Perspective

Coronary artery bypass grafting (CABG) *vs.* percutaneous coronary intervention (PCI) in the treatment of multivessel coronary disease: quo vadis? —a review of the evidences on coronary artery disease

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The optimal treatment of ischemic coronary artery disease (CAD) is still controversial. A number of randomized controlled trials (RCT) and several meta-analyses have been performed and are inspiring the current guidelines. However, a univocal consensus on the optimal therapeutic strategy for multivessel disease has still not been reached yet. We reviewed the current evidence on this topic, focusing on both RCT and meta-analyses. From both short and long-term studies, it emerges that in patients with multivessel disease, coronary artery bypass grafting (CABG) is associated with better survival, lower rates of major cardiovascular events (specifically myocardial infarction or stroke) and repeat revascularization as compared with percutaneous coronary intervention (PCI) with drug-eluting stents.

Keywords: Coronary artery bypass grafting (CABG); percutaneous coronary intervention (PCI); multivessel disease (MVD)

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Introduction

The optimal treatment of ischemic coronary artery disease (CAD) is still at the center of a heated 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 inspired the current guidelines, despite the presence of some unsolved questions (1). In this context, efforts have been undertaken in order 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 in mind (2-6). If the general consensus for LM disease seems to be trending towards the equivalence of PCI and CABG with regards 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-analyses (i.e., statistical underpower, selection bias, inclusion of both LM disease and MVD, etc.) could have conspired against the possibility to reach an unbiased conclusion. The difficulty in generalizing 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 available RCTs are often in disagreement, preventing a definitive analysis of the evidence on the topic at present. Therefore, we reviewed

the current literature and the available meta-analyses data 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 attesting to their superiority over bare metal stents (12), several trials have been published investigating PCI outcomes in comparison to CABG. The BEST investigators undertook an RCT to demonstrate non-inferiority of Everolimus eluting stent in respect to CABG. Despite being abandoned due to slow recruitment, the trials produced results from more than 800 patients, demonstrating an occurrence of the primary endpoint, a composite of death due to myocardial infarction (MI) 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 1,800 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 (14,15). The CARDia trial was the first examining the treatment of CAD in a subgroup of diabetic patients, demonstrating the superiority of CABG in this subset with combined rates of mortality, MI, stroke and repeated revascularization of 11.3% in the CABG group and 19.3% in the PCI group at 1 year (16). The FREEDOM trial confirmed these findings in 1,900 patients with complex MVD and diabetes, demonstrating comparatively worse 5-year rates of a composite outcome, including death from any cause, nonfatal MI, or nonfatal stroke, in the PCI group (26.6% *vs.* 18.7% in the CABG group). Despite the incidence of stroke being higher in CABG cohort, death and MI were significantly higher in the PCI group, leading to the conclusion that diabetic population would best benefit from CABG rather than PCI (17).

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 and high-complex CAD. Despite being underpowered, all-cause mortality was 5.0% for CABG and 21% for PCI at 2 years follow-up, while the risk for nonfatal MI was 15% for CABG and 6.2% for PCI (18) (*Table 1*).

The meta-analyses

Despite the significance of the conclusion reached by the aforementioned RCTs, several meta-analyses have been performed with the aim of circumventing the issues pertaining to being under-powered.

Our group performed a systematic review and meta-analysis of five RCTs, encompassing a total of 4,563 patients with MVD (19). PCI with DES was associated with a 154% increased relative risk of repeat revascularization, late mortality (increased by 51%) and MI (increased by 102%) when compared to CABG. On the hand, CABG was hampered by a 29% increase risk of stroke, but the absolute risk increase in stroke was minimal when compared with the absolute risk reduction in mortality and MI. A number-to-treat analysis demonstrated that placing 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 one extra stroke after an average follow-up of 3.4 years. Interestingly, subgroup analysis suggested that CABG would improve survival and minimize the risk of subsequent MI independent of the presence of diabetes. Conversely, the increased risk of stroke associated with CABG might be of clinical significance only in diabetic patients.

Moreover, the results of this meta-analysis refuted the existing dogmatic view that the survival benefit guaranteed by CABG is only relevant to three-vessel disease. Conversely, the benefit of CABG 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 (19).

Another large meta-analysis encompassing seven RCTs for a total 5,835 patients confirmed the results of the previously mentioned study, demonstrating a reduction in the mortality risk, MI and repeated revascularization in CABG versus first generation DES, at the expense of an increased stroke risk (20).

