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Are drug-eluting stents superior to bare-metal stents in patients with unprotected non-bifurcational left main disease? Insights from a multicentre registry

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Aims To compare long-term clinical outcome following drug-eluting stents (DES) or bare-metal stents (BMS) implantation on lesions located at the ostium or the shaft of the left main in a large real-world population. The advent of DES decreased the risk of unprotected left main coronary artery (ULMCA) restenosis when compared with BMS, but it is unclear if this advantage continues when non-bifurcational lesions are considered.

Methods and results The GISE-SICI registry is a retrospective, observational multicentre registry promoted by the Italian Society of Invasive Cardiology in which 19 high-volume participating centres enrolled 1453 consecutive patients who underwent percutaneous coronary intervention on ULMCA between January 2002 and December 2006. From the registry, a total of 479 consecutive patients with ostial and shaft lesions who underwent DES ($n = 334$) or BMS ($n = 145$) implantation were analysed with extensive multivariable and propensity score adjustments. At 3-year follow-up, risk-adjusted survival rates were higher in patients treated with DES than in those treated with BMS. The adjusted hazard ratio (HR) for the risk of mortality after DES implantation relative to BMS implantation was 0.37 (95% CI: 0.15–0.96, $P = 0.04$). The adjusted HR for the risk of cardiac mortality was 0.31 (95% CI: 0.09–1.04, $P = 0.06$). The adjusted 3-year rates of target lesion revascularization (TLR) were not significantly lower in the DES group than in the BMS group ($P = 0.60$).

Conclusion In a large population of patients with lesions located at the ostium or the shaft of the left main in a real-world setting, DES were associated with favourable clinical outcomes when compared with BMS, although there was no evidence of a significant reduction in TLR with DES vs. BMS.

Keywords Unprotected left main • Drug-eluting stent • Restenosis

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Introduction

Current guidelines consider coronary artery bypass surgery (CABG) a class I recommendation for treatment of patients with unprotected left main artery disease (ULMCA).[1–6] Even if randomized and registry data of percutaneous coronary intervention (PCI) with stent implantation demonstrate similar long-term outcome compared with surgery,[7] the effectiveness of PCI in reducing repeat revascularization is still a matter of debate.

Recent reports show dramatically conflicting results when the issue of in-stent restenosis is focused on high-risk lesions located at the distal bifurcation or at the ostium/shaft of the left main.[8–10] The advent of drug-eluting stents (DES) decreased the risk of ULMCA restenosis compared with bare-metal stents (BMS),[11–17] but it is unclear if this advantage continues when non-bifurcational lesions are considered.[18,19]

Therefore, the purpose of the present study was to compare long-term clinical outcome following DES or BMS implantation on lesions located at the ostium or the shaft of the left main in a large real-world population.

Methods

Study design

The 'GISE-SICI survey on ULMCA stenosis' is a retrospective, observational multicentre registry promoted by the Italian Society of Invasive Cardiology, in which 19 high-volume participating centres enrolled 1453 consecutive patients who underwent PCI on ULMCA between January 2002 and December 2006, either with DES [sirolimus-eluting stents (SES, Cypher, Cordis, Johnson & Johnson, Warren, NJ, USA) or paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA, USA)] or BMS. All data provided by each interventional centre were obtained from specially designed case report forms, centrally collected and assessed for quality. The inclusion criteria for the registry was the presence of a $\geq$50% stenosis of the left main which was not protected by a patent coronary bypass (CABG) in either left anterior descending or circumflex artery. The exclusion criteria were ST-segment elevation acute myocardial infarction (MI) or cardiogenic shock. Full details on the overall population have been already reported.[20] Only patients with a stenosis located at the ostium or shaft of left main, without any significant distal left main involvement, were included in the present analysis. Local institutional ethics committees approved the use of these data for this study. The authors had full access to the data and take full responsibility for their integrity.

Procedural and post-intervention practices

The decision to perform PCI instead of surgery was considered in the presence of suitable anatomy for stenting and preference by patient and referring physician for percutaneous approach, or in the presence of suitable anatomy and relative contraindications to surgery defined as a EuroSCORE (European System for Cardiac Operative Risk Evaluation) $\geq$6. The interventional strategy, as well as the choice of the various devices and the administration of therapies during the procedure, was left to the operator's discretion and current guidelines. Serum samples for cardiac enzymes were collected at baseline and at 8, 16, and 24 h after PCI. Patients underwent dual-antiplatelet therapy with aspirin and clopidogrel from a minimum of 1 month (BMS) to a maximum of 6–12 months according to local practice.

