Percutaneous Coronary Revascularization of Diabetic Patients in the Era of Drug-Eluting Stents

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Patients with diabetes have worse clinical outcomes following both surgical revascularization and percutaneous coronary intervention (PCI). Although coronary stenting has improved late outcomes (versus balloon angioplasty) following PCI, both angiographic restenosis and the requirement for repeat revascularization are increased in diabetics versus nondiabetics and limit the durability of PCI compared with surgery. Polymer-based drug-eluting stents (DES) have markedly reduced late coronary lumen loss and angiographic restenosis as well as the need for repeat revascularization when compared with conventional (non–drug-eluting) coronary stent deployment. Specifically, the CYPHER® sirolimus-eluting stent (Cordis Cardiology, Miami Lakes, FL) has demonstrated durable clinical and angiographic benefit for diabetic patients in both randomized clinical trials and postmarket surveillance registries. Data on the more recently approved paclitaxel-eluting TAXUS™ (Boston Scientific, Natick, MA) stent suggest similar efficacy for the treatment of diabetic patients. By markedly reducing restenosis, DES significantly improve or eliminate the major limitation of conventional stenting/PCI in diabetic patients. The advent of DES promises a paradigm shift from surgical revascularization in diabetic patients (especially those with multivessel disease) to PCI. Nevertheless, continued improvement in DES delivery as well as optimal adjunctive pharmacotherapy and control of hyperglycemia will be required to achieve the best clinical outcomes following PCI with DES in patients with diabetes.
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Key words: Angioplasty • Coronary artery bypass graft • Diabetes mellitus • Drug-eluting stents • Percutaneous coronary revascularization • Restenosis

Since the advent of percutaneous coronary intervention (PCI), restenosis has been considered the "Achilles' heel" and diabetes the "problem child" for the procedure. The presence of diabetes predicts adverse clinical outcomes following both percutaneous and surgical revascularization. The propensity of diabetic patients to experience adverse outcomes following revascularization

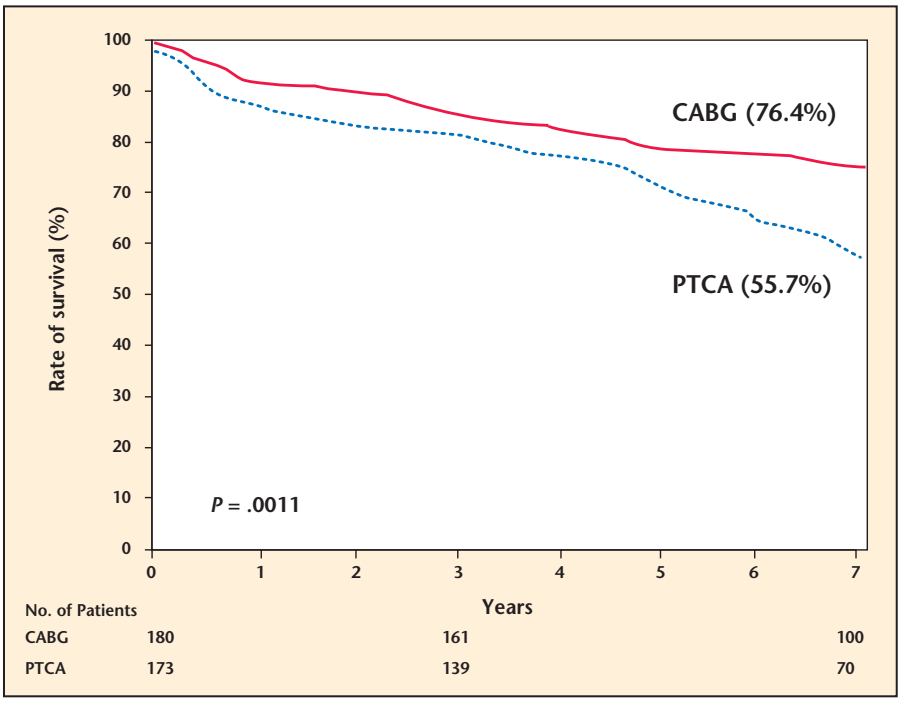
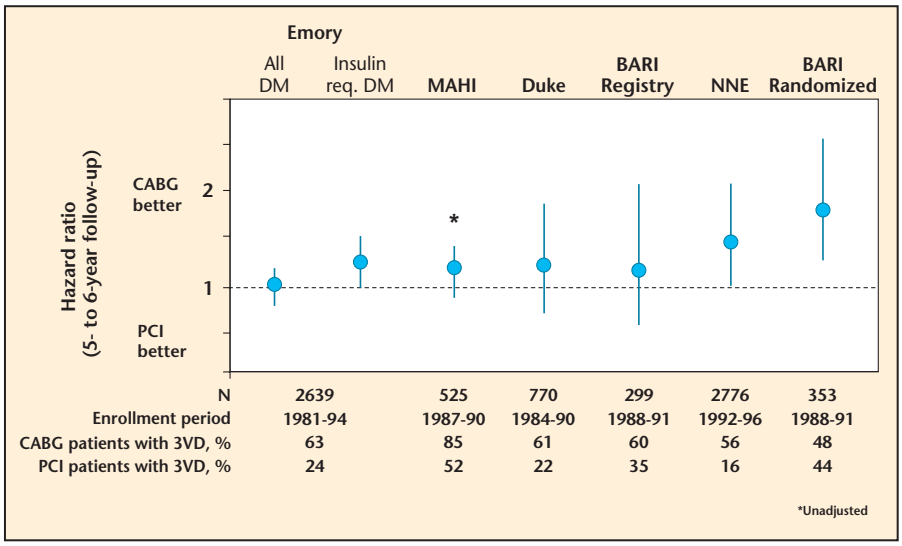


Figure 1. *Late survival in patients with treated diabetes in the Bypass Angioplasty Revascularization Investigation (BARI) trial. Late survival following multivessel revascularization was significantly increased by coronary artery bypass grafting (CABG) versus percutaneous transluminal coronary (balloon) angioplasty (PTCA). Reproduced with permission from the BARI Investigators.*[20]

has been ascribed to smaller-caliber target vessels, a greater degree of underlying vascular inflammation, a prothrombotic state, and more frequent associated risk factors. Furthermore, both the prevalence and extent of vascular disease are increased in patients with diabetes. Unfortunately, the prevalence of diabetes, obesity, and the associated metabolic syndrome has reached epidemic proportions in the United States.[1] Recent data suggest that immunity, inflammation, and heredity are related central pathogenic mechanisms in the development of insulin resistance, which characterizes the metabolic syndrome.[2,3] Insulin resistance may be further involved in the development of atherothrombotic disease through stimulation of plasminogen activator inhibitor-1 and alteration of endothelial function as well as through a direct mitogenic/growth factor–like effect of insulin on both vascular smooth muscle and neointimal cells.[4] In addition, maladaptive arterial remodeling (transmural vessel scarring or shrinkage) may contribute to more frequent restenosis following balloon angioplasty in diabetic patients.[5]

