction.

†Standardized difference = difference in means or proportions divided by standard error.

versus 19.0%; adjusted HR, 1.23 [95% CI, 0.94–1.62]; P=0.139) (Figure 2B) and to any MI (7.8% versus 5.3; adjusted HR, 1.60 [95% CI, 0.94–2.74]; P=0.085) (Figure 2C). Within any revascularization, differences were in terms of non–target vessel revascularization (non-TVR) (11.6% versus 6.0%; adjusted HR, 1.89 [95% CI, 1.20–2.99]; P=0.006), but not of TVR (12.8% versus 10.6%; adjusted HR, 1.35 [95% CI, 0.90–2.00]; P=0.14). No interaction was found in terms of TVR between diabetes and type of stent used at the time of the index revascularization (Table 3).

Low incidence of definite/probable stent thrombosis was found at 10 years without difference between patients with versus those without diabetes (2.3% versus 2.9%; adjusted HR, 0.81 [95% CI, 0.51–1.27]; P=0.61). No differences were found in terms of other end points.

Landmark analyses of POCE and its individual components are shown in Figure 3. There was insufficient evidence of a significant difference in the incidence of POCE in patients with diabetes versus those without (at the prespecified α of 0.05) either between 0 and 5 years (28.3% versus 20.4%; adjusted HR, 1.26 [95% CI, 0.96–1.66]; P=0.09) or between 5 and 10 years (25.0% versus 15.7%; adjusted HR, 1.35 [95% CI, 0.96–1.90]; P=0.08)

(Figure 3A). Specifically, in the first 5 years, any revascularization was higher in patients with diabetes versus those without (20.2% versus 12.8%; adjusted HR, 1.57 [95% CI, 1.13–2.19]; P=0.007), but not afterwards (5.7% versus 4.7%; adjusted HR, 1.62 [95% CI, 0.79–3.33]; P=0.19) (Figure 3D). No difference was found in terms of all-cause death and any MI either between 0 and 5 years or between 5 and 10 years (Figure 3B and 3C).

The 10-Year POCE, Mortality, and Revascularization Predictors in Patients With Diabetes