Sipahi and colleagues performed another review including six randomized studies (N=6,055), with their meta-analysis illustrating a significant reduction in total mortality, MI, and repeat revascularization with CABG compared with PCI (21). However, unlike the previous

Table 1 Overview of randomized controlled trials

Study (year of publication)	Country	Inclusion criteria	Syntax score mean (≥33)	Number of vessels diseased	Patients assigned		Mean age (years)	Male gender	Medically treated diabetes (on insulin)	Stents used	Median follow-up (years)
					CABG	DES-PCI					
CARDia, 2010 (16)	United Kingdom and Ireland	Diabetics with multivessel disease including PLAD	NR	3VD: 63% 2VD: 32% PLAD: 5%	242	248	64	74%	100% (38%)	SES (69%) BMS (31%)	1
FREEDOM, 2012 (17)	Multinational	Diabetes and stenosis of more than 70% in two or more major epicardial vessels	26 (19%)	3VD: 83% 2VD: 17%	947	953	63	71%	100% (32%)	SES (51%) PES (43%)	3.8
VA CARDS, 2013 (18)	US	Diabetics with multivessel disease including PLAD	22 (13%)	3VD: 63% 2VD: 24% PLAD: 13%	97	101	62	99%	100% (47%)	SES (20%) PES (35%) EES (18%) ZES (2%) MIXED (16%) BMS (1%)	2
SYNTAX*, 2014 (15)	Multinational	Significant stenosis in vessels supplying all three major epicardial territories	28, NR	3VD: 100% 2VD: 0%	549	546	64	80%	27% (11%)	PES	5
BEST TRIAL, 2015 (13)	South Korea, China, Malaysia, and Thailand	Stenosis of more than 70% of the vessel diameter in major epicardial vessels in the territories of at least two coronary arteries	24 (16%)	3VD: 77% 2VD: 23%	442	438	64	72%	41% (4%)	EES	2

*, subgroup analysis. 3VD, three-vessel disease; 2VD, two-vessel disease; PLAD, proximal left anterior descending artery disease; DES-PCI, drug-eluting stent percutaneous coronary intervention; CABG: coronary artery bypass grafting; BMS, bare-metal stent; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stent; EES, everolimus eluting stent; NR, not reported.

studies, these authors found a trend toward excess strokes with CABG, but this was not significant. The conclusions drawn suggest CABG as the best treatment option in patients with MVD compared with PCI, given the undisputable reduction in long-term mortality, MIs and repeat revascularizations, irrespective of the presence of diabetes (21).

An interesting work has been recently reported by Fanari and colleagues, who performed a meta-analysis of six RCTs and investigated the results of the long-term follow-up of the studies. Despite potential bias due to the presence of an additional RCT involving unprotected LM disease (22), this study demonstrated that at 1 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 (23).

An ad hoc meta-analysis on MVD in the diabetic population encompassing 14 studies (five RCTs and nine 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 favor percutaneous procedures (24).

A previous and 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 MI, and repeat revascularization (25).

In a meta-regression analysis using event rates as a dependent variable to test for an interaction between baseline clinical features (i.e., age, gender, diabetes mellitus, previous MI 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 (26).

An interesting point has been raised in meta-analyses and systematic reviews on CAD with respect to the comparison of outcomes in complete or incomplete revascularization. A large preliminary investigation, including 35 studies and 89,883 patients, demonstrated that complete revascularization is more commonly achieved with CABG rather than PCI, and that incompleteness of revascularization is associated to increased mortality and repeated revascularization independently on the mode of treatment (27). 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 (28).

More recently, Lee *et al.* in a meta-analysis of 3,280 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, MI, or stroke.

The results showed that CABG, as compared with PCI with DES, decreased long-term rates of the composite outcome and repeat revascularization, when compared with DES-PCI in LM or MVD, although the advantage of CABG was more pronounced in the latter subcategory (10).

Chang *et al.* reported the results of a patient-level meta-analysis comparing the effect of CABG versus PCI with DES on long-term mortality in 1,275 nondiabetic patients with multivessel CAD. Results showed superiority of CABG in terms of short and long-term mortality, MI and repeat revascularization, in absence of significant group differences as far as stroke was concerned. The conclusions drawn echoed previous results and demonstrated superiority of CABG also in nondiabetic patients with multivessel CAD (29).

In a pooled analysis of individual patient-level data of the SYNTAX and BEST randomized trials, Cavalcante *et al.* analyzed the outcomes of 1,166 patients in which 577 were randomized to PCI and 589 to CABG. In patients with MVD with proximal left anterior descending artery (LAD) involvement, CABG is associated with a significantly lower rate of cardiac death, MI and all-cause revascularization when compared with DES-PCI. There was no difference among the groups as far as all-cause mortality and stroke

were concerned, but the combined outcome of major adverse cardiovascular and cerebrovascular events (i.e., all-cause death, MI, stroke, revascularization) favored CABG. The authors concluded that in patients with MVD CABG was superior in terms of survival and cardiovascular events to drug-eluting stents at 5 years of follow-up (30).

