

## Stenting or Bypass Surgery: Overcoming the Quandary for Treatment Choice in Left Main Coronary Artery Disease in 2017

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**Received:** October 14, 2017; **Published:** October 26, 2017

### Abstract

Unprotected left main coronary artery disease (LMCA) found in 5-10% patients undergoing coronary angiography exposes patients to high risk for cardiovascular events. The optimal revascularization strategy for patients with LMCA disease of topic of continuing debate. For several decades, coronary artery bypass grafting (CABG) has been considered as the gold standard treatment of unprotected LMCA disease. However, because of large vessel caliber and anatomic accessibility, percutaneous coronary intervention (PCI) for LMCA has been attractive option for interventional cardiologists. With the marked improvement in technique and technology, PCI has been shown to be feasible for patients with unprotected LMCA stenosis. The recent introduction of drug-eluting stents (DESs), together with advances in pre procedural and post procedural adjunctive pharmacotherapies, has improved outcomes of PCI of these lesions. The two new dedicated randomized trials comparing CABG and PCI: the NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) with conflicting results, make both cardiac surgeons and interventional cardiologist happy and confused.

**Keywords:** *Left main coronary artery; Drug-eluting stent; Coronary artery bypass graft; Percutaneous Coronary Intervention*

**Abbreviations:** DS: Diameter Stenosis; DES: Drug-Eluting Stent; FFR: Fractional Flow Reserve; IVUS: Intra-Vascular Ultrasound; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention

Volume 1 Issue 3 October 2017

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### Introduction

Significant unprotected left main coronary artery disease (LMCA) is diagnosed in 5-10% patients undergoing coronary angiography. [1,2] LMCA disease extensive and coexisting disease is often complex. As it subtends a large amount of myocardium, significant, severe LMCA disease would reduce flow to large portion of the myocardium, placing the patient at high risk for life threatening left ventricular dysfunction, arrhythmias or hemodynamic compromise. [3] Early clinical trials demonstrated better survival with coronary artery bypass

**Citation:** Debabrata Dash. "Stenting or Bypass Surgery: Overcoming the Quandary for Treatment Choice in Left Main Coronary Artery Disease in 2017". *Therapeutic Advances in Cardiology* 1.3 (2017): 116-120.

graft surgery (CABG) compared to medical therapy in this subset, establishing CABG as the “gold standard” for the treatment. [4-7] The interventional cardiologists have been emboldened to test the feasibility of percutaneous coronary intervention (PCI) of LMCA mainly as a result of improved technical advances and stent technology. [8] Meta-analysis has revealed that PCI has similar five-year mortality and myocardial infarction, with a lower incidence of stroke and increased risk of repeat revascularization compared to CABG. [9,10] Up until recently, there is paucity of data comparing outcomes of PCI versus CABG in LMCA disease. The introduction of newer generation DES with proven improvements in both safety and efficacy has prompted the design of two new dedicated randomized trials comparing CABG and PCI: the NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) [11] EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization). [12]

### What is Unique about LMCA PCI?

It is a large artery and tends to have a high plaque volume. It also is prone to calcification. Plaque shift and incomplete stent expansion are therefore important technical considerations in LMCA PCI. Greater elastic tissue content of this artery explains elastic recoil and high restenosis following balloon angioplasty. Seventy percent of significant LMCA lesions involve the distal bifurcation. Intimal atherosclerosis in the LMCA bifurcation is accelerated primarily in area of low shear stress in the lateral wall close to the left anterior descending (LAD) and left circumflex (LCx) artery bifurcation. Thus, carina is usually free of disease, which can explain why single-stent strategy can be successfully performed in patients with no or moderate disease by angiography. [13]

