

## Outcomes with drug-eluting stents in diabetic patients

The relationship between diabetes mellitus and coronary artery disease is well established. The percentage of patients participating in clinical trials of percutaneous coronary intervention who have diabetes is quickly rising. Diabetic patients have a worse prognosis than nondiabetic patients, with generally greater rates of death, myocardial infarction and need for target lesion and vessel revascularization. Stenting has improved the outcome of diabetic patients receiving percutaneous coronary intervention. Compared with bare-metal stents, the use of drug-eluting stents in diabetic patients has resulted in a significant reduction in late lumen loss, binary restenosis, and clinically driven target vessel revascularization. The safety and efficacy of drug-eluting stents in diabetic patients is now well established; they are the preferred option in this subgroup in the absence of contraindications. New stent designs, polymers and drugs are resulting in better outcomes overall, but more research is required to define their relative efficacy relative to other treatment options in diabetics.

**KEYWORDS:** coronary artery disease ■ diabetes ■ drug-eluting stents

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The relationship between diabetes mellitus and coronary heart disease is well established. The prevalence of diabetes is quickly rising. Diabetics frequently have diffuse atherosclerosis with accelerated progression [1], more complex plaques and greater risk of thrombosis [2,3]. Multiple studies have demonstrated a worse prognosis for diabetics with coronary heart disease. Stenting has improved the prognosis of diabetic patients treated with percutaneous coronary intervention (PCI), largely due to a reduction in need for target vessel revascularization (TVR). Nevertheless, TVR is required more often in diabetics with bare-metal stenting compared with nondiabetics [4], and a significant benefit of drug-eluting stents (DES) with respect to reduction in TVR has been in the diabetic population [5]. The aim of this article is to summarize the current role of DES in the management of diabetic patients with coronary artery disease.

### Drug-eluting versus bare-metal stents in diabetic patients

Compared with bare-metal stents (BMS), the use of DES in diabetic patients has resulted in a significant reduction in late lumen loss, rates of binary restenosis, and clinically driven TVR [6]. In the original report of the Sirius trial by Moses *et al.*, at 270 days, the overall rate of target lesion revascularization (TLR) was reduced from 16.6% in patients treated with BMS, to 4.1% in those treated with sirolimus-eluting stent (SES) [7]. In the diabetic population, the rate of TLR

was reduced from 22.6 to 6.9% ( $p < 0.001$ ) in patients treated with SES, and in segment restenosis reduced from 50.7 to 17.6% ( $p < 0.001$ ). Nevertheless, the rate of TLR remained more than double for diabetics treated with SES compared with nondiabetics (6.9 vs 3.2%). Similarly, the 1-year results of the Scorpius study, a German multicenter investigation on the effectiveness of SESs in diabetic patients demonstrated a reduction in in-segment late lumen loss (0.17 vs 0.75 mm;  $p < 0.0001$ ), binary restenosis (8.8 vs 42.1%;  $p < 0.001$ , and TLR (5.3 vs 21.1%;  $p = 0.002$ ) in sirolimus-treated patients [8]. The Diabetes and Sirolimus-Eluting Stent (DIABETES) trial investigators compared in-segment late lumen loss in 160 diabetic patients who were randomized to sirolimus-eluting or bare-metal stenting [6]. At 9 months, late lumen loss was reduced from  $0.47 \pm 0.5$  mm for BMS to  $0.06 \pm 0.4$  mm for SESs ( $p < 0.001$ ). TLR was significantly lower in the sirolimus group (7.3 vs 31.3%;  $p < 0.001$ ) as were major adverse cardiac events (11.3 vs 36%;  $p < 0.001$ ). In a predefined intravascular substudy analysis of the same trial involving 140 lesions [9], in-stent neointimal hyperplasia area and volume were significantly reduced in the SES group, and this was accompanied by increase in vessel volume at stent edges, and increased late acquired incomplete stent apposition in 14.7% of the SES patients. All three of the previously mentioned trials utilized an first-generation thick strut BMS, that may have worsened outcomes in the control

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group. In an analysis of 14 randomized trials comparing sirolimus eluting stents to BMS by Kastrati *et al.*, the overall risk of death and the combined risk of death and myocardial infarction were found not to be significantly different for patients with either type of stent [10]. There was a significant reduction in the combined risk of death, myocardial infarction and re-intervention associated with SESs (hazard ratio [HR]: 0.43; 95% CI: 0.34–0.54). No significant interaction was noted between diabetes and any of the three end points in the study. A separate analysis of the risk of death in the subgroup of patients with diabetes demonstrated a HR associated with sirolimus use of 1.27 (95% CI: 0.83 ± 1.95;  $p = 0.26$ ). In a pooled analysis of data from the RAVEL and SIRIUS studies comparing SESs with BMS, Spaulding *et al.* demonstrated no significant differences between the two treatments in the rates of death, myocardial infarction, or stent thrombosis [11]. However, in the 428 patients with diabetes, a significant difference in the survival rate was observed in favor of the BMS group over the sirolimus-stent group (95.6 vs 87.8%; HR for death in the sirolimus-stent group, 2.9; 95% CI: 1.38 ± 6.10;  $p = 0.008$ ). The significance of this finding is uncertain, and has not been confirmed in other observations.

