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# Coronary Artery Revascularization in Patients with Diabetes

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### Keywords

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## Introduction

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 two decades.[1] Patients with diabetes have a two- to four-fold increased risk of coronary artery disease (CAD) over non-diabetic patients,[2] and 75% of diabetic patients die from a cardiovascular cause.[3] Diabetic patients commonly undergo percutaneous revascularization procedures, as 25-30% of all percutaneous coronary interventions (PCIs) are performed in patients with DM.[4] A diagnosis of DM is also considered equivalent to having CAD, since diabetic patients without a history of CAD have a 5-year cardiovascular mortality that is similar to that of non-diabetic patients who have a history of myocardial infarction (MI).[5] By current ACC/AHA guidelines, patients with DM are therefore treated as having a coronary artery disease equivalent.[6, 7] Previous review articles have summarized specific medical therapies for patients with diabetes.[8, 9] This review focuses on mechanisms of accelerated atherosclerosis, percutaneous and surgical revascularization strategies, and outcomes among patients with DM and CAD.

### Mechanisms Linking Diabetes, Atherosclerosis, and Outcomes After Coronary Revascularization

Diabetic patients have increased rates, extent, and complexity of atherosclerotic CAD.[8] After coronary revascularization, diabetics have an increased risk of target vessel failure and need for repeat interventions.[10] 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 transformation, and altered smooth muscle cell migration.[11-13] These mechanisms converge to create increased coronary artery plaque burden and more complex coronary artery disease (**Figure 1A**).

**Endothelial Dysfunction and Immune Cell Migration—**The endothelium plays a pivotal role in the maintenance of vessel tone and blood flow.[14] Disruption of endothelial cell homeostasis can increase smooth muscle cell, leukocyte and platelet activity.[15] The role

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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 (PI3K)-dependent activation of endothelial nitric oxide synthase (eNOS). NO promotes vasodilation but also possesses antiplatelet, antiproliferative, and antioxidant properties.[16] In healthy individuals, insulin induces PI3K 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.[17]

DM is also associated with increased production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) that bind to endothelial surface receptors and activate nuclear factor-κB (NF-κB) to induce transcription of endothelial cell adhesion molecules.[18] 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.[19] DM is also associated with an increase in advanced glycation end products (AGE), which result from the attachment of reducing sugars such as glucose to free amino groups via the Maillard reaction.[20] AGE induce endothelial cell signaling via receptors for AGE (RAGE).[21] Through their binding to RAGE, AGE can also induce the synthesis of proinflammatory cytokines and growth factors to increase tissue proliferation, induce modification of the endothelial cell extracellular matrix, and disrupt NO production. Production of AGE are known to be enhanced *in vivo* in the setting of hyperglycemia and are thought to mediate many of the complications of DM, including vascular dysfunction.[22]

**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, due to both increased neointimal hyperplasia and an increased propensity for thrombosis (Figure 1B). Accelerated rates of neointimal hyperplasia have been demonstrated in both rat[23] and human studies following angioplasty in type 2 DM.[24, 25] Increased neointimal hyperplasia in the diabetic artery following coronary intervention may result partly from increased production of transforming growth factor-β (TGF-β) and smooth muscle cell migration and proliferation caused by the hyperglycemic state.[24] Animal models of endovascular stent placement have also shown that diabetes is associated with increased extracellular signal-related kinase (ERK) activation but a reduction in Akt signaling.[26] Sirolimus, but not paclitaxel, activates Akt signaling, leading to increased smooth muscle cell proliferation in the setting of hyperglycemia.[27] These drug-specific signaling effects of antiproliferative agents may in part explain the differential efficacy of sirolimus-eluting stents in patients with diabetes (see below).

The neointima of patients with diabetes may also have biologic alterations that predispose to stent thrombosis: 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.[28] Platelets from diabetic patients are more reactive than those of non-diabetic patients, further increasing the risk of thrombosis.[29] Recent advances in antiplatelet therapies have been shown to be beneficial to both diabetic and non-diabetic patients in prevention of atherothrombosis,[30] and in certain studies antiplatelet agents have decreased the gap in thrombosis risk between diabetics and non-diabetics for endpoints such as stent thrombosis (see “Pharmacotherapy After Revascularization,” below).[31]

These findings emphasize that the choice of antiplatelet therapies, lipid-lowering therapies, method of glycemic control, and device choice for PCI must be considered as a whole when treating patients with diabetes. Due to the multiplicity and redundancy of pathophysiologic mechanisms in diabetics, no single therapy will be effective in all patients. Therapies that affect multiple pathophysiologic 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 Diabetes

Patients with DM and CAD are at high risk of subsequent cardiovascular events, regardless of symptoms.[32] 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 BARI 2D Trial compared prompt revascularization (either CABG or PCI) of patients with DM and stable CAD with concurrent aggressive medical treatment to aggressive medical treatment alone, as well as glycemic control strategies.[33] A total of 2,368 type 2 diabetic patients were enrolled and followed for 5 years. The primary endpoint of the trial was 5-year mortality, which demonstrated no difference between the revascularization plus medical treatment group vs. the initial medical treatment alone group. There was also no difference in outcomes between the two glycemic control strategy groups at 5 years.[34]