### Impact of the SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) Trial

The SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) trial was a large randomized study comparing PCI and CABG for patients with complex coronary artery disease and included a subset of 705 patients with LMCA. [14] SYNTAX trial has revolutionized decision-making in patients with LMCA disease by introduction of the SYNTAX score, a heart-team approach and evolving a close cooperation between both cardiac surgery and interventional cardiologist. For the left main subset, the 5-year outcome data reported that patients with a SYNTAX score > 33 had lower mortality and a lower rate of repeat revascularization with CABG compared with PCI, thus establishing CABG as the preferred revascularization method. Interestingly, the subgroup with low-to-intermediate SYNTAX scores (0-32) had a lower mortality and stroke rate with PCI with no difference in rate of repeat revascularization. [14]

The 2014 for European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guideline statement for myocardial revascularization makes Class 1 recommendation for PCI in setting of LMCA disease with SYNTAX score ≤ 22, II a recommendation with SYNTAX score 23-32 and Class III recommendation for SYNTAX score >32. [15]

### Dissecting the Implications of the EXCEL and NOBLE Trials

Both the EXCEL and NOBLE trials aim to compare PCI versus CABG for unprotected LMCA stenosis, they are not exactly the same [Table 1]. The EXCEL trial is an international, prospective, unblinded, randomized multicenter trial which enrolled 1,905 subjects in 131 centres. It was designed to establish the safety and efficacy of the everolimus-eluting stent [EES, (XIENCE PRIME™ or XIENCE V® or XIENCE Xpedition™ or XIENCE PRO™; Abbott Vascular, Santa, CA, USA)] in patients with significant LMCA disease. The NOBLE trial is an international, prospective, unblinded, randomized multicenter trial which randomized 1,200 patients in 36 centres. The biolimus-eluting stent BioMatrix™ (Biosensors, Morges, Switzerland) was the recommended study stent but other CE-marked DES could be used at operators' discretion.

In the EXCEL trial, the composite primary end point of all-cause death, stroke, or MI at 3 years occurred in 15.4% of patients treated with PCI and in 14.7% of patients undergoing CABG. The difference was significant for non-inferiority; but not for superiority. The patients with low- or intermediate-SYNTAX scores treated with an everolimus-eluting metallic stent (Xience, Abbott Vascular) had

comparable rates of death, stroke, or MI at 3 years when compared with patients treated with CABG surgery. [12] It is worth noting that the non-inferior margin used in EXCEL was too liberal (4.2%) and may have biased the results towards non-inferiority. [16] There was more peri procedural MI and STEMI in the CABG-treated patients at 30 days.

| <b>Variables</b>                              | <b>Excel Trial</b>   | <b>Noble Trial</b>  |
|---|--|---|
| Number of patients                            | 1905   | 1201  |
| Number of centers                             | 126  | 36  |
| Geographic region                             | 100% Europe  | 56% Europe, 40% North America, 4% others                                      |
| Anatomic characteristics                      | LMCA DS ≥ 70% or if 50-70% Then FFR <0.80 or IVUS MLA ≤ 6.0 mm <sup>2</sup> LMCA equivalent disease (Medina 0,1,1) with both ostial LAD and LCX ≥ 70% DS | LMCA DS ≥ 50% or FFR ≤ 0.80 and no more than 3 additional non-complex lesions |
| SYNTAX score inclusion                        | ≤ 32   | No restriction  |
| Primary end Point                             | Death, MI, stroke  | Death, MI, stroke or revascularization  |
| Included peri procedural MI                   | Yes  | No  |
| Stent   | 89% biolimus-eluting (Biomatrix™) 11% Gen DES  | 100% everolimus-eluting (XIENCETM)  |
| 3 yr definite ST rate                         | 0.7%   | 3%  |
| Definite ST < symptomatic graft occlusion     | Yes  | No  |
| Stroke: PCI vs CABG                           | Less with PCI  | More with PCI   |
| Worse PCI prognosis with highest SYNTAX Score | Yes  | No  |

