

Comparison of the Effectiveness of Percutaneous Intervention of the Left-Main Coronary Artery With Everolimus-Eluting Stents in Women -Vs- Men



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Everolimus-eluting stents are largely used for left main (LM) percutaneous coronary interventions (PCI). Long-term follow-up of patients who underwent LM PCI in a real world clinical setting, in particular women, have been scarcely reported. Consecutive patients who underwent unprotected LM PCI with EES at a single Institution from December 2006 to April 2016 were included. Main outcome assessed was the occurrence of major adverse cardiovascular events (MACE) as a composite of death, myocardial infarction or target lesion revascularization at follow-up. Overall, 589 patients (20.8% women) were included in the present analysis. Women were older, had lower body mass index and more frequently hypertensive compared with men. Main clinical presentation was stable coronary artery disease (CAD); unstable angina was more frequently observed in women compared with men, whereas ST-elevation myocardial infarction was less frequent. After 69.7 ± 28.3 months of follow-up, 47 patients overall experienced MACE (1.43 per 100*patients/year). MACE rate was higher in women compared with male patients, with a rate of 2.49 and 1.17 per 100*patients/year, respectively ($p = 0.015$). The difference was driven mainly by higher mortality in women (0.89 vs 0.15 per 100*patients/years, $p = 0.002$). At multivariable Cox regression, female gender was independently associated with an increased risk of MACE at follow-up (hazard ratio 2.21, 95% confidence interval 1.20 to 4.08, $p = 0.011$). In conclusion, EES can be safely and effectively adopted for LM PCI. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:1357–1362)

Coronary artery revascularization is the first-line treatment for patients with significant stenosis of the left main (LM) coronary artery.¹ Coronary artery bypass grafting (CABG) has represented for many years the gold standard for LM revascularization. Percutaneous coronary interventions (PCI), particularly with the use of latest generations of everolimus eluting stents (EES), has imposed itself as a viable and valuable alternative to CABG for patients with simple or intermediate anatomical coronary settings and for patients with contraindications to surgery.² Gender is seldom considered a relevant parameter when deciding the appropriate LM revascularization strategy (PCI vs CABG), as exemplified by current European Society of Cardiology guidelines on myocardial revascularization.¹ Nonetheless, several studies have reported in recent years that women might experience a worse prognostic outcome compared with men when undergoing LM PCI. Post hoc analyses from 2 large randomized clinical trials (RCTs) conducted in Western countries, in fact, have reported a higher rate of long-term adverse events in female patients who underwent LM PCI.^{2,3} This finding proved however inconsistent: RCTs and analyses of large registries conducted in Asian countries failed to find gender-related

differences,^{4,5} whereas registry analyses conducted in Western countries showed at most a trend toward a higher rate of adverse events in female patients.^{6–8} Given the uncertainty surrounding this topic, we conducted the present analysis to assess if LM PCI is associated with different outcomes in women compared with men who underwent coronary revascularization with EES, which represent one of the current state-of-the-art drug-eluting stent, in a real-world setting.⁹

Methods

Consecutive patients who underwent LM PCI with EES implantation at Centro Cardiologico Monzino, Milan, Italy from December 2006 to April 2016 were included in the present study.

Inclusion criteria were the presence of at least 1 angiographic characteristic: $\geq 50\%$ ostial or shaft unprotected LM stenosis; unprotected distal LM stenosis involving left anterior descending (LAD) or ostial LCx or both. Indications for coronary revascularization included stable angina, unstable angina, non-ST segment elevation myocardial infarction, ST-elevation myocardial infarction (STEMI), and cardiogenic shock. Definitions were revised according to current European Society of Cardiology guidelines.^{10–12} Cardiogenic shock was defined as the state of end-organ hypo-perfusion due to persistent hypotension in the presence of adequate cardiac filling pressures.¹³

Baseline clinical features were prospectively collected for each patient at the index event, along with medications at discharge. Main procedural data were recorded,

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See page 1362 for disclosure information.

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including, but not limited to, number, diameter, and length of implanted stents and, where applicable, bifurcation treatment techniques. Complete revascularization was defined as the treatment of every stenosis $\geq 70\%$ in a coronary branch with a diameter ≥ 2.0 mm. Use of intracoronary imaging was strongly recommended as per site protocol, although not mandatory. Need for intra-aortic balloon pump or other circulation support devices, as well as procedural and in-hospital complications, were recorded. Patients follow-up was performed by clinical outpatient visit or, where not possible, by telephone contact.