Follow-up

Information concerning in-hospital events was obtained from centralized databases of the participating institutions for those patients who stayed in local hospitals and from the hospital records or by telephone contacts for those transferred to another hospital after the procedure.

The clinical follow-up data related to medications and clinical status were prospectively collected until January 2008 through scheduled outpatient clinic evaluations. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information. All repeated coronary intervention (surgical and percutaneous) and re-hospitalization data were prospectively collected during follow-up using the centralized system of the participating institution or contacting directly the hospitals where the patients were admitted or referred.

Angiographic follow-up was suggested at 6 and 9 months after the index procedure in all consenting patients. It was performed at an earlier time if clinically indicated. All events were adjudicated by an independent, blinded endpoints committee.

Endpoints and definitions

Endpoints were the 3-year rates of all-cause mortality, cardiac mortality, myocardial infarction (MI), target lesion revascularization (TLR) and major adverse cardiac events (MACE). MACE were defined as the composite of all-cause mortality, MI, and TLR.

Acute coronary syndrome was defined as either unstable angina or non-ST-segment elevation MI (NSTEMI). An NSTEMI was defined as creatine kinase-MB enzyme elevation $\times$ 3 times the upper limit of the normal value; when in addition to enzyme elevation there were new pathological Q waves in the electrocardiogram, the event was defined as a ST-segment elevation MI (STEMI). Renal dysfunction was defined as serum creatinine levels $>$2 mg/dL. TLR was defined as any repeat percutaneous revascularization or surgical bypass of the original target lesion site.

Stent thrombosis was claimed in the presence of symptoms suggestive of an acute coronary syndrome and angiographic or pathological confirmation of thrombotic occlusion of the stented segment and categorized as early (within 30 days), late (after 30 days), and very late ($>$1 year), based on elapsed time since stent implantation.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviations or median and inter-quartile range (IQR), and were compared using Student's unpaired *t*-test or Mann–Whitney rank sum test, as appropriate. Categorical variables are presented as counts and percentages and were compared with the χ^2 test when appropriate (expected frequency $>$5). Otherwise, Fisher's exact test was used. Survival, survival-free from cardiac death, MI-free survival, and TLR-free survival were analysed by the Kaplan–Meier method and the log-rank test was used to evaluate differences between groups.

Analysis of independent predictors of death and cardiac death was performed with a Cox multivariable proportional hazard regression analysis. The assumption of the proportional hazard was verified by a visual examination of the log (minus log) curves and the linearity assumption was assessed by plotting the Martingale residuals against continuous covariates. The selection in the final model was based on a plausible association with mortality and availability in the data set $\geq$85%. Patients excluded owing to missing data accounted for $<$10%

(45 of 479). The variables considered as possible predictors included age, gender, diabetes, acute coronary syndrome, renal dysfunction, multivessel disease, left ventricular ejection fraction (LVEF), EuroSCORE, reference vessel diameter, lesion length, DES use among participating centre >75% as independent control variables and treatment group (DES vs. BMS) as the independent study variable of interest.

Propensity score methods

Control of potential confounders was attempted by developing a propensity score using logistic regression. The propensity score was the conditional probability of receiving either a DES or a BMS given a set of measured covariates.[21–23] In our context, it was computed for each of the patients using a logistic regression model including the following variables: age, diabetes mellitus, reference vessel diameter, and EuroSCORE. The selection of the variables, which formed a 'minimum relevant' information set according to standards of propensity score application in health-care outcome, was based on a close relation with both treatment effect and the choice of treatment as assessed by univariate analysis.

The population was then divided into quintiles according to the propensity score. Within each quintile, the mean propensity scores of BMS and DES groups were compared, as were their clinical and procedural characteristics. Covariate interactions and higher-order terms for the continuous variables proved unnecessary for the balance of baseline characteristics across quintiles. The model was well-calibrated (Hosmer–Lemeshow test = 0.77) with a good discrimination (*c*-statistic = 0.71).

The resulting propensity score was then used for adjustment in two ways. In the first case it was included in the Cox proportional hazard models for 3-year mortality and cardiac mortality as a linear term with the treatment group (DES or BMS) as a covariate. According to this procedure, final results were presented as adjusted hazard ratios.

In the second case, the Greedy 5→1 digit match algorithm was performed to select an equal number of patients (1:1 match) treated with DES and BMS on the basis of similar propensity scores.

