

Grand Rounds

Cardiovascular Disease in Diabetics: Pharmacology and Revascularization

SARANG S. MANGALMURTI, M.D.¹, AND MICHAEL E. FARKOUH, M.D.²

Abstract

Diabetes has become a public health crisis. With the incidence of obesity rising in the United States, the number of diabetics will grow considerably. Of greatest concern is the impact this trend will have on cardiovascular disease. Diabetics demonstrate accelerated coronary atherosclerosis, and the prognosis is worse following cardiac events. Moreover, our interventions have achieved uneven success in treating this subset of patients. This paper will review the metabolic abnormalities that promote atherosclerosis in diabetics and the current methods for treating and preventing the development of coronary artery disease in diabetics, principally through a combination of medications and revascularization.

Key Words: Diabetes, cardiovascular disease, insulin resistance, antiplatelet, dyslipidemia, hypertension, myocardial infarction, acute coronary syndrome, revascularization.

Introduction

DIABETES HAS BECOME a public health crisis. With the incidence of obesity rising in the United States, the prevalence of diabetes is expected to grow from 16 million cases to an estimated 22 million by 2025 (1). The effect of this on cardiovascular disease is unquestionable. Diabetic men have a threefold increase in the risk of cardiac disease compared to nondiabetics. And studies have shown that diabetics with no prior myocardial infarction have a risk of infarction similar to that of nondiabetics with a history of myocardial events (2); see Fig. 1 (3). Diabetic women are especially vulnerable and appear to lose their premenopausal protection from coronary artery disease (4). Unfortunately, our measures against cardiovascular disease have seen a smaller decline in cardiovascular mortality for diabetics compared to the general population.

Since more than 90% of diabetics are type 2, our prevention strategies begin by targeting

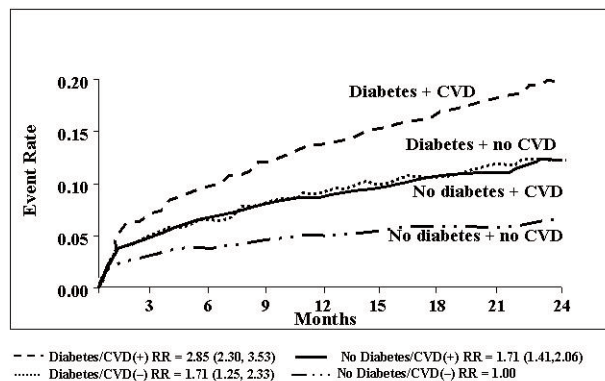


Fig. 1. Event rates, RR and CI for cardiovascular death (CVD) in diabetics and nondiabetics (n=8,013) with and without a history of CVD after hospitalization for coronary syndromes. RR = relative risk, CI = 95% confidence interval (3).

the constellation of metabolic derangements seen in these patients, collectively called “syndrome X” or the cardiovascular dysmetabolic syndrome (5). These include insulin resistance (from impaired glucose tolerance to hyperglycemia), dyslipidemia, hypercoagulability, and hypertension. Multiple drugs are utilized to slow the progression of atherogenesis in these patients. And the onset of symptomatic coronary artery disease heralds the need for revascularization, often with varying results in diabetics. The following discussion will review the metabolic predisposition to atherosclerosis in diabetics and highlight the pharmacologic and

¹Department of Medicine and ²Cardiovascular Clinical Research Center, New York University School of Medicine, New York, NY.

Address all correspondence to Michael E. Farkouh, M.D., F.A.C.C., Associate Director, Cardiovascular Clinical Research Center, New York University School of Medicine, 530 First Avenue, Suite 7G, New York, NY 10016.

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on October 16, 2002, and updated as of January 2004.

revascularization options that comprise their medical management.

Hyperglycemia

Hyperglycemia as a cause of vascular disease has been observed experimentally in animal models, and clinically through the benefits of tight glucose regulation. The Diabetes Control and Complications Trial (DCCT) demonstrated that aggressive glycemetic control in type I diabetics reduces the risk of microvascular complications including retinopathy, microalbuminuria, and clinical neuropathy by 76%, 39%, and 60%, respectively (6). A similar trend was seen in type 2 diabetics in the United Kingdom Prospective Diabetes Study (UKPDS), where fasting glucose levels of less than 108 mg/dL resulted in a 25% reduction in the risk of microvascular disease over 10 years (7).

The link between hyperglycemia and macrovascular disease, which was not clearly demonstrated in these large trials, has been shown in smaller studies. The San Antonio Heart Study showed a proportional increase in cardiovascular-related deaths with higher fasting blood glucose levels in type 2 diabetics (8). A similar result appeared for type I diabetics in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, where patients were followed for 10 years and demonstrated an 18% increase in cardiovascular mortality and a 1% increase in glycosylated hemoglobin (9).

