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PERCUTANEOUS INTERVENTION AND MYOCARDIAL REVASCULARIZATION IN PATIENTS WITH DM - ELEMENTS THAT SHOULD BE CONSIDERED

INTERVENÇÃO PERCUTÂNEA E REVASCULARIZAÇÃO MIOCÁRDICA NO PACIENTE COM DM - ELEMENTOS QUE DEVEM SER CONSIDERADOS

Marco Túlio de Souza[1]
Adriano Henrique Pereira Barbosa[1]
Adriano Caixeta[1,2]

1. Federal University of São Paulo, School of Medicine of São Paulo, Unifesp/EPM, Invasive Cardiology Sector, São Paulo, SP, Brazil.
2. Hospital Israelita Albert Einstein, São Paulo, SP, Brazil.

Correspondence:
Adriano Caixeta
Hosp. São Paulo - Setor de Hemodinamica. R. Napoleão de Barros, 715 - Vila Clementino, São Paulo, SP, Brazil. 04024-002
adriano.caixeta@einstein.br

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ABSTRACT

Coronary artery disease (CAD) is the leading cause of mortality and morbidity among patients with Diabetes Mellitus (DM). DM increases the risk of CAD and is an independent predictor of poorer outcomes after any method of coronary revascularization: percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The treatment of CAD in diabetics has important characteristics, and its presence should not be used in the choice of intervention method, especially in multiarterial patients and/or patients with unprotected left main stem disease. In addition to rigorous drug therapy being one of the fundamental pillars, the decision on the type of revascularization strategy should be made by a multiprofessional and multidisciplinary team ("Heart Team"), based on the clinical presentation, coronary anatomy, ischemic burden, left ventricular function, in-hospital surgical risk and individual patient risk.

Keywords: Diabetes mellitus; Angioplasty; Coronary disease; Myocardial revascularization.

RESUMO

A doença arterial coronariana (DAC) é a principal causa de mortalidade e morbidade entre os portadores de diabetes mellitus (DM). O DM aumenta o risco de DAC e é um preditor independente dos piores resultados após qualquer método de revascularização coronária: intervenção coronária percutânea (ICP) ou cirurgia de revascularização miocárdica (CRM). O tratamento da DAC em diabéticos possui características importantes e sua respectiva presença deve ser utilizada na escolha do método de intervenção, especialmente nos pacientes multiarteriais e/ou com lesão de tronco de coronária esquerda. Além da terapia medicamentosa rigorosa ser um dos pilares fundamentais, a decisão sobre a estratégia de revascularização deve ser tomada por uma equipe multiprofissional e multidisciplinar ("Heart Team"), baseando-se em elementos do quadro clínico, da anatomia coronária, carga isquêmica, função ventricular esquerda, risco cirúrgico hospitalar e do próprio paciente.

Descritores: *Diabetes mellitus; Angioplastia; Doenças das coronárias; Revascularização miocárdica.*

INTRODUCTION

Diabetes *mellitus* (DM) is a highly prevalent disease, and its significance lies on not only its increased incidence but also its direct relation to atherosclerosis.[1]

Coronary artery disease (CAD) is a leading cause of mortality and morbidity in patients with DM and responsible for over 75% of deaths in this population. Furthermore, it increases the risk of cardiovascular disease by two to four times and worsens the medical prognosis of the treated individuals, regardless of the established coronary revascularization procedure, when compared to patients without DM.[2]

CAD treatment in people with DM entails important particularities. Rigorous drug therapy is one of the fundamental pillars of the treatment, and the decision for revascularization strategy (percutaneous or surgical) must be based on the clinical condition, coronary anatomy, ischemic risk, left ventricular function, comorbidities, and the patient's preference. Patients must be provided with prior orientation as to the advantages and disadvantages of the therapy options (exclusive drug therapy, drug therapy associated with percutaneous treatment, and drug therapy associated with surgical treatment).[3]

THE ROLE OF THE "HEART TEAM" IN DECISION MAKING

The concept of the "Heart Team" or decision making by a multidisciplinary and multiprofessional collegiate team has become an essential and central topic in the treatment of cardiovascular diseases, especially CAD in complex patients (with multivessel disease and DM). The team is composed of a clinical cardiologist, interventional cardiologist, and cardiac surgeon, among others.

