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Long-Term Outcomes of Stenting the Proximal Left Anterior Descending Artery in the PROTECT Trial

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ABSTRACT

OBJECTIVES This study sought to compare the outcomes of patients undergoing drug-eluting stent implantation according to lesion location within or outside the proximal left anterior descending (LAD) artery.

BACKGROUND Proximal LAD artery involvement is considered uniquely in revascularization guidelines. The impact of LAD lesion location on long-term outcomes after revascularization is poorly understood in context of current percutaneous coronary intervention and medical therapy.

METHODS Among 8,709 patients enrolled in PROTECT (Patient Related Outcomes with Endeavor Versus Cypher Stenting Trial), a multicenter percutaneous coronary intervention trial, we compared the outcomes of 2,534 patients (29.1%) (3,871 lesions [31.5%]) with stents implanted in the proximal LAD to 6,172 patients (70.9%) (8,419 lesions [68.5%]) with stents implanted outside the proximal LAD.

RESULTS At the 4-year follow-up, death rates were the same (5.8% vs. 5.8%; $p > 0.999$), but more myocardial infarctions occurred in the proximal LAD group (6.2% vs. 4.9%; $p = 0.015$). The rate of clinically driven target vessel failure (TVF) (14.8% vs. 13.5%; $p = 0.109$), major adverse cardiac event(s) (MACE) (15.0% vs. 13.7%; hazard ratio: 1.1; 95% confidence interval: 0.97 to 1.31; $p = 0.139$), and stent thrombosis (2.1% vs. 2.0%; $p = 0.800$) were similar. Drug-eluting stent type had no interaction with MACE or TVF. In multivariate analysis, the proximal LAD was a predictor of myocardial infarction ($p = 0.038$) but not of TVF ($p = 0.149$) or MACE ($p = 0.069$).

CONCLUSIONS In this study of contemporary percutaneous coronary intervention, proximal LAD location was associated with higher rates of myocardial infarction during the long-term follow-up, but there were no differences in stent thrombosis, death, TVF, or overall MACE. This finding may suggest that, in the drug-eluting stent era, proximal LAD no longer confers a different prognosis than other lesion sites. (Randomized Study Comparing Endeavor With Cypher Stents [PROTECT]; NCT00476957) (J Am Coll Cardiol Intv 2017;10:548–56) © 2017 by the American College of Cardiology Foundation.

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The left anterior descending (LAD) artery supplies 45% to 55% of the left ventricle mass. Therefore, patients with LAD disease are thought to be at higher risk for future cardiovascular events. Appropriateness criteria and the revascularization guidelines use the LAD location to determine the best treatment (1,2). In the presence of ischemia when a lesion in the right coronary artery (RCA) or left circumflex artery is detected, we can continue with stenting. In contrast, location of the lesion in the proximal LAD identifies a higher risk subset of patients in whom the need for, and the method of, revascularization should be further discussed.

The data comparing outcomes after revascularization for proximal LAD versus nonproximal LAD are limited (3-6). It is not well understood whether the presence of LAD narrowings requiring revascularization still remains today a predictor of adverse outcome after percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) and with current medical therapy. Therefore, we aimed to compare long-term outcomes in patients with or without target lesions in the proximal LAD.

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We analyzed the 4-year outcomes in 8,709 patients who underwent coronary artery stenting in PROTECT (Patient Related Outcomes with Endeavor Versus Cypher Stenting Trial), classified according to lesion location within or outside the proximal LAD. We hypothesized that, in this large multinational trial, which encompasses a broad range of practice settings enrolling patients with single-vessel and multivessel disease, treatment of proximal LAD lesions would be associated with similar outcomes as treatment of nonproximal LAD lesions.

METHODS

PROTECT was an open-label, multicenter trial that randomized patients undergoing elective, unplanned, or emergency procedures in native coronary arteries to the Endeavor zotarolimus-eluting stent (E-ZES) (Medtronic, Santa Rosa, California) or the Cypher sirolimus-eluting stent (C-SES) (Cordis, Johnson & Johnson, Miami Lakes, Florida). The trial involved 196 participating hospitals in 36 countries across 5 continents and was conducted between May 21, 2007, and December 22, 2008. The study design has been described previously, and outcomes were previously published (7,8). The protocol was approved by the institutional ethical committee of each center and/or the centralized national ethical board in accordance with local regulations. This trial was registered with ClinicalTrials.gov (NCT00476957).

The present study included all patients from the PROTECT trial and compared the cohort of patients who received at least 1 stent in the proximal LAD with those who received stents only in nonproximal LAD locations. Proximal LAD was defined according to the Coronary Artery Surgery Study classification (9): end of left main to the first large septal or first diagonal, whichever is most proximal. In cases in which stents were implanted in the proximal LAD and another location, such as the RCA or left circumflex artery, they were categorized in the proximal LAD group.