Specifically, we sought to match each patient with DES to one with BMS who had a propensity score that was identical to five digits. If this could not be done, the algorithm then proceeded sequentially to the next highest digit match (a 4-, 3-, 2-, or 1-digit) on propensity score to make 'next-best' matches, in a hierarchical sequence until no more matches could be made. If a subject who received DES could not be matched to any subject who received BMS on the first digit of the propensity score, that subject with PCI was discarded from the matched analysis. Once a match was made, previous matches were not reconsidered before making the next match.

After all the propensity score matches were performed, we compared the baseline covariates between the two intervention groups. Continuous variables were compared with the use of the paired *t*-test or the Wilcoxon signed-rank test, as appropriate, and categorical variables were compared with the use of McNemar's test. The procedure yielded 119 well-matched pairs. Kaplan–Meier estimates were used to plot the rates of survival, survival free from cardiac death, TLR, and MACE in these groups of patients and differences between groups were analysed with the log-rank test.

Assessment of competing risk

Even if patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored, it is of note that simply censoring patients who experienced non-cardiac mortality at the time of their death can yield biased results for the analysis of cardiac mortality. Therefore, we applied a competing risk model on our matched data, so obtaining a non-parametric evaluation of the cumulative incidence of cardiac mortality taking into account the informative nature of censoring owing to competing risks.[24] Briefly, the cumulative incidence, accounting for competing risk events, was estimated in a two-step process. In the first step, we calculated the Kaplan–Meier estimates of the overall survival from all causes. In the second step the conditional probabilities of experiencing the event of interest were calculated.

Subgroup analyses

Subgroup analyses to determine the homogeneity of the associations of treatment with cardiac death and TLR were conducted using a two-stage approach: (i) we first estimated the effect of DES on cardiac mortality and TLR in each subgroup using Cox regression model, in each case adjusting for propensity score or DES implantation; (ii) then, we formally tested for first-order interactions using Cox proportional hazards models, entering interaction terms, and adjusting for propensity scores, separately for each subgroup. For the purposes of subgroup analyses, the volume of coronary angioplasty of each centre was dichotomized and treated as binary variable, based on the annual activity of the catheterization lab.[25]

For all analyses, a two-sided $P < 0.05$ was considered statistically significant. All data were processed using the Statistical Package for Social Sciences, version 15 (SPSS, Chicago, IL, USA).

Results

Study population

The 479 patients who fully satisfied the eligibility criteria represented 32.9% of the 1453 patients originally enrolled in the GISI-SICI registry who received stents to treat ostial or shaft lesions of unprotected left main coronary artery in the absence of cardiogenic shock or STEMI during the study period. Therefore, the study population consisted of 334 patients (69.7%) treated with DES and 145 patients (31.3%) treated with BMS. Use of DES among the 19 participating centres ranged from 50–100%. Overall, patients included in this study presented a high-risk profile, with similar characteristics with regard to those of the total population of the GISE-SICI registry: median age was 72 years, 28% had diabetes, 53% had multivessel coronary disease and 62% were admitted with a diagnosis of acute coronary syndrome. The median LVEF was 55 (45–60). The median EuroSCORE was 5 (3–7) and 46% of patients had a EuroSCORE ≥6. Left main disease was located at the ostium in 304 (63.5%) patients and involved shaft in 175 (36.5%) patients.

Table 1 reports baseline characteristics according to the type of stent (DES vs. BMS) used, before and after propensity matching. Before matching, no statistically significant difference was observed among baseline features except that patients in the DES subset were younger ($P < 0.001$), were largely diabetic ($P = 0.02$), had a lower EuroSCORE ($P < 0.001$), smaller vessels ($P < 0.001$) and more often underwent stenting on ostial lesions ($P = 0.04$) compared with those in the BMS data set. After matching, patients treated with DES or BMS were more similar with regards to all measured baseline characteristics.

Table 1 Clinical, anatomical, and procedural characteristics before and after propensity score matching

