Improved Survival in Asymptomatic Diabetic Patients With High-Risk Spect Imaging Treated With Coronary Artery Bypass Grafting

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Background—The Bypass Angioplasty Revascularization Investigation trial demonstrated that symptomatic diabetics with multivessel coronary artery disease had a survival advantage with initial coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI). No published study has examined different treatments and outcome in asymptomatic diabetics.

Methods and Results—This study group consisted of 826 asymptomatic diabetics (age 62±12 years; 76% men) without known coronary artery disease who had abnormal myocardial perfusion during stress single photon emission computed tomography (SPECT). SPECT images were classified as low-, intermediate-, and high-risk. Early revascularization (CABG or PCI ≤4 months after SPECT) was performed in 76 patients. Survival (follow-up, 5.3±3.3 years) was compared in patients treated with CABG, PCI, or medical therapy. Revascularization (CABG or PCI) was performed in 54 of 261 patients with high-risk scans and was independently associated with improved survival ($\chi^2=4.55; P=0.03$ after multivariate adjustment). Subset analysis demonstrated that the survival advantage was confined to patients treated with CABG (n=39), with a 5-year survival CABG at 85%, PCI at 72%, and medical therapy at 67% ($P=0.02$ for 3 groups). Although CABG was associated with better survival, mortality remained high (3% per year). There was no survival advantage by treatment for patients with less-severe SPECT abnormalities.

Conclusions—These nonrandomized data suggest that CABG improves survival in asymptomatic diabetic patients with high-risk SPECT, although revascularization was performed infrequently in these patients. These results parallel those of the Bypass Angioplasty Revascularization Investigation trial in symptomatic diabetic patients. (Circulation. 2005; 112[suppl I]:I-311–I-316.)

Key Words: diabetes ■ coronary disease ■ coronary artery bypass grafting

Cardiovascular disease accounts for ≈75% of deaths in diabetic patients.1,2 The optimal treatment of diabetic patients with coronary artery disease (CAD) remains uncertain.3 A subset analysis of the Bypass Angioplasty Revascularization Investigation (BARI) trial indicated that symptomatic diabetic patients with multivessel CAD have a survival advantage when treated with coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI).4 Ischemia is frequently silent in diabetic patients and is associated with an adverse prognosis.5–7 The high prevalence of silent ischemia in diabetic patients has led to recommendations for more aggressive screening for CAD.7–10 However, there are no published data comparing the outcome with revascularization or medical therapy of asymptomatic diabetic patients who have CAD identified through noninvasive screening. In a previous study from our laboratory, 58% of asymptomatic diabetic patients without clinical evidence of CAD had abnormal stress single photon emission computed tomography (SPECT) images.11,12 The purpose of this study was to compare the outcome of these patients treated by CABG versus PCI versus medical therapy alone.

Methods

Study Group
The Mayo Clinic Institutional Review Board approved this study. This study represents the third in a series of studies11,12 investigating silent CAD in diabetic patients. Initially, the Mayo Clinic Nuclear Cardiology database was used to identify 67,836 consecutive patients who underwent stress SPECT imaging between January 1986 and December 2000. The first study11 examined the yield of stress SPECT in asymptomatic diabetic patients without clinical evidence of CAD. The following exclusion criteria were, therefore, applied: current cardiovascular symptoms (n=22,124); clinical history of documented myocardial infarction (n=19,511); prior PCI or CABG (n=22,841); entities associated with false-positive perfusion defects

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(left bundle branch block or paced rhythm) (n=4406); significant valvular heart disease (n=5679); multiple studies (n=9736); technically suboptimal scans (n=2408); and refusal of research authorization (n=77). The remaining 1738 asymptomatic diabetic patients without clinical evidence of CAD were examined in the first study.11,12 The second study12 identified which asymptomatic diabetic patients would benefit most from screening SPECT imaging, examined the results of coronary angiography in patients referred for angiography, and evaluated the prognosis in these patients. There are limitations to using the database alone to accurately identify asymptomatic patients without prior evidence of CAD. The medical records of all 1738 patients were, therefore, reviewed by hand to exclude patients with prior cardiovascular symptoms (only current symptomatology was recorded in the database), past performance of coronary angiography at an institution other than the Mayo Clinic, or failure to meet the current criteria for the definition of diabetes. This exercise resulted in the exclusion of an additional 311 patients, yielding a study population of 1427 patients for the second study.12 For the third (present) study, we elected to restrict the analysis of the impact of revascularization to patients with abnormal myocardial perfusion. Patients with normal stress SPECT imaging (n=601) were, therefore, excluded, resulting in a study population of 826 patients.

