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

Corrado Tamburino1*, Maria Elena Di Salvo1, Davide Capodanno1, Antonio Marzocchi2, Imad Sheiban3, Massimo Margheri4, Aleardo Maresta5, Fabio Barlocco6, Giuseppe Sangiorgi7, Giancarlo Piovaccari8, Antonio Bartorelli9, Carlo Briguori10, Diego Ardissino10, Francesco Di Pede11, Angelo Ramondo12, Luigi Inglese13, Anna Sonia Petronio14, Leonardo Bolognese15, Alberto Benassi16, Cataldo Palmieri17, Aldo Patti18, and Stefano De Servi6

1Dipartimento di Cardiologia, Ospedale Ferrarotto, Università di Catania, via Citelli 6, 95124 Catania, Italy; 2Istituto di Cardiologia, Policlinico S. Orsola, Università di Bologna, Bologna, Italy; 3Divisione di Cardiologia, Ospedale Universitario Le Molinette, Torino, Italy; 4Dipartimento Cardiovascolare, Ospedale Careggi, Università di Firenze, Firenze, Italy; 5Dipartimento di Cardiologia, Ospedale S. Maria delle Croci, Università di Ravenna, Ravenna, Italy; 6Dipartimento di Malattie Cardiovascolari, Ospedale Civile, Legnano, Italy; 7Centro Emocolumbus, Milano, Italy; 8Dipartimento di Cardiologia, Ospedale degli Infermi, Rimini, Italy; 9Centro Cardiologico Monzino, Milano, Italy; 10Dipartimento di Cardiologia, Clinica Mediterranea, Napoli, Italy; 11Dipartimento di Cardiologia, Ospedale Civile, Mestre, Italy; 12Dipartimento di Scienze Cardiovascolari, Università di Padova, Padova, Italy; 13Cardiovascular Interventional Radiology Department, IRCCS Policlinico S. Donato, S. Donato Milanese, Milan, Italy; 14Dipartimento Cardio-Toracico, Ospedale Cisanello, Pisa, Italy; 15Dipartimento Cardiovascolare Ospedale S. Donato, Arezzo, Italy; 16Dipartimento di Cardiologia, Hesperia Hospital, Modena, Italy; 17Istituto di Fisiologia Clinica, CNR, Massa, Italy; and 18Dipartimento Cardiovascolare, Ospedale Cervello, Palermo, Italy

Received 26 August 2008; revised 12 December 2008; accepted 23 January 2009; online publish-ahead-of-print 10 March 2009

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

* Corresponding author. Tel: +39 (0) 957436201, Fax: +39 (0) 95362429, Email: tambucor@unict.it

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2009. For permissions please email: journals.permissions@oxfordjournals.org
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.\(^1\)–\(^8\),\(^19\)

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 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.

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.

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.

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 \(\chi^2\) 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 \(<10\%\).
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.

**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

| Characteristic                                      | 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    |
| Hypercholesterolaemia (%)                           | 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    |
| NSTMI (%)                                           | 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; NSTMI, non-ST-segment elevation acute myocardial infarction; LVEF, left ventricular ejection fraction; IQR, inter-quartile range.
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. 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, few data are available on the long-term outcome of patients with non-bifurcation stenosis.

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

In the recent study of Wood et al., 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 non-bifurcation left main disease is addressed. This is not surprising based on the statement that lesions with greater 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

### 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** | HR | 95% CI | **P-value** | **P-value** |
| 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 | 0.61 | 0.26–1.46 | 0.27 | 0.12 |
| 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 | 0.12 |
| 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 | 0.31 |
| 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 | 0.52 | 0.17–2.06 | 0.41 | 0.36 |
| 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 | 0.30 | 0.21–1.43 | 0.24 | 0.41 |
| 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 | 0.35 | 0.04–3.49 | 0.37 | 0.42 |
| 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 | 0.31 | 0.09–1.16 | 0.11 | 0.49 |
| 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 | 0.33 | 0.09–1.25 | 0.10 | 0.10 |

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

Acknowledgements

There are no funding sources to acknowledge. No medical writer or editor is involved in the creation of this manuscript.

