CABG vs PCI in Left Main Disease 2020: A Review Article

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Abstract:
Severe stenosis of the left main coronary artery (LMCA) generally occurs as a result of atherosclerosis and compromises the blood supply to a wide area of myocardium, thereby increasing the risk of serious adverse cardiac events. Revascularization for symptomatic significant left main (LM) coronary artery disease (CAD) has been the standard of care for more than 30 years. More recent advances in drug-eluting stents have begun to level the playing field between percutaneous coronary intervention (PCI) and coronary-artery bypass grafting (CABG), Current revascularization strategies for patients with significant LMCA disease include coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), both of which have a range of advantages and disadvantages. In general, PCI is associated with a lower rate of periprocedural adverse events and provides more rapid recovery, while CABG provides more durable revascularization. Most clinical trials comparing PCI and CABG for the treatment of LMCA disease have shown PCI to be non-inferior to CABG with respect to mortality and the serious composite outcome of death, myocardial infarction, or stroke in patients with low-to-intermediate anatomical complexities. Remarkable advancements in PCI standards, including safer and more effective stents, adjunctive intravascular imaging or physiologic evaluation, and antithrombotic treatment, may have contributed to these favorable results. This review provides an update on the current management of LMCA disease with an emphasis on clinical data and academic and clinical knowledge that supports the use of PCI in an increasing proportion of patients with LMCA disease.

Keywords: Coronary artery disease; Percutaneous coronary intervention; Coronary artery bypass; Angioplasty, balloon, coronary; Drug-eluting stents; Treatment outcome

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Introduction:

Obstructive left main coronary artery (LMCA) disease is associated with a high rate of morbidity and mortality as a result of compromised myocardial blood supply; therefore, revascularization by coronary artery bypass grafting (CABG) surgery has been regarded as standard treatment. Over the past 20 years, there have been considerable therapeutic developments in the technique of percutaneous coronary intervention (PCI) for the treatment of obstructive coronary artery disease (CAD), involving improvements in stent technology, procedural techniques and refinement, periprocedural anticoagulation, concomitant antiplatelet agents, and cardiovascular medication.[1, 2]

Several randomized clinical trials (RCTs) have been conducted to evaluate the potential therapeutic role of PCI as an alternative to standard CABG. With the introduction of first-generation drug-eluting stents (DESs), RCTs demonstrated that stenting achieved similar rates of mortality and hard clinical endpoints and a lower rate of stroke, although the rate of repeat revascularization was seen to be higher.[3-6] The development of second-generation DES was associated with improved efficacy and safety profiles compared with first-generation DES.[7, 8] Subsequent RCTs were conducted and PCI has achieved greater clinical recognition as a reasonable therapeutic modality.[9,10] These data may impact on future clinical guidelines for myocardial revascularization and will ultimately will lead to greater use of PCI worldwide. Importantly, when undertaking PCI of the LMCA, there is increasing awareness of the need to achieve optimal procedural outcomes through the use of available technologies, including safer and more effective stents, intravascular imaging, and physiological assessment.

This review provides an update on the current management of LMCA disease with an emphasis on clinical data and procedural knowledge to support the use of PCI in a growing proportion of patients.

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Randomized clinical trials

Key clinical trials comparing PCI and CABG from the first-generation DES era to the second-generation DES era are summarized in Table 1. The SYNTAX study was a key pivotal trial; in the LMCA subgroup, no significant differences were seen in the 5-year rate of major adverse cardiac and cerebrovascular events (MACCEs), mortality, or MI between PCI and CABG.4) However, the 5-year rate of repeat revascularization was higher after PCI and the rate of stroke was higher after CABG. The first LMCA-specific RCT (RECOMBAT) showed that the 5-year rate of MACCEs, death, MI, or stroke was similar between PCI and CABG, but the rate of target-vessel revascularization was significantly higher after PCI.6), 46) These trials prompted the initiation of two additional large-scale RCTs, EXCEL and NOBLE, which involved the use of contemporary DES.[9,10]