Insulin Resistance

For type 2 diabetics the presence of insulin resistance and hyperinsulinemia accelerates the development of atherosclerosis. One study showed hyperinsulinemia as an independent risk factor when adjusted for lipid profile, hypertension and family history (10). Studies of multiple ethnic groups have shown increased carotid intima-medial thickness (a reliable marker for coronary disease) in subjects with insulin resistance (11). Furthermore, impaired glucose tolerance (IGT), even without frank hyperglycemia, can increase the risk of heart disease (12). Since insulin resistance can precede clinically diagnosed diabetes by 10–15 years, this extensive period of atherogenic exposure may account for the higher rates of cardiovascular disease in type 2 diabetics.

There are multiple pharmacologic options for these patients, each utilizing a different mechanism for lowering blood glucose levels.

The major classes of drugs include: thiazolidinediones (troglitazone, rosiglitazone, pioglitazone); biguanides (metformin); and insulin secretagogues (sulfonylureas, repaglinide).

The thiazolidinediones act in the nucleus of muscle and adipose tissue to increase transcription and translation of surface glucose transporters. This augments insulin-mediated uptake of glucose, reducing glycosylated hemoglobin levels by as much as 1.5% (13). By sensitizing the action of circulating insulin, daily insulin requirements are reduced, sometimes by 50%, and the risk of hypoglycemia is lowered compared to other diabetic agents. Although these agents increase low-density lipoprotein (LDL) levels, they reduce triglycerides and small, dense LDLs (which are atherogenic), while raising high-density protein (HDL) levels and minimizing harmful oxidative changes to normal LDL (14). Disadvantages of this therapy include hepatotoxicity, weight gain, fluid retention and slow onset of action, with lowest glucose levels achieved 6–8 weeks after initiating therapy. All three thiazolidinediones are felt to be safe and equally efficacious as monotherapy or in conjunction with insulin (15), metformin (16), or sulfonylureas (17). Nevertheless, monotherapy with troglitazone is discouraged because of hepatotoxicity, which is lower with rosiglitazone and pioglitazone. The effect of thiazolidinediones in preventing coronary artery disease requires further study, but positive data has emerged from a randomized, controlled trial showing troglitazone reducing neointimal hyperplasia (a cause of stent restenosis) in diabetics receiving coronary stents (Table 1) (18).

Sulfonylureas target pancreatic beta cells, where they block potassium-adenosine triphosphate (K-ATP) channels, thereby increasing intracellular calcium and promoting the release of insulin. This method controls blood sugar but is worrisome, since it may induce hypoglycemia in patients. The UKPDS data revealed a 16% reduction in myocardial infarctions (MI) for patients treated with sulfonylurea or insulin, with no significant difference between the two agents. There was a 1–1.4% yearly rate of severe hypoglycemia in the sulfonylurea-treated group (7).

An additional concern emerges from trials showing an increased risk of MI and death in the setting of ischemia for patients taking sulfonylureas. The blocking of cardiac K-ATP channels is purported to reduce ischemic preconditioning, a phenomenon in which the heart becomes tolerant to further ischemia or reperfusion after an initial ischemic insult (19). This claim has been supported in a study showing increased in-hospi-

TABLE 1

IVUS Were Performed on 62 Stented Lesions in 52 Patients with NIDDM to Determine Whether Troglitazone (400 mg) Reduced Neointimal Tissue Proliferation after Coronary Stent Implantation*

IVUS Measurements after 6 months of treatment	Troglitazone (n=29 stents)	Control (n=33 stents)	p value
Stent area (mm ²)	7.3±1.8	7.3±2.3	0.7995
Lumen area (mm ²)	5.3±1.7	3.7±1.7	0.0002
Intimal area (mm ²)	2.0±0.9	3.5±1.8	<0.0001
Intimal index (%)	27.1±11.5	49.0±14.4	<0.0001

Reprinted with permission from J Am Coll Cardiol 2000; 36(5):1529–1535, Table 3 (18).

*IVUS = quantitative intravascular ultrasound studies

NIDDM = non-insulin-dependent diabetes mellitus.

$$\text{Intimal Index} = \frac{\text{Averaged Intimal Area}}{\text{Averaged Stent Area}} \times 100\%$$

Reduction in plasma glucose and insulin levels was significantly greater with troglitazone as compared to placebo ($p < 0.0001$ for both).

tal mortality of diabetics taking sulfonylureas and receiving percutaneous transluminal coronary angioplasty (PTCA) for acute MI. However, long-term mortality, risk of MI and need for coronary artery bypass graft (CABG) were no different between the two groups (20). This potential harm has also been disputed by the UKPDS data, which demonstrated no difference in myocardial events between the sulfonylurea group and the insulin group. Further study is necessary to resolve this issue.