		Before matching			After matching		
	Availability, *n* (%)	DES (*n* = 334)	BMS (*n* = 145)	*P*-value	DES (*n* = 119)	BMS (*n* = 119)	*P*-value
Age, median (IQR)	100	71 (62–78)	76 (68–82)	<0.001	76 (68–81)	75 (68–82)	0.81
Male (%)	100	73	67	0.19	68	66	0.68
Systemic hypertension (%)	94	65	70	0.35	64	69	0.46
Diabetes mellitus (%)	94	31	20	0.02	18	21	0.51
Hypercolesterolaemia (%)	94	57	52	0.32	54	50	0.47
Present or previous smoking habits (%)	93	34	29	0.23	26	28	0.74
Family history of coronary disease (%)	82	30	22	0.11	25	22	0.59
Acute coronary syndrome (%)	99	59	67	0.12	64	64	1.00
Unstable angina (%)	84	47	48		40	40	0.90
NSTEMI (%)	84	13	25		24	24	0.88
Chronic pulmonary disease (%)	77	9	7	0.66	10	7	0.43
Renal dysfunction (%)	96	12	17	0.14	15	15	0.95
Peripheral vascular disease (%)	69	20	25	0.32	26	26	1.00
EuroSCORE, median (IQR)	100	5 (2–7)	6 (4–8)	<0.001	6 (4–8)	6 (4–8)	0.36
EuroSCORE ≥6 (%)	100	41	59	<0.001	54	55	0.90
LVEF, median (IQR)	92	55 (45–60)	52 (40–60)	0.15	54 (42–60)	51 (40–60)	0.27
Lesion location	100			0.04			0.35
Ostium (%)		66	57		66	61	
Shaft (%)		33	43		34	39	
Multivessel disease (%)	91	56	47	0.09	56	50	0.37
Multivessel treatment (%)	70	30	24	0.27	30	27	0.65
Reference vessel diameter	98	3.7 (3.5–4)	4.0 (3.5–4.5)	<0.001	4.0 (3.5–4.1)	4.0 (3.5–4.1)	0.45
Lesion length	95	12 (8–13)	12 (8–13)	0.93	12 (8–13)	12 (8–13)	0.99

DES, drug-eluting stent; BMS, bare-metal stent; NSTEMI, non-ST-segment elevation acute myocardial infarction; LVEF, left ventricular ejection fraction; IQR, inter-quartile range.

