Drug-Eluting Stent for Left Main Coronary Artery Disease

The DELTA Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment

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Objectives The aim of this study was to compare, in a large all-comers registry, major adverse cardiac and cerebrovascular events (MACCE) after percutaneous coronary intervention (PCI) with first-generation drug-eluting stents (DES) versus coronary artery bypass grafting (CABG) in unprotected left main coronary artery (ULMCA) stenosis.

Background Percutaneous coronary intervention with DES implantation in ULMCA has been shown to be a feasible and safe approach at midterm clinical follow-up.

Methods All consecutive patients with ULMCA stenosis treated by PCI with DES versus CABG were analyzed in this multinational registry. A propensity score analysis was performed to adjust for baseline differences in the overall cohort.

Results In total 2,775 patients were included: 1,874 were treated with PCI versus 901 with CABG. At 1,295 (interquartile range: 928 to 1,713) days, there were no differences, at the adjusted analysis, in the primary composite endpoint of death, cerebrovascular accidents, and myocardial infarction (MI) (adjusted hazard ratio [HR]: 1.11; 95% confidence interval [CI]: 0.85 to 1.42; p = 0.47), mortality (adjusted HR: 1.16; 95% CI: 0.87 to 1.55; p = 0.32), or composite endpoint of death and MI (adjusted HR: 1.25; 95% CI: 0.95 to 1.64; p = 0.11). An advantage of CABG over PCI was observed in the composite secondary endpoint of MACCE (adjusted HR: 1.64; 95% CI: 1.33 to 2.03; p < 0.0001), driven exclusively by the higher incidence of target vessel revascularization with PCI.

Conclusions In our multinational all-comers registry, no difference was observed in the occurrence of death, cerebrovascular accidents, and MI between PCI and CABG. An advantage of CABG over PCI was observed in the incidence of MACCE, driven by the higher incidence of target vessel revascularization with PCI. (J Am Coll Cardiol Intv 2012;5:718–27) © 2012 by the American College of Cardiology Foundation

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Percutaneous coronary intervention (PCI) for unprotected left main coronary artery (ULMCA) lesions has a Class IIb indication, in high-risk surgical patients, according to recent guidelines (1). In this challenging subset of patients, PCI with drug-eluting stent (DES) implantation has been shown to be a feasible and safe approach at midterm clinical follow-up (2–10). Recently, results from multicenter registries have reported favorable outcomes at 3-year clinical follow-up (11–18). Moreover, single-center registries evaluating PCI with DES versus coronary artery bypass grafting (CABG) in this subset of patients have shown encouraging and comparable outcomes between these 2 treatment options, sustained up to 5 years of clinical follow-up (13). The noninferiority of PCI as compared with CABG in major adverse cardiac and cerebrovascular events (MACCE) at 12 months in this subset has been reported in the randomized SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) trial (19). Additionally, improved left ventricular ejection fraction (LVEF) in the PCI group when compared with CABG at 1-year follow-up was stated in the randomized LEMANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery) (20). The aim of the present study was to evaluate the long-term clinical outcomes of ULMCA PCI with DES in a "real-world" setting and compare these with the results of those undergoing CABG.

Methods

Consecutive "all comers" with ULMCA stenosis treated with PCI and "first generation" DES (sirolimus- and paclitaxel-eluting stents) implantation or CABG between April 2002 and April 2006 in 14 centers were retrospectively analyzed in this multinational registry. In all institutions, patients were evaluated by both interventional cardiologists and cardiac surgeons, and the decision to perform PCI or CABG was made 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. All data relating to hospital admissions, procedures, and outcomes were collected in each center with the hospital recording network. Information with regard to the clinical status at the latest clinical follow-up available was collected by clinical visits, telephone interviews, and referring physicians.

Dual antiplatelet therapy (i.e., aspirin 100 mg daily and clopidogrel 75 mg daily or ticlopidine 250 mg twice daily) was administered for at least 12 months in patients treated with PCI. In the Korean center, cilostazol was also prescribed. Detailed information on adherence as well as reasons and date for discontinuation of dual antiplatelet therapy were obtained in all patients. Angiographic follow-up was scheduled according to hospital practice or if a noninvasive evaluation or clinical presentation suggested ischemia. Data analysis was performed with the approval of the institutional ethics committees of the hospitals and/or universities involved.

Definitions. In this report, the following events were analyzed cumulatively at latest clinical follow-up available: cardiac and overall death, myocardial infarction (MI), cerebrovascular accident (CVA), target lesion revascularization (TLR), and target vessel revascularization (TVR). The occurrence of stent thrombosis (ST) was defined on the basis of the Academic Research Consortium definitions (21) in the PCI group. Stent thrombosis was defined as acute, subacute, late, and very late if the event occurred within 24 h, 30 days, <1 year, or >1 year, respectively, after the procedure. Deaths were classified as either cardiac or noncardiac. Cardiac death was defined as any death

Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CI = confidence interval

CK = creatine kinase

CVA = cerebrovascular accident

DES = drug-eluting stent(s)

EuroSCORE = European System for Cardiac Operative Risk Evaluation

HR = hazard ratio

IABP = intra-aortic balloon pump

IQR = interquartile range

IVUS = intravascular ultrasound

LVEF = left ventricular ejection fraction

MACCE = major adverse cardiac and cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

TLR = target lesion revascularization

TVR = target vessel revascularization

ULMCA = unprotected left main coronary artery

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due to a cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), procedure-related deaths, and death of unknown cause. Target lesion revascularization was defined as any repeat intervention of the target lesion or other complication of the target lesion. The target lesion was defined as the treated segment 5 mm proximally to the stent and 5 mm distally to the stent; TVR was defined as any repeat intervention of any segment of the target vessel, defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. Cerebrovascular accidents were defined as stroke, transient ischemic attacks, and reversible ischemic neurological deficits adjudicated by a neurologist and confirmed by computed tomography scanning.

