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VIEWPOINT

Controversies in the Indications of Percutaneous Angioplasty Or Coronary Artery Bypass Grafting In The Treatment Of Left Main Disease

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Introduction

Left main coronary artery (LMCA) disease is a high-risk clinical situation, since this artery is responsible for the irrigation of more than two-thirds of the myocardial tissue,[1] LMCA disease is associated with increased risk of adverse cardiac events.[2] Traditionally, the gold standard of treatment for significant LMCA disase, understood as a stenosis> 50%, is coronary artery bypass grafting (CABG) surgery.[3-7]

The technological evolution of percutaneous treatment and its safe application for LMCA disease in the PRECOMBAT study made it a viable alternative, initially restricted to patients at high surgical risk and with LMCA disease confined to the proximal portion of the trunk.[8] Subsequent studies have suggested the equivalence of percutaneous coronary intervention (PCI) and CABG in low and moderate complexity LMCA disease,[9] which was reflected in the most recent guidelines (Table 1). Clinical registries, with real-patient outcomes,[10-15] and long-term results from the EXCEL study,[16] contest this notion of equivalence between therapies in terms of mortality. The study was controversial, especially regarding the definition of clinical outcomes.

Motivated by recent studies showing divergent results on the comparison between surgical and percutaneous approach for LMCA disease, in this article we briefly review the results of the two forms of treatment, focusing on the recent evidences and controversies, but mainly on the lessons learned from these studies and their applicability in clinic care.

Coronary artery disease and myocardial revascularization

There is a tendency towards more conservative approaches in stable coronary artery disease (CAD), considering the absence of benefit from revascularization as demonstrated in the COURAGE trial[17] and, more recently, in the ISCHEMIA trial.[18] Even patients with areas of significant ischemia have not benefited from an invasive approach, so the tendency is to use revascularization to treat symptoms, without necessarily aiming to improve prognosis. In patients with CAD and severe ventricular dysfunction, the STICHES study demonstrated a reduction in long-term mortality from CABG compared with clinical treatment.[19] The ASCERT study, which was based on clinical records of CABG (n = 86244) and PCI (n = 103549), showed a relative risk reduction of mortality of 21% with CABG in the four years follow-up, when compared to PCI.[20] The results were observed in all subgroups of this large sample.

In the clinical trials mentioned above, patients with LMCA disease were not included. LMCA disease is present in 4 to 6% of all patients undergoing angiography and is associated with multivessel disease in approximately 70% of the cases.[21] The disease affects the distal portion of the LMCA in 60 to 94% of patients. When LMCA disease is

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Table 1 - Recommendations of the European Society of Cardiology (2018) and the American Heart Association (2017) guidelines for choosing the method of revascularization in patients with stable LMCA disease considering a scenario of favorable anatomy for both types of treatment (coronary bypass artery grafting and percutaneous coronary intervention) and a low surgical risk

Extension of coronary artery disease	Class and level of recommendation			
	CABG		PCI	
	ESC	AHA	ESC	AHA
LMCA disease with low SYNTAX score (0-22)	I (A)	I	I (A)	IIA
LMCA disease with intermediate SYNTAX score (22-33)	I (A)	I	II a (A)	IIB
LMCA disease with high SYNTAX score (≥33)	I (A)	I	III (B)	III

AHA: American Heart Association; ESC: European Society of Cardiology; LMCA: left main coronary artery disease; CABG: coronary bypass artery grafting; PCI: percutaneous coronary intervention

restricted to proximal or medial portions of the vessel, PCI is technically simpler than in distal lesions and is associated with low rates of restenosis.[1] The current recommendation is that all patients with stenosis ≥ 50% in the LMCA should undergo revascularization, regardless of the presence of symptoms or ischemia in functional tests.[4]

Anatomical particularities and severity of CAD are important factors when choosing the most adequate revascularization strategy.[22] Other variables should also be considered: ventricular function, form of presentation (acute or stable disease), chance of achieving complete revascularization, surgical risk and the patient's preference after being clarified about treatment options.

The indication for surgery in LMCA disease, in addition to the theoretical concept of the extensive myocardial area at risk, is based on subgroup analysis of two studies of surgical revascularization against clinical treatment, published in the 1980s.[3,5] Together, these studies included 185 patients with LMCA disease and demonstrated a mortality benefit at 5 and 10-year follow-up. These studies were conducted during a period when modern pharmacological treatment was not available, and only 66% of patients received some type of beta-blocker and 19% received acetylsalicylic acid (ASA).[1]

LMCA disease patients represent a high-risk group, but it is not homogeneous. These older studies identified subgroups that carry a worse prognosis, such as left main stenosis ≥ 70%, left ventricular dysfunction and previous infarction.[6,7] However, even the low-risk groups showed a very high mortality of around 20-30% in four years when treated conservatively.