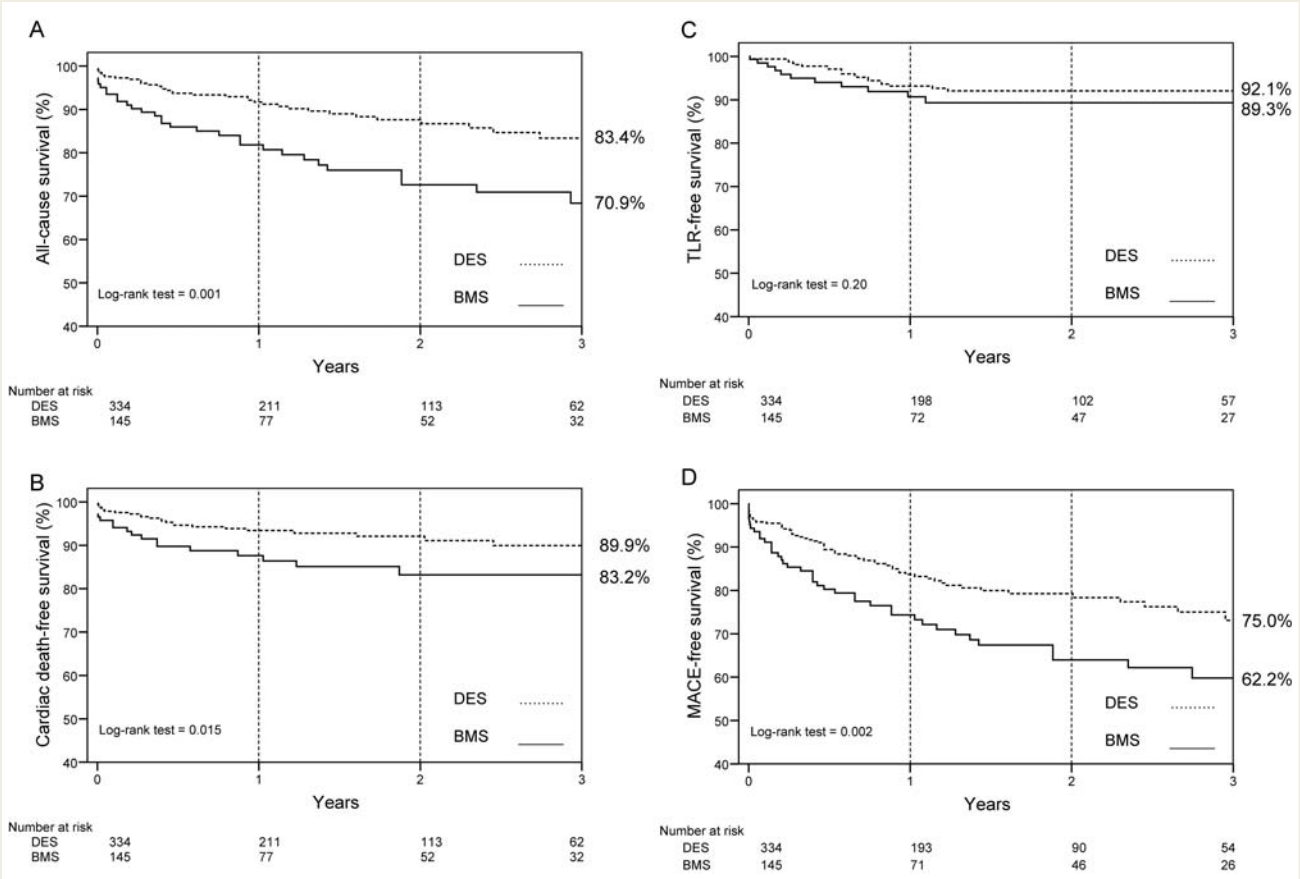

Figure 1 Actuarial rate of survival (*A*), survival free from cardiac death (*B*), target lesion revascularization (TLR) (*C*), and major adverse cardiovascular events (MACE) (*D*) at 3 years among patients who received drug-eluting stents or bare-metal stents.

Clinical outcome

Clinical outcome information was obtained for all patients. The average clinical follow-up was 455 (210–910) days. Angiographic follow-up was performed at 8 (6–10) months in 69% of patients treated with DES and 43% of patients treated with BMS. Definite subacute stent thrombosis occurred in one patient treated with BMS (0.6%), whereas definite late-stent thrombosis occurred in one patient treated with DES (0.3%). Kaplan–Meier analyses of 3-year survival and survival free from cardiac death, TLR, and MACE are shown in *Figure 1*. In the full pre-match cohort of patients, the MACE rate was significantly lower in the DES group [25.0% vs. 37.8%, hazard ratio (HR) 0.55; 95% CI 0.37–0.81, $P = 0.002$]. The beneficial effect was driven by a significant reduction in the overall mortality after DES implantation (16.6% vs. 29.1%, HR 0.46; 95% CI 0.29–0.73, $P = 0.001$). No significant differences in MI (4.2% vs. 3.4%, HR 1.41; 95% CI 0.49–4.06, $P = 0.52$) and TLR (7.9% vs. 10.7%, HR 0.63; 95% CI 0.31–1.28, $P = 0.20$) rates were observed between groups.

Cox multivariable regression models were used to correct for differences and independent predictors of mortality and cardiac mortality between treatment groups as shown in *Table 2*.

After correcting for independent predictors of adverse events, the adjusted HR for the risk of mortality after DES implantation relative to BMS implantation was 0.37 (95% CI 0.15–0.96, $P = 0.04$) and the adjusted HR for the risk of cardiac mortality after DES implantation relative to BMS implantation was 0.31 (95% CI 0.09–1.04, $P = 0.06$). Diabetes, EuroSCORE, and LVEF were found to be predictors of overall mortality, while diabetes, LVEF, and reference vessel diameter at baseline were the only predictors of cardiac death.

Propensity analysis

When the propensity score was used in the model as covariate, the adjusted HRs for the risk of mortality and cardiac mortality were 0.51 (95% CI 0.30–0.86, $P = 0.01$) and 0.42 (95% CI 0.22–0.81, $P = 0.01$), respectively (*Table 2*). Of note, when adjusted for propensity scores the magnitude of the statistical significance slightly increased.

Finally, in the matched cohort, DES were no longer associated with a significant reduction in 3-year all-cause mortality (19.9% vs. 26.2%, HR 0.62, 95% CI 0.33–1.18, $P = 0.15$), whereas a borderline significant advantage of DES vs. BMS was still observed in terms of cardiac mortality (7.8% vs. 17.2%, HR 0.42, 95% CI 0.17–1.01, $P = 0.047$). After adjusting for competing risk, cardiac mortality rates remained essentially unchanged (DES 7.7% vs. BMS 18.9%).

