Case Presentation
An asymptomatic and sedentary 58-year-old man with moderate overweight (body mass index, 29 kg/m²) and controlled hypertension was referred for a stress test. The patient had a highly positive stress test, with significant ST segment depression and tightening chest pain 2 minutes after the start of the exercise (40 Watts) followed by nonsustained ventricular tachycardia at rest. The physician hospitalized the patient into the coronary care unit for further evaluation. The echocardiogram was considered normal, without wall motion abnormalities, and serial troponin measurements remained normal. The patient was scheduled for next day coronary angiogram. In the morning, the laboratory evaluation included a fasting blood glucose value of 135 mg/dL, with a hemoglobin A1C of 7.4%, resulting in the likely diagnosis of previously unknown type 2 diabetes mellitus. Renal function was normal. The coronary angiogram showed a right-sided dominant coronary anatomy, with a focal lesion (75%) of the mid right coronary artery and with a fractional flow reserve (FFR) measured at 0.65. There were 2 focal and severe lesions in the left anterior descending artery (LAD), 1 proximal (95%) just before the first diagonal branch, which had also an intermediate ostial lesion, and 1 less tight lesion downstream (70%). FFR was not performed on the LAD because of the critical nature of the proximal lesion. The circumflex artery was a small artery without major branches. How would you manage this patient?

Background

Diabetes Mellitus and Coronary Artery Disease
Cardiovascular disease is the leading cause of morbidity and mortality in people with diabetes mellitus. Patients with diabetes mellitus have a 2- to 4-fold increase in risk of developing cardiovascular disease than those without diabetes mellitus, and also a 2- to 5-fold increase in mortality attributable to cardiovascular disease when compared with age- and sex-matched nondiabetic persons. Accelerated atherogenesis, blood abnormalities (altered platelet function, inflammation, hypofibrinolysis, and hypercoagulability), and myocardial vulnerability in diabetic patients are now considered as the causative factors for life-threatening cardiovascular events.

In coronary artery disease (CAD), atherosclerotic plaques can cause damage either with progressive evolution of the plaque volume leading to the narrowing of the lumen of the coronary arteries with subsequent ischemia, or with an unstable fissured plaque triggering local thrombosis, leading to an acute coronary syndrome.

Primary and secondary prevention of CAD remain unmet therapeutic challenges in diabetic patients. Drug management of CAD has evolved similarly for diabetic and nondiabetic patients, although the risk of complications and the long-term prognosis differ (Table 1).

Discovery of CAD in a Diabetic Patient
The presence of symptoms (typical angina or equivalents) in patients with type 2 diabetes mellitus has been associated with worse outcomes than in nondiabetic patients because it may indicate severe CAD. Silent myocardial ischemia discovered through resting ECG abnormalities, wall motion abnormalities in echocardiography, screening ischemic stress test, or FFR during
Coronary angiography, is more frequent in diabetic patients than nondiabetic patients and is associated with a worse prognosis. The management of CAD ranges from optimal medical therapy (OMT) to coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery (Figure 1).

**Medical Therapy Versus Revascularization**

Asymptomatic patients without ischemia or with limited ischemia should be treated with OMT only. However, there is uncertainty on therapeutic strategy when symptoms or moderate to severe ischemia are present. Advancements in both PCI and surgical techniques have continued to improve the safety and efficacy of coronary revascularization. However, results of randomized studies comparing myocardial revascularization with OMT only have been consistent in showing a lack of benefit of revascularization to reduce mortality or myocardial infarction in diabetic patients with stable CAD.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (n=2287) evaluated whether OMT plus PCI was better than OMT alone in patients with stable CAD who had objective evidence of myocardial ischemia and significant obstructive coronary lesions.\(^3,4\) The primary end point of death from any cause and nonfatal myocardial infarction (MI) during a median 4.6 years follow-up did not differ between the 2 treatment strategies, nor did the rates of MI or stroke. The 766 diabetic patients enrolled in the COURAGE trial had a higher rate of primary end points than nondiabetic patients (24.5% versus 16%), however no difference was found between the 2 therapeutics strategies in this subgroup of patients with rate of primary end points of 24.5% with OMT alone versus 25% with OMT plus PCI (hazard ratio, 0.99; 95% confidence interval, 0.73–1.32).\(^3\)

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (n=2368) evaluated whether PCI or CABG (choice left to the discretion of the treating physician) combined with OMT would be better than OMT alone in type 2 diabetic patients with stable CAD and angiographically documented CAD.\(^5\) The primary end point of all-cause mortality at 5 years follow-up did not differ between the 2 treatment strategies, nor did the rates of MI or stroke. Taken together, COURAGE and BARI-2D favor OMT alone in stable CAD patients and particularly in patients with diabetes mellitus.

