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VIEWPOINT

Drug-Eluting Stents for Diabetes Mellitus

A Rush to Judgment?

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The two pivotal U.S. trials of drug-eluting stents do not establish the principle that these stents are superior to thin-strut bare-metal stents for preventing repeat revascularization in patients with diabetes. Neither study was adequately powered to make this determination. Moreover, both studies used thick-strut stents known to have high restenosis rates as controls. Low angiographic follow-up underestimates the true target lesion revascularization rate in the Polymer-Based Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease (TAXUS-IV) trial because of the high incidence of silent ischemia in patients with diabetes. Optimal therapy for diabetic coronary disease should include a comprehensive approach directed toward metabolic normalization in addition to local stent-based therapy. (J Am Coll Cardiol 2005;45:479–83) © 2005 by the American College of Cardiology Foundation

Since the recent introduction of the Cypher (Cordis Corp., Warren, New Jersey) and Taxus Express (Boston Scientific, Natick, Massachusetts) drug-eluting stents (DES) into the U.S. market, these devices are now considered by many to be the standard of care for diabetic patients undergoing coronary stent placement. However, careful examination of the data from two pivotal U.S. trials, the Sirolimus-coated BX Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions (SIRIUS) trial and Polymer-Based Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease (TAXUS-IV) trial, demonstrate that this conclusion may not be supported by the data generated by these studies (1,2).

PATIENT DEMOGRAPHICS AND STUDY DESIGN

Diabetes mellitus was present in 26% of patients in the SIRIUS trial and in 32% of patients in the TAXUS-IV trial. The trial designs were similar in that they excluded higher-risk patients such as those with myocardial infarction, but were different in terms of requirement for angiographic follow-up. In the SIRIUS trial, approximately 67% of patients with diabetes underwent angiographic follow-up at 240 days. As a result, most target lesion revascularization (TLR) was angiographically as well as clinically determined. The design of TAXUS-IV trial was different in that the majority of diabetic patients in this trial (68%) did not receive angiographic follow-up. As a result, TLR rates in this trial were mostly clinically driven (i.e., on the basis of symptoms). This is an important fact for two reasons: 1) TLR rates are often higher in trials with angiographic rather than clinical follow-up and 2) clinical follow-up is notoriously unreliable in patients with diabetes because these patients are known to have significantly greater incidence of silent ischemia than their non-diabetic counterparts (3,4). In fact, TLR rates in this trial were approximately 50% higher in patients receiving angiographic rather than clinical follow-up and could probably be expected to be much higher within the diabetic subset (5). As a result of design differences, comparison of results between these trials is probably not possible.

Moreover, the importance of medical therapy to achieve recommended glycemic control targets and management of usual risk factors in these patients cannot be overstated and represent important potential confounding factors in interpreting any data from these trials (6,7). No information regarding the level of glycemic control of these patients as well as their medical regimen (e.g., number taking a statin) was given, and medical regimens were simplified into insulin-requiring versus non–insulin-requiring. The validity of subset analysis is uncertain given these uncontrolled-for variables.

In addition, neither trial was powered to determine differences in restenosis among patients with diabetes, and therefore any conclusions drawn carry a high risk that the differences observed may be due to chance alone (type I error). Subset analysis is not a substitute for adequately powered prospective randomized controlled studies in patients with type 2 diabetes undergoing coronary stent placement.

STUDY RESULTS

The SIRIUS trial. As for outcomes in the diabetic subset of each trial, in SIRIUS, the overall nine-month rate of angiographic restenosis among diabetic patients enrolled in the trial was 17.6% in the sirolimus-eluting stent (SES) arm versus 50.5% in the bare-metal stent (BMS) arm ($p < 0.001$) (Table 1) (8). The 270-day TLR rates were 22.3% in