Table 2 Predictors of mortality and cardiac mortality in the multivariable Cox proportional hazard analysis

	Hazard ratio (95% CI)	P-value
All-cause mortality		
Diabetes	3.10 (1.44–6.67)	0.004
EuroSCORE	1.36 (1.00–1.84)	0.048
Male gender	1.28 (0.59–2.78)	0.53
Renal dysfunction	1.14 (0.73–2.84)	0.35
DES use among centres >75%	1.11 (0.46–2.70)	0.82
Lesion length	1.01 (0.96–1.07)	0.68
Age	1.00 (0.93–1.07)	0.97
LVEF	0.96 (0.93–0.99)	0.006
Multivessel disease	0.93 (0.42–2.06)	0.65
Acute coronary syndrome	0.77 (0.25–2.34)	0.77
Reference vessel diameter	0.60 (0.28–1.25)	0.17
DES vs. BMS	0.37 (0.15–0.96)	0.04
Propensity-adjusted		
DES vs. BMS	0.51 (0.30–0.86)	0.01
Propensity score	0.99 (0.98–1.01)	0.43
Cardiac mortality		
Diabetes	2.86 (1.08–7.56)	0.03
Male gender	1.86 (0.65–5.38)	0.25
EuroSCORE	1.31 (0.91–1.88)	0.15
DES use among centres >75%	1.27 (0.41–3.95)	0.68
Acute coronary syndrome	1.04 (1.19–2.70)	0.96
Age	1.00 (0.92–1.08)	0.91
LVEF	0.96 (0.92–1.00)	0.03
Lesion length	0.96 (0.87–1.05)	0.36
Multivessel disease	0.92 (0.34–2.49)	0.86
Renal dysfunction	0.62 (0.19–2.70)	0.71
Reference vessel diameter	0.33 (0.12–0.88)	0.03
DES vs. BMS	0.31 (0.09–1.04)	0.06
Propensity-adjusted		
DES vs. BMS	0.42 (0.22–0.81)	0.01
Propensity score	1.01 (0.99–1.03)	0.59

DES, drug-eluting stent; BMS, bare-metal stent; LVEF, left ventricular ejection fraction.

Similar to the pre-match cohort, no difference was apparent in terms of TLR between DES- and BMS-matched groups (11.4% vs. 10.7%, HR 0.79, 95% CI 0.33–1.90, $P = 0.60$). In addition, no further advantages of DES vs. BMS were observed in terms of MI (5.9% vs. 2.1%, HR 1.72, 95% CI 0.49–6.05, $P = 0.39$) and composite of MACE (33.5% vs. 35.3%, HR 0.73, 95% CI 0.44–1.21, $P = 0.22$).

Subgroup analyses

Results of subgroup propensity-adjusted analysis of associations between DES implantation and risk of cardiac mortality or TLR at follow-up are reported in *Table 3*. The association of DES treatment and reduction of cardiac mortality was observed in a relatively wide spectrum of ULMCA patients. However, there were no significant interactions between DES and any of the subgroups, except for reference vessel diameter (P for interaction = 0.02). Conversely, the absence of treatment effect on TLR was consistent across all subgroups.

Discussion

The most important findings of the present study are: (i) ostial or shaft lesions account for about one-third (32.9%) of all percutaneous interventions involving ULMCA in a large multicentre registry; (ii) similar long-term rates of TLR and MACE are found when the two treatments are compared; (iii) although several statistical adjustments were attempted in order to address the issue of possible confounders between groups, suggesting that DES may be associated with a risk reduction of both mortality and cardiac mortality, their results are controversial and do not seem to provide a conclusive evidence of DESs superiority.

Current American Heart Association/American College of Cardiology and European Society of Cardiology guidelines consider ULMCA stenosis a class III indication of PCI when CABG is eligible.[1–6] Nevertheless, data from registries showed the safety and effectiveness of the percutaneous approach, especially in elective patients with preserved left ventricular systolic function and EuroSCORE <6.[26]

The advent of DESs has led to a dramatic change in the long term outcome of PCI, showing better results in comparison with BMSs, which reduced the incidence of acute complications following balloon angioplasty but were also associated with an unacceptable high rate of in-stent restenosis.[12–14]

The available studies comparing surgical and percutaneous treatment of ULMCA stenosis show no significant differences in survival, but higher rates of TLR in the group of patients undergoing PCI.[7–10] This finding is mostly explained by the high epidemiological frequency of bifurcation lesions in patients with ULMCA stenosis. Bifurcation represents the Achilles' heel of percutaneous treatment, commonly characterized by higher risk of restenosis than other lesion subsets. Lesion localization is obviously neither technically nor clinically determinant when the surgical approach is preferred.

To date, despite all the encouraging data on the safety of the percutaneous approach for ULMCA treatment,[2,4,7,8] few data are available on the long-term outcome of patients with non-bifurcation stenosis.