Although coronary stent deployment was observed to improve both angiographic and clinical late outcomes in diabetic cohorts when compared with standard balloon angioplasty, late restenosis and the requirement for revascularization following coronary stent deployment remains significantly more common in diabetics versus nondiabetics.[6-13] Early randomized comparative studies of percutaneous transluminal coronary (balloon) angioplasty (PTCA) and coronary artery bypass grafting (CABG) demonstrated an increased morbidity and mortality among diabetics compared with their nondiabetic counterparts.[14-19] Furthermore, the mode of revascularization appears to influence late survival (Figure 1). In the Bypass Angioplasty Revascularization (BARI) trial, survival to 7 years post revascularization was greater in diabetics randomly assigned to CABG (versus PTCA), par-

Figure 2. *Survival following revascularization in diabetics versus nondiabetics from multiple trials. In general, surgical revascularization has been associated with a trend toward improved late survival. MAHI, Mid America Heart Institute; BARI, Bypass Angioplasty Revascularization Investigation; NNE, Northern New England database; 3VD, triple-vessel disease; CABG, coronary artery bypass graft; DM, diabetes mellitus; PCI, percutaneous coronary intervention. Reproduced with permission from Niles et al.*[21]



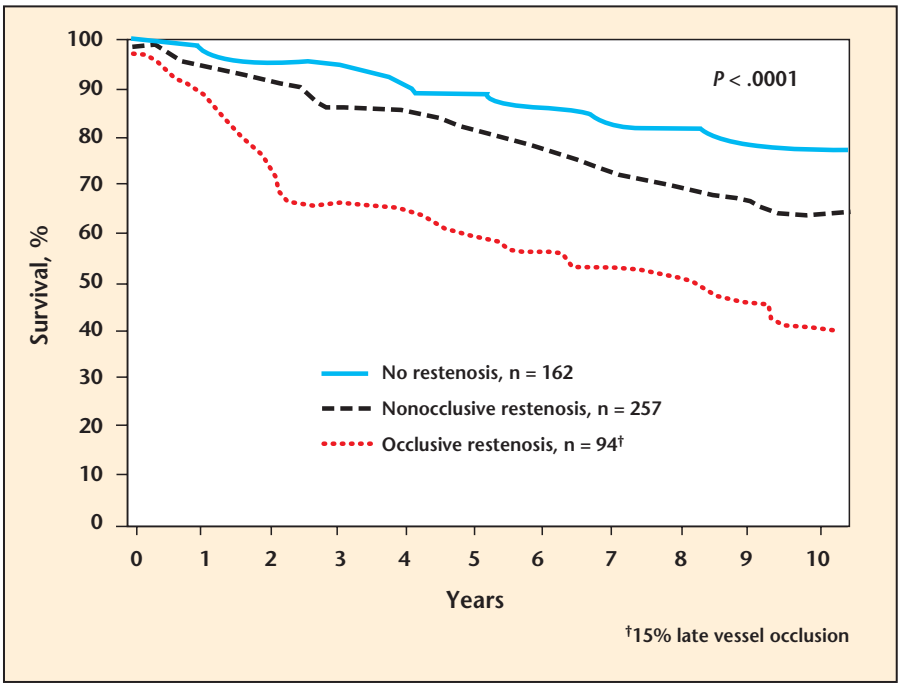
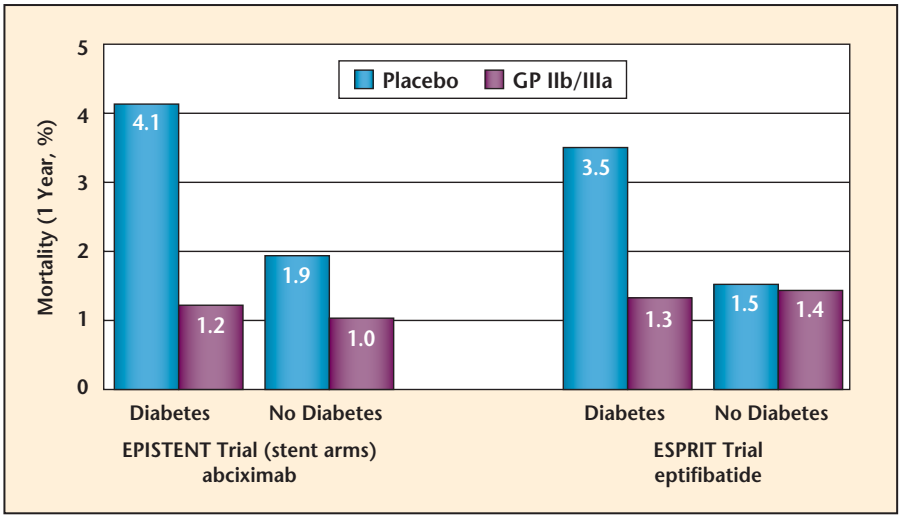


Figure 3. *Survival at late follow-up (mean 6.5 ± 2.4 yrs [SD]) by vessel patency following percutaneous coronary intervention. Survival is reduced in patients who have occlusive restenosis, which was observed in 15% of the total population. Both restenosis and occlusive restenosis were increased in diabetic patients. SD, standard deviation. Reproduced with permission from Van Belle et al.*[22]

ticularly diabetics treated with insulin.[20] This observation was supported by the results of the Coronary Angioplasty Versus Bypass Revascularization Investigation (CABRI).[19] In CABRI, the mortality of diabetic patients was twice that of nondiabetics and a trend for higher mortality to 4 years was observed in diabetics randomly assigned to treatment with PTCA versus CABG. Conversely, the Emory Angioplasty Versus Surgery Trial (EAST) did not demonstrate a survival advantage for diabetic patients randomly assigned to CABG versus PTCA revascularization for the numbers of patients evaluated.[17] Of note, however, at 8-year follow-up, death was observed in 7.3% of the CABG- and 10.7% of the PTCA-treated diabetic patients (P = .73). In general, late survival trends following multivessel revascularization in diabetics are less favorable for the percutaneous versus the surgical approach (Figure 2).[21]

More recently, stents have been demonstrated to improve midterm and late outcomes in diabetic patients by decreasing the frequency of restenosis.[6,11,22-26] In addition, stent deployment (versus PTCA) also reduced the frequency of total target vessel occlusion at the revascularization site by angiography performed at 6 months following treatment.[22] Indeed, the development of target vessel occlusion as the manifestation of restenosis following coronary stent deployment is more prevalent in diabetic versus nondiabetic patients and appears to adversely influence late survival (Figure 3).[22,27] Both the requirement for repeat revascularization and the composite clinical occurrence of cardiovascular death or myocardial infarction were reduced by stenting (compared with PTCA) in diabetic patients.[6,11,23,28,29] Despite the salutary effects of stent deployment, the recently available 2-year follow-up results in the diabetic cohort of the Arterial Revascularization Therapy Study (ARTS), which randomly assigned eligible patients with multivessel disease to treatment with either stents or CABG, demonstrated an increased requirement for repeat revascularization in patients

