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Left main stenting: do we need another study?

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Coronary artery bypass graft (CABG) surgery has long been adopted as the treatment of choice for patients with left main (LM) coronary obstructions. In the past, randomised trials and observational studies have shown an advantage in survival of CABG against medical treatment. Recent studies comparing CABG with percutaneous coronary intervention (PCI) suggested that angioplasty may play a role as an alternative choice. However, well designed randomised trials to evaluate the relative merits of both therapeutic approaches are lacking. In this article, we review the current scientific evidences and outline issues that currently still need to be addressed in comparing CABG versus PCI for the treatment of LM disease.

Introduction

Untreated left main (LM) coronary stenosis is a condition associated with a high mortality risk. Since the early days of coronary artery bypass grafting (CABG), surgery is regarded as the treatment of choice for LM obstructions. More recently, however, percutaneous coronary intervention (PCI) has been proposed as an alternative for this subset of patients. In the present article we revise the scientific evidence that form the basis for current treatment guidelines, and discuss the need for further clinical studies to assess the impact of modern therapeutic strategies on patients' outcomes.

Evidence supporting coronary artery bypass graft surgery as the gold-standard treatment for LM disease

In the late 1950s, the development of coronary angiography, and the consequent ability to assess the coronary anatomy *in vivo*,[1] ignited a wave of diagnostic and therapeutic possibilities that ultimately shaped much of cardiovascular medicine practiced today. Coronary bypass surgery was introduced only a few years after the availability of coronary angiography,[2] and was rapidly incorporated into routine practice worldwide.

A total of seven trials compared CABG with medical therapy between 1972 and 1984, with enrolment of 2,649 patients with or without LM disease.[3] A meta-analysis with individual data showed that, for the global population, the CABG group had a significantly lower mortality rate after 10 years (risk reduction 17% [95% confidence interval: 2-30%]; p=0.03), even when considering that the crossover from medical treatment to CABG was 41% during the follow-up period.[3] Patients with LM disease, however, comprised only 6.6% of the study population. In the LM subset of patients, the crossover to CABG was highest and the 10-year mortality reduction with CABG was 33% (95% confidence interval: 30% increase to 65% reduction) (p=0.24). Despite the lack of data from randomised trials, coronary surgery rapidly became the default therapy for LM stenosis. It is illustrative that the Coronary Artery Surgery Study (CASS), which was conducted approximately 10 years after the start of CABG surgery,[2] did not allow the randomisation of patients with a high degree LM stenosis.[4] Inclusion of that subset was judged to be unethical on the basis of prior subgroup analyses from the Veterans Administration Study and European Coronary Surgery Study Group. Remarkably, those two studies, in total, included less than a few dozen patients with LM disease treated with CABG.[4]

Because CABG was soon established as the default treatment for LM disease, little data is available on the natural history of patients with LM stenosis.[5] The CASS included a concomitant registry of 1,484 patients with LM disease who were not included in the randomised cohort.[6] The majority of patients in this registry was

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operated (1,153 patients) and only one-fifth of the patients were left on medical treatment.[6] Patients with LM stenosis that were treated medically had less angina and less severe coronary stenoses, but had significantly more heart failure and left ventricle dysfunction.[6] In the CASS registry, the surgical treatment did not show a significant survival benefit at 15 years compared to a non-operative strategy in "lower-risk" cases, i.e., those with normal left ventricle systolic function, non-stenotic right coronary artery, or intermediate LM stenosis (i.e., <60%).[6]

It is of note that medical treatment and risk factor modification have dramatically improved over the last four decades and have major clinical impact on outcomes.[7] Recent studies for patients with non-LM disease have therefore questioned the superiority of invasive treatment over a more conservative approach,[8] especially for low-risk patients.[9] On the other hand, operative techniques and results have also evolved. Recent studies have shown a consistent and progressive decrease over time in early and late mortality after CABG for LM stenosis.[10,11]

Coronary angioplasty: can it be a viable alternative for LM disease?

Percutaneous coronary intervention (PCI) was introduced approximately a decade after CABG, and was initially reserved for low-risk, non-complex patients with single-vessel coronary disease. However, an increase in expertise, pharmacology, and techniques, along with improvements in device technology, led to a plethora of scientific data that rapidly expanded the indications of PCI. Randomised studies in selected patients with multivessel coronary disease but without LM stenosis showed similar 5-year rates of death, myocardial infarction, or stroke after (bare metal) stenting, in comparison with surgery.[12]

Percutaneous coronary angioplasty for LM disease is frequently perceived as unsafe because periprocedural complications could have catastrophic consequences. Late restenosis may also hamper the durability of the intervention for LM stenosis to a higher extent than it would do for other anatomical scenarios. Therefore, balloon angioplasty has only been marginally applied for LM disease. The introduction of coronary stents reduced the risk of acute complications and restenosis and led to an increase in the use of PCI for patients with LM disease.