Metformin promotes glucose control in two ways: (a) by decreasing hepatic glucose release through an inhibition of gluconeogenesis, and (b) by increasing the sensitivity of peripheral tissue to insulin (21). In the UKPDS trial, metformin demonstrated significant reductions in all diabetes-related endpoints for obese diabetics. This finding, combined with its effect on promoting weight loss and reduced risk of hypoglycemia, supports metformin as a first line therapy, particularly for obese patients (22). Metformin also improves lipid and coagulation profiles. Decreased levels of LDL, triglycerides and plasminogen activator inhibitor-1 (PAI-1), which have been observed in treatment groups, may provide additional protection from cardiovascular disease (23). Lactic acidosis is a side effect, although rare, and limits the use of metformin in patients with chronic renal insufficiency, congestive heart failure, or hypoxia (24).

Hyperlipidemia

Dyslipidemia in diabetics involves elevated triglyceride levels and decreased HDL levels.

While LDL is typically normal in type 2 diabetics, it is often small and dense, with impaired antioxidant defenses. Glycosylation of protein and phospholipid components further increases its vulnerability to oxidative changes, a process that promotes atherogenesis (25).

Elevations of very low-density lipoproteins (VLDLs) are also seen. These VLDLs are the result of: (a) increased free fatty acid return to the liver due to obesity, which increases available quantities of fatty acids, and (b) insulin resistance, which decreases catabolism of fatty acids by peripheral tissue. In the liver, these fatty acids are used to generate triglyceride-rich VLDLs of varying sizes, which are atherogenic. Lipoprotein lipase, an enzyme responsible for eliminating VLDL within the circulation, is less active in diabetics, further contributing to VLDL increase (26).

Elevated VLDL is also involved in the pathogenesis of decreased HDL levels. With their triglyceride-rich cores, VLDLs promote the exchange of triglycerides for key cholesterol components in HDL, resulting in a triglyceride-laden HDL that is easily degraded by enzymes (27). Moreover, studies have shown that the circulating HDL in diabetic patients may be less effective in preventing coronary artery disease (CAD), by allowing the oxidation of LDL to occur unchecked (28). Altogether, these triglyceride-mediated changes in VLDL and HDL may account for hypertriglyceridemia as a risk factor for coronary disease in diabetics, but not in the general population.

Multiple trials have demonstrated benefits from treatment with hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors (simva-

TABLE 2

A Series of Clinical Trials Demonstrating the Risk Reduction of Major Coronary Events for Patients Treated with HMG-CoA Reductase Inhibitors (29–34)

Study	Drug	No. of Diabetics	Risk Reduction (nondiabetics)	Risk Reduction (diabetics)
Primary Prevention				
AFCAPS/TexCAPS	lovastatin	239	37% (all patients)	43%
Secondary Prevention				
Heart Protection Study	simvastatin	5963	27% (all patients)	27% * (p<0.0001)
CARE	pravastatin	586	23%	25% (p=0.05)
4S	simvastatin	202	32%	55% (p=0.002)
LIPID	pravastatin	782	25%	19%
4S-extended	simvastatin	483	32%	42% (p=0.001)

* A portion had no prior cardiovascular disease, thereby providing data for primary prevention.

statin, pravastatin) and fibric acid derivatives (gemfibrozil) as modes of lipid therapy. Subset analyses from these data show similarities in cardiovascular risk reduction for diabetics, compared to nondiabetics (Table 2) (29–34). The 4S and CARE trials yielded significant declines in the rates of death, nonfatal MI, and revascularization in diabetics treated with simvastatin and pravastatin, respectively, against placebo. The latter trial showed a 25% reduction in cardiac events over 5 years. Gemfibrozil is effective in raising HDL levels and lowering triglycerides, both of which are effective in limiting the progression of heart disease. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), a 22% reduction in cardiac deaths and nonfatal MIs combined was observed among diabetics treated with gemfibrozil against placebo. LDL levels were normal and unaffected during the treatment period (35). Similar benefits were seen years earlier in the Helsinki Heart Trial, indicating the importance of treating low HDL, even with normal LDL, as is seen in many type 2 diabetics (36).