A total of 4 years efficacy and safety data of 827 patients randomized to PES versus BMS are available from the TAXUS I, II, IV, V, and VI randomized trials [12]. At 4-year follow-up, there were no significant differences between PES and BMS in the rates of death (8.4 vs 10.3%, respectively,  $p = 0.61$ ), myocardial infarction (6.9 vs 8.9%,  $p = 0.17$ ), or stent thrombosis (1.4 vs 1.2%,  $p = 0.92$ ). In contrast to BMS, treatment with PES was associated with a significant and durable reduction in TLR over 4 years of follow-up (12.4 vs 24.7%,  $p < 0.0001$ ). This extended to both patients requiring and not requiring insulin treatment.

Randomized clinical trials constitute the highest level of evidence, but it is well known that patients included in these trials may not be comparable with those treated in every day clinical practice due to the many exclusion criteria in individual trials. This may be particularly pertinent to diabetic patients, in which certain subsets, such as long lesions and small vessels may be more important. The majority of these trials are not powered to assess safety end points, but rather combined safety/efficacy end points. As such, real world registries are critically important.

The 2-year results of paclitaxel-eluting stents (PESs) in patients with medically treated diabetes mellitus in the ARRIVE registries revealed

similar rates of TLR (8.2 vs 7.7%,  $p = 0.59$ ), stent thrombosis (2.65 vs 2.4%,  $p = 0.55$ ), and myocardial infarction (3.8 vs 3.0%,  $p = 0.09$ ) in diabetics and nondiabetics, respectively [13]. Likewise, the rate of TLR was similar in diabetics and nondiabetics treated with PES (8.2 vs 7.7%,  $p = 0.59$ ). Mortality was significantly higher in diabetic patients (9.7 vs 5.3%,  $p < 0.001$ ), a finding consistent in almost all studies of diabetic patients.

The Western Denmark Heart Registry compared the outcomes of 1,575 diabetic patients treated with drug-eluting and BMS [14]. The adjusted risk ratio for TLR for diabetics treated with drug-eluting compared with non DES at 2 years was 0.63 (0.47–0.85), while there were no significant differences for death, myocardial infarction, or overall stent thrombosis. The overall rate of TLR was 6.5% for patients treated with DES compared with 10.0% for patients treated with BMS. The REAL Registry investigators (REgistro AngiopLastiche coronariche Emilia-Romagna) observed a propensity-score adjusted reduction of TVR (HR: 0.66, 95% CI: 0.46–0.96;  $p = 0.041$ ) in 1648 diabetic patients (1,089 BMS, 559 DES) at 2 years without a significant difference in death or myocardial infarction [15]. They concluded that the use of DES was associated with a moderated reduction in the 2-year risk of TVR, but that benefit was limited to non-insulin diabetic patients. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) Registry investigators followed 47,000 patients who underwent stenting for up to 5 years and found no overall difference between the group that received DES and the group that received BMS in the combined end point of death or myocardial infarction, or the individual end points of death and myocardial infarction [16]. In the overall cohort, clinical restenosis at 1 year was significantly lower in those receiving DES (adjusted relative risk [RR], 0.43; 95% CI: 0.36–0.52); in the overall cohort, the number need to treat to prevent one clinical restenosis was 39. The incidence of clinical restenosis was highest among patients with diabetes who received BMS that were long (greater than 20 mm) and smaller (less than 3 mm); the rate of clinical restenosis was 8.3% points higher in this subgroup, and the number to treat with DES to prevent one restenosis was 10. The Massachusetts Data Analysis Center Registry compared the outcomes of 5051 patients who received DES or BMS over 18 months from 2003 to 2004, and who had complete 3-year follow-up [17]. Propensity analysis of 1:1 matched DES versus BMS (1476 DES:1476 BMS) revealed reductions in risk adjusted mortality (17.5 vs

20%, 95% CI: -6.0–-0.4;  $p = 0.02$ ), myocardial infarction (13.8 vs 16.9%; 95% CI: -5.6– -0.5;  $p = 0.02$ ) and TVR (18.4 vs 23.7%; CI: -8.3– -2.4%;  $p < 0.001$ ). They concluded that in a real-world diabetic population with mandatory reporting, DES were associated with reduced mortality, myocardial infarction, and revascularization rates at long-term follow-up compared with BMS. Cumulatively, these findings suggest a consistent and durable reduction in need for TLR in diabetic patients treated with DES compared with those treated with BMS. Intermediate term follow-up does not suggest a safety concern, but adequately powered studies with long term data are required to exclude possible survival and safety concerns.

### Comparing DES in patients with diabetes

Multiple clinical trials have attempted to address the comparative efficacy and safety of different stent platforms in diabetic patients. Importantly, most of the stent platforms have demonstrated significant improvement over their bare-metal counterparts, and while differences might exist, the consistent message has been that diabetic patients are a particular group that appear to benefit significantly from DES implantation.