The discussion is based on the patient's risk, hospital risk, anatomic and clinical Synergy Between PCI with Taxus and Cardiac Surgery (SYNTAX) score, and clinical opinion of each specialist. It is also based on evidence from studies in coronaropathy, with one common aim: the best treatment strategy for the patient (percutaneous, surgical, or even clinical) in the search for better quality of life. Therefore, the current guidelines[3] recommend the execution of the "Heart Team" as Class I in these groups of patients.

EVIDENCE ON THE DIFFERENT MEANS OF REVASCULARIZATION

Patients with DM represent around 30% of all patients undergoing revascularization procedures, whether surgical or percutaneous, and present with more unfavorable clinical progress compared with those without DM.

The *Bypass Angioplasty Revascularization Investigation 2 Diabetes* (BARI 2D)[4] study examined 2,368 patients with stable CAD and type 2 DM. The patients were randomized for percutaneous coronary interventional (PCI) revascularization or coronary artery bypass grafting (CABG) associated with optimized medical therapy vs. isolated optimized medical therapy. In five years, there was no difference in the survival rates (88.3% vs. 87.8%; p=0.97) or survival free of significant cerebrovascular and cardiovascular events (77.2% vs. 75.9%; p=0.7) between the groups. It is important to note that this was not a study directly comparing PCI and CABG. Moreover, more than 80% of the patients were asymptomatic, with the equivalent of functional classifications I or II of ischemic heart disease or angina. After five years, 42.1% of the patients of the isolated medical therapy group underwent myocardial revascularization (PCI or CABG). When the patients were examined separately using the revascularization strategy, in the subgroup of individuals who underwent surgery, a significant reduction was observed in the combined outcome of death or nonfatal acute myocardial infarction (AMI) and cerebrovascular accident (CVA) when compared with that in patients managed with only pharmacological therapy. This benefit was not identified in patients who underwent PCI. However, it is worth highlighting that, generally, the patients who preferred surgery as a revascularization option presented with a more extensive CAD, which was subsequently corroborated by the analysis of the angiographic risk score of the BARI-2D study and its impact on clinical outcomes. Furthermore, the use of drug-eluting stents (DESs) in patients who underwent PCI in this study was low (35%, limited to first-generation stents).

A meta-analysis of 10 randomized studies was conducted, and more than 7,800 patients with multivessel disease were compared for CABG or PCI. In the medical follow-up of five and nine years, the mortality among the patients was similar (15% vs. 16%, respectively, HR 0.91; 95% CI 0.82–1.02, p=0.12). In patients with DM, there were lower mortality rates for those undergoing CABG than those undergoing PCI. However, the forms of PCI did not meet the level recommended by the current guidelines (balloon angioplasty (PCI) was practiced only in six studies and conventional stems in the remaining studies).

The *Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease* (FREEDOM) study[6] randomized 1,900 patients with DM and multivessel disease (at least two lesions with >70% by coronary angiogram) for treatment through CABG or PCI. Patients with lesions on the left coronary artery (LCA) were excluded. Around 80% of patients had triarterial CAD, and over 65% had a moderate- to high-risk SYNTAX score, the mean age was 63 years, and 25% presented with AMI previously. Over 4% of patients presented with significant ventricular dysfunction (<40%). The mean EuroSCORE was 2.7 (low risk for perioperative complications). The combined primary outcome (mortality for all cases, nonfatal AMI or CVA) occurred more frequently in the PCI group (26.6% vs. 18.7%, p<0.001) in the five-year follow-up. The benefits of CABG were impelled by the AMI rates (13.9% vs. 6%, p=0.049) and all-cause mortality rates (16.3% vs. 10.9%, p=0.049). CVA was more frequent in the CABG group (2.4% vs. 5.2%, p=0.03). New revascularization rates were also higher in the PCI group (12.6% vs. 4.8%; HR 2.74; 95% CI 1.91–3.89; p>0.001). Two limitations of this study can be underscored: 1) The exclusion rates of patients in the study increased – from a total of 32,966 eligible patients, only 1,900 (less than 6%) were randomized, which limits its applicability to the real world and external validity. 2) Despite the use of DESs, they were of first generation, which are not currently used due to inferior results in terms of thrombosis, MACE, restenosis, and new revascularizations in contrast to that with new-generation DESs.

