Diabetes and Coronary Revascularization

Context  Patients with diabetes mellitus account for approximately 25% of the nearly 1.5 million coronary revascularization procedures performed each year in the United States and experience worse outcomes compared with nondiabetic patients.

Objectives  To summarize the current state of evidence comparing the effectiveness and safety of coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) in diabetic patients and to examine developments that may affect future outcomes in this high-risk group.

Evidence Acquisition  Using the key terms diabetes mellitus, revascularization, coronary artery bypass, angioplasty, and coronary intervention, we searched MEDLINE from 1985 to 2004 for all randomized controlled trials (RCTs) comparing CABG surgery and PCI that reported outcomes in diabetic patients. Bibliographies and the Web sites of cardiology conferences were also reviewed. Studies comparing drug-eluting stents and bare-metal stents were identified in a similar fashion. The literature was reviewed to identify clinical measures that may impact revascularization outcomes in diabetic patients.

Evidence Synthesis  We identified 6 RCTs comparing CABG surgery and PCI in a total of 950 diabetic patients. A mortality benefit for CABG over balloon-only PCI has been demonstrated in diabetic patients with multivessel coronary artery disease but has not been clearly established against stent-assisted PCI or in high-risk CABG patients. Use of glycoprotein IIb/IIIa receptor inhibitors has improved survival in diabetic patients undergoing PCI. Restenosis after PCI in diabetic patients has led to substantially higher repeat revascularization rates than after CABG. The use of drug-eluting stents has led to dramatic reductions in restenosis in diabetic patients. Ongoing RCTs comparing CABG and PCI using drug-eluting stents in diabetic patients will clarify the impact of these advances on outcomes.

Conclusions  There is a relative lack of data from RCTs specifically comparing CABG surgery and PCI as currently practiced in diabetic patients. The mortality advantage and decreased rates of revascularization seen with CABG in subgroups from early trials may not be applicable in the era of drug-eluting stents, glycoprotein IIb/IIIa inhibitors, and the latest medical therapies.

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coronary artery lesions, multivessel disease, and diffuse CAD. Diabetic patients are 2 to 4 times more likely to develop CAD than nondiabetic patients and to manifest this disease earlier in life. Individuals receiving medication for type 2 diabetes without known CAD have the same likelihood of experiencing an MI as those without diabetes but with a previous history of MI. Diabetic patients who have experienced an MI have a worse prognosis, particularly those treated with insulin.

In addition to optimal medical therapy, a significant proportion of diabetic patients with CAD are candidates for revascularization. Nearly 1.5 million revascularization procedures, CABG surgery or PCI, are performed each year in the United States. Approximately 25% occur in diabetic patients, who fare worse after either type of revascularization compared with those without diabetes. There is increased perioperative morbidity and mortality as well as long-term mortality in diabetic patients undergoing CABG, particularly among those treated with insulin. Diabetic patients undergoing PCI also have worse long-term survival and higher rates of repeat revascularization, primarily due to target-vessel restenosis.

**High-Risk Features of Diabetic Patients**

Although patients with diabetes frequently have concurrent risk factors, diabetes itself is a powerful independent risk factor for cardiovascular events. There are several pathophysiologic features of atherosclerosis in diabetic patients that contribute to their worse prognosis and unique response to coronary revascularization. Metabolic and hematologic abnormalities associated with type 2 diabetes include hyperglycemia, insulin resistance, dyslipidemia, inflammation, and thrombophilia. Platelets express more Gp IIb/IIIa receptors and are more prone to aggregation, particularly in the presence of hyperglycemia. Together these abnormalities contribute to development of hypertension, endothelial cell dysfunction, accelerated atherogenesis and, eventually, coronary thrombosis. Diabetic nephropathy, including reduced creatinine clearance and proteinuria, identifies patients with markedly decreased survival after coronary revascularization.

The anatomical patterns of CAD in diabetic patients may influence their prognosis and response to revascularization. Autopsy and angiographic studies have demonstrated that persons with diabetes more frequently have left main coronary artery lesions, multivessel disease, and diffuse CAD. Diabetic patients have smaller luminal diameters in segments adjacent to obstructive coronary lesions and more completely occluded segments. In addition to a greater atherosclerotic burden, diabetic patients have a larger amount of lipid-rich plaques, which may be more prone to rupture. In an angiographic study evaluating patients with unstable angina, those with diabetes had more fissured plaques and intracoronary thrombi. The coronary arteries of diabetic patients may be less able to adapt to significantly obstructive lesions. Diabetic patients have an impaired ability to develop coronary collaterals, which provide intrinsic bypass channels from one coronary segment or artery past an obstruction. Coronary arteries often undergo remodeling, which is an early compensatory enlargement at atherosclerotic sites to maintain luminal area and flow. However, intravascular ultrasound has shown that the coronary arteries of diabetic patients are less likely to undergo this favorable remodeling in response to atherosclerosis.