The first report comparing different drug-eluting platforms in diabetic patients came from Dibra *et al.*, who randomly assigned 250 patients to receive either PESs or SESs [18]. The primary end point of in-segment late luminal loss was 0.24 mm greater in the paclitaxel-treated group (0.67 vs 0.43 mm,  $p = 0.002$ ) compared with those treated with sirolimus; similarly, in-segment restenosis occurred more commonly in the paclitaxel treated group (16.5 vs 6.9%,  $p = 0.03$ ), and there was a trend toward greater need for TLR (12.0 vs 6.4%;  $p = 0.19$ ), suggesting a treatment benefit of sirolimus in the diabetic population. Similarly, Maeng *et al.* compared late lumen loss in a total of 153 diabetics randomized to sirolimus or paclitaxel eluting stents [19]. It was observed that 8-month angiographic in-stent late lumen loss was significantly less for the sirolimus treated diabetics (0.23 vs 0.44 mm,  $p = -0.025$ ). Windecker *et al.* conducted a randomized, single-blind comparing SES with PESs in 1012 patients undergoing PCI [20]. The primary end point (death from cardiac causes, myocardial infarction, or ischemia-driven TLR at 9 months) occurred less often in patients receiving SES (6.2 vs 10.8%, HR: 0.56; 95% CI: 0.36–0.86;  $p = 0.009$ ). The difference between SES and PES was more pronounced among the 201 patients with diabetes (HR: 0.31; 95% CI: 0.21–0.78), but the test for interaction

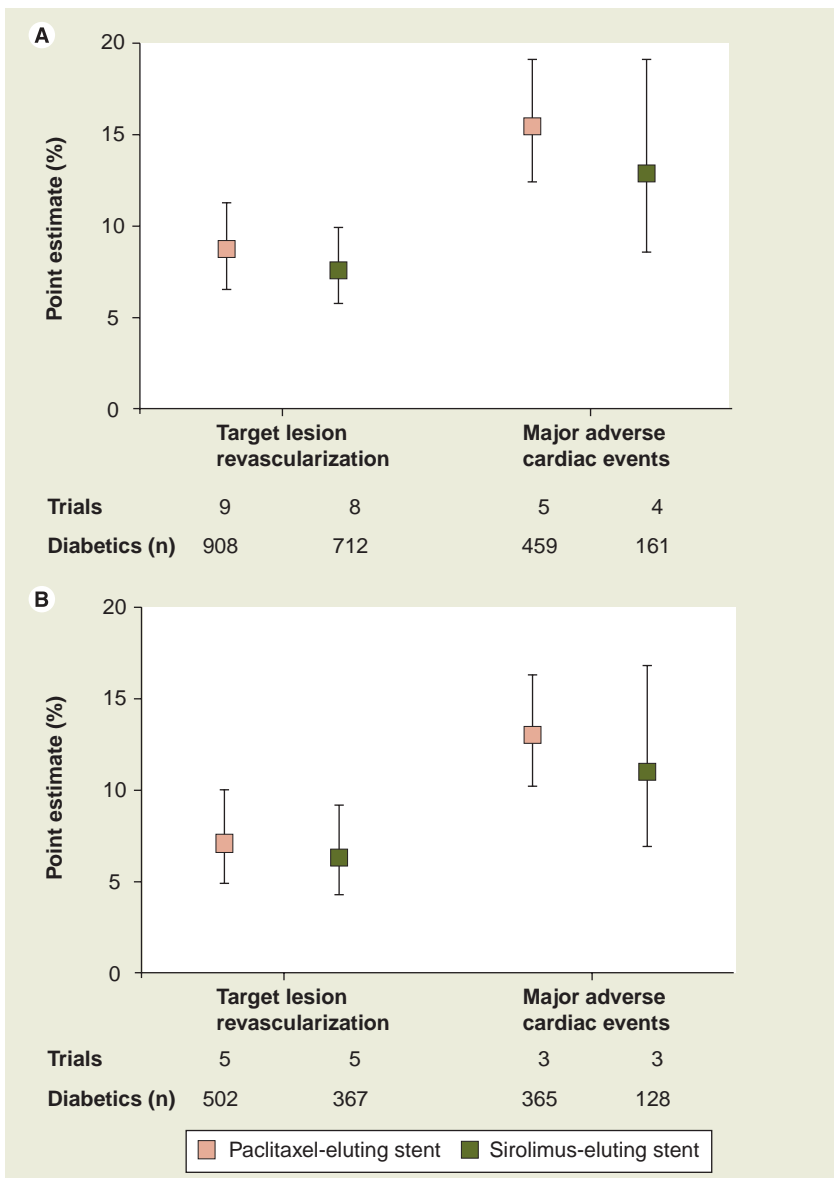
was not significant ( $p = 0.13$  for interaction). A large meta-analysis of sixteen randomized trials comparing the two stents also suggested a clear benefit for sirolimus with a reduction of reintervention (HR: 0.74; 95% CI: 0.63–0.87;  $p < 0.001$ ) and risk of stent thrombosis (HR: 0.66; 95% CI: 0.46–0.94,  $p < 0.02$ ), although the diabetic subgroup was not specifically addressed [21]. Lee *et al.* randomized 400 diabetic patients to receive either SES or PES [22]. The primary end point was in-segment restenosis at 6 months. A total of 6-month in-stent (3.4 vs 18.2%,  $p < 0.001$ ) and in-segment restenosis (4.0 vs 20.8%,  $p < 0.001$ ) and 9-month TLR (2.0 vs 7.5%,  $p = 0.017$ ) were significantly lower in the SES versus PES group. A recent report by the same group demonstrated durability of these results at 2 years [23]. In contrast, several large real world registries and meta-analyses have failed to demonstrate a consistent advantage of SES over PES in large patient cohorts. Stuckey *et al.* analyzed the outcomes of 3,935 patients without ST elevation in the STENT group who received SES ( $n = 1997$ ) or PES ( $n = 1938$ ) [24]. Propensity adjusted TVR (adjusted HR: 1.0; CI: 0.8–1.3;  $p = 0.90$ ) and Major adverse cardiac events (MACE) (Adjusted HR: 1.0, CI: 0.7–1.3;  $p = 0.77$ ) were similar in the two groups with follow-up of 2 years [23]. Similarly, the Registro Regionale Angioplastiche Emilia-Romagna Registry group reported equivalent propensity adjusted MACE (adjusted HR: 1.01, CI: 0.72–1.42;  $p = 0.96$ ) in 945 diabetic patients treated with SES ( $n = 606$ ) or PES ( $n = 339$ ) alone [25]. Reports from the SCAAR registry suggest similar rates of clinical restenosis for the Cypher, Taxus Express and Taxus Liberte stents, with a somewhat higher rate of restenosis for the Endeavor stent [26]. Restenosis as defined by the SCAAR registry was derived from any clinically driven angiographic follow-up reporting restenosis. Similarly, in the diabetic patients who underwent protocol-driven angiographic follow-up in the Endeavor IV trial, in-stent percent diameter stenosis at 8 months was greater among zotarolimus treated patients compared with those treated with paclitaxel (32.9 vs 21.1%,  $p = 0.023$ ), although clinical outcomes were similar in the larger cohort [27]. Mahmud *et al.* performed a meta-analysis incorporating over 11,000 patients utilizing randomized clinical trials and registries with diabetic patients receiving PES or SES [28]. In a total of 13 randomized clinical trials, similar point estimates for TLR (PES: 8.6%; 95% CI: 6.5–11.3; SES: 7.6%, 95% CI: 5.8–9.9) and MACE (PES: 15.4%; 95% CI: 12.4–19.1; SES: 12.9%, 95% CI: 8.5–19.2) were observed. In head to head trials (four trials), no