In-hospital non–Q-wave MI was defined as the elevation of the serum creatine kinase (CK) isoenzyme myocardial band that was 3× the upper limit of normal in the PCI group and 5× the upper limit of normal in the CABG group, in the absence of new pathological Q waves (22). In this analysis were included as cumulative MI: 1) all Q-wave MI that occurred during hospital stay and follow-up; and 2) all spontaneous MI occurring after hospital discharge. Q-wave MI was defined as the development of new pathological Q waves in 2 or more contiguous leads with or without CK or CK-myocardial band levels elevated above normal. Spontaneous MI was defined as the occurrence after hospital discharge of any value of troponin and/or CK-myocardial band greater than the upper limit of normal if associated with clinical and/or electrocardiogram change. Major adverse cardiac and cerebrovascular event was defined as the composite endpoint of death, CVA, MI, and TVR.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE)—which is based on patient-, cardiac-, and operation-related factors—was used to stratify the risk of death at 30 days.

Diagnostic angiograms were scored according to the SYNTAX score algorithm at the site laboratory (23). Patients were divided into low score (0 to 22), mid score (23 to 32), and high score (>32) groups.

Study endpoints. The primary study endpoint was the incidence of death (overall and cardiac), CVA, and MI at long-term follow-up. The secondary study endpoints were the occurrence of death (overall and cardiac), death and MI, MACCE, and TVR.

Statistical analysis. Data are presented as percentages and mean ± SD. In general, differences in proportions were tested with chi-square test or Fisher exact test, and differences in continuous variables were tested with a Student t test. Cumulative event curves were generated with the Kaplan-Meier method and compared by the log-rank test. Because of the nonrandomized nature of the study, a propensity score analysis was performed to minimize any selection bias due to the differences in clinical characteristics between the 2 treatment groups. Briefly, for each patient a propensity score indicating the likelihood of having PCI was calculated by the use of a nonparsimonious multivariable logistic regression. A propensity score, indicating the predicted probability of receiving a specific treatment conditional on the observed covariates, was then calculated from the logistic equation for each patient. Variables included in the logistic regression model to calculate the propensity score were age, sex, diabetes, smoking, family history of coronary artery disease, unstable angina, acute myocardial infarction, chronic kidney disease, LVEF, previous CABG, previous PCI, multivessel disease, and concomitant right coronary artery disease. The C-statistic was 0.78, and the Hosmer-Lemeshow test p value was 0.38, confirming good discrimination and calibration of the propensity score model. The individual propensity score was incorporated into Cox proportional hazards regression models as a covariate as well as treatment group to calculate the adjusted hazard ratio (HR). Also, the propensity scores were grouped into quintiles, and HR was compared across quintiles. In addition, to reduce the effect of treatment-selection bias and potential confounding in this observational study, we performed rigorous adjustment for significant differences in the baseline characteristics of patients with propensity-score matching using the following algorithm: 1:1 optimal match with a ±0.03 caliper and no replacement. Clinical outcomes in the matched population were analyzed with Cox proportional hazards regression stratified on matched-pairs. Multivariable Cox proportional-hazards regression modeling was performed to determine the independent predictors of the primary endpoint (death, CVA, or MI), MACCE, and death with purposeful selection of covariates. Variables associated at univariate analysis (all with a p value ≤0.1) and those judged to be of clinical importance from previous published reports were eligible for inclusion into the multivariable model-building process. The goodness of fit of the Cox multivariable model was assessed with the Grønnesby-Borgan-May test.

Results are reported as HR with associated 95% confidence interval (CI) and p value. All statistical analysis was performed with Stata (version 9.0, Stata Corporation, College Station, Texas).

Results

The baseline clinical characteristics are summarized in Table 1. In this "all comers" registry, 2,775 patients were included: 1,874 underwent PCI with implantation of "first-generation" DES, and 901 underwent CABG. Among the overall population, 2,187 patients were treated electively: 1,445 patients were treated with PCI, and 742 were treated with CABG. In the PCI group, 893 (47.6%) patients had paclitaxel-eluting stent implantation, and 893 (44.7%) had sirolimus-eluting stent implantation. Patients treated with PCI were more frequently male (73.9% vs. 63.6%; p < 0.01)