Although surgery's superiority was demonstrated in all SYNTAX score tertiles in the FREEDOM study, it is worth noting that the score's analysis was not previously planned and not even conducted by an independent angiography laboratory, which may significantly interfere with the results.

In the SYNTAX study, when the subgroup of patients with DM was examined (n=452), both revascularization strategies demonstrated similar occurrences in the combined outcome of death, nonfatal AMI, and CVA in the tertile of low angiographic complexity (SYNTAX score≤22). In the medium- and high-complexity tertiles, there were benefits favorable to surgery. In all subgroups, surgery demonstrated superiority in reducing the need for new revascularization procedures.

Table 1 compares the different means of revascularization (PCI vs. CABG in multivessel CAD). Presently, there are no randomized studies comparing revascularization strategies (CABG vs. new-generation DESs). The ongoing studies ISCHEMIA and FAME 3 shall answer this question in the near future.

SYNTAX SCORE

The multicentered, prospective SYNTAX[7] study compared PCI and CABG in complex patients with multivessel disease, whether the LCA was compromised or not. The SYNTAX score was developed in order to quantify angiographic complexity, taking into consideration (in addition to the number and location of lesions) the morphology of each stenosis. Accordingly, it adapted several

Table1. Comparison between PCI and CABG in multivessel CAD treatment.

	PCI	CABG
Advantages	Less invasive	Complete revascularization
	Improvement in symptoms	Possibility of revascularization of more complex lesions (e.g., chronic occlusions)
	Less internment time	
	Lower risk for complications	
	Possibility for repetition	Improvement in symptoms
Disadvantages	Greater rates for new revascularizations	More invasive
	Restenosis/thrombus/ intrastent	Greater mortality risk
	Incomplete revascularization	Longer internment time
		Higher initial cost

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

classifications, definitions, and prior scores to create a broad, practical, and comprehensive algorithm. In general, the SYNTAX score is unlike other scores because it provides additional value to characteristics of complexity such as tortuosity, calcification, bifurcation, occlusion, and thrombus, among others.

Nevertheless, the contribution of each coronary segment in supplying blood to the left ventricle is used as a multiplication factor. Stenoses ≥50% located on any coronary vessel ≥1.5 mm in diameter were considered, with the stenosis differentiated as nonocclusive (50%–90%) and occlusive (100%). In the case of occlusion, the presence (and degree) of collateral circulation was also assessed. In the five-year clinical follow-up, the SYNTAX score did not interfere significantly with the clinical outcomes of CABG. However, in those undergoing PCI, the MACE (and encephalic vascular accident) rate was 32.1% in the group with low score (0-22), 36% in those with intermediate score (23–32), and 44% in those with high score (≥33).

Therefore, the SYNTAX score demonstrates its usefulness in guiding clinical decisions, in addition to detailing CAD complexity. Moreover, the SYNTAX II score, which combines angiographic and clinical factors, can be used as a tool for discriminating and predicting mortality in the long-term follow-up of the SYNTAX study. The clinical variables that constitute SYNTAX II score are age, creatinine clearance, left ventricular function, sex, chronic obstructive pulmonary disease, and peripheral artery disease. Recent studies indicate that the SYNTAX II score has a better predictive value than the isolated anatomic SYNTAX score in complex patients with multivessel disease and/or left main CAD.[8]

Current guidelines recommend the use of SYNTAX I and II scores as Class I in the stratification of patients with multivessel disease and/or left main CAD undergoing PCI.

PCI IN PATIENTS WITH DM

The angiographic characteristics of patients with DM are presented in Table 2. In addition to these characteristics, these patients more frequently present with other associated comorbidities than those without DM: arterial hypertension, dyslipidemia, chronic kidney disease, peripheral artery disease, and heart failure.

