Type 2 diabetes mellitus (T2DM) is a major risk factor affecting coronary artery disease (CAD). In addition, 75% of T2DM patients die as a consequence of cardiovascular diseases, including CAD. In patients with T2DM, CAD is more likely to be a complex disease characterized by small, diffuse, calcified, multivessel disease (MVD) and often requires coronary revascularization in addition to optimal medical therapy to control angina. Regarding coronary revascularization, recent advances in the techniques and devices related to percutaneous coronary intervention (PCI) have expanded the indication of PCI to more complex lesions. Drug-eluting stents (DES) in particular have dramatically reduced the rate of restenosis and repeat revascularization. However, the morbidity and mortality of CAD in patients with T2DM continues to be high, even in this current DES era. 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 the lower repeat revascularization rate and lower incidences of myocardial infarction and mortality, it is not practical to perform CABG in all diabetic patients with MVD. Because CABG is highly invasive in contrast to PCI, selection of each revascularization therapy should depend on not only the lesion complexity but also a patient’s characteristics and comorbidities. In clinical trials, higher-risk surgical patients, such as the elderly and those with more comorbid diseases, have not been included. Therefore, selecting a revascularization therapy for CAD with T2DM requires a thorough discussion of the lesion characteristics and patient characteristics including age, comorbidities, cardio-pulmonary function, and frailty.

Recently, novel anti-diabetic drugs have been demonstrated to have effectiveness on reducing cardiovascular events, which was independent of the glucose-lowering effect. Furthermore, non-pharmacological interventions using exercise and diet during earlier stages of abnormal glucose metabolism might be beneficial in preventing the development or progression of T2DM and reducing the incidence of cardiovascular events.

Here, we provide novel insights into the following important and unresolved issues: 1) efficacy of the newer DESs in terms of repeat revascularization, incidences of myocardial infarction and mortality compare to CABG, and 2) what is the optimal medical therapy considering the positive results of novel anti-diabetic agents.

Revascularization Therapy

Advances in PCI have prompted its use in more complex lesions that had been previously 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-anal-
sis 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.\(^1\) Several clinical trials have been conducted in the United States and Europe to compare CABG with PCI using DES. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study was a prospective randomized trial that compared the efficacy of CABG and PCI with paclitaxel-eluting stents (PES) in patients with *de novo* left main coronary disease, 3-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.\(^1\) In the trial, 452 (25.1%) patients were diabetic and were included in a pre-specified sub-analysis. For the 3-year major adverse cardiac and cerebrovascular events in the diabetic cohort, the incidence was 37.0% and 22.9% in the PCI group and CABG group (*P* = 0.002), respectively. The rate of revascularization was also higher in the PCI group (PCI, 28.0% and CABG, 12.9%, *P* < 0.001).\(^2\) In 2012, a large-scale randomized trial, 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 PCI with mainly first-generation DES.\(^3\) The incidences of all-cause mortality and myocardial infarction were significantly higher in the PCI group during the mean follow-up of 5 years compared with the CABG group (PCI, 26.6% versus CABG, 18.7%). Based on these results, the recent guidelines from the European Cardiology Society for the management of T2DM patients stated that PCI for MVD was a Class IIb indication for relieving symptoms as an optimal medical therapy and comprehensive risk management 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.\(^4\) There was no significant difference between the PCI and CABG groups in cardiovascular events during the 5-year follow-up. These data indicated the importance of comprehensive risk management with glycemic control and administration of statins, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and antiplatelet therapy in T2DM patients with CAD. Guidelines for the management of diabetes mellitus from the American Diabetes Association, American College of Cardiology, and American Heart Association recommended 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 smoking cessation.\(^5\) However, a recent study examining the achievement of risk management in the large-scale clinical trials clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE), BARI-2D, and FREEDOM, showed unexpectedly low achievement rates, which indicated the difficulty of comprehensive risk management.\(^6\) 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.\(^7\) 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
<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of trial</th>
<th>Years of recruitment</th>
<th>Number of subjects</th>
<th>Type of PCI</th>
<th>Endpoint</th>
<th>Main results (PCI versus CABG)</th>
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<tbody>
<tr>
<td>ARTS I</td>
<td>Randomized</td>
<td>1997-1998</td>
<td>208</td>
<td>BMS</td>
<td>1 year freedom from death, stroke, MI or revascularization</td>
<td>63.4 versus 84.4% ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>MASS II</td>
<td>Randomized</td>
<td>1995-2000</td>
<td>115</td>
<td>N/A</td>
<td>1 year death</td>
<td>5.3 versus 6.8% ($P = 0.5$)</td>
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<tr>
<td>BARI-2D</td>
<td>Randomized</td>
<td>Comparison between revascularization and medical 2001-2005</td>
<td>1605</td>
<td>1st DES; 34.7% BMS; 56.0% Others; 9.3%</td>
<td>5 year freedom from death, MI, repeat revascularization</td>
<td>PCI versus medical (77.0 versus 78.9; $P = 0.15$) CABG versus medical (77.6 versus 69.5%; $P = 0.01$) $P$ for interaction 0.002</td>
</tr>
<tr>
<td>CARDIA</td>
<td>Randomized</td>
<td>2002-2007</td>
<td>510</td>
<td>1st DES; 61% BMS; 31%</td>
<td>1 year death, stroke, or MI</td>
<td>13.0 versus 10.5% ($P = 0.39$)</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>Randomized</td>
<td>2005-2007</td>
<td>452</td>
<td>1st DES</td>
<td>5 year death, stroke, MI, or revascularization</td>
<td>46.5 versus 29.0% ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>Randomized</td>
<td>2005-2010</td>
<td>1900</td>
<td>1st DES</td>
<td>1) 5 year death 2) 5 year death, nonfatal MI, or nonfatal stroke</td>
<td>1) 16.3 versus 10.9% ($P = 0.049$) 2) 26.6 versus 18.7% ($P = 0.005$)</td>
</tr>
</tbody>
</table>

Table. Clinical Trials of PCI With CABG in Diabetic Patients

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting; DES, drug-eluting stent; ARTS, Arterial Revascularization Therapies Study; BMS, bare metal stent; MACE, major adverse cardiovascular event; MI, myocardial infarction; MASS, Medicine, Angioplasty, or Surgery Study; and 1st DES, first generation DES.
properly achieved. Furthermore, non-pharmacotherapies including exercise, diet, and smoking cessation should be performed.

