CABG Versus PCI in the Treatment of Diabetic Patients Affected by Coronary Artery Disease
Which is the Best Option?
Francesco Nicolini,1 MD, Andrea Agostinelli,2 MD, Antonella Vezzani,2 MD, Filippo Benassi,2 MD, and Tiziano Gherli,1 MD

SUMMARY
Surgical coronary revascularization and percutaneous coronary intervention were demonstrated to be effective treatments for coronary artery disease. However, the optimal revascularization strategy remains unclear in certain patient subsets. The recently published Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial is a randomized study evaluating the use of CABG versus PCI in diabetic patients with multivessel coronary disease. The purpose of this study was to review the available literature based on randomized trials and observational studies in order to allow clinicians to make evidence-based decisions when treating diabetic patients with multivessel coronary disease. The current evidence suggests that CABG should remain the standard of care for this patient population. (Int Heart J 2014; 55: 469-473)

Key words: Coronary artery bypass grafting, Percutaneous coronary interventions, Diabetes mellitus

Diabetes mellitus (DM) is a key constituent of the metabolic syndrome, which is increasingly prevalent in Western countries; moreover, DM is a well-demonstrated independent risk factor for coronary heart disease. Patients with diabetes mellitus and coronary artery disease (CAD) often have severe and diffuse atherosclerotic involvement of multiple epicardial coronary arteries. It is therefore not surprising that DM is found in approximately one quarter of patients presenting for angiography following an acute coronary syndrome. Consequently, a large number of diabetic patients need multivessel coronary revascularization, either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).

Historically, the Bypass Angioplasty Revascularization (BARI) Investigators suggested improved outcomes with CABG versus PCI, confirmed by meta-analysis of randomized controlled trials of either balloon angioplasty or bare metal stents (BMS) versus CABG. Explanations of these results are largely based on the well documented higher rate of in-stent restenosis and subsequent target vessel revascularization with PCI. The introduction of drug-eluting stents (DES) in clinical practice led to a consistent reduction of in-stent restenosis and target vessel revascularization, even in diabetic patients, although no effect on mortality and myocardial infarction (MI) rates compared with BMS was reported.

Recent observational studies and a meta-analysis of these studies have suggested comparable outcomes of multivessel PCI with DES and CABG in diabetic patients. On the other hand, other observational single-center or registry studies demonstrated that the diabetic cohort receiving PCI experienced worse results than the CABG cohort in terms of both safety and efficacy. However, it is well known that retrospective studies provide a “real world” picture but their value is limited by the selection bias for treatment allocation related to their observational nature. Randomized controlled trials remain the benchmark for comparing the efficacy of both invasive treatments of these patients.

The focus of this review is to compare the results of PCI with CABG for the treatment of stable CAD in patients with DM.

Randomized Controlled Trials
Initial considerations about the optimal invasive treatment of diabetic patients affected by CAD were derived from results obtained by the Bypass Angioplasty Revascularization Investigation (BARI) trial (and registry), comparing revascularization strategies of CABG and PCI. This trial was designed in the era of old balloon angioplasty, but a significant difference was evident in the 5-year survival rates in the subgroup of randomized patients with medically treated DM, who had 65.5% survival in the PCI group and 80.6% survival in the CABG group. In the remaining randomized BARI population 5-year survival was described as essentially equal. These results were confirmed in the final 10-year follow-up with respective sur-
The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2 D) trial assigned 2368 patients with both type 2 diabetes and heart disease to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy. Patients were selected either for CABG or PCI as the more appropriate intervention, and followed for 5 years. The primary end points of death and a composite of death, myocardial infarction, or stroke did not differ significantly in the PCI population between the revascularization group and the medical therapy group. In the CABG patients, the rate of major cardiovascular events was significantly lower in the revascularization group compared with the medical therapy group. At 5 years, the rates of survival did not differ significantly between the revascularization group (88.3%) and the medical-therapy group (87.8%, P = 0.97). The BARI 2 D trial did not randomize the method of revascularization, which remained at the discretion of the cardiologist. The CABG population had more severe and complex coronary anatomy, received an internal mammary artery in 94.2% of patients and a mean of 3.0 ± 1.0 distal anastomoses were performed in this subgroup. On the other hand, only 34.7% of the patients who underwent PCI received a DES, 56.0% received a BMS, and 9.3% of the PCI patients did not receive any stent. In this subgroup a mean of 1.50 ± 0.8 lesions were attempted. In consideration of the intrinsic limitations of the study design and the absence of a statistically significant difference in mortality among CABG and PCI, it is difficult to draw any definitive conclusion about the optimal revascularization strategy in diabetic patients from this trial.