PROCEDURE. Treatment of coronary lesions was done in accordance with the manufacturer's instructions and local or national guidelines. Antiplatelet therapy with aspirin and clopidogrel (75 mg) or another thienopyridine derivative was started 3 days before the procedure or through a loading dose (clopidogrel 300 to 600 mg or its equivalent for other thienopyridine) for patients not yet taking these medications. During the procedure, 96.7% of patients were treated with clopidogrel, 0.27% were treated with ticlopidine, and 5.72% received another antiplatelet/antithrombin drug. Post-procedure, aspirin was prescribed indefinitely, and thienopyridine therapy was prescribed for a minimum of 3 months and up to 12 months (1,2), or for longer at the physician's discretion. Prolongation or reinstitution of thienopyridine therapy was allowed where clinically indicated.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

C-SES = Cypher sirolimus-eluting stent(s)

DES = drug-eluting stent(s)

E-ZES = Endeavor zotarolimus-eluting stent(s)

LAD = left anterior descending

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCA = right coronary artery

TVF = target vessel failure

Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck-Sharpe-Dohme, Novartis, Otsuka, Pfizer, Roche, The Medicines Company, and Vivus outside the submitted work; and grants and personal fees from Sanofi and Servier outside the submitted work. Dr. Wijns has received grants from Medtronic and Cordis J&J during the conduct of the study; grants from Boston Scientific, Biosensors, Terumo, MI-CELL, Pfizer, and Boehringer Ingelheim outside the submitted work; grants and non-financial support from Abbott Vascular, AstraZeneca, Biotronik, Cardio3 BioSciences, and St. Jude outside the submitted work; non-financial support from Volcano outside the submitted work; and has served as non-executive board member and stockholder of Cardio3 BioSciences (now Celyad), Argonauts, and Genae Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Baseline Patient Characteristics

	Proximal LAD (N = 2,534 Patients, N = 3,871 Lesions)	Nonproximal LAD (N = 6,172 Patients, N = 8,419 Lesions)	p Value
Age (yrs)	61.8 ± 10.8 (2,534)	62.3 ± 10.5 (6,172)	0.047
Body mass index (kg/m^2)	27.6 ± 4.5 (2,532)	27.9 ± 4.5 (6,171)	0.003
Male	76.0% (1,926/2,534)	76.5% (4,719/6,172)	0.657
History of smoking	52.8% (1,339/2,534)	59.5% (3,675/6,172)	<0.001
Current smoker	21.6% (547/2,534)	26.5% (1,635/6,172)	<0.001
Diabetes mellitus	26.9% (682/2,534)	28.0% (1,726/6,172)	0.329
Insulin dependent	6.5% (164/2,534)	7.2% (444/6,172)	0.247
Hypertension	61.9% (1,568/2,534)	64.9% (4,003/6,172)	0.009
Hyperlipidemia	60.1% (1,523/2,534)	63.3% (3,904/6,172)	0.006
Premature coronary artery disease in a first-degree relative	33.6% (732/2,180)	34.8% (1,867/5,358)	0.297
Previous MI	19.3% (489/2,534)	21.1% (1,302/6,172)	0.062
Previous coronary artery bypass graft surgery	1.9% (47/2,534)	6.1% (376/6,172)	<0.001
Previous percutaneous coronary intervention	9.5% (240/2,534)	13.8% (849/6,172)	<0.001
Previous stroke	3.0% (77/2,534)	3.1% (192/6,172)	0.892
Procedure indication			<0.001
All (acute) MI	25.1% (635/2,534)	26.2% (1,618/6,172)	
STEMI	9.8% (249/2,534)	8.0% (491/6,172)	
Non-STEMI	15.2% (386/2,534)	18.3% (1,127/6,172)	
Unstable angina	21.3% (539/2,534)	17.8% (1,099/6,172)	
Stable angina	48.8% (1236/2,534)	48.9% (3,020/6,172)	
Silent ischemia	4.9% (124/2,534)	7.0% (435/6,172)	
Left ventricular ejection fraction (%)	57.8 ± 13.2 (1,314)	58.8 ± 12.3 (3,174)	0.019
Serum creatinine (μmol/l)	86.9 ± 28.6 (2,364)	88.4 ± 37.5 (5,785)	0.053
Complex patients	63.3% (1,605/2,534)	55.9% (3,449/6,172)	<0.001

Values are mean ± SD (N) or % (n/N).
LAD = left anterior descending; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

All deaths and all triggers for suspected myocardial infarction (MI), stent thrombosis, or bleeding were adjudicated by a clinical events committee, which was composed of cardiologists who were not participating in the study, who were unaware of the assigned treatment, and who had access to case records as provided by the investigators and source documents such as angiograms, electrocardiographs, autopsy reports, and discharge letters. Strokes (not related to bleeding) were not adjudicated by the clinical events committee.

Cardiac biomarker data (creatine kinase, creatine kinase myocardial band [if creatine kinase was outside the normal range], and troponin) were obtained within 72 h of the procedure and at least once after the procedure. Centers were instructed to report all obtained biomarker values for event adjudication. A 3-year follow-up visit with electrocardiography was mandatory. Patient informed consent and source documentation of all reported events were monitored in all patients. Other data monitoring was done in 30% of randomly selected patients at all participating centers.