Table 1. Baseline Clinical Characteristics

	PCI Overall (N = 1,874)	CABG Overall (N = 900)	p Value
Male	1,385 (73.9)	572 (63.6)	<0.01
Age, yrs	65.8 ± 11.5	66.5 ± 9.8	0.24
Family history of CAD	546 (29.1)	228 (25.3)	0.038
Hypertension	1,200 (64.0)	609 (67.7)	0.061
Dyslipidemia	1,159 (61.8)	582 (64.7)	0.15
Smokers	847 (45.2)	384 (42.7)	0.22
Diabetes	520 (27.7)	306 (34.0)	<0.01
IDDM	115 (6.1)	65 (7.2)	
NIDDM	405 (21.6)	241 (26.8)	
Chronic kidney disease	137 (7.3)	37 (4.1)	<0.01
Clinical presentation			
Stable angina/silent ischemia	988 (52.7)	317 (35.2)	<0.01
Unstable angina	614 (32.8)	476 (52.9)	<0.01
NSTEMI	218 (11.6)	100 (11.1)	<0.01
STEMI	54 (2.9)	7 (0.8)	<0.01
Previous CABG	201 (10.7)	24 (2.7)	<0.01
Previous PCI	465 (24.8)	123 (13.7)	<0.01
LVEF	53.8 ± 12	53.3 ± 11.5	0.29
EuroSCORE	4.9 ± 3.6	5.1 ± 2.6	0.17

Values are n (%) or mean ± SD.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; IDDM = insulin-dependent diabetes mellitus; LVEF = left ventricular ejection fraction; NIDDM = noninsulin-dependent diabetes mellitus; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2. Angiographic and Procedural Characteristics

	PCI Overall (N = 1,874)	CABG Overall (N = 900)	p Value
Multivessel disease	1,495 (79.8)	848 (94.2)	<0.01
LAD/CX disease	1,211 (64.6)	758 (84.2)	0.037
RCA disease	684 (36.5)	627 (69.7)	
SYNTAX score	28.6 ± 14.3	38.9 ± 13.2	<0.01
Lesion location			
Ostial/shaft	744 (39.7)	374 (41.6)	0.23
Distal	1,130 (60.3)	526 (58.4)	0.36
True bifurcation	745 (39.8)	91 (10.1)	<0.01
Pre-dilation	821 (43.8)		
Atherectomy	25 (1.3)		
Rotablator	28 (1.5)		
Cutting balloon	167 (8.9)		
IABP	131 (7.0)	31 (3.4)	<0.01
IVUS	621 (33.1)		
IVUS guided procedure	161 (8.6)		
IVUS controlled procedure	460 (24.5)		
DES type (for LM lesion)			
Cypher	938		
Taxus	893		
Endeavor	4		
Xience V	43		
Mean stent diameter	3.44 ± 0.54		
Mean stent length	22.6 ± 19.4		
2-stent strategy	487 (43.1)		
Stenting technique			
Crush	196 (10.5)		
Mini-crush	53 (2.8)		
Culotte	40 (2.1)		
T stenting	135 (7.2)		
V stenting	63 (3.4)		
Post-dilation	867 (46.3)		
Max balloon diameter	3.6 ± 0.58		
Max pressure (atm)	15.7 ± 3.8		
Final kissing balloon	820 (43.8)		
GP IIb/IIIa			
Abciximab	201 (10.7)		
Eptifibatide	29 (1.5)		
Tirofiban	206 (11.0)		
Bivalirudin	47 (2.5)		
Vessels treated	1.4 ± 0.84	2.1 ± 0.9	<0.01
Lesions treated	1.5 ± 0.99		
Stent/lesion ratio	1.28 ± 0.65		
CABG beating heart		126 (14.0)	
Mean arterial graft		2 ± 1.02	
Mean venous graft		1.7 ± 1.2	
Graft/patient ratio		3.7 ± 1.6	
Complete revascularization		840 (93.3)	
Unintentional incomplete		33 (3.7)	
Mean hospital stay (days)		12.5 ± 11.2	

Values are n (%), n, or mean ± SD.

CX = circumflex artery; DES = drug-eluting stent(s); GP = glycoprotein; IABP = intra-aortic balloon pump; IVUS = intravascular ultrasound; LAD = left anterior descending artery; LM = left main; Max = maximum; RCA = right coronary artery; other abbreviations as in Table 1.

and had a family history of coronary artery disease (29.1% vs. 25.3%; p = 0.038), chronic kidney disease (7.3% vs. 4.1%; p < 0.01), previous CABG (10.7% vs. 2.7%; p < 0.01), and/or PCI (24.8% vs. 13.7%; p < 0.01) and presented with acute coronary syndromes (non–ST-segment elevation myocardial infarction 11.6% vs. 11.1% and ST-segment elevation myocardial infarction 2.9% vs. 0.8%). More patients treated with CABG had multivessel disease (94.2% vs. 79.8%; p < 0.01) and higher SYNTAX scores (38.9 ± 13.2 vs. 28.6 ± 14.3; p < 0.01). All the other baseline variables were similar.

The lesion and procedural characteristics are illustrated in Table 2. An intra-aortic balloon pump was more frequently used during PCI (7.0% vs. 3.4%; p < 0.01), most likely a reflection of the higher occurrence of emergency procedures in this group. Emergency procedures were performed in 429 (22.8%) patients in the PCI group versus 158 (17.5%) in the CABG group. A distal location was present in 1,130 (60.3%) of the patients treated with PCI: 745 (65.9%) were bifurcation lesions. Both branches were stented in 487 (43.1%) of the distal locations. An IVUS was performed in only 33.1% of the cases, varying considerably among the centers and reflecting the common practice during the study period.