difference in the likelihood for TLR (PES vs SES) was observed (odds ratio 1.37; 95% CI: 0.64–2.9,  $p = 0.42$ ). These results are demonstrated in FIGURE 1. The point estimates in 16 registries for TLR and MACE for PES and SES were also similar. Additional discrepancies have been identified by the recent presentation of the Spirit IV results, a large, multicenter randomized trial comparing the second generation everolimus-eluting stent to the first generation PES in 3687 patients [29,30]. This study demonstrated that target lesion failure was consistently reduced with the everolimus-eluting stents compared with paclitaxel stents in twelve

prespecified subgroups except in patients with diabetes (target lesion failure 6.4 vs 6.9%,  $p = 0.80$ ). Reduction in both TLR and stent thrombosis appeared significant for nondiabetic patients with the newer generation stent. Similar findings were reported in the Compare Study, which compared the everolimus-eluting stent to the Taxus Liberte [31]. This study also suggested a less robust result in a diabetic subgroup analysis. The results of these trials are demonstrated in FIGURES 2 & 3. The reasons for the discrepancy remain speculative, but could be due to the attenuation of the antimigratory effects of the mycin type drugs under high glucose conditions that are not observed with paclitaxel [32]. The clinical implications of these findings remain controversial [33], with small randomized trials with angiographic follow-up favoring reduction in late lumen loss with limus-based stent platforms (except the current generation of zotarolimus), but large randomized trials and clinical registries failing to demonstrate significant differences in safety and efficacy between the various platforms. Longer-term outcome data, particularly with the second-generation stents, will be crucial in defining potentially important clinical differences.

### Acute myocardial infarction

Routine stent implantation in diabetic patients with acute myocardial infarction significantly reduces restenosis and enhances survival free from TVR [34]. Whether DES improve outcomes over and above BMS in this setting, particularly in the diabetic patient, remains a point of intense interest. Clinical restenosis is less frequent in the patient with acute myocardial infarction, making the beneficial differences between BMS and DES less pronounced. Moreover, the frequency of stent thrombosis at 1 year is higher (more than 3%) for both BMS and DES in patients treated for acute myocardial infarction [35]. Moreover, delayed healing at sites of plaque rupture appears to be a significant contributor to late stent thrombosis, a finding that might be enhanced by DES [36]. Conversely, it has recently been suggested that diabetes may be associated with a lower rate of late stent malapposition, a potential cause of late stent thrombosis, after DES implantation in acute myocardial infarction [37]. Finally, despite high rates of TIMI grade flow 3 after primary PCI in diabetic patients, patients with diabetes are more likely to have abnormal myocardial perfusion as assessed by both incomplete ST segment resolution and myocardial blush grade [38]. A meta-analysis by Brar *et al.* has summarized trials



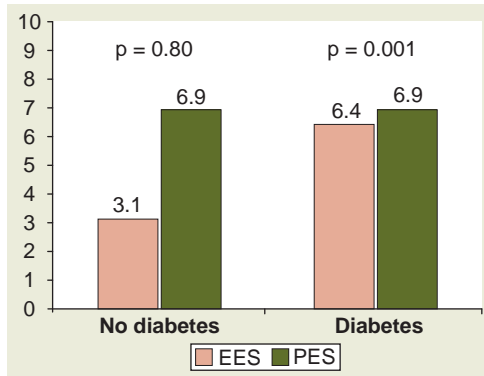
**Figure 1. Point estimates for target lesion revascularization and major adverse cardiac events for diabetic patients treated with drug-eluting stents in (A) all randomized controlled trials and (B) randomized controlled trials with Silber score >5.**

Bars indicate 95% confidence intervals. Reproduced with permission from [28].