Significant improvements in the field of coronary surgical revascularization with arterial conduits, and in perioperative management have resulted in better surgical outcomes after CABG. Similar advances in the field of interventional cardiology after BARI results, including the advent of DES, and newer antplatelet therapies have raised questions regarding the usefulness of these findings to contemporary patients undergoing PCI or CABG. Moreover, many contemporary studies supporting the superiority of CABG for patients with diabetes mellitus have been published.

A recent randomized trial comparing CABG versus PCI in diabetic patients was the Coronary Artery Revascularization in Diabetes trial. The trial was terminated early because of poor recruitment. At 1 year of follow-up, the composite rates of death, MI and stroke were 10.5% in the CABG group and 13.0% in the PCI group (P = 0.39), all-cause mortality rates were 3.2 and 3.2%, and the rates of death, MI, stroke or repeat revascularization were 11.3 and 19.3% (P = 0.02), respectively. The trial failed to show the noninferiority of PCI compared with CABG at 1 year, while the results of the 5-year follow-up are being awaited.

In 2011, the Arterial Revascularization Therapy Study (ARTS) I and II investigators published 5-year results of the 367 diabetic patients who were enrolled. These included 96 patients who underwent CABG, 112 who received a BMS, and 159 who received a DES. CABG patients reported fewer major adverse cardiac and cerebrovascular events when compared with BMS or DES. In the DES group, this difference was primarily due to the higher rate of repeat revascularizations.

The 10-year outcomes of patients enrolled in the Medicine, Angioplasty, or Surgery Study II (MASS II) trial have been recently published. This trial aimed to compare medical therapy, PCI, and CABG in 232 diabetic patients and 379 non-diabetic patients with multivessel CAD. Endpoints evaluated were overall and cardiac mortality. In a 10-year follow-up, more overall deaths occurred among patients with diabetes than among patients without diabetes (P = 0.001). In this follow-up, the 10-year mortality rates were 32.3% and 23.2% for diabetics and non-diabetics, respectively (P = 0.024). Regarding cardiac mortality, the 10-year cardiac mortality rates were 19.4% and 12.7%, respectively (P = 0.031). Considering only diabetic patients and stratifying this population by treatment strategies, the authors found mortality rates of 31.3% for PCI, 27.5% for CABG, and 37.5% for MT (P = 0.015 for CABG versus medical therapy) and cardiac mortality rates of 18.8%, 12.5% and 26.1%, respectively (P = 0.005 for CABG versus medical therapy). The authors concluded that among patients with stable multivessel CAD and preserved left ventricular ejection fraction, the 3 therapeutic strategies had high rates of overall and cardiac-related deaths among diabetic compared with non-diabetic patients. Better outcomes were observed in diabetic patients undergoing CABG compared to medical therapy in relation to overall and cardiac mortality in a 10-year follow-up.

Of 1800 patients in the SYNTAX trial, 452 had diabetes. The 5-year outcomes for the diabetic sub-group have been recently published. It is well known that the 5-year outcomes of the overall study population support the use of CABG in the setting of complex multivessel disease, but the superiority of CABG was even more evident in patients with diabetes. Among diabetic patients, PCI had worse results than CABG in terms of 5-year rates of major adverse cardiac or cerebrovascular events (MACCE) (46 versus 29%; P < 0.001) and repeat revascularization (35 versus 15%; P < 0.001). While there was no statistically significant difference in the individual components of MACCE because of the relatively small numbers, death (PCI: 19.5% versus CABG: 12.9%; P = 0.065) and MI (PCI: 9.0% versus CABG: 5.4%; P = 0.20) favored CABG while stroke was lower with PCI (PCI: 3.0% versus CABG: 4.7%; P = 0.34). The authors concluded that CABG should be the revascularization strategy of choice in patients with more complex coronary anatomy, particularly in diabetics.