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Abbreviations and Acronyms

BMS	= bare-metal stent
DES	= drug-eluting stents
ISAR-STEREO	= Intracoronary Stenting and Angiographic Results-Strut Thickness Effect on Restenosis Outcomes trial
PCI	= percutaneous coronary intervention
PES	= paclitaxel-eluting stent
PPAR	= peroxisome proliferator-activated receptor
RVD	= reference vessel diameter
SES	= sirolimus-eluting stent
SIRIUS	= Sirolimus-coated BX Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions
TAXUS-IV	= Polymer-Based Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease
TLR	= target lesion revascularization

the BMS arm and 6.9% in the SES arm ($p < 0.001$). The 270-day major adverse cardiac events evaluation revealed a 63% reduction in this end point among diabetic patients treated with SES versus those receiving BMS (25% BMS vs. 9.2% SES, $p < 0.001$).

In non–insulin-requiring patients, the angiographic in-segment restenosis rate was 12.3% in the SES arm and 50.7% in the BMS arm ($p < 0.001$) (Table 2). Target lesion revascularization was reduced in this group from 23.1% in the BMS arm to 4.3% in the SES arm ($p < 0.001$). The average reference vessel diameter (RVD) was 2.71 mm in the BMS arm and 2.63 mm in the SES arm (p = NS), with an average lesion length of 15 mm in the BMS arm and 13 mm in the SES arm (p = NS).

In insulin-requiring diabetic patients, the angiographic in-segment restenosis rate at 270 days was 50% in the BMS arm, which was not significantly different from 35% in the SES arm (Table 2). Target lesion revascularization rates were also not significantly different between the two arms (20.5% BMS vs. 13.2% SES, p = NS). The baseline RVD was 2.79 mm in the BMS arm and 2.77 mm in the SES arm (p = NS), with an average lesion length of 14.81 mm in the BMS arm and 14.5 mm in the SES arm (p = NS). Multiple logistic regression analysis revealed diabetes mellitus to be a significant predictor of TLR at 270 days (coefficient 0.5, odds ratio 1.65, $p = 0.03$) in diabetic patients treated with the Cypher stent.

The TAXUS-IV trial. The overall nine-month and one-year results from the TAXUS-IV trial have recently been published (2,5). However, specific information on patients with diabetes, including percent of patients in each arm with angiographic follow-up and nine-month TLR rates, has not yet been published in peer-reviewed journals. Approximately 136 of 423 diabetic patients enrolled in the trial underwent follow-up angiography. This represents 32% of the entire diabetic population enrolled in the trial. Mean lesion length was 14.4 mm in the paclitaxel-eluting stent (PES) arm and 14.4 mm in the BMS arm (p = NS). The average baseline RVD is not available. Nine-month angiographic data from this subset of patients revealed the angiographic restenosis rate to be 29.7% in the BMS arm and 5.8 in the PES arm ($p = 0.003$) among diabetic patients treated with oral medications. Among diabetics treated with insulin, the angiographic restenosis rate was 42.9% in the BMS arm and 7.7% in the PES arm ($p = 0.007$). One-year TVR rates for orally treated diabetics were 7.9% in the PES arm and 21.6% in the BMS arm ($p = 0.005$). For insulin-treated patients, TVR was 6.2% in the PES arm and 19.4% in the BMS arm ($p = 0.07$), with the confidence interval crossing beyond unity. It is interesting to note that the 12-month TVR rates for patients receiving the PES are actually lower in the insulin-treated population than in the oral-treated diabetic group, an unexpected result that runs counter to all previously published data (9–11). Because of differences in the design of this trial (i.e., number of patients with angiographic follow-up), it is unclear whether these results can be compared with those of the SIRIUS trial or other interventional trials involving coronary stent placement in which the majority of patients underwent follow-up angiography.