Clinical trials and guidelines recommendations

Surgical revascularization is a class I indication for treatment of LMCA disease, according to the guidelines of the American Heart Association (AHA)[23] and the European Society of Cardiology (ESC),[22] regardless of the complexity of the coronary lesions. More recent studies and registries have shown adequate results for the percutaneous treatment of ostial or medial LMCA disease when the anatomy is less complex. The two guidelines differ in degrees of recommendation. According to the ESC guidelines, PCI is a class I indication when anatomical complexity is low, defined as a SYNTAX score below 22 and a class IIA indication when SYNTAX score denotes a moderate complexity (score between 22 and 33). In the AHA guideline, these conditions receive class IIA and IIB indications, respectively. The procedure is not recommended (class III) when SYNTAX is equal to or greater than 33, being compatible with a complex anatomy, both in the ESC and the AHA guidelines. The guidelines also coincide in the recommendation to carry out an individualized assessment of each case, considering, in addition to the coronary anatomy, the surgical risk (calculated using the score of the Society of Thoracic Surgeons) and patient's preference. In this scenario, the role of the Heart Team, which receives class I indication in both guidelines, is fundamental.

The guidelines were based on pre-specified subgroups of patients with LMCA disease in the SYNTAX study[24,25] and in two less powerful studies: the LE MANS[26] and the PRECOMBAT[27] studies. These studies included a reduced sample (total of 1,410 in the sum of the three studies) and were performed when second-generation stents weren´t available. Two larger studies that specifically evaluated revascularization strategies for LMCA disease were the EXCEL[16] and the NOBLE trials[28] (Table 2). Even the most recent revascularization guidelines, published by the ESC in 2018,[22], were made without the availability of the long-term results of these studies,[29,30] but it gave a class recommendation for PCI in patients with low complexity LMCA disease, and maintained class IIA indication for moderate complexity anatomies.

The EXCEL study was the largest clinical trial to date regarding the treatment of LMCA disease; 1,905 patients from 126 centers spread across 17 different countries were randomized.[16] The primary outcome, a compound of death, stroke and myocardial infarction (MI), occurred in 22.0% of the patients in the PCI group and 19.2% in the CABG group (difference, 2.8 percentage points; 95% confidence interval [CI], -0.9 to 6.5; P = 0.13). In the five-year follow-up, but not in the prior publication with 3-year follow-up, PCI was associated with higher mortality, 13.0% vs. 9.9% (difference, 3.1 percentage points; 95% CI, 0.2 to 6.1), and the highest rate of repeat revascularization (16.9% vs. 10.0%; 95% CI, 3.7 to 10.0). CABG was associated with a higher rate of periprocedural MI, but with a lower risk of MI after surgery. The study was criticized for using its own definition of MI, as discussed later in this article. PCI was associated with a better quality of life and faster recovery in 30 days. In three years, however, the two modalities had similar results of quality of life.

In the NOBLE study, 1,201 patients were included in 36 European centers. The primary outcome was a composite of all-cause mortality, MI unrelated to the procedure, stroke

Table 2 – Main studies comparing percutaneous and surgical treatment in patients with left main coronary artery disease

Trial	Year	N	SYNTAX score	DM	Multivessel disease	Primary outcome (PCI vs CABG)	Main secondary outcomes (PCI vs CABG)
LE MANS	2008	105	N.D.	18%	91%	Change of LVEF (1 year): 3.3% vs 0.5% (p= 0.047)	No difference in mortality, MI, RR in 10 years
SYNTAX LM	2010	705	30	25%	68%	Death, stroke, RR (1 year): 15.8% vs 13.6% (P= 0.44)	5 years: Stroke: 1.5 vs 4.3 % (P = 0.03) RR: 26.7% vs 15.3% (P<0.001)
Boudriot	2011	201	23	36%	41%	Death, stroke, RR (1 year): 19.0% vs 13.0% (P= 0.19)	Similar rates of death, MI, stoke in 1 year (P for non inf. < 0.001) RR: 14 vs 5.9% (P for non inf. = 0.35)
PRECOMBAT	2011	600	25	32%	73%	Death, stroke, MI, RR (1 year): 8.7% vs 6.7% (P for non. = 0.01)	No difference in mortality, MI, stroke in 5 years RR: 13% vs 7.3% (P=0.02)
EXCEL	2017	1905	21	29%	51%	Death, stroke, MI in 3 years: 15.4% vs. 14.7% (P = 0.98)	Mortality in 5 years: 13.0% vs. 9.9% (difference, 3.1 percentage points; 95% CI, 0.2 a 6.1)
NOBLE	2017	1201	22	15%	N.D.	Death, stroke, MI, RR in 5 years: 29 % vs 19% (P=0.0066)	Similar rates of death and stroke in 5 years MI: 7 % vs 2% (P=0.004) NRE: 16 % vs 10% (P=0.032)