Hypertension

The presence of hypertension in diabetic patients significantly increases their risk of micro- and macrovascular complications, including retinopathy, nephropathy and cardiac disease. Several studies have demonstrated the benefits of blood pressure control in reducing these morbid sequelae. In the UKPDS trial, a target blood pressure of <150/85 resulted in a 24% risk reduction in diabetes-related endpoints (p=0.0046), including a 34% risk reduction (p=0.019) in combined macrovascular disease (MI, sudden death, stroke, and peripheral vascular disease) and a 37% reduction in risk of microvascular disease

(p=0.0092). The 21% reduction in MI was not statistically significant, but the risk of heart failure decreased by 56% (p=0.0043) (37).

In the UKPDS trial, these results were similar whether blood pressure was controlled with a beta-blocker (atenolol) or with an angiotensin-converting enzyme (ACE)-inhibitor (captopril), suggesting no advantage between different blood pressure regimens (38). However, recent data dispute this finding. The Captopril Prevention Project (CAPPP) trial demonstrated a statistically significant decrease in cardiac events, including MI and cardiovascular mortality, in diabetic patients treated with captopril vs. beta-blocker and diuretic therapy (39). Additionally, the Appropriate Blood Pressure Control in Diabetes (ABCD) trial showed fewer episodes of fatal and nonfatal MIs in diabetics taking enalapril vs. a calcium channel blocker (nisoldipine) (40).

For diabetics, ACE-inhibitors may exert cardiovascular protection beyond their blood pressure lowering effect. This was seen in the Heart Outcomes Prevention Evaluation (HOPE) trial, where 5-year rates of MI, stroke, and cardiovascular mortality were reduced in diabetics treated with enalapril compared to placebo (relative risk reduction=25%, p=0.0004). This benefit was disproportionately larger than the mean drop in systolic blood pressure (6 mm Hg). Since many of these patients also did not have baseline hypertension, enalapril may be cardioprotective through other mechanisms, possibly related to angiotensin II blockade. These are thought to include reduced vasoconstriction and left ventricular hypertrophy, improved endothelial function, decreased smooth muscle proliferation, and stabilization of coronary plaques (41).

The concept of further lowering blood pressure, even when patients are “normotensive,”

appears particularly beneficial in diabetics. The Hypertension Optimal Treatment (HOT) study yielded a 50% reduction in major cardiovascular events in diabetic patients with diastolic blood pressures of 80 mm Hg or less compared to pressures of 90 mm Hg or less. A similar improvement was seen for strokes, silent MIs, and cardiovascular mortality (42).

Beta-blocker treatment for diabetics has traditionally focused on post-MI patients, for whom mortality benefits have been proven (43). Yet there are concerns that these agents may be harmful to diabetics by masking hypoglycemic symptoms, raising lipid levels and worsening glucose tolerance. Recent data show no long-term effects on lipid profiles, although lower HDL levels and higher triglycerides were seen during the initial titration period (44). Furthermore, studies of MI patients treated with beta-blockers show no increase in complications related to their diabetes (45). Meanwhile, the benefits of treatment have become increasingly apparent. The Bezafibrate Infarction Prevention (BIP) study showed a 42% reduction in cardiac mortality in type 2 diabetics treated with beta-blockers. These patients had chronic CAD and remote histories of MI, suggesting a broader role for therapy beyond the immediate post-MI period (46).

Antiplatelet Drugs

Elevated levels of thromboxane, fibrinogen, PAI-1 and several coagulation factors suggest a link between diabetes and a procoagulant state (47). Antiplatelet therapy involves multiple pharmacologic agents, each with its own mechanism for platelet inhibition. The three major drugs used in cardiovascular disease include aspirin, clopidogrel and intravenous glycoprotein (GP) IIb/IIIa inhibitors.

Data from the BIP study suggest that diabetics derive even greater cardiovascular benefits from aspirin than do nondiabetics (48). One reason may have to do with elevated levels of thromboxane, a platelet aggregant, observed in diabetics and inhibited by aspirin therapy. For this reason, low-dose aspirin therapy is recommended as a primary prevention in diabetics with one other risk factor for coronary disease (49).

The role of additional antiplatelet agents is important for diabetics, since they experience increased mortality from acute coronary syndromes (ACS) (50). Clopidogrel (Plavix) blocks adenosine diphosphate-mediated platelet activation and subsequent aggregation. Its efficacy in acute coronary syndromes was demonstrated in the

Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, in which patients treated with aspirin plus clopidogrel, compared to aspirin alone, had significant risk reductions in cardiovascular mortality, nonfatal MI and stroke combined, as well as refractory ischemia (51). An extension of this effect was seen in patients receiving long-term clopidogrel therapy after percutaneous coronary intervention (PCI) (Fig. 2) (52). Necessity for target vessel revascularization within 30 days of PCI was also significantly less in the treated group (53). In both studies, diabetic subgroups also demonstrated these benefits.