Valgimigli *et al.*[27] compared two groups of patients undergoing PCI on ULMCA, according to the presence of distal ($n = 94$) or non-distal stenosis ($n = 36$). After a median follow-up of 587 days, the cumulative incidence of target vessel revascularization was 13% and 3% for distal and proximal lesions, respectively ($P = 0.02$). Distal lesion was identified as independent predictor of poor outcome in this subset of patients.

Chieffo *et al.*[28] recently reported results from a series of 147 consecutive patients with ostial or midshaft ULMCA stenosis who were electively treated with SES or PES implantation. The 2 years adverse events and restenosis rates were 7.4% and 0.9%, respectively. The authors identified the small sample size as a main limitation in their study, primarily because of the low

Table 3 Propensity score-adjusted hazard ratios for cardiac mortality or target lesion revascularization (TLR) associated with drug-eluting stent use for pre-specified subgroups of patients

	Cardiac death				TLR			
	HR	95% CI	*P*-value	*P*-value for interaction	HR	95% CI	*P*-value	*P*-value for interaction
Age <65	0.20	0.05–0.75	0.02	0.33	0.23	0.05–1.01	0.10	0.92
Age ≥65	0.54	0.26–1.13	0.10		0.61	0.26–1.46	0.27	
Male	0.39	0.18–0.86	0.02	0.14	0.52	0.20–1.36	0.18	0.10
Female	0.46	0.13–1.60	0.22		0.50	0.14–1.79	0.29	
Diabetes	0.54	0.18–1.59	0.26	0.13	0.63	0.10–3.87	0.62	0.18
Non-diabetes	0.35	0.15–0.85	0.02		0.49	0.21–1.13	0.09	
EuroSCORE <6	0.31	0.09–1.06	0.10	0.20	0.39	0.15–1.04	0.10	0.99
EuroSCORE ≥6	0.37	0.17–0.83	0.02		0.59	0.17–2.06	0.41	
Stable angina	0.23	0.06–0.90	0.03	0.52	1.01	0.27–3.77	0.99	0.36
ACS	0.53	0.24–1.17	0.12		0.30	0.21–1.43	0.24	
RVD ≥3.5 mm	0.54	0.26–1.11	0.10	0.02	0.51	0.23–1.16	0.11	0.15
RVD <3.5 mm	0.12	0.03–0.53	0.005		0.35	0.04–3.49	0.37	
Ostium	0.32	0.14–0.75	0.008	0.88	0.70	0.24–2.04	0.51	0.42
Shaft	0.69	0.24–2.00	0.50		0.31	0.09–1.16	0.11	
High volume centre	0.40	0.18–0.90	0.03	0.16	0.62	0.23–1.67	0.34	0.49
Low volume centre	0.44	0.14–1.45	0.18		0.33	0.09–1.25	0.10	

ACS, acute coronary syndrome; RVD, reference vessel diameter.

occurrence of the anatomical subset of non-bifurcation lesions in the general population.

In the recent study of Wood *et al.*,[29] the 2-year outcome of 31 patients undergoing DES implantation on the ostium/main stem of ULMCA was compared with the respective outcome for 69 patients with disease involving the bifurcation, showing that a substantial number of late adverse events occurred in both groups with equal frequency. The incidence of cardiac death and target vessel revascularization at 28 months was 22% in both the ostial and bifurcation groups. Based on the single centre, observational design of their study, the authors were urged to be cautious in their conclusions.

The present study reports data from the left main GISE-SICI registry that is, to the best of our knowledge, the largest available multicentre registry on ULMCA stenting. No study has been previously designed in order to specifically address the issue of long-term safety and efficacy of DES for patients with ostial or shaft lesions when compared with BMS.

Patients included in this analysis reflect the high-risk profile of a real-world population: 28% were diabetics, 53% had multivessel coronary disease, 62% were admitted with a diagnosis of acute coronary syndrome. It should also be emphasized that an increased surgical risk of the study population (46% had a EuroSCORE ≥6) was witnessed when compared with previous studies on ULMCA stenting.