Until the recent publication of the FREEDOM Trial, the relative benefits of CABG and PCI in patients with diabetes remained a matter of debate, particularly because, until the FREEDOM Trial, there was not a single trial in diabetic patients, adequately powered to give a definitive answer about the optimal coronary revascularization strategy in these patients. In fact the FREEDOM trial included more patients with diabetes than the total from all the subgroups from the other randomized trials. Patients in the FREEDOM trial were randomized to PCI with DES or CABG, with or without cardiopulmonary bypass. Any patient with diabetes and non–left main multivessel disease eligible for either CABG or PCI was enrolled, with very limited exclusion criteria. The primary end-point was a composite of all-cause mortality, nonfatal MI, and nonfatal stroke. In contrast to the SYNTAX trial, and most previously published randomized trials, repeat revascularization was not included in the composite primary endpoint. After a median follow-up of 3.8 years (minimum 2 years), CABG
showed a significant advantage in the primary outcome (18.7% versus 26.6%, \( P = 0.005 \)). The cause of the superiority of CABG was the reported lower rate of MI (6.0% versus 13.9%, \( P < 0.0001 \)) and all-cause mortality (10.9% versus 16.3%, \( P = 0.049 \)), compared with the PCI group. In line with previous literature, PCI was associated with a lower incidence of stroke (2.4% versus 5.2%, \( P = 0.034 \)). The relative risk of non-fatal stroke between CABG and PCI was 2.41 at 1 year, narrowing to 1.72 at 5 years.\(^{20}\) The early difference in stroke between the two strategies is almost certainly a consequence of the very well-recognized perioperative risk of stroke of CABG patients, who received a non-maximal anti-platelet medication in the postoperative period with respect to PCI patients.

All these findings provide a strong argument that patients with diabetes are better managed with CABG than with PCI. Interestingly, no interaction was found when patients were stratified by the SYNTAX score, suggesting that diabetic patients do better with CABG regardless of coronary disease complexity. In fact, the superiority of CABG over PCI remained across all of the prespecified subgroups except the geographic area of enrollment, although these subgroup analyses are severely underpowered to assess for differences in clinical outcome and must be interpreted with caution.

Trial data suggested that the advantage related to surgical revascularization for multivessel disease in DM was the wide use of internal mammary artery bypass grafting of the left anterior descending coronary artery. This strategy was associated with reduced mortality and a low rate of nonfatal myocardial infarction. There is significantly increased durability of internal mammary grafts, with 90% patency rates reported at 20 years\(^ {31-33} \) with the use of bilateral mammary arteries in comparison to saphenous vein grafts. However, CABG with bilateral internal mammary arteries (BIMA) is used only in 5% of cases in the United States and 10% in Europe.\(^ {22} \) A meta-analysis from Taggart, et al\(^ {23} \) reported outcomes of BIMA versus single internal mammary artery (SIMA) graft use. This analysis included studies with an incidence of diabetes in their cohorts between 4% and 21%. The authors reported an improved hazard ratio for death with BIMA versus SIMA grafts of 0.81%, although none of the included studies were randomized. Recently, Taggart, et al\(^ {24} \) have been investigating this issue with the Arterial Revascularization Trial, a randomized control study designed to compare SIMA versus BIMA with an intended 10-year follow-up. However, preliminary outcome data at 1 year are very interesting for patients with DM, because they show that 1.9% of BIMA and 0.6% of SIMA patients have wound dehiscence.

**Considerations on Randomized Controlled Trials**

The superiority of CABG over PCI for DM patients demonstrated in the randomized clinical trials (RCTs) must be interpreted in the context of the following important caveats. In the main examined trials only a small fraction of the overall population screened was finally enrolled in the studies (FREE- DOM trial 5%, SYNTAX Trial 41% overall, and diabetic subgroup 10.4%). Thus, these trials enrolled highly selected patient populations, not necessarily typical of those encountered in daily clinical practice. Exclusion enrollment criteria often included significant heart failure, cardiogenic shock, recent or acute ST-segment elevation MI, and previous revascularization. Moreover, the mean EUROSCORE (European System for Cardiac Operative Risk Evaluation) was 3.5, which signifies a relatively low to intermediate surgical risk for the enrolled patients. Due to these findings, the results of these trials should be applied only to the included diabetic subgroups with caution in extrapolating results to the excluded diabetic subgroups.