The main outcome assessed in the present analysis was the occurrence of major adverse cardiovascular events (MACE) at follow-up. MACEs were defined as a composite of death, myocardial infarction (MI) or target lesion revascularization (TLR). Single components of MACE, target vessel revascularization (TVR), and bleedings, defined according to Bleeding Academic Research Consortium (BARC) criteria, were the secondary outcomes.

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation and compared by nonparametric Mann-Whitney test. Qualitative variables were reported as number and

percentage and compared by means of Pearson's chi-square test or Fisher's exact test, as appropriate.

Survival estimates were computed by Kaplan-Meier methods; group comparisons were conducted using the log-rank test. Predictors of MACE were identified using a univariable Cox regression analysis. A multivariable model was built to identify the parameters independently associated with the occurrence of MACE at follow-up; all covariates with a statistically significant association with MACE at the univariable Cox regression analysis (with a 2-tailed p value < 0.10) or clinically relevant covariates were included in the final model. Analyses were conducted using SPSS software version 2.1 (IBM Corporation, Armonk, New York). A 2-tailed p value < 0.05 was considered statistically significant.

Results

The final study cohort was composed of 589 patients, of whom 122 (20.8%) were women. Detailed baseline clinical features are presented in Table 1. Most patients presented unprotected distal LM stenosis, whereas in 20% of the cases a non-LM vessel was treated during the same procedure. A single stent was implanted in 59.7% of the cases, whereas a

Table 1
Baseline clinical features and in-hospital outcomes

Variables	Overall (n = 588)	Women (n = 122)	Men (n = 466)	p Value
Age (years)	66.4 \pm 9.8	69.7 \pm 9.7	65.4 \pm 9.7	<0.001
BMI (Kg/mq)	26.1 \pm 3.6	25.7 \pm 4.4	26.3 \pm 3.4	0.039
Follow-up length (months)	69.7 \pm 28.3	68.1 \pm 28.4	70.4 \pm 28.0	0.383
Women	122 (20.8%)	—	—	
Hypertension	196 (33.3%)	55 (45.1%)	141 (30.3%)	0.002
Familiar history of CAD	141 (24.0%)	34 (27.9%)	107 (23.0%)	0.258
Smoke				
Active	90 (15.3%)	13 (10.6%)	77 (16.5%)	0.109
Former	248 (42.2%)	44 (36.1%)	204 (43.8%)	0.125
Dyslipidemia	211 (35.9%)	41 (33.6%)	170 (36.5%)	0.556
Diabetes mellitus	137 (23.3%)	29 (23.8%)	108 (23.2%)	0.890
Non-insulin dependent	126 (21.4%)	25 (20.5%)	101 (21.7%)	0.777
Insulin dependent	13 (2.2%)	4 (3.3%)	9 (1.9%)	0.368
Chronic kidney disease	16 (2.7%)	2 (1.6%)	14 (3.0%)	0.409
Previous coronary angioplasty	228 (38.8%)	47 (38.5%)	181 (38.8%)	0.949
Previous coronary bypass	97 (16.5%)	22 (18.0%)	75 (16.1%)	0.608
ST-elevation myocardial infarction	81 (13.8%)	9 (7.4%)	72 (15.5%)	0.021
Non-ST elevation myocardial infarction	21 (3.6%)	3 (2.5%)	18 (3.9%)	0.457
Unstable angina pectoris	43 (7.3%)	15 (12.3%)	28 (6.0%)	0.018
Stable coronary artery disease		94 (77.0%)	349 (74.9%)	0.623
Cardiogenic shock	8 (1.4%)	0 (0.0%)	8 (1.7%)	0.145
Intra-aortic balloon pump	14 (2.4%)	3 (2.5%)	11 (2.4%)	1
Cardiopulmonary support	4 (0.7%)	1 (0.8%)	3 (0.6%)	1.0
Stent-thrombosis (acute)	1 (0.2%)	1 (0.8%)	0 (0%)	0.207
Acute pulmonary oedema	1 (0.2%)	0 (0%)	1 (0.2%)	0.609
Acute kidney injury	1 (0.2%)	0 (0%)	1 (0.2%)	1.0
Cardiac biomarker increase	200 (34.0%)	38 (31.3%)	162 (34.8%)	0.453
Major bleeding (Bleeding Academic Consortium 3-5)	2 (0.3%)	0 (0%)	2 (0.4%)	1.0
Retroperitoneal hematoma	1 (0.2%)	0 (0%)	1 (0.2%)	1.0
Pseudoaneurysm	1 (0.2%)	0 (0%)	1 (0.2%)	1.0
Death	2 (0.3%)	1 (0.8%)	1 (0.2%)	0.372
Periprocedural Myocardial infarction	84 (14.3%)	15 (12.3%)	69 (14.8%)	0.480

Values are expressed as mean \pm standard deviation or number (%), as appropriate.