The low incidence of short-term adverse events after stenting for unprotected LM stenosis indicates that, at least for selected patients and in experienced hands, PCI for LM stenosis is a safe procedure.[13] The use of DES has further improved the results. A recent meta-analysis with 44 studies (10,342 patients) evaluated the late outcomes of patients undergoing percutaneous coronary intervention with bare metal stents (BMS) or drug-eluting stents (DES).[14] The rate of re-intervention was lower with DES compared to BMS, at six to 12 months, at two years, and at three years, with a tendency towards a decreased risk of late death and myocardial infarction.[14]

Most experience with DES for LM disease has been accumulated with first generation sirolimus- or paclitaxel-eluting stents.[14] Recently, second generation DES have been shown to be clinically superior than paclitaxel-eluting stents,[15-17] and at least non-inferior compared to sirolimus-eluting stents.[18] Newer generations of DES use advanced metallic platforms with improved mechanical performance, which may further improve the outcome in complex LM stenoses.

In contrast to surgery, the outcomes after percutaneous treatment are highly modulated by the morphology and anatomy of the target atherosclerotic lesions. Percutaneous treatment of the distal left main bifurcation remains challenging and is an important risk factor for future complications, potentially more than doubling the rate of late re-interventions.[19] Thus far, no bifurcational strategy has significantly decreased the hazardous impact of distal LM stenosis. Recently, much emphasis has been placed on the use of a single stent at the main branch, reserving a two-stent approach only for selected cases.[20,21]

Guidance with intravascular ultrasound has been suggested to decrease late mortality after DES implantation.[22] A more liberal use of intravascular ultrasound or fractional flow reserve should also be advocated at the time of the diagnostic catheterisation, for patients with LM disease. The angiographic quantification of luminal stenosis may be particularly challenging for LM lesions.[23,24] Ambiguous lesions at the LM, including those of intermediate stenosis (i.e., <60-70% stenosis) or located at the ostium should most probably undergo further invasive testing, instead of relying solely on the angiographic appearance for the decision making.[25,26] There are compelling data suggesting that CABG in non-critically diseased coronary arteries may occlude and potentially have catastrophic consequences.[27] Moreover, data from early studies suggest that native atherosclerotic progression appears to be higher in grafted than in non-grafted vessels.[28]

How much data is currently available comparing CABG versus PCI for LM disease?

Only one single randomised study has been conducted to specifically compare the outcomes of patients with LM stenosis treated with either PCI or CABG.[29] The Study of Unprotected Left Main Stenting Versus Bypass Surgery (LEMANS) randomised 105 patients with LM stenosis to treatment with CABG or PCI.[29] The LEMANS pre-defined the change in left ventricular ejection fraction at 12 months as the primary endpoint for comparison between the two treatment arms. Importantly, in LEMANS only one-third of the patients were treated with DES and the rate of left internal mammary artery grafting was only 72% in CABG patients. A significant increase in ejection fraction was observed only in the PCI group (3.3±6.7% after PCI vs. 0.5±0.8% after CABG; p=0.047). Angioplasty was associated with a shorter hospitalisation time and a lower risk of 30-day adverse events and, after one year, the incidence of combined events was comparable. At 28±9.9 months of follow-up, there was a trend towards better survival after PCI, even though data on more prolonged follow-up time were not available.[29]

The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial was a randomised trial that included "all-comers" with triple vessel or LM disease for treatment with CABG or PCI with paclitaxel-eluting stents.[30] A total

