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DIABETES AND CARDIOVASCULAR DISEASE (S MALIK, SECTION EDITOR)

Percutaneous Versus Surgical Interventions for Coronary Artery Disease in Those with Diabetes Mellitus

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Abstract Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies that causes long-term damage of various organs including the cardiovascular system. A consistent observation shows that DM amplifies the risk of cardiovascular events by 4- to 6-fold. Since coronary artery disease (CAD) in diabetic patients exhibits diffuse and accelerated lesions, invasive revascularization continues to be a challenge and has worse outcomes than patients without DM. Owing to the pathogenesis of DM and the presence of severe endothelial dysfunction, investigators have been trying to find new treatment modalities that could target the treatment of the disease rather than the treatment of the lesion. Until new treatment modalities are proven and gain acceptance, invasive revascularization remains to be the choice of treatment in such patients. The focus of this review is to compare the results of percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) for the treatment of stable CAD in patients with DM.

Keywords Percutaneous coronary intervention · PCI · Surgical intervention · Coronary bypass surgery · CABG · Diabetes mellitus · Coronary artery disease · Treatment · Ischemic heart disease · Revascularization · External counterpulsation · EECP · Guideline committee · Multivessel disease · Guidelines

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Introduction

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Decreased nitric oxide bioavailability, the hallmark of insulin resistance, is multifactorial (impaired nitric oxide synthesis, trapping of nitric oxide reactive oxygen species) and has been associated with the procoagulant state, reduced protection afforded by ischemic preconditioning, extensive nature of coronary artery disease (CAD) and myocardial function impairment observed in diabetic patients. These factors not only increase the predisposition to CAD but are also responsible for severe consequences of thrombotic events [1]. Prothrombotic and proinflammatory states, in adjunct to endothelial dysfunction and metabolic disorders, such as hyperglycemia, dyslipidemia, obesity, insulin resistance, and oxidative stress, are key features of the accelerated atherosclerotic process observed in patients with DM. The prothrombotic status is the consequence of multiple conditions, including increased platelet reactivity; increased levels of procoagulant agents such as fibrinogen, tissue factor, von Willebrand factor, platelet factor 4, factor VII; decreased concentrations of endogenous anticoagulants including protein C, and antithrombin III; and impaired endogenous fibrinolysis secondary to elevated levels of plasminogen activator inhibitor-1 [2–4]. Additional metabolic conditions that may enhance platelet reactivity include obesity (via insulin resistance, augmented cytosolic calcium concentration, and increased oxidative stress), dyslipidemia, systemic inflammation, and endothelial dysfunction. The latter, a characteristic feature of DM, is mediated by hyperglycemia, increased free fatty acid production, altered lipoproteins, insulin resistance, and hypertension [2]. The

effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs including cardiovascular system.

Diabetes mellitus is considered to be a pandemic by the World Health Organization. During the last decade its prevalence increased by 40 % in industrialized countries and almost tripled in developing countries [5, 6]. It has been estimated that the global prevalence of DM among adults will be 7.7 % (439 million individuals) in 2030 [7]. In the USA, the costs related to DM have been estimated at $172 billion in 2007–$116 billion for direct and $58 billion for indirect medical costs such as disability and work loss–while they are expected to rise to $192 billion by 2020 [8].

A consistent observation shows that DM amplifies the risk of cardiovascular events by 4–6 fold. Cardiovascular events are responsible for 75 % of all hospitalizations and 80 % of all deaths in diabetic patients [9]. DM is present in 25 %–30 % of patients admitted with acute coronary syndromes, in 15 %–25 % of patients undergone for coronary revascularization, and in more than 30 % of patients hospitalized with cardiogenic shock [10]. An example of the deleterious impact of DM on cardiovascular prognosis was observed in a Danish population-based study of 3.3 million people showing that DM patients without a history of CAD had the same 5-year mortality as non-DM patients without a history of myocardial infarction [11]. DM is considered as a risk equivalent to CAD, and DM itself is the main cause of accelerated atherogenesis and atherothrombosis [3].