Hospital and long-term MACCE. Periprocedural MI occurred in 88 (4.7%) of the patients treated with PCI versus 213

(23.6%) with CABG. Of these, Q-wave MI was detected in only 11 patients with PCI versus 15 in the CABG group. In-hospital death occurred in 41 (2.2%) patients in the PCI group versus 29 (3.2%) of the CABG group: cardiac death was adjudicated in 33 (1.7%) patients in the PCI versus 20 (2.2%) in the CABG group. A periprocedural CVA occurred in 4 (0.2%) patients treated with PCI and in 12 (1.3%) of those undergoing CABG. Target vessel revascularization was performed in 15 (0.8%) patients treated with PCI versus 3 (0.3%) patients treated with CABG.

Clinical follow-up was obtained overall in 95% of the patients (2-year follow-up was available in 90% of PCI patients and in 87% of CABG patients).

At a median follow-up of 1,295 (interquartile range [IQR]: 928 to 1,713) days, 103 patients (11.4%) in the CABG group versus 264 (14.1%) in the PCI group died. Among them, 61 (6.8%) were adjudicated as cardiac deaths in the CABG cohort and 140 (7.5%) in the PCI group. During follow-up, 33 (4.0%) patients in the CABG arm experienced an MI compared with 75 (3.7%) in the PCI group. Target vessel revascularization was performed in 290 (15.5%) of the patients treated with PCI versus 44 (5.2%) with CABG. Of these, TLR occurred in 192 (10.2%) in the PCI versus 36 (4.3%) in the CABG group. Cerebrovascular accident occurred in 25 patients (2.9%) in the CABG group and in 30 (1.6%) in the PCI group. Definite ST occurred in 20 (1.06%) patients: 6 subacutely, 9 late, and 5 very late. Probable ST was adjudicated in 12 (0.6%) patients, and possible ST was adjudicated in 8 (0.4%) patients. In-hospital and follow-up MACCE are illustrated in Table 3.

Study endpoints. At a median of 1,295 (IQR 928 to 1,713) days of clinical follow-up, no difference in the primary endpoint of death, CVA, and MI was observed (17.6% PCI vs. 16.9% CABG; unadjusted HR: 1.11; 95% CI: 0.89 to 1.36; p = 0.38; adjusted HR: 1.11; 95% CI: 0.85 to 1.42; p = 0.47). Furthermore, no significant differences were found in mortality (unadjusted HR: 1.29; 95% CI: 1.01 to 1.65; p = 0.04; adjusted HR: 1.16; 95% CI: 0.87 to 1.55; p = 0.32) and the composite endpoint of death and MI (16.7% in PCI vs. 13.9% in CABG; unadjusted HR: 1.22; 95% CI: 0.98 to 1.53; p = 0.07; adjusted HR: 1.25; 95% CI: 0.95 to 1.64; p = 0.11).

An advantage of CABG over PCI was observed in the composite secondary endpoint of MACCE (30.3% in the PCI group vs. 20.1% in the CABG group; unadjusted HR: 1.58; 95% CI: 1.32 to 1.90; p < 0.0001; adjusted HR: 1.64; 95% CI: 1.33 to 2.03; p < 0.0001), driven by the benefit of CABG in terms of TVR (unadjusted HR: 3.65; 95% CI: 2.57 to 5.19; p < 0.0001; adjusted HR: 3.51; 95% CI: 2.40 to 5.13; p < 0.0001) as well as TLR (unadjusted HR: 2.78; 95% CI: 1.89 to 4.10; p < 0.0001; adjusted HR: 2.65; 95% CI: 1.73 to 4.04; p < 0.0001). No differences in the study endpoints were observed in the elective population compared with overall results. Additionally, when the propensity score analysis was performed according to quintiles, the results were consistent with the overall analysis. Kaplan-Meier survival curves for the primary endpoint of death, MI, and CVA; death; death or MI; and MACCE are illustrated in Figure 1.

Multivariate analysis for predictors of primary and secondary study endpoints. At Cox regression multivariable analysis, age (1.03; 95% CI: 1.00 to 1.04; p = 0.009), EuroSCORE (1.06; 95% CI: 1.01 to 1.10; p = 0.02), SYNTAX score (1.02; 95% CI: 1.01 to 1.03; p < 0.0001), emergency procedures (0.68; 95% CI: 0.48 to 0.95; p = 0.02), and need for intra-aortic balloon pump (IABP) (1.85, 95% CI: 1.27 to 2.68; p = 0.001) were found to be predictors of the composite primary endpoint of death, MI, and CVA (Table 4).

Predictors of death were age (1.03; 95% CI: 1.01 to 1.05; p = 0.001), LVEF (0.98, 95% CI: 0.97 to 0.99; p = 0.02), SYNTAX score (1.03, 95% CI: 1.02 to 1.04; p < 0.0001), presentation with acute MI (1.62; 95% CI: 1.03 to 2.53; p = 0.04), and the need for IABP support (2.0; 95% CI: 1.35 to 2.97; p = 0.001).