While the BARI 2D Trial was not designed to compare CABG vs. PCI, there was a significant decrease in the rate of composite cardiovascular events when CABG revascularization was compared to 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.[34] Of note, this study was carried out during the first clinical use of DES. Approximately 35% of diabetic patients undergoing PCI as part of the BARI 2D Trial received DES, while the remainder received either a 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 (42% at 5 year follow up in the BARI 2D trial) may eventually require revascularization. The initial 2009 Appropriate Use Criteria (AUC) document for coronary revascularization included diabetes as a clinical decision point for the type of revascularization (e.g., CABG vs. PCI), but the presence of diabetes did not alter the appropriateness of a given method of revascularization.[35] The 2012 AUC update does not include diabetes as a variable for the appropriateness of revascularization or method of revascularization, but instead uses the SYNTAX score to stratify decision-making.[36] Current AUC for revascularization therefore remain primarily based on patient symptoms, documentation of ischemia, and anatomic extent of disease. The presence of diabetes in a given patient, however, may be an important clinical factor to take into account for scenarios in the “uncertain” range, where the presence of diabetes may identify a patient as having a higher risk profile who may therefore benefit from closer clinical monitoring and possible revascularization.

## Clinical Trials Comparing Surgical Revascularization to Percutaneous Coronary Intervention in Patients with Diabetes

A number of large-scale trials have compared CABG to PCI (Table 1). These trials have been conducted in parallel with development of new PCI technologies and refinement in surgical techniques, including angioplasty (BARI trial), bare metal stents (ARTS-I), and most recently, first generation drug-eluting stents (SYNTAX trial). Each of these trials

included a large percentage of patients with DM. More recently, the FREEDOM trial specifically randomized patients with DM to CABG or PCI.

The Bypass Angioplasty Revascularization Investigation (BARI) Trial compared the safety and efficacy of coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) in a randomized population of patients with multivessel disease. This trial, which enrolled 1,829 patients, showed that diabetic patients who underwent CABG had increased rates of 10-year survival and decreased rates of MI compared to those who underwent PTCA.[37] Contemporaneous smaller trials yielded conflicting results, with some finding increased survival of diabetic patients undergoing CABG vs. PTCA,[38-40] and others finding no difference in survival of diabetic patients treated with CABG vs. PCI.[41-44]

Application of BMS or early generation DES led to improved outcomes of PCI among diabetic patients, thereby narrowing the outcomes gap with CABG. The Arterial Revascularization Therapies Study (ARTS-I and -II) compared the safety and efficacy of CABG vs. BMS (ARTS-I) and CABG vs. SES (ARTS-II) in patients with and without DM. Among patients with DM, there was no difference in 3-year MACCE between CABG, BMS and SES, but CABG and SES each showed decreased rates of death and MI when compared to BMS historical comparisons.[45] At 5-year follow-up, SES-treated patients had lower rates of MACCE than those 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 when compared to CABG.[46] Similarly, in the Coronary Artery Revascularization in Diabetes (CARDia) Trial, PCI (either BMS or DES) was compared to CABG in diabetic patients with multivessel disease and demonstrated that there were no differences in death, MI, or stroke when comparing PCI and CABG. 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.[47]

The Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) study examined the use of the TAXUS PES vs. CABG for treatment of diabetic and non-diabetic patients with multivessel disease. In agreement with many other studies, this study found that diabetic patients had increased rates of major adverse cardiac and cerebrovascular events (MACCE) and revascularization when compared to non-diabetic patients.[48] Furthermore, both diabetic and non-diabetic patients treated with PES demonstrated increased rates of MACCE and repeat revascularization when compared to those treated with CABG out to final five year follow up.[49] 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 non-inferior to CABG in terms of all MACCE endpoints. Therefore, PCI may be an acceptable alternative to CABG in diabetic patients with lower disease complexity.[50]

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial, a randomized trial of 1900 patients with multivessel disease and DM, examined the use of PCI (primarily first-generation PES or SES) vs. CABG.[51] Patients with DM who underwent CABG had a decreased incidence of MI (6.0% vs. 13.9%) and all-cause mortality (10.9% vs. 16.3%) at 5 years compared to those who underwent PCI. However, patients randomized to CABG did have increased rates of stroke (5.2% vs. 2.4%). Of note, there was no interaction between SYNTAX score and outcomes among the overall population, suggesting the increased event rates among patients randomized to PCI was not related to the anatomic complexity of disease at the time of revascularization. The FREEDOM trial enrolled lower surgical risk patients with preserved

ejection fractions, and the conclusions of the trial may therefore 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 high surgical risk patients have not been studied in any of the trials reviewed here, it is reasonable that a multidisciplinary heart team evaluate high surgical risk patients for the best revascularization strategy. In many of these cases, PCI may remain the preferred strategy due to the less invasive nature of this approach.

Upcoming randomized studies of second-generation stents will continue to address important questions regarding revascularization strategies in patients with diabetes. The Evaluation of Xience Prime™ or Xience V™ stents versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial will enroll approximately 2600 patients with left main disease and a SYNTAX score of ≤ 32 to compare the Xience Prime EES vs. CABG.[52] Patients with DM will be a pre-specified 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 vs. 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.

