Differential Influence of Diabetes Mellitus on Increased Jeopardized Myocardium After Initial Angioplasty or Bypass Surgery

Bypass Angioplasty Revascularization Investigation

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Background—Data are absent that compare midterm angiographic outcome between patients with and without diabetes after initial percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft surgery (CABG). Importantly, diabetes mellitus may differentially influence long-term survival after PTCA or CABG.

Methods and Results—Patients with multivessel coronary disease who were previously enrolled in the Bypass Angiopathy Revascularization Investigation to compare initial PTCA versus CABG (n=1829) and who had a reduction in jeopardized myocardium after initial revascularization and at least 1 angiogram during 5-year follow-up were analyzed (n=897). This included 369 CABG-treated patients (16% with diabetes) and 528 PTCA-treated patients (18% with diabetes). The influence of diabetes on angiographic increase in percentage of jeopardized myocardium after initial revascularization with either PTCA or CABG was investigated. Among PTCA patients, the mean percentage increase in total jeopardized myocardium was significantly greater in those with diabetes than in those without at 1-year protocol-directed angiography (42% versus 24%, P=0.05) and on the first clinically performed (unscheduled) angiogram within 30 months (63% versus 50%, P=0.01) but not at 5-year protocol-directed angiography (34% versus 26%, P=0.33). This excess midterm risk associated with diabetes persisted after statistical adjustment. In contrast, among CABG patients, diabetes was not associated with percentage increase in jeopardized myocardium at any angiographic follow-up interval.

Conclusions—Presence of diabetes differentially influences worsening of jeopardized myocardium after initial PTCA compared with CABG. This differential effect occurs irrespective of whether follow-up angiography is undertaken for clinical or nonclinical purposes. (Circulation. 2002;105:1914-1920.)

Key Words: angiography ■ angioplasty ■ bypass surgery ■ diabetes mellitus ■ follow-up studies

Diabetes mellitus is associated with development and increased prevalence of coronary artery disease.1–3 Reports from observational registries suggest that patients with diabetes treated with angioplasty4–6 and bypass surgery4–6 have poorer adjusted long-term survival than similarly treated patients without diabetes. The relative benefit of surgical versus percutaneous revascularization is uncertain with some observational studies suggesting that among patients with diabetes, bypass surgery results in superior adjusted long-term survival compared with angioplasty,5,7,8 whereas other studies fail to confirm this advantage.4–6 Similar uncertainty exists among randomized trials that involve subgroups of patients with diabetes. The Bypass Angiography Revascularization Investigation (BARI) trial showed a definite survival advantage associated with bypass surgery,9 the Emory Angioplasty versus Surgery Trial10 and Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) trial11 suggested a trend that favors bypass surgery, and the Randomized Intervention Treatment of Angina trial12 showed no survival advantage with bypass surgery.

The relatively poor long-term survival among patients with diabetes treated with angioplasty has been the target of...
multiple studies, including angiographic analyses. Diabetes has been shown to increase restenosis rates,13–14 12-month target lesion revascularization procedures,15 and stent thrombosis after acute MI16 and is associated with new arterial narrowing17 and coronary artery disease progression.18 However, no published reports have simultaneously compared midterm angiographic findings between subgroups of patients with and without diabetes and treated with angioplasty and bypass surgery. Therefore, we compare angiographic outcome between patients with and without diabetes in the BARI trial after initial revascularization with either angioplasty or bypass surgery. We further stratify this analysis according to whether follow-up angiography was performed at protocol-directed intervals (1- or 5-year follow-up) or at unscheduled intervals in response to ischemic symptoms (within 30 months of follow-up).

Methods

Study Design
Study participants were selected from BARI, details of which have been published.19 Briefly, patient eligibility required severely symptomatic angiographically confirmed multivessel coronary artery disease suitable for initial revascularization; absence of severe left main disease and presence of multi-territory coronary disease; and clinically important targets feasible by both angioplasty and surgery. No requirement existed for equivalent or complete revascularization. Conventional balloon angioplasty was the only percutaneous technique used.