utilizing DES in the setting of acute myocardial infarction up to 2008 [39]. A total of 13 randomized trials were identified. Compared with BMS, DES significantly reduced TVR (RR: 0.44; 95% CI: 0.35–0.55), without increasing death (RR: 0.97; 95% CI: 0.73–1.28), myocardial infarction (RR: 0.82; 95% CI: 0.64 to 1.05), or stent thrombosis (RR: 0.97; 95% CI: 0.73–1.28). These results were durable over 2 years. The Korean Acute Myocardial Infarction Registry (KAMIR) study prospectively enrolled 4416 patients who underwent primary PCI with DES [40]. PES was inferior to SES in the overall population with regard to the occurrence of MACE and TLR. In the diabetic subgroup, however, MACE was not significantly different between PES and SES (14.5 vs 12.3%,  $p = 0.217$ ) matched by propensity score. The HORIZONS study prospectively enrolled 3006 patients with ST elevation myocardial infarction to receive paclitaxel eluting stents or BMS in a 3:1 randomization [35]. The two primary end points were the 12 month rate of TLR for ischemia, and a composite safety outcome measure of death, reinfarction, stroke, or stent thrombosis. Patients receiving paclitaxel eluting stents had significantly lower 12 month rates of ischemia driven TLR (4.5 vs 7.5%; HR: 0.59; 95% CI: 0.43–0.83;  $p = 0.002$ ) with non inferior rates of the composite safety end point. The rate of ischemia driven TLR was significantly reduced in the diabetic subgroup (5.2 vs 11.2%,  $p = 0.03$ ) with no difference in the primary safety outcome measure (10.2 vs 12.5%,  $p = 0.18$ ). These results are summarized in TABLE 1. Cumulatively, these findings to date suggest that DES may be of particular benefit in diabetic patients in the setting of acute myocardial infarction. More data are needed to determine if one platform is superior to another in diabetic patients with acute myocardial infarction. Until that time, it seems reasonable to consider drug-eluting implantation a reasonable default strategy in diabetics in the setting of acute myocardial infarction.

### Stenting versus coronary artery bypass graft surgery for multivessel CAD

One area of intense controversy involves the appropriate use of DES versus coronary artery bypass surgery and/or medical therapy for diabetic patients with multivessel coronary artery disease. The Bypass Angioplasty Revascularization Investigation (BARI) compared PCI with conventional angioplasty with

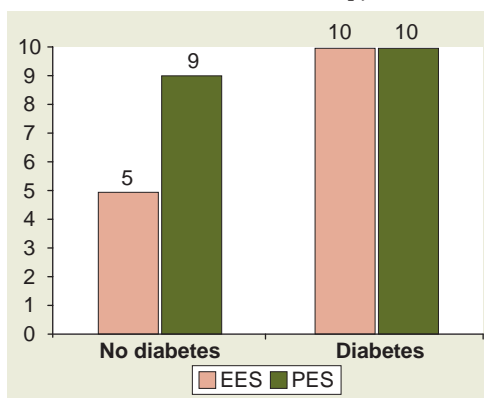


**Figure 2. Primary end point (cardiac death, myocardial infarction and ischemia-driven target lesion revascularization) in diabetic and nondiabetic patients randomized to a second-generation everolimus-eluting stent or first-generation paclitaxel-eluting stent.**

EES: Everolimus-eluting stent; PES: Paclitaxel-eluting stent.

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coronary artery bypass graft surgery (CABG) [41]. While the study reported no overall differences in the long-term rates of death and myocardial infarction, there was a significantly better 5-year survival with CABG compared with PCI in diabetic patients. These results were noted to be durable at 10 years [42], and these findings were subsequently confirmed in a meta-analysis of over 7000 patients incorporating multiple smaller trials. More recently, the BARI 2D Study Group randomly assigned 2368 patients with both Type 2 diabetes and stable ischemic heart disease to undergo either prompt revascularization with intensive medical therapy or intensive



**Figure 3. Primary end point (all-cause mortality, myocardial infarction and target vessel revascularization) in diabetic and nondiabetic patients randomized to a second-generation everolimus-eluting stent or second-generation paclitaxel-eluting stent.**

EES: Everolimus-eluting stent; PES: Paclitaxel-eluting stent.

Reproduced with permission from [31].

Table 1. 1-year outcomes in the HORIZONS-AMI trial

|                  | Diabetic            |                     |         | Nondiabetic          |                     |         |
|------------------|---------------------|---------------------|---------|----------------------|---------------------|---------|
|                  | PES<br>(n = 364; %) | BMS<br>(n = 114; %) | p-value | PES<br>(n = 1892; %) | BMS<br>(n = 635; %) | p-value |
| TLR              | 5.20                | 11.20               | 0.03    | 4.60                 | 7.00                | 0.02    |
| TVR              | 7.20                | 12.20               | 0.1     | 5.80                 | 8.30                | 0.03    |
| Death, all-cause | 6.10                | 7.20                | 0.7     | 3.00                 | 2.90                | 0.88    |
| Cardiac death    | 5.00                | 4.50                | 0.82    | 1.90                 | 2.40                | 0.48    |
| Reinfarction     | 3.40                | 5.60                | 0.32    | 3.70                 | 4.40                | 0.49    |
| Stroke           | 1.70                | 2.80                | 0.49    | 0.90                 | 0.30                | 0.14    |
| MACE             | 13.50               | 18.90               | 0.18    | 15.00                | 14.80               | 0.41    |
| Stent thrombosis | 3.10                | 4.50                | 0.49    | 3.40                 | 3.20                | 0.86    |

