Left Main Coronary Disease

Current evidence for drug-eluting stent placement in unprotected left main coronary disease.

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After the introduction of coronary stents, several reports have demonstrated the feasibility of unprotected left main coronary artery (LMCA) stenosis with percutaneous interventional approaches.[1] More recently, drug-eluting stents (DESs), in conjunction with advances in periprocedural and postprocedural adjunctive pharmacotherapies, have improved outcomes of percutaneous coronary interventions (PCIs) for such a complex coronary lesion.[2-15] However, there is growing concern about the long-term safety of DESs. In particular, late stent thrombosis is a serious problem that has been reported more frequently in DES than bare-metal stent (BMS) implantation.[16-19] Therefore, we need to examine carefully the safety as well as the efficacy of DES use compared with BMS use or coronary artery bypass graft surgery (CABG).

SAFETY

Mortality, Myocardial Infarction, and Stent Thrombosis

Table 1 depicts the results of recent registries demonstrating the outcomes of DES implantation for unprotected LMCA stenosis. It is clear that none of the clinical studies showed a significant increase in the cumulative rates of death or myocardial infarction (MI) in DES implantation for unprotected LMCA, as compared with BMS implantation. In three clinical studies comparing the outcomes of DES with those of BMS, the incidences of death, MI, or stent thrombosis were comparable in the two stent types during the procedure and at follow-up.[3,4,6] Of interest, in a study by Valgimigli et al, DES was associated with significant reduction in both the rate of MI (hazard ratio, .22; *P*=.006) and composite of death and MI (hazard ratio, .26; *P*=.004) compared with BMS.[6] Considering that restenosis can lead to acute MI in 3.5% to 19.4% of patients,[20,21] the significant reduction of restenosis achieved by DES use might contribute to the better outcome of DESs. A previous study noted that restenosis in the LMCA with stenting could present as late mortality.[22] In addition, more frequent repeat revascularization to treat BMS restenosis, in which CABG is the standard of care in the unprotected LMCA, may also be related to the increase in clinical events compared with DES.

> "Bifurcation DES placement has been an independent predictor of stent thrombosis in multivariate analysis."

In a series of LMCA DES studies, the incidence of stent thrombosis at 1 year ranged from 0% to 4% and was not statistically different from that in BMS.[3,4,6] Recent pooled data from randomized clinical trials for native coronary lesions showed a modest increase in stent thrombosis after DES implantation versus BMS between 1 and 4 years; however, the overall incidence was not statistically different.[17,18] Therefore, although it is very hard to evaluate the true incidence of stent thrombosis in this particular subgroup, further studies with a larger population and longer follow-up are warranted. Until such clinical trials are complete, rigorous use of the antiplatelet combination aspirin and thienopyridine for at least 1 year and meticulous follow-up of clinical features are recommended after DES placement in the LMCA. In particular, for patients receiving multiple stents or complex stenting at the bifurcation, or having antiplatelet resistance, a high loading dose and lifelong administration of clopidogrel with aspirin should be considered. Bifurcation DES placement has been an independent predictor of stent thrombosis in multivariate analysis.[16,19]

Predictably, periprocedural and long-term mortality

TABLE 1. OUTCOMES OF UNPROTECTED LMCA STENOSIS WITH DES

	Chieffo et al[4]		Valgimigli et al[6]		Park et al[3]		De Lezo et al[2]	Price et al[15]
Stent type	SES or PES	BMS	SES or PES	BMS	SES	BMS	SES	SES
No. of patients	85	64	95	86	102	121	52	50
Age	63	66	64	66	60	58	63	69
Ejection fraction	51%*	57%	41%	42%	60%	62%	57%	–
Acute MI	–	–	17%	20%*	9.80%	6.60%	–	–
Bifurcation involvement	81%*	58%	65%	66%	71%*	43%	42%	94%
Two-stent technique	74%	–	40%*	15%	41%*	18%	18%	89%
Initial Clinical Outcomes								
Follow-up	In-hospital		30 days		In-hospital		In-hospital	In-hospital
Death	0%	0%	11%	7%	0%	0%	0%	0%
MI	6%	8%	4%	9%	7%	8%	4%	8%
Stent thrombosis	0%	0%	0%	0%	0%	0%	0%	4%
Target vessel revascularization	0%	2%	0%	2%	0%	0%	0%	6%
Any events	–	–	15%	19%	7%	8%	4%	10%
Long-Term Clinical Outcomes	**Cumulative**		**Cumulative**		**Cumulative**		**Cumulative**	**After Discharge**
Mean follow-up (mo)	6	6	17	12	12	12	12	9
Death	4%	14%	14%	16%	0%	0%	0%	10%
MI	–	–	4%*	12%	7%	8%	4%	2%
Stent thrombosis	.10%	0%	–	–	0%	0%	0%	0%
Target vessel revascularization	19%	31%	6%*	12%	2%*	17%	2%	38%
Any events	–	–	24%*	45%	8%*	26%	–	44%

