The DELTA 2 Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention With New-Generation Drug-Eluting Stents in Patients With Obstructive Left Main Coronary Artery Disease

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Abstract: OBJECTIVES The aim of this study was to evaluate clinical outcomes of unprotected left main coronary artery percutaneous coronary intervention (PCI) with new-generation drug-eluting stents in a "real world" population. BACKGROUND PCI of the unprotected left main coronary artery is currently recommended as an alternative to coronary artery bypass grafting (CABG) in selected patients. METHODS All consecutive patients with unprotected left main coronary artery stenosis treated by PCI with second-generation drug-eluting stents were analyzed in this international, all-comers, multicenter registry. The results were compared with those from the historical DELTA 1 (Drug Eluting Stent for Left Main Coronary Artery) CABG cohort using propensity score stratification. The primary endpoint was the composite of death, myocardial infarction (MI), or stroke at the median time of follow-up. RESULTS A total of 3,986 patients were included. The mean age was 69.6 ± 10.9 years, diabetes was present in 30.8%, and 21% of the patients presented with acute MI. The distal left main coronary artery was involved in 84.6% of the lesions. At a median of 501 days (17 months) of follow-up, the occurrence of the primary endpoint of death, MI, or cerebrovascular accident was lower in the PCI DELTA 2 group compared with the historical DELTA 1 CABG cohort (10.3% vs. 11.6%; adjusted hazard ratio: 0.73; 95% confidence interval: 0.55 to 0.98; $p = 0.03$). Of note, an advantage of PCI was observed with respect to cerebrovascular accident (0.8% vs. 2.0%; adjusted hazard ratio: 0.37; 95% confidence interval: 0.16 to 0.86; $p = 0.02$), while an advantage of CABG was observed with respect to target vessel revascularization (14.2% vs. 2.9%; adjusted hazard ratio: 3.32; 95% confidence interval: 2.12 to 5.18; $p < 0.0001$). CONCLUSIONS After a median follow-up period of 17 months, PCI with new-generation drug-eluting stents was associated with an overall low rate of the composite endpoint of death, MI, or cerebrovascular accident.

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The DELTA 2 Registry

A Multicenter Registry Evaluating Percutaneous Coronary Intervention With New-Generation Drug-Eluting Stents in Patients With Obstructive Left Main Coronary Artery Disease

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate clinical outcomes of unprotected left main coronary artery percutaneous coronary intervention (PCI) with new-generation drug-eluting stents in a "real world" population.

BACKGROUND PCI of the unprotected left main coronary artery is currently recommended as an alternative to coronary artery bypass grafting (CABG) in selected patients.

METHODS All consecutive patients with unprotected left main coronary artery stenosis treated by PCI with second-generation drug-eluting stents were analyzed in this international, all-comers, multicenter registry. The results were compared with those from the historical DELTA 1 (Drug Eluting Stent for Left Main Coronary Artery) CABG cohort using propensity score stratification. The primary endpoint was the composite of death, myocardial infarction (MI), or stroke at the median time of follow-up.

RESULTS A total of 3,986 patients were included. The mean age was 69.6 ± 10.9 years, diabetes was present in 30.8%, and 21% of the patients presented with acute MI. The distal left main coronary artery was involved in 84.6% of the lesions. At a median of 501 days (≈17 months) of follow-up, the occurrence of the primary endpoint of death, MI, or cerebrovascular accident was lower in the PCI DELTA 2 group compared with the historical DELTA 1 CABG cohort (10.3% vs. 11.6%; adjusted hazard ratio: 0.73; 95% confidence interval: 0.55 to 0.98; $p = 0.03$). Of note, an advantage of PCI was observed with respect to cerebrovascular accident (0.8% vs. 2.0%; adjusted hazard ratio: 0.37; 95% confidence interval: 0.16 to 0.86; $p = 0.02$), while an advantage of CABG was observed with respect to target vessel revascularization (14.2% vs. 2.9%; adjusted hazard ratio: 3.32; 95% confidence interval: 2.12 to 5.18; $p < 0.0001$).

CONCLUSIONS After a median follow-up period of 17 months, PCI with new-generation drug-eluting stents was associated with an overall low rate of the composite endpoint of death, MI, or cerebrovascular accident. (J Am Coll Cardiol Intv 2017;10:2401–10) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CI = confidence interval

CVA = cerebrovascular accident

DES = drug-eluting stent(s)

HR = hazard ratio

MACCE = major adverse cardiac and cerebrovascular events(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TLR = target lesion revascularization

TVR = target vessel revascularization

ULMCA = unprotected left main coronary artery

Percutaneous treatment of unprotected left main coronary artery (ULMCA) disease evolved over time and currently is accepted as an alternative to coronary artery bypass grafting (CABG) in selected patients (1). In this challenging subset of patients, percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has been demonstrated to be feasible and safe at midterm clinical follow-up (2–21).

