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

Antonio Sergio Rocha, Paulo Dutra and Andrea De Lorenzo*

Instituto Nacional de Cardiologia, Rua das Laranjeiras 374, City: Rio de Janeiro, PostalCode: 22240006, Country: Brazil

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 disese, 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 1 [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 baloon 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.

*Address correspondence to this author at the Instituto Nacional de Cardiologia, Rua das Laranjeiras 374, City: Rio de Janeiro, PostalCode: 22240006, Country: Brazil; Tel: 55-21-30372172; Fax: 55-21-30372172; E-mail: andlorenzo@hotmail.com

1573-403X/10 $55.00+.00

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]. Sorajja *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 ≥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 baloon 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.

REFERENCES

[1] King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025. Prevalence, numerical estimates, and projections. Diabetes Care 1998; 21: 1414-31.

[2] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53.

[3] Lotufo PA, Gaziano JM, Chae CU, *et al*. Diabetes and all-cause and coronary heart disease mortality among U.S. male physicians. Arch Intern Med 2001; 161: 242-7.

[4] Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229-34.

[5] Bulugahapitiya U, Siyambalapitiva S, Sithole J, Idris I. Is diabetes a coronary risk equivalente? Systematic review and meta-analysis. Diabet Med 2009; 26: 142-8

[6] Aronson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. J Am Coll Cardiol 1996; 27: 528-35.

[7] Nahser PJ, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. Circulation 1995; 91: 635-40.

[8] Winocour PD. Platelet abnormalities in diabetes mellitus. Diabetes 1992; 41(Suppl 2): 26-31.

[9] Strano A, Davi G, Patrono C. *In vivo* platelet activation in diabetes mellitus. (review). Semin Thromb Haemost 1991; 17: 422-5.

[10] Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease pathophysiology, clinical consequences, and medical therapy: part I. Circulation 2003; 108: 1527-32.

[11] Ceriello A. Coagulation activation in diabetes mellitus: a role of hyperglycemia and therapeutic prospects. Diabetologia 1993; 36: 1119-25.

[12] Sobel BE, Woodcock-Mitchell J, Schneider DJ, Holt RE, Marutsuka K, Gold H. Increased plasminogen activator inhibitor type-1 in coronary artery atherectomy specimens from type-2 diabetic compared with nondiabetic patients. Circulation 1998; 97: 2213-21.

[13] Burke AP, Kolodgie FD, Zieske A, *et al*. Morphologic findings of coronary atherosclerotic plaques in diabetics. A postmortem study. Arterioscler Thromb Vasc Biol 2004; 24: 1266-71.

[14] Goraya TY, Leibson CL, Palumbo PJ, *et al*. Coronary atherosclerosis in diabetes mellitus. A population-based autopsy study. J Am Coll Cardiol 2002; 40: 946-53.

[15] Berry C, Tardif JC, Bourassa MG. Coronary heart disease in patients with diabetes. Part I: recents advances in prevention and noninvasive management. J Am Coll Cardiol 2007; 49: 631-42.

[16] Stone KE, Chiquette E, Chilton RJ. Diabetic endovascular disease: role of coronary artery revascularization. Am J Cardiol 2007: 99(suppl I): 105B-112B.

[17] Nicholls SJ, Tuzcu M, Kalidindi S, *et al*. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling. A pooled analysis of 5 intravascular ultrasound trials. J Am Coll Cardiol 2008; 52: 255-62.

[18] Ledru F, Ducimetière P, Battaglia S, *et al*. New diagnostic criteria for diabetes and coronary artery disease: insights from an angiographic study. J Am Coll Cardiol 2001; 37: 1543-50.

[19] Barsness GW, Peterson ED, Ohman EM, *et al*. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. Circulation 1997; 96: 2551-6.

[20] Alderman EL, Corley SD, Fisher LD, *et al*. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the coronary artery surgery study (CASS). CASS participating investigators and Staff. J Am Coll Cardiol 1993; 22: 1141-51.

[21] Thourani VH, Weintraub WS, Stein B, Gebhar SSP, Craver JM, Guyton RA. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. Ann Thorac Surg 1999; 67: 1045-52.

[22] Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1996; 94: 1818-25

[23] Reeder GS, Holmes DR, Lennon RJ, Larson TS, Frye RL. Proteinuria, serum creatinine, and outcome of percutaneous coronary intervention in patients with diabetes mellitus. Am J Cardiol 2002; 89: 760-4.

[24] Singh SK, Desai ND, Petroff SD, *et al*. The impact of diabetic status on coronary artery bypass graft patency. Insights from the radial artery patency study. Circulation 2008; 118: S222-5.

[25] Leavitt BJ, Sheppard L, Maloney C, *et al*. Effect of diabetes and associated conditions on long-term survival after coronary artery bypass graft surgery. Circulation. 2004; 110 [Suppl I]: II-41-II-44.

[26] Van Belle E, Ketelers R, Bauters C, *et al*. Patency of Percutaneous Transluminal Coronary Angioplasty Sites at 6-Month Angiographic Follow-Up. A Key Determinant of Survival in Diabetics after Coronary Balloon Angioplasty. Circulation 2001; 103: 1218-24.

