REVIEW

The Contemporary Role of Percutaneous Coronary Intervention in Left Main Disease Management

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Abstract

Since the 1980s coronary artery bypass grafting (CABG) has been considered as the gold standard for treating left main disease. The continuous evolution of tools and techniques concerning coronary angioplasty and the advent of drug-eluting stents (DES) have established percutaneous coronary intervention (PCI) as a possible alternative to CABG. Initial randomized studies that were conducted during the previous decade, with main representative the SYNTAX study, compared conventional CABG to PCI with first generation DES and showed non-inferiority regarding hard clinical outcomes. The results of two randomized studies comparing CABG versus PCI with second generation DES were simultaneously published in the end of 2016 to further support PCI as a credible alternative to CABG for patients with left main disease with low and intermediate SYNTAX scores. A Heart Team is indispensable to best evaluate the anatomic parameters of coronary lesions, the clinical variables and the technical possibilities regarding disease complexity in order to define the ideal revascularization strategy for each patient in the elective setting. Percutaneous treatment for left main disease has been increasingly performed during the last decade, since the procedural steps and optimal techniques for left main PCI are nowadays standardized and well described in expert consensus documents and therefore should be respected and applied in order to optimize patient outcomes. ***Rhythmos 2018;13(3):48-53***.

Key words: coronary artery disease; left main disease; percutaneous coronary intervention; coronary artery bypass grafting

Abbreviations: CABG = coronary artery bypass grafting; DES = drug-eluting stents; IVUS = intravascular ultrasonography; LAD = left anterior descending; LCX = left circumflex; LM = left main; MACE = major acute cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; POT = proximal optimization technique

INTRODUCTION

Coronary artery bypass grafting (CABG) has been considered as the gold standard for treating left main (LM) disease since the 1980s, after clinical studies had proven its superiority over medical treatment concerning mortality.[1] During the first two and a half decades of percutaneous coronary intervention (PCI) the results of CABG could not be challenged by simple balloon angioplasty and bare-metal stents. However, the continuous evolution of tools and techniques and the arrival of drug-eluting stents (DES) have progressively established PCI as a possible alternative to CABG.

Significant LM lesions represent about 5% of the lesions revealed at coronary angiography and are predominantly distal affecting the left main bifurcation (in almost 4 out of 5 of cases).[2] In up to 25% of cases, a distal trifurcation exists due to the presence of an intermediate branch. It is estimated that the LM usually supplies more than 75% of the left ventricular myocardium in cases of right dominant coronary circulation.[3] Importantly, the size of the normal LM and its bifurcation into the left anterior descending (LAD) and the left circumflex (LCX) is predictable using fractal geometry and Finet's law (the LM diameter roughly equals the two thirds of the sum of the proximal LAD diameter plus the proximal LCX diameter).[4] The LM has unique anatomic features which should be taken into account during clinical practice and intervention.[5]

EVIDENCE-BASE FOR LEFT MAIN PCI

Four randomized studies from the previous decade which compared conventional CABG to PCI with first generation DES and showed non-inferiority have contributed to the current recommendations and clinical practice regarding LM revascularization.[6-9] Most importantly, the subgroup analysis of 705 patients with LM disease of the SYNTAX study that randomized patients to CABG or PCI with a first generation paclitaxel-eluting stent (Taxus Express, Boston Scientific) showed comparable results for the two strategies concerning the advent of major acute cardiovascular events (MACE) composite end-point (death, MI, cerebrovascular accident and repeated revascularization) at 1 year follow-up (CABG 13.7% *vs* PCI 15.8%, p=0.44).[8] At 5-year follow-up there was no significant difference in mortality (CABG 14.6% *vs* PCI 12.8%, p=0.53) and MI (CABG 4.8% *vs* PCI 8.2%, p=0.10), while CABG was associated with a higher incidence of stroke (CABG 4.3% *vs* PCI 1.5%, p=0.03) and a lower risk of repeated revascularization (CABG 15.5 % *vs* PCI 26.7%, p = 0.001), but without significant difference in the composite MACE outcome (CABG 31% *vs* PCI 36.9%, p = 0.12).[10,11] Furthermore the results for MACE were comparable for the two techniques among patients with a SYNTAX score <22 (CABG 30.4% *vs* PCI 31.5%, p = 0.74) and among those with SYNTAX score 23-32 (32.7% *vs* 32.3%, p = 0.88). Among patients with a SYNTAX score >32 CABG was associated with favorable results regarding mortality (CABG 14.1% *vs* PCI 20.9%, p=0.11) and a significantly lower rate of repeat revascularization (11.6% *vs* 34.1%, p< 0.001), but with a higher risk of stroke (4.9% *vs* 1.6%, p=0.13).[10,11]