The noninferiority of PCI compared with CABG in terms of major adverse cardiac and cerebrovascular events (MACCE) in patients with ULMCA disease was reported in the randomized SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial in the era of first-generation DES (22,23). Recently, the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial demonstrated the noninferiority of PCI with second-generation DES versus CABG in patients with ULMCA disease and intermediate to low SYNTAX scores with respect to death, cerebrovascular accident (CVA), or myocardial infarction (MI) at 3 years (24). Conversely, higher rates of the primary endpoint of death, CVA, MI, or any repeat coronary revascularization with PCI were reported in the NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trial at 5 years of follow-up (25).

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Patterns of use and clinical outcomes of PCI with new-generation DES in real-world practice remain unclear. Therefore, the aim of the present study was to evaluate clinical outcomes of ULMCA PCI with second-generation DES in a "real world" setting and compare these with CABG from the historical DELTA 1 (Drug Eluting Stent for Left Main Coronary Artery) registry (2).

METHODS

The DELTA 2 registry included "all comers" patients with ULMCA disease treated with PCI and new-generation DES between March 2006 and December 2015 at 19 centers in 7 countries. New-generation DES included in the registry were the following: everolimus-eluting stents (XIENCE, Abbott Vascular, Santa Clara, California; PROMUS, Boston Scientific, Natick, Massachusetts; and SYNERGY Boston Scientific), zotarolimus-eluting stents [Endeavor, Resolute Integrity, and Resolute Onyx, Medtronic, Santa Rosa, California), biolimus-eluting stents (Nobori, Terumo, Tokyo, Japan; and BioMatrix, Biosensors, Newport Beach, California), and sirolimus-eluting stents (Ultimaster, Terumo; and Orsiro, Biotronik, Bülach, Switzerland).

At all institutions, patients were evaluated by both interventional cardiologists and cardiac surgeons, and the decision to perform PCI or CABG was made as in the DELTA 1 registry on the basis of: 1) hemodynamic conditions; 2) lesion characteristics; 3) vessel size; 4) the presence of comorbidities; 5) quality of arterial and/or venous conduits for grafting; and 6) patient and/or referring physician preferences. In all cases, the selected revascularization approach seemed suitable to guarantee complete revascularization (2). All data related to hospital admissions, procedures, and outcomes were collected at each center within the hospital recording network. Information on clinical status at the latest clinical follow-up was collected by clinical visits, telephone interviews, and referring physicians. Dual-antiplatelet therapy was administered according to hospital and physician practice. Angiographic follow-up was scheduled according to hospital practice or if a noninvasive evaluation or clinical presentation suggested ischemia.

DEFINITIONS. Study definitions of the DELTA 2 registry were consistent with the previously published DELTA 1 registry (2). The following events were analyzed cumulatively at the latest clinical follow-up available: all-cause and cardiac death, MI, CVA, target lesion revascularization (TLR), and target vessel revascularization (TVR). The occurrence of stent

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thrombosis was defined on the basis of the Academic Research Consortium criteria (26).

Diagnostic angiograms were scored according to the SYNTAX score algorithm at the site laboratory according to hospital practice (27). A true bifurcation was defined as a Medina classification of 1.1.1, 0.1.1, or 1.1.0.

STUDY ENDPOINTS. The study endpoints used in the DELTA 2 registry were consistent with those in the DELTA 1 registry (2). The primary composite study endpoint was the incidence of all-cause death, MI, or CVA at median time of follow-up. The secondary endpoints were the occurrence of death, death or MI, MACCE, TLR, and TVR.

COMPARISON WITH THE HISTORICAL DELTA 1 CABG COHORT. The DELTA 1 registry was a multicenter registry evaluating PCI versus CABG for left main coronary artery treatment (2). The study population included consecutive all-comers patients with ULMCA stenosis treated with PCI and "first-generation" DES implantation or CABG between April 2002 and April 2006 at 14 centers worldwide. The surgical cohort of the DELTA 1 population was used in this study as a historical surgical group and compared with the DELTA 2 (28,29). The DELTA 2 registry did not include a parallel contemporary CABG group.

STATISTICAL ANALYSIS. Individual patient data were pooled in a single pre-specified structured dataset and analyzed. Baseline characteristics are reported as number (percentage), mean ± SD, or median (interquartile range). Event rates with 95% confidence intervals (CI) and absolute rate differences at follow-up were estimated using the Kaplan-Meier method as time to first event. Predictors for endpoint events were estimated using multivariate Cox regression analysis including all variables with p values <0.10 in univariate analysis and using a rule of 1:10 covariates per number of events to avoid overfitting. To account for pre-treatment difference between the DELTA 2 cohort and the historical DELTA 1 CABG cohort, a propensity score was generated by means of a logistic regression model. Calibration of the logistic regression model was assessed using the Hosmer-Lemeshow test. The following covariates were included in the logistic regression model to generate the propensity score: age, male sex, diabetes, smoking history, family history of coronary artery disease, acute MI (ST-segment elevation MI or non-ST-segment elevation MI), previous CABG, previous PCI, and right coronary artery disease. Subsequently, Cox regression models stratified by quintiles of propensity score were performed to estimate adjusted differences between treatments (PCI vs. CABG). To account for intercenter heterogeneity, center identifiers were included as a covariate within the Cox regression models. The proportionality assumption of the Cox regression models was tested using the Schoenfeld residual method. Multicollinearity across covariates in the multivariate model was assessed using the variance inflation factor, with values >10 indicating significant multicollinearity. A p value <0.05 was considered to indicate statistical significance. Analyses were performed using Stata version 14.0 (StataCorp, College Station, Texas) and SPSS version 21.0 (SPSS, Chicago, Illinois).