**Comparing CABG vs Balloon-Only PCI**

There are no prospective RCTs that compare CABG surgery and PCI specifically in diabetic patients. However, there are several RCTs comparing these revascularization strategies that reported outcomes for subgroups of diabetic patients (TABLE 1). No trial included patients with significant (>50%) lesions in the left main coronary artery. Among the trials, the Bypass Angioplasty Revascularization Investigation (BARI) has received the most attention. This study compared CABG with balloon-only PCI as the initial treatment strategy in patients with multivessel CAD in need of revascularization. Overall, CABG and PCI yielded similar rates of in-hospital mortality (1.3% vs 1.1%, P<.01) and 5-year survival (89.3% vs 86.3%, P=.19), although those who underwent PCI required substantially more additional revascularization procedures.

Among treated diabetic patients (n=353) in the BARI trial there was a 15% absolute survival advantage for CABG (P=.003) at 5 years. However, this trial was conducted prior to the availability of coronary stents and intravenous platelet Gp IIb/IIIa inhibitors. Also, the trial did not designate aggressive postprocedural medical management now known to improve survival, such as the
use of angiotension-converting enzyme inhibitors, β-blockers, antiplatelet therapy, and statins.

The Emory Angioplasty vs Surgery (EAST)\(^2\) and the Coronary Angioplasty vs Bypass Revascularization Investigation (CABRI)\(^3\) trials enrolled patients similar to those in the BARI trial. Subgroup analyses of diabetic patients showed that CABG tended to show better long-term survival over balloon-only PCI (Table 1). Perhaps due to inadequate sample size, this result did not reach statistical significance in either trial. In contrast, the Randomized Intervention Treatment of Angina (RITA-1) trial showed a trend toward more death in diabetic patients who underwent CABG vs balloon-only PCI.\(^2\) Of note, in this trial, 32% of diabetic patients had single-vessel CAD only.

### Explaining the Mortality Benefit of CABG

There are several explanations for the apparent long-term superiority of CABG surgery over PCI in diabetic patients with multivessel CAD. Internal mammary artery (IMA) grafts provide better long-term patency than saphenous vein grafts and were used in 81% of the diabetic patients in the BARI trial. In fact, the survival advantage of CABG in diabetic patients was limited to those who received at least 1 IMA graft.\(^3\) The completeness of revascularization is another important factor. Diabetic patients in the BARI trial had a similar mean number of significant lesions in both the CABG and PCI groups (3.5 vs 3.4). However, while 87% of all intended vessels were successfully bypassed, only 76% of significant lesions were successfully treated with PCI.\(^3\)

Bypass grafts may render future ischemic events to be less often fatal. An analysis of all BARI-eligible diabetic patients (n=641) revealed that the likelihood of a spontaneous Q-wave MI was similar after PCI or CABG (about 8%-9%) in the first 5 years.\(^3\) However, the risk of death after a spontaneous Q-wave MI was substantially less in patients who underwent CABG (adjusted relative risk, 0.09; 95% confidence interval, 0.03-0.29; \(P<.001\)). Those who underwent CABG but did not experience a subsequent spontaneous Q-wave MI gained less protection from death (adjusted relative risk, 0.65; 95% confidence interval, 0.45-0.94; \(P=.02\)). The risk of death in each group was even lower when an IMA graft was used. Complete revascularization was achieved more frequently with CABG. These results suggest that CABG, particularly when an IMA graft was used,

### Table 1. CABG Surgery vs PCI in Diabetic Patients: Subgroups From Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Profile</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITA-1,(^2^9) 1993</td>
<td>1- to 3-Vessel CAD Angina or ischemia</td>
<td>CABG (n = 53)</td>
<td>24.2 at 6.5 y (P=.09)</td>
</tr>
<tr>
<td>EAST,(^2^9) 1994</td>
<td>Multivessel CAD Referred for revascularization LVEF &gt;25%</td>
<td>CABG (n = 30)</td>
<td>10.0 at 3 y</td>
</tr>
<tr>
<td>CABRI,(^3^0) 1995</td>
<td>Multivessel CAD Angina or ischemia LVEF &gt;35%</td>
<td>CABG (n = 60)</td>
<td>12.5 at 4 y</td>
</tr>
<tr>
<td>BARI,(^3^1,(^3^2) 1996</td>
<td>Multivessel CAD Angina or ischemia</td>
<td>CABG (n = 180)</td>
<td>11.1 at 7 y</td>
</tr>
<tr>
<td>ARTS,(^3^3,(^3^4) 2001</td>
<td>Multivessel CAD Angina or ischemia LVEF &gt;30%</td>
<td>CABG (n = 96)</td>
<td>3.1 at 1 y*</td>
</tr>
<tr>
<td>AWESOME,(^3^5,(^3^6) 2001</td>
<td>Medically refractory unstable angina High CABG risk (prior heart surgery, MI &lt;35%, age &gt;70 y, or balloon pump use)</td>
<td>CABG (n = 79)</td>
<td>35 at 1 y†</td>
</tr>
</tbody>
</table>