## Drug Eluting Stents in Patients with Diabetes

DES are associated with a decreased rate of restenosis compared to BMS in both diabetic and non-diabetic patients.[53-56,57, 58] Pooled analysis of these studies has raised some controversy regarding the relative efficacy of different DES types in DM. A recent mixed-treatment comparison meta-analysis of 42 randomized trials that included 10,714 patients with DM found that DES as a whole were associated with a 37-69% reduction in target vessel revascularization (TVR) compared to BMS, but the magnitude of this reduction varied with stent type.[59] 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 (PES)—**A large meta-analysis examined the outcomes of BMS vs. the first generation TAXUS PES in five prospective, randomized trials enrolling 2,797 patients (TAXUS Clinical Program). The authors demonstrated similar 5-year safety and efficacy between PES and BMS in diabetic patients.[54, 60] In the TAXUS IV study, PES decreased the overall rates of target vessel failure (TVF), target lesion revascularization (TLR) and major adverse cardiovascular events (MACE) in diabetic and non-diabetic patients.[61] Additional studies demonstrated no difference in rates of stent thrombosis (ST), MI, death or neointimal proliferation in diabetic and non-diabetic patients treated with PES.[62] Importantly, patients with type 2 DM who required insulin therapy were at increased risk for MACE, TVF and TVR when compared to those with Type 2 DM who were treated with oral medications.

**Sirolimus Eluting Stents (SES)—**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 vs. BMS in a small group of diabetic patients. Treatment with SES led to a reduction in 5-year overall MACE, mostly attributable 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.[56] A combined analysis of four randomized trials comparing SES to BMS with five years of follow up found no difference in overall rates of MACE among

the overall study population. However, patients with DM treated with SES had significantly higher rates of death due to cardiac causes than patients treated with BMS (15.9% vs. 9.0%).[63] This finding has raised the concern of possible increased stent thrombosis 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.[64]

**Comparisons of PES and SES Among Patients with Diabetes—**A mixed comparison meta-analysis comparing SES, PES and BMS in 3,852 diabetic patients found that the two 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 non-diabetic patients.[55] 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.[65, 66] Further stratification of diabetic patients into those 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 TVR for treatment of diabetic patients.[59]

## Second-Generation DES

Second-generation DES have optimized drug deliverability while seeking to minimize TLR as well as 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 (EES)—**Initial studies with follow-up angiography demonstrated decreased rates of angiographic restenosis among diabetic patients treated with EES as compared to PES. A pooled study comparing the use of the Xience V EES and TAXUS LIBERTÉ™ PES (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 as compared to PES, without any effect on safety outcomes.[58] Further studies demonstrated that EES were associated with decreased neointima formation, lumen loss and vessel narrowing in diabetic patients, as measured by intravascular ultrasound, when compared to PES.[67]

These findings concur with recent studies in which EES decreased rates of ST up to one year following treatment in diabetic patients when compared to PES, with similar composite TLR-MACE outcomes between the stent types.[68] In the 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 similar safety outcomes to SES.[69]

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 vs. the first-generation TAXUS LIBERTÉ PES. Strikingly, non-diabetic patients receiving EES had decreased mortality, MI, ST, and TLR as compared to PES in the overall population, whereas there were no differences in efficacy or safety outcomes between the two stent platforms among patients with diabetes (Figure 2).[70] These unexpected differential effects in patients with diabetes versus those without diabetes 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 PES in diabetic patients with 3 or fewer de novo lesions, even though marked increases in efficacy were shown in the non-diabetic population.[71] 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 (ZES)—**The ENDEAVOR IV trial examined the second-generation Endeavor™ zotarolimus-eluting stent (E-ZES) in patients with a single de novo lesion and demonstrated non-inferiority of E-ZES to the TAXUS PES in both diabetic and non-diabetic patient populations in terms of safety, efficacy and clinical outcomes.[72, 73] However, the percentage of in-stent restenosis was increased in diabetic patients treated with E-ZES compared to non-diabetic patients treated with E-ZES. Further stratification revealed that this effect was independent of whether insulin was necessary to treat a patient's diabetes. Additional comparisons between diabetic and non-diabetic patients treated with E-ZES in the E-FIVE Registry demonstrated that diabetic patients had significantly higher rates of MACE, TLR, TVF, and early ST than non-diabetic patients at one year, and that insulin dependence led to increased MACE and TVF when compared to non-insulin dependent diabetic patients.[74]

**Comparisons of PES, SES and ZES—**Direct comparison of E-ZES with SES in the SORT OUT III Trial demonstrated that treatment with E-ZES was associated with increased rates of MACE, as well as TVR and TLR in both diabetic and non-diabetic patients at 18 months, but these increases were much greater in the diabetic population.[75] In comparison, the PROTECT study showed comparable levels of definite ST at 3 years in both diabetic and non-diabetic populations treated with E-ZES and SES,[76] suggesting similar long-term safety outcomes between the two stents.