The following persons and institutions have contributed to this work: M.E.D.S., D.C., C.T. (Ospedale Ferrarotto, Catania, Italy); L.B., G. Falsini (Ospedale Civile, Areezo, Italy); T. Palmerini, A.M. (Policlinico S. Orsola, Bologna, Italy); S. Vecchio, M.M. (Ospedale Careggi, Firenze, Italy); F.B., S.D.S. (Ospedale Civile, Legnano, Italy); C.P. (Ospedale Pasquiniucci, Massa, Italy); F.D.P., P. Buja (Ospedale Civile, Mestre, Italy); P. Ravagnani, A.B. (Ospedale Monzino, Milano, Italy); G.S. (Centro Emocolumbus, Milano, Italy); Giuseppe D’Anniballe, A.B. (Hesperia Hospital, Modena, Italy); D. Tavano, C.B. (Clinica Mediterranea, Napoli, Italy); M. Pepe, A.R. (Policlinico Universitario, Padova, Italy); A.P., V. Filippone (Ospedale Cervello, Palermo, Italy); L. Vignali, D.A. (Policlinico, Parma, Italy), M. De Carlo, A.S.P. (Ospedale Cisanello, Pisa, Italy); G. Vecchi, A.M. (Ospedale S. Maria delle Croci, Ravenna, Italy); A. Santarelli, G.P. (Ospedale degli Infermi, Rimini, Italy); C. Fantoni, L.I. (Ospedale civile, S. Donato Milanese); D. Siliano, G. Biondi-Zoccai, I.S. (Ospedale Universitario Le Molinette, Torino, Italy).

Conflict of interest: none declared.

References

1. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB III, Morrison DA, O’Neil WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 Guideline update for percutaneous coronary intervention. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:1–121.
2. King SB III, Smith SC, Hirshfeld JW, Jacobs AK, Morrison DA, Williams DO. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline update for percutaneous coronary intervention. J Am Coll Cardiol 2008;51:172–209.
3. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug J-E, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for percutaneous coronary interventions. The Task Force for percutaneous coronary interventions of the European Society of Cardiology. Eur Heart J 2005;26:804–847.
4. Caracciola EA, Davis KB, Sogoli G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main coronary artery disease: long-term CASS experience. Circulation 1995;91:2325–2334.
5. D’Allonnes FR, Corbineau H, Le Breton H, Leclercq C, Lagueurrier A, Daubert C. Isolated left main coronary artery stenosis: long-term follow up in 106 patients after surgery. Heart 2002;87:544 –548.
6. Eagle KA, Guyton RA, Dawoodz R, Edwards PH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC. ACC/AHA 2004 Guidelines update for coronary artery bypass graft surgery. Circulation 2004;110:1168–1176.
21. Rosembaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. Biometrika 1983; 70:41–55.

22. Rosembaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity scores. J Am Stat Assoc 1984; 79:516–24.

23. Rubin DB. Estimating causal effects from large data sets using propensity scores. Am Intern Med 1997; 127:757–763.

24. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer 2004; 91:1229–1235.

25. Tamburino C. Elenco generale delle procedure effettuate nei laboratori italiani nel 2007. Giornale Italiano di Cardiol Invasiva 2008; 13:2–12.

26. Lefering R, Silvestri M, Bedossa M, Elchsoon H, Brunel P, Koning R, Chevailer B. The French Registry of unprotected left main coronary artery treatment. Am J Cardiol 2003; 92(suppl):31L.

27. Valgimigli M, Malaguti P, Rodriguez-Granillo GA. Garcia-Garcia HM, Pold J, Tsuchida K, Regar E, Van der Giessen WJ, De Jaegere P, De Feyter P, Serruys PW. Distal left main coronary artery is a major predictor of outcome in patients undergoing percutaneous intervention in the drug-eluting stent era. An integrated clinical and angiographic analysis based on the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registries. J Am Coll Cardiol 2006; 47:1503–1537.