Between August 1988 and July 1991, 4017 eligible patients from 18 clinical centers across North America were recruited, of whom 1829 agreed to undergo random assignment to either coronary artery bypass graft surgery (CABG; n=914) or percutaneous transluminal coronary angioplasty (PTCA; n=915). Because this is a study of mid-to-late success of revascularization, only those patients who achieved some initial anatomic benefit (at least 1 graft placed during surgery or 1 lesion successfully dilated) and who had at least 1 follow-up angiogram available for analysis are included. This design yielded 369 CABG patients (41% of total) of whom 58 (16%) had a history of treated diabetes and 528 PTCA patients (57%) of total of whom 97 (18%) had a history of treated diabetes. Patient diabetes status was established according to whether they were receiving insulin or oral hypoglycemic medication for treatment of diabetes at study entry.

Follow-Up Angiography
Follow-up angiography in BARI was performed under 2 circumstances: protocol and clinically indicated (ie, not protocol directed). For protocol-directed angiography, 4 clinical sites at 1 year and at 5 years obtained follow-up angiograms on consecutive randomized patients who consented to have follow-up angiography. Of 347 surviving patients at 1-year follow-up sites, 270 (78%) had protocol-directed angiography;20 of 512 surviving patients at 5-year follow-up sites, 407 (79%) had protocol-directed angiography. Non–protocol-directed angiograms were routinely obtained at all 18 clinical sites to evaluate the causes and impact of clinical symptoms.

Angiographic Evaluation
The Core Angiographic Laboratory at Stanford University evaluated all entry, percutaneous procedure, intercurrent, and follow-up angiograms for anatomic distribution and severity of all coronary lesions (assessed with calipers) and for effects of angioplasty and bypass grafts on myocardial perfusion distal to lesions. The total percentage of left ventricular myocardium jeopardized was determined by the overall percentage of the coronary perfusion territory compromised by stenoses ≥50%.20,21 Briefly, to quantify the total coronary perfusion territory, the native coronary distribution was graded from distal terminating arteries (vessels >1.5 mm diameter), which were each sized as insignificant, small, medium, or large (range 0 to 3). The sum of all terminal arteries reflects the global coronary distribution to left ventricular myocardial territory. The percentage of myocardium jeopardized (range 0% to 100%) is the fraction of the terminal arteries compromised by lesions ≥50%. This quantity was computed from entry and 1- and 5-year angiograms and from intecurrent or postangioplasty angiograms. Myocardial jeopardy after surgery was calculated assuming that all arterial and vein grafts placed were initially patent. Angioplasty, if successful (<50% residual stenosis, ≥20% change in stenosis, and TIMI 3 flow), was considered to alleviate jeopardy distal to all treated stenosis. On follow-up angiography, coronary grafts, if not compromised by ≥50% stenosis, were considered to relieve jeopardy in the native vessel and its branches in both anterograde and retrograde directions.

To illustrate the percentage increase in total jeopardized myocardium after initial revascularization, a hypothetical example is provided. If a patient had 80% total myocardium jeopardized before revascularization, 20% initially after revascularization, and 40% at follow-up angiography, the percentage increase in total jeopardized myocardium during follow-up would be (40%−20%)/(80%−20%) =20%/60% =0.33 (33.3%). In calculating this quantity, theoretical negative values and those exceeding 100% were truncated at 0% and 100%, respectively.

Statistical Analysis
Differences in baseline clinical and angiographic characteristics between study patients and all other randomized BARI patients were compared by Student’s t tests for continuous variables and Fisher’s exact test for categorical variables. Similarly, comparisons of mean myocardial jeopardy scores between patients with and without diabetes at baseline and percentage increases in total jeopardized myocardium during follow-up were compared by Student’s t tests and were stratified by initial mode of revascularization (PTCA or CABG) and type of angiogram. Polychotomous logistic regression models were fit to estimate the independent effect of diabetes, expressed as odds ratios, on the percentage increase in total jeopardized myocardium during follow-up. For non–protocol-directed angiography, results are presented with the first angiogram within 30 months of follow-up. Results were similar when the first angiogram during entire follow-up and the first angiogram within 1 year were evaluated.

Results

Baseline Characteristics
The 897 study patients who had either protocol- or non–protocol-directed angiography differed from the 932 other BARI patients. Study patients were less likely to have received CABG as their initial revascularization (41% versus 58%) and less likely to be ≥65 years of age at study entry (35% versus 43%) and to have a history of treated diabetes (17% versus 21%), congestive heart failure (7% versus 10%), or peripheral vascular disease (7% versus 10%). However, study patients had a similar prevalence of 3-vessel disease (40% versus 43%) and mean number of lesions ≥50% stenosis as all other BARI patients (3.5 versus 3.5).