A direct comparison of SES, PES and E-ZES in type 2 diabetes 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, as compared to either PES or SES, led to increased 3-year rates of MACE, due largely to a higher rate of TLR.[57] Similar results were found in the Swedish Coronary Angiography and Angioplasty Register (SCAAR) study.[77]

**Resolute Zotarolimus-Eluting Stent (R-ZES)—**Recently, the latest-generation Resolute™ ZES (R-ZES) became the first DES to gain an FDA 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.[78] FDA approval was based on a pre-specified performance goal in diabetic patients.[79] The study population included 878 diabetic and matched control subjects from the Global Resolute Clinical Trial Program. A pre-specified performance goal of 14.5% TVF, which included cardiac death, MI not attributable to other vessels, and TVR, was implemented based on a meta-analysis of published studies in diabetic patients treated with first-generation SES and PES stents and data from pooled Endeavor studies.

At 1-year follow-up, the R-ZES TVF rate in diabetic patients was superior (7.8%) to the pre-specified 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 non-diabetic patient populations and, importantly, the rates of ST were not significantly different between diabetic patients and non-diabetic patients. Further stratification of the diabetic population into patients requiring treatment with insulin demonstrated that TLF rates in the non-insulin treated population remained similar to those in the non-diabetic population, while 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 to other DES types and found no significant differences in clinically driven outcomes. In the TWENTE Trial, the safety and efficacy of R-ZES was compared to that of the Xience V EES in an all-comers population. This trial demonstrated the overall non-inferiority of R-ZES as compared to EES, and there were no significant differences in the primary endpoint of TVF between R-ZES and EES in the subset of diabetic patients.[80]

These initial trials with the R-ZES provide encouraging results for patients with diabetes undergoing PCI. The pre-specified analysis of outcomes for patients with DM treated with RZES did not include the higher risk cohorts of patients treated in the RESOLUTE All Comers or RESOLUTE International trials.[81, 82] Real-world outcomes among patients with diabetes 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 to first-generation DES.

## Pharmacotherapy After Revascularization in Patients with Diabetes

Although patients with diabetes 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.[83] Close attention must be paid to secondary risk reduction after both CABG and PCI with a goal of meeting current guideline directed therapies for control of hypertension, cholesterol, smoking cessation, and hemoglobin A1C. Current guidelines for diabetic patients recommend a target blood pressure of <130/80 mm Hg, LDL <100 mg/dl for established CAD and <70 mg/dL in the highest risk patients, immediate smoking cessation, and strong consideration of aspirin therapy.[84] Although strict glucose control for reduction of 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 five years.[85] It remains uncertain whether specific medications are favored for control of glucose in patients with diabetes and CAD. Although DM requiring insulin is associated with increased cardiovascular event rates after PCI, it is uncertain whether the increased event rates are due to insulin use or confounded by the presence of more severe diabetes. Recent research has also suggested that metformin may be associated with impaired re-endothelialization after PCI, although no clinical studies have yet investigated whether metformin increases rates of restenosis or target lesion failure after PCI.[86]