of 1,800 patients were enrolled in SYNTAX, which included 705 patients who had LM disease. Although this was a pre-specified subgroup, the analysis of LM patients should only be regarded as hypothesis generating. After one year, the rate of major cardiac and cerebrovascular events in the subset with LM disease was similar between CABG and PCI (13.7% versus 15.8% respectively; p=0.44). The incidence of stroke was higher in the CABG arm (2.7% versus 0.3%; p=0.009), while re-intervention was higher in the PCI arm (6.5% versus 11.8%; p=0.02), with no significant differences for other clinical endpoints at one year.[30] The 3-year outcomes of the SYNTAX LM substudy have been recently presented (P.W. Serruys, oral presentation at the TCT meeting, Washington DC, USA, 2010), showing similar survival (91.6% versus 92.7%; p=0.6) and myocardial infarction (4.1% versus 6.9%; p=0.1) between the CABG and the PCI groups respectively, even though the PCI group tended to have a higher incidence of infarctions between two and three years (0% versus 1.5%; p=0.06). After three years, the cumulative risk of stroke was still higher in the CABG group (4.0% versus 1.2%; p=0.02) and the cumulative rate of re-intervention was higher among PCI patients (11.7% versus 20.0%; p=0.004), even though the difference in cerebrovascular complications or repeat revascularisation between the study arms was basically restricted to the first year of follow-up. It is important to realise that, in clinical studies conducted according to the intention-to-treat principle, adverse events start to be computed immediately after the randomisation. Therefore, it is of utmost importance for investigators to focus on decreasing the time lag between inclusion and the effective treatment. In SYNTAX, LM patients undergoing PCI received the assigned treatment significantly faster than the CABG group (6.0 days versus 14.7 days respectively; p<0.001),[30] even though such delay in the surgical groups was clearly decreased in comparison with early clinical trials.[3]

The SYNTAX study also tested the prognostic ability of a scoring system based on coronary morphology (e.g., number of lesions, total occlusion, bi/trifurcations, aorto-ostial stenosis, tortuosity, lesion length, calcification, thrombus, and small vessels/diffuse disease). In the LM subset included in the SYNTAX trial, a higher baseline anatomic complexity predicted worse outcomes with PCI, but did not affect the outcomes after CABG.[30] However, recent analyses have suggested that angiographic complexity only partially modulates the long-term outcomes after PCI for LM stenosis and that complementary evaluation of the clinical profile might better the ability to predict future complications.[31,32]

A recent meta-analysis included 2,905 patients from eight clinical studies (two randomised trials and six non-randomised studies) comparing CABG versus PCI using DES for patients with unprotected LM disease.[33] At 1-year, there was no significant difference between CABG and PCI in terms of mortality, or the composite endpoint of death, myocardial infarction, or stroke. However, the risk for re-interventions was significantly lower among patients treated with CABG.[33] Indeed, in a long-term observational study, even after five to 10 years, stenting showed similar survival, infarction, and stroke rates, compared to CABG.[34] However, the rate of repeat revascularisation was still lower with CABG, even after the introduction of DES.[34]

Left main stenting: do we need another study?

The best treatment for LM disease has yet to be defined. Thus far, the accumulated evidence to guide the therapeutic choice for these patients is derived from clinical practice, observational surveys, small or outdated randomised studies, or substudies of larger trials. However, no single study conducted to date has addressed the important issues listed in Table 1, leaving several gaps in clinical knowledge. Hopefully, the future Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL) trial will help filling the gap of information about the best therapeutic strategy for LM disease.[35] The EXCEL will randomise approximately 2,500 patients with LM stenosis, judged to be amenable to either CABG or PCI by consensus of a Heart Team. Patients will be followed-up to five years, and the trial is adequately powered in sequentially tracking non-inferiority and superiority regarding the occurrence of the composite primary endpoint of death, MI, or stroke.

Table 1. Guidelines for optimising the CABG versus PCI comparison.

- The decision whether a patient is eligible for randomisation must be made by consensus among all treating physicians, the so-called "Heart Team".
- Patients who are eventually not randomised should be included in a parallel registry.
- Subgroups for future analysis should be pre-specified.
- Study hypothesis and endpoints should be carefully chosen. Left main coronary disease is assumed to be a potentially lethal condition. Ideally, a trial should be adequately powered to evaluate mortality after CABG or PCI.
- Regardless of allocated invasive treatment, optimal medical treatment must be universally instituted, which includes but is not restricted to aggressive risk factor and life-style modification strategies.
- Use of advanced surgical techniques should be strongly reinforced, including the maximisation of arterial conduit grafting.
- Time between randomisation and the allocated treatment should be short.
- PCI should be performed with the last generation stents, with demonstrated improved clinical performance compared to early generation ones.
- PCI techniques should follow strict guidelines to avoid suboptimal interventional results, especially in cases with distal bifurcation involvement.
- Adjunctive diagnostic methods (FFR and IVUS) should be liberally used for selecting patients for study entry (ambiguous lesions) as well as for guiding the percutaneous interventional strategy.
- Adequate adjunctive antithrombotic therapy must be used during and after PCI to optimise early and late results.

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