The Intracoronary Stenting and Angiographic Results-Strut Thickness Effect on Restenosis Outcomes (ISAR-STEREO) trial. In both the SIRIUS and TAXUS-IV trials, the bare-metal control arm stents had very high restenosis rates likely related to the stent design, which overemphasized the superiority of drug delivery stents. The strut thickness of both the BX Velocity (Cordis Corp., Johnson & Johnson, Warren, New Jersey) and the Express stent is significantly larger than that of the thin-strut stents such as the Multi-Link. Randomized trials have shown strut thickness to be an important

Table 1. Diabetic Subset Analysis: SIRIUS (1) Versus ISAR-STEREO (12,13)

	SIRIUS			ISAR-STEREO		
	BMS	**SES**	**p Value**	**Thin S**	**Thick S**	**p Value**
Angiographic restenosis	50.5% n = 101	17.6% n = 85	< 0.001	19.7% n = 76	37.9% n = 95	0.01
TLR	22.3% n = 148	6.9% n = 131	< 0.001	9.0% n = 122	21.9% n = 128	0.005

BMS = bare-metal stent; ISAR-STEREO = Intracoronary Stenting and Angiographic Results trial; SES = sirolimus-eluting stent; SIRIUS = Sirolimus-coated BX Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions trial; Thin S = thin-strut stent; Thick S = thick-strut stent; TLR = target lesion revascularization.

Table 2. SIRIUS: Results From Insulin-Requiring Versus Non–Insulin-Requiring Diabetic Patients (8)

	Non–Insulin-Requiring			Insulin-Requiring		
	BMS (n = 104)	SES (n = 93)	p Value	BMS (n = 44)	SES (n = 38)	p Value
Angiographic restenosis*	50.7% n = 73	12.3% n = 65	< 0.001	50% n = 28	35% n = 20	0.38
TLR	23.1%	4.3%	< 0.001	20.5%	13.2%	0.56
MACE	26.0%	6.5%	< 0.001	22.7%	15.7%	0.58

*In segment.
MACE = major adverse cardiac events; TLR = target lesion revascularization; other abbreviations as in Table 1.

determinant of angiographic restenosis and TLR in both diabetic and non-diabetic patients. Data from two randomized controlled clinical trials, the ISAR-STEREO and ISAR-STEREO-2 trials, confirmed that reduced stent strut thickness is associated with significantly improved angiographic and clinical restenosis rates (12,13). In these trials patients were randomized to thin-strut (Multi-Link, Guidant Corp., Advanced Cardiovascular Systems, Santa Clara, California) versus thick-strut (Multi-Link Duet) (ISAR-STEREO trial) or BX Velocity (ISAR-STEREO-2 trial) stent implantation and underwent six-month follow-up angiography. Rates of angiographic follow-up for diabetic patients in these trials were approximately 70%. Combined diabetic subset data from the 171 patients receiving angiographic follow-up in these trials reveal six-month angiographic restenosis rates to be 37.9% in the thick-strut bare-metal arm (Duet or BX Velocity) and 19.7% (Multi-Link) in the thin-strut bare-metal arm ($p = 0.01$). The six-month TLR in the 250 diabetic patients followed was 21.9% in the thick-strut arm and 9% in the thin-strut arm ($p = 0.005$) (A. Kastrati, personal communication, April 13, 2004). In summary, the results using thin-strut stents in diabetic patients in this trial compare favorably with those obtained with the SES in diabetic patients in the SIRIUS trial (Table 1).

Angiographic restenosis and TLR across the trials. Although data from the two pivotal U.S. trials using DES appear impressive at first glance, the confidence intervals for angiographic restenosis and TLR overlap when comparing the data from these trials with the data from the ISAR-STEREO trial (Fig. 1). It remains unclear whether either