The results of the SYNTAX study validated the SYNTAX score that had been proposed on 2005.[8,12] It is a score calculated according to the anatomic complexity of coronary artery disease and thus used to evaluate the risk and possible outcome of PCI, according to the results of SYNTAX study. This score however has several drawbacks: its reproducibility is difficult, it is time consuming to calculate, it does not include clinical variables or ischemia documentation and its prognostic value is not calibrated.[13] The current recommendations for myocardial revascularization are largely based on the results of the SYNTAX study and propose the use of the SYNTAX score in order to select the most suitable revascularization strategy for each patient.[14] Yet, it is logical that in clinical practice decisions cannot be based only on a score that describes the anatomic complexity of coronary artery disease, but also in multiple other clinical parameters. The advent of the second-generation DES that clearly outperformed first-generation DES in multiple clinical studies regarding the rates of restenosis and stent thrombosis, along with the progress in the techniques and tools of PCI, have created doubt about the validity of the guidelines which are based on results of studies conducted during the previous decade.

The revascularization of significant LM lesions holds naturally a class IA recommendation according to the last European guidelines for myocardial revascularization published in 2014.[14] According to the abovementioned data in the same guidelines regarding severe LM disease, PCI holds a class IB recommendation for patients with a SYNTAX score <22, a class IIA recommendation for patients with SYNTAX score 22-32 and finally a class III recommendation for patients with SYNTAX score >32, while CABG holds a class IB recommendation irrespective of the SYNTAX score.[14]

At the end of 2016, two very significant new randomized studies comparing CABG to PCI with second generation DES were simultaneously published, EXCEL and NOBLE (Table 1 shows their main results along with those of SYNTAX LM). The EXCEL study comprised 1905 patients presenting with LM disease and had a non-inferiority design.[15] The DES that was used in the PCI arm was a second-generation fluoropolymer-based cobalt–chromium everolimus-eluting stent (Xience, Abbott) and patients with a SYNTAX score <32 were included. The EXCEL investigators used a contemporary second-generation DES, which has shown a very low incidence of stent thrombosis and restenosis and they frequently used intravascular ultrasonography (IVUS) to guide stent placement and optimization. In the other study arm contemporary surgical techniques were used with arterial revascularization procedures and off-pump CABG being performed in many patients.

The primary end-point was a composite of MACE including all cause death, stroke and MI. At 3 years the primary end-point was met in 15.4% of the PCI arm and in 14.7% of the CABG arm patients, leading to the conclusion that PCI was non-inferior to CABG (p=0.02 for non-inferiority). Of note, the secondary end-points of death, stroke or MI at 30 days were met in 4.9% patients of the PCI arm and in 7.9% of patients of the CABG arm ($p < 0.001$ for non-inferiority, $p = 0.008$ for superiority). This trend was reversed after the first month with MACE found in 23.1% of patients in the PCI arm and 19.1% of patients in the CABG arm ($p = 0.01$ for non-inferiority, $p = 0.10$ for superiority).[15]

The NOBLE study had also a non-inferiority design that randomized 1201 patients with left main disease to CABG or PCI.[16] The primary MACE end-point included repeated revascularization, non-procedural MI, stroke and all-cause mortality. In contrast to EXCEL this study concluded that CABG was superior to PCI. At 5 years MACE were met in 28% of PCI patients and in 18% of CABG patients (hazard ratio 1.51, 95% confidence interval 1.13-2.0) which was beyond the non-inferiority limit (p=0.044). These results were driven by an increased risk of non-procedural MI (p=0.004) and repeated revascularizations (p=0.03) in the PCI arm, with the repeated revascularizations being included in the primary end point in NOBLE trial but not in EXCEL.[15,16]

These apparently contradictory results between the EXCEL and NOBLE studies that try to find the answer to the same clinical question are explained by the differences regarding their design. The EXCEL study had a shorter follow-up period and its primary composite end-point did not include repeated revascularizations (that are known to be systematically met more often after PCI compared to CABG) but included procedural MIs (defined by troponin elevations of >5 times above the upper limit of normal which are often met after CABG). Under these conditions PCI was found non-inferior to CABG for the revascularization in case of LM disease.