BMS: Bare-metal stent; MACE: Major adverse cardiac events; PES: Paclitaxel-eluting stent; TLR: Target lesion revascularization; TVR: Target vessel revascularization. Reproduced with permission from Elsevier. Data from [62].

medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy [43,44]. Primary end points were the rate of death and a composite of death, myocardial infarction, or stroke. Randomization was stratified according to the optimal method of revascularization chosen by the physician, either CABG or PCI. Of the 798 patients selected for the PCI stratum, 55% received a BMS and 35% received a DES. At 5 years, there was no significant difference in survival between those assigned to the revascularization group versus the medical therapy group (88.3 vs 87.8%,  $p = 0.97$ ), or between the insulin-sensitization group and insulin-provision group (88.2 vs 87.9%,  $p = 0.89$ ). In the those patients enrolled in the PCI stratum, at 5 years there was no difference in the primary end point between the revascularization group and those randomized to optimal medical therapy. In the CABG stratum, the rate of major cardiovascular events was significantly lower in the revascularization group compared with medical therapy (22.4 vs 30.5%,  $p = 0.01$ ) primarily due to a reduction in the rate of nonfatal myocardial infarction. Importantly, 42% crossed over to some form of revascularization during the 5 years of follow-up, stressing the importance of close observation in the medical treatment group. It is important to note that this was not a study comparing PCI to CABG in diabetics. The clinical relevance of the PCI stratum to contemporary practice has been questioned due to the late transition to DES during the course of the study.

Mehran *et al.* compared in hospital and 1-year outcomes in diabetic and nondiabetic patients undergoing multivessel stenting in 689 patients receiving BMSs [45]. Despite a high technical success rate, diabetic patients, especially those treated with insulin, had higher in hospital CABG, higher

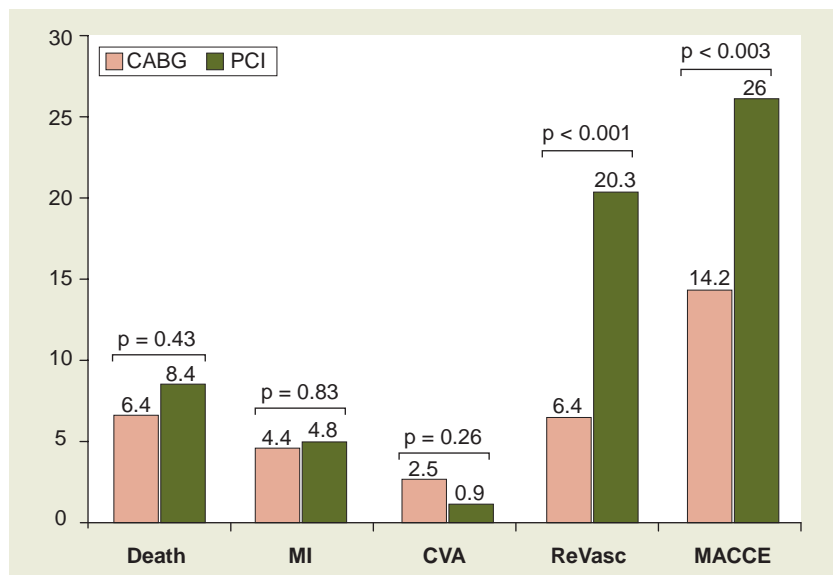
subsequent revascularization rates, and lower 1-year survival than non diabetic patients. The Arterial Revascularization Study (ARTS-I) compared multivessel coronary artery stenting with CABG [46]. The subgroup of diabetic patients required more repeat revascularization procedures, and there was a trend toward higher mortality at 5 years. ARTS-II was designed to evaluate the SES versus ARTS-I [47]. Despite more extensive disease, the overall MACE-free survival in diabetic patients at 1 year in ARTS-II was similar to ARTS I-CABG. Specifically, MACE free survival was 84.3% for ARTS II vs 85.4% for ARTS I-CABG in the diabetic subset ( $p = 0.86$ ). While the need for repeat revascularization was higher, this was offset by insignificantly lower rates of death and myocardial infarction. These results appear sustained at 3 years [48]. The Coronary Artery Revascularization in Diabetes (CARDia) trial compared the safety and efficacy of PCI in patients with diabetes and symptomatic multivessel disease against CABG [49]. Of the 510 patients, 38% were treated with insulin, 60% of the patients were treated for three vessel disease, and 69% received SES. Statins and aspirin were used in 85% at 1 year. The primary outcome was a composite of all cause mortality, myocardial infarction, and stroke. At 1 year of follow-up, the composite rate was 10.5% in the CABG group, and 13.0% in the PCI group (HR: 1.25; 95% CI: 0.75–2.09;  $p = 0.39$ ). When the patients who underwent CABG were compared with the subset of patients who received DES, the primary outcome rates were 12.4% in the CABG group, and 11.6% in the PCI group (HR: 0.93, 95% CI: 0.51–1.71;  $p = 0.82$ ). Longer-term follow-up is required to determine if these comparable outcomes persist. The Synergy between PCI with Taxus and cardiac surgery (SYNTAX) study compared CABG with the TAXUS Express PES stent