TABLE 1 Baseline Clinical Characteristics (n = 3,986)

Age, yrs	69.6 ± 10.9
Male	2,969 (74.5)
Body mass index, kg/m^2	26.6 ± 4.9
Hypertension	3,118 (78.2)
Dyslipidemia	2,898 (72.7)
Diabetes	1,226 (30.8)
Insulin dependent diabetes	300 (7.6)
Smoking history (current and former)	1,423 (35.7)
Family history of CAD	1,059 (28.7)
Chronic kidney disease	1,199 (31.2)
Previous MI	1,115 (28.2)
Previous CABG	329 (8.3)
Previous PCI	1,639 (41.5)
LVEF, %	53.4 ± 11.3
EuroSCORE 1	3.7 (1.8-6.9)*
EuroSCORE 2	1.3 (0.9-2.8)*
Clinical presentation	
Stable angina/silent ischemia	2,546 (63.9)
Unstable angina	604 (15.2)
NSTEMI	588 (14.8)
STEMI	248 (6.2)

Values are mean ± SD, n (%), or median (interquartile range), calculated with available sample data. *EuroSCORE 1 was available in 1,100 patients and EuroSCORE 2 in 868 patients.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

RESULTS

The baseline clinical characteristics of the study population are summarized in Table 1. A total of 3,986 patients were included. The mean age was 69.6 ± 10.9 years, diabetes was present in 30.8%, and chronic kidney disease was present in 31.2%. Of note, 14.8% of the patients presented with non-ST-segment elevation MI and 6.2% with ST-segment elevation MI.

TABLE 2 Lesion and Procedural Characteristics (n = 3,986)

Multivessel disease	2,962 (74.3)
LAD/LCx disease	3,497 (87.7)
RCA disease	1,925 (48.3)
SYNTAX score	27.0 ± 10.6*
Lesion location	
Ostial/shaft only	614 (15.4)
Involving distal bifurcation	3,372 (84.6)
True bifurcation	1,586 (39.8)
Procedure	
Elective	2,860 (71.8)
Urgent/emergent	1,126 (28.2)
Radial access	1,568 (39.3)
Number of vessels treated	1.6 ± 0.7
Number of lesions treated	1.9 ± 1.0
Intravascular ultrasound	1,437 (36.1)
Intra-aortic balloon pumping	269 (6.7)
Pre-dilation	2,530 (71.1)
Rotablator	235 (6.1)
Drug-eluting stent type	
Everolimus-eluting stent	2,986 (74.9)
Zotarolimus-eluting stent	364 (9.1)
Biolimus-eluting stent	521 (13.1)
Sirolimus-eluting stent	115 (2.9)
Left main coronary artery stent diameter, mm	3.59 ± 0.37
Total stent length, mm	27.1 ± 19.6
Double-stenting	753 (20.4)
Crush	42
Mini-crush	159
Culotte	176
T-stenting	348
V-stenting	28
Post-dilation	3,452 (86.6)
Maximum balloon diameter, mm	4.0 ± 0.5
Maximum pressure, atm	18.5 ± 4.7
Kissing balloon inflation	1,780 (48.2)

Values are n (%) or mean ± SD, calculated with available sample data. *SYNTAX score was available in 2,132 patients.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

TABLE 3 Major Adverse Cardiac and Cerebrovascular Events in Hospital and During Clinical Follow-Up (n = 3,986)

In-hospital events	
Cardiac death	43 (1.1)
Noncardiac death	10 (0.3)
Myocardial infarction	158 (4.0)
Target lesion revascularization	10 (0.3)
Target vessel revascularization	15 (0.4)
Cerebrovascular event	7 (0.2)
MACCE	211 (5.3)
Follow-up events	
Cardiac death	210 (5.3)
Noncardiac death	119 (3.0)
Myocardial infarction	92 (2.3)
Target lesion revascularization	311 (7.8)
Target vessel revascularization	515 (12.9)
Cerebrovascular event	32 (0.8)
MACCE	846 (21.2)

Values are n (%). Numbers of events during follow-up are cumulatively counted at latest clinical follow-up.

MACCE = major adverse cardiac and cerebrovascular event(s).

