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**Coronary artery disease in type 2 diabetes mellitus: Recent treatment strategies and future perspectives**

Naito R *et al.* Coronary artery disease in type 2 diabetes mellitus

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**Abstract**

Patients with type 2 diabetes mellitus (T2DM) are at a higher risk of developing coronary artery disease (CAD) than are non-T2DM patients. Moreover, the clinical outcomes in CAD with T2DM are poor despite improvements in medications and other interventions. Coronary artery bypass grafting is superior to percutaneous coronary intervention in treating multivessel coronary artery disease in diabetic patients. However, selecting a revascularization strategy depends not only on the lesion complexity but also on the patient’s medical history and comorbidities. Additionally, comprehensive risk management with medical and non-pharmacological therapies is important, as is confirmation regarding whether the risk-management strategies are being appropriately achieved. Furthermore, non-pharmacological interventions using exercise and diet during the earlier stages of glucose metabolism abnormalities, such as impaired glucose tolerance, might be beneficial in preventing the development or progression of T2DM and in reducing the occurrence of cardiovascular events.

**Key words**: Diabetes; Multivessel disease; Percutaneous coronary intervention; Drug-eluting stents; Comprehensive risk management

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**Core tip:** Clinical outcomes in coronary artery disease with type 2 diabetes mellitus (T2DM) are poor despite improvements in medications and other interventions. Although coronary artery bypass grafting is superior to percutaneous coronary intervention in multivessel coronary artery disease with T2DM, selecting the revascularization strategy depends not only on the lesion complexity but also on the patient’s medical history and comorbidities. In these patients, comprehensive risk management with medical and non-pharmacological therapies is indispensable, and confirming whether such risk management is being appropriately achieved is also important. Furthermore, interventions with exercise and diet therapy during the early stages of glucose abnormalities might be effective in preventing the development or progression of T2DM and in reducing the occurrence of cardiovascular events.

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**INTRODUCTION**

Patients with type 2 diabetes mellitus (T2DM) have a higher risk of developing coronary artery disease (CAD) than do patients without T2DM[1]. Additionally, 75% of T2DM patients die as a consequence of cardiovascular diseases, including CAD[2]. In patients with T2DM, CAD tends to be a more complex disease characterized by small, diffuse, calcified, multivessel involvement (multivessel disease, MVD)[3,4] and often requires coronary revascularization in addition to optimal medical therapy to control angina[5]. Regarding coronary revascularization, recent advances in the techniques and devices used during percutaneous coronary intervention (PCI) have expanded the indication of PCI to more complex lesions[6-8]. In particular, drug-eluting stents (DES) have reduced the restenosis and repeat revascularization rates[9,10]. However, the morbidity and mortality of CAD in patients with T2DM continues to be high, even in the current DES era[11]. Although most clinical trials comparing outcomes among T2DM patients with MVD have shown that coronary artery bypass grafting (CABG) was superior to PCI in terms of repeat revascularization and the incidence of myocardial infarction and mortality[12-17] (Table 1), it is not feasible to perform CABG in all diabetic patients with MVD. Because CABG is highly invasive in contrast to PCI, selecting a revascularization therapy depends not only on the lesion complexity but also on a patient’s medical history and comorbidities. SYNTAX score is a reliable score to assess coronary anatomical features and lesion complexity[16]. EuroSCORE is also a useful scoring system that is based on the clinical background information of an individual patient, which might predict the operative mortality for patients undergoing cardiac surgery[18]. Recently, revised versions of these two scoring systems were proposed. Because combining the SYNTAX score and other clinical variables have been demonstrated to be more accurate in identifying the risk of patients with complex CAD compared with the SYNTAX score alone, the SYNTAX score II was constructed, which included the original SYNTAX score and the following variables: the presence of unprotected left main CAD, female gender, chronic obstructive pulmonary disease, age and left ventricular ejection fraction[19]. Similarly, EuroSCORE II is an updated version of the original EuroSCORE, reconstructed from a large database of 22381 consecutive patients undergoing cardiac surgery in 43 countries in 2010 using a logistic regression model[20]. These scoring systems may provide additional and reliable information to better decide revascularization strategies. In clinical trials, higher-risk surgical patients, such as the elderly and those with more comorbid diseases, have been excluded. Therefore, selecting a revascularization therapy for CAD with T2DM requires a thorough discussion of the patient’s coronary anatomical features and lesion characteristics, age, and comorbid conditions.

