Editorial

Stenting or bypass surgery for unprotected left main coronary artery disease—still a long rally to go

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Coronary artery disease (CAD) is still major cause of mortality and morbidity in western country (1,2). With the advancement of percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) is not the only choice of revascularization for CAD (1,2). The left main coronary artery (LMCA) arises from aortic sinus and supplies the around 70% myocardium in patients with right dominant type and 100% in patients with left dominant type (3). Therefore, severe LMCA stenosis will reduce coronary perfusion to large portion of the myocardium and may cause terrible consequences. The definition of LMCA stenosis is the reduction by more than 50% in the luminal diameter of LMCA (4). Patients with LMCA stenosis are associated with higher mortality, and LMCA stenosis is a strong independent predictor of mortality and morbidity in patients with CAD (1,2,5-7). The average diameter of LMCA is usually more than 3 mm (8), implying LMCA is theoretically considered suitable for coronary stenting. However, the complex anatomy of LMCA may associate with periprocedural complications and restenosis of PCI (9,10). Furthermore, most LMCA lesions are at distal site presenting as bifurcation or trifurcation lesions, which is challenging for PCI. Given that patients with isolated LMCA stenosis are rare, and most patients with LMCA stenosis are associated with severe double or triple vessel disease, complete revascularization by CABG is still the golden standard for treating unprotected LMCA stenosis (1,2) although intravascular ultrasound-guided PCI is considered a reasonable alternative nowadays (11).

With improvement of the design in PCI devices such as drug eluting stent (DES) and pharmacological treatment, more and more evidences shows that PCI is a safe and effective revascularization strategy for patients with unprotected LMCA stenosis and multivessel CAD in short term period. Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) study is the first large-scale randomized trial comparing the long-term outcomes after LMCA stenting with first generation DES to CABG in patients with unprotected LMCA stenosis (12). There was no significant different between PCI and CABG in mortality and major advanced cardiac and cerebral events (MACCE) in patients with unprotected LMCA stenosis in low/intermediate SYNTAX score (<33) although target lesion revascularization (TLR) rate is higher in PCI group than CABG group. However, CABG provided better long-term outcome including survival rate in patients with high SYNTAX score (≥33). Interestingly, among patient cohort of multi-vessel CAD but no critical LMCA stenosis, CABG was superior to PCI in cardiac death, TLR, and MACCE. This finding suggests that stenting at LMCA may secure the upstream coronary artery flow and provide adequate perfusion to the large territory of left coronary artery system. Importantly, the results of Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) (13) and Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization (EXCEL) (14) are consistent with the results of LMCA stenosis cohort in SYNTAX study. *Table 1* lists the randomized clinical trials comparing PCI and CABG in patients with unprotected LMCA stenosis.

Table 1 List of randomized clinical trials comparing PCI and CABG in patients with unprotected LMCA stenosis

Trial name (Ref.)	Patient number (n)	Study period (years)	Rate of DES stent	Age (years)	Syntax score	Mortality (%)	MACCE (%)
LE MANS trial (15)	PCI (n=53); CABG (n=52)	10	PCI: 35% DES; CABG: 81% LIMA	PCI: 60.6; CABG: 61.3	PCI: 25.2 8.7; CABG: 24.7 6.8	PCI: 21.6; CABG: 30.2	PCI: 52.2; CABG: 62.5
EXCEL trial (13)	PCI (n=948); CABG (n=957)	5	PCI: 100%; CABG: unknown LIMA	PCI: 66; CABG: 66	PCI: 21 [15–26]; CABG: 20 [15–25]	PCI: 8.5; CABG: 10.5	N/A
PRECOMAT trial (12)	PCI (n=232); CABG (n=201)	5	PCI: 100% sirolimus DES; CABG: 93.6% LIMA	PCI: 61.8; CABG: 62.7	PCI: 24.4 9.4; CABG: 25.8 10.5	PCI: 6.1; CABG: 6.4	PCI: 16.7; CABG: 12.4
SYNTAX trial (11)	PCI (n=221); CABG (n=196)	5	PCI: 100% DES; CABG: N/A	N/A	N/A	PCI: 7.9; CABG: 15.1	PCI: 31.3; CABG: 32.1

BMS, bare-metal stent; CABG, coronary artery bypass surgery; DES, drug eluting stent; EXCEL trial, The Evaluation of Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization; LE MANS trial, Left Main Coronary Artery Stenting; LIMA, left internal mammary artery; MACCE, major advanced cardiac and cerebral events; N/A, not available; PCI, percutaneous coronary intervention; PRECOMBAT trial, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX trial, Synergy between PCI with Taxus and Cardiac Surgery.