A second key point is that these RCTs mostly used first-generation DES. Although a previous study showed a sustained clinical benefit after sirolimus eluting-stents (SES) implantation,\(^ {25} \) little is known about long-term angiographic outcomes, and concerns have been raised about the late restenosis of SES.\(^ {26} \) Recent studies have suggested the possibility of “late catch-up” phenomenon after SES implantation,\(^ {27,28} \) which was significantly more pronounced with SES than with BMS in the recent study of Natsuki, et al.\(^ {29} \) “Late catch-up” phenomenon is strictly related to late adverse events such as late stent thrombosis and late target-lesion revascularization and then may be an important explanation of the worse results of these DES first-generation with respect to CABG. Whether CABG will confirm superiority over PCI with newer-generation DES in diabetic patients remains a matter of debate. Recent data from a registry study of a large series of patients\(^ {30} \) showed a lower event rate in diabetic patients with the use of second-generation stents (everolimus) compared with first-generation stents, mainly due to a lower incidence of stent thrombosis and mortality.

An important explanation for long-term durability and improved clinical efficacy of CABG may be related in part to the “completeness of revascularization.” Several studies have demonstrated that incomplete revascularization is an independent predictor of MACE and repeat revascularization.\(^ {13} \) An important limitation of the reported trials was that they did not evaluate the impact of the degree of revascularization (compared between CABG and PCI) on outcomes. In the CARDia Trial\(^ {16} \) 65% of PCI patients had 3-vessel disease, of whom 88% had complete revascularization. On average, 3.6 stents (a mean total stent length of 71 mm) were implanted per patient. In the CABG group, 60% of patients had 3-vessel disease, of whom 90% underwent complete revascularization. In the ARTS-II cohort, completeness of revascularization was lower for patients treated with DES versus BMS (68.6% for BMS versus 59.9% for DES-treated patients and 77.4% for CABG-treated patients with diabetes; \( P = 0.017 \)).\(^ {17} \) Moreover, complete revascularization was achieved in 41% of PCI and 74% of CABG in the MASS Trial, respectively.\(^ {30} \) A recent post-hoc analysis from the 4-year outcomes of the SYNTAX Trial and Registry showed that angiographic complete revascularization was achieved in only 52.8% of the PCI arm and 66.9% of the CABG arm.\(^ {12} \) Patients with incomplete revascularization had a significantly higher risk of death, MI, and repeat revascularization in both the PCI and CABG groups.

Finally, an important aspect is the duration of dual antiplatelet therapy in diabetic patients who undergo multivessel stenting. The suboptimal dual antiplatelet therapy duration in some trials may have contributed to a higher MI rate (stent thrombosis) or death. In fact the duration of therapy was variable, ranging at 1 year from 50% in the CARDia trial to 90% in the FREEDOM Trial. Furthermore, newer thienopyridines, including prasugrel and ticagrelor, were not used in these trials. It has been well established that prasugrel (and perhaps ticagrelor) had a particular advantage in the diabetic subgroup.\(^ {34,35} \)
Registry and observational studies: Evidence from “real world” registries supports the advantages of CABG over PCI in patients with diabetes and multivessel CAD. In 2001 a large regional database of 7159 consecutive patients with diabetes who underwent CAGB in northern New England was published. A large percentage of patients (38.6%) had the same characteristics of the patients randomized in the BARI trial. After adjusting for differences in baseline clinical characteristics, in this cohort PCI had significantly greater mortality than CAGB (HR: 1.49; 95% CI: 1.02–2.17; P = 0.037). Moreover, the mortality risk was greater with PCI in patients with more severe and diffuse CAD.

