Diabetes mellitus (DM) is caused by inadequate insulin secretion or an inability to respond appropriately to secreted insulin, which leads to chronic hyperglycemia. An estimated 171 million people worldwide have DM, and the prevalence of DM will more than double over the next 2 decades. Patients with DM have a 2- to 4-fold increased risk of coronary artery disease (CAD) over nondiabetic patients, and 75% of diabetic patients die as a result of a cardiovascular cause. Diabetic patients commonly undergo percutaneous revascularization procedures; 25% to 30% of all percutaneous coronary interventions (PCIs) are performed in patients with DM. A diagnosis of DM is also considered equivalent to having CAD because diabetic patients without a history of CAD have a 5-year cardiovascular mortality that is similar to that of nondiabetic patients who have a history of myocardial infarction (MI). According to current American College of Cardiology/American Heart Association guidelines, patients with DM are therefore treated as having a CAD equivalent. Previous review articles have summarized specific medical therapies for patients with DM. This review focuses on mechanisms of accelerated atherosclerosis, percutaneous and surgical revascularization strategies, and outcomes among patients with DM and CAD.

Mechanisms Linking DM, Atherosclerosis, and Outcomes After Coronary Revascularization
Diabetic patients have increased rates, extent, and complexity of atherosclerotic CAD. After coronary revascularization, diabetics have an increased risk of target vessel failure (TVF) and need for repeat interventions. Altered inflammatory pathways stemming from the effects of hyperglycemia, insulin resistance, and altered free fatty acid metabolism predispose diabetic patients to endothelial dysfunction, thrombogenesis, monocyte activation, foam cell formation, and altered smooth muscle cell migration. These mechanisms converge to create increased coronary artery plaque burden and more complex CAD (Figure 1A).

Endothelial Dysfunction and Immune Cell Migration
The endothelium plays a pivotal role in the maintenance of vessel tone and blood flow. Disruption of endothelial cell homeostasis can increase smooth muscle cell, leukocyte, and platelet activity. The role of hyperglycemia and insulin resistance in endothelial cell dysfunction is multifactorial. Endothelial cells control vessel tone by the regulated production of nitric oxide (NO) via phosphoinositol-3 kinase–dependent activation of endothelial NO synthase. NO promotes vasodilation but also possesses antiplatelet, anti proliferative, and antioxidant properties. In healthy individuals, insulin induces phosphoinositol-3 kinase signaling, leading to the production of NO and increased NO bioavailability. However, in patients with type 2 DM, the production of NO is impaired, leading to a decrease in vasodilation.

DM is also associated with increased production of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 that bind to endothelial surface receptors and activate nuclear factor-κB to induce transcription of endothelial cell adhesion molecules. The increase in adhesion molecule expression enhances binding of leukocytes and platelets to the surface of the endothelium, leading to increased thrombogenesis. Increased leukocyte migration to sites of coronary plaque may also promote local plaque inflammation and plaque instability.

Platelet Activation
Platelet activity is enhanced in patients with DM, with increased expression of P-selectin on the platelet surface and glycation of platelet surface receptors leading to increased platelet adhesion. DM is also associated with an increase in advanced glycation end products (AGEs), which result from the attachment of reducing sugars such as glucose to free amino groups via the Maillard reaction. AGEs induce endothelial cell signaling via receptors for AGEs. Through their binding to receptors for AGEs, AGEs can also induce the synthesis of proinflammatory cytokines and growth factors to increase tissue proliferation, to induce modification of the endothelial cell extracellular matrix, and to disrupt NO production. Production of AGEs is known to be enhanced in vivo in the setting of hyperglycemia and is thought to mediate many of the complications of DM, including vascular dysfunction.

Restenosis and Stent Thrombosis
The above mechanisms are associated with the increased development of clinically significant CAD among patients with DM. Patients with DM also have higher rates of adverse events after PCI as a result of both increased neointimal hyperplasia and an increased propensity for thrombosis (Figure 1B). Accelerated rates of neointimal hyperplasia...
have been demonstrated in both rat and human studies after angioplasty in type 2 DM. Increased neointimal hyperplasia in the diabetic artery after coronary intervention may result partly from increased production of transforming growth factor-β and smooth muscle cell migration and proliferation caused by the hyperglycemic state. Animal models of endovascular stent placement have also shown that DM is associated with increased extracellular signal-related kinase activation but a reduction in Akt signaling. Sirolimus, but not paclitaxel, activates Akt signaling, leading to increased smooth muscle cell proliferation in the setting of hyperglycemia. These drug-specific signaling effects of antiproliferative agents may in part explain the differential efficacy of sirolimus-eluting stents (SES) in patients with DM (see below).