Nevertheless, a recent systematic review featured in *The Lancet* by Head and colleagues, including 11 randomized trials and involving a total of 11,518 patients, illustrated equivalence in the long-term safety outcomes between the modalities of revascularization for unprotected LM disease. Conversely, the benefit of CABG was restricted to complex MVD and diabetic patients (31) (*Table 2*).

Discussion

The optimal treatment strategy for CAD remains controversial, as illustrated by the contradictory conclusions reached even in the context of meta-analyses of the same RCTs. Although some standpoints, such 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 of the mode of revascularization adopted. Consequently, conspicuous sample sizes are required to achieve significance, given the diminishing power of these studies. On one side, this calls for new event-driven designed trials, and on the other, it makes the interpretation and reliability of the results reached by both RCTs and their systematic reviews/meta-analyses rather difficult. 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 the 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

Table 2 Overview of meta-analyses

Author, date	Studies included	Total number of patients	Years at follow-up	Mortality	Myocardial infarction (MI)	Stroke or cerebrovascular event	Repeat revascularization (RR)	Notes
Hakeem *et al.*, 2013 (25)	4 RCTs	3,052	4 years	Favors CABG	Favors CABG	Favors PCI	Favors CABG	CABG in diabetic patients with MVD at low to intermediate surgical risk (EuroSCORE <5) is superior to MVD PCI with DES
Garcia *et al.*, 2013 (27)	35 studies	89,883	–	–	–	–	–	Complete revascularization is more commonly achieved with CABG than PCI Incomplete revascularization has increased mortality and RR independently on the mode of treatment
Al Ali *et al.*, 2014 (20)	7 RCTs; MVD + LMD	5,835	6 months–5 years	Favors CABG	Favors CABG	Favors PCI	Favors CABG	In MVD patients, CABG reduced the risk of mortality, but increased stroke In patients with LM disease, CABG reduced revascularization risk and increased stroke risk

Table 2 (*continued*)

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Author, date	Studies included	Total number of patients	Years at follow-up	Mortality	Myocardial infarction (MI)	Stroke or cerebrovascular event	Repeat revascularization (RR)	Notes
Sipahi *et al.*, 2014 (21)	6 RCT	6,055	4.1 years	Favors CABG	Favors CABG	Non-significant	Favors CABG	CABG is superior to PCI independently on diabetes
Lim *et al.*, 2014 (24)	5 RCT; 9 OBS	5,000	3 to 5 years	Favors CABG	Favors CABG	30 days: favours PCI; 1–5 years: non-significant	Favors CABG	Cardiovascular/cerebrovascular event were 1.71 times higher in the DES/PCI
D'Ascenzo *et al.*, 2014 (26)	20 RCT; aimed at correlating risk factors	12,844	30 days to 1 year	Favors CABG	Favors CABG	Favors PCI	Favors CABG	PCI reduces the risk of stroke in female patients: PCI has increased risk of RR risk in women and in those with diabetes
Fanari *et al.*, 2015 (23)	6 RCT	5,123	1 and 5 years	1-year: non-significant; 5-year: favors CABG	1 year: non-significant; 5 years: favours CABG	Favors PCI	Favors CABG	Increased death in diabetics with PCI
Zimarino *et al.*, 2016 (28)	28 studies	83,695	4.7 ± 4.3 years	–	–	–	–	CR confers benefit on outcomes more evident in diabetics
Benedetto *et al.*, 2016 (19)	5 RCT	4,563	3.4 years	Favors CABG	Favors CABG	Favors PCI	Favors CABG	PCI increase mortality by 51%; PCI increase MI by 102%; CABG increase stroke by 29%
Lee *et al.*, 2016 (10)	3 RCT; MVD + LMD	3,280	5 years	MVD: favors CABG; LMD: non-significant	MVD: favors CABG; LMD: favors CABG	Non-significant	Favors CABG	Overall CABG educed long-term rates of the composite of all-cause death, myocardial infarction, or stroke in patients with LMD and MVD Benefit of CABG more pronounced in MVD
Chang *et al.*, 2016 (29)	BEST + SYNTAX in non-diabetics	1,275	62 months	Favors CABG	Favors CABG	No differences	Favors CABG	CABG, as compared with DES-PCI educed the long-term risk of mortality in nondiabetic patients with MVD CAD
Cavalcante *et al.*, 2017 (30)	BEST + SYNTAX	1,166	5 years	Favors CABG	Favors CABG	No differences	Favors CABG	In MVD with proximal LAD involvement, CABG has lower rates of the composite endpoint of death, MI or stroke
Head *et al.*, 2018 (31)	11 RCT; MVD + LMD	11,518	5 years	Favors CABG in complex MVD and diabetes; LMD: non-significant	–	–	–	CABG benefit restricted to MVD + diabetes Equivalence for LMD Equivalence for MVD in non-diabetic patients