2 stent-technique approach for LM bifurcation was used in one quarter of the patients. Final kissing balloon was performed in 36.0% of the cases. Complete procedural data are reported in Table 2. Periprocedural MI occurred in about 14% of the patients, whereas severe complications were rare, as only 2 major bleedings (Bleeding Academic Research Consortium 3), 1 retroperitoneal hematoma, 1 femoral artery pseudoaneurysm and 2 in-hospital deaths occurred. After a mean follow-up of 69.7 ± 28.3 months, 47 (7.97%) patients experienced MACE, accounting for a rate of 1.43 per 100*patients/year. More specifically, 10 patients died, 27 patients had TLR, 19 had MI. Moreover, 22 patients were reported having TVR. MACE occurred more frequently in women compared with men, as 16 of 122 (13.1%) women and 31 of 465 (6.6%) men experienced MACE at follow-up, accounting for an event rate of 2.49 and 1.17 per 100*patients/year, respectively ($p = 0.015$, Figure 1). The difference was driven mainly by higher mortality rate in female patients (0.89 vs 0.15 per 100*patients/years, $p = 0.002$, Figure 2). A trend, albeit nonsignificant, toward higher rate of TVR was observed in male patients (0.15 vs 0.79 per 100*patients/years, $p = 0.066$; Figure 2). No differences were observed for MI and TLR (Figure 2). At univariable Cox regression analysis, female gender was associated with an increased risk of MACE at follow-up, with a hazard ratio 2.07 (95% confidence interval 1.13 to 3.79, $p = 0.018$; Figure 3). After controlling for potential confounders in a multivariable model, female gender was confirmed as independently associated with an increased

risk of MACE at long-term follow-up (hazard ratio 2.21, 95% confidence interval 1.20 to 4.08, $p = 0.011$). Cumulative stent length was also independently associated with a higher rate of MACE at follow-up, whereas larger diameter of the stent implanted in the LM related to a lower rate (Figure 3).

Discussion

For more than a decade, LM stenting has been completely investigated and upgraded from an experimental and controversial treatment up to a recommended revascularization strategy in a certain subset of patients.² More importantly, LM stenting has been adopted before in clinical routine practice reporting at least a comparable outcome when compared with CABG with regard to safety outcomes such as survival, incidence of MI, or stroke and it has been commonly used in patients who are not eligible or who refuse CABG. This immense progress was possible due to technological improvements over time, the availability of first- and second-generation drug-eluting stents, intravascular imaging techniques, bifurcation lesion treatment technique concept-evolution, and growing experience of operators.

The present study confirms the safety and feasibility of percutaneous revascularization of LM stenosis with EES in a real-world context. With our results, we showed hence that patients who underwent PCI of LM at a high-volume center report a very favorable short- and especially very long-term (up to 10 years) prognosis according to MACE