In the EXCEL study, the primary composite endpoint of death, stroke, or MI at 3 years was similar between PCI and CABG (p value for non-inferiority=0.02; p value for superiority=0.98).[9] PCI was associated with a lower incidence of major periprocedural adverse events (i.e., major arrhythmias, infections, reoperations, bleeding, or transfusions). PCI was also associated with a more rapid recovery and greater improvement in quality of life at 30 days than was CABG, although both procedures resulted in similar quality of life and angina relief at 3 years.11) In the NOBLE trial, the primary composite endpoint of all-cause mortality, nonprocedural MI, stroke, or repeat revascularization at 5 years was significantly higher after PCI than after CABG (29% vs. 19% exceeding the limit for non-inferiority, respectively). The difference in favor of CABG was statistically significant (p value for superiority=0.007) and was driven by significantly higher rates of nonprocedural MI, repeat revascularization, and stroke in the PCI arm.[10]

There may be several explanations for the inconsistent results seen in the EXCEL and NOBLE studies.[11] First, different types of DES were used. In EXCEL a thin-strut, fluoropolymer-based CoCr-EES was employed, which was associated with the lowest risk of stent thrombosis of all available DES.[12] The NOBLE study used first-generation, thicker-strut, stainless-steel, sirolimus-eluting Cypher stents (11%) or the biolimus-eluting Biomatrix Flex stent (89%). A substantial difference in the rate of definite stent thrombosis (0.7% in EXCEL vs. 3% in NOBLE) suggests the differential performance of stenting for LMCA disease. Secondly, the soft clinical endpoint of repeat revascularization was adopted as the key component of the primary endpoint in the NOBLE study. The majority of previous studies have consistently shown that the rate of repeat revascularization is significantly higher after PCI than after CABG. Therefore, the selection of this primary composite outcome may unfairly penalize the PCI stratum. The SYNTAX trial showed that the increase in repeat revascularization in the PCI group did not directly translate into an increase in the incidence of death or MI.[13] Thirdly, the definitions used for components of the primary composite outcomes differed between the studies, particularly the definition of MI. The Society for Cardiovascular Angiography and Interventions -defined clinically relevant MI definition was used in EXCEL,[14] while periprocedural MI was disregarded in NOBLE. Finally, in the NOBLE study, the rate of stroke was more than two times higher after PCI than after CABG, which is not in agreement with the findings of previous clinical trials comparing PCI and CABG. This observation lacks a clear explanation and biologic plausibility and is, therefore, likely to be due to a chance effect.[15]

Currently in the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial is the largest study comparing coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) in the treatment of low-complexity left main disease. The 5-year outcomes have recently been published. The composite primary outcome occurred in 22.0% of the PCI patients and in 19.2% of the CABG patients (95% confidence interval, -0.9-6.5; p = 0.13), and the authors conclude that there is no significant difference between the two treatments.[16]

However, in the EXCEL trial, there was a significant excess mortality in the PCI arm (13.0% vs. 9.9%, odds ratio 1.38 [1.03-1.85]). The authors attribute this difference to chance because no difference was found in definite cardiovascular deaths. Although we agree that the analysis is underpowered and there was no adjustment for multiple testing, the large difference in the most important outcome cannot be simply ignored, especially because adjudication of the cause of death in open-label trials is notoriously open to bias.[17]

In addition, in the EXCEL trial, perioperative myocardial infarction (MI) was a main driver of the primary outcome at 3 and 5 years, being in large part the cause of non-proportional hazards at 5 years and of the neutral results. In the EXCEL trial, the authors used an original definition that allows a purely enzymatic diagnosis of perioperative MI and increases by 100% the enzymatic threshold in the PCI group but not in the CABG group, clearly disadvantaging surgery. In fact, the rate of perioperative MI after surgery in similar trials that used the generally adopted universal definition were clearly lower: 1.7% in FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) and 2.9% in SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) versus 6.2% in the EXCEL trial.