Considering this issue, several important and as yet unresolved questions are raised including the following: (1) whether the newer DES are superior or similar in terms of repeat revascularization, incidence of myocardial infarction and mortality; (2) what can be done in conjunction with optimal medical and revascularization therapy to improve patient outcomes; and (3) whether early detection and intervention for CAD patients with undiagnosed T2DM or impaired glucose tolerance may improve mortality. In this editorial, we aim to provide novel insights into each of these specific questions and to consider the directions for future research.

**REVASCULARIZATION THERAPY - THE POTENTIAL OF NEWER DRUG-ELUTING STENTS AND BIORESORBABLE VASCULAR SCAFFOLDS**

First, it is essential to understand what types of outcome measures were used in clinical trials to evaluate the effectiveness of a given revascularization strategy or to determine the superiority of one revascularization therapy over another. Clinical trials for cardiovascular diseases often use a composite assessment of major adverse cardiovascular events as outcome measures including all-cause mortality, myocardial infarction, stroke and repeat revascularization. Because death and myocardial infarction are considered to be hard and preferably primary endpoints, whereas repeat revascularization is a less hard and secondary endpoint according to the severity of each case, the primary and secondary endpoints should be treated as two distinct endpoints.

Advances in PCI have prompted the selection of this procedure in more complex lesions that previously had been indicated for CABG. However, MVD in T2DM patients is associated with a high incidence of repeat revascularization after PCI with DES; therefore, CABG remains superior to PCI in such lesions. A meta-analysis has demonstrated that the superiority of CABG to PCI with balloon angioplasty or bare metal stents in terms of all-cause mortality was greater in patients with than without T2DM[21].

To date, several clinical trials have been conducted at 85 centers in the USA and Europe to compare CABG and PCI with DES. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) was a prospective randomized trial that compared the efficacy of CABG and PCI with paclitaxel-eluting stents (PES) for patients with de-novo left main coronary disease, three-vessel disease or both, which were considered equally suitable for CABG or PCI by both a cardiac surgeon and an interventional cardiologist at each center[22]. In the trial, 452 (25.1%) of the study population patients were diabetic, and these patients were included in a pre-specified sub-analysis. For 3-year major adverse cardiac and cerebrovascular events in the diabetic cohort, the incidence was 37.0% in the PCI group and 22.9% in the CABG group (*P* = 0.002). The rate of revascularization was also higher in the PCI group (PCI, 28.0% and CABG, 12.9%, *P* < 0.001)[23]. In 2012, a large-scale randomized trial known as the future revascularization evaluation in patients with diabetes mellitus (FREEDOM) trial was conducted. A total of 1900 diabetic patients with MVD were randomly assigned to CABG or to PCI with mainly sirolimus-eluting stents (SES) and PES[17]. The incidence of all-cause mortality and myocardial infarction was significantly lower in the CABG group during the mean follow-up period of 5 years compared with the DES group (CABG, 18.7% *vs* DES, 26.6%). Based on these results, the latest guidelines from the European Cardiology Society for the management of T2DM patients stated that PCI for MVD was a Class indication for relieving symptoms as an alternative to CABG in patients with low SYNTAX scores[24]. However, in the FREEDOM trial, almost all patients in the PCI group were treated with first-generation DES that were replaced by newer-generation DES used in current clinical practice. The newer generation DES have overcome the critical issue of stent thrombosis; in particular, the everolimus-eluting stent (EES) reduced myocardial infarction and stent thrombosis compared with other DES in a meta-analysis[25]. Recently, Bangalore and colleagues reported a meta-analysis of 68 randomized clinical trials to compare clinical outcomes in CAD patients with T2DM between those who received CABG and DES, including SES, PES and EES[26]. All-cause mortality was higher in the patients who received SES and PES compared with CABG, whereas the mortality rates in the EES group were similar to those of the CABG group [reference rate ratio to CABG, 1.31, 95% confidence interval (CI): 0.74-2.29]. These results should be carefully interpreted because they were generated from an indirect comparison of individual clinical trials. Ongoing randomized trials in evaluation of the Xience Prime or Xience V stents versus coronary artery bypass surgery for the effectiveness of left main revascularization (EXCEL) and bypass surgery versus everolimus-eluting stent implantation for approaching multivessel disease (BEST) aim to determine the effectiveness of EES. EXCEL is a randomized trial comparing EES and CABG in patients with left main trunk lesions and SYNTAX scores of 32 or less. The BEST trial aims to compare EES and CABG in MVD. In both trials, a sub-analysis for diabetic patients is intended.