Table 2
Procedural clinical features and in-hospital outcomes

Variables	Overall (n = 588)	Women (n = 122)	Men (n = 466)	p Value
Left main narrowing				0.665
Ostium/Shaft	111 (18.9%)	25 (20.5%)	86 (18.5%)	
Left main – left descending	399 (68%)	85 (69.7%)	315 (67.6%)	
Left main – circumflex	69 (11.8%)	11 (9.0%)	58 (12.4%)	
Left main – intermediate branch	8 (1.4%)	1 (0.8%)	7 (1.5%)	
Guiding catheter				
6-French	393 (66.7%)	72 (59%)	320 (68.7%)	0.044
7-French	197 (33.4%)	49 (40.2%)	148 (31.8%)	0.080
No of implanted stents				0.417
1	349 (59.7%)	72 (59%)	278 (59.9%)	
2	145 (24.8%)	33 (27%)	112 (24.1%)	
≥ 3	91 (15.5%)	17 (14%)	74 (16%)	
Cumulative stent length (mm)	53.7 ± 38.4	52.6 ± 39.9	54.4 ± 38.1	0.533
Left main stent diameter (mm)	3.7 ± 1.5	3.7 ± 0.4	3.7 ± 1.7	0.635
Direct stenting	67 (11.4%)	12 (9.8%)	55 (11.8%)	0.543
Side branch stent	147 (25%)	30 (24.6%)	117 (25.1%)	0.925
Crush/Minicrush	62 (10.5%)	14 (46.7%)	48 (41.7%)	
Culotte	0 (0%)	0 (0%)	0 (0%)	
T-and-protrusion (TAP)	10 (10.7%)	2 (6.7%)	8 (7%)	
T-stenting	14 (2.4%)	4 (13.3%)	10 (8.7%)	
V-stenting	7 (1.2%)	1 (3.3%)	6 (5.2%)	
Reverse crush	1 (0.2%)	0 (0%)	1 (0.9%)	
Tryton	51 (8.7%)	9 (7.4%)	42 (9%)	
Final kissing-balloon	212 (36%)	44 (36.1%)	168 (36.1%)	0.998
Thrombus detection	3 (0.5%)	0 (0%)	3 (0.6%)	1.0
Non-left main Percutaneous coronary intervention	118 (20%)	20 (16.4%)	98 (21%)	0.255
Complete revascularization	354 (60.1%)	73 (59.8%)	280 (60.1%)	0.960
No reflow	9 (1.5%)	9 (1.9%)	0 (0%)	0.216

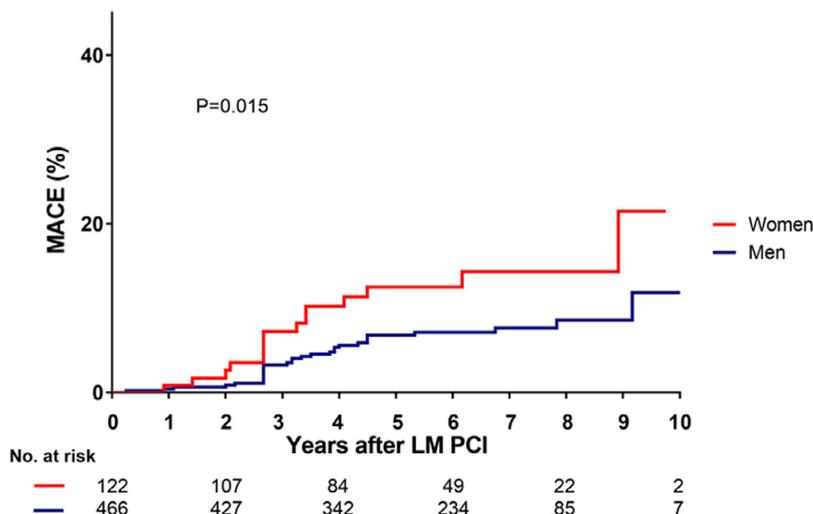


Figure 1. Rate of major adverse cardiovascular events at follow-up. LM = left main; MACE = major adverse cardiovascular event; PCI = percutaneous coronary intervention.