It is important to highlight that 1) all the cardiac outcomes in the EXCEL trial (including non-periprocedural MI whose definition was not substantially modified) are in favor of surgery, and 2) although the main rationale provided by the authors for the definition used was the prognostic relevance of periprocedural MI, in the EXCEL trial, no excess death was found in the surgical group despite a significantly higher incidence of perioperative MI.

Other relevant considerations come into play when interpreting the EXCEL results. Unlike the homogeneous PCI treatment arm in which all patients received everolimus-eluting stents, the CABG arm has important variations that should be factored in. Approximately 30% of patients in the surgical arm of the EXCEL trial underwent off-pump CABG, which, compared with on-pump CABG, was associated with a significantly increased risk of 3-year all-cause mortality (8.8% vs. 4.5%; hazard ratio 1.94; 95% confidence interval, 1.10-3.41).18 In addition, despite guideline recommendations for multiarterial grafting. 19, 20 only 24% of EXCEL patients received bilateral internal thoracic artery grafts, and fewer than 7% received radial artery grafts.[21]

In summary, the EXCEL results are to be interpreted with caution because of the study design features that disadvantage CABG. The modern-day CABG that achieves complete revascularization with multiarterial grafting remains a very competitive and durable therapy if not the gold standard intervention for patients with left main disease.[22]

Meta-analyses

In a meta-analysis of the four largest studies of LMCA revascularization with follow-up available at 3–5 years, incorporating data from the EXCEL and NOBLE trials, the hazard ratio (HR) for death, stroke, or MI with PCI compared with CABG was neutral (1.06) in a random-effects model (p=0.60).53) Based on individual patient data reconstruction, the Kaplan-Meier estimates of death, stroke, or MI at 5 years were 18.3% for PCI and 16.8% for CABG (p=0.52). No statistically significant subgroup interaction for this combined outcome was noted across studies based on the generation of DES used for PCI (p value for interaction=0.25). There were no significant differences in the pooled effects for death (HR, 1.04; p=0.77) and cardiac death (HR, 1.00; p=0.99). The endpoints of MI and stroke also did not differ between the PCI and CABG groups (HR, 1.48; p=0.17 and 0.87; p=0.72, respectively), but these outcomes were confounded by high heterogeneity across the trials. Repeat revascularization was consistently higher following PCI in all trials, leading to a pooled HR of 1.70 (p<0.001). In another meta-analysis, including all the six trials available to date, missing data were collected by the principal investigators, enabling further subgroup analyses.23) PCI was found to significantly reduce death, MI, or stroke by 36% within 30 days. PCI reduced periprocedural MI by 33%, but this effect was offset by 93% more spontaneous MIs beyond 30 days after the procedure. Cardiac death differed in relation to angiographic complexity in that it tended to be lower with PCI among patients with low SYNTAX scores and higher in patients with high SYNTAX scores.

A recent large-scale, pooled analysis of individual patient data reported a comparable treatment effect for PCI and CABG with regard to all-cause mortality up to 5 years in selected patients participating in RCTs.24) This analysis included 11 RCTs involving 11,518 patients who were assigned to undergo PCI (n=5,753) or CABG (n=5,765). The 5-year rate of all-cause mortality was 11.2% after PCI and 9.2% after CABG (HR, 1.20; 95% CI, 1.06–1.37; p=0.004). Interestingly, the 5-year all-cause mortality differed significantly between the two interventions in patients with multivessel disease (11.5% after PCI vs. 8.9% after CABG; HR, 1.28; 95% CI, 1.09–1.49; p=0.002), including in those with diabetes (15.5% vs. 10.0%, respectively; HR, 1.48; 95% CI, 1.19–1.84; p=0.0004), but not in those without diabetes (8.7% vs. 8.0%, respectively; HR, 1.08; 95% CI, 0.86–1.36; p=0.49). By contrast, the 5-year rate of all-cause mortality was similar between the two groups in patients with LMCA disease (10.7% after PCI vs. 10.5% after CABG; HR, 1.07; 95% CI, 0.87–1.33; p=0.52), regardless of diabetes status and SYNTAX score.[25]

Revascularization guidelines

Existing clinical practice guidelines continue to advocate CABG surgery as the singular class I indication for myocardial revascularization of LMCA disease. However, more recent RCTs and registry studies support PCI as a reasonable alternative in selected patients with less complex LMCA anatomy.