PTCA Patients
Among the 229 PTCA patients who had at least 1 protocol-directed 1- and/or 5-year angiogram, the mean percentage of jeopardized myocardium was similar between patients with and without diabetes at both study entry (58% versus 60%) and immediately after initial angioplasty (13% versus 15%) (Table 1). However, at protocol-directed 1-year angiography
patients with diabetes had a higher percentage increase in jeopardized myocardium than patients without diabetes (42% versus 24%, \( P = 0.05 \)) (Table 1, Figure 1). At protocol-directed 5-year angiography (\( n = 195 \)), the percentage increase in jeopardized myocardium was similar between patients with and without diabetes (34% versus 26%, \( P = 0.33 \)) (Table 1). The attenuated difference in jeopardized myocardium between 1- and 5-year protocol-directed angiography reflected, at least in part, the requirement of surviving to 5 years and the frequent repeat PTCA (39%) and intercurrent bypass surgery (17%) among the 195 patients with 5-year angiography who initially received PTCA.

Among the 355 PTCA patients who had at least 1 non–protocol-directed angiogram within 30 months (mean follow-up 6.7 months), the mean number of significant lesions (4.1 versus 3.5, \( P = 0.002 \)) and percentage of jeopardized myocardium increased (50 (41) versus 63 (38), \( P = 0.01 \)).

### Table 1. Angiographic Assessment of PTCA-Treated Patients by Diabetes Status

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic Patients</th>
<th>Diabetic Patients</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-directed angiography (( n = 199 ))</td>
<td>(n=199)</td>
<td>(n=90)</td>
<td>0.06</td>
</tr>
<tr>
<td>Lesions ( \geq 50% ) stenosis at baseline angiogram</td>
<td>3.2 (1.2)</td>
<td>3.3 (1.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Percent JM at study entry procedure</td>
<td>60 (15)</td>
<td>58 (17)</td>
<td>0.57</td>
</tr>
<tr>
<td>Lesions attempted at initial angioplasty</td>
<td>2.4 (1.0)</td>
<td>2.4 (0.9)</td>
<td>0.80</td>
</tr>
<tr>
<td>Percent JM immediately after angioplasty</td>
<td>15 (16)</td>
<td>13 (15)</td>
<td>0.54</td>
</tr>
<tr>
<td>Percent JM mitigated by angioplasty</td>
<td>75 (25)</td>
<td>79 (21)</td>
<td>0.47</td>
</tr>
<tr>
<td>Angiogram at 1-year follow-up* (( n = 199 ))</td>
<td>(n=109)</td>
<td>(n=19)</td>
<td>0.05</td>
</tr>
<tr>
<td>Percent JM on 1-year angiogram</td>
<td>25 (22)</td>
<td>26 (24)</td>
<td>0.19</td>
</tr>
<tr>
<td>Percent increase in JM†</td>
<td>24 (35)</td>
<td>42 (41)</td>
<td>0.05</td>
</tr>
<tr>
<td>Angiogram at 5-year follow-up‡ (( n = 173 ))</td>
<td>(n=173)</td>
<td>(n=19)</td>
<td>0.33</td>
</tr>
<tr>
<td>Percent JM on 5-year angiogram</td>
<td>25 (22)</td>
<td>26 (25)</td>
<td>0.90</td>
</tr>
<tr>
<td>Percent increase in JM†</td>
<td>26 (35)</td>
<td>34 (39)</td>
<td>0.33</td>
</tr>
<tr>
<td>First non–protocol-directed angiogram within 30 months (( n = 273 ))</td>
<td>(n=273)</td>
<td>(n=82)</td>
<td></td>
</tr>
<tr>
<td>Lesions ( \geq 50% ) stenosis at baseline angiogram</td>
<td>3.5 (1.4)</td>
<td>4.1 (1.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Percent JM at study entry procedure</td>
<td>62 (16)</td>
<td>67 (16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Lesions attempted at initial angioplasty</td>
<td>2.4 (1.1)</td>
<td>2.4 (1.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>Percent JM immediately after angioplasty</td>
<td>19 (18)</td>
<td>23 (20)</td>
<td>0.14</td>
</tr>
<tr>
<td>Percent JM mitigated by angioplasty</td>
<td>69 (26)</td>
<td>66 (26)</td>
<td>0.73</td>
</tr>
<tr>
<td>Months from study entry to follow-up angiography</td>
<td>7.0 (6.8)</td>
<td>5.9 (5.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Percent JM on follow-up angiogram</td>
<td>41 (24)</td>
<td>51 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent increase in JM†</td>
<td>50 (41)</td>
<td>63 (38)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are mean (SD).
JM indicates jeopardized myocardium.
*Actual time interval: 10.1 months to 15.4 months.
†As defined in Methods.
‡Actual time interval: 4.0 years to 5.5 years.
dized myocardium (67% versus 62%, \(P=0.03\)) at study entry were higher in patients with diabetes than in those without (Table 1). Despite this differential atherosclerotic burden, the mean number of lesions attempted was similar between patients with and without diabetes (2.4 versus 2.4), and immediately after initial angioplasty, the percentage of jeopardized myocardium was similar (23% versus 19%, \(P=0.14\)) (Table 1, Figure 2A). On the first non–protocol-directed angiogram within 30 months, the mean percentage increase in total jeopardized myocardium was significantly greater in patients with diabetes than in those without (63% versus 50%, \(P=0.01\)) (Table 1, Figure 2). In multivariable analysis, diabetes was associated with an approximate 2-fold higher adjusted risk of an increase in percentage of jeopardized myocardium during follow-up on the basis of the first follow-up angiogram (protocol- or non–protocol-directed) obtained within 30 months (Table 2).