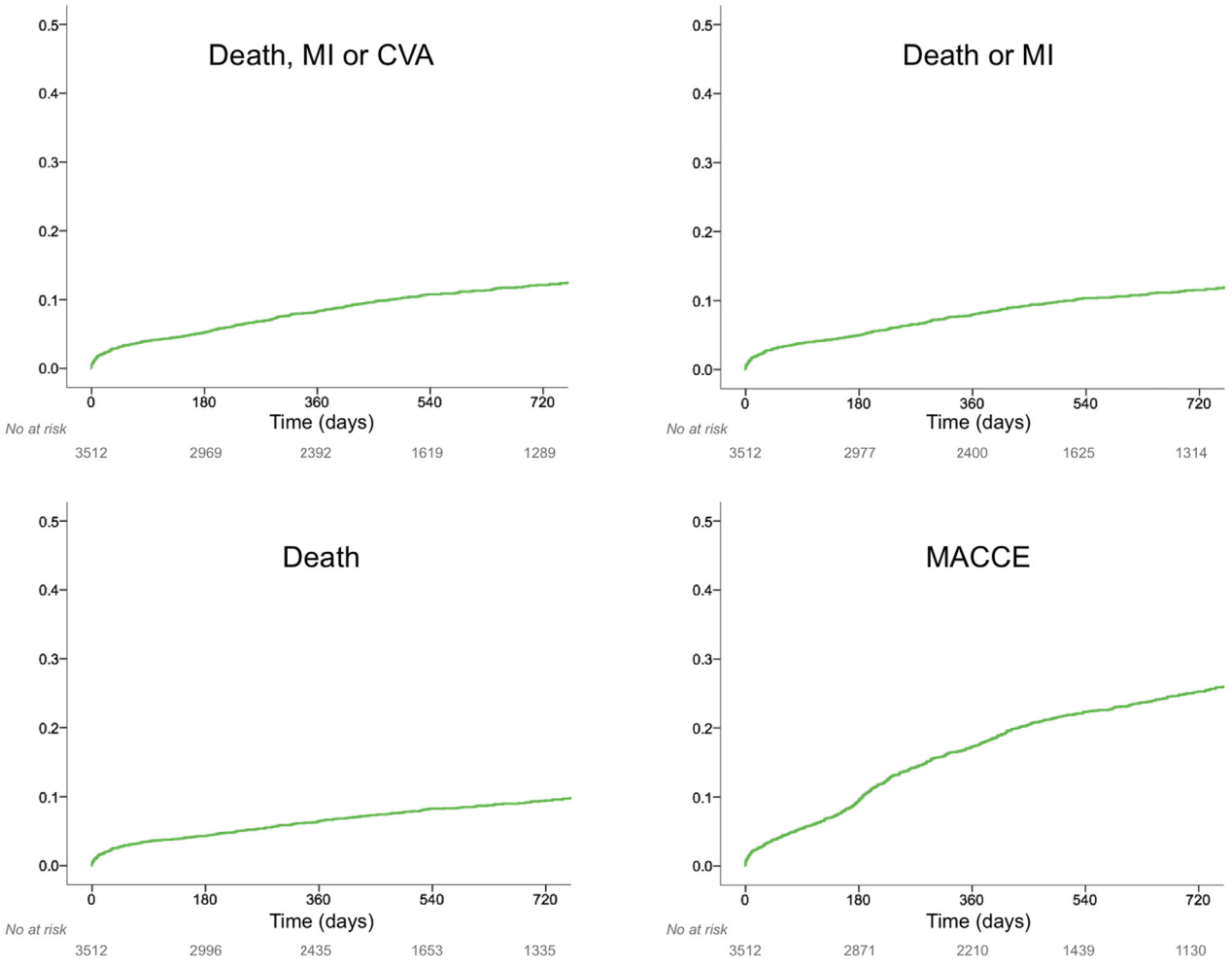
Angiographic and procedural characteristics are illustrated in Table 2. The distal left main coronary artery was involved in 84.6% of the lesions. The prevalence of urgent or emergent procedures was 28.2%, and a radial approach was chosen in 39.3% of the procedures. A total of 2,986 patients (74.9%) received everolimus-eluting stents, 364 (9.1%) zotarolimus-eluting stents, 521 (13.1%) biolimus-eluting stents, and 115 (2.9%) sirolimus-eluting stents. Intravascular ultrasound was used in 36.1% of the cases. In the majority of the cases, a provisional approach was used; double-stenting was performed in only 753 patients (20.4%). When a 2-stent approach was chosen, final kissing balloon inflation was used in most of the cases (83.9%).

HOSPITAL AND FOLLOW-UP CLINICAL OUTCOMES. In-hospital death occurred in 53 patients (1.3%), and the rate was significantly lower in elective cases (elective vs. urgent or emergent, 0.5% vs. 3.6%; $p < 0.001$). Death was considered of cardiac origin in 43 patients (1.1%). Periprocedural MI occurred in 158 patients (4.0%), and in-hospital CVA occurred in 7 (0.2%). In-hospital TVR was performed in 15 (0.4%) and TLR in 10 (0.3%) patients.