LVEF: left ventricular ejection fraction; N: number of included patients; DM: diabetes mellitus; MI: myocardial infarction; RR: repeat revascularization and repeat revascularization.[28] The event rate estimated by Kaplan-Meier over five years was 28% for PCI and 19% for CABG (Hazard ratio [HR] 1.58 [95% CI 1.24–2.01]). CABG was superior to PCI for the primary outcome (P = 0.0002), due to the lower rate of MI unrelated to the procedure and less need for new revascularization.

Panoulas et al.,[31] published a retrospective analysis of 6,383 consecutive patients undergoing CABG or PCI with contemporary technology.[3]

[1] All patients were from the same center in the United Kingdom between 2007 and 2015. The average follow-up was 3.3 years. Left main disease represented 30.6% of the sample in the CABG group and 13.4% in the total sample, which underwent both Cox regression analysis and propensity score matching to reduce the effects of selection bias and other confounding factors. Surgery showed a mortality benefit (HR 3.24, 1.37 to 7.71), more pronounced than in the group of patients with three-vessel disease (HR 2.49, 1.22 to 5.1). Mortality in the study by Panoulas et al.,[31] was higher than that reported in the meta-analysis by Head et al.,[9] as would be expected when real-patients results are compared with randomized clinical trials. This article also showed the excellent results of CABG in the contemporary era: 2.1% of in-hospital mortality and 95.7% of one-year survival.

Head et al.[9] carried out a meta-analysis with individual data of the 11 clinical trials published up to July 2017 which compared PCI and CABG for treatment of LMCA disease.[9] A total of 11,518 patients were included, 4,478 (38.8%) with LMCA disease. They found similar five-year mortality in the groups (10.7% PCI vs 10.5% CABG , HR 1. 07, 95%CI 0.87–1.33; P = 0.52), regardless of the SYNTAX score and the presence of diabetes.

Incomplete revascularization is associated with increased mortality,[32] which may explain the benefit of surgical revascularization in patients with a more complex anatomy, reflected as a high SYNTAX score. The Heart Team, in other words, a thoughtful discussion of the best procedure for each individual patient by a clinical cardiologist, an interventional cardiologist and a cardiovascular surgeon, is crucial in complex scenarios, as occurs in patients at high surgical risk (mortality estimated ≥ 8%),[1,22] always based on current guidelines. On the other hand, it must be considered that some factors known to influence surgical results, such as frailty and social support, are not present in the scores traditionally used.[33]

Few studies have compared different angioplasty techniques that could potentially affect the outcomes. There is a consensus that drug-eluting stents should be used,[22] as they reduce complications when compared to bare-metal stent, especially when the implant is performed using IVUS.[34] The DK-CRUSH V study[35] demonstrated better results in one year with the double kissing crush technique when compared with provisional stenting, in terms of treatment failure (5% versus 10.7%, P = 0.02) and risk of stent thrombosis (0.4% versus 3.3%, P = 0.02). These technical details are important and may have an influence on clinical outcomes and should be specifically addressed in upcoming trials.

Controversies and perspectives

The publication of the 5-year results of the EXCEL study brought controversies.[29] In this article, the risk of death, MI and stroke was similar between surgical and catheter revascularizations (19.2% with CABG and 22% with PCI; P = 0.13). The list of authors, however, did not include David Taggart, the Principal Investigator of the surgical group. He requested the removal of his name from the publication for two reasons: the primary endpoints of the study had been altered to favor PCI, and reduction in mortality, observed in favor of surgery (13.0% versus 9.9%, OR 1.38; 95% CI 1.03 –1.85; p = 0.002), had not been the central focus of the publication. Another point of controversy was the definition used for MI in the study, which was not in accordance with the universal definition of infarction.[36] The study developed and applied a new criterion, which had no previous evidence of clinical relevance. Its definition disfavors the surgical result, since small enzymatic changes are expected in the postoperative period, due to manipulation of myocardial tissue, without necessarily representing a clinically significant myocardial injury.[37]

The definition of MI can significantly change the incidence of periprocedural infarction. Cho et al.[38] demonstrated that in PCI, as compared with CABG, the incidence of infarction varies according to the applied criteria: 18.7% against 2.9% using the second universal definition, 3.2% against 1.9% using the third universal definition and 5.6% against 18.3% according to the Society for criteria Cardiovascular Angiography and Interventions criteria. Accordingly, the incidence of perioperative MI in the EXCEL study (6.2%)[16] was much higher than that observed in the FREEDOM (1.7%) and SYNTAX (2.9%) studies. The biochemical definition of infarction and the inclusion of this variable as a part of the primary outcome statistically favors PCI. In addition, previous studies comparing CABG and PCI have not clearly shown that periprocedural infarction influences long-term outcomes.[39] However, after the 30-day period, the risk of death, stroke or heart attack was 44% higher in the PCI group than in the CABG group (11.5% vs 7.9%; p = 0.02).