At multivariate analysis, age (HR, 1.05 [95% CI, 1.03–1.07]) and previous MI (HR, 3.17 [95% CI, 1.73–5.78]) were independent predictors of 10-year POCE. Age (HR, 1.14 [95% CI, 1.10–1.17]) and previous smoker (HR, 1.72 [95% CI, 1.05–2.81]) were independent predictors of 10-year mortality. At competitive risk analysis, hyperlipidemia (HR, 0.43 [95% CI, 0.23–0.80]), manual thrombectomy (HR, 0.53 [95% CI, 0.29–0.97]), IIb/IIIa inhibitor at procedure (HR, 2.00 [95% CI, 1.13–3.52]), and number of stents (HR, 0.25 [95% CI, 0.07–0.93]) were independent predictors of 10-year revascularization.
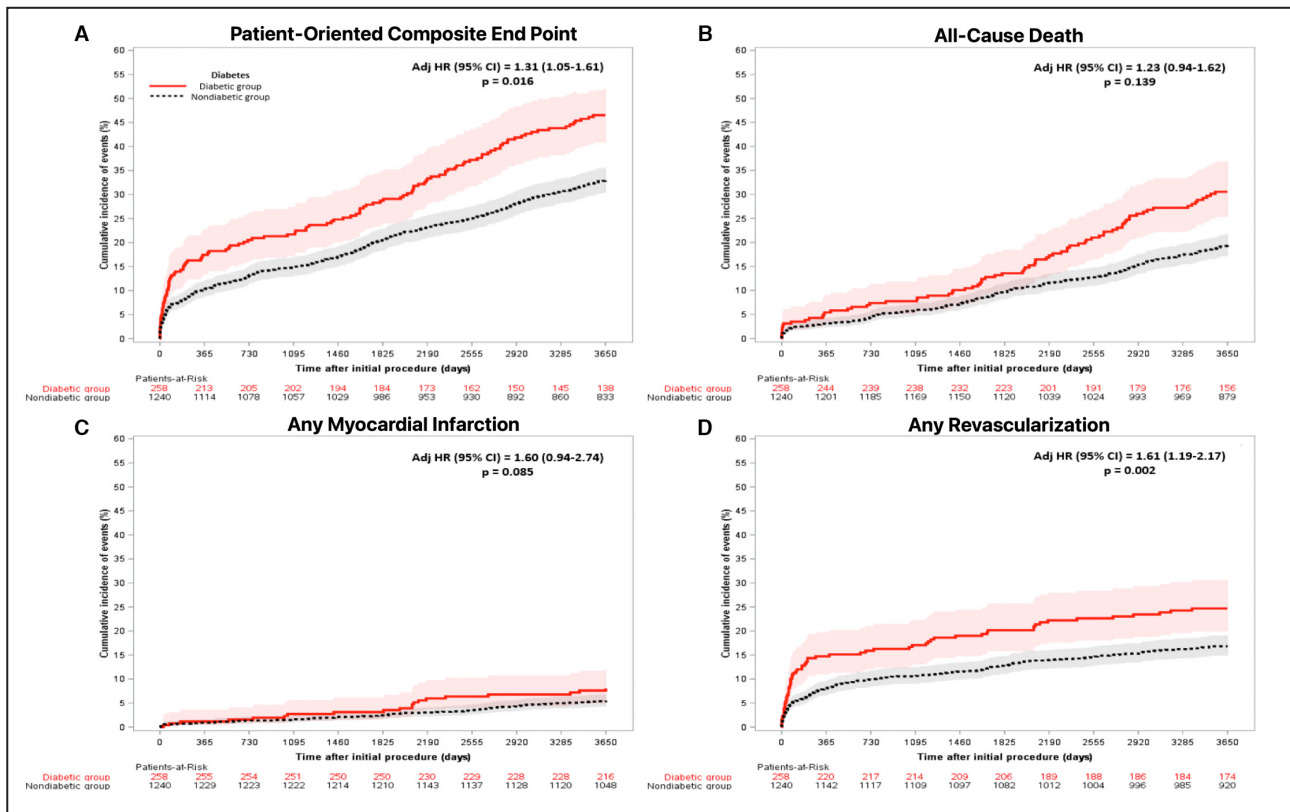
Figure 2.   The 10-year time-to-event curves for the primary end point and its individual components.
Cumulative 10-year incidence is shown with Kaplan-Meier yearly event rates. Patient-oriented outcome (**A**) and its individual components: all-cause death (**B**), any myocardial infarction (**C**), or any revascularization (**D**). Adj indicates adjusted; and HR, hazard ratio.

The 10-Year POCE, Mortality, and Revascularization Predictors in Patients Without Diabetes

At multivariate analysis, age (HR, 1.04 [95% CI, 1.03–1.05]), previous MI (HR, 1.52 [95% CI, 1.04–2.24]), and multivessel disease (HR, 1.34 [95% CI, 1.01–1.78]) were independent predictors of 10-year POCE. Age (HR, 1.10 [95% CI, 1.08–1.11]), unfractionated heparin at procedure (HR, 1.43 [95% CI, 1.01–2.02]), and low-molecular-weight heparin at procedure (HR, 1.78 [95% CI, 1.14–2.78]) were independent predictors of 10-year mortality. No independent predictors of 10-year revascularization were found at competitive risk multivariate analysis.

DISCUSSION

The main findings of this substudy of the EXAMINATION-EXTEND trial can be summarized as following: (1) at 10-year follow-up, patients with STEMI who have diabetes have worse clinical outcomes compared with those without diabetes, mainly attributable to higher incidence of any revascularization; (2) within any revascularization, non-TVR was more common in patients with diabetes versus those without; (3) specifically looking at the landmark analyses, the cumulative incidence of any revascularization was significantly higher in patients with diabetes in the time between 0 and 5 years of follow-up, but not between 5 and 10 years, compared with patients without diabetes; and (4) in patients with diabetes, age and previous MI were the independent predictors of POCE.