During follow-up (median 501 days; interquartile range: 318 to 1,002 days; clinical follow-up rate 88.1%), all-cause death occurred in 329 patients (8.3%). Among them, 210 (5.3%) were adjudicated as cardiac deaths. TVR was performed in 515 patients (12.9%) and TLR in 311 patients (7.8%). Definite stent thrombosis occurred in 28 patients (0.7%), of which 6 were acute, 5 subacute, 13 late, and 4 very late. Probable stent thrombosis occurred in 23 patients (0.6%). In-hospital and follow-up MACCE are illustrated in Table 3. Kaplan-Meier curves for the primary endpoint of death, MI, or CVA, death, death or MI, and MACCE are illustrated in Figure 1.

MULTIVARIATE ANALYSIS FOR PREDICTORS OF PRIMARY AND SECONDARY ENDPOINTS. On Cox regression multivariate analysis, age (HR: 1.03; 95% CI: 1.01 to 1.02; $p = 0.003$), dyslipidemia (HR: 0.70; 95% CI: 0.51 to 0.96; $p = 0.02$), diabetes (HR: 1.51; 95% CI: 1.12 to 2.02; $p = 0.006$), chronic kidney disease

FIGURE 1 Time-to-Event Curves for Death, MI, or CVA; Death or MI; Death; and MACCE in the Overall Population



CVA = cerebrovascular accident; MACCE = major adverse cardiac and cerebrovascular event(s); MI = myocardial infarction.

(HR: 1.58; 95% CI: 1.16 to 2.15; p = 0.004), left ventricular ejection fraction (HR: 0.96; 95% CI: 0.95 to 0.97; p < 0.001), emergent or urgent procedure (HR: 1.83; 95% CI: 1.33 to 2.52; p < 0.001), femoral access (HR: 1.68; 95% CI: 1.17 to 2.42; p = 0.005), and requirement for Rotablator (HR: 1.73; 95% CI: 1.02 to 2.94; p = 0.04) were found to be predictors of the composite primary endpoint of death, MI, and CVA (Online Table 1).

Predictors of MACCE were diabetes (HR: 1.72; 95% CI: 1.43 to 2.07; p < 0.001), left ventricular ejection fraction (HR: 0.98; 95% CI: 0.97 to 0.99), multivessel disease (HR: 1.35; 95% CI: 1.00 to 1.82; p = 0.049), emergent or urgent procedure (HR: 1.34; 95% CI: 1.07 to 1.67; p = 0.01), femoral access (HR: 1.27; 95% CI: 1.02 to 1.58; p = 0.03), requirement for intra-aortic balloon pump (HR: 1.78; 95% CI: 1.33 to 2.38; p < 0.001), pre-dilation (HR: 0.82; 95% CI: 0.67 to 0.99; p = 0.04), requirement for Rotablator (HR: 1.87; 95% CI: 1.34 to 2.60; p < 0.001), left main coronary artery stent diameter (HR: 0.70; 95% CI: 0.53 to 0.92; p = 0.01), and performance of bifurcation double-stenting (HR: 1.37; 95% CI: 1.09 to 1.72; p = 0.007) (Online Table 2).

Predictors of TVR were age (HR: 0.98; 95% CI: 0.97 to 0.99; p = 0.001), diabetes (HR: 1.84; 95% CI: 1.48 to 2.29; p < 0.001), requirement for Rotablator (HR: 1.90; 95% CI: 1.26 to 2.87; p = 0.002), left main coronary artery stent diameter (HR: 0.57; 95% CI: 0.41 to 0.79; p = 0.001), and performance of bifurcation

TABLE 4 Unadjusted and Adjusted Outcomes Between DELTA 2 and Historical DELTA 1 Coronary Artery Bypass Grafting Cohort

	DELTA 2 (n = 3,986)	CABG (n = 901)	ARD (95% CI)	Univariate HR (95% CI)	Adjusted HR* (95% CI)	p Value†
Death, MI, or CVA	312 (10.3 [9.2 to 11.5])	101 (11.6 [9.6 to 13.9])	−1.3 (−2.4 to −0.4)	0.82 (0.66 to 1.03)	0.73 (0.55 to 0.98)	0.03
Death	240 (7.8 [6.9 to 8.9])	68 (7.9 [6.3 to 9.9])	−0.1 (−1.0 to 0.6)	0.96 (0.73 to 1.26)	0.78 (0.56 to 1.09)	0.15
MI	79 (2.8 [2.3 to 3.5])	25 (2.9 [2.0 to 4.3])	−0.6 (−0.8 to 0.3)	0.87 (0.56 to 1.37)	0.89 (0.49 to 1.63)	0.71
CVA	22 (0.8 [0.5 to 1.2])	17 (2.0 [1.3 to 3.2])	−1.2 (−2.0 to −0.8)	0.33 (0.18 to 0.63)	0.37 (0.16 to 0.86)	0.02
Death or MI	300 (9.9 [8.9 to 11.0])	89 (10.3 [8.4 to 12.5])	−0.4 (−1.5 to 0.5)	0.91 (0.72 to 1.15)	0.77 (0.57 to 1.04)	0.09
TVR	402 (14.2 [12.9 to 15.6])	23 (2.9 [1.9 to 4.3])	11.3 (11.0 to 11.3)	5.11 (3.35 to 7.77)	3.32 (2.12 to 5.18)	<0.0001
TLR	241 (8.5 [7.5 to 9.6])	21 (2.6 [1.7 to 4.0])	5.9 (5.6 to 5.9)	3.23 (2.07 to 5.05)	2.39 (1.45 to 3.94)	0.001
Definite/probable ST	49 (1.6 [1.2 to 2.1])	–	–	–	–	–
MACCE	652 (21.6 [20.2 to 23.2])	120 (13.9 [11.7 to 16.3])	7.7 (6.9 to 8.5)	1.64 (1.48 to 1.82)	1.16 (0.92 to 1.46)	0.20