DATA COLLECTION. The PROTECT trial was sponsored by Medtronic, and the Medtronic Bakken Research Center (Maastricht, the Netherlands) was responsible for study management. The steering committee designed the study in collaboration with the sponsor. An independent academic research organization (Cardialysis, Rotterdam, the Netherlands), blinded to the patients' study stent assignment, was responsible for the organization of meetings involving the clinical events committee and data safety monitoring board and for the data analysis. All data collection, data analysis, data interpretation, and writing of the report were done by independent groups, and the sponsor had only oversight of these activities.

DEFINITIONS. Major adverse cardiac events (MACE) included all-cause death, MI (Q-wave and non-Q-wave), emergent coronary artery bypass graft (CABG) surgery, or repeat clinically indicated target lesion percutaneous or surgical revascularization. Target vessel failure (TVF) included cardiac death, target vessel MI (Q-wave and non-Q-wave), or clinically driven target vessel revascularization by percutaneous or surgical methods. Target lesion failure included death from cardiac causes, target vessel MI, and target lesion revascularization. Stent thrombosis was defined according to the Academic Research Consortium definition and listed as definite/probable stent thrombosis (10).

Patients were defined as "complex" if they met at least 1 of the following clinical or lesion characteristics: renal insufficiency or failure (defined as creatinine ≥140 μmol/l [1.6 mg/dl]), left ventricular ejection fraction <30%, the occurrence of an acute MI within the previous 72 h, >1 lesion per vessel, ≥2 vessels with stents, a lesion measuring >27 mm, bifurcation, bypass grafts, in-stent restenosis, unprotected left main artery, lesions with thrombus, or total occlusion (pre-procedure TIMI [Thrombolysis In Myocardial Infarction] flow grade 0).

STATISTICAL ANALYSIS. Dichotomous and categorical variables were reported as counts and percentages; between-group differences were assessed with the Fisher exact test for dichotomous variables and Cochran-Mantel-Haenszel Modified Ridit Scores for categorical variables. Continuous variables were reported as mean ± SD and were compared with a 2-sample Student *t* test. All analyses were performed according to the intention-to-treat principle in the entire enrolled study population. The incidence of clinical outcomes was calculated using the Kaplan-Meier method and compared using the log-rank test.

For each event, a multivariate model was constructed that examined the effect of several

individual baseline clinical and angiographic characteristics, including proximal LAD target lesion, on outcomes (MACE, TVF, MI). On first pass, the model includes all variables simultaneously. Covariates with a p value of <0.25 ('entry p value') are retained in the model, which is then rerun to identify covariates with a p value of <0.15 ('stay p value') (stepwise selected model). This model provides a set of important, predictive variables and avoids multi-collinearity. For all outcomes, a 2-sided p value of <0.05 represents statistical significance. We also performed a sensitivity analysis using a random effect model to account for the large number of hospitals in the clinical study from 36 different countries. The results of this analysis were consistent with the primary results (data not shown). All analyses were performed with SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Among the 8,709 patients enrolled in PROTECT, 2,534 patients (29.1%) (3,871 lesions [31.5%]) were implanted with stents in the proximal LAD, and 6,172 patients [70.9%] (8,419 lesions [68.5%]) were implanted with stents outside the proximal LAD. Compared with patients in the nonproximal LAD cohort, the cohort of patients with proximal LAD stenting was slightly younger, had fewer atherosclerotic risk factors, had fewer previous coronary revascularization procedures, and more of these patients had unstable angina (Table 1). The denominators are different for certain characteristics in Table 1: left ventricular ejection fraction, serum creatinine levels, and family history of coronary artery disease were not collected for all patients, because the protocol did not require patients to undergo echocardiography or a creatinine blood test at baseline, and some centers did not report family history of coronary artery disease.

Table 2 provides lesion characteristics of patients treated in the proximal and nonproximal LAD cohorts. The proximal LAD cohort included patients with additional coronary lesions in locations other than the proximal LAD: the left circumflex artery was treated in 9.9% and the RCA in 10.5% of the 3,871 total lesions. In the nonproximal LAD cohort, the mid or distal LAD was treated in 31.6% of the 8,419 lesions.

As compared with the nonproximal LAD cohort, lesions in the proximal LAD cohort more often involved a bifurcation, had less tortuosity, and were located in a reference vessel of larger diameter. Patients in the proximal LAD cohort also had more lesions treated (1.5 ± 0.8 vs. 1.3 ± 0.7; p < 0.001), more stents implanted (1.7 ± 1.0 vs. 1.6 ± 0.9; p < 0.001), and a longer overall stent length (33.5 ± 22.1 vs. 30.3 ± 20.1; p < 0.001). The stent diameter and stent length per lesion were similar.