Previous studies have shown worse PCI outcomes in patients with diabetes versus those without up to 5 years of follow-up.[8,13–15] Our study extends this observation to a longer-term outcome of 10 years in a particularly interesting population of patients with STEMI. As a matter of fact, patients with STEMI represent a population with an acute thrombotic milieu, in whom follow-up may vary much, with some patients asymptomatic for many years and some others with many recurrent events. These varying events at follow-up are known to be influenced by the type of stent implanted at the culprit event up to 5 years, but not thereafter, where clinical factors, such as diabetes, may be more important than drug-eluting stent in determining such late outcomes.[10,16] Our study, specifically focusing on 10-year outcomes, shows that diabetes plays a continuous active role in determining outcomes in patients

Table 3. Clinical Events at 10 Years

	Patients with diabetes (n=258)	Patients without diabetes (n=1240)	Adjusted HR (95% CI)*
10-y Follow-up			
Patient-oriented composite end point, n (%)†	120 (46.5)	409 (33.0)	1.31 (1.05–1.61)
All-cause death, n (%)‡	76 (29.5)	235 (19.0)	1.23 (0.94–1.62)
Cardiac	42 (16.3)	124 (10.0)	1.15 (0.79–1.67)
Myocardial infarction, n (%)§	20 (7.8)	66 (5.3)	1.60 (0.94–2.74)
Target vessel related	11 (4.3)	41 (3.3)	1.45 (0.72–2.93)
Non–target vessel related	9 (3.5)	25 (2.0)	1.76 (0.76–4.05)
Revascularization, n (%)	63 (24.4)	206 (16.6)	1.61 (1.19–2.17)
Target lesion	21 (8.1)	86 (6.9)	1.38 (0.84–2.26)
Target vessel	33 (12.8)	131 (10.6)	1.35 (0.90–2.00)
Non–target vessel	30 (11.6)	75 (6.0)	1.89 (1.20–2.99)
Definite/probable stent thrombosis, n (%)‖	6 (2.3)	37 (2.9)	0.81 (0.51–1.27)

HR indicates hazard ratio.

*Adjusted for age, sex, previous smoker, arterial hypertension, hyperlipidemia, and body mass index.

†Combined end point of all-cause death, any recurrent myocardial infarction, and any revascularization.

‡Death was adjudicated according to the Academic Research Consortium definition.

§Myocardial infarction was adjudicated according to the World Health Organization extended definition.

‖Stent thrombosis was defined according to the Academic Research Consortium definition.

with STEMI, with POCE curves continuing to diverge over time, either during the first 5 years or between 5 and 10 years of follow-up (Figure 3A).

Overall, impaired outcomes of patients with STEMI who have diabetes are mainly driven by a high incidence of any revascularization: the profound metabolic disorder associated with diabetes determines a more aggressive and extensive coronary atherosclerosis that is inevitably associated with a higher incidence of revascularization beyond the culprit STEMI lesion treated in the initial acute event.[17,18] Non-TVR is the more common event recorded within the revascularization events of patients with diabetes versus those without (11.6% versus 6.0%).

Of note is that revascularization related to diabetes seems to be time dependent, with a higher incidence in any revascularization in the first 5 years of follow-up but not after (Figure 3D). The early interaction between STEMI proinflammatory state and glycemic metabolic disorder may explain this higher incidence of revascularization in the first years from the index event.[19,20] A slow and late achievement of optimization in diabetes medical treatment may also explain the reduced incidence of revascularization recorded between 5 and 10 years, compared with the first 5 years of follow-up.

Eventually, looking specifically at patients with diabetes, age and history of previous MI resulted as independent predictors of POCE. Considering independent predictors of mortality and revascularization either in patients with or in those without diabetes, whereas some appear easy to explain (eg, age and previous smoker as independent predictors of mortality in

patients with diabetes), some others may be the result of a play of chance and should be carefully interpreted (eg, such as use of unfractionated heparin or low-molecular-weight heparin at the time of the index procedure as independent predictor of mortality for patients without diabetes).

Despite the advancements of STEMI reperfusion strategies and medical therapy, there is still a gap in the long-term outcomes between patients with and without diabetes. Future clinical investigations should focus on either dedicated stents or pharmacological treatment, which may be able to improve over time prognosis of patients with STEMI who have diabetes.[21–23]