Values are n (% [95% CI]) or hazard ratio (95% CI). All endpoints were evaluated at 501 days of follow-up. *Adjusted hazard ratios generated with Cox models including center identifiers as a covariate and stratified by quintiles of propensity score. †Adjusted p value.

ARD = absolute risk difference; CI = confidence interval; DELTA = Drug Eluting Stent for Left Main Coronary Artery; HR = hazard ratio; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

double-stenting (HR: 1.50; 95% CI: 1.13 to 1.97; p = 0.004) (Online Table 3).

COMPARISON BETWEEN DELTA 2 AND HISTORICAL DELTA 1 CABG PATIENTS. Baseline differences between DELTA 2 PCI (n = 3,986) and historical DELTA 1 CABG (n = 901) patients are summarized in Online Table 4. Patients in the DELTA 2 cohort were older; were more frequently male; more frequently had hypertension, dyslipidemia, and histories of CABG and PCI; and more often presented with non-ST-segment elevation MI or ST-segment elevation MI.

Considering the difference in follow-up duration (median 501 days in DELTA 2 and 1,524 days in DELTA 1 CABG), all endpoints were compared at 501 days of follow-up. The propensity score model was well calibrated (goodness-of-fit test, p = 0.12).

Unadjusted and adjusted outcomes between the DELTA 2 PCI and historical DELTA 1 CABG cohorts are illustrated in **Table 4 and Figures 2A and 2B**. The risk for the primary endpoint of death, MI, and CVA was lower in the PCI group. In particular, PCI was associated with lower risk for cerebrovascular events. Conversely, an advantage of CABG was observed with respect to repeated coronary revascularization. Indeed, no significant difference was observed in MACCE.