BMS, bare-metal stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.
**P<.05 between DES (SES and/or PES) versus BMS*

rates depend strongly on the patient's clinical presentation. In the ULTIMA registry, which included 279 patients treated with BMSs, 46% of whom were inoperable or at high surgical risk, the in-hospital mortality rate was 13.7%, and the 1-year incidence of all-cause mortality was 24.2%.[23] On the other hand, in the 32% of patients with low surgical risk (age <65 years, ejection fraction >30%), there were no periprocedural deaths and a 1-year mortality rate of 3.4%. Similarly, in the DES implantation group, high surgical risk, represented by a high EuroSCORE or Parsonnet score, was an independent predictor of death or MI.[12,13] Therefore, a lot of attention should continue to be paid in the procedure for patients considered to be at high surgical risk. The PCI procedure should be performed by experienced interventionists with the aid of intravascular ultrasound, mechanical hemodynamic support in some cases, and optimal adjunctive pharmacotherapies, after judicious selection of patients.

EFFECTIVENESS

Angiographic Restenosis and Repeat Revascularization

Compared with BMS use, DES use reduced the incidence of angiographic restenosis and, subsequently, the need of repeat revascularization in unprotected LMCA stenosis.[3,4,6] In early pilot studies, the 1-year incidence of repeat revascularization in DES implantation was 2% to 19%, as compared with 12% to 31% in BMS implantation (Table 1). In a long-term study up to 2 years, the incidence of repeat revascularization remained steady without a significant observation of the "late catch-up" phenomenon of late restenosis, which had been noted after coronary brachytherapy.[24]

The risk of restenosis was significantly influenced by lesion location. DES treatment in the ostial and shaft LMCA lesions had a very low incidence of angiographic or clinical restenosis.[25] In a study including 144 patients with ostial or shaft stenoses in three cardiac centers, angiographic restenosis and target vessel revascularization at 1 year occurred in one patient (1%) and two patients (1%), respectively. Although the lack of availability of DES sizes bigger than 3.5 mm imposed an overdilation strategy to match LMCA reference diameter, there were no cases of cardiac death, MI, or stent thrombosis in this study.

An important limitation of DES implantation for

TABLE 2. NONRANDOMIZED COMPARISON OF DES TO CORONARY ARTERY BYPASS SURGERY

	Chieffo et al[11]		Lee et al[6]		Palmerini et al[3]	
Treatment type	SES or PES	CABG	SES	CABG	SES	CABG
No. of patients	107	142	50	123	157	154
Age	64	68	72	70	73*	69
Ejection fraction	52%	52%	51%	52%	52%	55%
EuroSCORE or Parsonnet score	4.4	4.3	18*	13	6*	5
Initial Clinical Outcomes						
Follow-up	In-hospital		30 days		30 days	
Death	0%	2%	2%	5%	3.20%	4.50%
MI	9%	26%	0%	2%	4.50%	1.90%
Target vessel revascularization	0%	2%	0%	1%	.60%	.60%
Any events	–	–	0%	8%	–	–
Cerebrovascular accident	0%	1.40%	2%*	17%	–	–
Long-Term Clinical Outcomes	**After Discharge**		**Kaplan-Meier**		**Cumulative**	
Mean follow-up (mo)	12	12	6	6	14	14
Death	2.80%	6.40%	4%	13%	13.40%	12.30%
MI	.90%	1.40%	–	–	8.30%	4.50%
Target vessel revascularization	19.6%*	3.60%	7%	1%	25.5%*	2.60%
Cerebrovascular accident	.90%	.70%	–	–	–	–
Any events	–	–	11%	17%	–	–