Figure 4. *Mortality to 1 year in diabetic and nondiabetic patients enrolled in the EPISTENT and ESPRIT placebo-controlled randomized trials of platelet glycoprotein (GP) IIb/IIIa blockade administration for percutaneous coronary intervention. The increased mortality in diabetics (vs nondiabetics) appears to be normalized by adjunctive platelet GP IIb/IIIa blockade. Reproduced with permission from Lincoff.*[35]



treated percutaneously.[30,31] Of note, the composite occurrence of death, myocardial infarction, and stroke to 2 years was similar for both stenting and CABG (16.1% vs 14.6%, respectively). Furthermore, recent registry analyses suggest that ischemic event-free survival and even survival alone (single endpoint) are decreased following multivessel coronary stenting in diabetics compared with nondiabetic patients but are similar in diabetics treated with either oral agents or insulin.[29,32,33]

The presence of diabetes is a significant predictor of death to 6-month follow-up after PCI for acute myocardial infarction.[34] Interestingly, the mortality "hazard" conferred by diabetes to 1 year following coronary stenting may be "normalized" to that observed in nondiabetics through the use of periprocedural adjunctive platelet glycoprotein (GP) IIb/IIIa receptor blockade (Figure 4).[35,36] Because diabetics have higher ischemic event rates to 30 days, 6 months, and 1 year following coronary stent deployment (vs nondiabetics), periprocedural platelet GP IIb/IIIa blockade appears to provide preferential benefit, particularly following multivessel stenting in this population (Figure 5).[37,38] The late quantitative angiographic and clinical follow-up of the diabetic cohort in the Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) trial suggested that there was a reduction in target vessel revascularization and an increase in net coronary lumen gain associated with periprocedural abciximab administration.[39] This observation heightened interest and investigation into differences among diabetics (versus nondiabetics) in platelet vitronectin (αvß3) receptor function and regulation. It was hypothesized that non-GP IIb/IIIa (nonplatelet) effects of abciximab on the inflammatory

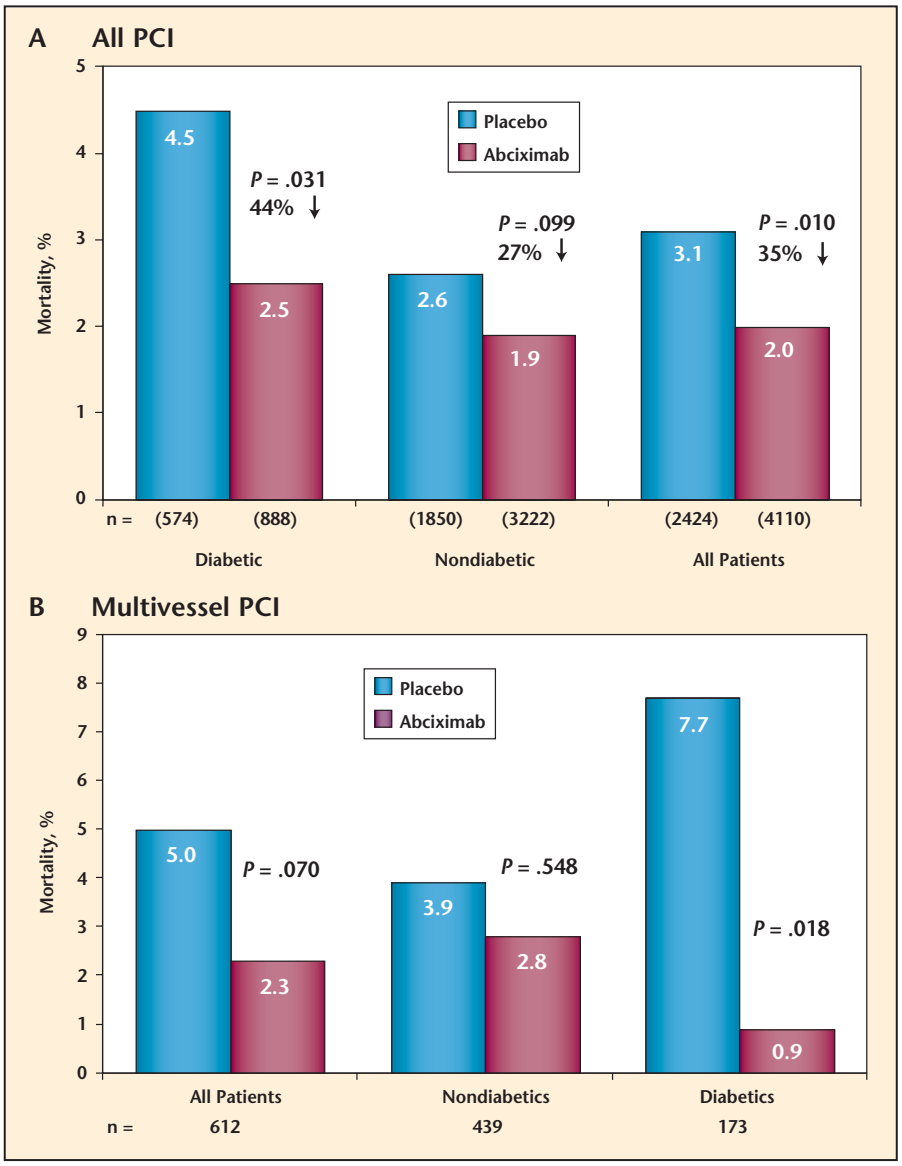


Figure 5. (A) *Mortality to 1 year following percutaneous coronary intervention (PCI) by diabetic status and abciximab (vs placebo) treatment in the pooled analysis of the EPIC, EPILOG, and EPISTENT trials.* **(B)** *Mortality to 1 year is significantly less in diabetic patients who received periprocedural abciximab (vs placebo), particularly those undergoing multivessel PCI. Data from Bhatt et al.*[37]

response to vessel injury and/or smooth muscle cell migration/proliferation might be etiologic in providing this apparent selective benefit.[40-42] Unfortunately, subsequent randomized clinical trial evaluations of abciximab for coronary stenting did not demonstrate a reduction in the neointimal proliferative response or angiographic restenosis in diabetic patients.[43-45] Indeed, subsequent studies utilizing quantitative coronary angiography demonstrated a relationship between both the presence and type of diabetes and binary (> 50%) late angiographic restenosis following stenting.[46,47] Both diabetes (vs nondiabetes) and insulin requirement (vs non–insulin requirement) were associated with an increased inci-

dence of restenosis. The relatively high frequency of clinical and angiographic restenosis prompting repeat revascularization has marred the comparative late benefit of conventional coronary stent deployment compared with CABG.