The neointima of patients with DM may also have biological alterations that predispose to stent thrombosis (ST): When visualized by optical coherence tomography, the neointima in diabetic patients has a low-signal pattern that may be associated with increased proteoglycan content and organized thrombi. Platelets from diabetic patients are more reactive than those of nondiabetic patients, further increasing the risk of thrombosis. Recent advances in antiplatelet therapies have been shown to be beneficial to both diabetic and nondiabetic patients in the prevention of atherothrombosis, and in certain studies, antiplatelet agents have decreased the gap in thrombosis risk between diabetics and nondiabetics for end points such as ST (see Pharmacotherapy After Revascularization in Patients With DM below).

These findings emphasize that the choice of antiplatelet therapies, lipid-lowering therapies, and method of glycemic control must be considered as a whole when treating patients with DM. As a result of the multiplicity and redundancy of pathophysiological mechanisms in diabetics, no single therapy will be effective in all patients. Therapies that affect multiple pathophysiological mechanisms such as weight loss and exercise are likely to be the most effective treatments in the long term.

### Appropriateness and Timing of Revascularization in Patients With DM

Patients with DM and CAD are at high risk of subsequent cardiovascular events, regardless of symptoms. Whether such patients with stable CAD should undergo prompt revascularization is an important clinical question with broad implications for risk stratification and treatment. The prospective, randomized Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial compared prompt revascularization (either coronary artery bypass graft surgery [CABG] or PCI) of patients with DM and stable CAD with concurrent aggressive medical treatment with aggressive medical treatment alone, as well as glycemic control strategies. A total of 2368 patients with type 2 DM were enrolled and followed up for 5 years. The primary end point of the trial was 5-year mortality, which demonstrated no difference between the revascularization plus medical treatment group and the initial medical treatment alone group. There was also no difference in outcomes between the 2 glycemic control strategy groups at 5 years.

Although the BARI 2D trial was not designed to compare CABG and PCI, there was a significant decrease in the rate of composite cardiovascular events when CABG revascularization was compared with the medical therapy alone group that was not seen in the PCI group. This suggested that there was a benefit to prompt revascularization in diabetic patients in whom CABG was the preferred revascularization treatment but that this benefit was not seen in those in whom PCI was the preferred treatment. Of note, this study was carried out during the first clinical use of drug-eluting stents (DES). Approximately 35% of diabetic patients undergoing
PCI as part of the BARI 2D trial received DES, and the remainder received either a bare metal stent (BMS; 56%) or no stent (9%).

The results of the BARI 2D trial suggest that an initial strategy of medical therapy is reasonable in patients with DM and stable CAD, with the recognition that a large percentage of such patients (38% at the 5-year follow-up in the BARI 2D trial) may eventually require revascularization. The initial 2009 appropriate use criteria document for coronary revascularization included DM as a clinical decision point for the type of revascularization (eg, CABG versus PCI), but the presence of DM did not alter the appropriateness of a given method of revascularization.35 The 2012 appropriate use criteria update does not include DM as a variable for the appropriateness of revascularization or method of revascularization but instead uses the Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) score to stratify the presence of DM did not alter the appropriateness of a given method of revascularization. The 2012 appropriate use criteria update does not include DM as a variable for the appropriateness of revascularization or method of revascularization but instead uses the Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) score to stratify the presence of DM did not alter the appropriateness of a given method of revascularization.35 The 2012 appropriate use criteria update does not include DM as a variable for the appropriateness of revascularization or method of revascularization but instead uses the Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) score to stratify the presence of DM did not alter the appropriateness of a given method of revascularization.35

**Clinical Trials Comparing Surgical Revascularization and PCI in Patients with DM**

A number of large-scale trials have compared CABG with PCI (Table 1). These trials have been conducted in parallel with the development of new PCI technologies and refinement in surgical techniques, including angioplasty (the BARI trial), BMS (Arterial Revascularization Therapies Study [ARTS]-I), and most recently, first-generation DES (the SYNTAX trial). Each of these trials included a large percentage of patients with DM. More recently, the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial specifically randomized patients with DM to CABG or PCI.