TABLE 2 Lesion and Procedure Characteristics

	Proximal LAD (N = 2,534 Patients, N = 3,871 Lesions)	Nonproximal LAD (N = 6,172 Patients, N = 8,419 Lesions)	p Value
Vessel location per lesion			<0.001
LAD (mid and distal)	79.2 (3,067/3,871)	31.6 (2,660/8,419)	
Left circumflex	9.9 (383/3,871)	28.7 (2,414/8,419)	
Right coronary artery	10.5 (405/3,871)	38.3 (3,221/8,419)	
Left main	0.4 (16/3,871)	1.0 (88/8,419)	
Bypass graft	0.0 (0/3,871)	0.4 (36/8,419)	
In-stent restenosis	1.0 (39/3,871)	1.1 (89/8,418)	0.849
Lesion type			0.277
Restenosis after previous PTCA	0.3 (11/3,871)	0.4 (33/8,418)	
In-stent restenosis	1.0 (39/3,871)	1.1 (89/8,418)	
Total stent length per patient, mm	33.5 ± 22.1	30.3 ± 20.1	<0.001
Chronic total occlusion*	2.2 (85/3,871)	3.1 (260/8,416)	0.006
Bifurcation	21.0 (812/3,871)	14.3 (1,203/8,416)	<0.001
Moderate/severe calcification	29.2 (1,131/3,871)	28.9 (2,428/8,416)	0.684
Moderate/severe tortuosity	18.8 (729/3,870)	24.7 (2,087/8,414)	0.684
TIMI flow grade 0/1	13.3 (516/3,871)	15.7 (1,326/8,416)	<0.001
Thrombus	8.1 (313/3,871)	7.6 (640/8,416)	0.364
ACC/AHA lesion class B2/C	56.1 (2,170/3,870)	54.1 (4,550/8,415)	0.039
Reference vessel diameter (mm)	3.0 ± 0.5 (3,866)	2.9 ± 0.5 (8,400)	<0.001
Minimum lumen diameter (mm)	0.5 ± 0.4 (3,866)	0.5 ± 0.4 (8,403)	0.001
Diameter stenosis (%)	82.5 ± 12.5 (3,867)	82.9 ± 13.0 (8,408)	0.069
Lesion length (mm)	17.7 ± 8.6 (3,866)	17.7 ± 9.4 (8,400)	0.808
Procedure characteristics			
No. of vessels treated per patient	1.3 ± 0.5 (2,534)	1.2 ± 0.4 (6,172)	<0.001
No. of lesions treated per patient	1.5 ± 0.8 (2,534)	1.3 ± 0.7 (6,172)	<0.001
No. of stents per patient	1.7 ± 1.0 (2,534)	1.6 ± 0.9 (6,172)	<0.001
No. of stents per lesion	1.1 ± 0.4 (3,871)	1.2 ± 0.5 (8,419)	0.009
Lesions with pre-dilatation	67.5 (2,612/3,871)	68.9 (5,801/8,419)	0.117
Post-procedure characteristics			
Residual stenosis (%)	2.0 ± 9.0 (3,868)	2.1 ± 10.0 (8,414)	0.319
TIMI flow grade 2/3	99.6 (3,854/3,871)	99.4 (8,365/8,418)	0.245

Values are % (n/N) or mean ± SD. *TIMI flow grade 0, no unstable angina, no myocardial infarction within 72 h.
ACC/AHA = American College of Cardiology/American Heart Association; PTCA = percutaneous coronary angioplasty; TIMI = Thrombolysis In Myocardial Infarction.

Lesion success, defined as attainment of <50% residual stenosis of the target lesion, was achieved in 99.6% in the proximal LAD cohort versus 99.4% in the nonproximal LAD cohort (p = 0.149). Procedure success, defined as attainment of <50% residual stenosis of all the target lesions and no in-hospital MACE, was achieved in 97.0% in the proximal LAD group versus 97.0% in the nonproximal LAD group (p = 0.961).

CLINICAL OUTCOMES. Table 3 provides clinical outcomes in patients in the proximal LAD and nonproximal LAD cohorts. There was a high rate of follow-up of the participants in this study: 99% for 1 year, 98% for 2 and 3 years, and 97% for 4 years.

TABLE 3 Clinical Outcomes to 4 Yrs in Patients Treated for Proximal LAD Vs. Nonproximal LAD

	30 Days			6 Months			1 Yr		
	Proximal LAD (n = 2,525)	Nonproximal LAD (n = 6,156)	p Value	Proximal LAD (n = 2,520)	Nonproximal LAD (n = 6,133)	p Value	Proximal LAD (n = 2,518)	Nonproximal LAD (n = 6,112)	p Value
MACE	3.4 (86)	2.9 (181)	0.273	5.4 (137)	4.6 (282)	0.110	7.5 (188)	6.2 (376)	0.027
Death	0.7 (17)	0.3 (19)	0.025	1.1 (28)	0.8 (48)	0.162	1.7 (42)	1.3 (79)	0.190
Cardiac death	0.6 (16)	0.3 (18)	0.035	1.0 (24)	0.6 (37)	0.089	1.3 (33)	0.9 (56)	0.102
MI	3.0 (77)	2.5 (152)	0.140	3.6 (90)	2.7 (166)	0.036	3.9 (99)	2.8 (174)	0.010
TV MI	3.0 (77)	2.4 (148)	0.088	3.5 (89)	2.6 (160)	0.023	3.8 (95)	2.7 (166)	0.010
Emergent CABG	0.1 (2)	0.2 (10)	0.528	0.1 (3)	0.2 (11)	0.769	0.3 (8)	0.2 (13)	0.347
TLF	3.4 (85)	2.8 (171)	0.143	5.3 (133)	4.3 (261)	0.041	7.0 (177)	5.6 (341)	0.011
TVF	3.5 (89)	3.0 (187)	0.252	6.1 (154)	5.1 (313)	0.067	8.7 (219)	7.0 (430)	0.009
Clinically driven TLR	0.5 (12)	0.5 (28)	0.863	2.0 (50)	1.6 (96)	0.169	3.5 (88)	2.6 (157)	0.022
Clinically driven TVR	0.6 (16)	0.8 (50)	0.418	2.8 (71)	2.6 (159)	0.557	5.3 (133)	4.3 (261)	0.047
Stent thrombosis	0.8 (21)	0.6 (36)	0.191	1.0 (25)	0.7 (42)	0.139	1.2 (29)	0.8 (50)	0.138
Hemorrhagic stroke while on clopidogrel	0.0 (1)	0.1 (5)	0.679	0.1 (2)	0.1 (8)	0.734	0.1 (3)	0.2 (13)	0.425