MVD, multivessel disease; LMD, left main disease; CR, complete revascularization; DES-PCI, Drug-eluting stents percutaneous coronary intervention; OBS, observational; RCT, randomized controlled trial; CABG, coronary artery bypass grafting; CAD, cardiovascular disease.

endpoint of mortality (32). Even the most recent study by Head *et al.* (31) with a sample size of more than 11,500 patients, despite confirming the superiority of CABG for MVD in diabetic patients, is not in agreement with the meta-analyses published immediately prior by Chang *et al.* (29) and Cavalcante *et al.* (30).

An interesting point that is emerging from the analysis of the literature is that of the issue of incomplete revascularization in the two modes of revascularization. Very recently, Hannan *et al.* reported the results of an interesting registry analysis on the outcomes of incomplete revascularization in PCI in a very large cohort of patients (33). 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 incomplete revascularization was an independent predictor of mortality in the PCI group. Interestingly, in the SYNTAX trial, incomplete revascularization did not increase the risk of death or cardiac adverse events in the CABG arm of the study (34). These results reflect the findings of an analysis of the NICOR database including 13,701 patients who underwent CABG. After propensity score matching, incomplete revascularization did not increase all-cause death in the group (35). The mechanisms underlying this apparent inefficacy of PCI in incomplete revascularization still remains unsolved. Chronic total occlusion—which is difficult to manage percutaneously—and post-procedural MI exacerbate the already incomplete revascularization, have been advocated as culprit factors in determining mortality in PCI (36).

These events might similarly occur in surgical settings, however, they do not constitute a significant risk factor for CABG patients. From the BARI trial, we learnt that grafting left internal mammary artery (LIMA) to LAD determines survival independently of the presence of other grafts and that it seems that there is no direct numeric correlation between grafts and coronary lesions to achieve clinical benefit (37). On the other hand, arterial grafts have been shown to release high quantities of nitric oxide (NO), a known inducer of angiogenesis, and this is thought to be one of the factors at the crux of the superior outcomes of these conduits in CABG (38). It has been hypothesized that intramyocardial delivery of NO through the graft, together with the neoangiogenic drive initiated by the reperfusion, may account for the creation of a progressively spreading microvascular network of neocapillaries within the affected myocardium. These territorially expand from the region directly subjected to revascularization to the adjacent territories, therefore restoring the function of ungrafted regions (39).

This hypothesis finds a clinical correlate in the analysis of the NICOR registry, in which large territories that are tributaries of the right coronary artery or the circumflex artery remain unrevascularized leading to a reduction in late survival (35). More *ad hoc* studies are required to elucidate the pathophysiological mechanisms and the consequent optimal strategy to be adopted in these circumstances.

Another point of discussion centers on the fact that the currently available RCTs are comparing the newest generation of stenting technology with a relatively "old-fashioned" operation; the patency rate and durability of venous grafts is widely known to be limited. On account of the evidence testifying to 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 is even more significant when noting that the majority of the trials and reviews, despite showing non-inferiority of PCI with 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 compelling results would arise from the comparison of the long-term data of multiple arterial grafting trials, such as the ART trial (40), with the long-term durability of the newest generation DES.

Summarizing the current evidence from the largest RCTs, SYNTAX demonstrated superiority of CABG in cases of SYNTAX scores >22 (15). The BEST (13) and FREEDOM (17) trials showed the same superiority, irrespective of the SYNTAX score. A large patient level meta-analysis, combining the results of SYNTAX and BEST trials, concluded that CABG offers improved outcomes when compared to DES-PCI in both and non-diabetic and in MVD (2 or 3 vessels involved) with proximal LAD involvement (30).

In conclusion, CABG remains the best revascularization strategy in MVD, conferring reduced mortality and repeat revascularization risk. The absolute risk increases 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 be considered carefully when translating the results to the real-life scenarios, which are often inclusive of variegate case mixes with multiple comorbidities. In this context, the importance of the Heart Team is profound.

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Footnote

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