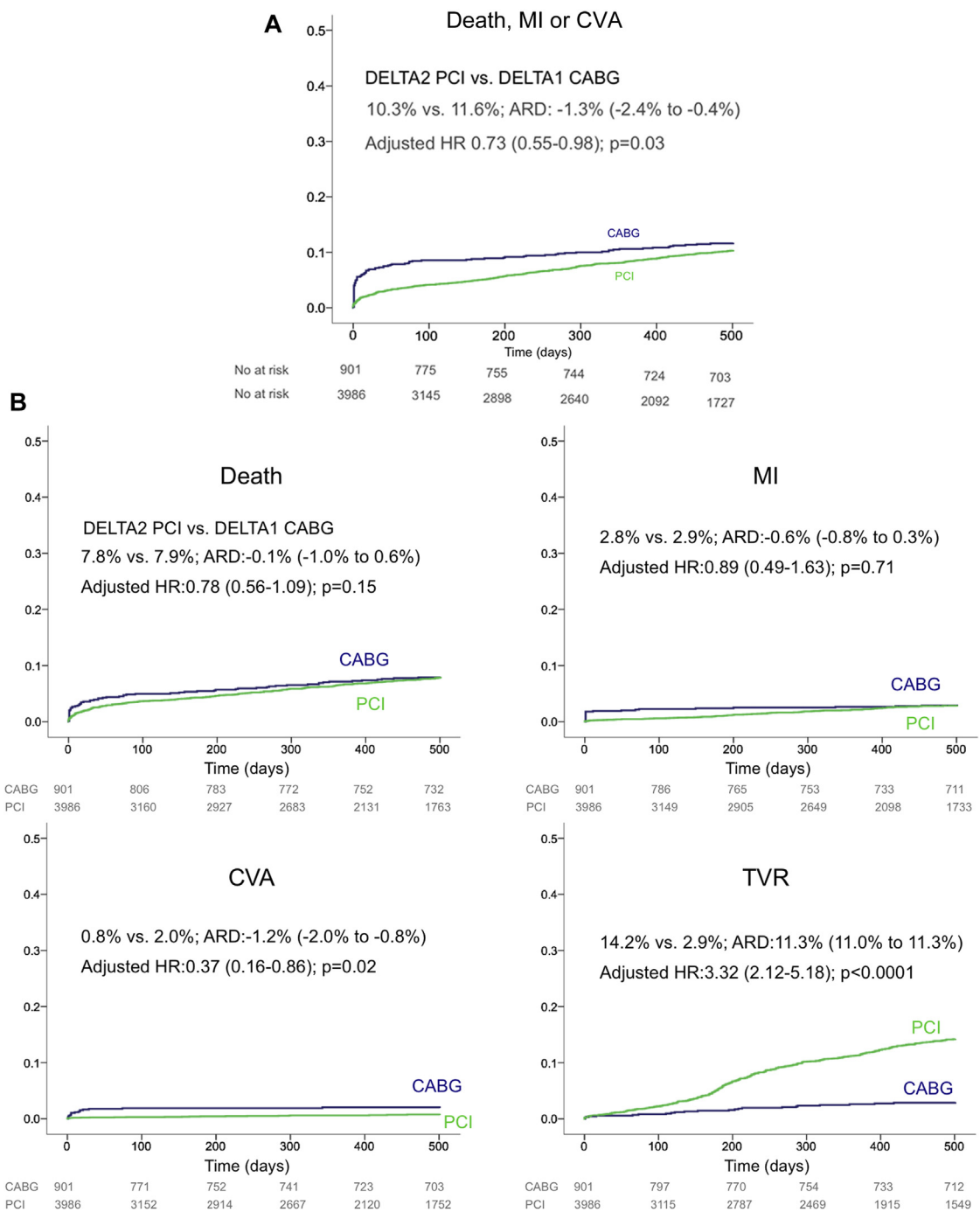
DISCUSSION

The main findings of this large, all-comers international registry study evaluating all consecutive PCI procedures with new-generation DES in ULMCA lesions are as follows. 1) At a median time of follow-up of 501 days, the primary endpoint (death, MI, or CVA) occurred in 416 (10.4%) patients. Cumulative all-cause mortality was 8.3%. MI was observed in 92 (2.3%) and CVA in 32 (0.8%) patients. 2) The secondary endpoint of MACCE occurred in 846 patients (21.2%), driven mostly by TVR (12.9%) and TLR (7.8%). 3) At a median time of follow-up of 501 days, the occurrence of the primary endpoint of death, MI, or CVA was lower in the PCI DELTA 2 cohort compared with the historical DELTA 1 CABG cohort. In particular, PCI was associated with lower risk for cerebrovascular events. Conversely, an advantage of CABG was observed with respect to repeated coronary revascularization. Indeed, no difference was observed in MACCE.

Current guidelines recommend PCI as an alternative to CABG in selected patients (1). In this challenging subset of patients, PCI with DES implantation has been shown in several registries to be a feasible and safe approach at mid- and long-term follow-up (2–21).

The study population included in DELTA 2 is a real-world population including patients usually excluded from randomized clinical trials. Chronic kidney disease was present in 31.2% of the patients, and the clinical presentation was non-ST-segment elevation MI in 14.8% and ST-segment elevation MI in 6.2% of the patients. Moreover, urgent or emergent procedures were performed in 28.2% of the patients, and the Rotablator was required in 6.1%. Furthermore, the majority of patients (74.3%) had multivessel disease, distal left main coronary artery bifurcation disease was present in 84.6%, and the mean SYNTAX score was 27.0 ± 10.6. Despite a high clinical and lesion risk profile, the primary endpoint occurred in only 416 patients (10.4%). Femoral access was found in our registry to be an independent predictor of the primary endpoint, in alignment with current research (30–32). Clearly we cannot exclude

FIGURE 2 Time-to-Event Curves



(A) Time-to-event curves for composite events of death, myocardial infarction (MI), or cerebrovascular accident (CVA) in DELTA 2 (Drug Eluting Stent for Left Main Coronary Artery) versus DELTA 1 coronary artery bypass grafting (CABG) cohort. ARD = absolute risk difference; HR = hazard ratio. **(B)** Time-to-event curves for death, MI, CVA, and target vessel revascularization (TVR) in DELTA 2 versus DELTA 1 CABG cohort.

that this finding was due to selection bias, as femoral access was chosen by the operators in more complex procedures.

In DELTA 2, a 2-stent strategy was chosen by the operators in a minority of cases (20.4%), reflecting the current standard of care in bifurcation treatment (33). Although several randomized clinical trials have evaluated the optimal stenting strategy (34-39) in non-left main coronary artery bifurcations, few data are available about the optimal stenting strategy of left main coronary artery bifurcations. Several observational studies have suggested that a single-stent strategy may be superior to a 2-stent strategy also in the setting of left main coronary artery bifurcation, but these studies are naturally confounded by selection bias. The ongoing EBC MAIN (European Bifurcation Club Left Main) study is the first randomized multicenter clinical trial so far comparing true ULMCA bifurcation treatment with a planned single- versus dual-stent strategy with respect to death, TLR, and MI at 1 year (NCT02497014).

COMPARISON BETWEEN DELTA 2 AND HISTORICAL DELTA 1 CABG PATIENTS. In the SYNTAX trial, elective PCI using first-generation DES for the left main coronary artery had a similar occurrence of the primary endpoint of MACCE compared with CABG in the subset of patients with ULMCA disease (22,23). Recently in the EXCEL trial, PCI with new-generation DES showed similar rates of the primary endpoint of death, MI, or stroke at 3 years compared with CABG (24). However, the rate of repeat revascularization was greater in the PCI group (12.6% vs. 7.5%, $p < 0.001$).