in nondiabetic and diabetic patients with complex left main and/or three-vessel disease [50,51]. Of the 1800 randomized patients, 459 had diabetes, of which 40% were treated with insulin. The primary end point was a composite of death from any cause, stroke, myocardial infarction, or repeat revascularization in the 12 months following randomization. In diabetic patients, the 1-year composite MACCE rate was significantly higher after PES treatment compared with CABG. These results are summarized in **Figure 4**. There was not a significant difference in the composite rate of death/stroke/or myocardial infarction between the PES and CABG group in diabetics (10.1 vs 10.3%,  $p = 0.98$ ). The difference in outcome was driven by repeat revascularization (20.3 vs 6.4%,  $p < 0.001$ ) in the PES group. Both diabetic and nondiabetic patients had increased mortality in the subset with the highest complexity (Syntax score  $>33$ ). Moreover, repeat revascularization rates after PES treatment tended to increase with increasing lesion complexity, particularly in diabetic patients. A nonstatistically significant trend towards higher mortality was also noted in insulin requiring diabetics treated with PES over CABG. In conclusion, DES implantation appears to be a reasonable alternative to CABG in diabetic patients with multivessel disease with low or intermediate Syntax scores, while CABG may be the preferred strategy in those individuals with high Syntax scores or insulin-requiring diabetes.

The Future Revascularization Evaluation in patients with Diabetes Mellitus: Optimal management of Multivessel disease (FREEDOM) is an NHLBI sponsored multicenter randomized trial comparing PCI with DES to the standard of care, CABG, in 1900 patients, combined with optimal medical management [101]. The primary outcome is the composite of all cause mortality, nonfatal myocardial infarction and stroke. Patients will be followed up to 5 years. The choice of DES is at the discretion of the operator. This will be a pivotal study for defining the role of DES in the multivessel management of patients with diabetes. Until this trial is complete, coronary artery bypass surgery would appear to be favored over PCI with DES, particularly those that require insulin, and those with increased interventional complexity.

### Second-generation drug-eluting coronary stents

The second generation of DES have been recently approved, and are gaining traction in the interventional community. Newer stents that incorporate a variety of design alterations are also on the



**Figure 4. A total of 12-month outcomes of medically treated diabetic patients with left main or three vessel disease randomized to coronary artery bypass graft surgery or percutaneous coronary intervention with Taxus.**

CABG: Coronary artery bypass graft surgery; PCI: percutaneous coronary intervention.

Reproduced with permission from [51].

horizon over the next several years. The second-generation stents differ from their first-generation platforms by employing thinner struts, which may result in reduced vessel wall injury [52], and greater endothelialization [53]. Durable polymers employed in early stent designs may be associated with inflammation and allergic reactions, a potential suspect for late stent thrombosis in some cases, and are being replaced by more biocompatible and biodegradable polymers [54,55]. The SPIRIT IV trial, as previously noted, which compared the first-generation paclitaxel-eluting Express II stent to the second-generation everolimus-eluting stent, demonstrated a reduction in target vessel failure at 1 year in 12 prespecified subgroups except patients with diabetes. The COMPARE study randomized 1800 consecutive patients at one center to the second-generation everolimus-eluting stent to the second-generation PES (Liberte) [49]. The primary end point was a composite of safety and efficacy (all cause mortality, myocardial infarction and TVR) within 12 months. The primary end point occurred less frequently in the everolimus-eluting stent (6 vs 9%, RR: 0.69; 95% CI: 0.50–0.95,  $p = 0.02$  for superiority). However, as in SPIRIT III and SPIRIT IV, subgroup analysis in the 325 diabetic patients revealed no difference in the primary end point for diabetics, as the rate was 10% in both. The conclusions of the authors were that PES should no longer be used in everyday clinical

practice. Nonetheless, the data that exist do not support an important difference in outcome in diabetic patients between the limus-eluting second-generation stents and first- and second-generation paclitaxel stents. Further follow-up studies are needed to sort through the long-term impact of the predominately 1-year datasets. Whether next-generation stents, which employ other limus analogs, polymer-free and prohealing technologies, and thinner strut and biodegradable stents, will have an impact on future outcomes remains to be seen.

### Stent thrombosis & optimal antiplatelet therapy

Previous studies have suggested that diabetic patients are at increased risk for stent thrombosis [56]. The mechanisms for this may be multiple, including increased multiple comorbidities, as well as upregulation of platelet membrane proteins such as the P2Y<sub>12</sub> receptor [57]. Furthermore, patients with Type 2 diabetes mellitus appear to have reduced *in vitro* responsiveness to antiplatelet agents. Angiolillo *et al.* randomized suboptimal responders to standard clopidogrel treatment with diabetes to standard (75 mg) or high (150 mg) daily maintenance dosing [58]. After 30 days of treatment, maximal adenosine diphosphate induced platelet aggregation was reduced in the 150-mg group compared with the 75-mg group. However, suboptimal clopidogrel response was still present in 60% of patients on the 150-mg regimen. Furthermore, high on treatment platelet reactivity has been shown to be associated with an increase in cardiovascular events [59]. Newer agents, such as prasugrel and ticagrelor, overcome some of the inherent limitations of clopidogrel, and show promise, particularly in diabetic patients. In the TRITON-TIMI 38 [60] investigation, patients with acute coronary syndromes undergoing PCI were randomized to dual antiplatelet therapy with aspirin and either clopidogrel or prasugrel following stent implantation [60]. The primary end point of the study was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The primary end point was observed in 9.9% of patients without diabetes, 13.4% of patients with diabetes not using insulin, and 18.3% of patients requiring insulin (*p* for trend < 0.0001). Patients with diabetes had a higher rate of stent thrombosis (definite/probable according to the Academic Research Consortium; 2.8 vs 1.4%; HR: 1.95; 95% CI: 1.47–2.59; *p* < 0.0001). A 14% reduction in the primary end point occurred in nondiabetics and a 30% reduction occurred in diabetic patients (*p* < 0.001). A substantial