Intravenous GPIIb/IIIa inhibitors target the final step in platelet aggregation, where fibrinogen binds glycoprotein IIb/IIIa and promotes cross-linking of platelet molecules (53). The PRISM-PLUS study showed decreased mortality, myocardial infarction and refractory ischemia after 7 days in diabetics with unstable angina treated with a GPIIb/IIIa plus heparin vs. heparin alone (54). A meta-analysis of six GPIIb/IIIa trials, including PRISM-PLUS, demonstrated a 30-day mortality reduction from 6.2% to 4.6% ($p=0.007$) in diabetics with ACS and an even greater benefit in diabetics undergoing PCI. No survival difference was seen between therapies for nondiabetics (55).

Myocardial Infarction

Management of acute MI in diabetics is of special concern, since they have a higher incidence and a higher mortality from these events.

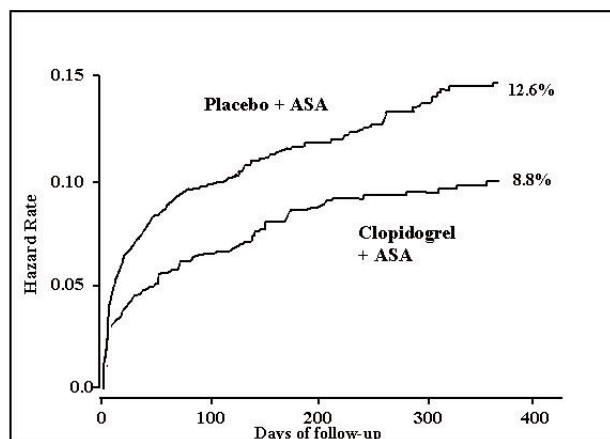


Fig. 2. Long-term clopidogrel therapy in 2,658 patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention showed a 31% risk reduction in cardiovascular death and myocardial infarction ($p=0.002$). ASA = aspirin. Reprinted with permission from Elsevier, *Lancet* 2001; 358:527–533 (52).

Thrombolytic therapy has the same, if not greater short-term benefits for diabetics vs. nondiabetics in spite of their elevated coagulation factors. Multiple angiographic studies have demonstrated similar patency rates between these two groups 90 minutes after thrombolysis (56). And an analysis of all thrombolytic trials demonstrated a non-significant, but increased 35-day survival rate for diabetics (57).

Novel approaches for improving survival after myocardial infarction include aggressive glucose control with insulin during the peri-infarct period. The DIGAMI trial randomized diabetic patients with acute MIs to insulin infusion for 24 hours upon hospitalization, followed by three months of subcutaneous insulin therapy. This was compared to standard glucose control therapy. A 30% and 28% reduction in mortality was seen in the insulin infusion group after 1 and 3.4 years of follow-up, respectively (58).

Revascularization

Coronary revascularization, through angioplasty or CABG, is critical to any long-term survival strategy for patients with cardiovascular disease. Diabetes poses a unique challenge by accelerating the development of multi-vessel atherosclerosis before and after these procedures (59). The effect this has on the management of diabetics is seen in results from the Bypass Angioplasty Revascularization Investigation (BARI) trial. This study demonstrated that 5-year survival rates were significantly improved for diabetics with multi-vessel disease treated with CABG (survival rate 80.6%) compared to balloon angioplasty (65.5% survival, $p=0.003$). This difference was not seen in the nondiabetic subset. The benefits of surgery could be explained by more widespread coronary disease in diabetics, and higher rates of restenosis after PTCA (60). Interestingly, other trials do not confirm this result. A prospective nonrandomized study at Duke University found no difference in 5-year survival between diabetics with multi-vessel disease treated with CABG compared to PTCA (61). Furthermore, an examination of outcomes among BARI registry patients yielded similar 7-year mortality rates (26%) between CABG and PTCA-treated diabetics when physicians chose the modality of revascularization, selecting PACA for 65% of all patients (62). Regardless of the therapy, diabetics still demonstrate higher mortality rates than nondiabetics after PCI, resulting in large part from higher rates of restenosis.

The problem of restenosis is being addressed through advances in PCI techniques, including antiplatelet administration and coronary stent placement. The EPIC and EPILOG trials demonstrated a reduction in acute ischemic complications after angioplasty with the administration of a GPIIb/IIIa inhibitor (63). The latter trial showed a continuation of benefits six months after therapy (64).