Since CAD in diabetic patients exhibits certain characteristics which confer an increased risk, such as more diffuse and accelerated lesions, with longer lesion lengths, greater plaque burden, and smaller vessel size, invasive revascularization continues to be a challenge and have worse outcomes than patients without DM [11]. Due to the pathogenesis of DM and the presence of severe endothelial dysfunction, investigators have been trying to find new treatment modalities that could target the treatment of the disease rather than the treatment of the lesion. One such new treatment modality which is under investigation as a first line treatment of choice before performing any invasive revascularization in patients with DM and CAD is Enhanced External Counterpulsation Therapy (EECP) [12••, 13]. Until new treatment modalities have been proven and gain acceptance invasive revascularization remains to be the choice of treatment along with the medical management in patients with CAD and DM.

Certain factors affect the choice of invasive revascularization procedures in diabetic patients. These factors include the clinical presentation (stable angina pectoris vs acute coronary syndrome), left ventricular function, coronary anatomy (left main disease, localization of the lesions, extent of the CAD, suitability for coronary artery bypass grafting (CABG) anastomoses, history of previous CABG, malignancies, coagulation disorders, chronic obstructive pulmonary disease, peripheral arterial disease, chest deformities, prior radiation exposure, presence of valvular heart disease, and patient preference. Until recently, comparative data between percutaneous coronary intervention (PCI) and CABG in DM were limited to subgroup analyses of randomized trials. Now, the results of randomized trials are available both on myocardial revascularization in stable and unstable angina and on drug-eluting stent (DES)-based PCI vs CABG in diabetic patients. The focus of this review is to define the role of PCI and CABG in the management of diabetic patients with stable CAD.

Percutaneous vs Surgical Revascularization in Patients with CAD and DM

CAD in those with diabetes has been shown to be more aggressive and to be associated with an impaired event-free survival, compared with those without diabetes, after both CABG and PCI because of smaller vessel sizes, longer lesion length, greater plaque burden, and a possibly differently acting restenotic cascade than in non-diabetic patients [14••, 15]. Given this higher-risk profile, which is most often associated with multivessel disease, CABG has been regarded by some as a preferred revascularization method because of its ability to bypass this large amount of plaque burden and to achieve more complete revascularization rates, making the need for repeat revascularizations less likely [14••, 16].

Many trials have demonstrated CABG to be superior compared with PCI in high-risk patient subgroup. A propensity analysis of long-term survival after surgical or percutaneous revascularization in 6033 patients with multivessel disease and high-risk features (diabetes or left ventricular dysfunction) showed that PCI had 2.3 times higher mortality rate than CABG at 5-year follow-up [17]. Niles et al published the results of survival of patients with diabetes and multivessel disease after surgical or PCI [18]. Their results showed that in 2766 risk matched diabetic patients PCI increased 5-year mortality by 1.5–3.9 times. In a retrospective cohort study of 6320 procedures, Pell et al compared the survival following CABG vs PCI in diabetic and non-diabetic patients [19]. Results showed that PCI had 3.6 times higher mortality rates at 2-year follow-up in patients with diabetes.

In a recent study of patients with multivessel disease and ≥5 years of follow-up, CABG was found to have a significant survival advantage over patients undergoing stent implantation [20]. This advantage was maintained among most subgroups, including males, those >65 years of age, patients without a history of PCI, CABG, or myocardial infarction, nondiabetic patients, diabetic patients, patients with an EF >40 %, patients

with either 2- or 3-vessel disease, and for both complete and incomplete PCI. The only subgroups in which the survival advantage trended toward stent implantation were those with a previous history of coronary revascularization (either previous CABG or PCI). CABG patients also experienced fewer repeat revascularizations (CABG or PCI) and myocardial infarction, and 41 % fewer events for the composite end point of major adverse cardiovascular events. These results are consistent with the reports of other studies [17, 21, 22]. However, it should be noted that most of the prior trials of CABG vs PCI included outdated technology and techniques for both procedures—this is often why trials such as Bypass Angioplasty Revascularization Investigation (BARI) [23] are no longer given the same weight.

Most of the randomized clinical trials report similar 5-year mortality rates for both CABG and PCI [21, 24–33, 34••, 35–39]. Why the results differ between the observational studies of patients seen in typical clinical practice and these randomized trials has been addressed before (such as randomized trials eliminate selection bias, and involve independent data safety monitoring board, core laboratories, and clinical event committees; registry data can be complementary in that a broader cross-section of patients are enrolled, but are subject to selection bias and an inability to adjust for unmeasured confounders). Patient selection could possibly explain the differing results. Typically, clinical trial participants are required to meet strict inclusion and exclusion criteria. They often have less comorbidity and may not represent the average patient presenting for a coronary intervention. Another possible explanation for the non-significant difference in mortality between the treatments may be limited to insufficient power of these trials [16]. Nonetheless, the Stent or Surgery Trial (SOS) which was a randomized, controlled trial comparing PCI with CABG for patients with multivessel disease found a survival advantage for patients randomized to CABG at a median follow-up of 2 years. At a median follow-up of 6 years, a continuing survival advantage was observed for patients managed with CABG [22]. Other randomized trials, such as the BARI study, also have found a survival advantage for CABG among certain subgroups of patients such as diabetic patients [33].