Regarding other novel devices, bioresorbable vascular scaffolds (BVS) may be a candidate treatment of CAD in diabetic patients. BVS are novel intra-coronary devices that have potential advantages over metallic DES in terms of adverse coronary events such as stent thrombosis because unlike metallic DES, no uncovered struts or polymers exist after the scaffolds are resorbed[27].To date, only a single clinical study has reported on the efficacy of BVS in diabetic patients. Muramatsu *et al*[27] compared BVS and EES in diabetic patients using different clinical trials of each device and reported that the incidence of the clinical outcome, which was a composite of cardiac death, target vessel MI, or ischemia-driven target lesion revascularization, was similar between BVS and EES in diabetic patients (3.9% for the BVS *vs* 6.4% for EES, *P* = 0.38)[28].As described by the authors, the data analysis was performed using different pooled data and the study population number was quite small (*n* = 102 in the BVS group and 172 in the EES group). Further studies in a larger cohort of diabetic patients are required to demonstrate the safety and efficacy of BVS.

**COMPREHENSIVE RISK MANAGEMENT AND INTERVENTIONS**

Because clinical outcomes in T2DM patients with CAD are poor, aggressive medical and non-pharmacological therapies are indispensable, regardless of the revascularization strategy pursued. The bypass angioplasty revascularization investigation in type 2 diabetes (BARI-2D) trial examined and compared long-term clinical outcomes between medical therapy alone and revascularization by PCI or CABG in T2DM patients[14]. No significant difference was observed between the PCI and CABG groups in all-cause mortality or in the event-free survival rates for cardiovascular events during the 5-year follow-up period. These data indicated the importance of comprehensive risk management with glycemic control and the administration of statins, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and antiplatelet therapy in T2DM patients with CAD[21]. Guidelines for the management of diabetes mellitus from the American Diabetes Association, the American College of Cardiology and the American Heart Association recommend the following prevention strategies for CAD: blood pressure 130/80 mmHg or less, low-density lipoprotein cholesterol (LDL-C) below 100 mg/dL (below 70 mg/dL for CAD patients) and prompt smoking cessation[29-31]. However, a previous study examining the achievement of risk management in the large-scale clinical trials of clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE), BARI-2D and FREEDOM, showed unexpectedly low achievement rates[32]. One-year risk management achievement rates (LDL-C < 100 mg/dL, (70 mg/dL in the FREEDOM trial), systolic blood pressure < 130 mmHg, glycated hemoglobin < 7.0% and smoking cessation) were 18%, 23% and 8% in the COURAGE, BARI-2D and FREEDOM trials, respectively. Although the achievement rate was not originally included in the clinical trial endpoints, these results prompted us to review our clinical practices regarding not only adherence to evidence-based medical therapy but also whether risk management is being properly achieved. Furthermore, non-pharmacotherapeutic strategies including exercise, diet and smoking cessation should be pursued.