TABLE 3 Continued

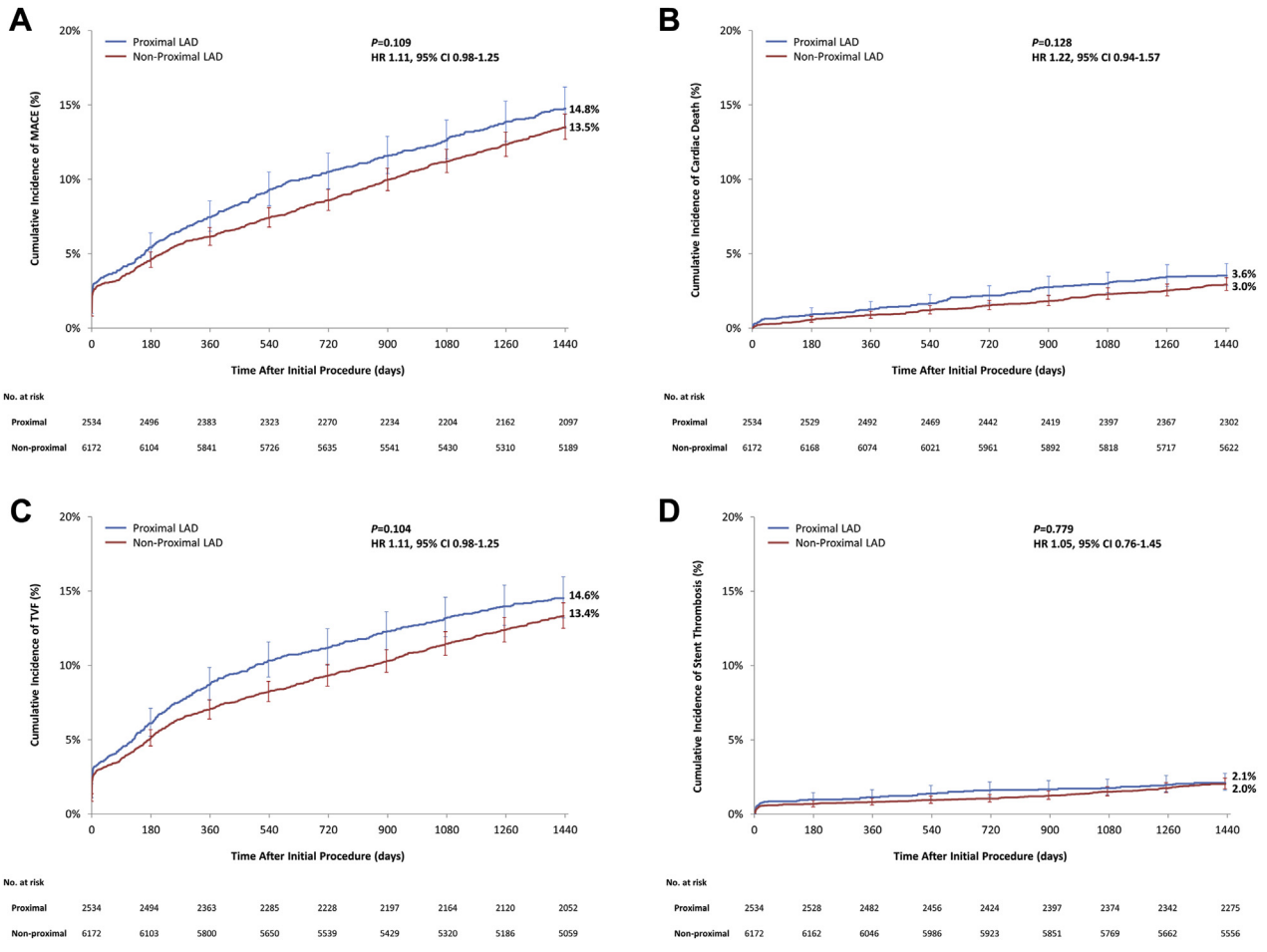
	2 Yrs			3 Yrs			4 Yrs		
	Proximal LAD (n = 2,507)	Nonproximal LAD (n = 6,084)	p Value	Proximal LAD (n = 2,491)	Nonproximal LAD (n = 6,041)	p Value	Proximal LAD (n = 2,459)	Nonproximal LAD (n = 5,973)	p Value
MACE	10.5 (264)	8.6 (526)	0.007	12.7 (317)	11.3 (684)	0.070	15.0 (369)	13.7 (821)	0.139
Death	3.2 (79)	2.8 (169)	0.357	4.4 (109)	4.3 (261)	0.907	5.8 (143)	5.8 (348)	>0.999
Cardiac death	2.2 (56)	1.6 (95)	0.037	3.1 (76)	2.3 (141)	0.059	3.6 (89)	3.0 (178)	0.132
MI	4.8 (120)	3.3 (201)	0.001	5.4 (134)	4.1 (249)	0.013	6.2 (152)	4.9 (290)	0.015
TV MI	4.3 (107)	3.0 (184)	0.005	4.7 (117)	3.6 (219)	0.023	5.3 (130)	4.2 (248)	0.024
Emergent CABG	0.4 (9)	0.2 (14)	0.357	0.4 (11)	0.3 (17)	0.297	0.5 (12)	0.4 (21)	0.344
TLF	9.3 (234)	7.1 (435)	<0.001	11.0 (274)	8.9 (535)	0.003	12.3 (302)	10.4 (620)	0.013
TVF	11.2 (281)	9.3 (568)	0.009	13.3 (331)	11.5 (696)	0.023	14.8 (363)	13.5 (805)	0.127
Clinically driven TLR	4.8 (121)	3.4 (207)	0.002	5.5 (138)	4.2 (253)	0.007	6.1 (150)	4.9 (291)	0.024
Clinically driven TVR	7.1 (178)	5.9 (361)	0.045	8.4 (209)	7.3 (440)	0.080	9.4 (230)	8.6 (513)	0.272
Stent thrombosis	1.6 (40)	1.1 (64)	0.039	1.8 (44)	1.5 (91)	0.391	2.1 (52)	2.0% (121)	0.800
Hemorrhagic stroke while on clopidogrel	0.1 (3)	0.3 (17)	0.220	0.2 (4)	0.3 (20)	0.260	0.2 (5)	0.4 (22)	0.290