As new evidence has become available, guideline recommendations for LMCA revascularization have slowly evolved over time in both Europe and the US . Recently, the 2018 European Society of Cardiology guidelines incorporated compelling data from the EXCEL and NOBLE trials, as well as the results of the pooled analysis.[26] The 2018 European guideline indicates the same class of recommendation, but all evidence levels have been upgraded to level A. For PCI in LMCA with intermediate anatomical complexity, the previous class IIa recommendation was maintained in view of the incomplete 5-year follow-up in the two largest RCTs in this setting. In the future, the guideline will propose less restrictive indications for PCI, thereby expanding the patient pool that might be eligible for PCI. In addition, given that SYNTAX score was not an important factor for decision-making regarding optimal revascularization and to differentiate the comparative outcomes between CABG and PCI in the EXCEL and NOBLE studies, it may be debated whether the SYNTAX score can play a pivotal role in decision-making regarding LMCA revascularization.

The heart team approach

Regardless of which method of revascularization is used, current guidelines highlight the importance of a ‘heart team’ approach to the management of LMCA disease. The heart team evaluates the risks and benefits of PCI, surgery, or medical treatment alone, taking into account the patient’s informed preference . In general, PCI offers more rapid recovery and a lower early adverse event rate, whereas CABG offers more durable revascularization. However, the relative outcomes of PCI vs. CABG can be attributed to a complex interplay of patient comorbidities, coronary anatomic complexity, and ventricular function, in addition to other less tangible factors such as operator expertise and compliance with medication. The complexity and extent of coexisting CAD with the intention of achieving complete revascularization should also be considered by the heart team. Previous evaluation has shown that major adverse cardiovascular events are higher in patients with incomplete revascularization than in those with complete revascularization regardless of the revascularization strategy.[27] The heart team approach is critical when evaluating the risks and benefits of surgery in high- and extreme-risk populations. Additional clinical factors that are not included in most risk models also need to be considered by the heart team when making management recommendations, including frailty, cognitive status, surgical recovery and social support, quality of life, life expectancy, patient preference, and any potential concerns regarding tolerance or adherence with long-term dual antiplatelet therapy.

Conclusions:

Over the past 20 years, significant advancements in stent technology, technical refinement, image and physiological guidance, and adjunctive drug therapy have led to progressive improvements in outcomes following PCI in patients with LMCA disease. In the contemporary clinical setting, LMCA PCI has become a viable option in daily practice not only for patients with less complex clinical and anatomic characteristics (i.e., isolated left main disease, ostial or shaft left main disease, or additional less complex CAD), but also for patients with complex clinical and anatomic characteristics (i.e., distal LMCA bifurcation or those with acute MI or unsuitability for CABG).

Which approach will be of most benefit to individual patients with LMCA disease should be decided by the local heart team, which comprises a general cardiologist, interventional cardiologist, and cardiac surgeon. The heart team will consider the clinical circumstances, any technical issues, and the likelihood of safely achieving complete revascularization with each procedure. It will also be important to consider the patient’s own preference once the procedures have been explained in full.

Current joint European guidelines equivalently recommend PCI and CABG for patients with LM disease of low anatomic complexity (Class IA) and less strongly support PCI in lesions of intermediate (Class IIA) and high complexity (Class IIIA).

Generally, I believe the long-term outcomes with CABG are superior for more complex anatomic LM disease. PCI is preferable for patients with more noncardiac comorbidities, particularly in the shorter term. A heart-team approach is helpful to balance these issues. Shared decision-making is essential for patients who strongly prefer a less-invasive initial approach despite higher risks for later events.

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