In this regard, 2 of the largest trials of CABG vs PCI ever performed, FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) and SYNTAX trials (the Synergy between PCI with TAXUS and Cardiac Surgery), both using drug-eluting stents (DES), and minimally invasive surgery have been initiated [14••].

FREEDOM Trial is still ongoing however, the SYNTAX Trial (the Synergy between PCI with TAXUS and Cardiac Surgery) results have been recently published showing that PCI with TAXUS (paclitaxel-eluting) stenting was inferior to CABG with respect to the primary composite of death, stroke, myocardial infarction, or repeat revascularization among patients with left main and or 3-vessel disease [40••]. The trial was conducted at 62 sites in Europe and 23 sites in the US and had an 'all-comers' design instead of a highly selected population to reflect, as much as possible, real world conditions. Limited exclusion criteria included previous interventions, acute myocardial infarction with creatine phosphokinase (CPK)–myocardial band >2× or concomitant cardiac surgery. Investigators randomized 1800 subjects to CABG (n=897) or PCI (n=903). Approximately 28 % had diabetes, 33 % prior myocardial infarction, and 29 % recent unstable angina. The average number of lesions was 4.4 with 66 % qualifying on the basis of 3-vessel disease only, 3 % with left main only, and 31 % with both left main and 3-vessel disease. Average stent implantation per patient was 4.6 with 48 % receiving 5 stents. The primary end point of the trial, the rate of Major Cardiovascular or Cerebrovascular Event Rate (MACCE as defined by all -cause death, cerebrovascular accident, documented myocardial infarction, or any repeated revascularization) at 12 months, occurred in more patients undergoing PCI than CABG (18 % vs 12 %; P=0.0015). The prespecified DM-subgroup analysis showed that, driven by an increased rate of repeat revascularization (6.4 % vs 20.3 %, P<0.001), the 1-year death, stroke, myocardial infarction, or repeat revascularization rate was significantly higher among DM patients treated with DES than with CABG while no difference between the groups was observed in the rate of death, stroke, or myocardial infarction. The mortality rate was higher after PCI (13.5 %) than after CABG (4.1 %, P= 0.04) in DM patients with highly complex lesions (ie, SYNTAX score ≥33), in those with the lowest SYNTAX score tertile the 1-year death, stroke, myocardial infarction, or repeat revascularization rate did not differ between CABG and PCI (18.3 vs 20.3 %) [40••].

The CARDia (Coronary Artery Revascularization in Diabetes) Trial compared PCI (~1/3 BMS and ~2/3 DES) and CABG in 510 DM patients with multivessel CAD. At 1 year, the primary endpoint of death, myocardial infarction, and stroke (13 % vs 10.5 %, P=0.393) did not differ among the groups while the need of repeat revascularization was significantly higher in the PCI group (12 % vs 2 %, P<0.001) [41••].

Daemen et al published the results of ARTS (the Arterial Revascularisation Therapy Study)-II trial in diabetic patients with multivessel disease and reported similar outcomes between DES (DES = Sirolimus-eluting stent) and CABG [34••]. The advent of DES has revolutionized the field of interventional cardiology. On the other hand off-pump CABG (OPCAB) has also emerged as an established technique with specific benefits, such as shorter operating time, rapid recovery from surgery, and lower rates of