Myriad attempts to reduce in-stent restenosis through systemically administered pharmacotherapy have met with modest, if any, success. Most recently, cilostazol administered orally for 6 months (vs placebo) was associated with reduction in late binary angiographic restenosis in diabetics for both in-stent (15.25% vs 35.25%, respectively; $P \leq .0131$) and in-segment (in-stent plus 5 mm margins) analyses (16.95% vs 36.99%, respectively; $P = .0108$).[48] Nevertheless, the concept of providing high local tissue concentrations of a therapeutic agent while minimizing/eliminating systemic toxicity is intuitively attractive. The advent of polymer-based, drug-eluting coronary stent devices represents a major advance in catheter-based revascularization for all patients, including diabetics. Drug-eluting stents (DES) offer a potential solution to the higher rates of repeat revascularization and restenosis observed following conventional stent deployment in diabetics. Furthermore, any preferential benefit of surgical revascularization over stenting could be eliminated by targeted pharmacotherapy to reduce the inflammatory-neointimal proliferative response to stent-vessel injury.

The recent availability of polymer-based DES may provide preferential clinical benefit for patients with diabetes mellitus because of the higher rates of repeat revascularization that follow PCI in this population. In the initial experience from the Randomized Study with the Sirolimus Eluting Bx-Velocity Balloon Expandable Stent (RAVEL) trial with the sirolimus-eluting CYPHER® stent (Cordis Cardiology, Miami Lakes, FL), preferential benefit for reduction in binary (> 50%) angiographic restenosis was observed in the diabetic cohort (0% vs 41.7%, respectively; $P = .002$) for the CYPHER versus the Bx Velocity® stent (Cordis Cardiology).[49] These salutary results were confirmed in the diabetic cohort (n = 279) of the Sirolimus Coated Bx Velocity Stent in Treatment of Patients with De Novo Coronary Artery Lesions (SIRIUS) trial, which demonstrated a reduction in binary angiographic restenosis (in-lesion) for the CYPHER versus the Bx Velocity stent (17.6% vs 50.5%, respectively; $P < .001$). Similarly, target lesion revascularization (TLR) at 1-year follow-up was reduced by the CYPHER versus the Bx Velocity stent (8.4% vs 26.5%, respectively; $P = .0002$).[50] Indeed, CYPHER stent deployment (versus Bx Velocity) was associated with a similar magnitude of reduction in 12-month TLR (70%-80%) irrespective of lesion length, reference vessel size, or diabetic status (Table 1).[50] Presently, a wealth of clinical and angiographic data from randomized clinical trials as well as postmarket surveillance registries offer support for these initial observations of durable benefit following CYPHER stent deployment in diabetic patients.

Diabetic patients enrolled in the SIRIUS trial demonstrated significant reductions in both angiographic (binary restenosis, late coronary

Table 1
Percent Reduction in 12-Month Target Lesion Revascularization with Sirolimus-Eluting Versus Bx Velocity Stent by Lesion Length, Vessel Size, and Diabetic Status

Diabetic Status/Vessel Size	Lesion Length: < 12 mm, %	≥ 12 mm but ≤ 15 mm, %	> 15 mm, %
Nondiabetics			
RVD > 3.0 mm	78.5	78.1	77.5
2.5 mm ≤ RVD < 3.0 mm	77.6	77.1	76.2
RVD < 2.5 mm	76.6	76.0	74.7
Diabetics			
RVD > 3.0 mm	77.2	76.7	75.6
2.5 mm ≤ RVD < 3.0 mm	75.8	75.0	73.4
RVD < 2.5 mm	74.1	73.1	71.0

RVD, reference-vessel diameter.
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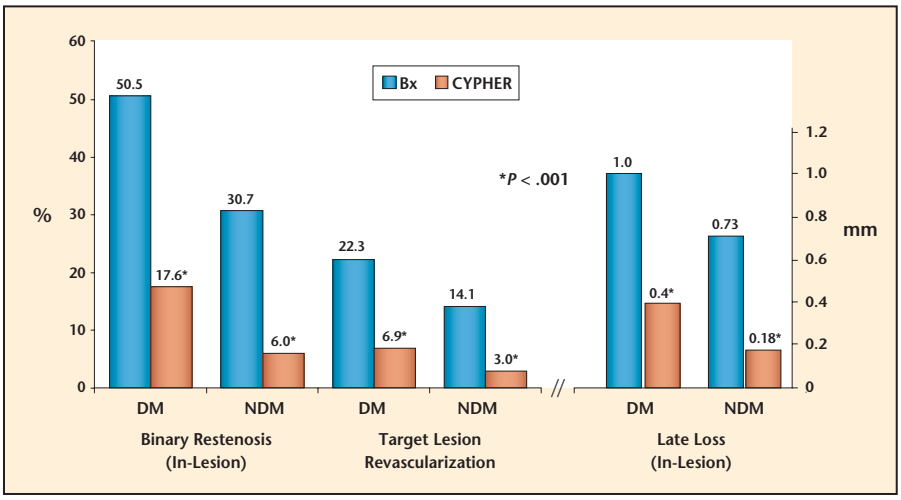


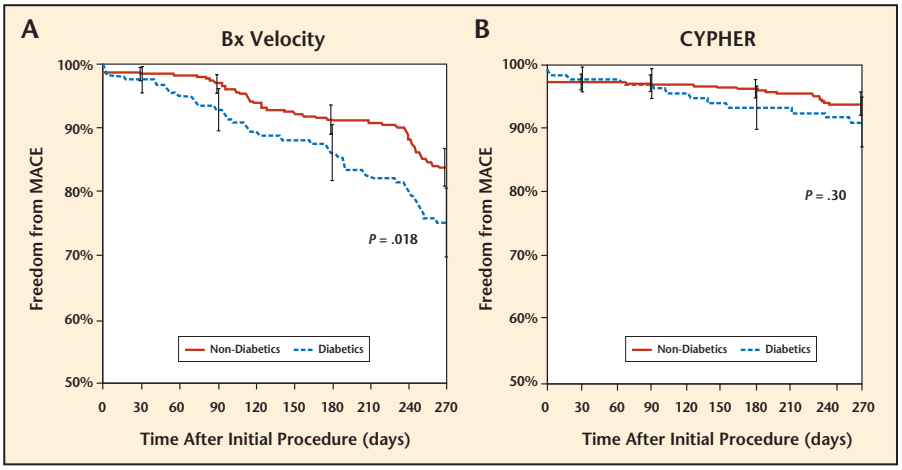
Figure 6. *Late clinical and angiographic outcomes by diabetic status and randomly assigned treatment strategy (Bx vs CYPHER stent) in the SIRIUS trial. Diabetics demonstrated an increased incidence of adverse clinical and angiographic outcomes, which was significantly reduced by treatment with the CYPHER stent. DM, diabetes mellitus; NDM, non–diabetes mellitus. Data from Moussa et al.*[51]

lumen loss) and clinical (TLR) restenosis at late follow-up in favor of the CYPHER versus the Bx Velocity stent (Figure 6).[51] In the SIRIUS trial, although diabetics had a higher incidence of adverse outcomes following coronary stent deployment versus nondiabetics, substantial benefit was observed in diabetic patients treated with the CYPHER compared with the Bx Velocity stent. Indeed, no difference in major adverse cardiovascular event (MACE)-free survival to 9 months was observed by diabetic status (P = .30) in patients treated with the CYPHER stent (Figure 7). Conversely, in patients who were treated with the Bx Velocity (non–drug-eluting) stent, the presence of diabetes was associated with a significant (P = .018) reduction in MACE-free survival. As noted previously, the magnitude of reduction in clinical coronary restenosis (TLR) by the CYPHER stent was not influenced by lesion length, reference vessel diameter, or diabetic status.[50] This salutary effect of the CYPHER stent on clinical restenosis in diabetic patients has been consistent across clinical trials as well as postmarket surveillance registries (Figure 8). In the cumulative clinical experience involving diabetic patients treated with the CYPHER stent, TLR was observed in only 0%-7.0% and the reduction in TLR conferred by CYPHER (versus Bx Velocity) ranged from 70%-100% (Figure 8).