Due to their similar design and simultaneous publication, the different results of these two trials generated a lot of discussion. In particular, it has been speculated that differences in primary endpoint selection, differences in periprocedural MI definitions and available follow-up lengths might have played a major role. In addition, different DES were used (e.g., a thin-strut cobalt–chromium everolimus-eluting stent in the EXCEL trial vs a thicker-strut stainless steel biolimus-eluting stent in about 90% of NOBLE trial patients). The possible

relevance of this issue is suggested by a striking difference in the definite stent thrombosis rate observed in the two trials (0.7% in EXCEL and 3% in NOBLE). Most importantly it should be noted that despite the discrepancies in these two studies with new generation DES the repeated revascularization rates in the PCI arm were almost two times inferior compared to the PCI arm of SYNTAX study, a sign that confirms the improved performance of the new generation DES.

Recently, Palmerini et al published the results of a meta-analysis of all 6 available trials including 4.686 randomized patients (also collecting key missing data in order to enable subgroup analyses). After a median follow-up of 39 months, there were no significant differences between PCI vs CABG in the risk of all-cause mortality or cardiac mortality. Unsurprisingly long-term cardiac death differed in relation to angiographic complexity, such that the relative risk for mortality tended to be lower with PCI compared to CABG among patients in the lower SYNTAX score tertile, similar in the intermediate tertile, and higher in the upper SYNTAX score tertile. Finally, and consistently with previous results, both procedures resulted in similar long-term composite rates of death, MI, or stroke, with PCI offering an early safety advantage and CABG demonstrating greater durability.[17]

LEFT MAIN PCI STRATEGY AND TECHNIQUE ISSUES

According to the European guidelines, myocardial revascularization is indicated for patients with LM angiographic stenosis >50% and documentation of myocardial ischemia.[14] When LM stenosis severity is uncertain from angiography, it should be assessed without hesitation in the catheterization laboratory with the use of adjunctive devices for intravascular imaging or physiologic assessment. Among various modalities, intravascular ultrasound minimal lumen area >6 mm^2 and FFR >0.80 are well-known acceptable criteria for deferring left main revascularization.[18,19]

European guidelines highlight the critical role of the multi-disciplinary Heart Team in the treatment decision for stable or stabilized patients with unprotected LM disease in whom revascularization is being planned electively or semi-electively.[14] In the emergency setting, however, myocardial revascularization must be performed as soon as possible, since CABG is usually not a viable option.

Of note, the need for hemodynamic support devices is anticipated to be higher for patients with severe LM disease, either in the setting of elective PCI (especially in cases with depressed left ventricular function) or in emergency cases due to acute coronary syndromes. In some circumstances, rapid and effective deployment of hemodynamic support devices can be life-saving during complications of left main interventions. Accordingly, it is important that these are immediately available and can be inserted and activated quickly, which requires a high level of organization and sufficiently trained staff in the cath lab beyond the physician skills and experience. An LM PCI example is presented in Figures 1-3.

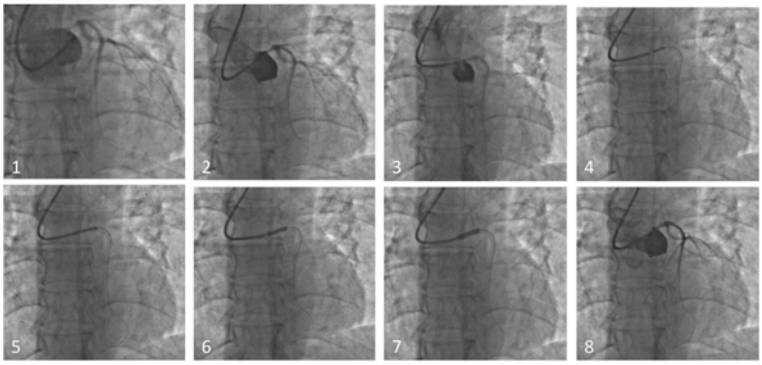

Figure 1. LM PCI example. Critical ostial stenosis of a diffusely atheromatous short LM (1) treated with transradial PCI. The lesion being resistant is pre-dilated with progressively increasing in diameter non-compliant balloons (2-6) and finally with a scoring balloon (7). The result is satisfactory and the LM is now sufficiently prepared for stenting, yet with a linear dissection throughout its length extending into the proximal LAD (8). The next procedural steps are shown in Fig. 2. LAD = left anterior descending; LM = left main

