Editorial

Very long-term follow-up for left main coronary artery stenting: a missing piece of the jigsaw puzzle

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Significant left main coronary artery (LMCA) stenosis, which is defined as a 50% diameter stenosis that corresponds to a 75% area stenosis of the LMCA, is found in approximately 5–10% of all coronary angiograms performed for symptomatic coronary artery disease (1,2). Data obtained before the modern age of pharmacotherapy of coronary artery disease suggested that significant LMCA stenosis has a very grim prognosis when treated medically, with a mortality rate of 50% within 3 years of diagnosis (3,4). Coronary artery bypass surgery (CABG) offered superior and durable survival advantage over medical therapy, which was supported by very long term follow-up data up to 10 years' post-bypass (5,6). After these seminal works, CABG was accepted as the gold standard—and perhaps the singular—treatment for significant LMCA stenosis. This assumption was never questioned until the recent technical developments had allowed safe and durable revascularization with percutaneous coronary intervention (PCI).

As the LMCA supplies the majority of blood flow to the left ventricle, an acute closure of the vessel during or after the procedure nearly uniformly leads to catastrophic events. High elasticity of the LMCA vastly increases the rate of elastic recoil following balloon dilatation (7). These two features of LMCA intervention makes the vessel a highly unattractive target for sole balloon angioplasty, which was noted by Grüntzig himself in his original description of percutaneous transcatheter balloon angioplasty (8). With the advent of stents, however, the rates of abrupt vessel closure dropped dramatically, paving the way for PCI for unprotected LMCA stenosis.

Short and long-term follow-up data for unprotected LMCA stenting

Bare-metal stents (BMS) offered high periprocedural success rate that offered an option for revascularization in patients deemed high risk for surgical revascularization or when the LMCA occlusion was acute as a result of myocardial infarction (MI). Short and mid-term follow up data for BMS, however, had indicated target lesion revascularization (TLR) rates as high as 20%, and higher mortality rates compared to CABG.

Following the introduction of drug-eluting stents (DES), the interest for percutaneous LMCA intervention was renewed as the need for repeat revascularization was significantly lower in patients treated with a DES. The prespecified subgroup analysis of the SYNTAX trial that compared paclitaxel eluting stents with CABG showed that neither major adverse cardiovascular or cerebrovascular events (MACCE), nor mortality was significantly different in patients treated with DES, as compared to patients treated with CABG (9). The five year results of the PRECOMBAT trial, which was a dedicated study that only included patients with an unprotected LMCA stenosis (10) showed a mortality rate of 5.7% with sirolimus eluting stents. The MAIN-COMPARE registry, which was the largest registry that had directly compared unprotected LMCA stenting with CABG, demonstrated that event-free survival was 88.5% for BMS and 87.3% for DES groups (11). A common theme that was constantly observed in all registries and randomized controlled trials (RCTs) was a higher TLR rate in PCI group, which necessitated repeat

intervention or CABG, but this high TLR rate did not translate into an increase in mortality (9-12). Although TLR rate was higher for both BMS and DES, the rate of stent thrombosis was low at short and long term, with the majority of studies had reported a definite stent thrombosis rate of <2%. In the MAIN-COMPARE registry, 11 of 784 patients who underwent DES implantation had experienced definite stent thrombosis at 5 years (1.4%), and only 4 them had very late stent thrombosis although older-generation DES were used at the time of registry. A recent study utilizing newer-generation DES platforms (everolimus and zotarolimus coated stents) for unprotected LMCA disease reported 1-year mortality rates similar to older-generation DES, but with a possible reduction in MI (13). More data on the safety and comparative efficiency for newer-generation DES will be available after the completion of the EXCEL (Evaluation of Xience Prime or Xience V Versus CABG for Effectiveness of Left Main Revascularization) study.

