



## EDITORIAL COMMENT

## Left main disease: Have late trial results changed our knowledge and practice?



### Doença do tronco comum: os resultados tardios dos ensaios mudaram o nosso conhecimento e prática?

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In this issue of the *Journal*, Manuel Martins presents a thorough review of the best available evidence on percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) for the treatment of left main (LM) coronary artery disease (CAD).<sup>1</sup> In this regard, we will briefly discuss the main findings of each of the trials reviewed.

The SYNTAX trial used first-generation drug-eluting stents and was a landmark trial in cardiovascular medicine. It established the SYNTAX score (SS) as a tool for decision-making in the treatment of CAD and defined which ranges of SS are amenable to both PCI or CABG or better treated by one of the techniques. The 12-month outcomes show that with SS lower than 32, PCI appeared to be similar to CABG, so its less invasive nature made it preferable in most cases. With an SS of 33 or more, CABG was preferable since rates of major adverse cardiac and cerebrovascular events (MACCE) were lower. It is important to note that stroke was more frequent in CABG and repeat revascularization (RR) more frequent in PCI. At five years the results were similar. In its long-term findings (the SYNTAXES trial), which looked mainly at all-cause mortality, similar results were obtained for both

treatments, and SS was not found to influence long-term mortality.

The EXCEL trial compared everolimus-eluting stents to CABG in LM disease with a SS of 32 or less. It showed that 30-day outcomes were favorable to PCI, but the difference was mainly due to periprocedural myocardial infarction. This was related to the definition of periprocedural myocardial infarction, which was changed during the trial. This alteration led to a public conflict among the investigators of the trial, with the lead surgical researcher withdrawing his name from the final publication. Furthermore, the five-year results of this trial were apparently favorable to PCI: symptomatic graft occlusion rates were higher than symptomatic stent restenosis (unlike the findings of the SYNTAX trial, probably due to the use of newer-generation stents). With apparently no clear difference being found between the two revascularization strategies regarding primary outcomes, the less invasive nature of PCI suggested it should be the preferred strategy with a SS under 32, but fine-tuning of the statistical analysis using Bayesian methods has since suggested the opposite conclusion from the EXCEL data, namely that the mean difference for the primary composite outcome was 3% lower for CABG than for PCI, and five-year mortality was slightly lower with CABG than with PCI. Similar

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results were later obtained using Bayesian methods for other previous studies comparing CABG and PCI studies.<sup>2</sup> These inconsistencies in the EXCEL trial led the European Association of Cardiothoracic Surgery to remove its endorsement of the recommendations on LM disease published in the 2018 European Society of Cardiology/European Association for Cardio-thoracic Surgery myocardial revascularisation guidelines, which were based on the EXCEL trial findings.

The EXCEL trial nonetheless managed to offer well-performed recruitment and a good follow-up of a large number of patients and is not to be dismissed as without value.

The NOBLE trial showed a higher event rate for CABG in the first 30 days, and a changing event rate over the five years of the trial. It failed to show the non-inferiority of PCI at five years, due to higher rates of non-procedural MI and revascularization at five years. Interestingly, it also showed higher MACCE rates in PCI patients with lower SS ( $\leq 22$ ).

One-, two-, five- and 10-year results have been published from the PRECOMBAT trial, which was carried out in South Korea. Overall it showed similar outcomes for both revascularization strategies, but with persistently higher ischemia-driven revascularization rates for PCI patients at two, five and 10 years. Other MACCE outcomes were similar and no interaction of SS with MACCE was found.

After summarizing these findings, is a definite conclusion possible? First, CABG is undeniably more aggressive, and the higher rates of stroke, blood transfusion and extended hospital stay associated with it are to be expected. It is also reasonable to assume that a higher SS reflects a patient with greater atherosclerotic burden, so CABG is able to protect these more complex patients more effectively in the long term, since it also protects against future lesions. We find from the SYNTAX trial that low- and intermediate-risk patients are equally suited for CABG and PCI, but stroke is more frequent in the immediate and long term with CABG, while the RR rate is higher with PCI. From the EXCEL trial, despite its shortcomings, we find that despite a higher RR rate for PCI at three years, overall the results were similar in both treatments, and the same was found at five years, except when RR was considered (higher in the PCI group). This is a constant finding in modern trials that is also seen in PRECOMBAT: RR is the main drawback of PCI, while surgical morbidity (and sometimes the stroke rate) is the main

handicap of CABG. These results were corroborated in the meta-analysis by Ahmad et al. mentioned in Martins' paper: most outcomes are similar at five years except RR.

This finding of higher RR rates in PCI has a very different meaning depending on whether the redo procedure is a PCI or a redo CABG, since the latter is normally a complex situation with a high risk in patients for whom normally available donor vessels for grafting may be scarce, while a redo PCI is, excluding anatomically very complex patients, simpler and less risky. Nowadays most patients who undergo RR after CABG receive a PCI, and the risk is not necessarily higher.

So the way forward for surgery is to diminish its morbidity (since it is already the most effective and complete treatment). Potential areas of improvement include total arterial grafting, off-pump surgery, intraoperative graft assessment with transit time flowmetry (graft quality control is a serious drawback of surgery compared to PCI), and improvements in transfusion practices and intensive care. On the other hand, the area in which PCI needs to improve is clearly the RR rate, which may be achieved with better intraprocedural quality control, better patient education and new stents and medical therapy.

Meanwhile, while these large trials suggest PCI may be very safe and effective in many patients, CABG will often still be the best option in young patients with low SS and good clinical status or with low therapeutic adherence.

## Conflicts of interest

The author has no conflicts of interest to declare.

## References

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