[27] Van Belle E, Abolmaali K, Bauters C, McFadden EP, Lablanche JM, Bertrand ME. Restenosis, late vessel occlusion and left ventricular function six months after balloon angioplasty in diabetic patients. J Am Coll Cardiol 1999; 34: 476-85.

[28] Weintraub WS, Kosinski AS, Brown CL, King III SB. Can restenosis after coronary angioplasty be predicted from clinical variables? J Am Coll Cardiol 1993; 21: 6-14.

[29] Abizaid A, Kornowski R, Mintz GS, *et al*. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardio. 1998; 32: 584-9.

[30] Moussa I, Leon MB, Baim DS, *et al*. Impact of sirolimus eluting stents on outcome in diabetic patients. A SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy Circulation 2004; 109: 2273-8.

[31] Scheen AJ, Warzee F, Legrand VM. Drug-eluting stents: meta-analysis in diabetic patients. Eur Heart J 2004; 25. 2167-8.

[32] Stettler C, Alleman S, Wandel S, *et al*. Drug eluting stent and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ 2008; 337: a1331.

[33] Lemos PA, Serruys PW, van Domburg RT, *et al*. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "Real World". The Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry Circulation 2004; 109: 190-5.

[34] Pinto STL, Steinberg DH, Roy PK, *et al*. Observations and outcomes of definite and probable drug-eluting stent thrombosis seen at a single hospital in a four-year period. Am J Cardiol 2008; 102: 298-303.

[35] Iakovou I, Schmidt T, Bonizzoni E, *et al*. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293: 2126-30.

[36] Soares PR, Hueb WA, PA, Lopes N, *et al*. Coronary Revascularization (Surgical or Percutaneous) Decreases Mortality After the First Year in Diabetic Subjects but not in Nondiabetic Subjects With Multivessel Disease. An Analysis From the Medicine, Angioplasty, or Surgery Study (MASS II). Circulation 2006; 114: I420-4.

[37] Sorajja P, Chareonthaitawee P, Rajagopalan N, *et al*. Improved Survival in Asymptomatic Diabetic Patients With High-Risk Spect Imaging Treated With Coronary Artery Bypass Grafting. Circulation 2005; 112: I-311-6.

[38] BARI 2D Study Group, Frye RL, August P, *et al*. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009; 360: 2503-15.

[39] Kim LJ, King SB, Kent K, *et al*. Factors related to the selection of surgical versus percutaneous revascularization in diabetic patients with multivessel coronary artery disease in the BARI 2D (Bypass Angioplasty Revascularization Investigation Type 2 Diabetes) trial. J Am Coll Cardiol 2009; 2: 384-92.

[40] Schwartz L, Kip KE, Alderman E, *et al*. Baseline coronary angiographic findings in the bypass angioplasty revascularization investigation 2 diabetes trial (BARI 2 D). Am J Cardiol 2009; 103: 632-8.

[41] Gersh BJ, Frue RL. Methods of coronary revascularization - things may not be as they seem. N Engl J Med 2005; 352: 2235-7.

[42] Ong ATL, Serruys PW. Complete revascularization. Coronary artery bypass graft surgery versus percutaneous coronary intervention. Circultaion 2006; 114: 249-55.

[43] Di Carlo A, Perna AM, Pantoni L, *et al*. Clinically relevant cognitive impairment after cardiac surfery: a 6-month follow-up study. J Neurol Sci 2001; 188: 85-93.

[44] Barber PA, Hach S, Tippen LJ, Ross L, Merry AF, Milsom P. Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocogntive decline after cardiac surgery. Stroke 2008; 39: 1427-33.

[45] MaKhann GM, Grega MA, Borowicz Jr LM, Baumgartner WA, Selnes OA. Stroke and encephalopathy after cardiac surgery. An uptade. Stroke 2006; 37: 562-71.

[46] The BARI investigators. The final 10-year follow-up results from the BARI randomized trial. J Am Coll Cardiol 2007; 49: 1600-6.

[47] Serruys PW, Ong AT, van Herwerden LA, *et al*. Five year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Studies (ARTS) randomized trial. J Am Coll Cardiol 2005; 46: 575-81.

[48] Booth J, Clayton T, Pepper J, Nugara F, *et al*. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease. Six-year follow-up for the Stent or Surgery Trial (SOS). Circulation 2008; 118: 381-8.

[49] Banning AP, Wetaby S, Morice MC, *et al*. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitxel-eluting stents. J Am Coll Cardiol 2010; 55: 1067-75

[50] Kapur A, Hall RJ, Malik IS, *et al*. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010; 55: 432-40.

[51] Farkoub ME, Dangas G, Leon MB, *et al*. Design of the future revascularization evaluation in patients with diabetes mellitus: optimal management of multivessel disease (FREEDOM) trial. Am Heart J 2008: 155: 215-23.

[52] Pereira AL, Lopes NHM, Soares PR, *et al*. Clinical judgment and treatment options in stable multivessel coronary artery disease. Results from the one-year follow-up of the MASS II (Medicine. Angioplasty, or Surgery Study II). J Am Coll Cardiol 2006; 48: 948-53.

[53] Hueb W, Lopes NH, Gersh BJ, *et al*. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASSII). A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2007; 115: 1082-9.

Received: May 12, 2010 Revised: May 31, 2010 Accepted: May 31, 2010