CABG, coronary artery bypass grafting; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.
**P<.05 between DES (SES and/or PES) versus CABG.*

unprotected LMCA stenosis has been the involvement of distal bifurcation. In previous studies, the majority of repeat revascularizations were performed in patients with bifurcation stenosis.[3,4,6] A recent study assessing the outcomes of LMCA DESs showed that the risk of target vessel revascularization was sixfold (95% confidence interval, 1.2 to 29) in bifurcation stenosis compared with nonbifurcation stenosis (13% vs 3%).[12] The risk of bifurcation stenosis was highlighted in a recent study by Price et al; the target lesion revascularization rate after sirolimus-eluting stent implantation was 44%.[15] In this study, 94% of patients (44 of 50) had lesions at the bifurcation, and 98% underwent serial angiographic follow-up at 3 and/or 9 months. This discouraging result cautioned the efficacy of DES and alarmed the need for meticulous surveillance of angiographic follow-up in PCI for LMCA bifurcation stenosis. However, this study was limited by the exclusive use of a complex stenting strategy (two stents in both branches) in 84% of patients, which may increase the need of repeat revascularization. However, there was a debate;[26] a recent report proposed that complex stenting techniques (using two or more stents to treat the bifurcation) might be associated with a higher occurrence of restenosis compared with a simple stenting technique (a single stent in the LMCA and LAD, crossing over the circumflex origin).[10] Taken together, before the best treatment strategy for LMCA bifurcation stenting is settled, the simple stenting approach (LMCA to left anterior descending artery with optional treatment in the circumflex artery) is recommended in patients with either a relatively patent or a diminutive circumflex artery. Future stent platforms specifically designed for bifurcation lesions will provide better scaffolding and more uniform drug delivery to the bifurcation LMCA stenosis and may yield better outcomes than either one or two conventional stents.

COMPARISON WITH BYPASS SURGERY

The current guideline for unprotected LMCA treat-

ment is CABG, and elective PCI for patients who are treatable with bypass surgery is a contraindication.[27] The guideline recommendation is based on the 20-year-old clinical trials.[28,29] These studies demonstrated a definite benefit of survival of CABG in LMCA stenosis compared with medical treatment. However, application of these results to current practice may not be appropriate because surgical technique, as well as medical treatment in these studies, is outdated by today's standards, and no randomized comparisons between PCI and CABG have been conducted. The lack of data on the current CABG procedure used in unprotected LMCA stenosis further precludes a theoretical comparison of the two revascularization strategies.

> "Randomized trials comparing DES to CABG are underway and will provide answers to many of the uncertainties that remain for LMCA patient selection and therapy."

Recently, several nonrandomized studies comparing the safety and efficacy of DES treatment for unprotected LMCA stenosis compared with CABG were published (Table 2). Chieffo et al retrospectively compared the outcomes of 107 patients undergoing DES placement with 142 patients undergoing CABG.[11] They showed that DES was associated with nonsignificant benefit in mortality (odds ratio, .331; *P*=.167) and significantly lower incidence of the composites of death and MI (odds ratio, .260; *P*=.0005), and death, MI, and cerebrovascular accident (odds ratio, .385; *P*=.01) at 1-year follow-up. Conversely, CABG was correlated with a lower occurrence of target vessel revascularization (3.6% vs 19.6%; *P*=.0001). These findings were supported by a study by Lee et al, who reported 50 patients with DES placement and 123 patients with CABG.[9] In this study, although the DES group had slightly higher surgical risk, the rate of mortality and MI at 30 days was comparable between the two treatments. At 1-year follow-up, the DES group had nonsignificantly better clinical outcomes compared with CABG, reflected by overall survival (96% vs 85%) and survival freedom from death, MI, target vessel revascularization, and adverse cerebrovascular events (83% vs 75%). However, the freedom from repeat revascularization at 1 year remained nonsignificantly higher for the CABG group compared to the DES group (95% vs 87%). The results of a recent multicenter registry were in agreement with the previous two reports.[14] The PCI group treated with BMSs or DESs (60%) had a similar incidence of death and/or MI but a higher incidence of target lesion revascularization compared with the CABG group. However, these studies are inherently limited by the unavoidable biases due to the nonrandomized and retrospective study design. Furthermore, longer-term follow-up is required to better determine the relative durable benefit of CABG. Randomized trials comparing DES to CABG are underway and will provide answers to many of the uncertainties that remain for LMCA patient selection and therapy.

CONCLUSION

The current registry studies, although limited by a nonrandomized study design, small sample size, and short-term follow-up, have demonstrated promise for the procedure and midterm safety and effectiveness of DES use for LMCA stenosis, as compared with the treatment of BMS or CABG. In our opinion, PCI with DES use for LMCA will progressively increase and can be recommended as a reliable alternative to bypass surgery for patients with unprotected LMCA stenosis, especially as the first-line therapy for ostial or shaft stenosis. Although bifurcation stenosis remains challenging for the percutaneous approach, we are still optimistic because further research on novel procedural techniques, new dedicated stent platforms, and optimal pharmacotherapies may improve the outcomes. With the upcoming randomized clinical trials comparing PCI to CABG for unprotected LMCA stenosis, more confidence in the long-term safety, durability, and efficacy of PCI will accrue in the near future. ■

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