Abbreviations: ARTS, Arterial Revascularization Therapy Study; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; BARI, Bypass Angioplasty Revascularization Investigation; CABG, coronary artery bypass graft surgery; CABRI, Coronary Angioplasty vs Bypass Revascularization Investigation; CAD, coronary artery disease; EAST, Emory Angioplasty vs Surgery Trial; Gp, glycoprotein; IMA, internal mammary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; RITA-1, Randomized Intervention Treatment of Angina.

\(*\)Combines absolute rates of repeat CABG and PCI.

\(†\)Includes revascularization or unstable angina.
provided greater protection from death after ischemic events in diabetic patients studied in the BARI trial.

In a single-institution study, angiographic follow-up after PCI showed that diabetic patients are more likely to develop new coronary lesions compared with nondiabetic patients, particularly in instrumented vessels. Jeopardized myocardium is defined as the total territory of myocardium supplied by arteries with at least one 50% stenosis. The amount of jeopardized myocardium decreases initially following revascularization but subsequently increases due to restenosis, graft failure, or formation of new vessel lesions. In the BARI trial, diabetic patients had more jeopardized myocardium initially after PCI than after CABG, as well as at follow-up angiography. These results suggest that, in BARI trial participants with diabetes, CABG may provide better protection from vulnerable plaques compared with PCI.

Another single-institution angiographic study demonstrated that diabetic patients have higher rates of completely occlusive restenosis after PCI, a finding that independently correlated with increased long-term mortality. While diabetic patients in the BARI trial had markedly more restenosis after PCI, graft patency in those undergoing CABG surgery was not influenced by diabetic status. The long-term mortality advantage of CABG over PCI in diabetic patients therefore may in part be due to a more durable restoration of flow to the diseased arteries treated. The risk associated with repeat revascularization procedures due to restenosis after PCI may also negatively impact long-term survival.

As part of the BARI trial, eligible patients who elected not to undergo randomization were followed up in a registry. More diabetic patients chose PCI (n = 182) than CABG (n = 117). There was no significant mortality difference between those who received PCI or CABG at 5 years (14.4% vs 14.9%, P = .86). However, the patients with diabetes who underwent CABG had a higher prevalence of 3-vessel CAD and a greater number of significant lesions, including in the proximal left anterior descending artery. An analysis adjusted for worse clinical risk factors and angiographic profiles did not demonstrate an advantage for either strategy (relative risk of PCI, 1.24; 95% confidence interval, 0.71-2.18). These data from the BARI registry suggest that it may be reasonable to use the angiographic profile in diabetic patients to help select the type of revascularization.

### Improving Outcomes in Diabetic Patients Undergoing PCI

A potentially serious limitation of the aforementioned trials is that they were conducted in the era prior to widespread use of stents and Gp IIb/IIIa inhibitors. The use of coronary stents has reduced the incidence of abrupt vessel closure following balloon angioplasty and has decreased restenosis rates. The Arterial Revascularization Therapy Study (ARTS) compared multivessel coronary artery stenting with CABG surgery. In a subgroup of diabetic patients (n = 208) there was no statistically significant difference in mortality at 1 or 3 years between the 2 groups (Table 1). However, diabetic patients who underwent PCI required more repeat revascularization procedures. The greater need for CABG following PCI (10.0% vs 2.0%; P < .05) was attributed to a less complete revascularization (70.5% vs 84.1%; P < .001) achieved with stent-assisted PCI vs CABG. In the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial, patients at high surgical risk were randomized to receive PCI or CABG. In a subgroup of diabetic patients (n = 144), there was no statistically significant difference in survival throughout a 5-year follow-up period (Table 1). Stents (54%) and Gp IIb/IIIa inhibitors (11%) were permitted in the PCI group.