28. Chieffo A, Park SJ, Valgimigli M, Kim YH, Daemen J, Sheiban I, Truffa A, Montorfano M, Airoldi F, Sangiorgi G, Carolino M, Michiev L, Lee CW, Hong MK, Park SW, Moretti C, Bonizzone E, Rogacka R, Serruys PW, Colombo A. Favorable long-term outcome after drug-eluting stent implantation in non bifurcation lesions with unprotected left main coronary artery. A multicenter registry. Circulation 2007; 116:558–162.

29. Wood FO, Saylors E, Schneider J, Joe RL, Tift Mann J. Unprotected left main disease managed with drug-eluting stents: long term outcome of 100 patients with increased surgical risk. Cath Cardiol Int 2008; 71:533–538.

30. Beauford RB, Saunders CR, Luncerof TA, Niemeier LA, Shah S, Karanam R, Pendergast T, Burns P, Sardar F, Goldstein DJ. Multivessel off-pump revascularization in patients with significant left main coronary artery stenosis: early and mid-term outcome analysis. J Card Surg 2005; 20:112–118.

31. Biondi-Zoccai GG, Lotrionte M, Moretti C, Meliga E, Agostini P, Valgimigli M, Migliorini A, Antonucci D, Carrié D, Sangiorgi G, Chieffo A, Colombo A, Price MJ, Teirstein PS, Christiansen EH, Abatte A, Testa L, Gunn JP, Burzotta F, Laidoito A, Trevi GP, Sheiban I. A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease. Am Heart J 2008; 155:274–283.

32. Holm F, Lubiana JC, Semrad M, Rohac J, Vondracek V, Miller I, Vanek I, Golan L, Ashchermann M. Main clinical and surgical determinants of in-hospital mortality after surgical revascularization of left main coronary artery stenosis: 2 year retrospective study (1998–1999). J Mal Vascul 2004; 29:89–93.

33. Lu JC, Grayson AD, Pullan DM. On-pump versus off-pump surgical revascularization for left main stem stenosis: risk adjusted outcomes. Ann Thorac Surg 2005; 79:136–142.

34. Sheiban I, Meliga E, Moretti C, Fumagalli A, Omede` P, Sciuto F, Grossomarras W, Trevi G. Sirolimus-eluting stents vs. bare metal stents for the treatment of unprotected left main coronary artery stenosis. Eurointervention 2006; 2:356–362.

35. Chieffo A, Montorfano A. Treatment of unprotected left main coronary artery disease with drug-eluting stents: is it time for a randomized trial? Nat Clin Pract Cardiovasc Med 2005; 2:396–400.

36. Li M, Zhang Y, Ren H, Zhang Y, Zhu X. Effect of clopidogrel on the inflammatory progression of early atherosclerosis in rabbits model. Atherosclerosis 2007; 194:348–356.

37. Cuiuffet G, Lombardini R, Pirro M, Lupattelli G, Mannarino E. Clopidogrel: hemorheological effects in subjects with subclinical atherosclerosis. Clin Hemorheol Microcirc 2001; 25:31–39.

38. Park SJ, Hong MK, Lee CW, Kim JJ, Song JK, Kang DH, Park SW, Mintz GS. Elective stenting of unprotected left main coronary artery stenosis: effect of debulking before stenting and intravascular ultrasound guidance. Am J Cardiol 2001; 88:1054–1060.

39. Agostoni P, Valgimigli M, Van Mieghem CA, Rodriguez-Granillo GA, Aoi K, Ong AT, Tsuchida K, McFadden EP, Lighthart JM, Smits PC, De Jaegere P, Sianos G, Van der Giessen WJ, De Feyter P, Serruys PW. Comparison of early outcome of percutaneous coronary intervention for unprotected left main coronary artery disease in the drug-eluting stent era with versus without intravascular ultrasonic guidance. Am J Cardiol 2005; 95:644–647.

40. Ong AT, Serruys PW, Lee CW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van ES GA, Kleijne J, Koglin J, Russell ME. The SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006; 151:1194–1204.