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# **CABG vs PCI in the Treatment of Multivessel Coronary Disease: quo vadis?**

## **A review of the evidences**

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### **Introduction**

The optimal treatment of ischemic coronary artery disease (CAD) is still at the center of a vivid debate. A number of randomized trials (RCTs) and a plethora of retrospective studies investigated the outcomes and risk/benefit balance of the two accepted approaches in CAD, namely percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) surgery. These trials have been inspiring the current guidelines, despite the presence of some unsolved questions(1). In this context several efforts have been lavished to elucidate the best treatment for unprotected left main(LM) disease and up to date meta-analyses of RCTs have been performed with this aim (2-6). If the general consensus for LM disease seems to be trending towards the equivalence of PCI and CABG as regard to safety outcomes with an increase in repeat revascularization in PCI and a marginal increase in strokes in CABG (7-11), in the more common situation of multivessel disease (MVD) an acceptable level of agreement has not been reached yet. Several confounding factors inherent to the nature of both RCT and meta-analysis (i.e. statistical underpower, selection bias, inclusion of both left main disease and MVD etc) could have conspired against the possibility to reach an unbiased conclusion. The difficulty to generalise the results to the real-life scenario of CAD might have played an additional role. Moreover, the currently published systematic reviews cumulating the results of the same available RCTs are often in disagreement allowing to perceive the lack of definitive evidence on this topic at the moment. Therefore, we reviewed the current literature and the available meta-analyses on the comparison between PCI and CABG focusing on MVD only.

## **The clinical trials**

Since the advent of drug eluting stents (DES) and the evidence testifying their superiority to bare metal stents(12), several trials have been published investigating PCI outcomes in comparison to CABG. The BEST investigators undertook a RCT to demonstrate non-inferiority of Everolimus eluting stent in respect to CABG. Despite being abandoned for slow recruitment, the trials produced results from more than 800 patients demonstrating an occurrence of the primary endpoint, a composite of death myocardial infarction, or target-vessel revascularization at 2 years, of 11.0% in the patients in the PCI group and of 7.9% in those in the CABG group with a still significant difference at longer follow up (median, 4.6 years (15.3% of the patients in the PCI group and in 10.6% of those in the CABG group))(13)

The SYNTAX trial tested non-inferiority of PCI versus CABG in 1800 patients. Non-inferiority criteria were not met as rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG). This was thought to be due to an increased rate of repeat revascularization (13.5% vs. 5.9) in the PCI group(14)

The CARDia trial was the first examining the treatment of CAD in the subgroup of diabetic patients demonstrating the superiority of CABG in this subset with combined rates of mortality, myocardial infarction, stroke and repeated revascularization of 11.3% in the CABG group and 19.3% in the PCI group at 1 year(15). The FREEDOM trial confirmed these findings in 1900 patients with complex MVD and diabetes demonstrating worse 5-year rates of a composite outcome, including death from any cause, nonfatal myocardial infarction, or nonfatal stroke, in the PCI group (26.6% vs 18.7% in the CABG group). Despite the incidence of stroke was higher in CABG, death and myocardial infarction were significantly higher in the PCI group, leading to the conclusion that diabetic population would best benefit from CABG than PCI(16).

Subsequently, the VA-CARDS investigators reported the results of a randomized trial comparing interventions exclusively with drug-eluting stents and surgery in patients with diabetes with high-complex coronary artery disease. Despite underpowered, all-cause mortality was 5.0% for CABG

and 21% for PCI at 2 years follow-up, while the risk for nonfatal myocardial infarction was 15% for CABG and 6.2% for PCI(17) (Table 1)

### **The meta-analyses**

Despite the significance of the conclusion reached by the mentioned RCTs, several meta-analyses have been performed with the aim to circumvent the issues of under-powering hindering the design of the clinical trials.

Our group performed a systematic review and meta-analysis of 5 RCTs including a total of 4563 patients with MVD(18). PCI with DES was associated with a 154% increased relative risk of repeat revascularization, late mortality (increased by 51%) and MI (increased by 102%) in respect to CABG. On the other side CABG was hampered by a 29% increase risk of stroke, but the absolute risk increase in stroke was minimal in comparison with the absolute risk reduction in mortality and MI. A number-to-treat analysis demonstrated that preferring CABG over DES-PCI in 100 subjects, 3–4 deaths, 4–5 MI and 8–9 repeat revascularizations would be prevented at the expense of 1 extra stroke after an average follow-up of 3.4 years. Interestingly, subgroup analysis suggested the idea that CABG would improve survival and minimize the risk of subsequent MI independently on the presence of diabetes. Conversely, the increased risk of stroke associated to CABG, might be of clinical significance only in diabetic patients.