reduction in stent thrombosis at 450 days was observed regardless of diabetic status, and was 48% lower in diabetics treated with prasugrel (2.0 vs 3.6%; *p* = 0.007, *p* interaction = 0.63). Although no major increase in major or minor hemorrhage was seen in the diabetic subgroup according to treatment, prasugrel was associated with a 43% increase in non-CABG-related major hemorrhage (*p* = 0.02) in the overall trial, and no interaction was observed between treatment and diabetic status for major hemorrhage. In the PLATElet inhibition and patient Outcomes trial (PLATO) [61], the reversible direct P2Y<sub>12</sub> inhibitor ticagrelor was compared with clopidogrel in patients with STEMI and non-STEMI acute coronary syndromes; in the diabetic subgroup, the reduction in the composite primary end point (death from vascular causes, myocardial infarction or stroke at 360 days) was consistent with the overall trial, and without significant diabetes status-by-treatment interaction. (HR: 0.88; 95% CI: 0.76–1.03). There was no increase in major bleeding. Stent thrombosis was lower in diabetics treated with ticagrelor (1.6 vs 2.4%, HR: 0.65; 95% CI: 0.36–1.17; *p* = NS). As in the TRITON-TIMI-38 investigation, diabetics in the PLATO trial had higher overall event rates compared with non diabetics. Cumulatively, these data suggest that diabetes is associated with higher rates of adverse cardiac events and stent thrombosis, and that more potent platelet inhibition is associated with a reduction in event rates. Ongoing clinical research evaluating the trade off between more aggressive platelet suppression and increased risk of bleeding will be important to optimizing outcomes in diabetic patients. At present, selection of agents based on careful analysis of individual patient benefit/risk seems prudent.

### Conclusion

Stenting has improved the outcome of patients with ischemic heart disease and diabetes mellitus. Diabetic patients who undergo PCI have higher rates of late lumen loss, binary restenosis, and the need for TVR. Stenting has reduced these complications over conventional PCI by eliminating elastic recoil, and creating a greater net gain. Neointimal hyperplasia is greater in diabetics receiving stents, and the use of drug-eluting platforms which inhibit this, make DES ideal for this patient subset. While some randomized studies have demonstrated differences between drug-eluting platforms with regard to outcomes in diabetic patients, other randomized trials and clinical registries have failed to demonstrate large differences in outcomes among the



different stents. Furthermore, the true long-term outcomes of different platforms remains under careful scrutiny at this time. While DESs have improved outcomes in diabetic patients predominately by a reduction in ischemia driven TLR, they have not shown a demonstrable impact on mortality in randomized trials. In patients with more advanced multivessel and complex disease, CABG continues to demonstrate an advantage, particularly in the diabetic population with high lesion complexity and insulin use. Ongoing studies will hopefully provide more clarity. Randomized trials utilizing DES in patients with acute myocardial infarction show promise, but will require continued study with longer follow-up, and continued development in stent design to help avoid potential pitfalls mediated by lack of vascular healing.

### Future perspective

Diabetic patients with coronary artery disease represent a challenging subset of patients as evidence by their higher rates of adverse cardiac events regardless of the treatment strategy utilized.

Continued improvements in stent technology and in adjunctive medical therapies has the potential to narrow the gap between coronary revascularization surgery and PCI with DES for patients with more advanced disease. Stabilization of arterial segments not covered by stents, and eliminating those factors associated with late stent thrombosis and the requirement for prolonged dual antiplatelet therapy are progressively within reach.

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## Executive summary

### Introduction

- Diabetic patients with coronary heart disease have a worse prognosis compared with nondiabetic patients, and coronary stenting has improved the prognosis in these patients due to a reduction in need for target vessel revascularization.

### Drug-eluting versus bare-metal stents in diabetic patients

- Compared with bare-metal stents, the use of drug-eluting stents in diabetic patients has resulted in a significant reduction in late lumen loss, rates of binary restenosis, and clinically driven target vessel revascularization.

### Comparing drug-eluting stents in patients with diabetes

- Drug-eluting stents differ in design, polymer and drug, resulting in the potential for different outcomes.
- Randomized trials and registries with both first- and second-generation platforms have yielded conflicting results as to best options with regard to stent choice in the diabetic population.

### Acute myocardial infarction

- The role of drug-eluting stents in acute myocardial infarction remains controversial owing to lower overall benefit combined with increased safety concerns, but diabetic patients may benefit disproportionately in this subgroup.

### Stenting versus coronary artery bypass graft surgery for multivessel disease in diabetics

- Diabetics with multivessel CAD, particularly those with increased lesion complexity, appear to benefit more with coronary artery bypass graft surgery.

### Second-generation stents in diabetics

- Despite the promise of newer technologies, clinical trials to date have suggested a leveling effect between drug-eluting platforms in this subgroup.

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