Regarding the efficacy of strict glucose control with anti-diabetic drugs on reducing cardiovascular events, large-scale randomized trials conducted in the early 2000s have shown that intensive glucose control did not consistently reduce cardiovascular events. Since 2006, dipeptidyl peptidase-4 (DPP-4) inhibitors have been available as novel anti-diabetic drugs, which had a different mechanism of glucose-lowering compared with other agents such as sulfonylurea. To date, the results from 3 large-scale clinical trials (SAVOR, EXAMINE and TECOS) using different DPP-4 inhibitors have been reported (Figure 1). A consistent finding was that the DPP-4 inhibitor group was non-inferior to conventional glucose-lowering therapy for the primary outcomes of cardiovascular death, myocardial infarction, stroke, and/or hospitalization for unstable angina. However, hospitalization for heart failure was more likely in the DPP4 inhibitor group in SAVOR and EXAMINE, which was not observed in TECOS. Another class of novel anti-diabetic drugs is the glucagon-like peptide-1 (GLP1) receptor agonists that stimulate insulin secretion in a glucose-dependent manner and reduce glucagon secretion. A large-scale clinical trial has compared the efficacy of lixisenatide to that of the control on cardiovascular outcomes in patients with T2DM and ACS. This trial was designed to investigate both the noninferiority and superiority of lixisenatide to controls, however, it could only demonstrate the noninferiority. On the other hand, two large clinical trials (LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial and SUSTAIN-6 (Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes)), which aimed to assess the primary prevention effect of a glucagon-like peptide 1 analogue added to standard care compared to placebo in T2DM, showed a statistically significant reduction in a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. In the LEADER trial, a total of 9340 patients with T2DM were randomly assigned to liraxatinide with standard care or placebo. The primary endpoint (a composite of cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke) occurred in 13.0% and 14.9% in the liraxatinide group and the placebo group during the median follow-up of 3.8 years (hazard ratio 0.87; 95% confidence interval 0.78-0.97) (Figure 2). In the SUSTAIN-6 trial, a total of 3297 patients with T2DM, 83.0% of which had cardiovascular disease, were randomly allocated to semaglutide added to standard care or placebo. The rate of a composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was significantly lower in the semaglutide group (hazard ratio 0.74, 95% confidence interval 0.58-0.95). The other novel anti-diabetic drug was a sodium glucose cotransporter 2 (SGLT2) inhibitor that reduces renal glucose reabsorption and results in increased urinary glucose excretion as well as diuresis. Empagliflozin, a selective inhibitor of SGLT2, reduces glycated hemoglobin, systolic blood pressure without a heart rate increase, and body weight. In 2015, a striking result was reported by the EMPA-REG OUTCOME trial whose aim was to examine the effects of empagliflozin on cardiovascular events compared to standard-of-care therapy. They demonstrated the superiority of empagliflozin in reducing cardiovascular events, in particular cardiovascular death and hospitalization for heart failure (Figure 3). These recent clinical trials (EMPA-REG, LEADER, and SUSTAIN 6) have shed light on the cardiovascular protective effect of

Figure 1. Cardiovascular outcomes for DPP-4 inhibitors. Three DPP-4 inhibitors were consistently non-inferior to conventional glucose-lowering therapy for the primary endpoints of cardiovascular death, myocardial infarction, stroke, and/or hospitalization for unstable angina.
Consider that patients with T2DM tend to have macro- and microvascular complications, and the clinical outcomes of CAD patients are poor. Interventions are desirable during the earlier stages of T2DM, such as impaired glucose tolerance (IGT). Progression to diabetes was observed in 10% of IGT patients. However, it has not been fully elucidated whether IGT in CAD patients could be a treatment target for secondary prevention. Also, the effects of anti-diabetic agents including SGLT2 inhibitors and GLP-1 receptor agonists on reducing progression to diabetes or the incidence of cardiovascular events in this subset of patients are undetermined. 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. Thus, aggressive surveys for diabetes and IGT are needed in CAD patients. In current clinical practice, although diabetes testing with fasting blood glucose and glycated hemoglobin are routinely checked, the glucose tolerance test is not frequently performed in CAD patients unless fasting blood glucose or glycated hemoglobin levels are above the upper limits of normal. To detect diabetes at an earlier stage, diabetes testing with blood glucose, glycated hemoglobin, and glucose tolerance are considerably important.

Conclusions: In this review, the selection of appropriate coronary revascularization therapies and optimal medical therapy for comprehensive risk management in T2DM patients with CAD are described. When selecting revascularization strategies in this subset of patients, cardiologists and cardiac surgeons must thoroughly discuss as a heart team, based not only the complexity of the lesions but also the characteristics of the patient. Comprehensive risk management with medical and non-pharmacological therapies should be performed and confirm whether risk management is properly achieved. Novel anti-diabetic drugs (SGLT2 inhibitors and GLP1 antagonists) could be beneficial in reducing cardiovascular events, which might play an important role in optimal medical therapy. Furthermore, non-pharmacological interventions with exercise, calorie intake restriction, and smoking cessation might also be beneficial in preventing the development and progression of atherosclerosis.

References