SPECT Imaging
These methods have been described previously.11,12 Patients underwent exercise treadmill testing (n=373) or pharmacological stress with adenosine or dipyridamole (n=402) or dobutamine (n=51). The SPECT images were displayed in 3 orthogonal planes (short axis, horizontal long axis, and vertical long axis). Radioisotope uptake in each segment was graded by a consensus of 2 experienced observers using a 5-point scoring system (0=absent; 1=severely decreased; 2=moderately decreased; 3=mildly decreased; and 4=normal) as described previously.11-15

Coronary Angiography, Left Ventricular Ejection Fraction, and Revascularization
Decisions to proceed with coronary angiography and revascularization were at the discretion of the attending clinicians. Data on “early” coronary angiography performed within 3 months after stress SPECT imaging has been reported previously.12 This time cut point has traditionally been used to characterize coronary angiography decisions that are likely strongly influenced by the results of stress SPECT imaging. Significant CAD was defined as a luminal stenosis of ≥50% in the left main coronary artery or ≥70% in left anterior descending artery, left circumflex artery, right coronary artery, or major branches.12,16 Left ventricular ejection fraction was ascertained by review of the medical record for standard methods that used radioisotope imaging, echocardiography, or invasive ventriculography within 3 months of SPECT imaging and before revascularization with either PCI or CABG. Early revascularization was defined as CABG or PCI performed ≤1 month after coronary angiography. This time frame was selected, because elective revascularization procedures at the Mayo Clinic in general are performed within 1 month of coronary angiography. These cut points have been used in prior studies comparing treatment modalities of patients with CAD.17,18

Follow-Up Data
Vital status was ascertained by review of Mayo Clinic registration records and interrogation of the Social Security Death Index. The mean follow-up was 5.7±3.3 years.

Statistical Analysis
Cardiovascular survival was estimated using the Kaplan-Meier method. The log-rank test was used to compare survival curves. Because of the limited number of patients who underwent PCI, analyses were performed for all patients who underwent revascularization combined (CABG or PCI) versus medical therapy alone and CABG versus PCI versus medical therapy alone. Multivariate models were constructed using the Cox proportional hazard models. Forward stepwise techniques were used to identify variables independently associated with the end points. Candidate variables were age, male gender, body mass index, peripheral arterial disease, renal insufficiency, hypertension, smoking, hyperlipidemia, left ventricular ejection fraction, and revascularization. Contingency tables were analyzed for association with a $\chi^2$ test. Comparisons of continuous variables were made with a Wilcoxon rank sum test. Statistical significance was P<0.05.

Results
Baseline Characteristics
The mean age for the study population was 62±12 years (76% men). Seven-hundred seventeen (86.8%) patients had type II diabetes; 381 patients (46.1%) used insulin (Table 1). A high-risk SPECT scan was present in 261 patients (32%). The mean SSS for patients with high-risk scans was 38.8±6.7. For patients without high-risk perfusion scans, the mean SSS was 51.6±2.5. Two hundred twenty-nine patients (27.7%) underwent coronary angiography, including 138 (60.3%) patients with high-risk SPECT scans. Seventy-six patients were treated with early revascularization, consisting of CABG in 48 and PCI in 28. Fifty-four of the 261 patients with high-risk scans (21%) underwent revascularization. Among the patients who underwent CABG, a left internal mammary graft was used in 92% of patients, and the mean number of vessels bypassed was 3.2±1.0. Among the 28 patients who had PCI, 42 total segments were treated, and stents were used in 34 of these segments. The number of patients who underwent 1-, 2-, and 3-vessel PCI were 24, 4, and zero, respectively. Overall, multivessel CAD, peripheral arterial disease, and CAD involving the left main and proximal left anterior descending segments were more common in patients who underwent CABG (Table 1).

Survival
We initially examined survival by treatment in the entire study population. Survival was similar in patients treated with revascularization versus medical therapy (P=0.28) for the entire population (Figure 1). Given the much higher referral to angiography and revascularization in patients with high-risk SSS, the second analysis was restricted to patients with high-risk scans. Survival was greater among asymptomatic diabetics who underwent CABG (5-year survival, 67% [95% CI, 60% to 74%; P=0.02 versus revascularization group). Subgroup analysis of the patients with high-risk scans by mode of revascularization found the greatest survival among asymptomatic diabetics who underwent CABG (5-year survival, 85%; [95% CI, 73% to 98%) versus those who underwent PCI (5-year survival, 72%; [95% CI, 52% to 100%) or medical therapy alone (5-year survival, 67%; [95% CI, 50% to 74%; P=0.02 for 3-group comparison) (Figure 3). Mortality in the CABG group remained high at 3% per year. Among the patients without high-risk perfusion abnormalities, there was no difference in survival according
to treatment (Figure 4) \((P=0.89\) for medical versus revascularization). For patients with high-risk SSS, the variables associated with mortality are shown in Table 2. By multivariate analysis, the impact of revascularization on the survival of patients with high-risk perfusion scans remained significant after adjustment for age, peripheral arterial disease, and renal insufficiency, which were independent predictors of death in these patients (Table 2).

