Choosing a Revascularization Strategy in Patients with Diabetes and Stable Coronary Artery Disease: A Complex Decision

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Abstract: Diabetes mellitus is associated with well-known increases in cardiovascular morbidity and mortality. In diabetics with stable coronary artery disease, the best therapeutic option is widely discussed. Current studies comparing surgical to percutaneous revascularization have been unable to definitely demonstrate any significant advantage of one strategy over the other regarding the prevention of cardiac death or acute myocardial infarction. Therefore, even taking into account clinical and angiographic information as well as the risks determined by each type of treatment, the decision regarding the best therapeutic strategy in diabetics with stable coronary artery disease is still complex.

Keywords: Coronary artery bypass graft surgery, coronary artery disease, diabetes mellitus.

INTRODUCTION

According to data from the WHO, from 1995 to 2005 the world’s adult population will increase 64%, while the number of diabetic patients will increase 122%. In developed countries, the number of adults with diabetes mellitus (DM) will increase 42%, while in developing countries the increase will be of 170% [1]. In general terms, it is estimated that the prevalence of DM will increase from 2.8% in 2000 to 4.4% in 2030 [2]. These data underscore the importance of prevention, treatment and control of the disease, especially if we take into account the 2 to 4 times higher cardiovascular mortality found in these individuals [1-4] and the 65% of cardiovascular deaths in diabetics, most of these related to coronary artery disease (CAD) [5].

RELATIONSHIP BETWEEN DIABETES AND CORONARY ARTERY DISEASE AND ITS IMPLICATIONS ON THE TREATMENT FOR CORONARY ARTERY DISEASE

DM has been associated with accelerated atherosclerosis due to a number of factors, such as endothelial dysfunction [6], decreased coronary flow reserve [7], increased platelet activity [8-10], increased levels of fibrinogen and factor VII [11], decreased fibrinolytic activity and of antithrombin III [11] and increased levels of plasminogen activator inhibitor I [12]. Morphologic characterization of the coronary arteries of diabetic patients who died suddenly has found a greater burden of atherosclerotic plaque, increased lipid cores, as well as increased macrophage and T-lymphocyte infiltration when compared to non-diabetics with sudden death [13].

In asymptomatic diabetics, significant coronary artery obstructions have been found in over 75% of the patients, and multivessel involvement in over 50% [13,14]. Moreover, DM is associated with a higher prevalence of left main coronary artery disease but less collateral circulation [15,16]. Coronary lesions in diabetics are generally more calcified than in nondiabetics [16], and compensatory arterial remodelling is often inadequate [17].

All of the former contribute to the peculiar angiographic aspects of DM (diffuse and often distal atherosclerotic involvement of coronary arteries), to the increased risk of adverse coronary events and of incomplete coronary revascularization, either surgical or percutaneous [18-22]. The presence of diabetic nephropathy identifies a subgroup of patients with reduced survival after coronary artery bypass [23]. Moreover, after bypass surgery, vascular grafts (especially venous) occlude more frequently in diabetics than in non-diabetics [24,25].

In patients undergoing balloon percutaneous coronary intervention (PCI), restenosis is more frequent among diabetics, and that also has an impact on long-term survival [26-28]. Coronary stents also have an increased incidence of restenosis, especially in insulin-dependent diabetics; this is also related to higher rates of death, acute myocardial infarction (AMI) and the need for repeated revascularization in diabetic patients, compared to non-diabetics [29]. In addition, although pharmacologic stents have reduced restenosis and the need for repeat revascularization when compared to bare-metal stents, the incidence of restenosis and repeat revascularization have also been consistently higher in diabetics compared to non-diabetics [30-32]. Diabetes mellitus is an independent risk factor for major cardiovascular events after PCI [33] and for pharmacologic stent thrombosis [34,35].

Therefore, DM is associated with an increased risk of adverse events no matter which type of myocardial revascularization is chosen, either surgical or percutaneous. The question that follows is if there is any benefit of myocardial revascularization over medical treatment in diabetics with stable CAD.
Regarding that question, a retrospective analysis of diabetic patients included in the MASS II study has demonstrated that myocardial revascularization, compared to medical treatment, reduced the risk of death between the first and fifth years of follow-up. However, considering the whole follow-up, from randomization to five years, there was no difference among the 3 treatment groups [36]. Soriaja et al., in an observational study in which asymptomatic diabetics were followed for 5 years and stratified into low, intermediate or high risk according to stress myocardial perfusion SPECT, have found that surgical revascularization, when compared to medical treatment, was only favored in high-risk patients [37].