Diabetic patients who have undergone PCI may also benefit from more intensive antiplatelet therapy. The TRITON-TIMI 38 and PLATO trials both found an overall improvement in net clinical outcomes for prasugrel or ticagrelor compared to clopidogrel after PCI.[87, 88] Subgroup analyses of patients from these trials with DM reported that diabetics have equal or greater relative reduction in MACE compared to patients without diabetes. In the TRITON TIMI-38 trial, patients with diabetes 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 diabetes treated with ticagrelor in the PLATO trial, although these results were not statistically significant. Treatment of diabetic patients with prasugrel in the TIMI-38 trial was also associated with a significant reduction in the risk of stent thrombosis (2.0% vs. 3.6%, $p<0.001$) among this high-risk cohort.[87] Strong consideration should therefore be given towards 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 diabetes and to improve clinical outcomes in this challenging patient population. Further characterization of the signaling mechanisms that link diabetes to restenosis after percutaneous intervention could lead to development of novel anti-restenotic agents specific to diabetic patients. While CABG remains superior to PCI among patients with diabetes who are candidates for surgical revascularization (and particularly for those with higher angiographic disease complexity), the gap between CABG and PCI has narrowed over time. Advances in stent technology including bioresorbable stents may further minimize the risk of target lesion failure and the long-term risk of stent thrombosis.[89] Additionally, invasive assessment of lesion significance with fractional flow reserve will help with identifying hemodynamically important lesions that benefit most from revascularization. Such a strategy may have important prognostic utility in reclassifying patients with apparent three-vessel disease into functional one- or two-vessel CAD.[90, 91] As the prevalence of diabetes continues to rise, development of new treatment strategies and increased recognition of the association between diabetes and outcomes after revascularization will help identify novel treatments for this high-risk cohort of patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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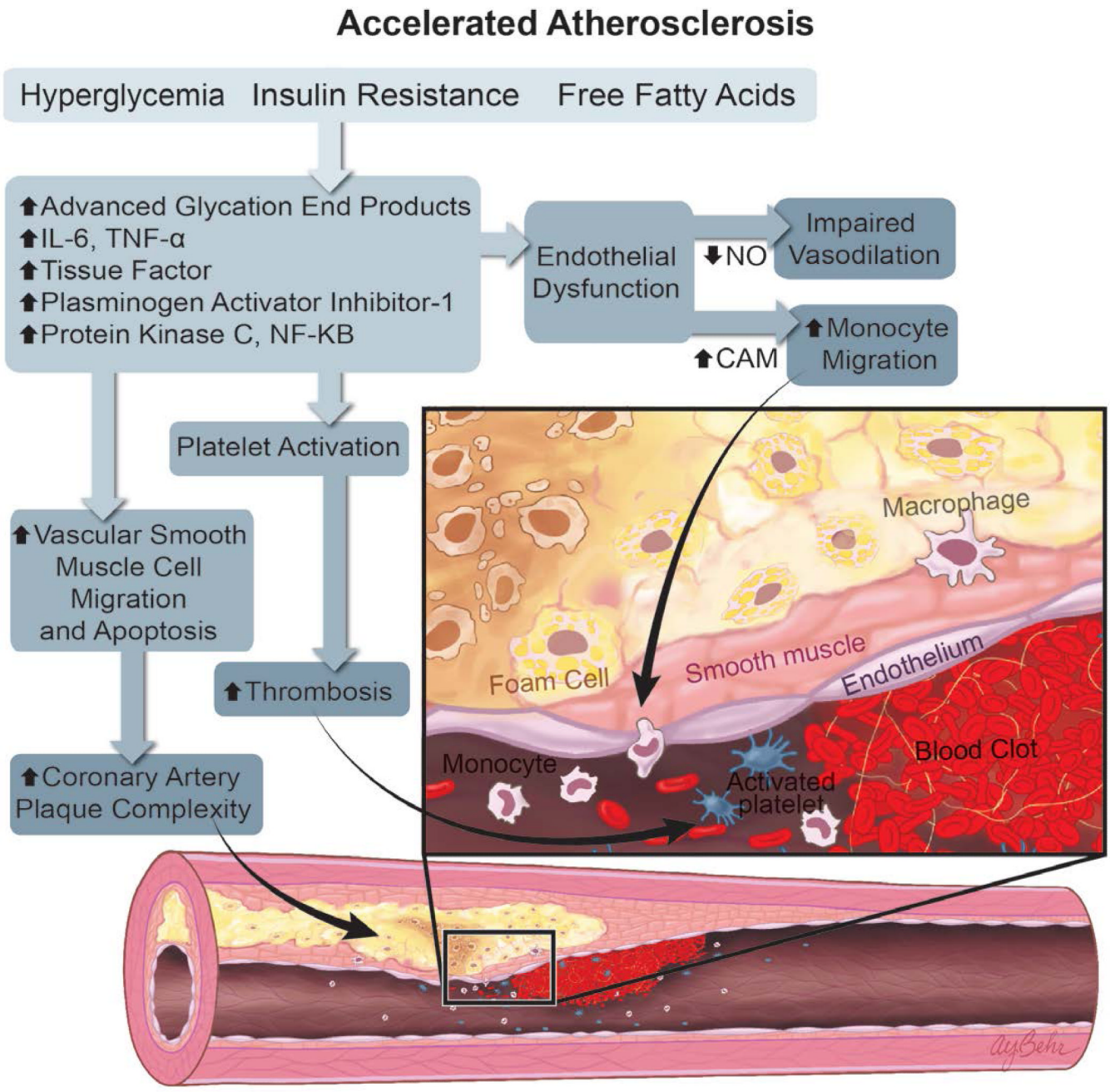