The BARI trial compared the safety and efficacy of CABG and percutaneous transluminal coronary angioplasty in a randomized population of patients with multivessel disease. This trial, which enrolled 1829 patients, showed that diabetic patients who underwent CABG had increased rates of 10-year survival and decreased rates of MI compared with those who underwent percutaneous transluminal coronary angioplasty.37 Contemporaneous smaller trials yielded conflicting results, with some finding increased survival of diabetic patients undergoing CABG compared with percutaneous transluminal coronary angioplasty,38-40 and others finding no difference in survival of diabetic patients treated with CABG versus PCI.41-44

**Table 1. Major Recent Studies Comparing PCI With CABG Among Patients With DM**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Study Period</th>
<th>Type of PCI</th>
<th>Patients per Arm, n</th>
<th>Patients With DM, n (%)</th>
<th>Follow-Up, y</th>
<th>Primary End Point in DM</th>
<th>Outcome in DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS or DES</td>
<td></td>
<td>BMS</td>
<td>600 BMS</td>
<td>208 (17.3)</td>
<td>5</td>
<td>Composite MACCEs</td>
<td>CABG&lt;BMS</td>
</tr>
<tr>
<td>ARTS-I</td>
<td>1997–1998</td>
<td>Cypher SES</td>
<td>607 SES</td>
<td>255 (21.0)</td>
<td>5</td>
<td>Composite MACCEs</td>
<td>CABG&lt;SES&lt;BMS</td>
</tr>
<tr>
<td>ARTS-II</td>
<td>2003–2003</td>
<td>Cypher SES</td>
<td>605 CABG (from ARTS-I)</td>
<td>2368 (100)</td>
<td>5</td>
<td>All-cause mortality</td>
<td>Similar outcomes for medical therapy and revascularization</td>
</tr>
<tr>
<td>BARI 2D</td>
<td>2000–2008</td>
<td>PTCA/PCI/DES</td>
<td>1605 PCI</td>
<td>510 (100)</td>
<td>5</td>
<td>Composite all-cause death, nonfatal MI, and nonfatal stroke</td>
<td>No difference between CABG and PCI</td>
</tr>
<tr>
<td>CARDia</td>
<td>2002–2007</td>
<td>BMS or Cypher SES</td>
<td>256 PCI</td>
<td>452 (25.1)</td>
<td>3</td>
<td>Composite MACCEs</td>
<td>Increased MACCEs in PCI</td>
</tr>
<tr>
<td>DES</td>
<td></td>
<td>TAXUS PES</td>
<td>903 PES</td>
<td>1900 (100)</td>
<td>5</td>
<td>Composite all-cause mortality, MI, and stroke</td>
<td>CABG better for DM in all outcomes</td>
</tr>
<tr>
<td>PRECOMBAT</td>
<td>2004–2009</td>
<td>Cypher SES</td>
<td>300 SES</td>
<td>192 (32)</td>
<td>1</td>
<td>Composite MACCEs</td>
<td>No difference between PCI and CABG</td>
</tr>
<tr>
<td>EXCEL</td>
<td>2010–current</td>
<td>Xience V EES</td>
<td>3000 CABG</td>
<td>2600 (estimated)</td>
<td>Ongoing</td>
<td>Composite all-cause mortality, MI, and stroke</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

ARTS indicates Arterial Revascularization Therapies Study; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; BMS, bare metal stent; CABG, coronary artery bypass graft; CARDia, Coronary Artery Revascularization in Diabetes; DES, drug-eluting stent; DM, diabetes mellitus; EES, everolimus-eluting stent; EXCEL, Evaluation of Xience Prime or Xience V Stents Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; E-ZES, Endeavor zotarolimus-eluting stent; FREEDOM, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; PES, paclitaxel-eluting stent; PCI, percutaneous coronary intervention; PRECOMBAT, Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; PTCA, percutaneous transluminal coronary angioplasty; R-ZES, Resolute zotarolimus-eluting stent; SES, sirolimus-eluting stent; and SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.
Application of BMS or early-generation DES led to improved outcomes of PCI among diabetic patients, thereby narrowing the outcomes gap with CABG. ARTS-I and ARTS-II compared the safety and efficacy of CABG versus BMS (ARTS-I) and CABG versus SES (ARTS-II) in patients with and without DM. Among patients with DM, there was no difference in 3-year major adverse cardiac and cerebrovascular events (MACCEs) between CABG, BMS, and SES, but CABG and SES each showed decreased rates of death and MI compared with BMS historical comparisons. At the 5-year follow-up, SES-treated patients had lower rates of MACCEs than patients previously randomized to BMS, but CABG remained superior to both PCI strategies. SES was also associated with an increased risk of repeat revascularization at 5 years compared with CABG. Similarly, in the Coronary Artery Revascularization in Diabetes (CARDia) Trial, PCI (either BMS or DES) was compared with CABG in diabetic patients with multivessel disease and demonstrated that there were no differences in death, MI, or stroke when PCI and CABG were compared. However, treatment with PCI in diabetic patients was associated with an increased incidence of late MI and the need for repeat revascularization at 1 year.