Moreover, the results of this meta-analysis dispelled the dogma assuming that the survival benefit guaranteed by CABG is only relevant to three vessel disease. Conversely, CABG benefit was also significant in the presence of two vessel disease and/or proximal left descending artery disease. On the other hand, data showed that the increased risk of subsequent MI following DES-PCI was likely to be significant only in cases of three vessel disease(18).

Another large meta-analysis including 7 randomized controlled trials for a total 5,835 patients confirmed the results of the previously mentioned study, demonstrating a reduction in the mortality

risk, myocardial infarction and repeated revascularization in CABG versus first generation DES at the expense of an increased stroke risk(19).

Sipahi and colleagues performed another review including 6 randomized studies (N= 6055) and their meta-analysis showed a significant reduction in total mortality, MI, and repeat revascularization with CABG compared with PCI(20). However, unlikely the previous, these authors only found a trend toward excess strokes with CABG which was not significant. Conclusion drawn pointed at CABG as the best treatment option in patients with MVD compared with PCI because leading to an undisputable reduction in long-term mortality and myocardial infarctions and to reduction in repeat revascularizations, regardless presence of diabetes(20).

An interesting work has been more recently reported by Fanari and colleagues, who performed a meta-analysis of 6 RCTs and investigated the results of the long-term follow-up of the studies.

Despite potentially biased because of the presence of an additional RCT involving unprotected LM disease(21), this study demonstrated that at one year PCI was associated with a significantly higher incidence of target vessel revascularization, lower incidence of stroke and no difference in death or MI compared to CABG. However, at 5 years, PCI was associated with a higher incidence of death and MI. Increased mortality in the PCI group was mainly found in diabetics(22).

An ad hoc meta-analysis on MVD in the diabetic population including 14 studies (5 RCT and 9 observational) documented a much higher risk of repeat intervention and adverse cardiovascular /cerebrovascular events in the DES/PCI cohort compared to CABG, although early morbidities seemed to favour percutaneous procedures(23).

A previous similar study on diabetic population confirmed that CABG in diabetic patients with MVD at low to intermediate surgical risk (defined as EUROSCORE <5) is superior to MVD PCI with DES. Despite an increase in stroke risk, CABG reduced overall death, nonfatal myocardial infarction, and repeat revascularization(24).

In a meta-regression analysis using event rates as a dependent variable to test for an interaction between baseline clinical features (age, gender, diabetes mellitus, previous myocardial infarction

and ejection fraction) and choice of revascularization, D'Ascenzo et al. concluded that PCI significantly reduces the risk of stroke compared to CABG particularly in female patients, but the risk of revascularization is increased with PCI, especially in women and in those with diabetes(25). An interesting point raised by the literature of meta-analysis and systematic review in CAD regards the comparison of outcomes in complete or incomplete revascularization. An initial large study including 35 studies and 89,883 patients, demonstrated as complete revascularization is more commonly achieved with CABG than PCI and that incompleteness of revascularization is associated to increased mortality and repeated revascularization independently on the mode of treatment(26). Subsequently, Zimarino and colleagues echoed those results in another meta-analysis of 28 studies reporting on clinical outcomes of MVD patients treated with complete and incomplete revascularization, with extensive (>80%) use of stents for PCI or arterial conduits in CABG. They achieved similar results and demonstrated a larger clinical benefit of complete revascularization in diabetic patients. Interestingly, the survival benefit and reduction in relative risk of cardiovascular events was better in the patients enrolled in the more recent studies(27).

More recently, Lee et al. in a meta-analysis of 3280 patients pooled results from the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease), PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery vs. Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease), and SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trials. The study was focused on a composite outcome including of all-cause death, myocardial infarction, or stroke. The results showed that CABG, as compared with PCI with DES, decreased long-term rates of the composite outcome and repeat revascularization as compared with DES-PCI in left main or MVD, although the advantage of CABG was more pronounced in the latter subcategory(10).

Nevertheless, in a very recent systematic review appeared in The Lancet by Head and colleagues including 11 randomised trials and involving a total of 11 518 patients, equivalence in the long-term

safety outcomes was demonstrated between the modalities of revascularization for unprotected LM disease. Conversely, the benefit of CABG was restricted to complex MVD and diabetic patients(28) (Table 2).