perioperative stroke [42, 43]. Recent studies report favorable outcomes at 4–5 years follow-up after OPCAB with total arterial revascularization using the bilateral internal mammary arteries [44–47]. However, there are few data to compare the long-term efficacy and outcome of these advanced revascularization therapies (ie, DES and OPCAB) for diabetic patients with multivessel disease. Briguori et al reported the superiority of OPCAB at 1-year follow-up compared with DES; however, multivessel stenting was performed in only 65 % of patients and the follow-up period was limited to a year [48••]. In a recently published single center, nonrandomized registry, 208 diabetic patients with multivessel disease were examined (DES = Sirolimus-eluting stent group: n=92, OPCAB group: n=116). The occurrence of major adverse cardiac and cerebrovascular events (MACCE, defined as all-cause death, non-fatal myocardial infarction, cerebrovascular event, and repeat revascularization) was compared between the 2 groups. Fasting blood glucose level, type of diabetic treatment, and the prevalence of diabetic major vascular complications were similar between groups. The DES group had a significantly higher prevalence of 2-vessel disease and a significantly lower prevalence of 3-vessel disease compared with the OPCAB group. During the follow-up period (mean: 42± 8 months), the cumulative MACCE was similar between the 2 groups (27 % vs 23 %, P=0.492). However, consistent with the results of previous studies, the rate of revascularization was significantly higher in the DES group than the OPCAB group (21 % vs 6.9 %, P=0.003) [49••].

Recently, the American College of Cardiology (ACC), and the Centers for Medicare and Medicaid Services (CMS) collaborated to develop ASCERT, a comparative-effectiveness study of surgery vs PCI in stable coronary atherosclerosis patients. Among patients 65 years of age or older who had 2-vessel or 3-vessel coronary artery disease without acute myocardial infarction, 86,244 underwent CABG and 103,549 underwent PCI. The median follow-up period was 2.67 years and the mean age was 74 years. At 1 year, there was no significant difference in adjusted mortality between the groups (6.24 % in the CABG group as compared with 6.55 % in the PCI group; risk ratio, 0.95; 95 % confidence interval [CI], 0.90 to 1.00). At 4 years, there was lower mortality with CABG than with PCI (16.4 % vs 20.8 %; risk ratio, 0.79; 95 % CI, 0.76 to 0.82). For high risk patients—75 years or older, diabetic, ejection fraction <50 %, and glomerular filtration rate <60 mL/min/1.73 m^2, bypass surgery was associated with lower 4-year mortality than PCI (risk ratio=0.72). Investigators concluded that among older patients with multivessel coronary disease that did not require emergency treatment, there was a long-term survival advantage among patients who underwent CABG as compared with patients who underwent PCI. [50]

Impact of Diabetic Treatment and Age on the Clinical Outcomes

It is important to keep in mind that patients requiring insulin for the treatment of diabetes are more susceptible to adverse cardiac events [51]. Voudris et al assessed the long-term results after DES implantation in non-insulin-dependent diabetic patients compared with insulin-dependent patients [52••]. A total of 610 consecutive diabetic patients (mean age 65±9 years) underwent PCI with DES implantation. They were classified into 2 groups according to their diabetic treatment: (1) non-insulin-dependent patients (477); (2) insulin-dependent patients (133). The primary endpoint was the composite of death, non-fatal myocardial infarction, bypass surgery, and target lesion revascularization. Clinical follow-up for more than 12 months (median 29 months) was achieved in 597/610 patients (98 %). During clinical follow-up, no significant differences in the incidence of death or non-fatal myocardial infarction were observed, but target lesion revascularization, and bypass surgery were more frequent in the insulin-dependent group (8.5 % vs 3.4 %, P= 0.01, and 4.7 % vs 1.3 %, P=0.01, respectively). The event-free survival was lower in the insulin-dependent group (hazard ratio: 0.52; 95 % confidence interval, 0.31–0.85, P=0.01) as a result of the need for repeat revascularization with either PCI or CABG. Even though the implantation of DES in diabetic patients may provide a reduced risk of restenosis and TLR, DM remains a significant risk factor for restenosis after both BMS and DES implantation [53–55], Restenosis and disease progression are the 2 major processes blamed for the higher rates of repeat revascularization and mortality after PCI in diabetic patients. These processes are affected in part by the metabolic dysregulation resulting from insulin resistance and chronic hyperglycemia [56]. There are a number of mechanisms that can explain the higher restenosis rate in diabetic patients. Hyperglycemia, which is the dominant abnormality in insulin-dependent diabetic patients directly, causes endothelial dysfunction by decreasing the production of endothelium-derived relaxing factor, increasing oxidative stress by vascular protein glycation and free radical formation, and decreasing prostacyclin production. In addition, lipoprotein abnormalities may impair endothelium-dependent relaxation; moreover, greater growth factor stimulation occurs in diabetic patients. All these mechanisms may also lead to pronounced intimal hyperplasia, the main mechanism of restenosis in diabetic patients [51, 57–63].