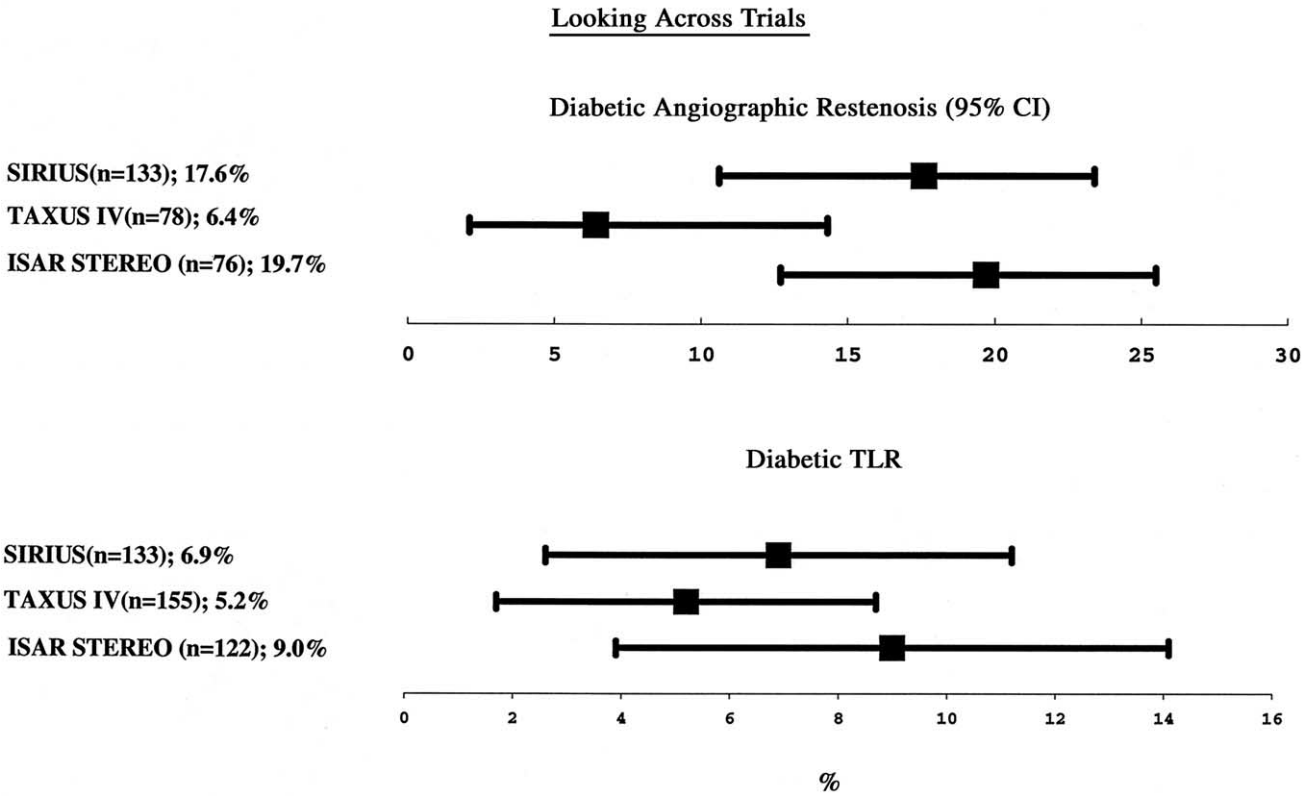

Figure 1. Comparison of rates of angiographic restenosis and target lesion revascularization (TLR) for diabetic patients enrolled in the Sirolimus-coated BX Velocity Balloon-Expandable Stent in the treatment of Patients with De Novo Coronary Artery Lesions (SIRIUS) (1), Polymer-Based Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease (TAXUS-IV) (2), and Intracoronary Stenting and Angiographic Results (ISAR-STEREO) (12,13) trials (95% confidence intervals [CI] are illustrated).

DES commercially available in the U.S. randomized against a thin-strut stent of the Multi-Link design would show significant benefit in patients with diabetes. Moreover, the TAXUS-IV study results for diabetic patients are not easily comparable with the other two studies in which rates of follow-up angiography were much higher.