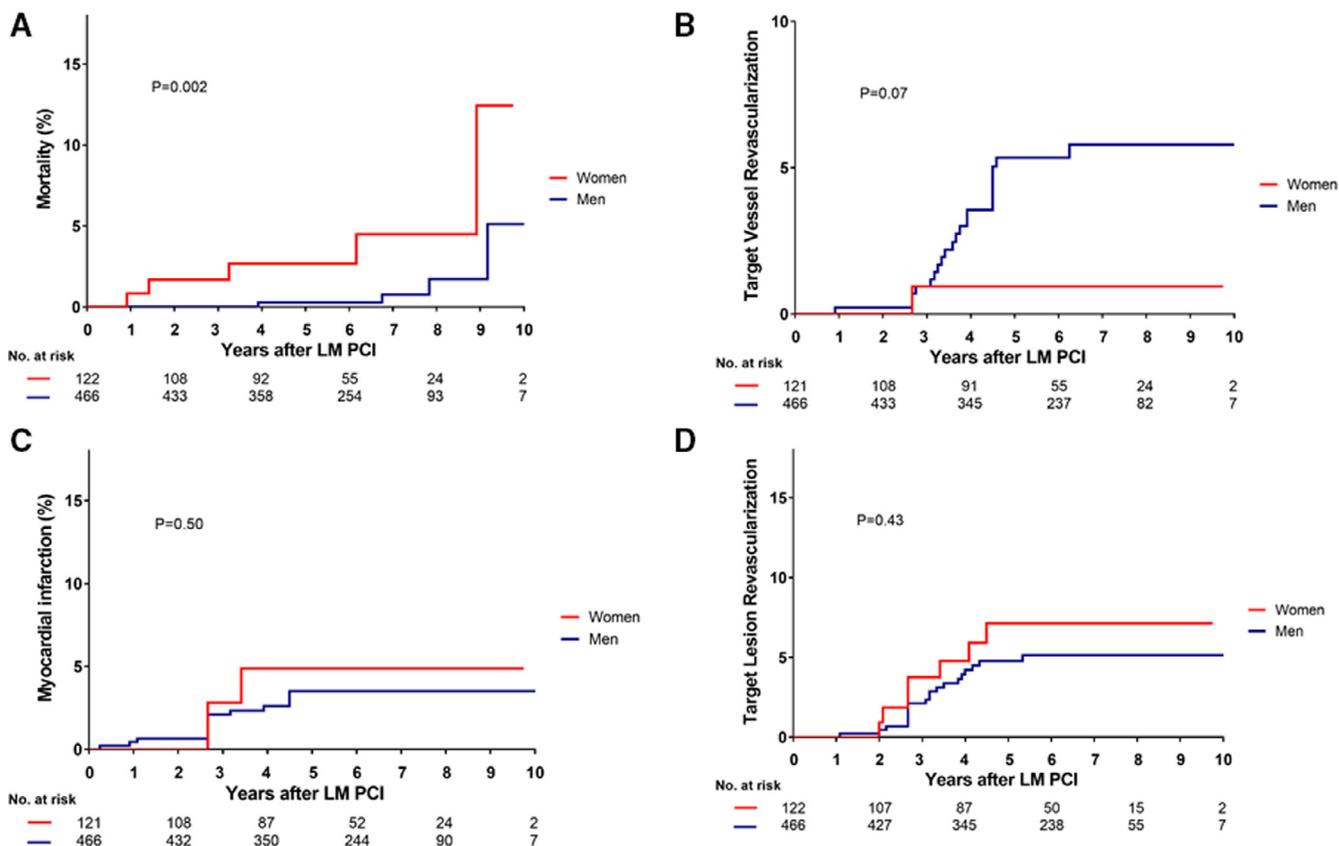


Figure 2. Mortality (panel a), rate of target vessel revascularization (panel b), myocardial infarction (panel c) and target lesion revascularization (panel d) at follow-up.

and mortality rate. These data are in line with recent literature findings, particularly with those emerged in the EXCEL trial, which was conducted using the same kind of drug-eluting stents assessed in the present study.³ Of interest, we showed that, with current technology, EES implantation can be performed in the majority of the cases with the use of standard-sized 6-French catheters, a relevant factor in terms of access-site complications and use of radial way.¹⁴

The only available data showing probability of 10-year survival and MACCE-free survival were reported in the LE MANS registry, a multicenter, prospective study randomly assigning 105 patients with unprotected LM stenosis to PCI or CABG, demonstrating favorable very long-term (up to 10 years) safety and MACCE-free survival rates in the PCI group (34.7% vs 22.1%, p=0.06). It must be highlighted that the overall cohort included a wide spectrum of coronary