The SYNTAX study examined the use of the TAXUS paclitaxel-eluting stents (PES) versus CABG for the treatment of diabetic and nondiabetic patients with multivessel disease. In agreement with many other studies, this study found that diabetic patients had increased rates of MACCEs and revascularization compared with nondiabetic patients. Furthermore, both diabetic and nondiabetic patients treated with PES demonstrated increased rates of MACCEs and repeat revascularization compared with those treated with CABG out to the final 5-year follow-up. These results suggested that in patients with complex disease (as determined by the SYNTAX score), CABG remains the preferred method of revascularization over PES. However, for patients with lower disease complexity (SYNTAX score ≤22), PCI was noninferior to CABG in terms of all MACCE end points. Therefore, PCI may be an acceptable alternative to CABG in diabetic patients with lower disease complexity.

The FREEDOM trial, a randomized trial of 1900 patients with multivessel disease and DM, examined the use of PCI (primarily first-generation PES or SES) versus CABG. Patients with DM who underwent CABG had a decreased incidence of MI (6.0% versus 13.9%) and all-cause mortality (10.9% versus 16.3%) at 5 years compared with those who underwent PCI. However, patients randomized to CABG had an increased rate of stroke (5.2% versus 2.4%). Of note, there was no interaction between SYNTAX score and outcomes among the overall population, suggesting that the increased event rate among patients randomized to PCI was not related to the anatomic complexity of disease at the time of revascularization. The FREEDOM trial enrolled patients at lower surgical risk with preserved ejection fractions; therefore, the conclusions of the trial may not be applicable to patients at higher risk for surgery with comorbidities such as left ventricular dysfunction, stroke, renal insufficiency, neuropathy, peripheral arterial disease, and frailty. Because patients at high surgical risk have not been studied in any of the trials reviewed here, it is reasonable that a multidisciplinary heart team should evaluate patients at high surgical risk for the best revascularization strategy. In many of these cases, PCI may remain the preferred strategy owing to the less invasive nature of this approach.

Upcoming randomized studies of second-generation stents will continue to address important questions about revascularization strategies in patients with DM. The Evaluation of Xience Prime or Xience V Stents Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial will enroll ≥2600 patients with left main disease and a SYNTAX score of ≤32 to compare the Xience Prime everolimus-eluting stents (EES) with CABG. Patients with DM will be a prespecified subgroup of this study. Additionally, the Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Disease (BEST) trial (NCT00997828) will examine the use of the Xience V EES versus CABG in patients with multivessel disease. Analysis of the diabetic subgroups of the FREEDOM, EXCEL, and BEST trials will shed further light on the safety and efficacy of second-generation DES in patients with DM.

**DES in Patients With DM**

DES are associated with a decreased rate of restenosis compared with BMS in both diabetic and nondiabetic patients. Pooled analysis of these studies has raised some controversy about the relative efficacy of different DES types in DM. A recent mixed-treatment comparison meta-analysis of 42 randomized trials that included 10714 patients with DM found that DES as a whole were associated with a 37% to 69% reduction in target vessel revascularization compared with BMS, but the magnitude of this reduction varied with stent type. In the following discussion, we review recent data on the efficacy of first-, second-, and newer-generation DES platforms among patients with DM. In each case, we highlight the available data comparing stents types among patients with DM (Table 2).

**First-Generation DES**

**Paclitaxel-Eluting Stents**

A large meta-analysis examined the outcomes of BMS versus the first-generation TAXUS PES in 5 prospective, randomized trials enrolling 2797 patients (TAXUS Clinical Program). The authors demonstrated similar 5-year safety and efficacy between PES and BMS in diabetic patients. In the TAXUS IV study, PES decreased the overall rates of TVF, target lesion revascularization (TLR), and major adverse cardiovascular events (MACEs) in diabetic and nondiabetic patients. Additional studies demonstrated no difference in rates of ST, MI, death, or neointimal proliferation in diabetic and nondiabetic patients treated with PES. Importantly, patients with type 2 DM who required insulin therapy were at increased risk for MACEs, TVF, and target vessel revascularization compared with patients with type 2 DM who were treated with oral medications.