These observations are supported by more recent data from the Direct Stenting Using the Sirolimus-Eluting Stent (DIRECT) trial, in which the strategy of direct stenting (versus predilatation) with the CYPHER stent was employed.[52] Patients enrolled into the DIRECT trial were compared with the historical cohort of patients treated with the CYPHER stent from the SIRIUS trial. Quantitative coronary angiography was performed at 8 months following stent deployment in both the DIRECT and SIRIUS trials. The strategy of direct stenting versus predilatation was associated with lower rates of binary (in-lesion) restenosis in nondiabetics (5.3% vs 6.0%; P = 1.00), non–insulin-dependent diabetics (10.3% vs 13.8%; P = .76), and, particularly, insulin-dependent diabetics (0% vs 35.0%, P = .03). The DIRECT trial suggests the importance of operator technique for deploying the CYPHER stent, especially in diabetic patients. These data support the concept that minimizing the extent of endoluminal injury beyond the confines of the drug-delivery platform by eliminating the predilatation process (when possible) has clinical/angiographic benefit.

The "real-world" clinical practice experience with CYPHER coronary stenting from the e-CYPHER registry

Figure 7. *The reduction in major adverse cardiovascular event (MACE)-free survival observed in diabetics (vs nondiabetics) treated with the bare-metal Bx Velocity stent* **(A)** *was eliminated in patients who received treatment with the CYPHER stent in the SIRIUS trial* **(B)**. *Diabetic patients treated with the CYPHER stent demonstrated an incidence of late MACE events similar to that in nondiabetic patients. Reproduced with permission from Moussa et al.*[51]



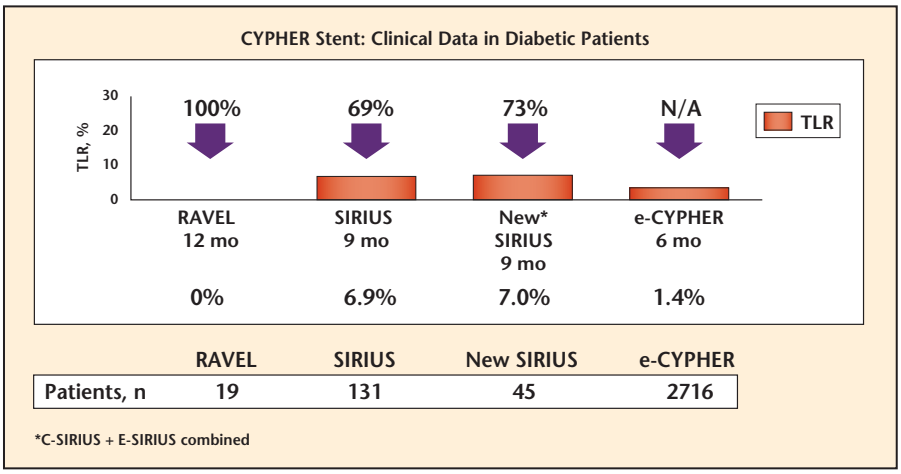


Figure 8. *Clinical restenosis (target vessel revascularization) across multiple randomized controlled trials and in the e-CYPHER postmarket surveillance registry. Target lesion revascularization (TLR) is consistently low (0%-7%) following CYPHER stent deployment as is the reduction in TLR observed (70%-100%) following deployment of the CYPHER versus the Bx Velocity stent.*

has recently been updated in 3438 patients.[53] Despite the fact that diabetics were older and had more associated risk factors, including multivessel disease and number of stents deployed per patient as well as smaller reference vessel diameters and longer lesion lengths versus nondiabetic patients enrolled in this registry (Table 2), clinical TLR to 6 months follow-up was observed in only 1.4% of diabetics and 0.9% of nondiabetics (P = not significant). Total MACE to 6 months were observed in only 4.2% of 2716 diabetic patients followed up for 6 months post CYPHER stent deployment (Figure 9). These data are similar to the preliminary real-world experience from the BRIDGE registry of CYPHER stenting in diabetic patients. In BRIDGE, 6-month clinical follow-up in 547 diabetic patients with average reference vessel diameter of 2.80 mm and lesion length of 18.4 mm demonstrated TLR in 3.5% and MACE in 5.9%.[54] The expanding database for CYPHER stent use in diabetics suggests safe and durable clinical benefit in the form of low MACE and TLR rates as well as minimal late coronary lumen loss (0.20-0.30 mm) by quantitative coronary angiography.

The more recently Food and Drug Administration–approved and –released polymer-based slow-release paclitaxel-eluting TAXUS™ stent (Boston Scientific, Natick, MA) has also demonstrated efficacy for the treatment of diabetic patients. Late (9-month) quantitative angiographic follow-up in the TAXUS IV trial, in which patients were treated with either the TAXUS paclitaxel-eluting stent or the bare metal Express™ stent (Boston Scientific), demonstrated a significant reduction in binary restenosis in the analysis segment from 34.5% to 6.4% (P = .0001) in all medically treated diabetic patients and from 42.9% to 7.7% (P = .0065) in insulin-requiring diabetics.[55] Furthermore, clinical restenosis as reflected by the requirement for target vessel revascularization to 1-year follow-up was reduced in both insulin-requiring (from 19.4% to 6.2%; P = .07) and oral medication–treated (21.6% to 7.9%; P = .005) diabetic patients following treatment with the Express versus the TAXUS stent, respectively. Indeed, the presence of diabetes mellitus was not an independent predictor for late TLR by multivari-

Table 2
Selected Baseline Clinical and Procedural Characteristics in Diabetic and Nondiabetic Patients Enrolled in the e-CYPHER Postmarket Surveillance Registry for Use of the CYPHER Stent

Characteristic	Diabetics (n = 3438)	Nondiabetics (n = 8670)	*P* Value
Age	62.2 ± 10.4	60.6 ± 11.7	< .0001
Female gender	28.9%	19.4%	< .0001
History of hypertension	70.9%	58.1%	< .0001
Body mass index > 30	17.7%	11.1%	< .0001
Prior CVA/TIA	3.7%	2.7%	< .005
Multivessel disease	59.7%	54.8%	< .001
No. of stents/patient	1.4 ± 0.7	1.3 ± 0.7	< .0001
Multilesion procedure	18.8%	16%	= .0002
LMS lesion	1.6%	2.4%	< .005
Estimated reference diameter (mm)	28 ± 0.4	29 ± 0.4	< .0001
Estimated lesion length (mm)	17.8 ± 9.3	17.0 ± 8.7	< .0001

CVA, cerebrovascular accident; LMS, left main stem; TIA, transient ischemic attack.