Predictors of MACCE were PCI (1.38; 95% CI: 1.01 to 1.89; p = 0.046), EuroSCORE (1.05; 95% CI: 1.02 to 1.09; p = 0.005), SYNTAX score (1.01; 95% CI: 1.01 to 1.02; p < 0.0001), need for IABP support (2.06; 95% CI: 1.52 to 2.79; p < 0.0001), and distal ULMCA disease (1.34; 95% CI: 1.04 to 1.72; p = 0.02).

Propensity matched analysis. After propensity-score matching was performed, there were 602 matched pairs of patients in both treatment groups. Baseline clinical and lesion characteristics of the matched groups are shown in the Online

Table 3. Cumulative Incidence of MACCE in the Overall Population

	PCI Overall (N = 1,874)	CABG Overall (N = 900)
In-hospital events		
Cardiac death	33 (1.7)	20 (2.2)
Noncardiac death	8 (0.5)	9 (1)
Myocardial infarction	88 (4.7)	213 (23.6)
Target lesion revascularization	0 (0)	0 (0)
Target vessel revascularization	15 (0.8)	3 (0.3)
Cerebrovascular accident	4 (0.2)	12 (1.3)
MACCE	148 (7.9)	257 (28.4)
Events at follow-up		
Cardiac death	140 (7.5)	61 (6.8)
Noncardiac death	124 (6.6)	42 (4.6)
Myocardial infarction	75 (3.7)	33 (4)
Target lesion revascularization	192 (10.2)	36 (4.3)
Target vessel revascularization	290 (15.5)	44 (5.2)
Cerebrovascular accident	30 (1.6)	25 (2.9)
MACCE	659 (34.9)	205 (23.5)

Values are n (%).

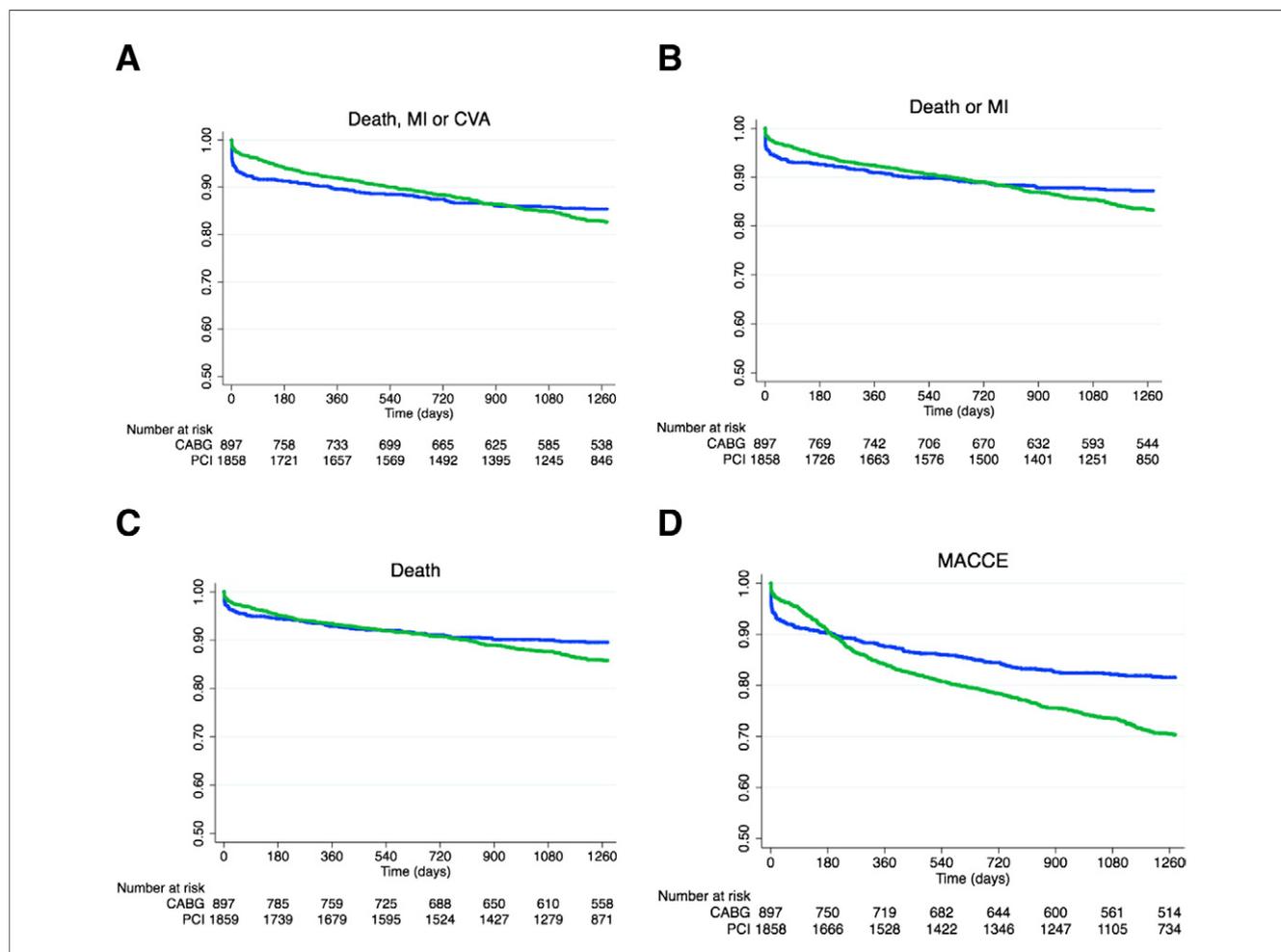MACCE = major adverse cardiac and cerebrovascular events; other abbreviations as in Table 1.