Values are % (n). MACE included all-cause death, MI (Q-wave and non-Q-wave), emergent CABG surgery, or repeat clinically indicated target lesion percutaneous or surgical revascularization. CABG = coronary artery bypass graft; MACE = major adverse cardiac events; TV MI = MI not clearly attributable to a nontarget vessel; TLF = target lesion failure; TLR = target lesion revascularization; TVF = target vessel failure; other abbreviations as in Table 1.

MACE was higher in the proximal LAD cohort at 1, 2, and 3 years, but not at 4 years (15.0% vs. 13.7%; p = 0.139) (hazard ratio: 1.1 [95% confidence interval (CI): 0.97 to 1.31]; p = 0.139). At 30 days, cardiac mortality was higher in the proximal LAD cohort (0.6% vs. 0.3%; p = 0.035), but this was not observed at later time points (3.6% vs. 3.0%, hazard ratio: 1.2 [95% CI: 0.91 to 1.61]; p = 0.132). At 4 years of follow-up, target lesion failure was 12.3% in the proximal LAD cohort versus 10.4% in the nonproximal LAD cohort (p = 0.127), whereas TVF was similar 14.8% versus 13.5% (p = 0.127) (hazard ratio: 1.1 [95% CI: 0.98 to 1.33]; p = 0.109). More MI occurred in the proximal LAD group (6.2% vs. 4.9%; p = 0.015) (**Table 3**). **Figure 1** provides the cumulative incidence of events (Kaplan-Meier estimates) in patients in the proximal LAD and nonproximal LAD cohorts.

Patients with an E-ZES had a lower incidence of definite or probable stent thrombosis both in the proximal LAD cohort (1.5% vs. 2.7%; p = 0.050) and the nonproximal LAD cohort (1.6% vs. 2.4%; p = 0.027). There were no other differences in clinical outcomes between the E-ZES and C-SES arms in both the proximal and nonproximal LAD cohorts. Yet in the proximal LAD there were numerically fewer target lesion failures and TVFs (11.5% vs. 13.0% [p = 0.269] and 14.4% vs. 15.1% [p = 0.649]) in the C-SES arm versus the E-ZES arm and numerically more target vessel MI and cardiac death (Online Table 1). The same efficacy-safety trend, although less pronounced, was observed in the nonproximal LAD cohort. Online Tables 2 and 3 show the baseline and lesion characteristics for patients with proximal LAD versus nonproximal LAD stent treatment, stratified by stent type.

FIGURE 1 4-Year Cumulative Incidence of Events Stratified by Proximal LAD Patients Versus Nonproximal LAD



Based on Kaplan-Meier analysis: **(A)** major adverse cardiac events (MACE); **(B)** cardiac death; **(C)** target vessel failure (TVF); **(D)** stent thrombosis; CI = confidence interval; HR = hazard ratio; LAD = left anterior descending.