**Sirolimus-Eluting Stents**

The German Multicenter Randomized Single Blind Study of the CYPHER Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery
Lesions (SCORPIUS) trial examined the safety and efficacy of SES versus BMS in a small group of diabetic patients. Treatment with SES led to a reduction in 5-year overall MACEs, attributable mostly to a decrease in 5-year TLR. Safety endpoints of all-cause mortality, cardiac death, MI, and ST were similar between SES and BMS in diabetic patients.63 A combined analysis of 4 randomized trials comparing SES and BMS with 5 years of follow-up found no difference in overall rates of MACEs among the overall study population. However, patients with DM treated with SES had significantly higher rates of deaths resulting from cardiac causes than patients treated with BMS (15.9% versus 9.0%).62 This finding has raised the concern of possible increased ST rates among patients with DM treated with SES, although other studies have suggested decreased rates of mortality among diabetic patients treated with first-generation DES.63

### Table 2. Major Studies Comparing DES Types Among Patients With DM

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Study Period</th>
<th>Type of PCI</th>
<th>Patients per Arm, n</th>
<th>Patients With DM, n (%)</th>
<th>Follow-Up, y</th>
<th>Primary End Point in DM</th>
<th>Outcome in DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIRIT V</td>
<td>2006–2007</td>
<td>XIENCE EES vs TAXUS PES</td>
<td>218 EES</td>
<td>324(100)</td>
<td>1</td>
<td>In-stent late loss</td>
<td>PES increased late loss</td>
</tr>
<tr>
<td>ESSENCE-DIABETES</td>
<td>2008–2009</td>
<td>XIENCE EES vs Cypher SES</td>
<td>149 EES</td>
<td>300(100)</td>
<td>1</td>
<td>Angiographic in-segment late loss</td>
<td>No difference between EES and SES</td>
</tr>
<tr>
<td>PROTECT</td>
<td>2007–2008</td>
<td>E-ZES vs Cypher SES</td>
<td>4357 ZES</td>
<td>2410(28)</td>
<td>3</td>
<td>Stent thrombosis</td>
<td>ZES better in all patients, no difference between DM and non-DM</td>
</tr>
<tr>
<td>NAPLES-DIABETES</td>
<td>2005–2007</td>
<td>E-ZES vs TAXUS PES vs Cypher SES</td>
<td>75 ZES</td>
<td>226(100)</td>
<td>3</td>
<td>Composite MACEs</td>
<td>Increased MACEs in ZES vs PES and SES</td>
</tr>
<tr>
<td>SCAAR</td>
<td>2004–2008</td>
<td>E-ZES vs TAXUS PES vs Cypher SES</td>
<td>3531 ZES</td>
<td>8231(23)</td>
<td>4</td>
<td>Restenosis</td>
<td>Increased restenosis with ZES</td>
</tr>
<tr>
<td>RESOLUTE US</td>
<td>2008–2009</td>
<td>R-ZES vs E-ZES</td>
<td>1402 R-ZES</td>
<td>374(25)</td>
<td>1</td>
<td>TLF and composite TVF</td>
<td>No difference between E-ZES and R-ZES in DM or non-DM</td>
</tr>
<tr>
<td>TWENTE</td>
<td>2008–2010</td>
<td>E-ZES vs XIENCE V EES</td>
<td>697 ZES</td>
<td>301(22)</td>
<td>1</td>
<td>TVF</td>
<td>No difference between ZES and EES</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent; DM, diabetes mellitus; EES, everolimus-eluting stent; ESSENCE-DIABETES, Comparison of Everolimus-Eluting Stent vs Sirolimus-Eluting Stent in Patients With Diabetes Mellitus; E-ZES, Endeavor zotarolimus-eluting stent; MAC, major adverse cardiovascular event; MI, myocardial infarction; NAPLES-DIABETES, Novel Approaches for Preventing or Limiting Events in Diabetic Patients; PES, paclitaxel-eluting stent; R-ZES, Resolute zotarolimus-eluting stent; SCAAR, Swedish Coronary Angiography and Angioplasty Register; SES, sirolimus-eluting stent; SPIRIT, A Clinical Evaluation of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Coronary Artery Lesions; TLF, target lesion failure; TVF, target vessel failure; and ZES, zotarolimus-eluting stent.