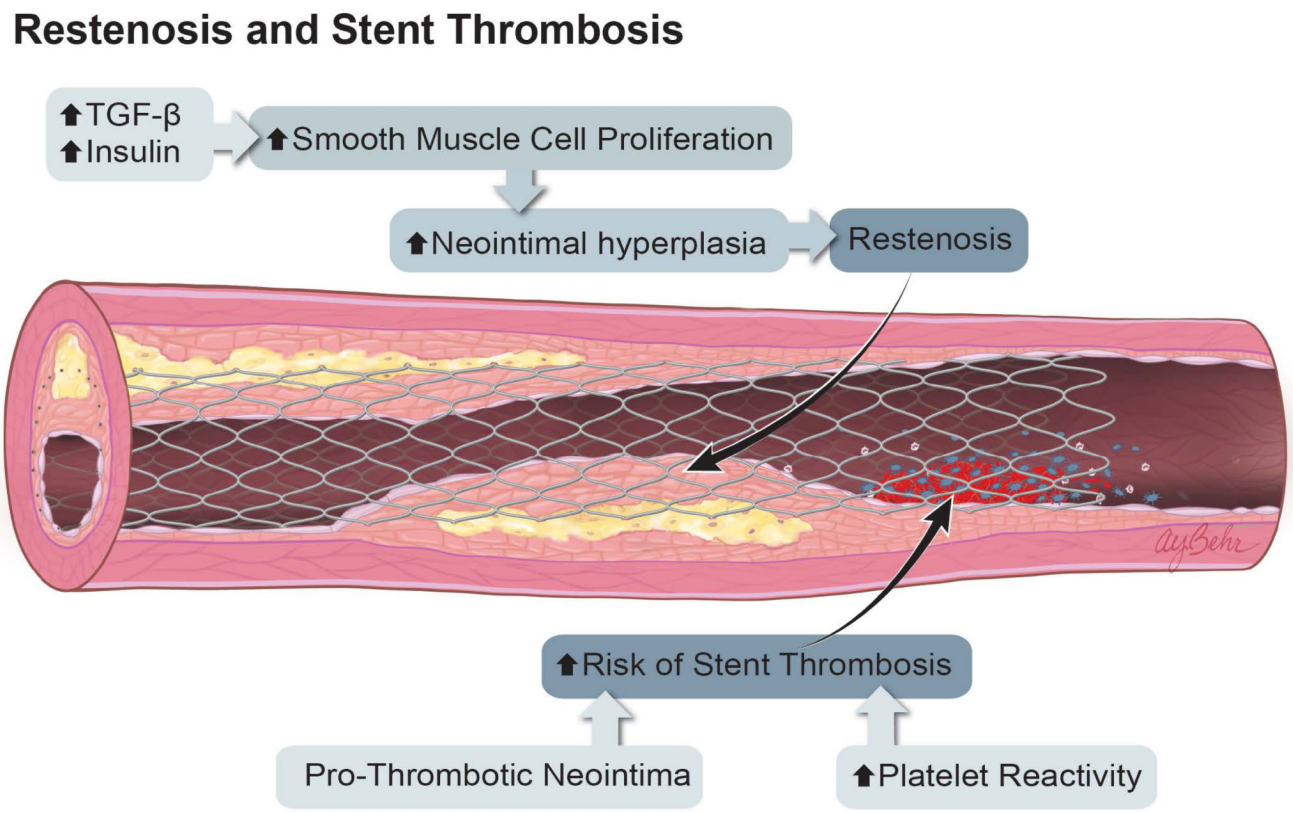


**Figure 1.**
Mechanisms of Atherosclerosis and Restenosis in Diabetes. A. The combination of hyperglycemia, insulin resistance, and increased circulating free fatty acids activate multiple inflammatory pathways, leading to endothelial dysfunction, increased monocyte activation and localization to sites of nascent plaque, increased vascular smooth muscle cell migration, and apoptosis. These inflammatory pathways also increase platelet activation, leading to an increased risk of atherothrombosis and coronary artery plaque complexity. B. After percutaneous coronary intervention, elevated levels of insulin and TGF-β promote greater smooth muscle cell proliferation, neointimal hyperplasia, and restenosis. Patients with DM may also have prothrombotic neointima, as well as increased platelet reactivity. The sum of these effects results in an increased risk of stent thrombosis.