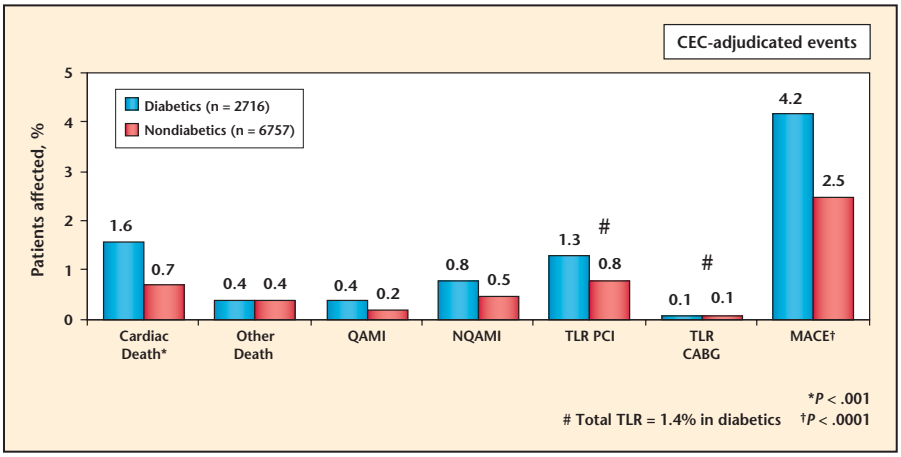


Figure 9. *Clinical outcomes to 6 months follow-up in the e-CYPHER registry. Despite the presence of more complex clinical and procedural demographics in diabetic (vs nondiabetic) patients (Table 2), cumulative target vessel revascularization was observed in only 1.4% of diabetics versus 0.9% of nondiabetics (P = not significant). CEC, clinical events committee; QAMI, Q-wave acute myocardial infarction; NQAMI, non–Q-wave acute myocardial infarction; TLR, target lesion revascularization; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MACE, major adverse cardiovascular events (death, acute myocardial infarction, PCI, or CABG).*

able analysis following TAXUS stent deployment.[55,56] The reduction in angiographic and clinical restenosis in TAXUS-treated patients was associated with a lower incidence of late (not periprocedural) myocardial infarction as well.

DES in Diabetic Patients: General Measures

The use of DES in diabetic patients does not negate the potential benefits to be derived by periprocedural adjunctive therapy with platelet GP IIb/IIIa blockade. These powerful treatments (DES and GP IIb/IIIa receptor inhibition) should be considered complementary in their salutary effects. Platelet GP IIb/IIIa inhibitor therapy reduces periprocedural myocardial infarction and the need for urgent repeat revascularization. Conversely, the benefits provided by DES are manifest late, and include reductions in angiographic as well as clinical coronary restenosis. Furthermore, recent data from meta-analyses of randomized, placebo-controlled clinical trials have demonstrated a survival advantage at 30 days and 6 months following PCI performed with adjunctive GP IIb/IIIa inhibitor therapy.[57,58] The survival benefit associated with GP IIb/IIIa blockade is particularly evident in high-risk patient subsets (including diabetics) and following abciximab (versus small-molecule GP IIb/IIIa receptor antagonist) administration.[59,60] No survival advantage has yet been observed following DES versus conventional stent deployment.[49,50,55] For these reasons, adjunctive therapy with GP IIb/IIIa inhibition should be administered based on periprocedural risk assessment during PCI with DES. Similarly, extended (≥ 1 year) oral therapy with combination aspirin and a thienopyridine may be especially beneficial in diabetic patients following DES deployment.[61,62] Concomitant therapy with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin), angiotensin-converting enzyme inhibitor, or angio-

Main Points

- Early randomized comparative studies of percutaneous transluminal coronary (balloon) angioplasty (PTCA) and coronary artery bypass grafting demonstrated an increased morbidity and mortality among diabetics compared with their nondiabetic counterparts.
- Both the requirement for repeat revascularization and the composite clinical occurrence of cardiovascular death or myocardial infarction were reduced by stenting, compared with PTCA, in diabetic patients.
- Drug-eluting stents offer a potential solution to the higher rates of repeat revascularization and restenosis observed following conventional stent deployment in diabetics.
- In the cumulative clinical experience involving diabetic patients treated with the CYPHER stent, target lesion revascularization (TLR) was observed in only 0%-7.0% and the reduction in TLR conferred by CYPHER (versus Bx Velocity) ranged from 70%-100%.
- Drug-eluting stents and glycoprotein IIb/IIIa receptor inhibition should be considered complementary treatments.
- Modifications in the CYPHER stent delivery system designed to enhance stent delivery are in progress and will be available in the near future. Similarly, the availability of smaller-diameter CYPHER stents, which have demonstrated low levels of late lumen loss and binary restenosis, may be particularly applicable to the diabetic patient population.

tensin receptor blocker should also be mandated in diabetic patients if clinically tolerated.

Last, but certainly not least, close control of diabetes can improve clinical outcomes. If possible, control of diabetes should optimally be achieved prior to PCI. Recent data suggest that both fasting blood glucose (> 110 mg/dL) and levels of glycosylated hemoglobin (HgA_{1C}) > 7.0% are associated with an increase in both late mortality and the requirement for repeat revascularization following PCI.[63-65] These data suggest that closer control of blood glucose (HgA_{1C} < 7.0%) may improve clinical outcomes in follow-up post PCI. Most recently, it has been suggested that insulin-sensitizing medications may have more salutary effects on late clinical outcomes than insulin-providing medications among diabetic patients who do not require exogenous insulin therapy.[66,67] This novel class of agents—thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor-α and/or -γ agonists—has demonstrated anti-inflammatory actions in both diabetic and nondiabetic patients.[68,69] Suppression of inflammatory cytokine production (sCD40L, C-reactive protein, E-selectin, von Willebrand factor) has been demonstrated following TZD administration and may specifically address the heightened levels of vascular inflammation central to the pathobiology of diabetic patients. More recently, the insulin sensitizer metformin was associated with improved event-free survival compared with nonsensitizer therapies in diabetic patients treated with oral medications who had undergone coronary stenting.[70] Furthermore, the TZD rosiglitazone has demonstrated antiplatelet effects, which may contribute to the clinical benefit observed following treatment with this agent and which were not correlated with the known effects of rosiglitazone on insulin resistance.[71]

Careful attention must be paid to optimal periprocedural and late adjunctive pharmacotherapy including the use of platelet GP IIb/IIIa inhibition with abciximab as well as the concomitant and extended administration of statins, clopidogrel, and angiotensin-converting enzyme inhibitors, which all have demonstrated salutary effects on periprocedural and late clinical outcomes following coronary stent deployment.