Limitations

This is a post hoc analysis, and the results should be interpreted with caution, as potential confounding factors cannot be excluded. However, it is the first 10-year report on patients with STEMI who have diabetes. No data about estimated glomerular filtration rate, hemoglobin A1c, and blood pressure, glycemic control, or change in diabetic therapy over time are available. No data were collected about patients without diabetes who developed diabetes during the follow-up. This study was performed in the "clopidogrel era," which may affect the clinical outcomes, especially in this high-risk group of patients; impact of dual antiplatelet therapy on such long-term outcome is, however, small. Eventually, we did not perform an analysis about the type of stent implanted and outcomes, as such analysis would not make any sense because of small
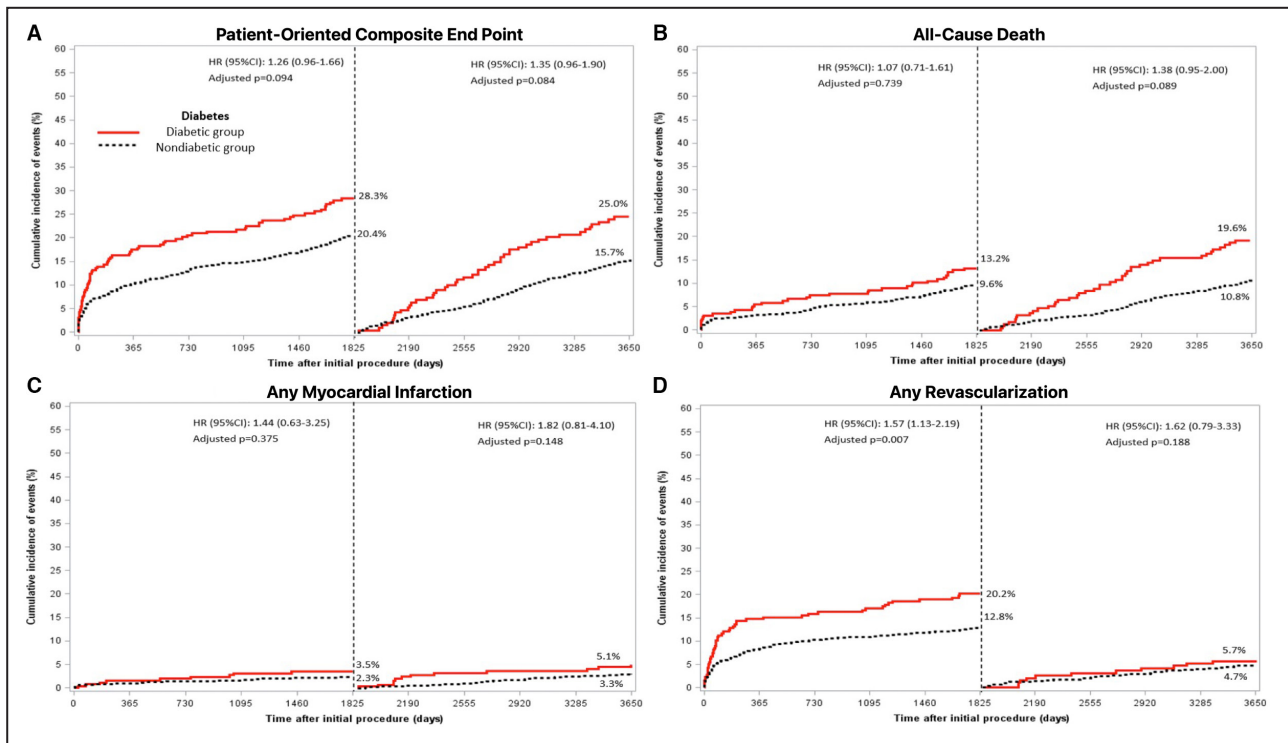
Figure 3. Landmark analysis of patient-oriented outcomes after ST-segment–elevation myocardial infarction.
This figure shows a landmark analysis, from 0 to 5 and from 5 to 10 years, for patient-oriented composite end point (**A**) and its individual components: all-cause death (**B**), any myocardial infarction (**C**), or any revascularization (**D**). HR indicates hazard ratio.

number of patients to be compared and because bare metal stents are rarely used in daily clinical practice; nevertheless, an interaction analysis between type of stent and diabetes was negative.

CONCLUSIONS

In this 10-year follow-up of patients with STEMI treated with primary PCI, patients with diabetes exhibit a worse clinical outcome compared with patients without diabetes. This was mainly driven by a higher incidence of any revascularization in the first 5 years. Future studies should be focused on either dedicated stents on population with diabetes or specific long-term pharmacological treatments.

ARTICLE INFORMATION

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