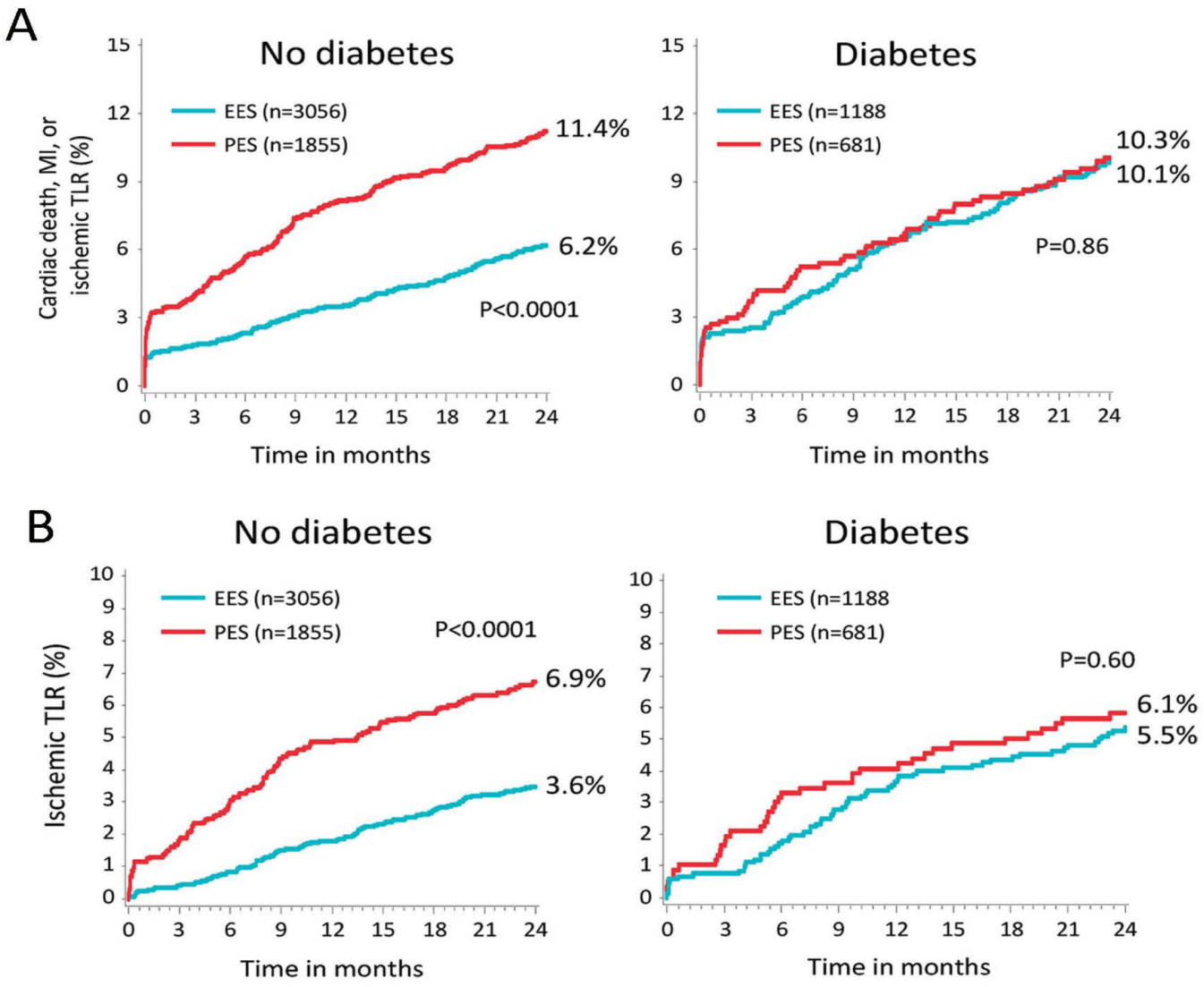


**Figure 2.**

Differential Outcomes After PCI Among Patients with and without Diabetes in the SPIRIT and COMPARE Trials. Pooled analysis of the SPIRIT and COMPARE trials demonstrate a significant interaction effect of diabetes on the outcomes of everolimus-eluting stents (EES) vs. paclitaxel-eluting stents (PES). Top panel: Among patients without diabetes, the rates of cardiac death, MI, or ischemic TLR were significantly lower for EES compared to PES. In comparison, there was no difference in outcomes of EES vs. PES among patients with DM. Bottom panel: Among patients without diabetes, EES were associated with significantly decreased rates of ischemic TLR. There was no difference in rates of ischemic TLR among patients with diabetes. (Reproduced, with permission, from Stone et al, Circulation 2011;124:893-900.)

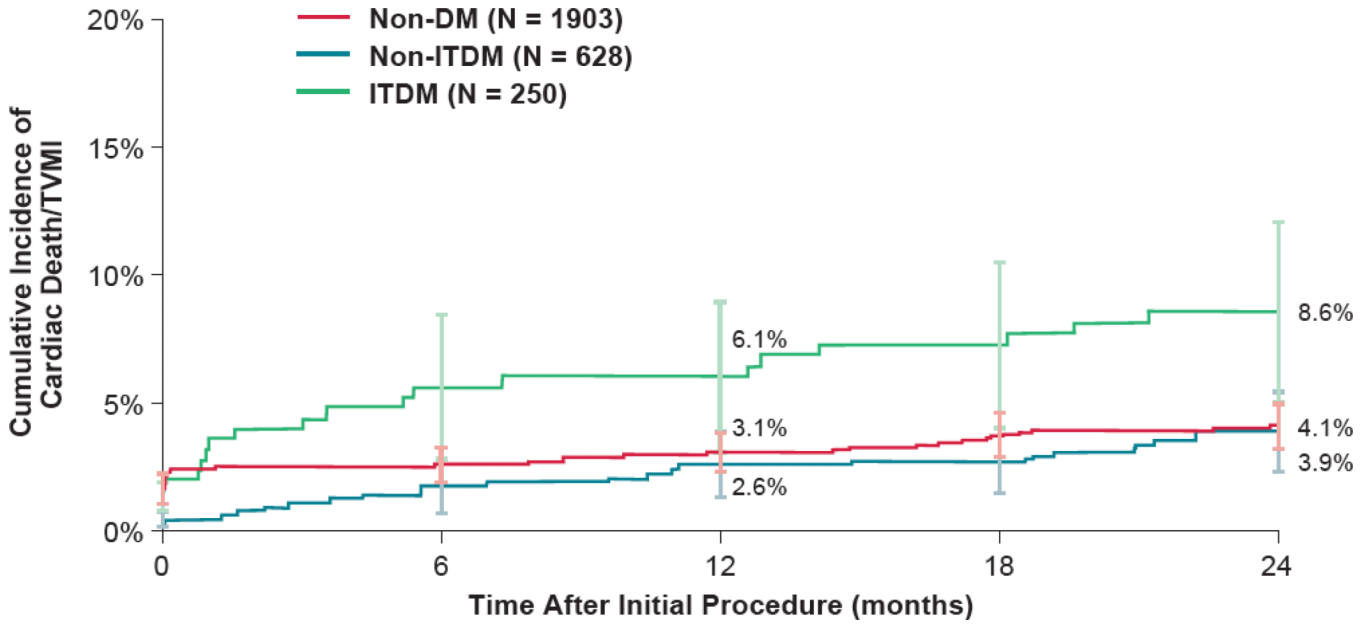


**Figure 3.**

Outcomes After PCI Among Patients with Diabetes Treated with Resolute Zotarolimus-Eluting Stents. During two-year follow-up, the rates of cardiac death or target vessel MI were similar between patients without diabetes and those with diabetes who did not require treatment with insulin (non-ITDM). In comparison, patients with diabetes who required treatment with insulin (ITDM) had significantly higher rates of cardiac death or target vessel MI at two years of follow-up. (Reproduced, with permission, from Silber et al J. Am. Coll. Cardiol. Intv, 2013; 6:357-368.)