Recently, the ASCERT registry investigators have provided strong evidence that CAGB, in comparison with PCI, offers a strong survival benefit as well as a marked reduction in MI and repeat revascularization in patients with intermediate and more severe CAD.

These results are similar to those reported by our previous registry study. The aim of our investigation was to compare 5-year clinical outcomes of CAGB versus PCI in a real world population of diabetic patients with multivessel CAD consisting of 2885 multivessel coronary diabetic patients who had undergone revascularization (1466 CAGB and 1419 PCI, respectively). The 5-year incidences of MACCE (mortality, acute MI, stroke, and repeat revascularization) were assessed and the cumulative incidence functions of death and TVR were analyzed in order to evaluate the competing risk of AMI on death and TVR. The same analyses were applied to the propensity score matched subgroup of patients undergoing CAGB or complete revascularization with DES only. PCI had higher mortality for all causes (HR: 1.8, 95% CI 1.4–2.2, P < 0.0001), AMI (HR: 3.3, 95% CI 2.4–4.6, P < 0.0001) and TVR (HR: 4.5, 95% CI 3.4–6.1, P < 0.0001). No significant differences emerged for stroke (HR: 0.8, 95% CI 0.5–1.2, P = 0.26). The higher incidence of acute MI was the main cause of higher mortality in the PCI group. The results did not change when comparing CAGB with PCI patients receiving complete revascularization with DES only.

These results have been confirmed by other retrospective and cohort studies, both in the treatment of diabetic patients affected by multivessel CAD or unprotected left main coronary artery.

It has been demonstrated that there is significantly increased durability of internal mammary grafts, with 90% patency rates reported at 20 years with the use of bilateral mammary arteries in comparison to saphenous vein grafts. Recently, Moshkovitz et al investigated the outcomes of DES and BIMA grafting in diabetic patients with multivessel CAD. The outcomes of diabetic patients who underwent left-sided arterial revascularization with BIMA grafting (226 patients) were evaluated and compared with those of diabetic patients who underwent PCI with DES (Cypher) (271 patients). The 5-year reintervention-free survival (Kaplan-Meier 86% versus 65%, log rank P < 0.000) and major adverse cardiovascular events–free survival (81% versus 54%, P < 0.0001) were significantly better in the BIMA group. The PCI group was associated with decreased adjusted survival (hazard ratio 3.01, 95% confidence interval: 1.59 to 5.73, P < 0.000) and increased risk of target vessel reinterventions (hazard ratio 7.00, 95% confidence interval: 3.1 to 15.70). The adjusted risk of MACE increased with the number of DES-treated vessels. The authors’ conclusions demonstrated significantly better long-term adjusted survival and outcomes of diabetic patients who underwent CAGB with BIMA grafting compared with diabetic patients who underwent PCI with DES.

Conclusions: Several medical device companies are competing to produce newer technologies aimed at improving PCI procedures, particularly in small coronary arteries. Such innovations include thin-strutted stents, drug-coated balloons, and biodegradable stent systems. These devices may improve the results of PCI in the future, although, to date, none of these techniques have been sufficiently validated to justify a radical change in clinical practice.

In diabetic patients affected by CAD, the evidence derived from both RCTs and “real world” studies generally favors CAGB over PCI, particularly in those patients with severe and diffuse CAD. FREEDOM is the most recent of several important trials in patients with DM with multivessel coronary disease. At 5-year follow-up, CAGB was found to be beneficial with regard to the composite primary endpoint as well as all secondary endpoints. The results of the FREEDOM trial support upgrading of the current American Heart Association recommendation to class I (level of evidence: B) in favor of CAGB for diabetic patients with multivessel coronary disease. The 2011 American Heart Association/American College of Cardiology guidelines update recommend a “Heart Team” approach, with the implicit understanding that each patient’s case takes into account surgical and interventional risks, long-term outcomes, and patient preferences.

Based on the current study, CAGB is preferred for the most favorable long-term outcomes in high-risk SYNTAX Score patients without high surgical risk. In patients who are high risk for surgery, or have low-severity CAD, PCI remains an attractive and feasible option. We should finally decide the revascularization strategy after fully considering the treatment results and emergency treatment systems at each institution.

References