**CABG Patients**

Among the 241 CABG patients who had at least 1 protocol-directed 1- and/or 5-year angiogram, the mean percentage of jeopardized myocardium at study entry was higher in patients with diabetes than in patients without diabetes (66% versus 60%, \(P=0.05\)) (Table 3). The more extensive arteriosclerosis in CABG patients with diabetes resulted in more extensive revascularization, with an average of 3.0 grafts placed in patients with diabetes and 2.7 grafts placed in patients without diabetes \((P=0.04)\). Thus, immediately after bypass surgery, the percentage of jeopardized myocardium was similar between CABG patients with and without diabetes (7% versus 7%) (Table 3).

In contrast to PTCA patients, at protocol-directed 1-year angiography \((n=132)\), the percentage increase in jeopardized myocardium was similar between CABG patients with and without diabetes (11% versus 15%, \(P=0.25\)) (Table 3, Figure 1). Similarly, at protocol-directed 5-year angiography \((n=196)\), the percentage increase in jeopardized myocardium was similar between patients with and without diabetes (26% versus 25%, \(P=0.88\)) (Table 3).

Among the 103 CABG patients who had at least 1 non–protocol-directed angiogram within 30 months (mean

**TABLE 2. Polychotomous Logistic Regression of Effect of Diabetes on Percentage Increase in Total Jeopardized Myocardium During Follow-Up (PTCA Patients—First Angiogram Within 30 Months Used)**

<table>
<thead>
<tr>
<th>% Increase in Jeopardized Myocardium</th>
<th>% of Patients With Specified Increase in Jeopardized Myocardium</th>
<th>Polychotomous Logistic Regression Models (Effect of Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-diabetic Patients ((n=333))</td>
<td>Diabetic Patients ((n=88))</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>0</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>1–49</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>50–99</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>100</td>
<td>26</td>
<td>35</td>
</tr>
</tbody>
</table>

*Model with intercept and diabetes only.
†Adjusted for percentage of myocardium jeopardized before initial PTCA, reduction in jeopardized myocardium after initial PTCA, in-hospital repeat revascularization, days from initial PTCA to angiographic assessment, and protocol or nonprotocol angiographic assessment.
‡Adjusted for partial model variables† plus history of CHF, body mass index, number of lesions >50%, and number of attempted lesions.
\(\$P<0.10, |P<0.05, \text{and } \|P<0.01.\)
follow-up 12.9 months), the mean number of significant lesions at study entry was nonsignificantly higher in patients with diabetes than in patients without diabetes (3.9 versus 3.4, \(P=0.18\)), although the percentage of jeopardized myocardium was similar (64% versus 61%, \(P=0.52\)) (Table 3).