The study's lead author, Gregg Stone, agreed that mortality was higher in the ACTP group, but diminished the importance of the finding by claiming that the study had no statistical power to assess mortality, despite the large relative difference of 38%. Although the EXCEL study had 1,905 patients, the initial plan was to include 2,634 patients, but it was reduced due to a lower than expected recruitment rate.

Following the emergence of controversies related to the EXCEL study, the European Society of Cardiothoracic Surgery withdrew its support for the myocardial revascularization guidelines,[5] claiming that it is not safe to recommend decision making on LCMA disease treatment based on the local Heart Team. In response, the study sponsors called for an independent audit to analyze the results.

Due to these statements, other societies have also issued statement on LMCA disease treatment. American surgeons, through the Society of Thoracic Surgeons, reported that the final interpretation of the outcomes of the EXCEL study should await independent analysis. The Brazilian Society of Cardiovascular Surgery accompanied the European society and suggested that the recommendations in the LMCA disease chapter of the European guideline should be disregarded.

On the other hand, the ESC maintained its position, claiming that the guidelines are also based on other studies, but that it could be changed accordingly to new evidence. Meanwhile, interventional cardiology societies, both Brazilian (SBHCI) and American (SCAI) have supported the current the guidelines. They believe that there isn´t enough evidence to justify a new recommendation.

Conclusions

It is widely recognized that the left main is easily accessible by catheter, making it possible to perform PCI safely and with good immediate results when the lesion is in the proximal or medial part of the artery. The question is whether medium and long-term results are equivalent to the surgical results, which have been supported by clinical studies and registries through decades of follow-up.

Previous clinical registries, *i.e.*, data obtained outside clinical trials, showed higher rates of MI, higher rates of cardiovascular events and higher medium and long-term mortality when PCI was compared with CABG. Meanwhile, recent clinical trials have shown the viability of percutaneous treatment, with immediate outcomes similar to surgical ones, especially in cases of low anatomy complexity, as in proximal lesions away from the bifurcation and in the absence of significant disease of other major vessels.

However, survival curves between the two forms of treatment dissociate in favor of greater survival in the surgical series during longer follow-up, as is generally observed when the PCI and CABG are compared. Difference becomes clearer as the complexity of the lesions increases and are highlighted when the anterior descending artery is also affected, in patients with diabetes and in the presence of ventricular dysfunction.

Such evidence must be considered in choosing the best option for each patient. PCI should be chosen for patients with less complex anatomy, elderly with reduced life expectancy, patients at high surgical risk, patients with important comorbidities, and for situations when the immediate clinical benefit is more important than the long-term results. We summarize this approach in a flowchart (Figure 1).

Individualization of treatment, including a complete review by the Heart Team composed of enlightened professionals with no conflict of interests and who prioritize patient´s benefit is fundamental for good practice in the treatment of left main disease.

Author contributions

Conception and design of the research: Kalil RAK, Sant´Anna RT, Salles FD. Writing of the manuscript: Kalil RAK, Sant´Anna RT, Salles FD. Critical revision of the manuscript for intellectual content: Kalil RAK, Sant´Anna RT, Salles FD.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

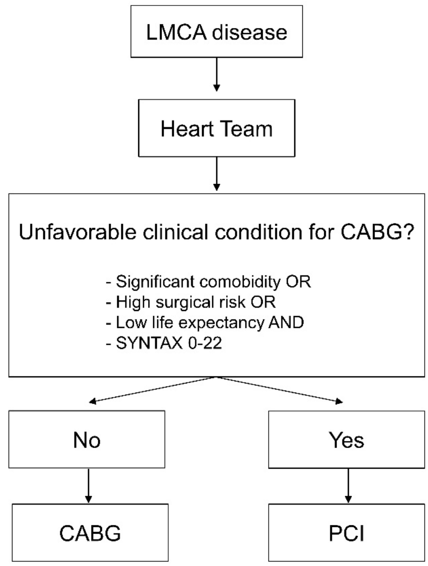

Figure 1 – Flowchart of the approach proposed for left main disease. LMCA: left main coronary artery; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention (PCI)

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