More than half of the patients with AMI do not know they have DM. The prevalence of DM in the general population is around 10%, while in interventional cardiology laboratories, it is estimated that approximately 25% of patients treated with PCI have DM.[9] Furthermore, the presence of DM increases the risk of kidney injury and complications after PCI.[10]

Complete or incomplete PCI: immediate or staged

Complete revascularization, whenever technically possible, must be performed, regardless of the type of approach (PCI or CABG). A substudy of the SYNTAX[11] confirmed, in the four-year follow-up, the benefit of this strategy: patients with multivessel disease were randomized for PCI or CABG treatment. Major adverse cardiac events occurred more frequently in incompletely revascularized patients, in both the PCI (39.9% vs. 26.6%; p=0.02) and surgical groups (27.8% vs. 18.7%; p=0.01).

The probable benefit of PCI for all vessels in the index procedure or even during the same internment is in the ACS scenario. The number of patients with multivessel disease is increasing, and around 50% of patients with AMI with ST-segment elevation have lesions on arteries other than those related to the infarction. Four randomized studies were conducted: PRAMI with 465 patients and 23 months of follow-up, CvLPRIT with 296 patients and 12 months of follow-up, DANAMI-3/PRIMULTI with 627 patients and 27 months of follow-up, and the most recent Compare-Acute with 885 patients and 12 months of follow-up. PCI of the non-culprit vessel was not conducted in the index procedure of PRAMI and Compare-Acute, during internment in DANAMI-3, or at any moment in CvLPRIT. The indication for non-culprit lesions was >50% in PRAMI and >70% in CvLPRIT or guided by the fractional flow reserve in DANAMI-3 and Compare-Acute. The primary outcome, impelled mainly by the need for new revascularization, was to infer in favor of complete revascularization in the four studies. The main question was regarding the moment of execution, during either the index procedure or the hospital phase. The European guidelines recommend complete revascularization during internment (*Class IIa, evidence level A*).[12]

TYPE OF STENTS UTILIZED IN PCI

In contemporary interventional cardiology, several studies and meta-analyses illustrate the superiority of new-generation DESs in contrast to that of the first-generation DESs and bare-metal stents (BMSs), especially in patients with DM. They are superior in terms of both efficacy and safety, with a striking reduction in the occurrence of adverse events, including nonfatal AMI, thrombosis, and new revascularization of a target lesion in all clinical scenarios.[13,14] In a

Table 2. Angiographic characteristics of patients with DM.

Greater prevalence of multivascular lesions
Greater prevalence of lesions in the left coronary artery (LCA)
Greater prevalence of total lesions
More serious and diffuse atherosclerosis plaques
More occurrences in distal vessels
Less collateral formation
Smaller reference diameter for the vessel
Greater prevalence of vulnerable plaques

DM: Diabetes *Mellitus*.

recently published study, with a follow-up of five years, the new-generation everolimus-eluting stent presented lower mortality rates than BMS.[15] These new-generation DESs have biocompatible or biodegradable polymers, combined with metallic platforms with finer stems.

A recent meta-analysis involving 3,582 patients with DM treated with PCI and BMS or DES showed that the use of the latter reduced the need for new interventions in the target lesion by more than 60%.[16] Another very recent meta-analysis involving 42 randomized studies and 22,844 patients with DM revealed that the new-generation DESs decreased restenosis rates by 37% to 69% in contrast to that with bare-metal stents.[17]

Duration of dual antiplatelet therapy (DAPT) in DM patients with CAD undergoing PCI.

The duration of DAPT after PCI has been cause for discussion, and the presence of DM must be taken into consideration in the duration. In general, the American guidelines[18] published in 2016 and European[19] guidelines published in 2017 recommend, as Class 1, DAPT for six months and BMS for 30 days for stable patients after a DES implant and DAPT for 12 months for patients in the ACS scenario with or without elevation and regardless of the type of treatment (clinical, PCI, or CABG).