Comparisons of PES and SES Among Patients With DM
A mixed-comparison meta-analysis comparing SES, PES, and BMS in 3852 diabetic patients found that the 2 DES types were associated with lower mortality in diabetic patients than BMS, but as suggested by other studies, mortality in diabetic patients remained higher than in nondiabetic patients.58 SES also showed an advantage over PES for ST and longer event-free follow-up in diabetic patients at 1 year. When these results were followed to 5 years, the early advantage of SES was lost in the general population, but SES remained advantageous for diabetic patients.64,65 Further stratification of diabetic patients into those requiring insulin and those not requiring insulin has shown that patients with DM who require insulin treatment have the highest rates of restenosis regardless of stent type. The above-mentioned mixed-treatment comparison also favored SES over PES in a head-to-head comparison of the outcome of target vessel revascularization for the treatment of diabetic patients.10

Second-Generation DES
Second-generation DES have optimized drug deliverability while seeking to minimize TLR and the risk of ST. Numerous studies have examined the relative efficacy of second-generation DES among patients with DM. Overall, these studies have found that event rates among diabetic patients remain higher than for the general population but that most of this effect on outcomes is driven by the subset of patients with DM who require insulin therapy.

Everolimus-Eluting Stents
Initial studies with follow-up angiography demonstrated decreased rates of angiographic restenosis among diabetic patients treated with EES compared with PES. A pooled study comparing the use of the Xience V EES and TAXUS Liberté PES (A Clinical Evaluation of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Coronary Artery Lesions [SPIRIT] V diabetic study) determined that the rate of angiographic lumen loss, which reflects the degree of neointimal hyperplasia, was reduced in diabetic patients treated with EES compared with PES without any effect on safety outcomes.66 Further studies demonstrated that EES were associated with decreased neointima formation, lumen loss, and vessel narrowing in diabetic patients as measured by intravascular ultrasound compared with PES.66 These findings concur with recent studies in which EES decreased rates of ST up to 1 year after treatment in diabetic
patients compared with PES, with similar composite TLR-MACE outcomes between the stent types.\textsuperscript{65} In the Comparison of Everolimus-Eluting Stent vs Sirolimus-Eluting Stent in Patients With Diabetes Mellitus (ESSENCE-DIABETES) trial comparing EES and SES in diabetic patients, EES was associated with decreased in-segment lumen loss, restenosis rates, and ST in diabetic patients while maintaining safety outcomes similar to SES.\textsuperscript{68}

Other studies have suggested that EES may have less relative benefit among patients with DM. A pooled analysis of the SPIRIT II, SPIRIT III, SPIRIT IV, and Comparison of the Everolimus Eluting XIENCE-V Stent With the Paclitaxel Eluting TAXUS Liberté Stent in All-Comers (COMPARE) trials evaluated the second-generation EES system, Xience V/ PROMUS, versus the first-generation TAXUS Liberté PES. Strikingly, nondiabetic patients receiving EES had decreased mortality, MI, ST, and TLR compared with those receiving PES in the overall population, whereas there were no differences in efficacy or safety outcomes between the 2 stent platforms among patients with DM (Figure 2).\textsuperscript{69} These unexpected differential effects in patients with DM versus those without DM highlight the as-yet uncertain mechanistic links between stent drug elution and adverse events after PCI. Similarly, the SPIRIT IV trial demonstrated no difference in efficacy between EES and SES in diabetic patients with \( \leq 3 \) de novo lesions, even though marked increases in efficacy were shown in the nondiabetic population.\textsuperscript{70} Consistent with other studies, patients with DM who required insulin had higher rates of these adverse outcomes than patients with DM treated with oral agents.

**Zotarolimus-Eluting Stents**

The Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease (ENDEAVOR) IV trial examined the second-generation Endeavor zotarolimus-eluting stent (E-ZES) in patients with a single de novo lesion and demonstrated noninferiority of E-ZES to the TAXUS PES in both diabetic and nondiabetic populations treated with E-ZES and SES,\textsuperscript{73} suggesting similar long-term safety outcomes between the 2 stents. A direct comparison of SES, PES, and E-ZES in type 2 DM patients was undertaken in the Novel Approaches for Preventing or Limiting Events in Diabetic Patients (NAPLES-Diabetes) Trial. Results from this trial indicated that treatment of diabetic patients with E-ZES compared with either SES or PES led to increased 3-year rates of MACEs, largely as a result of a higher rate of TLR.\textsuperscript{74} Similar results were found in the Swedish Coronary Angiography and Angioplasty Register (SCAAR) study.\textsuperscript{76}