A pooled analysis from 3 trials (n = 1462) investigating the use of the Gp IIb/IIIa inhibitor abciximab with PCI in diabetic patients showed a 2% absolute mortality reduction (4.5% vs 2.5%, P = .03) at 1 year. Furthermore, diabetic patients in a meta-analysis from 6 studies (n = 6458) investigating various Gp IIb/IIIa inhibitors in acute coronary syndromes showed a 1.6% absolute mortality reduction (6.2% vs 4.6%, P = .007) at 30 days. This mortality benefit was greater in diabetic patients (n = 1279) who underwent PCI during the index hospitalization (4.0% vs 1.2%, P = .002).

In a recent study, diabetic patients undergoing planned PCI (n = 701), primarily with bare-metal stents, were pretreated with high-dose clopidogrel (600 mg) at least 2 hours before the procedure. Patients with recent acute coronary syndromes were excluded. The addition of abciximab to pretreatment clopidogrel did not lower the composite incidence of death or MI at 1 year (8.3% vs 8.6%, P = .91). This trial may have been underpowered to detect a significant difference. However, the use of abciximab did reduce the incidence of target-lesion revascularization (23.2% vs 30.4%, P = .03) at 1 year. The applicability of this effect with more frequent use of drug-eluting stents is unknown.

Restenosis is the driving force behind the increased need for repeat revascularization in diabetic patients following PCI. Patients with diabetes exhibit increased intimal hyperplasia after PCI, which correlates with the degree of hyperglycemia. Diabetic patients with optimal glycemic control after PCI have rates of target vessel revascularization similar to those without diabetes. This suggests that medical therapy aimed at improved glycemic control might improve PCI outcomes. The thiazolidinediones, a newer class of insulin-sensitizing agents, have shown promise in reducing intimal hyperplasia and clinical restenosis rates in diabetic patients undergoing PCI with bare-metal stents. This effect may be independent of glycemic control.

The introduction of drug-eluting stents has further changed the landscape for PCI, with significant reductions in angiographic restenosis rates and need for repeat revascularization procedures. Drug-eluting stents implanted in diabetic patients have reduced restenosis rates in the target vessel with both rapamycin-eluting and
paclitaxel-eluting stents (TABLE 2). Rates of angiographic restenosis and need for target-lesion revascularization in diabetic patients are substantially lower than for nondiabetic patients receiving bare-metal stents. However, these rates are still higher in diabetic patients than in nondiabetic patients receiving drug-eluting stents. The potential impact of this reduction in restenosis on mortality, particularly in multivessel PCI, is unknown.

**Primary PCI in Diabetic Patients**

Patients with diabetes experiencing an acute MI with electrocardiographic evidence of ST-segment elevation presented to the hospital later than patients without diabetes and are more likely to have congestive heart failure.8,16 Coronary artery bypass graft surgery in the setting of an ST-segment elevation MI is typically reserved for cases of failed PCI or for mechanical complications from the MI. Primary PCI may be preferred over thrombolytic therapy in diabetic patients presenting with an ST-segment elevation MI. In a pooled subset analysis from 11 RCTs of diabetic patients (n=367) randomized to receive primary PCI or thrombolytic therapy, an invasive strategy led to a significant reduction in death or nonfatal MI at 30 days (9.2% vs 19.3%, P<.05).53 The relative benefit of primary PCI was greater in diabetic patients compared with nondiabetic patients. These data were reported before the availability of stents or Gp IIb/IIIa inhibitors.

In an observational study of diabetic patients, PCI performed with frequent stenting (94.2%) and use of Gp IIb/IIIa inhibitors (63.1%) was, compared with fibrinolysis, associated with lower 1-year rates of death or reinfarction (19.4% vs 36.4%, P=0.007).54 In a nonrandomized group of diabetic patients undergoing primary PCI with stenting (n=53), the use of abciximab was associated with lower mortality (0% vs 16.7%, P=0.02) at 6 months, as well as reduced rates of reinfarction and repeat revascularization.57

### Improving Outcomes in Diabetic Patients Undergoing CABG

Rigid glycemic control in diabetic patients undergoing CABG surgery improves outcomes. The use of a continuous insulin infusion has correlated with reduced perioperative mortality compared with subcutaneous insulin.58 A recent RCT compared continuous glucose-insulin-potassium (GIK) infusion to