However, these results need to be interpreted with caution and should be individualized, knowing that there are limitations to these 2 trials. The high crossover rates from OMT to revascularization suggest that revascularization was just deferred in one third of the patients randomized to a conservative approach. Also, not all of the subsets of patients with stable CAD commonly encountered in clinical practice were represented in these 2 trials. So, the results may not be applicable to all diabetic patients. Documented ischemia was not mandatory for enrollment in either trial. Therefore, many patients with severe ischemia underwent revascularization shortly after angiography, before they could be enrolled in the trial. In contrast, patients without significant ischemia may have been randomized more easily. Finally, the highest risk patients with severe presentation, those with complex CAD or left main artery disease or arrhythmic or hemodynamic
instability, were not enrolled in the COURAGE or BARI 2D trials. Neither were patients for whom revascularization was required for prompt control of severe angina.

Neither OMT nor revascularization overrides the fact that diabetic patients with CAD experience worse outcomes compared with nondiabetic CAD patients. The only situation in which revascularization is not debated is with a clinical presentation of ST-elevation myocardial infarction or non ST-elevation acute coronary syndrome.

**CABG or PCI Revascularization**

In the absence of multivessel disease or a lesion involving the left main, PCI is a simple and efficient technique to revascularize 1 vessel. As soon as the left main artery or 2 major epicardial vessels are involved, especially the LAD, discussion for the technique of revascularization must occur. The benefit of off-pump CABG in diabetics is still debated.6

The failure of PCI to show superiority over CABG in multivessel disease was initially attributed to the use of bare-metal stents, inadequate antiplatelet therapy to prevent stent thrombosis, and absence of optimal OMT for secondary prevention. The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial (n=1800) comparing PCI with the first generation of drug (paclitaxel) eluting stent (DES) with CABG for treating patients with previously untreated 3-vessel or left main coronary artery disease (or both) concluded that CABG was the best option for patients with 3-vessel with or without associated left main CAD.7 In the 452 diabetic patients of the SYNTAX trial, the 1-year major adverse cardiac and cerebrovascular event rate was higher with PCI-DES than with CABG, a difference driven by an increase in repeat revascularization that reached 20.3% in diabetic PCI patients versus 6.4% in diabetic CABG patients (P<0.001). Moreover, mortality in diabetic patients was higher in the PCI arm when compared with CABG (13.5% versus 4.1%, P=0.04).8

In the more recently published Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, 1900 diabetic patients with multivessel disease eligible for both revascularization techniques were randomized to PCI with DES (paclitaxel and sirolimus) versus CABG.9 The primary end point of all-cause mortality, nonfatal MI, or stroke over a mean 3.8 years follow-up favored CABG, with 18.7% of events at 5 years with CABG versus 26.6% with PCI (P=0.005). All cause mortality was lower with CABG at 5 years (10.3% versus 16.3% P=0.049). Repeat revascularization (13% versus 5% P<0.001) and nonfatal MI (13.9% versus 6.0% P<0.001) were higher with PCI. PCI had a lower rate of stroke (2.4% versus 5.2% P<0.001). These results from SYNTAX and FREEDOM are compelling in favor of CABG for patients with triple vessel disease (only 15% had 2-vessel disease in FREEDOM). The only subgroup of patients in whom PCI seems to do equally well with PCI, albeit with a higher rate of repeat revascularization, is the group with left main disease when isolated or with 1-vessel disease.10

Data on the best revascularization option for left main disease should be provided by the ongoing Evaluation of Xience Prime versus Coronary Artery Bypass