Furthermore, placement of coronary stents during angioplasty significantly lowers restenosis rates in simple lesions for both diabetics and nondiabetics, as demonstrated by the STRESS and BENESTENT trials (65). The BENESTENT study showed a 22% restenosis rate after stent insertion compared to 32% for angioplasty alone ($p=0.02$), with benefits also seen after 5-year follow-up (66, 67).

A combination of stent and antiplatelet therapy demonstrates the most significant mortality benefits. The EPISTENT trial compared outcomes after 6 months for patients treated with stent combined with abciximab (GPIIb/IIIa inhibitor), abciximab and angioplasty, or stent placement alone. There was a 50% reduction in mortality, nonfatal MI and repeat revascularization for diabetics receiving stent and abciximab vs. stent and placebo. Diabetics also showed lower rates of repeat target vessel revascularization after treatment with stent and abciximab (8.1%) vs. angioplasty and abciximab (18.4%, $p=0.008$) or stent alone (16.6%, $p=0.02$) (68).

Even with the advent of coronary stents, CABG appears to be more beneficial in diabetics compared to PCI. In the Arterial Revascularization Therapy Study (ARTS) trial, diabetics receiving CABG surgery had significantly fewer cardiac events (84.4% event-free survival) at one year than those treated with multi-vessel stenting (63.4% event-free survival, $p<0.001$). One reason was the greater need for repeat revascularization procedures in the PCI group due to stent restenosis. The addition of a GPIIb/IIIa inhibitor may improve outcomes for diabetics receiving multi-vessel stenting, but this requires further study (69).

Preventing stent restenosis is the current challenge in coronary revascularization. Restenosis, which is accelerated in diabetics, results from neointimal hyperplasia secondary to smooth muscle proliferation. Many oncologic agents are being studied for their effect on inhibiting this process, including paclitaxel, c-myc, sirolimus, actinomycin-D, tacrolimus and dexamethasone. For example, sirolimus binds to its intracellular receptor protein FKBP₁₂ in target

TABLE 3

Angiographic and Clinical Data for Diabetic Subsets in Two Trials Testing Sirolimus-Eluting Stents (70, 71)

	Sirolimus	Control	p Value
RAVEL	n=19	n=25	
Late luminal loss (mm)	0.07	0.82	<0.001
Cardiac events (%) (at 12 months, all patients)	5.8	28.8	<0.001
SIRIUS	n=131	n=148	
In-segment restenosis (%)	17.6	50.5	<0.001
Target lesion revascularization (%)	6.9	22.3	<0.001

“Late luminal loss” denotes the difference between minimal lumen diameter immediately after procedure and at six months.

cells, resulting in elevations of p^{27kip1}, a cyclin-dependent kinase inhibitor. This reduces phosphorylation of cell-cycle progression protein Rb (retinoblastoma protein), thereby inducing cell cycle arrest and inhibition of vascular smooth muscle proliferation (53). These drugs, however, have shown little success when given systemically, leading to the development of *in-situ* delivery systems such as drug-eluting stents. Local administration of these drugs allows higher doses to be given with less concern for the toxic side effects associated with systemic delivery. Favorable results have been achieved in clinical trials using sirolimus-eluting stents for patients with and without diabetes (Table 3). Results of the RAVEL trial demonstrated significantly reduced rates of neointimal hyperplasia in patients treated with sirolimus-coated stents versus non-coated stents. This resulted in a reduction of stent restenosis at six months with no patients showing greater than 50% stent narrowing in the sirolimus group compared to 25% ($p < 0.001$) in the standard group. Diabetics in this study experienced similar benefits, showing 0% restenosis with sirolimus but 41.7% restenosis without the drug ($p = 0.002$) (70).

The SIRIUS trial randomized 1,058 patients (279 diabetics) to sirolimus-coated stents vs. standard stents, and followed clinical endpoints at 9 months. Diabetics showed statistically significant reductions in the rates of restenosis and repeat revascularization (Table 3) in addition to decreased MI and death (71). The FREEDOM Trial will investigate whether drug-eluting stents can improve outcomes in diabetics with multi-vessel disease when compared to CABG.

Future Directions

Diabetes poses a unique and pressing challenge in the management of cardiovascular disease. The BARI-2D trial will address many unanswered questions in this area, including the role of

revascularization in stable, and even asymptomatic, CAD in diabetics. Patients will be randomized to aggressive medical management combined with revascularization (CABG or PCI) vs. aggressive medical management only. The study will also examine outcome differences between an insulin-based approach to glycemic control and an insulin-sensitizing strategy, which targets insulin resistance (72). In the future, the clinical effects of new pharmacologic agents, such as the thiazolidinediones, in preventing development and progression of cardiovascular disease will need to be addressed. Moreover, the potential negative impact of current pharmacologic agents in diabetics, such as sulfonylurea in acute myocardial infarctions, requires further study. And with the advent of drug-eluting stents, many of the same management questions and dilemmas addressed in prior clinical trials with diabetics will be revisited.