**INTERVENTIONS FOR IMPAIRED GLUCOSE TOLERANCE**

Considering that patients with T2DM tend to have macro- and microvascular complications and that the clinical outcomes of CAD patients are poor, interventions are desirable during the earlier stages of T2DM, such as impaired glucose tolerance (IGT). We understand that IGT is not simply an early stage of T2DM but rather an important state predisposing to T2DM. In fact, progression to diabetes was observed in 10% of IGT patients[33]. Additionally, it was suggested that IGT itself might have an impact on CAD morbidity and mortality[34]. However, it is not fully elucidated whether IGT in CAD patients might be a treatment target for secondary prevention the effects of anti-diabetic agents on reducing progression to diabetes or the incidence of cardiovascular events in such patients. Nevertheless, non-pharmacological therapies such as nutrition and exercise are important even in IGT patients.Previous studies reported that about one-third of CAD patients who had not been diagnosed with diabetes were actually diabetic[35,36]. Thus, aggressive evaluation for diabetes and IGT are required in CAD patients. In current clinical practice, although fasting blood glucose and glycated hemoglobin diabetes testing is routinely performed, the glucose tolerance test is not frequently performed in CAD patients unless the fasting blood glucose or glycated hemoglobin levels are above the upper limits of normal. To detect diabetes at an earlier stage, blood glucose, glycated hemoglobin and glucose tolerance tests for diabetes are considerably important.

**CONCLUSION**

When selecting revascularization strategies in diabetic patients, physicians must thoroughly consider not only a patient’s coronary artery lesions but also his/her medical history. Additionally, comprehensive risk management with medical and non-pharmacological therapies should be performed and the proper achievement of risk management should be confirmed. Furthermore, non-pharmacological interventions through exercise and diet therapy during the earlier stages of glucose metabolism abnormalities such as IGT may also be beneficial in preventing the development or progression of T2DM and in reducing the occurrence of cardiovascular events by either primary or secondary prevention of CAD.

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**Table 1 Clinical trials of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Trial | Type of trial  years of recruitment | Number of study population | Type of PCI | Endpoint | Main results  (PCI *vs* CABG) |
| ARTS Ι[12] | Randomized  1997-1998 | 208 | BMS | 1 yr freedom from death, stroke, MI or revascularization) | 63.4% *vs* 84.4% (*P* < 0.001) |
| MASS ΙΙ[13] | Randomized  1995-2000 | 115 | N/A | 1 year death | 5.3% *vs* 6.8% (*P* = 0.5) |
| BARI-2D[14] | Randomized  Comparison between revascularization and medical  2001-2005 | 1605 | 1st DES; 34.7%  BMS; 56.0%  Others; 9.3% | 5 yr freedom from death, MI, repeat revascularization | PCI *vs* medical (77.0 *vs* 78.9; *P* = 0.15)  CABG *vs* medical (77.6% *vs* 69.5%; *P* = 0.01)  *P* for interaction 0.002 |
| CARDIa[15] | Randomized  2002-2007 | 510 | 1st DES; 61%  BMS; 31% | 1 yr death, stroke, or MI | 13.0% *vs* 10.5% (*P* = 0.39) |
| SYNTAX[16] | Randomized  2005-2007 | 452 | 1st DES | 5 yr death, stroke, MI, or revascularization | 46.5% *vs* 29.0% (*P* < 0.001) |
| FREEDOM[17] | Randomized  2005-2010 | 1900 | 1st DES | 1. 5 yr death 2. 5 yr death, nonfatal MI, or nonfatal stroke | 1. 16.3% *vs* 10.9% (P = 0.049) 2. 26.6% *vs* 18.7% (*P* = 0.005) |

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; DES: Drug-eluting stent; ARTS: Arterial revasucularization Therapies Study; BMS: Bare metal stent; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; MASS: Medicine, Angioplasty, or Surgery Study; 1st DES: First generation DES.