### Table 2. Selected Studies of Comparison of Revascularization Methods in Diabetic Patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Patient Group</th>
<th>Patients Follow-Up</th>
<th>PCI, %</th>
<th>CABG, %</th>
<th>P Value</th>
<th>MACCE (Including Repeat Revasc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al12</td>
<td>Registry</td>
<td>2007</td>
<td>Diabetic 205</td>
<td>LIMA, %</td>
<td>Follow-Up</td>
<td>10</td>
</tr>
<tr>
<td>Briguori et al13</td>
<td>Registry</td>
<td>2007</td>
<td>Diabetic 218</td>
<td>DES 100%</td>
<td>1 yr</td>
<td>5.9</td>
</tr>
<tr>
<td>Hannan et al14</td>
<td>Registry</td>
<td>2008</td>
<td>Diabetic 6100</td>
<td>DES 100%</td>
<td>N/A</td>
<td>6.9</td>
</tr>
<tr>
<td>Yang et al15</td>
<td>Registry</td>
<td>2008</td>
<td>Diabetic 352</td>
<td>DES 100%</td>
<td>1 yr</td>
<td>3.8</td>
</tr>
<tr>
<td>CARDIA16</td>
<td>Specific RCT</td>
<td>2008</td>
<td>Diabetic 510</td>
<td>DES 71%</td>
<td>1 yr</td>
<td>2.2</td>
</tr>
<tr>
<td>BARI 2D17</td>
<td>Indirect comparison</td>
<td>2009</td>
<td>Diabetic 953</td>
<td>DES 35%</td>
<td>5 yr</td>
<td>10.8</td>
</tr>
<tr>
<td>SYNTAX7</td>
<td>Subgroup analysis RCT</td>
<td>2009</td>
<td>Diabetic 452</td>
<td>DES 100%</td>
<td>5 yr</td>
<td>19.5</td>
</tr>
<tr>
<td>FREEDOM6</td>
<td>Specific RCT</td>
<td>2012</td>
<td>Diabetic 1900</td>
<td>DES 100%</td>
<td>5 yr</td>
<td>16.3</td>
</tr>
<tr>
<td>Wu et al18</td>
<td>Registry</td>
<td>2013</td>
<td>Diabetic 5784</td>
<td>DES 100%</td>
<td>5 yr</td>
<td>32.5</td>
</tr>
</tbody>
</table>

**BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes trial; CABG, coronary artery bypass graft; CARDIA, Coronary Artery Revascularization in Diabetes trial; DES, drug-eluting stent; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial; LIMA, left internal mammary artery; MACCE, major cardiovascular and cerebral events including repeat revascularization, with the exception of the registry of Hannan et al, which only provided Death or myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized, controlled trial; and SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery trial.**

*P<0.05.*

†After adjustment for propensity score for registries.
Diabetic Patients with CAD

<table>
<thead>
<tr>
<th>Diabetic patient with CAD and needing revascularization</th>
<th>PCI preferred</th>
<th>CABG preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single or two vessel disease, (non-proximal LAD, non-left main)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High surgical risk (comorbidities)</td>
<td></td>
<td></td>
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<tr>
<td>Contraindication to surgery</td>
<td></td>
<td></td>
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<tr>
<td>Elderly patients (&gt;65 yr) or frailty</td>
<td></td>
<td></td>
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<tr>
<td>MV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal LAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent restenosis (with DES in major arteries)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Choice of revascularization therapy in diabetic patients with CAD. CABG indicates coronary artery bypass graft; CAD, coronary artery disease; LAD, left anterior descending artery; and PCI, percutaneous coronary intervention.

Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial comparing CABG with PCI using the Xience everolimus eluting stent in 2500 patients (NCT01205776).

What Type of Revascularization?

Improvement in rates of repeat revascularization and lower rates of stent thrombosis with DES have influenced physician’s choice in the type of revascularization for diabetic patients. This is particularly true with the second-generation of DES using everolimus.11 PCI is also more attractive to patients with its percutaneous approach, its lower rate of stroke, and shorter length of hospital stay. According to the results of registries and randomized studies comparing the 2 techniques (Table 2) and in the absence of contraindication to surgery, PCI can be envisioned in diabetic patients with single or 2-vessel disease without complex lesions, when the proximal LAD is not involved.9,10 Patients presenting with ST-elevation myocardial infarction should undergo primary PCI of the culprit lesion only and then be reconsidered once stabilized for CABG if there is multivessel disease involving the LAD. For non-ST-elevation acute coronary syndrome, the choice is more difficult. These patients can be considered like stable CAD patients in terms of revascularization. Based on the recent results of the FAME-2 trial supporting the use of FFR measurement in stable CAD,20 FFR-guided PCI should be used more thoroughly to evaluate lesions in diabetic patients who are identified with multivessel disease.

How to Choose?

In low-risk stable CAD patients, the strategy of initial OMT is safe and should be the default approach. The choice can be PCI in diabetic patients with single or 2-vessel disease without involvement of the LAD. Discussion of the patient’s case with a multidisciplinary heart team should be considered to weigh the benefit and risk of PCI versus CABG (Figure 2).

Case Resolution

The patient was diagnosed with type 2 diabetes mellitus and CAD with multivessel disease. Although asymptomatic, the results of the stress test with possible life-threatening ventricular tachycardia made us consider the patient suitable for revascularization, and CABG was chosen as a first choice by the staff and accepted by the patients after explanation. He underwent revascularization with CABG using bilateral mammary artery grafts with an excellent immediate result and discharge without complications.

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Disclosures

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