References

1. Mokdad AH, Serdula MK, Dietz WH, et al. The spread of the obesity epidemic in the United States, 1991–1998. *JAMA* 1999; 282:1519–1522.
2. Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior history of myocardial infarction. *N Engl J Med* 1998; 339:229–234.
3. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000; 102(9):1014–1019.
4. Nathan DM. Long-term complications of diabetes mellitus. *N Engl J Med* 1993; 328:1676–1685.
5. Haffner S, Taegtmeier H. Epidemic obesity and the metabolic syndrome. *Circulation* 2003; 108(13):1541–1545.
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependant diabetes mellitus. *N Engl J Med* 1993; 329:977–986.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352(9131):837–853. Erratum in *Lancet* 1999; 354(9178):602.

8. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality, The San Antonio Heart Study. *Diabetes Care* 1998; 21(7):1167–1172.
9. Klein R, Klein BE, Moss SE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XVI. The relationship of C-peptide to the incidence and progression of diabetic retinopathy. *Diabetes* 1995; 44:796–801.
10. Despres J-P, Lamarche B, Mauriege P, et al. Hyperinsulinemia is an independent risk factor for ischemic heart disease. *N Engl J Med* 1996; 334:952–957.
11. Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. *Circulation* 1996; 93:1809–1817.
12. Jarrett RJ, McCartney P, Keen H. The Bedford Study: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 1982; 22(2):79–84.
13. Patel J, Miller E, Patwardhan R, et al. Rosiglitazone improves glycemic control when used as monotherapy in type 2 diabetic patients. *Diab Med* 1998; 15(Suppl 2):S38.
14. Ghazzi MN, Perez JE, Antonucci TK, et al. The Troglitazone Study Group. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. *Diabetes* 1997; 46:433–439.
15. Schwartz S, Raskin P, Fonseca V, et al. for the Troglitazone and Exogenous Insulin Study Group. Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med* 1998; 338:861–866.
16. Inzucchi SE, Maggs DG, Spollett GR, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 1998; 338:867–872.
17. Horton ES, Whitehouse F, Ghazzi MN, et al. The Troglitazone Study Group: Troglitazone in combination with sulfonylurea restores glycemic control in patients with type II diabetes. *Diabetes Care* 1998; 21:1462–1469.
18. Takagi T, Akasaka T, Yamamuro A, et al. Troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with non-insulin dependent diabetes mellitus: a serial intravascular ultrasound study. *J Am Coll Cardiol* 2000; 36(5):1529–1535.
19. Cleveland JC, Meldrum DR, Cain BS, et al. Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium. *Circulation* 1997; 96(1):29–32.
20. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999; 33(1):119–124.
21. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; 333(9):550–554.
22. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352(9131):854–865. Erratum in *Lancet* 1998; 352(9139):1557.
23. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects: a study of two ethnic groups. *Diabetes Care* 1993; 16:621–629.
24. Stang, MR, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care* 1999; 22:925–927.
25. Lyons TJ. Glycation and oxidation: a role in the pathogenesis of atherosclerosis. *Am J Cardiol* 1993; 71:26B–31B.
26. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann Intern Med* 2001; 135(6):447–459.
27. Ginsberg HN. Diabetic dyslipidemia: basic mechanisms underlying the common hypertriglyceridemia and low HDL cholesterol levels. *Diabetes* 1996; 45(Suppl):27S–30S.
28. Gowri MS, Van der Westhuyzen DR, Bridges SR, Anderson JW. Decreased protection by HDL from poorly controlled type 2 diabetic subjects against LDL oxidation may be due to the abnormal composition of HDL. *Arterioscler Thromb Vasc Biol* 1999; 19(9):2226–2233.
29. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/Tex-CAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279(20):1615–1622.
30. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339(19):1349–1357.
31. Pyorala K, Pedersen DR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997; 20(4):614–620. Erratum in *Diabetes Care* 1997; 20(6):1048.
32. Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1999; 159(22):2661–2667.
33. Collins R, Armitage J, Parish S, et al. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361(9374):2005–2016.
34. Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial: The Care Investigators. *Circulation* 1998; 98(23):2513–2519.
35. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; 341:410–418.
36. Koskinen P, Manttrai M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992; 15:820–825.
37. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 38. *BMJ* 1998; 317(7160):703–713. Erratum in *BMJ* 1999; 318(7175):29.
38. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 39. *BMJ* 1998; 317(7160):713–720.
39. Hansson L, Lindholm LH, Niskanen L, et al., for the Captopril Prevention Projects (CAPPP) study group. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; 353:611–616.
40. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; 338(10):645–652.

41. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342:145–153.
42. Hansson L, Zanchetti A, Carruthers SG, et al., for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998; 351:1755–1762.
43. Kjekshus J, Gilpin E, Cali G, et al. Diabetic patients and beta-blockers after acute myocardial infarction. *Eur Heart J* 1990; 11:43–50.
44. Lakshman MR, Reda DJ, Materson BJ, et al. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Department of Veterans Affairs Cooperative Study Group on Anti-hypertensive Agents. *Arch Intern Med* 1999; 159:551–558.
45. Chen J, Marciniak TA, Radford MJ, et al. Beta-blocker therapy for secondary prevention of myocardial infarction in elderly diabetic patients. Results from the National Cooperative Cardiovascular Project. *J Am Coll Cardiol* 1999; 34:1388–1394.
46. Jonas M, Reicher-Reiss H, Boyko V, et al. Usefulness of beta-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary artery disease. Bezafibrate Infarction Prevention (BIP) Study Group. *Am J Cardiol* 1996; 77:1273–1277.
47. Vinik AI, Erbas T, Park TS, et al. Platelet dysfunction in type 2 diabetes. *Diabetes Care* 2001; 24(8):1476–1485.
48. Harpaz D, Gottlieb S, Graff E, et al. Effects of aspirin treatment on survival in non-insulin-dependent diabetic patients with coronary artery disease. Israeli Bezafibrate Infarction Prevention Study Group. *Am J Med* 1998; 105:494–499.
49. American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care* 2001; 24:562–563.
50. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000; 102:1014–1019.
51. Yusuf S, Zhao F, Mehta SR, et al., and 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(7):494–502. Errata in *N Engl J Med* 2001; 345(23):1716 and *N Engl J Med* 2001; 345(20):1506.
52. Mehta SR, Yusuf S, Peters RJ, et al., and Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358(9281):527–533.
53. Marks AR. Sirolimus for the prevention of in-stent restenosis in a coronary artery. *N Engl J Med* 2003; 349(14):1307–1309.
54. PRISM-PLUS. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998; 338(21):1488–1497. Erratum in *N Engl J Med* 1998; 339(6):415.
55. Roffi M, Chew DP, Mukherjee D, et al. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation* 2001; 104(23):2767–2771.
56. Woodfield SL, Lundergan CF, Reiner JS, et al. Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-1 experience. *J Am Coll Cardiol* 1996; 28:1661–1669.
57. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet* 1994; 343(8893):311–322. Erratum in *Lancet* 1994; 343(8899):742.
58. Malmberg K, for the DIGAMI Study Group. Prospective randomised study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997; 314:1512–1515.
59. Kip KE, Faxon DP, Detre KM, et al. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1996; 94:1818–1825.
60. 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(4):217–225. Erratum in *N Engl J Med* 1997; 336(2):147.
61. Barsness GW, Peterson ED, Ohman EM, et al. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. *Circulation* 1997; 96(8):2551–2556.
62. Feit F, Brooks MM, Sopko G, et al. Long-term clinical outcome in the Bypass Angioplasty Revascularization Investigation Registry: comparison with the randomized trial. BARI Investigators. *Circulation* 2000; 101(24):2795–2802.
63. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994; 330(14):956–961.
64. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997; 336(24):1689–1696.
65. Savage MP, Fischman DL, Schatz RA, et al. STRESS Investigators. Stent Restenosis Study. Coronary intervention in the diabetic patient: improved outcome following stent implantation compared with balloon angioplasty. *Clin Cardiol* 2002; 25(5):213–217.
66. Serruys PW, De Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; 331:489–495.
67. Kiemeneij F, Serruys PW, Macaya C, et al. Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. *J Am Coll Cardiol* 2001; 37(6):1598–603.
68. Lincoff AM, Califf RM, Moliterno DJ, et al., for the Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators (EPIS-TENT). Complementary clinical benefits of coronary artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. *N Engl J Med* 1999; 341:319–327.
69. Abizaid A, Costa MA, Centemero M, et al., for the Arterial Revascularization Therapy Study Group. 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; 104(5):533–538.
70. Morice MC, Serruys PW, Sousa JE, et al., and RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346(23):1773–1780.
71. Moses JW, Leon MB, Popma JJ, et al., and SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; 349(14):1315–1323.
72. Sobel BE, Frye R, Detre KM. Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial. Burgeoning dilemmas in the management of diabetes and cardiovascular disease: rationale for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Circulation* 2003; 107(4):636–642.