**Table 1: NOBLE and EXCEL Trials: Differences.**

In contrast, in the NOBLE trial, treatment with PCI using predominantly a biolimus-eluting stent (Biomatrix Flex, Biosensors) was associated with a significantly higher rate of major adverse cardiac and cerebrovascular events (MACCE) at 5 years when compared with CABG. Individually, all-cause mortality was comparable between the two treatments, while nonprocedural MI and the need for a repeat coronary revascularization were higher among those treated with PCI. Stroke rates were higher among the CABG patients at 30 days but numerically higher among PCI patients at 5 years. [11]

One must keep in mind that the benefit of CABG is often seen after extended follow-up. [17] Both studies had a median follow-up duration of 3.1 years, which is relatively short, hence longer term follow-up is needed before any concrete conclusion is drawn. In the EXCEL trial, by the time one gets out over 3 years, death begins to split in favour of CABG. It is going to become statistically significant once the median follow-up is extended up to 5 years.

EXCEL recruited 704 more patients than NOBLE. The mean SYNTAX score of EXCEL was 20.6 ± 6.2 versus NOBLE which was 22.5, but most notably they had similar rates (81%) of bifurcation disease. Procedural data was not reported regarding technical aspects of PCI such as use of support devices, bifurcation strategy, or need for rotational atherectomy. IVUS guidance was used in 77% of cases in EXCEL compared to 47% pre-stent and 77% post-stent in NOBLE. Both NOBLE and EXCEL did not find any significant difference in all-cause-mortality or cardiac-death between PCI and CABG. However, there was more spontaneous MI in the PCI group (6%) in NOBLE, which contributed to its composite endpoint. In EXCEL there were similar rates of spontaneous MI in the PCI group (4.3%). This difference in rates of spontaneous MI in the PCI groups between the two studies may be due to different stents used between the two trials. In

Noble, 11% of the patients who underwent PCI received a 1<sup>st</sup> generation DES. The 2<sup>nd</sup> generation DES biolimus-eluting stent (BES) was not introduced as the “stent of choice” until well into enrollment. Moreover, subsequent meta-analysis has demonstrated that the BES has an inferior safety profile compared to the EES. [17] Higher definite stent thrombosis rate could be attributed to different stents used. In NOBLE, there was a 2% definite stent thrombosis rate compared to EXCEL which had a 0.7% rate of stent thrombosis. [18] In NOBLE, the higher rate of spontaneous MI and revascularization set the primary composite endpoint in favor of CABG as compared to PCI of LMCA. Similar rates of spontaneous MI between the treatment arms and non-inclusion of revascularization in the primary composite endpoint, led EXCEL investigators to conclude that PCI and CABG conferred a similar benefit.

### Take Home Message

PCI and CABG confer a similar survival benefit in revascularization of LMCA over intermediate-term follow-up. In patients with low-or intermediate-SYNTAX scores, PCI is an acceptable, perhaps even preferred alternative to CABG because of early and profound advantage in terms of primary endpoint events, specifically a lower risk of MI. Repeat revascularization is more likely with PCI compared to CABG. Many patients will choose that option because they don't perceive additional PCI as negatively as they do surgery. Both PCI and CABG fare quite well when performed by experienced operators at experienced centers. This, in fact, is a testimony to the value of Heart Team approach. Patient discussion should center on risks and benefits of both the procedures and include the important use of long term dual antiplatelet. Higher rate of bifurcation in LMCA disease further reinforces the need for having an experienced heart team, familiar with current best practices and techniques to achieve optimal outcomes. Longer-term follow-up data from both trials in due time would provide further insights into the durability of the results for both PCI and CABG. The decision between PCI and CABG for LMCA revascularization should be based on weighing the benefits and risks of both the procedures and taking patient preference into consideration. LMCA PCI is a high-risk subset and requires special skill sets. The interventionalists contemplating LMCA PCI should be comfortable with management of coronary calcification, strategies for complex bifurcation, use of intravascular ultrasound, optical coherence tomography, and hemodynamic support devices.

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