The LE MANS (Left Main Coronary Artery Stenting) trial was the first prospective randomized study to compare left main stenting (n=52) to CABG (n=53) in patients with unprotected LMCA stenosis. There was no significant different of short-term survival rate between PCI and CABG group in patients with LMCA stenosis in low to intermediate SYNTAX score (<33). However, the repeat revascularization rate was higher in PCI group than CABG group during the 28±9.9 months of follow-up (relative risk: 1.27; 95% confidence interval: 1.05–1.54; P<0.01). Notably, PCI provided better improvement of left ventricular ejection fraction (LVEF) than CABG group (P=0.04) (15). Recently, Dr. Buszman and his colleagues published the 10-year outcomes of LE MANS study in Journal of the American College of Cardiology Cardiovascular Interventions (16). The major findings are that PCI with stenting demonstrated equivalent outcomes in the very long-term as compared to CABG in patients with unprotected LMCA obstruction and low to intermediate SYNTAX score (<33). In addition, there was no significant between PCI and CABG groups in myocardial infarction (8.7% *vs.* 10.4%; P=0.62), stroke (4.3% *vs.* 6.3%; P=0.68) and repeat revascularization (26.1% *vs.* 31.3%; P=0.64). LE MANS study is the first randomized study to prove that PCI also provide similar very long-term outcomes in patients with unprotected LMCA stenosis and low to intermediate SYNTAX score (<33). Although their findings are interesting with clinical meaning, and provide us a new evidence and concept to manage the patients with unprotected LMCA stenosis, there are some issues that should be discussed.

Instead of DES, 65% of patients in PCI group in LE MANS study received bare metal stent (BMS) during PCI, which is not recommended by established guidelines. This finding is different to previous studies (17-19). Surprisingly, mortality (21.6% *vs.* 30.2%), repeat revascularization (26.1% *vs.* 31.3%), and MACCE (51.1% *vs.* 64.4%) were similar between two groups. These findings were different from previous studies, which found CABG group is with less TVR revascularization rate (12-14). On the other hand, there was only 72% of patients received left internal mammary artery (LIMA) graft to left anterior descending artery in CABG group in this study, which is apparently lower than those in other studies (>95%) (12,13). The LIMA graft provides long-term patent rate than saphenous vein graft in patients undergoing CABG and leads to better clinical outcomes (20). This difference may explain why CABG group in LE MANS study did not could not reduce repeat vascularization rate in LE MANS study. Furthermore, LVEF is one of secondary endpoint in the LE MANS study, and PCI group provided better LVEF preserved function than CABG group in the first year and maintain the LVEF function after 10 years. Nevertheless, 35% patients did not echocardiography in this study which initially enrolled only 105 patients. It may be not adequately

powered to exam this primary endpoint. Finally, the penetration and adherence rate with anti-platelet therapy, beta-blocker, angiotensin inhibition, and statin therapy was high in both groups in the LE MANS trial. Optimal risk factor modification is crucial to reduce mortality and morbidity in patients with stable CAD (21), suggesting optimization of medical therapy together with selection of appropriate revascularization therapy is mandatory to order to achieve better long-term clinical outcomes in this specific patient group.

Similar to SYNTAX study, the LE MANS trial showed that PCI with optimal medical therapy is not inferior to CABG among patients with unprotected LMCA stenosis and low to intermediate SYNTAX score (<33) in 10 years after index procedure. Given that graft failure rate may as high as 50% at 10 years after CABG (22), PCI is promising to catch up with CABG in this long rally! However, answers for several questions remains unclear: (I) the comparison between PCI with 2nd generation DES and CABG in long-term outcomes; (II) PCI *vs*. CABG in non-bifurcation LMCA stenosis; (III) whether chronic total occlusion may have an impact in procedural success and clinical outcomes this patient population? (IV) why PCI has different outcomes in the patient cohorts with and without LMCA stenosis in SYNTAX study? (V) optimal duration of dual anti-platelet therapy in the era of 2nd generation DES and bioabsorbable vascular scaffold. Further large scale, long-term clinical trials or registries are warranted to investigate these important issues.

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Footnote

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