Figure 1. Freedom From Cardiac and Cerebrovascular Events in PCI Versus CABG in the Overall Population

Freedom from cardiac death, myocardial infarction (MI), and cerebrovascular accidents (CVA) **(A)**; from death and MI **(B)**; from death **(C)**; and from major adverse cardiac and cerebrovascular events (MACCE) **(D)** after percutaneous coronary intervention (PCI) **(green line)** versus coronary artery bypass grafting (CABG) **(blue line)** in the overall population. Patients at risk at different times are reported below each graph.

Appendix. For the 602 matched pairs, there was no significant difference between the PCI and CABG groups in the risk of the primary endpoint of death, CVA, and MI (HR: 0.91; 95% CI: 0.66 to 1.26; p = 0.57). Furthermore, no significant differences were found in mortality (HR: 1.0; 95% CI: 0.70 to 1.43; p = 1.0)

Table 4. Predictors of the Primary Endpoint at Cox Multivariable Analysis

	HR	95% CI	p Value
PCI vs. CABG	0.98	0.67–1.44	0.94
Age	1.02	1.00–1.04	0.009
LVEF	0.99	0.97–1.00	0.06
EuroSCORE	1.06	1.01–1.10	0.02
SYNTAX score	1.02	1.01–1.03	<0.0001
Elective	0.68	0.48–0.95	0.02
IABP	1.85	1.27–2.68	0.001

Adjusted for presence of sex and chronic kidney disease.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

and the composite endpoint of death and MI (HR: 1.02; 95% CI: 0.72 to 1.42; p = 0.93).

An advantage of CABG over PCI was observed in the composite secondary endpoint of MACCE (HR: 1.35; 95% CI: 1.03 to 1.76; p = 0.03), driven by the benefit of CABG in terms of TVR (HR: 2.96; 95% CI: 1.84 to 4.74; p < 0.0001) as well as TLR (HR: 2.0; 95% CI: 1.18 to 3.38; p = 0.009).

Kaplan-Meier survival curves for the primary endpoint of death, MI, or CVA; death; death or MI; and MACCE in the propensity score matched groups are illustrated in Figure 2.

Discussion

The main findings of this large multicenter, multinational, "all comers" registry are: 1) no difference was found at a median follow-up of 1,295 (IQR 928 to 1,713) days in the
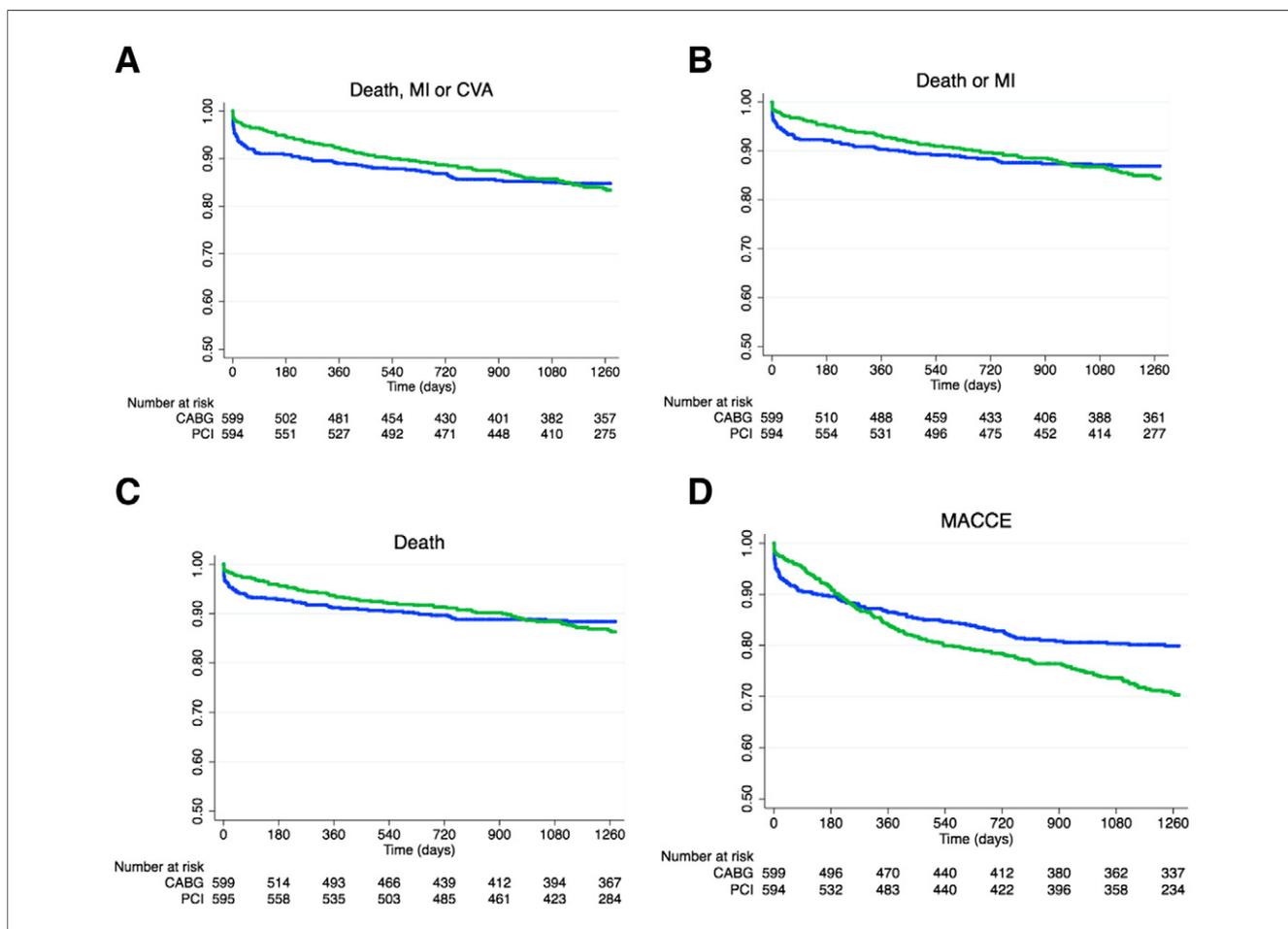
Figure 2. Freedom From Cardiac and Cerebrovascular Events in PCI Versus CABG in the Propensity Score-Matched Groups