**Comparisons of PES, SES, and ZES**

Direct comparison of E-ZES with SES in the Randomized Clinical Comparison of the Endeavor and the Cypher Coronary Stents in Non-selected Angina Pectoris Patients (SORT OUT III) trial demonstrated that treatment with E-ZES was associated with increased rates of MACEs, target vessel revascularization, and TLR in both diabetic and nondiabetic patients at 18 months, but these increases were much greater in the diabetic population.\textsuperscript{74} In comparison, the Patient Related OuTcomes with Endeavor versus Cypher stenting Trial (PROTECT) study showed comparable levels of definite ST at 3 years in both diabetic and nondiabetic populations treated with E-ZES and SES,\textsuperscript{75} suggesting similar long-term safety outcomes between the 2 stents.

A direct comparison of SES, PES, and E-ZES in type 2 DM patients was undertaken in the Novel Approaches for Preventing or Limiting Events in Diabetic Patients (NAPLES-Diabetes) Trial. Results from this trial indicated that treatment of diabetic patients with E-ZES compared with either SES or PES led to increased 3-year rates of MACEs, largely as a result of a higher rate of TLR.\textsuperscript{73} Similar results were found in the Swedish Coronary Angiography and Angioplasty Register (SCAAR) study.\textsuperscript{76}
Resolute ZES

Recently, the latest-generation Resolute ZES (R-ZES) became the first DES to gain a Food and Drug Administration labeling indication for patients with DM. The R-ZES sought to improve on E-ZES with controlled drug release over a longer time period while maintaining the safety outcomes observed with E-ZES.77 Food and Drug Administration approval was based on a prespecified performance goal in diabetic patients.78 The study population included 878 diabetic and matched control subjects from the Global Resolute Clinical Trial Program. A prespecified performance goal of 14.5% TVF, which included cardiac death, MI not attributable to other vessels, and target vessel revascularization, was implemented on the basis of a meta-analysis of published studies in diabetic patients treated with first-generation SES and PES stents and data from pooled Endeavor studies.

At the 1-year follow-up, the R-ZES TVF rate in diabetic patients was superior (7.8%) to the prespecified performance goal of 14.5% (P<0.001). In results from the 2-year follow-up to this pooled study, R-ZES continued to perform similarly in both diabetic and nondiabetic patient populations, and importantly, the rates of ST were not significantly different between diabetic patients and nondiabetic patients. Further stratification of the diabetic population into patients requiring treatment with insulin and those not requiring insulin demonstrated that TLF rates in the non–insulin-treated population remained similar to those in the nondiabetic population, whereas the rate of TLF was increased in the insulin-treated population (Figure 3). These findings emphasize that insulin dependence plays an important role in determining the safety and efficacy of DES in diabetic patients.

Recent trials have also compared R-ZES with other DES types and found no significant differences in clinically driven outcomes. In the The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting SteNt Study: Head-to-head Comparison of Clinical Outcome After Implantation of Second Generation Drug-eluting Stents in a Real World Scenario (TWENTE) trial, the safety and efficacy of R-ZES were compared with those of the Xience V EES in an all-comers population. This trial demonstrated the overall non-inferiority of R-ZES compared with EES, and there were no significant differences in the primary end point of TVF between R-ZES and EES in the subset of diabetic patients.79

These initial trials with the R-ZES provide encouraging results for patients with DM undergoing PCI. The prespecified analysis of outcomes for patients with DM treated with R-ZES did not include the higher-risk cohorts of patients treated in the RESOLUTE All Comers or RESOLUTE International trials.80,81 Real-world outcomes among patients with DM and more complex lesions may therefore be associated with higher target lesion event rates during long-term follow-up. However, current data support improved outcomes of R-ZES in patients with DM compared with first-generation DES.

Pharmacotherapy After Revascularization in Patients With DM

Although patients with DM are at high risk for recurrent cardiovascular events after revascularization, a number of studies have shown that these patients are not adequately managed for modifiable risk factors.82 Close attention must be paid to secondary risk reduction after both CABG and PCI with a goal of meeting current guideline-directed therapies for the control of hypertension, cholesterol, and hemoglobin A1C, and smoking cessation. Current guidelines for diabetic patients recommend a target blood pressure of <130/80 mm Hg, low-density lipoprotein <100 mg/dL for established CAD and <70 mg/dL in the highest-risk patients, immediate smoking cessation, and close consideration of aspirin therapy.83 Although strict glucose control for reducing cardiovascular events has met with mixed results in randomized trials, a goal hemoglobin A1C of <7% is a reasonable target for patients with a life expectancy exceeding 5 years.84 It remains uncertain whether specific medications are favored for control of glucose in patients with DM and CAD. Although DM requiring insulin is associated with increased cardiovascular event rates after PCI, it is uncertain whether the increased event rates are attributable to insulin use or are confounded by the presence of more severe DM. Recent research has also suggested that metformin may be associated with impaired reendothelialization after PCI, although no clinical studies have yet investigated whether metformin increases rates of restenosis or target lesion failure after PCI.85