The duration may be extended or reduced according to the patient's ischemic/hemorrhagic risks, and the decision regarding the ideal time is based mainly on personal risk. Two scores were developed to aid in the decision over the period. DAPT score 2016[18] was fundamental in predicting the patient's ischemic risk and encompasses nine variables (age, tobacco addiction, DM, AMI with ST-segment elevation at presentation, prior AMI/stent, first-generation DES, stent diameter<3 mm, ejection fraction<30%, PCI of saphenous vein grafts). Each variable is assigned points varying from -2 to +2. Each patient has a total ≥2 and has to tolerate and tolerated DAPT for 12 months, which can be extended for up to 30 months for the benefit of reducing ischemic events (NNT=34) at the expense of a slight increase in bleeding (NNT for damages=227). If the score is <2, DAPT is maintained for 12 months because, in these patients, the ischemic risks remain the same with an extension and the risk of bleeding increases significantly (NNT for damages=64).

PRECISE-DAPT score 2017[19] was developed to estimate hemorrhagic risks and consists of five variables (hemoglobin level, white blood cell count, age, creatinine clearance, and prior bleeding history), which can total from 0 to 100. In patients with values ≥25, DAPT can be used for a shorter period (three to six months). If this period is extended, it does not reduce ischemic events and also increases the risk for bleeding (NNT for damages=38). If the score is <25, DAPT may be extended for 12–24 months and decreases the risk of ischemic events (NNT = 65) without increasing the risk for bleeding.

CABG IN PATIENTS WITH DM

Patients with DM present with greater perioperative morbidity, such as kidney failure and infection of the operative wound. The survival rate is also lower for this subgroup of patients. In distinct studies, patients with DM present with greater mortality in 30 days (5% vs 2.5%), five years (22% vs. 12%), and ten years (50% vs. 29%) in contrast to those with DM.[20] Surgical risk may be predicted by the EuroSCORE or STS. Local surgical mortality rates must be taken into consideration when deciding on the type of revascularization.

One of the more serious complications of CABG is encephalic vascular accident. This complication has a mortality rate of 21%, twice as much internment time, and greater need for domestic care. The main predictors are diabetes (OR 2.59), hypertension (OR 2.31), advanced age (OR 1.75 by decade), and prior neurological disease (OR 3.19).

Surgical revascularization presents benefits in contrast to clinical treatment with respect to the decrease in mortality rate in subgroups of patients with significant ischemic risks, such as the presence of stenosis in the LCA, involvement of the left anterior descending artery, left ventricular dysfunction, large mass of myocardial ischemia, and low ischemic threshold. The studies that generated this hypothesis have confounders common to most pragmatic studies: insufficient use of arterial grafting, significant crossing over of clinical to surgical patients, and small sample sizes. The MASS II study followed patients for 10 years and unveiled a decrease in cardiac deaths, infarctions, and angina. In the STICH study, in 1,212 patients with an ejection fraction lower than 35%, excluding stenosis of the LCA, surgery was superior to clinical treatment in reducing overall mortality or hospitalization, without reducing mortality for the overall population. Nevertheless, under the "protocol" analysis, excluding patients allocated to clinical treatment but crossed for surgical (17%) or percutaneous (6%) revascularization, there was a decrease in mortality for surgical treatment (HR 0.70; 95% CI 0.58–0.84; P<0.001). In patients with acute coronary syndrome and who underwent CABG, the SYNTAX score's role is limited.

Thus, if surgical treatment is preferred, at least one arterial graft must be used, preferably the internal mammary artery to the left anterior descending artery. The utilization of bilateral internal mammary artery bypass grafting in people with DM is controversial due to the increased risk of infectious complications in the sternum. An alternative would be to use radial arteries in patients with an elevated risk for infection since studies reveal a better survival rate for venous grafting.

CONCLUSION

The presence of DM increases CAD risk and is recognized as an independent predictor of worse clinical outcomes after any coronary revascularization method (PCI or CABG). The presence of DM alone must not be a watershed for deciding on the type of intervention to apply in patients with multivessel disease and/or patients with lesions on the LCA. The decisions over which method to adopt must be made collegiately by a "Heart Team," considering the SYNTAX I and II scores, in-hospital surgical risk, and patient's risk.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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