BARI 2D is the only study which has compared medical treatment to myocardial revascularization in diabetics [38]. This study included 2,368 diabetic patients with stable CAD, either symptomatic or not, who were randomized to intensive medical treatment or to intensive medical treatment plus percutaneous or surgical revascularization. The study demonstrated that there were no significant differences among treatment strategies regarding mortality or the incidence of major adverse cardiovascular events [38]. However, revascularization significantly reduced major adverse cardiovascular events among patients selected for a strategy of surgical revascularization, but that was not true for patients selected for percutaneous revascularization. That difference was determined by a higher incidence of nonfatal acute myocardial infarction in medically treated patients [38].

One interesting aspect of this study was that the type of revascularization (surgical or percutaneous) was left at the discretion of the study’s investigators, in a way that the choice of bypass surgery or PCI was based on angiographic criteria such as the location and extent of coronary lesions, as well as clinical and demographic variables [39]. Therefore, most patients undergoing bypass had higher angiographic severity (more 3-vessel disease, more \( \geq 70\% \) lesions, more proximal lesions of the left anterior descending artery, as well as type C lesions), were older, with more previous coronary interventions [39]. It was not surprising, then, that patients treated with PCI had similar prognosis to those medically treated, since they had less extensive and severe CAD, as well as normal LV function [40]. Finally, that study was not designed and therefore was not powered either to compare revascularization strategies or to compare PCI or surgery to medical treatment, and regarding superiority of one of the treatment strategies it should be considered hypothesis-generating.

**TAKING ALL THIS INTO CONSIDERATION, WHICH IS THE BEST REVASCULARIZATION STRATEGY FOR DIABETIC PATIENTS WITH STABLE CAD AND NORMAL LV FUNCTION?**

Theoretically, coronary artery bypass grafting surgery (CABG) is advantageous since grafts bypass the proximal 2/3 of the coronary arteries, where most plaque ruptures occur, generating clinical events, while PCI offers target-lesion treatment, leaving other plaques unprotected [41]. In addition, CABG also provides complete revascularization more often than PCI, what may lead to less repeat revascularization procedures and less angina during follow-up [42]. On the other side, CABG may have complications, and even those considered mild and reversible may prolong hospitalization [43,44]; the short-term risk of cerebrovascular accidents (CVA) is also increased [45].

The Bypass Angioplasty Revascularization Investigation Study (BARI) has demonstrated that in 10 years of follow-up diabetics patients had the highest benefit with CABG (57.9\% of survival) compared to balloon PCI (45.5\%). However, that was true only for patients who received internal mammary grafts in the LAD artery [46]. Other two randomized trial, ARTS [47] and SoS [48], in which bare metal stents were used, have shown similar results, that is, that diabetic patients who underwent CABG had lower 5-year mortality than those who had PCI. In the ARTS study, 5-year mortality in diabetics was 13.4\% for those who underwent PCI and 8.3\% for those who had CABG, while in SoS the 6-year mortality was 17.6\% for PCI and 5.4\% for CABG. Also, in a substudy of 452 patients from the SYNTAX study, CABG determined a lower incidence of composite endpoints (death, AMI, CVA or repeat revascularization) compared to PCI, but there was no difference regarding the incidence of death or AMI [49]. However, even though these 4 studies suggest that CABG is the best revascularization strategy for diabetics, they were not designed to evaluate specific revascularization strategies in this patient group, and therefore did not have enough statistical power to draw definitive conclusions about that issue.

Recently, the CARDia (Coronary Artery Revascularization in Diabetes) study tried to address the efficacy and safety of PCI compared to CABG in diabetics with symptomatic, multivessel or complex single-vessel CAD [50]. Patients were followed for a median of 1 year; 65\% of those undergoing PCI had 3-vessel CAD, and of these, 88\% had complete myocardial revascularization, with pharmacologic stents in 69\% of cases and a mean of 3.6 stents per patient. In the CABG group, 60\% had 3-vessel CAD, 90\% of whom had complete myocardial revascularization, with 94\% with internal mammary grafts to the LAD artery and a mean of 2.9 grafts per patient. The primary endpoint of the study was the combination of death, nonfatal AMI or CVA, and the secondary endpoint included repeat revascularization. At 1 year, no statistically significant difference was found between treatment strategies regarding the primary endpoint, but considering the secondary endpoint a significant difference in favor of CABG was found, due to increased repeat revascularization procedures in the PCI group. Nonetheless, the short follow-up and small patients number somewhat limit the study’s conclusions.

Therefore, it is clear that with all amount of information we have, and before the results of the FREEDOM study [51] are available, clinical judgment may be the best way to decide about the best revascularization strategy in diabetics with stable CAD and preserved LV function. Pereira et al. [52] studied the ability of clinical judgment to predict the incidence of cardiovascular end-points in patients with multivessel CAD [53] and showed that when clinical decision pointed against PCI, but due to randomization patients underwent that strategy (discordant status), these patients had more composite endpoints than those in the concordant
status. As the authors pointed out, it seemed that physicians could identify patients who would be suited or not to PCI.

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