Freedom from cardiac death, myocardial infarction (MI), and cerebrovascular accidents (CVA) **(A)**; from death and MI **(B)**; from death **(C)**; and from major adverse cardiac and cerebrovascular events (MACCE) **(D)** after percutaneous coronary intervention (PCI) **(green line)** versus coronary artery bypass grafting (CABG) **(blue line)** in the propensity score matched groups. Patients at risk at different times are reported below each graph.

occurrence of the primary endpoint (death, MI, and CVA) between PCI with DES implantation and CABG for ULMCA disease both in the propensity analysis as well as in the propensity matched analysis; 2) there is still an advantage of CABG over PCI in terms of MACCE that is exclusively driven by a lower incidence of repeat revascularization; 3) PCI in this particular subset of patients can be considered a safe procedure, and this is testified to by the low occurrence of ST and mortality despite the "all comers" design; and 4) age, LVEF, EuroSCORE, SYNTAX score, emergency procedures, and need for hemodynamic support were found to be correlated to the occurrence of death, MI, and CVA.

Encouraging long-term results have been reported for PCI with DES implantation in this particular lesion subset (2–8,10,24). Moreover, several observational, nonrandomized registries (5,11,22) have shown no difference in the occurrence of MACCE between patients treated with DES

compared with the ones treated with CABG in this subset of patients up to 5 years of clinical follow-up (13,16).

Promising results were reported from randomized trials comparing first-generation DES versus CABG (19,25,26). In the SYNTAX trial, patients were stratified according to the presence of ULMCA disease (19) and randomized to CABG (n = 348) or PCI with paclitaxel-eluting stents (n = 357). In the ULMCA subgroup, MACCE at 12 months was comparable between PCI and CABG (13.7% vs. 15.8%; p = 0.44). Moreover, although the rate of repeat revascularization among patients with ULMCA disease was significantly higher in the PCI group (11.8%, vs. 6.5%; p = 0.02), this result was offset by a significantly higher rate of stroke in the CABG subgroup (2.7%, vs. 0.3%; p = 0.01) (19). The results have been recently confirmed at 4 years (presented November 7, 2011 at the Transcatheter Therapeutics Scientific Sessions, San Francisco, California).

It is important to consider that SYNTAX, PRECOMBAT (Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease), and also MAIN COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization) (19,25,27) do not have an "all-comers" design, and patients with ACS and cardiogenic shock were excluded. Our registry does have an "all comers" design; no patients were excluded, including those admitted with ACS, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. Moreover, in this study—which to the best of our knowledge is the largest thus far—only patients exclusively treated with DES were included (n = 1,874): of these 1,445 were treated electively, compared with 901 patients treated in this way by CABG.

Because of the nonrandomized nature of our study, an adjusted analysis with the propensity score was performed to take into account the differences in baseline clinical characteristics. At a median clinical follow-up of 1,295 (IQR 928 to 1,713) days, no difference was observed in the primary endpoint of death, CVA, and MI. Similarly, no significant differences were found in mortality and the composite endpoint of death and MI. Conversely, the advantage of CABG over PCI was observed in the composite secondary endpoint of MACCE (adjusted HR: 1.64; 95% CI 1.33 to 2.03; p < 0.0001), exclusively driven by the lower need of TVR (adjusted HR: 3.51; 95% CI 2.40 to 5.13; p < 0.0001) and TLR (adjusted HR: 2.65; 95% CI 1.73 to 4.04; p < 0.0001). In addition, after propensity score matching was performed for the entire population, no difference in the primary study endpoint of death, CVA, and MI was confirmed (HR: 0.99; 95% CI 0.73 to 1.33; p = 0.97).