**Possible Mechanisms and Explanations**

Diabetes mellitus is associated with lipid, platelet, and coagulation abnormalities that contribute to atherogenesis and thrombogenesis and diffuseness of coronary atherosclerosis. Intuitively, the accelerated atherogenesis associated with diabetes would be expected to manifest in both angioplasty and bypass surgery patients with diabetes, but we did not observe this in surgery patients. From a measurement standpoint, initially "nonsignificant" native lesions that progress to 50% among CABG-treated patients would not contribute to the total percentage of myocardium jeopardized so long as bypass grafts that were placed remained patent. However, among PTCA-treated patients, untreated lesions <50% that ultimately progressed to \(\geq 50\%\) would give the appearance of loss of initial revascularized myocardium, perhaps to a greater extent among patients with diabetes because of more prevalent diffuse and rapidly progressive disease.

Clinically, the endothelial dysfunction, platelet and coagulation abnormalities, and metabolic disorders associated with diabetes mellitus may contribute substantially to the complex healing process after arterial wall injury. Indeed, diabetes mellitus has been associated with a higher incidence...
of restenosis in some\textsuperscript{13,14} but not all studies\textsuperscript{26} that involve nonstented lesions and in some\textsuperscript{14} but not all studies\textsuperscript{33} that involve stented lesions, with the primary postulated mechanism being exaggerated intimal hyperplasia in both stented and nonstented lesions.\textsuperscript{13,14} In contrast, there are very little current data that compare short- and mid-term loss of graft patency between CABG patients with and without diabetes.

**Clinical Implications**

The greater increase in jeopardized myocardium among patients with diabetes after initial revascularization with angioplasty but not bypass surgery is consistent with the early divergence in mortality observed between PTCA and CABG patients with diabetes in the BARI trial.\textsuperscript{9} Still, a direct causal relationship between higher mortality among patients with diabetes and greater restenosis, vascular healing sequela, and possible early accelerated arteriosclerosis cannot be established, because, unlike the randomized trial, the present study is based on survivors only, and the requirement for follow-up angiography compromises the inherent comparability between patients randomly assigned to either PTCA or CABG. Still, the survival requirement implicit in undergoing follow-up angiography may have resulted in selective removal of some of the most severely diseased patients with diabetes. This may underestimate the true relative difference in increase in jeopardized myocardium after initial angioplasty between patients with and without diabetes.

Use of conventional angioplasty only in BARI does not permit evaluation of the potential benefit of new percutaneous technologies, including stenting and coated stents. Thus, our results may be used as a benchmark against which the relative performance of stenting and coated stents can be judged between patients with and without diabetes. Still, in BARI, a broad range of patients was enrolled, including those with complex multilesion disease and small vessels; these patients are typically underrepresented or absent in clinical trials that involve stenting or coated stents.

Finally, the adverse effect of diabetes on increased jeopardized myocardium after initial angioplasty was not evident at protocol-directed 5-year angiography. We postulate that this absence of late effect is predominantly the result of selection bias and frequent intercurrent revascularization before the 5-year angiogram rather than equivalent progression of atherosclerosis between PTCA patients with and without diabetes. Indeed, among randomized BARI patients not included in the present study who received initial PTCA (n=391), crude 5-year mortality was 45% in those with diabetes compared with 13% in those without diabetes. Moreover, among PTCA study participants with 5-year protocol-directed angiography, 49% had undergone repeat PTCA or bypass surgery before 5-year angiography.

**Study Limitations**

All study patients experienced a reduction in jeopardized myocardium at the initial revascularization procedure and underwent follow-up angiography. The effect of these selection criteria was a modestly less-diseased group of patients than all BARI-randomized patients; thus, results may not generalize to all patients with severe multivessel disease. Additionally, the requirement for follow-up angiography resulted in a relatively small group of patients who initially underwent CABG, particularly when subdivided by diabetes status.

**Conclusions**

After initial revascularization, diabetes adversely impacts midterm increase in percentage of jeopardized myocardium among PTCA-treated patients but not among CABG-treated patients. This differential effect occurs irrespective of whether follow-up angiography is undertaken for clinical or nonclinical purposes. The independent influence of this greater increase in total jeopardized myocardium on the relatively poor long-term survival among angioplasty patients with diabetes and multivessel disease requires investigation.

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