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**Table 2. Outcomes With Drug-Eluting US Bare-Metal Stents in Diabetic Patients**

| Abbreviations: Abbreviations: DIABETES, Diabetes and Sirolimus Eluting Stent Trial; LVEF, left ventricular ejection fraction; SIRIUS, Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With de novo Coronary Artery Lesions. *Includes unpublished data (M. Sabaté, MD, written communication, January 17, 2005). †Death from cardiac cause, myocardial infarction, or target-lesion revascularization. ‡Measured at 6 months in the SIRIUS trial. §§Target-lesion and target-vessel revascularization were defined as clinically driven coronary artery bypass graft surgery or percutaneous coronary intervention for restenosis or closure of the target lesion or vessel, respectively. ©2005 American Medical Association. All rights reserved. (Reprinted) JAMA, March 23/30, 2005—Vol 293, No. 12 1505
### Box. Strategies to Improve Outcomes in Diabetic Patients Undergoing Coronary Revascularization

**CABG**
- If possible, use ≥1 arterial conduit, preferably an internal mammary artery, with preference given to anastomoses to the left anterior descending artery.
- Maintain rigid perioperative glycemic control (serum glucose <200 mg/dL [11.1 mmol/L]) with continuous insulin infusion.

**PCI**
- Drug-eluting stents, with either rapamycin or paclitaxel, are strongly recommended.
- Glycoprotein IIb/IIIa inhibitors are strongly recommended, especially during an acute coronary syndrome.

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

Achieve a target serum glucose level of 125 to 200 mg/dL (6.9-11.1 mmol/L) against standard therapy (serum glucose <250 mg/dL [13.9 mmol/L]). Patients treated with GIK infusion developed fewer perioperative infections and atrial fibrillation and experienced shorter hospital stays. Over 2 years, patients treated with GIK infusion also had a significantly improved survival rate and fewer recurrent ischemic events.

Different surgical techniques have been investigated in diabetic patients. The use of multiple arterial conduits, including bilateral IMA grafts, appears to improve the long-term results of CABG. A recently published observational cohort showed improved 10-year survival and lower rates of recurrent MI and repeat CABG in diabetic patients with preserved left ventricular function who received bilateral IMA grafts. Additionally, there was no significant difference in the incidence of sternal wound infections, a concern that historically has limited the application of this approach. In recent years, there has been an increased use of "off-pump" CABG, ie, without cardiopulmonary bypass and cardiac arrest. An analysis of 346 diabetic patients who underwent off-pump CABG showed reduced complications but no survival advantage compared with randomized controls who underwent on-pump CABG.

### Medical Management of Diabetic Patients

Aggressive cardiovascular risk factor modification is essential in the management of diabetic patients, including cigarette smoking cessation as well as control of blood pressure and cholesterol levels. Angiotensin-converting enzyme inhibitors have been shown to reduce cardiovascular events in diabetic patients, independent of their blood pressure–lowering effect. Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce cardiovascular events in diabetic patients, irrespective of manifest CAD or a high baseline low-density lipoprotein cholesterol level. The use of antiplatelet agents significantly reduces vascular events in diabetic patients. The use of β-blockers in diabetic patients with CAD is associated with improved survival, even in those without a previous MI.

A recent trial investigated the use of GIK infusion for 24 hours in patients with ST-segment elevation MI primarily treated with thrombolytic therapy. Survival at 30 days was not improved in diabetic patients treated with GIK infusion. In contrast, the use of a glucose-insulin infusion followed by an extended course of subcutaneous insulin has been shown to improve long-term survival in diabetic patients presenting with an acute MI. The long-term impact of intensive glycemic control on cardiovascular outcomes in all diabetic patients is less established.

### Future Directions

Two important RCTs sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health are ongoing that compare PCI and CABG surgery in diabetic patients. The BARI 2 Diabetes (BARI 2D) trial is investigating 2600 diabetic patients with mild angina or documented myocardial ischemia and at least 1 significant (>50%) angiographic lesion. Using a 2 × 2 factorial design, patients are randomly assigned to 2 glucose management regimens—an insulin-sensitizing strategy vs an insulin-providing one, and medical therapy vs medical therapy with mechanical revascularization. The physician and the patient determine the type of revascularization: either PCI or...
CONCLUSIONS

Coronary revascularization has a prominent role in managing the heavy burden of CAD in the expanding population of diabetic patients. A host of unfavorable pathophysiological and anatomical features of atherosclerosis in patients with diabetes has contributed to their worse prognosis and poorer response to revascularization. Several early studies comparing CABG surgery vs balloon-only PCI in subgroups of diabetic patients with multivessel CAD demonstrated a survival advantage and fewer repeat revascularization procedures with an initial surgical strategy. However, advances in medical therapy, PCI technology, and surgical techniques demand a continual reassessment of the treatment strategies for CAD available to diabetic patients. Ongoing clinical trials comparing coronary revascularization strategies specifically in diabetic patients will help define the optimal management strategy.

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