Higher rates with PCI for the primary endpoint of all-cause mortality, nonprocedural MI, any repeat coronary revascularization, and stroke were reported in the NOBLE trial (25). However, as recently demonstrated by Capodanno et al. (40), there is an important difference in the prognostic role between repeat revascularization and the other components of MACCE, such as death, MI, and stroke.

In the DELTA 2 registry, there was no parallel contemporary CABG group. The surgical cohort of the DELTA 1 population was therefore used in this study as a historical surgical group and compared with DELTA 2. Patients in the DELTA 2 cohort were older; were more frequently male; more frequently had hypertension, dyslipidemia, and histories of CABG and PCI; and more often presented with non-ST-segment elevation MI or ST-segment elevation MI. More patients treated with CABG in DELTA 1 had higher SYNTAX scores and elective procedure. Notably, in the DELTA 1 CABG cohort, 187 patients (27.7%) had complete arterial revascularization. In the EXCEL trial, 24.8% of patients in the CABG group had complete arterial revascularization, not significantly different from what was reported in SYNTAX and also in the DELTA 1 CABG cohort and despite the protocol recommendation to aim for complete arterial revascularization.

A propensity score was generated by means of a logistic regression model to adjust for differences in the 2 study populations. Considering the difference in follow-up duration (median 501 days in DELTA 2 and 1,524 days in DELTA 1 CABG), all endpoints were compared at 501 days of follow-up. The occurrence of the primary endpoint of death, MI, and CVA was lower in the DELTA 2 PCI cohort compared with the historical DELTA 1 CABG cohort. In particular, PCI was associated with lower risk for cerebrovascular events. Conversely, an advantage of CABG was observed in terms of repeated coronary revascularization. Indeed, no difference was observed in MACCE. Our results are comparable with those reported from randomized trials, although our study population was a real-world population including patients who, because of clinical presentation, comorbidities, or anatomic complexity, would have been excluded from randomized controlled trials.

STUDY LIMITATIONS. First, given the observational, retrospective design our findings precludes causal inferences.

Second, because of the "all-comers" multicenter design, there may have been differences among centers in the strategy regarding patient selection for PCI or CABG.

Third, comparisons between PCI with new-generation DES and CABG are based on contemporary and historical cohorts, respectively, with different enrolling centers and patterns of practice. As such, intercenter heterogeneity between cohorts may be substantial, and more sophisticated methods to account for intercenter heterogeneity, such as multilevel hierarchical modeling, could not be performed. We attempted to attenuate the effect of intercenter heterogeneity by including trial identifiers as a covariate within the propensity-stratified Cox model.

Fourth, data were collected at each center within the hospital network, and adjudication of the outcomes was largely dependent on individual institutions. Therefore we cannot exclude that in the absence of site monitoring and a formal clinical events committee adjudication underreporting of MACCE may have occurred.

Fifth, despite the implementation of non-parsimonious propensity score adjustment between

revascularization strategies, our effect estimates are subject to residual confounding bias. However, our findings were consistent with randomized controlled trial data in terms of magnitude and direction of the effects on both primary and secondary outcomes.

Sixth, given the lack of standardized, prospective data collection, our findings are also subject to substantial intercenter variability and possibly underestimation of the event rates.

Seventh, data on medication regimens and adherence, which are known to influence long-term outcomes after coronary revascularization, were not available.

Finally, the follow-up time for comparisons between the DELTA 2 PCI cohort and the DELTA 1 CABG cohort was relatively short (501 days); longer clinical follow-up may abrogate the early advantage observed with PCI.

CONCLUSIONS

In the large, international, multicenter all-comers DELTA 2 registry, PCI with new-generation DES was associated with acceptable rates of the composite endpoint of death, MI, or CVA as well as the secondary endpoint of MACCE. The occurrence of the primary endpoint of death, MI, or CVA was lower in the PCI DELTA 2 group compared with the historical DELTA 1 CABG cohort. An advantage of PCI was observed with respect to CVA, while an advantage of CABG was observed with respect to TVR and TLR occurrence.

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PERSPECTIVES

WHAT IS KNOWN? Percutaneous treatment of ULMCA disease has been accepted as an alternative to CABG in selected patients.

WHAT IS NEW? At a median time of follow-up of 501 days, the occurrence of the primary endpoint of death, MI, or CVA in patients with ULMCA disease was lower with PCI with new-generation DES compared with a historical CABG cohort. In particular, PCI was associated with lower risk for cerebrovascular events. Conversely, an advantage of CABG was observed in terms of repeated coronary revascularization.

WHAT IS NEXT? Extended follow-up from randomized controlled trials and observational studies is needed to evaluate the long-term comparative effectiveness of PCI versus CABG in patients with ULMCA disease.

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