## **Discussion**

The optimal treatment strategy for CAD remains controversial as testified by the contradictory conclusions reached even in the context of meta-analyses of the same RCTs. Although some standpoints, as the higher risk of repeat revascularization and cardiovascular event in DES-PCI remain consistent throughout the literature, the hard endpoints regarding early mortality, long-term survival and strokes are constantly put in doubt by subsequent study sub-analyses. The reason underlying this uncertainty might find its root in the low power and statistical bias inherent in some of the studies included in the systematic reviews. The mortality rate of treated CAD has dramatically reduced over the years independently on the mode of revascularization adopted. Consequently, conspicuous sample size are required to achieve significance diminishing the power of these studies. If on a side this demands for new event-driven designed trials, on the other makes very difficult the interpretation and reliability of the results reached by both RCTs and their systematic reviews and meta-analyses. The composite primary endpoint of major cerebrovascular and cardiac adverse events (MACCE) recurrently described in every RCT represents a product of this issue and has been introduced to avoid the power limitations of these trials.

From the review of both trials and meta-analyses it appears that the main pillar sustaining the benefit of CABG compared to PCI is the reduced rate of repeat revascularizations, as the weight of the lower rate of MACCEs is jeopardized by the relative increased incidence of stroke in this group. However, repeat revascularization is considered a “soft” endpoint and no trial seems to have been adequately powered to assess the more important endpoint of mortality(29). Even the most recent

study by Head et al. recruiting a sample size of more than 11.500 patients, despite confirming the superiority of CABG for MVD in diabetic patients has been criticized (vedi Articolo di Domenico Pagano che mi dicevi...scusa ma non lo riesco a trovare)

An interesting point emerging from the analysis of the literature is the issue of incomplete revascularization in the two modes of revascularization. Very recently, Hannah et al. reported the results of an interesting registry analysis on the outcomes of incomplete revascularization(IR) in PCI in a very large cohort of patients(30). The results of the study somehow echo the conclusion of the most recent follow-up of the SYNTAX study by Milojevic et al. in which authors demonstrated that IR was an independent predictor of mortality in the PCI group. Interestingly, in the SYNTAX trial, IR did not increase the risk of death or cardiac adverse events in the CABG arm of the study(31). These results reflect the findings of an analysis of the NICOR database including 13701 patients undergone CABG, in which after propensity score matching, IR did not increase all-cause death in the overall group(32). Interrogatives regarding the mechanisms underlying this apparent inefficacy of PCI in IR still remains unsolved. Chronic total occlusion, difficult to manage percutaneously, and post-procedural MI, exacerbating the already incomplete revascularization, have been advocated as a culprit factors in determining mortality in PCI(33). However, despite these events might similarly occur in surgical settings, they do not constitute a significant risk factor for CABG patients. From the BARI trial we learnt that grafting LIMA to LAD determines survival independently by the presence of other grafts and that it seems there is no a direct numeric correlation between grafts and coronary lesions to achieve clinical benefit(34). On the other side, arterial grafts, have been shown to release high quantity of nitric oxide(NO), a known inducer of angiogenesis, and this is thought to be one of the factors at the basis of the superior outcome of these conduits in CABG(35). It has been hypothesized that intramyocardial delivery of NO through the graft together with the neoangiogenetic drive initiated by the reperfusion might account for the creation of a progressively spreading microvascular network of neocapillaries within the affected



myocardium, territorially expanding from the region directly subjected to revascularization to the adjacent territories, therefore restoring function of ungrafted regions(36). This hypothesis finds a clinical correlate in the analysis of the NICOR registry in which when large territories tributary of the right coronary artery or the circumflex artery remain unrevascularized late survival was reduced(32). More ad hoc studies are required to elucidate the pathophysiological mechanisms and the consequent optimal strategy to be adopted in this circumstances.

Another point of discussion relies on the fact that the currently available RCTs are comparing the newest generation of stenting technology with a relatively “old-fashioned” operation in which the patency rate and durability of venous grafts is widely known to be limited. On account of the evidence testifying the longer-term durability of CABG performed with a total arterial technique, a more adequate comparison would be performed among the newest stenting technology and more modern grafting strategies (i.e. total arterial revascularization).

This point acquires even more significance when noting that the majority of the trials and reviews, despite showing non-inferiority of PCI in respect to CABG for the safety endpoints in the immediate postoperative period, fail to demonstrate a sustained benefit of percutaneous interventions over the long-term. CABG seems to outperform PCI in the long-term with conduits known to have a limited life. We could imagine that even more interesting results would arise from the comparison of the long-term data of multiple arterial grafting trials, as the ART trial(37), with the long-term durability of the newest generation DES.

In conclusion, CABG remains the best revascularization strategy in MVD especially in diabetics, as carrying reduced mortality and repeat revascularization risk. The absolute risk increase in stroke

associated with CABG does not outweigh the benefit in the long-term survival achievable with this technique of revascularization.

The conclusions reached by the currently available studies should anyway be considered carefully when translating the results to the real life scenario which is constituted by a variegated case mix with multiple comorbidities. In this context, the importance of the Heart Team emerges even more significantly.

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