**Table 1**

Major Recent Studies Comparing PCI with CABG Among Patients with Diabetes.

| Trial Name | Study Period | Type of PCI | # Patients per Arm | # With DM (%) | Follow-up | Primary Endpoint in DM | Outcome in DM |
|---|---|---|---|---|---|---|---|
| ***BMS or DES*** | | | | | | | |
| **ARTS-I** | 1997-1998 | BMS | 600 BMS<br>605 CABG | 208 (17.3) | 5 yr | Composite MACCE | CABG<BMS |
| **ARTS-II** | 2003-2003 | Cypher SES | 607 SES<br>605 CABG (from ARTS-I) | 255 (21.0) | 5 yr | Composite MACCE | CABG<SES<BMS |
| **BARI 2D** | 2000-2008 | PTCA/BMS/DES | 1605 PCI<br>763 CABG | 2368 (100) | 5 yr | All-cause mortality | Similar outcomes for medical therapy or revascularization |
| **CARDia** | 2002-2007 | BMS or Cypher SES | 256 PCI<br>254 CABG | 510 (100) | 5 yr | Composite of all-cause death, non-fatal MI, non-fatal stroke | No difference between CABG and PCI |
| ***DES*** | | | | | | | |
| **SYNTAX** | 2005-2007 | Taxus PES | 903 PES<br>897 CABG | 452 (25.1) | 3 yr | Composite MACCE | Increased MACCE in PCI |
| **FREEDOM** | 2005-2010 | Taxus PES or Cypher SES | 953 PCI<br>947 CABG | 1900 (100) | 5 yr | Composite all-cause mortality, MI and stroke | CABG better for DM in all outcomes |
| **PRECOMBAT** | 2004-2009 | Cypher SES | 300 SES<br>300 CABG | 192 | 1 yr | Composite MACCE | No difference between PCI and CABG |
| **EXCEL** | 2010-current | Xience V<br>EES | 2600 (estimated) | Ongoing | 3 yr | Composite all cause mortality, MI, stroke | Ongoing |

CABG=Coronary artery bypass graft; BMS=Bare metal stent; DES= drug-eluting stent; SES=Sirolimus-eluting stent; EES=Everolimus-eluting stent; PES=Paclitaxel-eluting stent; E-ZES=Endeavor zotarolimus-eluting stent; R-ZES=Resolute zotarolimus-eluting stent

**Table 2**

Major Studies Comparing DES Types Among Patients with Diabetes.

| Trial Name | Study Period | Type of PCI | # Patients per Arm | # with DM (%) | Follow-up | Primary Endpoint in DM | Outcome in DM |
|---|---|---|---|---|---|---|---|
| **SPIRIT V** | 2006-2007 | Xience EES vs. Taxus PES | 218 EES<br>106 PES | 324 | 1 yr | In-stent late loss | PES increased late loss |
| **ESSENCE-DIABETES** | 2008-2009 | Xience EES vs. Cypher SES | 149 EES<br>151 SES | 300 | 1 yr | Angiographic in-segment late loss | No difference between EES and SES |
| **PROTECT** | 2007-2008 | Endeavor ZES vs. Cypher SES | 4357 ZES<br>4352 SES | 2410 | 3 yr | Stent thrombosis | ZES better in all pts, no difference between DM and non- DM |
| **NAPLES-DIABETES** | 2005-2007 | Endeavor ZES vs. Taxus PES vs. Cypher SES | 75 ZES<br>75 PES<br>76 SES | 226 | 3 yr | Composite MACE | Increased MACE in ZES vs. PES and SES |
| **SCAAR** | 2003-2006 | Endeavor ZES vs. Taxus PES vs. Cypher SES | 333 ZES<br>2852 PES<br>1569 SES | 9710 | 4 yr | Death and MI | No difference between stent types or DES vs. BMS |
| **RESOLUTE US** | 2008-2009 | Resolute ZES vs. Endeavor ZES | 1402 R-ZES<br>2270 E-ZES (historical) | 374 | 1 yr | TLF and Composite TVF | No difference between E-ZES and R-ZES in DM or non-DM |
| **TWENTE** | 2008-2010 | Endeavor ZES vs. Xience V EES | 697 ZES<br>694 EES | 301 | 1 yr | TVF | No difference between ZES and EES |

SES=Sirolimus-eluting stent; EES=Everolimus-eluting stent; PES=Paclitaxel-eluting stent; E-ZES=Endeavor zotarolimus-eluting stent; R-ZES=Resolute zotarolimus-eluting stent