Since patients treated with BMS presented a high-risk profile than those treated with DES, three contemporary methods of adjustments (using covariate, propensity score as covariate or propensity score matching) were performed in order to account for possible confounders and hardly challenge the consistency of results with regards to mortality and cardiac mortality. Overall, the three methods agree on the evidence of a trend for a reduction of mortality with DES vs. BMS, whose magnitude ranges from 58–69% for death from cardiac causes. This is consistent with the observation of a recently published meta-analysis.[30]

However, in the present study this evidence was not always corroborated by a clear statistical significance across all types of adjustment ($P = 0.04$, $P = 0.01$ and $P = 0.15$ for all-cause mortality and $P = 0.06$, $P = 0.01$ and $P = 0.047$ for cardiac mortality, respectively). In the absence of a conclusive demonstration of DES superiority, our findings on safety outcomes need to be interpreted with caution and should be considered as hypothesis-generating.

The available studies on surgical ULMCA treatment reported a 1-year mortality of 6–14%.[6,31–33] This outcome was reduced to 0–5% by the advent of DES,[16,34,35] at a price of a TLR rate of 0–14%,[15,16,33–35] that was mainly driven by a high rate of distal lesions restenosis. Bifurcations account for the main part of the lesions included in these studies. In our experience, the localization at ostial and shaft ULMCA allows to get over the limits of previous registries. Thus, our results on the subject of TLR support the hypothesis that the well-documented effectiveness of DES in reducing the need for repeat revascularization in patients who undergo PCI for treatment of coronary artery disease is questionable when the issue of non-bifurcation left main disease is addressed. This is not surprising based on the statement that lesions with greater reference vessel diameter, short length, and simple morphology are not generally characterized by high risk of repeat revascularization *per se*. Therefore, it seems reasonable to observe that the supposed advantage of DES on BMS in reducing repeat

revascularization of patients treated with PCI on left main, should be reviewed when patients with distal bifurcation lesions are excluded from the analysis. Of interest, in this study the absence of a real advantage of DES in reducing TLR ($P = 0.60$) was consistent across multiple pre-specified subgroups.

The reason why DES vs. BMS show a trend in reducing mortality, while not reducing TLR, is unexpected. However, some possible explanations may be considered. First of all, the 19 participating centres started to enrol patients when DES were not available or their penetration was low. This scenario, in which BMS were the stents of choice, could have common ground with the ascending phase of the learning curve for ULMCA PCI. Thus, in our experience, DES could have taken advantage from their enhanced and improved use on the plateau of the learning curve and from a general technical improvement in PCI stenting. In addition, patients treated with DES could have benefited from a closer angiographic follow-up than those treated with BMS, suggesting the need for routine angiographic follow-up after ULMCA treatment.

Another possible explanation for DES superiority in reducing mortality may be related to ancillary medical therapy. Although no data on patients adherence to medical treatment are available in GISE-SICI registry, prolonged double-antiplatelet therapy could be responsible of better outcomes independently from its prescription to prevent stent thrombosis.[36,37]

Finally, the most important limitation of the present study is the lack of a random assignment to treatment groups. Evaluating the impact of a specific treatment using a registry can lead to incorrect conclusions because of the influence of unassessed confounding variables [e.g. co-morbidities, terminal illness, low socio-economic status, intravascular ultrasound (IVUS) guidance]. In this study, each treatment was not assigned randomly but by specific criteria in each case, generating an unavoidable risk of bias regarding treatment selection and the possible prognosis. In order to partly compensate for the baseline and angiographic imbalance between groups, we performed extensive adjustments both with multivariate analysis and propensity score, making residual selection biases unlikely. However, it is impossible to know if these adjustments are appropriate or if the relevant characteristics have been correctly identified, since only randomization can provide an unbiased estimation of the effects of a treatment.

Systematic IVUS was not conducted in all patients at the time of PCI. Some available data observe that IVUS could be useful in order to achieve optimal sizing of lesion and good implantation of stent during PCI but, to date, IVUS utilization does not seem to significantly reduce the incidence of both ISR and TLR at long-term follow-up.[38,39] No data adequately address the issue of safety when IVUS guidance is employed.

Analysis of recently completed trials[40] or further specifically designed study with adequate power are expected and strongly encouraged in order to clarify the role of stent type in left main coronary disease not involving bifurcation and give answers on the presence and the magnitude of DES superiority in reducing mortality independently of its effect on revascularization.

Based on the results of our study, we conclude that patients with ostial or shaft ULMCA disease treated with stent-supported PCI have comparable outcome in terms of MACE and repeat revascularization when DES or BMS are deployed. The observational finding of a potential improved survival with DES vs. BMS suggests the need for large prospective trials with clinical primary endpoints.

A further comparison between surgical and percutaneous treatment of non-bifurcation ULMCA lesions could drive to an update of guidelines, improving the actual class recommendation for ostial and shaft ULMCA stenosis.

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