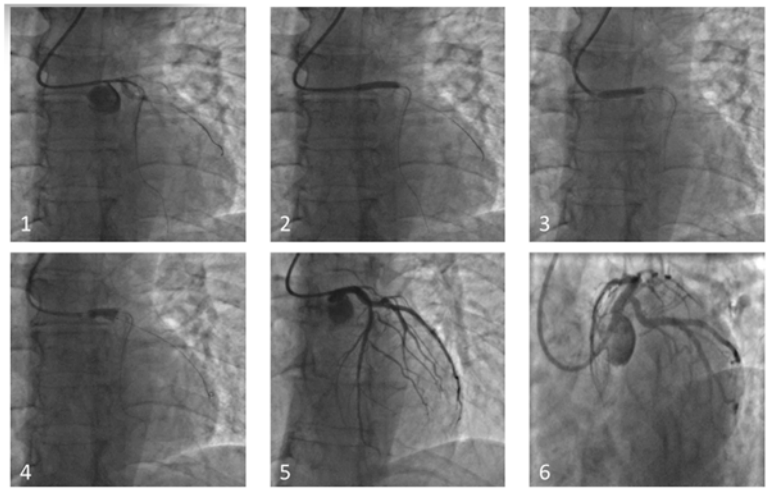

Figure 2. Left main PCI example (continued). A DES is positioned to cover the LM from the ostium to the proximal LAD and deployed (1,2). It is then post-dilated with a large non-compliant balloon until the carina of the LM bifurcation in order to perform the proximal optimization technique (POT) to obtain a good apposition of the stent in the LM (3), a kissing balloon inflation is performed (4) and a final POT is repeated as in 3. The balloons used for each of these procedural steps must be appropriately sized non-compliant balloons in order to obtain a good angiographic result as in this case (5,6).

The selection of a DES that will adapt correctly to the LM anatomy is recognized as a critical step for successful PCI. Accordingly, the individual patient's LM anatomy assessment by IVUS is strongly recommended whenever angiography is unclear and there are doubts about stent sizing (Fig. 3). In LM ostium/mid-shaft disease where the DES will not extend distally beyond the bifurcation it should be selected according to the LM diameter. Knowledge of DES platform characteristics is pivotal during LM stenting procedures. DES from different manufactures are available with different diameter ranges, thus large diameter stents whose nominal range falls within the typical LM size (4.5-5 mm) should be readily available together with non-compliant balloons of diameters more than 4mm (mainly 4.5mm and 5mm, but up to 6mm could be needed in some cases).

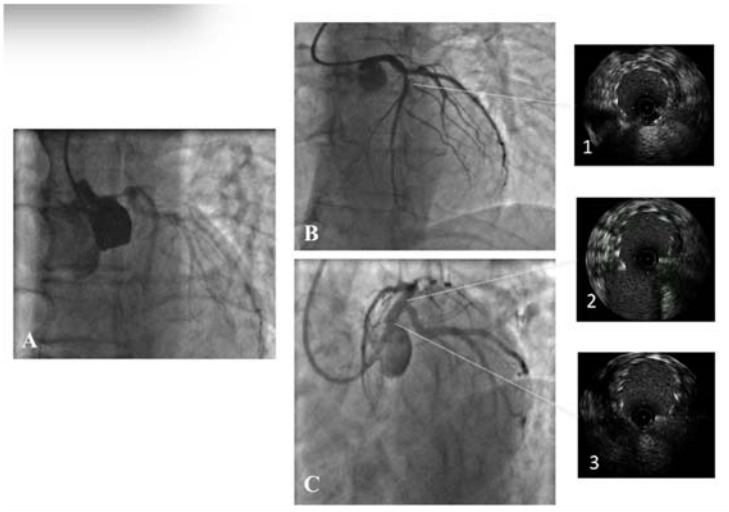

Figure 3. Left main PCI example (continued). The diffusely diseased LM with a critical ostial stenosis (A) has been treated with PCI to obtain a good angiographic result (B, C). Intravascular ultrasound control verified good stent expansion and apposition in the proximal LAD (1), with good opening of the stent cells at the LCX ostium (2) and also good stent expansion and apposition in the LM body (3).

Bench tests have confirmed the ability of different contemporary DES platforms with a nominal size of 3-4 mm to maintain structural integrity when expanded to higher diameters, but to a limit more or less defined for each platform.[20] In the more common situation of PCI to tackle bifurcation lesions, the LM coverage must be achieved with the same DES which is implanted into either the LAD or the LCX and consequently the stent size is selected according to the distal vessel diameter, so that 3-4 mm DES are usually considered. As a next pivotal step stent expansion in the LM is recommended according to the proximal optimization technique (POT) and by using an appropriately sized non-compliant balloon at high pressure for post-dilation.[21] Whether and when it is necessary to perform stent side-cell re-crossing, dilatation and eventual kissing balloon inflation after POT is debated and examined in a case-by-case basis. Side branch ostium angiographic stenosis after main vessel stenting may be the result of carina shift, a phenomenon that may not signify functional perturbation. According to expert consensus as a general principle kissing balloon inflation should be undertaken if a suboptimal result in the side branch ostium is clearly recognized or the possibility exists for downstream PCI in the future.[21]