DUAL ANTIPLATELET THERAPY AND STENT THROMBOSIS. The rate of adherence to dual antiplatelet therapy was high. The use of dual antiplatelet drugs at discharge (96.7% and 96.4% [p = 0.583]) and at 6 months' follow-up (95.1% and 95.1% [p = 0.936]) was similar in both groups. At 1 year, the rate was 88.8% in the proximal LAD group and 87.3% in the nonproximal LAD group (p = 0.059); at 2 years it was 38.0% and 35.8% (p = 0.063); at 3 years, 30.5% and 29.7% (p = 0.48); and at 4 years, 29.2% and 26.8% (p = 0.028), respectively. The bleeding rate was similar.

Definitive and probable stent thrombosis was similar for both the proximal and nonproximal LAD cohorts (1.2% vs. 0.8% at 1 year [p = 0.19] and 2.1% vs. 2.0% at 4 years [p = 0.28], respectively) (Figure 1). Hemorrhagic stroke while on clopidogrel was low for both cohorts (0.1% vs. 0.2% [p = 0.425] at 1 year and 0.2% vs. 0.4% [p = 0.290] at 4 years).

MULTIVARIATE ANALYSES. Multivariate analyses was conducted on baseline variables associated with MACE (Table 4), TVF (Table 5), and MI (Appendix Table 4) at 4 years. Stent placement at the proximal LAD was not found to have a statistically significant correlation with higher TVF (p = 0.15) or MACE (p = 0.069). However, there was a significant correlation with MI (p = 0.038).

DISCUSSION

In this prospective, multinational, multicenter, randomized study with 8,709 patients treated with DES for single-vessel and multivessel disease, there was no

TABLE 4 Baseline Patient and Lesion Characteristics Correlated With Major Adverse Cardiac Events at 4 Years by Multivariate Analysis

	Multivariate	
	OR	p Value
Age (yrs)	1.032	<0.001
Diabetes mellitus	1.451	<0.001
Hypertension	1.212	0.008
Previous peripheral vascular disease	1.654	<0.001
Previous MI	1.165	0.055
Previous PCI	1.257	0.014
Previous CABG	1.304	0.045
Calcified lesion (moderate/severe vs. none/mild)	1.409	<0.001
Bifurcation lesion	1.147	0.073
Pre-procedure reference vessel diameter, mm	0.898	0.125
Multiple vessels vs. single vessel	–	–
Multiple lesions vs. single lesion	–	–
Tortuosity (moderate/severe vs. none)	–	–
Proximal LAD	1.138	0.069
BMI	–	–
Current smoker	1.352	<0.001
History of hyperlipidemia	–	–
Procedure indication (acute MI or UA vs. stable angina or silent ischemia)	1.102	0.140
LVEF percent	0.992	0.002
Pre-TIMI (0 or 1 vs. 2 or 3)	–	–
Lesion class (B2 or C vs. A or B1)	–	–
Total stent length per patient	1.010	<0.001
Pre-procedure minimum lumen diameter	–	–
Pre-procedure diameter stenosis (%)	–	–
No. of vessels treated per patient	–	–
No. of lesions treated per patient	–	–

The multiple regression used an entry criterion of 0.25 and a stay criterion of 0.15. For the binary variables above, ORs are calculated by comparing "yes" vs. "no" if no specification.

BMI = body mass index; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; UA = unstable angina; other abbreviations as in Tables 1 and 2.

TABLE 5 Multivariate Analysis on TVF to 4 Years for PROTECT Patients

	Multivariate	
	OR	p Value
Age (yrs)	1.015	<0.001
Diabetes mellitus	1.349	<0.001
Hypertension	1.365	<0.001
Previous peripheral vascular disease	1.266	0.081
Previous MI	–	–
Previous PCI	1.424	<0.001
Previous CABG	1.288	0.061
Calcified lesion (moderate/severe vs. none/mild)	1.512	<0.001
Bifurcation lesion	1.202	0.016
Pre-procedure reference vessel diameter, mm	0.775	<0.001
Multiple vessels vs. single vessel	1.979	0.002
Multiple lesions vs. single lesion	–	–
Tortuosity (moderate/severe vs. none)	–	–
Proximal LAD	1.111	0.143
BMI	–	–
Current smoker	1.265	0.004
History of hyperlipidemia	–	–
Procedure indication (acute MI or UA vs. stable angina or silent ischemia)	–	–
LVEF percent	0.991	<0.001
Pre-TIMI (0 or 1 vs. 2 or 3)	0.859	0.079
Lesion class (B2 or C vs. A or B1)	–	–
Total stent length per patient	1.010	<0.001
Pre-procedure minimum lumen diameter	–	–
Pre-procedure diameter stenosis (%)	–	–
No. of vessels treated per patient	0.643	0.026
No. of lesions treated per patient	–	–

Abbreviations as in Tables 1, 2, and 4.

difference in the rates of death, MACE, or TVF at 4 years according to intervention at a proximal LAD or nonproximal LAD lesion site. The occurrence of the predefined primary endpoint—namely, stent thrombosis—was not dependent on whether a proximal LAD or nonproximal LAD site was treated with a DES. However, stenting of proximal LAD lesions was associated with significantly higher rates of MI compared with stenting of nonproximal LAD lesions.