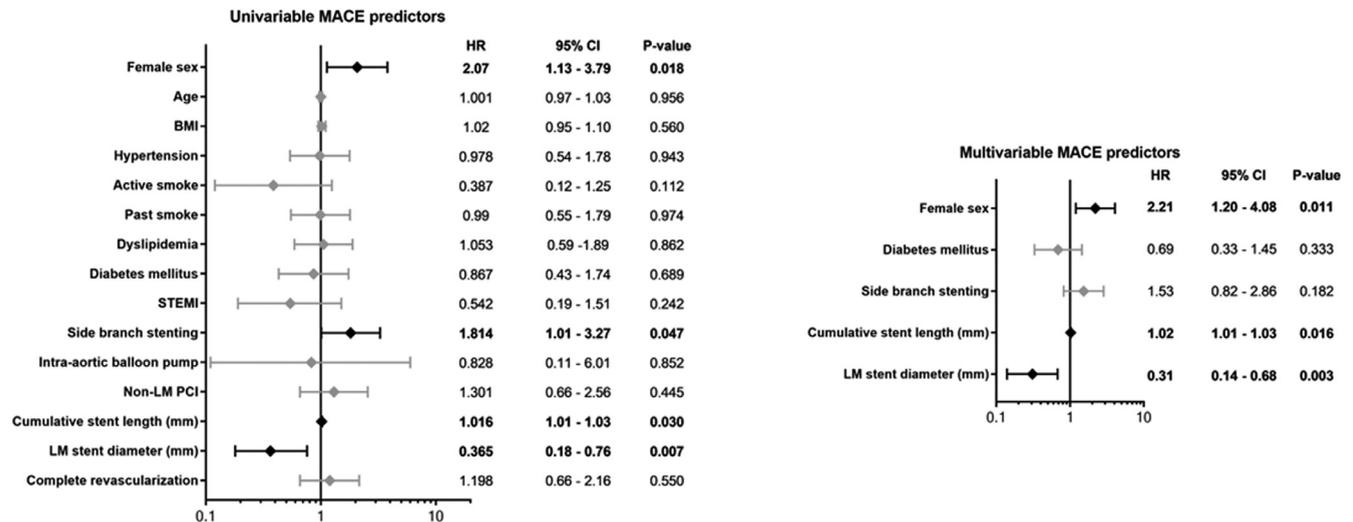


Figure 3. Univariate (*panel a*) and multivariate (*panel b*) analysis evaluating the baseline parameters independently associated with the occurrence of major adverse cardiovascular events (MACE) at follow-up.

BMI = body mass index; LM = left main; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

disease as well as acute coronary syndromes.¹⁵ Patients in the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization registry,¹⁶ who received bare metal stent (BMS) for LM with less complex coronary artery disease, showed a 10-year survival probability at 83.1%, which is nearly identical to the current report.

Our study aimed in particular to assess gender-related differences regarding the outcome of patients treated with LM PCI. Previous subanalyses of the SYNTAX and EXCEL trial reported a higher rate of adverse events at follow-up in women compared with men.^{3,4,17} In particular, these differences were observed only for PCI and not for CABG. However, gender-related differences after LM PCI were inconsistently confirmed in other settings, particularly in registry-based analyses.^{6,7} Such inconsistencies between RCTs and clinical registries might be due to the misrepresentation of real-world populations frequently encountered with RCTs, which happens to affect in particular female patients.^{18,19} It is also possible that differences in patients' selection and clinical or interventional procedures between different studies might have led to these slight differences. Our results, which are based on a registry analysis, are consistent with the findings of the EXCEL trial, which used EES as selected study devices. The higher rate of MACE observed in women was guided primarily by higher mortality, as no significant differences were observed in terms of MI and TLR. These differences might be explained by a prevalence of unstable clinical setting and older age in women compared with men, findings that alone could have at least partially explained higher MACE rate and mortality. Age and clinical presentation, however, failed to emerge as independently related to MACE at follow-up at multivariable analysis. Other baseline differences observed at baseline between men and women, such as hypertension and body mass index were not sufficient to explain the different rates of MACE at follow-up, as shown by the same multivariable Cox regression analysis. It has to be

acknowledged, however, that given the retrospective setting, some unknown confounding might have contributed to these differences in outcomes.²⁰ From a procedural standpoint, no significant differences were observed between women and men in terms of LM segment treated, number, length, and diameter of stents implanted, one versus double-stenting in LM lesion treatment, type of bifurcation technique adopted, high-pressure postdilatation, use of intracoronary imaging guidance, and concomitant non-LM vessel PCI. The only significant procedural difference observed between men and women regarded indeed the type of guiding catheters used, as men were treated more frequently with standard 6-French catheters compared with women.

The present study has several limitations. First, the retrospective design and lack of randomization might limit the detection of potential known and unknown confounding despite the performance of multivariable adjustment, as already reported in the discussion. Second, despite the high number of patients included and the guideline-driven management of patients, the present is a single-center analysis, thus some findings might depend on center's own peculiar proceedings. Moreover, included patients were treated during a relatively long time-span, thus potential technical, pharmacological and procedural technical changes over the course of the years might have influenced the outcomes of the patients and not being accounted for. Third, Syntax score, as well as arterial access site information, were not systematically recorded. Fourth, a direct comparison of PCI against surgical revascularization was beyond the aims of the study and was therefore not performed.

In conclusion, EES can be safely and effectively adopted for LM percutaneous revascularization, with a low rate of adverse events at long-term follow-up. Women might experience a worse prognostic outcome compared with men following PCI of LM and should therefore be carefully selected and monitored before undergoing LM PCI. The present findings, however, deserve further validation in a prospective setting.

Disclosures

Antonio Bartorelli received minor speaker's fee from Abbott Vascular. The other authors have no conflict of interest to declare.

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