Very long-term data for the feasibility of unprotected left main stenting: the LE MANS trial

One piece of critical data missing for unprotected LMCA interventions is the very long term (10 years or more) follow-up results, which is available for CABG (14). As CABG was considered as the benchmark therapy for revascularization of unprotected LMCA stenosis, until recently, very long term data on unprotected LMCA interventions were limited and biased as only patients that did not accept CABG or patients who deemed too risky for surgical intervention were included to registries and retrospective studies. In the ASAN-MAIN registry (15), 10-year results for BMS indicated that even implantation of BMS is safe for unprotected LMCA stenosis as cardiac mortality at 10 years (6.9%) was similar to CABG (11.0%, P=0.1). As expected, both repeat revascularization (43.1% *vs.* 6.7%, P<0.001) and TLR (24.9% *vs.* 4.9%, P<0.001) was higher in BMS group compared to CABG. While the results of ASAN-MAIN registry had hinted that stents (even BMS) are a safe alternative to CABG for unprotected LMCA lesions, as aforementioned before, retrospective data is inherently biased and data from RCTs should be available before establishing the safety of percutaneous interventions for unprotected LMCA.

In this regard, the LE-MANS RCT (16) was the first study that had reported 10 years results for unprotected LMCA intervention, as compared to CABG. The initial study group included 52 patients allocated to PCI (35 patients with DS and 17 patients with BMS) and 53 patients allocated to CABG groups. At 10 years, the investigators have reported that the survival rate was close to 70% in PCI group, and MACCE-free survival was numerically better for PCI (OR: 1.57, P=0.1). In contrast to previous studies and registries that had reported more repeat revascularization and a higher TLR for percutaneous interventions, the LE-MANS trial found that the rate of repeat revascularization was comparable between PCI and CABG groups (P=0.46), mainly due to an increase in repeat revascularizations in CABG group two years after the operation. Finally, the authors had reported a higher ejection fraction in PCI group as compared to CABG group (54.9%±8.3% *vs.* 49.8%±10.3%; P=0.07), although this latter finding did not reach statistical significance.

Perhaps the most important finding of the LE MANS study was the demonstration of a similar survival rate in PCI and CABG groups both in the short, long and very long terms (16), thereby suggesting that the excellent short-term results obtained with PCI is durable and safe, even 10 years after the index revascularization. As the number of patients included in LE MANS study was relatively low (n=52 for PCI and n=53 for CABG groups), these preliminary findings should be regarded as hypothesis-generating rather than definite in the absence of data from larger RCTs, such as SYNTAX or PRECOMBAT (9,10). The analysis of SYNTAX score for LE MANS cohort revealed that all patients included in the study had syntax scores <32 (low and middle SYNTAX groups). A similar finding was also reported in the 5-year data of the SYNTAX study, suggesting that patients with less complex lesions or lesions limited to LMCA have a survival rate similar to CABG after LMCA interventions (9). Therefore, these "excellent" very-long term results of the LE MANS study should be interpreted in this context, and are not necessarily applicable to patients with more complex lesions (i.e., bifurcation lesions) or those with extensive coronary artery disease.

A more controversial finding from the LE MANS study was the similarity of TLR and repeat revascularization in PCI and CABG groups, which was not supported by previous registry and RCT data (9,10,16,17). Special subsets of patients, such as patients with LMCA aorto-osteal or shaft lesions, or patients treated with provisional one-stent technique for distal bifurcations lesions, were known to have comparable (11,17-19) TLR rates with CABG. The angiographic properties of the patients included in the

LE MANS study were similar to other studies reported in the literature, and patients with a distal LMCA stenosis received bifurcation stents as needed (13,16). Therefore, neither patient characteristics nor the interventional techniques could explain this exciting yet extraordinary findings. As aforementioned before, the number of patients included in the LE MANS study was limited, so the results should be interpreted with caution and more data from larger studies should be waited before suggesting a similar revascularization rate in PCI and CABG groups in the long term.

Conclusions

While there are abundant data on short and long term survival following unprotected LMCA intervention, data on very long-term survival after unprotected LMCA stenting was notably missing. In this regard, the LE MANS trial was the first RCT that provided evidence for the efficiency and safety of stents in the very-long term. As the number of patients included in the study was quite low (only 52 patients were randomized to the PCI group), statistical power of the study was severely limited. The very-long term safety and efficiency of stents will be better defined in the future as more data emerges from the large RCTs and studies. Other surprising findings of the LE MANS study, such as the similar repeat revascularization rate in PCI and CABG groups, definitely needs further data as the majority of large studies and RCTs conducted so far had suggested an increase in TLR and repeated revascularization in PCI patients followed-up for short and long term.

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Footnote

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