DIABETES AND RISK OF ATHEROSCLEROSIS PROGRESSION

Although the goals of DES are to lower restenosis at the stented site, the therapy is local and obviously will do nothing to prevent progression of coronary disease at other sites. In addition to restenosis, non-culprit lesion progression is another important factor underlying adverse outcomes seen in diabetic patients after percutaneous coronary intervention (PCI) (14). A large number of these patients undergo repeat PCI at a site different from that of the initially treated lesion (15). The Arterial Revascularization Therapies Study (ARTS) demonstrated a two-fold higher mortality in diabetic patients with multi-vessel disease undergoing PCI versus coronary artery bypass surgery (16). A significant reason for this was non-culprit lesion progression. In the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial, which examined the effect of tranilast on restenosis prevention after coronary stenting, diabetic patients had a 33% increase over non-diabetic patients in new lesion formation over the next nine months (17). Moreover, adverse clinical events, including myocardial infarction and death, were more frequent in diabetic versus non-diabetic patients. In addition to its as-yet-unproven benefit for diabetic patients in terms of lowering restenosis, the long-term benefit of DES in these patients may be limited by their inability to retard non-culprit lesion progression. Newer systemic therapies that combat both restenosis and progression of atherosclerosis are needed and may in the end be the best solution for patients with diabetes.

EFFECT OF DIABETES ON VASCULAR BIOLOGY: SYSTEMIC VERSUS LOCAL THERAPY

Hyperglycemia and insulin resistance are the two crucial metabolic abnormalities defining type 2 diabetes mellitus (18). Together these pathophysiologic alterations drive both atherosclerosis and excessive neointimal formation after coronary intervention. Any therapy based on the pathobiology of this disease must target both of these processes. Reliance on local antiproliferative therapy using either paclitaxel or sirolimus may treat local responses to stent-induced injury through prevention of smooth-muscle cell proliferation, but they do not target the underlying systemic derangements that affect the entire coronary circulation. New approaches using systemic therapies to target insulin resistance, inflammatory signaling, endothelial dysfunction, and prothrombotic state are needed in order to significantly improve outcomes in this patient population. The glitazones are agonists of the peroxisome proliferator-activated receptor (PPAR)-gamma, have multiple beneficial effects on vascular cells, and are commercially available for the treatment of type 2 diabetes (19). These drugs are known to: 1) inhibit smooth-muscle cell growth and migration; 2) limit the production of proinflammatory and proatherosclerotic cytokines; 3) improve defects in fibrinolysis by decreasing fibrinogen and plasminogen activator inhibitor-1 levels; and 4) reduce insulin levels by improving insulin sensitivity in a variety of tissues (20,21). Haffner et al. (22) reported that in patients with type 2 diabetes, treatment with 26 weeks of the PPAR-gamma oral agonist rosiglitazone resulted in significantly lower levels of C-reactive protein and matrix metalloproteinase-9 compared with diabetic patients receiving placebo. These findings suggest a potential beneficial effect on overall atherosclerotic risk. Another group of studies by Minamikawa et al. (23) and Koshiyama et al. (24) demonstrated that type 2 diabetic patients treated with PPAR-gamma agonists troglitazone or pioglitazone demonstrated a significant decrease in common carotid intima-to-media ratio compared with control patients, suggesting a potent inhibitory effect on progression of early atherosclerosis.

Study limitations. There are limitations to drawing conclusions from a non-randomized comparison because the patient population and other demographic features (such as the incidence of smoking and the severity of diabetes) may differ between trials. Definite conclusions can only be drawn from a prospective randomized trial in diabetic patients comparing thin-strut BMS to DES.

Conclusions. In summary, the two pivotal U.S. trials of DES, the SIRIUS and TAXUS-IV trials, do not establish the principle that DES are superior to well-designed thin-strut BMS in terms of lowering repeat revascularization. Neither study was adequately powered to determine differences within the diabetic subsets of these trials. Moreover, both trials compared DES to BMS with excessively high restenosis rates, exaggerating any differences observed. The impressive angiographic results regarding restenosis rates and TLR in the diabetic subset of the TAXUS-IV trial are in part related to the relatively low angiographic follow-up rate. Finally, revascularization in diabetic patients utilizing coronary stent implantation will also require systemic therapy to address alterations in underlying pathobiology responsible for both atherosclerosis progression and aggressive neointimal formation.

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