The effectiveness of DES, especially in insulin-dependent diabetic patients, has been a matter of debate. In the RESEARCH registry, diabetic patients constituted 1 of the few subgroups in which evidence of benefit did not reach statistical significance and diabetes mellitus remained an independent predictor of adverse events and clinically

driven target vessel revascularization (TVR) [64]. In a recently published study, only DM was an independent predictor for angiographic restenosis after sirolimus-eluting stent implantation [65]. Furthermore, in a meta-analysis of 4 trials specifically addressing the effects on restenosis of implanting BMS or DES in diabetic and nondiabetic patients, DM remained an independent risk factor for restenosis, suggesting that the use of DES does not fill the gap between diabetic and non-diabetic patients [54].

In a recent real-world multicenter registry, no benefit was demonstrated among insulin-dependent diabetic patients after DES implantation, whereas non- insulin-dependent diabetic patients showed substantial improvements in the 2-year relative risk of major adverse cardiac events and TVR [66••]. Similarly, the SIRIUS trial failed to demonstrate a benefit from sirolimus-eluting stent use in the subgroup of insulin-dependent diabetic patients, owing to the high incidence of edge effect [67]. Another single-center study results showed that patients who had insulin-dependent DM manifested a higher prevalence of restenosis compared with patients who did not require insulin for their diabetes treatment [52••]. Likewise, in the EVASTENT matched-cohort registry, insulin therapy was an independent predictor of TLR [68]. In contrast, the DIABETES trial has demonstrated similar repeat revascularization rates among both non-insulin-dependent diabetic patients and insulin-dependent diabetic patients [52••].

An increasing severity of CAD in diabetic patients is associated with higher mortality [69, 70]. Voudris et al showed no significant difference in the incidence of death and non-fatal myocardial infarction between the insulin-dependent and non-insulin dependent diabetic patients however, the event free survival was lower in insulin-dependent diabetic patients, mainly as a result of the greater risk of new revascularization [52••]. These results were similar to those from a pooled analysis of 5 randomized trials, where rates of all-cause mortality, cardiac, and non-cardiac death were similar for DES and BMS in insulin-dependent diabetic patients and non-insulin-dependent diabetic patients [71•]. In contrast, Ortolani et al reported insulin-dependent DM as an independent predictor of all-cause death/acute myocardial infarction at 2-year follow-up [66••]. Moreover, in a very recent study, insulin use was an independent predictor for death, TVR, and composite outcome (death, nonfatal myocardial infarction, or TVR) [72].

Recently, Legrand et al evaluated the prognostic impact of age on the procedural results and subsequent clinical outcomes in patients with multivessel disease treated either by CABG or by PCI with or without DES, based on data of the Arterial Revascularization Therapies Study (ARTS) part I and part II. Three-year clinical outcome of ARTS I patients randomized to PCI with BMS (n=600) or CABG (n=605), and matched patients treated by PCI with DES (DES = sirolimus-eluting stents) in ARTS II (n=607) were reviewed according to 4 age quartiles. Endpoints were measured in terms of major adverse cardiac and cerebrovascular events (MACCE) during hospital stay and up to 3 years. Diabetes was the strongest independent predictor of MACCE among PCI treated patients (P<0.02), but did not affect 3-year outcomes following CABG [73•].