Conclusions

Drug-eluting stents offer a major advance in the percutaneous catheter–based coronary revascularization of diabetic patients. Late follow-up of the diabetic patients treated with the CYPHER sirolimus-eluting stent demonstrates safety as well as durable clinical benefit. Both target vessel revascularization and angiographic restenosis are markedly reduced following CYPHER stent deployment when compared with the results of conventional stenting. The CYPHER stent design and ethylene-vinyl acetate–butyl methacrylate polymer provide predictable sirolimus elution and reliable dose distribution irrespective of target vessel diameter. The durable benefit of CYPHER stent deployment in diabetic patients appears comparable to that provided by CABG, but definitive comparisons await the results of a randomized, controlled trial. The initial results of TAXUS stent deployment in diabetics demonstrate clinical and angiographic benefit (versus conventional stenting), and late clinical follow-up evaluation is forthcoming. The reliability of paclitaxel dose distribution and elution from Translute™ polymer (Boston Scientific) for target vessels > 3.0 mm remains to be determined in the diabetic patient population. Modifications in the CYPHER stent delivery system designed to enhance stent delivery are in progress and will be available in the near future. Similarly, the availability of smaller-diameter CYPHER stents (2.25 mm), which have demonstrated low levels of late lumen loss and binary restenosis, may be particularly applicable to the diabetic patient population. In addition, careful attention must be paid to optimal periprocedural and late adjunctive pharmacotherapy including the use of platelet GP IIb/IIIa inhibition with abciximab as well as the concomitant and extended administration of statins, clopidogrel, and angiotensin-converting enzyme inhibitors, which all have demonstrated salutary effects on periprocedural and late clinical outcomes following coronary stent deployment. Thus, the optimal strategy for percutaneous revascularization in diabetic patients must include DES in combination with adjunctive pharmacotherapies. ■

References

1. Kereiakes DJ, Willerson JT. Metabolic syndrome epidemic. *Circulation*. 2003;108:1552-1553.
2. Haffner S, Taegtmeyer H. Epidemic obesity and the metabolic syndrome. *Circulation*. 2003;108:1541-1545.
3. Reilly MP, Rader DJ. The metabolic syndrome—more than the sum of its parts? *Circulation*. 2003;108:1546-1551.
4. Beckman J, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287:2570-2581.
5. Kornowski R, Mintz GS, Lansky AJ, et al. Paradoxic decreases in atherosclerotic plaque mass in insulin-treated diabetic patients. *Am J Cardiol*. 1998;81:1298-1304.
6. Van Belle E, Bauters C, Hubert E, et al. Restenosis rates in diabetic patients: a comparison of coronary stenting and balloon angioplasty in native coronary vessels. *Circulation*. 1997;96:1454-1460.

7. Wong SC, Baim DS, Schatz RA, et al for the Palmaz-Schatz Stent Study Group. Immediate results and late outcomes after stent implantation in saphenous vein graft lesions: the multicenter U.S. Palmaz-Schatz stent experience. *J Am Coll Cardiol*. 1995;26:704-712.
8. Carrozza JP, Kuntz RE, Fishman RF, Baim DS. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. *Ann Intern Med*. 1993;118:344-349.
9. Elezi S, Schuhlen H, Wehinger A, et al. Stent placement in diabetic versus non-diabetic patients: six month angiographic follow-up [abstract]. *J Am Coll Cardiol*. 1997;29:188A.
10. Okoi H, Nosaka T, Kimura T, et al. Coronary stenting in diabetic patients: early and follow-up results [abstract]. *J Am Coll Cardiol*. 1997; 29:455A.
11. Van Belle E, Perie M, Braune D, et al. Effects of coronary stenting on vessel patency and long-term clinical outcome after percutaneous coronary revascularization in diabetic patients. *J Am Coll Cardiol*. 2002;40:410-417.
12. Rozenman Y, Sapoznikov D, Mosseri M, et al. Long-term angiographic follow-up of coronary balloon angioplasty in patients with diabetes mellitus. *J Am Coll Cardiol*. 1997; 30:1420-1425.
13. Savage MP, Fischman DL, Schatz RA, et al. Coronary intervention in the diabetic patient: improved outcome following stent implantation compared with balloon angioplasty. *Clin Cardiol* 2002;25:213-217.
14. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med*. 1996;335:217-225.
15. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease. *Circulation*. 1997;96:1761-1769.
16. Detre KM, Guo P, Holubkov R, et al. Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation*. 1999;99:633-640.
17. King SB 3d, Lembo NJ, Weintraub WS, et al. Randomized trial comparing coronary angioplasty with coronary bypass surgery: Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med*. 1994;331:1044-1050.
18. Hamm CW, Reimers J, Ischinger T, et al. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. *N Engl J Med* 1994;331:1037-1043.
19. The CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularization Investigation). *Lancet*. 1995;346:1179-1184.
20. The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol*. 2000;35:1122-1129.
21. Niles NW, McGrath PD, Malenka D, et al. Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary revascularization: results of a large regional prospective study. *J Am Coll Cardiol*. 2001;37:1008-1015.
22. Van Belle E, Ketelers R, Bauters C, et al. Patency of percutaneous transluminal coronary angioplasty sites at 6-month angiographic follow-up: a key determinant of survival in diabetes after coronary balloon angioplasty. *Circulation*. 2001;103:1218-1224.
23. Lincoff AM. Does stenting prevent diabetic arterial shrinkage after percutaneous coronary revascularization? *Circulation*. 1997;96:1374-1377.
24. Aronson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. *J Am Coll Cardiol*. 1996; 27:528-535.
25. Kornowski R, Mintz GS, Kent KM, et al. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia: a serial intravascular study. *Circulation*. 1997;95:1366-1369.
26. Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol*. 1998;32:584-589.
27. Van Belle E, Abolmaali K, Bauters C, et al. Restenosis, late vessel occlusion and left ventricular function six months after balloon angioplasty in diabetic patients. *J Am Coll Cardiol*. 1999;34:476-485.
28. Vetrovec GW. Don't blame the stents. *J Am Coll Cardiol*. 2004;43:1355-1357.
29. Mehran R, Dangas GD, Kobayashi Y, et al. Short- and long-term results after multivessel stenting in diabetic patients. *J Am Coll Cardiol*. 2004;43:1348-1354.
30. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117-1124.
31. Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation*. 2001;14:533-538.
32. Mathew V, Holmes DR. Outcomes in diabetics undergoing revascularization: the long and the short of it. *J Am Coll Cardiol*. 2002;40:424-427.
33. Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol*. 1998; 32:584-589.
34. Harjai KJ, Stone GW, Boura J, et al. and Primary Angioplasty in Myocardial Infarction (PAMI) Investigators. Comparison of outcomes of diabetic and nondiabetic patients undergoing primary angioplasty for acute myocardial infarction. *Am J Cardiol*. 2003; 91:1041-1045.
35. Lincoff AM. Important triad in cardiovascular medicine: diabetes, coronary intervention and platelet glycoprotein IIb/IIIa receptor blockade. *Circulation*. 2003;107:1556-1559.
36. Lincoff AM, Califf RM, Moliterno DJ, et al. The Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. *N Engl J Med*. 1999;341:319-327.
37. Bhatt DL, Marso SP, Lincoff AM, et al. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol*. 2000;35:922-928.
38. Bhatt DL, Chew DP, Topol EJ. The importance of intravenous antiplatelet therapy with abciximab during percutaneous coronary intervention in diabetic patients. *Cardiovasc Rev Rep*. 2001;21:161-164.
39. Marso SP, Lincoff AM, Ellis SG, et al. Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) diabetic sub-study. *Circulation*. 1999;100:2477-2484.
40. Coller BS. Binding of abciximab to αVß3 and activated αMß2 receptors: with a review of platelet-leukocyte interactions. *Thromb Haemost*. 1999;82:326-335.
41. Mickelson JK, Ali MN, Kleiman NS, et al. Chimeric 7E3 Fab (ReoPro) decreases detectable CD11b on neutrophils from patients undergoing coronary angioplasty. *J Am Coll Cardiol*. 1999;33:97-106.
42. Kereiakes DJ, Runyon JP, Broderick TM, Shimshak TM. IIb's are not IIb's. *Am J Cardiol*. 2000;85:23C-31C.
43. ERASER Investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). *Circulation*. 2000; 102:E110.
44. Hausleitter J, Kastrati A, Mehill J, et al. Abciximab administration for the prevention of angiographic restenosis in small coronary arteries: results from the randomized ISAR-SMART-2 trial. *J Am Coll Cardiol*. 2004;43:37A.
45. Chen W-H, Kaul U, Leung S-K, et al. A randomized placebo-controlled trial of abciximab for prevention of in-stent restenosis in diabetic patients after coronary stenting. *J Am Coll Cardiol*. 2004;43:51A.
46. Schofer J, Schluter M, Rau T, et al. Influence of treatment modality on angiographic outcome after coronary stenting in diabetic patients: a controlled study. *J Am Coll Cardiol*. 2000; 35:1554-1559.
47. Alonzo JJ, Duran JM, Gimeno F, et al. Influence of the presence and type of diabetes mellitus on the initial and long-term outcome after coronary stenting [abstract]. *J Am Coll Cardiol* 2000;35:77A.
48. Douglas JS Jr, Holmes DR, Kereiakes DJ, et al. Cilostazol for Restenosis Trial: a randomized, double-blind study following coronary artery stent implantation. *Circulation*. 2003;108:2723. Available at http://circ.ahajournals.org/cgi/content/full/108/21/2723 (accessed online 05/20/04).
49. Regar E, Serruys PW, Bode C, et al. Angiographic findings of the multicenter Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. *Circulation*. 2002;106:1949-1956.
50. Holmes DR Jr, Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation*. 2004;109: 634-640.
51. Moussa I, Leon MB, Baim D, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx

Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation*. 2004;109:2273-2278.
52. Moses JW, Leon MB, Popma JJ, et al. Matched comparison of direct stenting to predilation with the sirolimus-eluting Bx Velocity™ stent. *J Am Coll Cardiol*. 2004;43:97A.
53. Lotan C, Sousa E, Urban P, et al. Sirolimus-eluting stent implantation in routine clinical practice: a 12-month follow-up report from the international e-CYPHER registry. *J Am Coll Cardiol*. 2004;43:97A.
54. Commeau P. Safety and efficiency registry of Bx Velocity Cypher™ stent in the Revascularization of patients with significant risk of restenosis (BRIDGE) registry. Presented at the 16th Annual Scientific Symposium—Transcatheter Cardiovascular Therapeutics. September 29, 2004. Washington, DC.
55. Stone GW, Ellis SG, Cox DA, et al for the TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation*. 2004;109:1942-1947.
56. Hermiller JB, Raizner A, Cannon L, et al for the TAXUS-IV investigators. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS IV trial. *J Am Coll Cardiol*. In press.
57. Kong DF, Hasselblad V, Harrington RA, et al. Meta-analysis of survival with platelet glycoprotein IIb/IIIa antagonists for percutaneous coronary interventions. *Am J Cardiol*. 2003; 92:651-655.
58. Karvouni E, Katritsis DG, Ioannidis JPA. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. *J Am Coll Cardiol*. 2003;41:26-32.
59. Topol EJ, Lincoff AM, Kereiakes DJ, et al. Multi-year follow-up of abciximab therapy in three randomized, placebo-controlled trials of percutaneous coronary revascularization. *Am J Med*. 2002;113:1-6.
60. Kereiakes DJ, Lincoff AM, Anderson KM, et al. Abciximab survival advantage following percutaneous coronary intervention is predicted by clinical risk profile. *Am J Cardiol*. 2002; 90:628-630.
61. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
62. Steinhubl S, Berger PB, Mann JT 3d, et al; CREDO Investigators. Clopidogrel for the reduction of events during observation. *JAMA*. 2002;288:2411-2420. *Erratum in JAMA*. 2003 26;289:987.
63. Muhlestein JB, Anderson JL, Horne BD, et al. Effect of fasting glucose levels on mortality rate in patients with and without diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention. *Am Heart J*. 2003;146:351-358.
64. Corpus RA, George PB, House JA, et al. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol*. 2004;43:8-14.
65. Hasadai D, Rizza RA, Grill DE, et al. Glycemic control and outcome of diabetic patients after successful percutaneous coronary revascularization. *Am Heart J*. 2001;141:117-123.
66. McGuire DK, Newby LK, Bhapkar MV, et al. Association of diabetes mellitus and glycemic control strategies with clinical outcomes after acute coronary syndromes. *Am Heart J*. 2004; 147:246-252.
67. Osman A, Otero J, Brizolara A. Effect of rosiglitazone on restenosis after coronary stenting in patients with type 2 diabetes. *Am Heart J*. 2004;147:e23.
68. Varo N, Vicent D, Libby P, et al. Elevated plasma levels of the atherogenic mediator soluble CD40 ligand in diabetic patients: a novel target of thiazolidinediones. *Circulation*. 2003;107:2664-2669.
69. Sidhu JS, Cowan D, Kaski J-C. The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and fibrinogen levels in non-diabetic coronary artery disease patients. *J Am Coll Cardiol*. 2003;42:1757-1763.
70. Kao J, Tobis J, McClelland RL, et al; Investigators in the Prevention of Restenosis With Tranilast and Its Outcomes Trial. Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. *Am J Cardiol*. 2004; 93:1347-1350.
71. Sidhu JS, Cowan D, Tooze JA, Kaski JC. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reduces circulating platelet activity in patients without diabetes mellitus who have coronary artery disease. *Am Heart J*. 2004;147:e25.