Diabetic patients who have undergone PCI may also benefit from more intensive antiplatelet therapy. The Trial to Assess

Figure 3. Outcomes after percutaneous coronary intervention among patients with diabetes mellitus (DM) treated with Resolute zotarolimus-eluting stents. During the 2-year follow-up, the rates of cardiac death and target vessel myocardial infarction (TVMI) were similar between patients without DM and those with DM who did not require treatment with insulin (non-ITDM). In comparison, patients with DM who required treatment with insulin (ITDM) had significantly higher rates of cardiac death and target vessel MI at 2 years of follow-up. Reprinted from Silber et al83 with permission from the publisher. Copyright © 2013, Elsevier B.V. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) and Platelet Inhibition and Patient Outcomes (PLATO) trials both found an overall improvement in net clinical outcomes for prasugrel or ticagrelor compared with clopidogrel after PCI.65,67 Subgroup analyses of patients from these trials with DM reported that diabetics have relative reductions in MACEs equal to or greater than reductions in patients without DM. In the TRITON-TIMI 38 trial, patients with DM treated with prasugrel had a greater net clinical benefit than the overall population, with an observed improvement in outcomes for both insulin-requiring and non–insulin-requiring diabetic patients. Similar trends were observed among the cohort of patients with DM treated with ticagrelor in the PLATO trial, although these results were not statistically significant. Treatment of diabetic patients with prasugrel in the TRITON-TIMI 38 trial was also associated with a significant reduction in the risk of ST (2.0% versus 3.6%; P<0.001) among this high-risk cohort.66 Strong consideration should therefore be given to administering prasugrel or ticagrelor as part of a dual antiplatelet strategy after PCI in diabetic patients while weighing the possible increased risk of bleeding.

Future Directions

Although modern revascularization strategies have greatly improved the outcomes of patients with DM and CAD, much work remains to better understand the underlying mechanisms of CAD in the setting of DM and to improve clinical outcomes in this challenging patient population. Further characterization of the signaling mechanisms that link DM to restenosis after percutaneous intervention could lead to the development of novel antirestenotic agents specific to diabetic patients. Although CABB remains superior to PCI among patients with DM and multivessel disease who are candidates for surgical revascularization (and particularly for those with higher angiographic disease complexity), the gap between CABB and PCI has narrowed over time. Advances in stent technology, including biodegradable stents, may further minimize the risk of target lesion failure and the long-term risk of ST.69 Additionally, invasive assessment of lesion significance with fractional flow reserve will help identify hemodynamically important lesions that benefit most from revascularization. Such a strategy may have important prognostic utility in reclassifying patients with apparent 3-vessel disease into functional 1- or 2-vessel CAD.70 As the prevalence of DM continues to rise, the development of new treatment strategies and increased recognition of the association between DM and outcomes after revascularization will help identify novel treatments for this high-risk cohort of patients.

Acknowledgments

We thank Chantelle Rein-Smith, PhD, and Robin WhitSELL, BA, BPh, for their assistance in the preparation of this manuscript and Amanda Behr, MA, CMI, for assistance in the preparation of Figure 1.

Sources of Funding

Dr Armstrong was supported by American Heart Association grant 11CRP7260031. Dr Rutledge was supported by the National Institutes of Health–National Institute on Aging (NIH-NIA) AG039094 and the Richard A. Harrison Endowed Chair in Diabetes Research.

Disclosures

Dr Rogers is a consultant for Medtronic and Boston Scientific. The other authors report no conflicts.

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Silber S, Serruys PW, Leon MB, Meredith IT, Windecker S, Neumann FF, Belardi J, Widimsky P, Massaro J, Novack V, Yeung AC, Saito S.


Key Words: diabetes mellitus • myocardial revascularization • percutaneous coronary intervention
Coronary Artery Revascularization in Patients With Diabetes Mellitus
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Circulation. 2013;128:1675-1685
doi: 10.1161/CIRCULATIONAHA.113.002114

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/15/1675

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