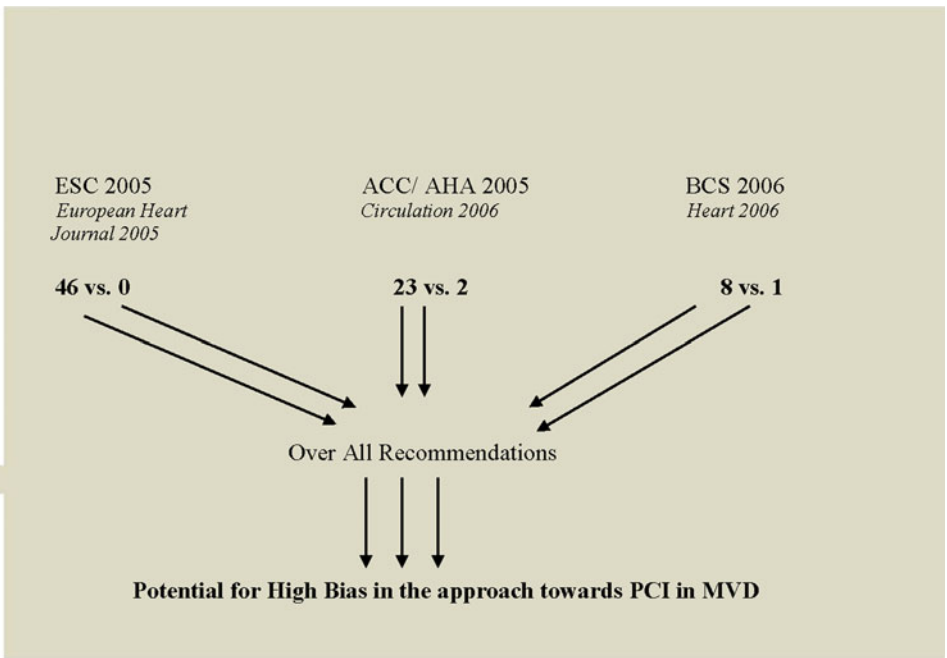

Fig. 1 Number of cardiologists vs surgeons in the Guideline Committees and Recommendations for PCI. ACC = American College of Cardiology; AHA = American Heart Association; BCS = British Cardiac Society; ESC = European Society of Cardiology. (With permission from: Soran O, Manchanda A, Schueler S. Percutaneous coronary intervention vs coronary artery bypass surgery in multivessel disease: a current perspective. Interactive CardioVascular and Thoracic Surgery. 8 2009;666–72) [14••]

Cost Effectiveness

Since the presentation of DES to the medical community, its use gained a rapid acceptance among interventional cardiologist. In 2003, eleven health economists did a systemic review and economic evaluation on stents [74]. They clearly stated that in the absence of substantive clinical evidence of the superiority of stenting with DES over CABG for 2- and 3-vessel disease, to encourage the widespread use of DES will drive up the cost of stenting and if allowed to displace CABG, reduce the gain in quality and possibly duration of life arising from CABG in the long term.

In a cost-effectiveness analysis of 1720 patients who were allocated to PCI, CABG or either therapy were followed for 7 years. It was concluded that while the medical therapy and CABG were cost-effective at a conventional quality-adjusted life year of $60,000, PCI was not cost-effective, and the additional benefit of stenting over best medical therapy was 'too small to justify the additional cost' [75]. These findings are consistent with a previous report by the UK Health Technology Assessment Group, who also questioned whether the additional costs of DES were justifiable, warning that the widespread use of DES might reduce the gain in quality and possibly the duration of life arising from CABG in the long term. In 2006, the use of DES was 89 % and 80 % in Europe and in the US, respectively, and the off-label use of DES was 60 %. After FDA warnings these ratios dropped by 20 %–25 % in 2007 [14••].

Conclusions

In determining a treatment strategy for a patient with CAD, there are a variety of considerations that need to be made when selecting the appropriate treatment to prevent iatrogenic fulminans [76]. Patients with DM often have multiple cardiovascular risk factors and require multiple cardiac and diabetes medications. Aggressive glycemic control has a beneficial effect on microvascular but not macrovascular endpoints. In addition, aggressive lowering of systolic blood pressure produces no advantage over treatment 130 mmHg; therefore, special attention should be paid to glucose and blood pressure control. Since the clinical outcomes differ according to the treatment choice it is essential to ensure that every patient receives balanced advice and therapy that is most cost effective in the long term.

It is extremely important to establish a multidisciplinary team of general cardiologists, interventional cardiologists, and cardiothoracic surgeons to ensure that the most appropriate advice is offered including recommendation for stenting. Until recently, representation of cardiothoracic surgeons in the various Guidelines Writing Committees on the use of PCI vs CABG in management of CAD was unbalanced (Fig. 1). Although not sufficient, steps have been undertaken recently to increase the representation of cardiothoracic surgeons in the Guidelines Writing Committees to represent an unbiased opinion.

FREEDOM trial is now underway, which may address many of the limitations of previous studies, and be more relevant to contemporary practice. Until then, currently available data emphasize the fact that patients with CAD and DM derive more benefit from CABG than from PCI in the long term.

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enhanced-external-counterpulsation-therapy-in-the-management-of-coronary-artery-disease. *This book chapter reviews the role of EECP Therapy in CAD and it`s mechanism of action which is different than invasive revascularization. The author underlined the need to initiate a randomized clinical trial to ascertain the efficacy of EECP therapy combined with drug therapy as a first line treatment before any invasive revascularization in selected group of patients with CAD.*

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