Similarly, there remained an advantage of CABG in the composite endpoint of MACCE driven by repeated revascularizations. The lower need for revascularization in this group suggests that at least "first generation" DES (exclusively used in this preliminary phase of our experience from 2002 to 2006) are still an imperfect solution, unable to completely eliminate restenosis in complex settings, such as bifurcation lesions and multivessel disease. It is important to underline that the higher incidence of TVR in the PCI group did not translate into a higher incidence of the "hard endpoints" like death, MI, or CVA. In our opinion, the need for repeated revascularization should not be considered only as the "Achilles' heel" of the technique but also as a characteristic that does not have any impact on hard endpoints and can be easily repeated as compared with the need for repeated CABG. It might be fair to point out that routine angiographic follow-up was part of this initial protocol to detect early left main in-stent restenosis and that many TLR and TVR were angiographically rather than clinically driven. The low rate of IVUS guidance (33.1%) as

well as the lack of properly sized post-dilation could clearly have played an important role in the occurrence of TLR in the PCI group. Moreover, the need for "two stent techniques" as intention-to-treat in 43.1% of the patients is a measure of the high incidence of complex distal bifurcation lesions in our registry and could help to explain the overall 10.0% TLR rate in the PCI group.

In our study, there was a significant difference in SYNTAX scores between the PCI and CABG groups (28.6 ± 14.3 vs. 38.9 ± 13.2, respectively; p < 0.01). Interestingly, in such experienced centers, the extent of coronary artery disease guided the choice of the treatment even before the introduction of the SYNTAX score, with the SYNTAX trial that reported worse clinical outcome in the subgroup of patients with a score >33. Clearly, the application of the SYNTAX score gives credibility to our practice, helping the operator and referring physician to decide upon the optimal therapeutic option in this subset of patients.

From a safety perspective, the overall and cardiac mortality (14.1% vs. 11.4% and 7.5% vs. 6.8% in PCI and CABG, respectively) are quite reassuring, considering the high-risk profile of the patients included in the analysis. Age, SYNTAX score, LVEF, acute MI, and the need for IABP were all correlated with mortality in multivariable analysis.

In addition, the rate of definite ST was 1.06%, a value comparable to previous series. In our registry, the information on symptomatic graft occlusion in the CABG group is not available; however, if we consider the 2.8% rate reported in a previous series (13), a 1.6% of definite and/or probable ST is reassuring.

According to the SYNTAX score (19), also in our study the incidence of CVA was greater in the CABG group (Table 3).

Considering these encouraging long-term results and the technical developments in PCI—"second generation" DES; higher use of IVUS and fractional flow reserve; new imaging techniques, such as optimal coherence tomography; assessment of clopidogrel responsiveness and more effective antiplatelet drugs (prasugrel, ticagrelor) as well as in CABG (higher percentage of off-pump and no-touch techniques)—there is now a clear need for a prospective, randomized trial adequately powered to evaluate the optimal revascularization treatment in unprotected ULMCA lesions.

The EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial is currently randomizing 2,600 patients with ULMCA disease and a SYNTAX score of ≤32 to CABG versus second-generation DES (XIENCE Prime, Abbott Vascular, Temecula, California). The primary endpoint is the composite incidence of death, MI, or stroke at a median follow-up duration of 3 years, powered for sequential noninferiority and superiority testing. Questions remain unanswered with regard to the need to include

revascularization in the primary endpoint and the exclusion of patients with extensive triple vessel disease, in addition to left main stenosis.

Study limitations. The major limitation is that this is an observational study. A propensity score adjustment was performed to adjust for the differences in baseline clinical and lesion characteristics between the 2 study groups. In addition a propensity-score matching was also performed.

Another limitation was that, because of the retrospective nature of the study, we could not analyze all the baseline angiography films to calculate the SYNTAX score in all patients (overall 2,064 of 2,775 films were analyzed). Also, it was not possible calculate the rate of symptomatic graft occlusion in the CABG group.

Further limitations are the length of clinical follow-up and the type of stent used.

We acknowledge that, in our registry, the proportion of patients undergoing PCI is double that of those undergoing CABG in this registry. This phenomenon might reflect the practice of selected high-volume tertiary centers, as the ones included in our study.

Conclusions

In this large "all-comers" multinational registry evaluating CABG versus PCI with "first generation" DES, no difference was observed in the primary endpoint of death, CVA, and MI, at a median of 1,295 days of clinical follow-up. Rates of repeat revascularization were still higher among patients who underwent PCI than among those who underwent CABG. In selected cases and in highly competent tertiary centers, PCI for ULMCA disease can be considered a safe and effective procedure, with encouraging results at long-term follow-up, and might possibly be considered a feasible alternative to CABG.

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Key Words: coronary artery bypass graft ■ drug-eluting stent ■ left main coronary artery disease ■ percutaneous coronary intervention.

▷ **APPENDIX**

For supplementary materials, please see the online version of this article.