The rate of follow-up was high, and all analyses were done by an independent research organization. Multivariate analysis as well as a stepwise selection model showed that proximal LAD location did not predict MACE or TVF, although for MACE there was a numerical difference (p = 0.07). These results are consistent with an analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation) trial, in which disease in the proximal LAD did not influence death or MI [11].

In this study, a high-risk population representing a real-life mixture of patients was treated. In both the proximal LAD and nonproximal LAD groups, >50% of patients had acute coronary syndrome and multivessel disease, and one-third had diabetes. Discussion in a heart team forum was not required; participating centers practiced their local routine.

Two relatively large meta-analyses examining the method of revascularization of the proximal LAD location have not shown differences in mortality, MI, or stroke between PCI and CABG. One of these studies included 6 randomized, controlled trials and 2 nonrandomized studies with a total of 1,952 patients with isolated proximal LAD lesions who were followed for up to 4 years (5), and the other, 9 randomized controlled trials involving 1,210 patients with isolated proximal LAD lesions followed for up to 5 years (6). These studies used bare metal stents in the PCI arm and demonstrated a 3-fold increase in recurrent

angina and a 5-fold increase in repeat revascularization with PCI as compared with CABG. In the meta-analysis performed by Kapoor et al. (6), the 5-year repeat revascularization rate of patients undergoing CABG for isolated proximal LAD disease was 7.3% at 5 years, compared with 33.5% in their PCI arm, whereas in the current study the TVF rate was 14.8% at 4 years.

There are no randomized studies comparing the long-term outcomes of PCI with CABG for isolated proximal LAD lesions. Hannan et al. (12) examined the New York Percutaneous Coronary Interventions Reporting System for patients who underwent CABG surgery and received DES for isolated proximal LAD disease. Among 715 of 5,340 patients (13.4%), they reported no differences in mortality or in a combination of mortality, MI, and/or stroke using propensity-matched comparisons; however, CABG patients had significantly lower repeat revascularization rates. The angiographic patency of the internal mammary artery has been documented to be >90% at 2 decades of follow-up (13–16). Furthermore, there is a long-term survival benefit of a single internal mammary artery in patients with multivessel coronary artery disease, especially with bilateral internal mammary arteries, compared with PCI using bare metal stents (14–16).

Such studies are unlikely to be performed; therefore, we have to reach these conclusions from indirect comparisons (17–20). Our study is a post hoc, nonrandomized comparison; all patients underwent PCI and no patient underwent CABG. Yet we found that outcomes in >2,500 patients treated with DES in the proximal LAD were similar to the outcomes of >6,100 patients with lesions in other coronary arteries, which currently are treated ad hoc and do not require further discussion before decision and intervention.

STUDY LIMITATIONS. The comparison of patients with and without a proximal LAD target lesion was a post hoc analysis. As such, it should be considered as hypothesis generating, and the results should be interpreted cautiously. We cannot exclude the presence of unmeasured selection bias. There are several known and unknown confounders with significant impact on the endpoints, and even sophisticated statistical methods cannot eliminate potential selection bias (i.e., dual antiplatelet therapy use, bleeding, anemia, transfusion, dementia, prior revascularization, prior stroke, and noncardiac surgery). Lesion success was defined as attainment of <50% residual stenosis, which today represents an outdated definition. Our findings are applicable only to those patients who fulfilled the inclusion and exclusion criteria of the PROTECT trial. In the proximal LAD group, more lesions were treated and more stents were implanted; however, we cannot exclude the possibility that, as a result of the guidelines, the potentially higher risk proximal LAD patients in PROTECT were treated differently than other patients. We do not have information regarding heart failure and quality of life, as an event in the proximal LAD may be associated with greater myocardial damage than one in other coronary artery locations.

DES have reduced markedly the risk of repeat revascularization. Interestingly, in the present analysis, the use of a DES with stronger antiproliferative properties (C-SES) in the proximal LAD did not improve clinical prognosis despite a higher long-term adherence to dual antiplatelet therapy. Similar to what was observed in the PROTECT trial (7,8), DES-specific properties and dual antiplatelet therapy regimen remain determinant for clinical outcomes (mainly stent thrombosis) independent of lesion location (proximal LAD vs. nonproximal LAD).

CONCLUSIONS

The discussion of how best to treat the patient with a proximal LAD lesion remains a topic of debate (21–26). In the present study, we found that long-term outcomes for MACE, mortality, and TVF were similar regardless of whether the target lesion was in the proximal LAD or not. The nonsignificant interaction between stent type (E-ZES vs. C-SES) and lesion location (proximal LAD vs. nonproximal LAD) suggests that these results are independent of stent type. This finding may suggest that proximal LAD lesion may not confer a substantial additional risk in the DES era.

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PERSPECTIVES

WHAT IS KNOWN? Proximal LAD artery involvement significantly impacts the recommendations for revascularization.

WHAT IS NEW? In patients treated with drug eluting stents in the proximal LAD, the 4-year event rate was similar to patients treated in other coronary artery tree locations.

WHAT IS NEXT? In the DES era, proximal LAD no longer confers a different prognosis than other lesion sites.

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KEY WORDS angioplasty, coronary artery disease, decision making, guidelines, left anterior descending artery, stent

APPENDIX For supplemental tables, please see the online version of this article.