Provisional stenting is the recommended technique for distal LM disease not involving both branches and usually one stent is needed (Fig. 1-3). When both LAD and LCX ostia are significantly diseased, the choice of stent technique is of great importance, it should depend on the individual patient's anatomical characteristics and the operator's skill, but certainly the chances of needing two stents for both LM branches are quite high. The expert consensus is that the vast majority of true bifurcation anatomies can be approached using a stepwise provisional technique which includes the potential to end with double stenting if needed. Expert consensus suggests that T/TAP or culotte are adequate techniques for bail-out side branch stenting. Whenever a second stent is implanted, the performance of high-pressure kissing inflation is mandatory and may benefit from a sequential strategy where the two balloons are firstly individually dilated to high pressures (to ensure ostial LAD and LCX expansion), followed by a simultaneous balloon inflation at lower pressures (to avoid LM overstretch). Since kissing balloon inflation is associated with proximal stent segment oval shape deformation, repeat final POT to obtain circular stent expansion of the DES is advisable, whenever long kissing balloon overlap in the left main stent occurs.[21] Among different techniques for elective double stenting, DK-Crush has become increasingly popular since it reduces the final kissing inflation failure rate as compared with the classic stent crush technique. A recent trial conducted in centers experienced with this technique reported better one-year target vessel failure rates as compared with provisional stenting.[22]

Intracoronary imaging (IVUS or optical coherence tomography) and functional (pressure wire-based) assessments are useful to optimize left main PCI, since there is a relationship between suboptimal LM PCI results and adverse clinical outcomes. As compared with angiographic guidance, IVUS-guided LM stenting has been found to be associated with a clinically detectable benefit, so that its use is strongly recommended.[23] For

instance, IVUS was extensively used in the EXCEL and NOBLE trials [15,16]

Intensive follow-up strategies should be considered for patients who have undergone successful LM PCI, especially when complex procedures with double-stent techniques have been used.

Conclusions

For the revascularization in case of LM disease PCI is supported by robust clinical data as a viable alternative to CABG among patients with low and intermediate SYNTAX scores. However, CABG still holds a long-term benefit, mainly concerning the need for repeated revascularization procedures. A Heart Team is indispensable to best evaluate the anatomic parameters of coronary lesions, the clinical variables and the technical environment in order to define the ideal revascularization strategy for each patient. When LM PCI is decided it should be performed with great attention to technical details and a low threshold for intravascular imaging guidance in order to optimize the result and patient outcomes.

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Table 1. Most important randomized studies that define the current role of PCI for left main (LM) disease.

Study	**Year**	**Patients**	**DES Generation**	**DES type**	**Primary endpoint (PCI vs CABG)**	**Secondary endpoints (PCI vs CABG)**
SYNTAX LM[11]	2010	705	First	TAXUS	*At 1 year:* Death, CVA, MI, or repeat revascularization: 15.8% vs. 13.7%, *p*=NS.	*At 5 years:* 1. Death, CVA, MI, or repeat revascularization: 36.9% vs. 31%, *p*=NS 2. Death/CVA/MI: 19% vs 20.8%, *p*=NS 3. Death: 12.8% vs 14.6%, *p*=NS 4. CVA: 1.5% vs 4.3%, *p*=0.03 5. MI: 8.2% vs 4.8%, *p*=0.10 6. Repeat revascularization: 26.7% vs 15.5%, *p*<0.001
EXCEL[15]	2017	1905	Second	XIENCE	*At 3 years:* Death, CVA, or MI: 15.4% vs 14.7%, *p* for non-inferiority = 0.02, *p*=NS for superiority	*At 3 years:* 1. Death, stroke, MI, or repeat revascularization: 3.1% vs 19.1%, *p* for non-inferiority = 0.01 2. Death: 8.2% vs 5.9%, *p*=0.11 3. CVA: 2.3% vs 2.9%, *p*=NS 4. MI: 8.0% vs 8.3%, *p*=NS 5. Repeat revascularization: 12.6% vs 7.5%, *p*<0.001
NOBLE[16]	2017	1201	Second	BioMatrix	*At 5 years:* Death, CVA, or non-procedural MI, repeat revascularization: 29% vs 19%, *p*=0.0066	*At 5 years:* - Death: 12% vs 9%, *p*=NS - CVA: 5% vs 2%, *p*=0.073 - Non-procedural MI: 7% vs 2%, *p*=0.004 - Repeat revascularization: 16% vs 10%, *p*=0.032

CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; DES = drug-eluting stent(s); LM = left main; MI = myocardial infarction; NS = non-significant; PCI = percutaneous coronary intervention