### Discussion

For screening procedures to be justifiable in asymptomatic populations, the following criteria need to be fulfilled: (1) high prevalence of disease; (2) accuracy of the screening procedure; and (3) the intervention offered to the high-risk patients (and not to the general population) results in improved outcome. This study is the third in a series to evaluate the value of screening stress SPECT in asymptomatic diabetics.\textsuperscript{11,12} The first study showed a high prevalence of abnormal and high-risk SPECT scans in these patients.\textsuperscript{11} The second study demonstrated a high prevalence of severe CAD at angiography and a poor prognosis in patients with high-risk SPECT scans.\textsuperscript{12} The present investigation shows that CABG improves survival in asymptomatic diabetic patients with high-risk SPECT imaging.

No prior study has addressed the prognostic impact of revascularization in a purely asymptomatic diabetic population. In the randomized BARI study, 98% of patients, most of whom were unstable, had angina.\textsuperscript{19} In the recently published AHA/ACC 2004 Guideline Update for Coronary Artery Bypass Graft Surgery,\textsuperscript{20} CABG is recommended for asymptomatic patients with a large area of myocardial ischemia. This recommendation is based on expert opinion and is not

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Medical (N=750)</th>
<th>CABG (N=48)</th>
<th>PCI (N=28)</th>
<th>(P) Value Overall</th>
<th>(P) Value CABG vs Medical</th>
<th>(P) Value CABG vs PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, years</td>
<td>61.6±12.5</td>
<td>61.0±10.4</td>
<td>63.7±10.3</td>
<td>0.64</td>
<td>0.40</td>
<td>0.29</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>564 (75.2)</td>
<td>38 (79.2)</td>
<td>22 (78.6)</td>
<td>0.77 (0.54)</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>30.2±6.8</td>
<td>28.2±5.5</td>
<td>28.2±5.4</td>
<td>0.05 (0.06)</td>
<td>0.40</td>
<td>0.74</td>
</tr>
<tr>
<td>LVEF, n (%)</td>
<td>56.6±12.1</td>
<td>57.2±13.6</td>
<td>57.0±8.3</td>
<td>0.95 (0.88)</td>
<td>0.87</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Diabetic history

| Diabetes duration (years)     | 12.6±10.9       | 16.6±14.5  | 14.0±10.8 | 0.06 (0.10)         | 0.69                        |                       |
| Type I diabetes, n (%)        | 95 (12.7)       | 10 (20.8)  | 4 (14.3)  | 0.27 (0.11)         | 0.48                        |                       |
| Insulin use, n (%)            | 344 (46.1)      | 23 (47.9)  | 14 (50.0) | 0.89 (0.80)         | 0.86                        |                       |
| Oral agent, n (%)             | 296 (39.8)      | 20 (41.7)  | 10 (35.7) | 0.88 (0.80)         | 0.61                        |                       |
| Gly-HgbB, n (%)               | 9.2±2.7         | 9.9±3.3    | 9.9±2.9  | 0.09 (0.15)         | 0.87                        |                       |
| Hypertension, n (%)           | 520 (69.3)      | 29 (60.4)  | 18 (64.3) | 0.38 (0.20)         | 0.74                        |                       |
| Hyperlipidemia, n (%)         | 390 (52.0)      | 21 (43.8)  | 14 (50.0) | 0.53 (0.27)         | 0.60                        |                       |
| Smoker, n (%)                 | 448 (59.7)      | 28 (58.3)  | 16 (57.1) | 0.95 (0.85)         | 0.92                        |                       |
| Family history of CAD, n (%)  | 203 (27.1)      | 16 (33.3)  | 4 (14.3)  | 0.20 (0.35)         | 0.07                        |                       |
| Renal insufficiency, n (%)    | 197 (26.9)      | 8 (17.0)   | 10 (35.7) | 0.18 (0.14)         | 0.07                        |                       |
| PAD, n (%)                    | 282 (37.8)      | 21 (43.8)  | 13 (46.4) | 0.48 (0.41)         | 0.82                        |                       |

SPECT SSS, n (%)  

| Low-risk (53–55)              | 256 (34.1)      | 1 (2.1)    | 2 (7.1)   | <0.001             | <0.001                      | 0.01                   |
| Medium-risk (48–52)           | 287 (38.3)      | 8 (16.7)   | 11 (39.3) |                       |                             |                       |
| High-risk (>74)               | 207 (27.6)      | 39 (81.3)  | 15 (53.6) |                       |                             |                       |
| Coronary angiography (%)      | 155 (20.7)      | 48 (100)   | 28 (100)  | <0.001             | <0.001                      | <0.001                 |
| No. of diseased vessels       |                |            |           | <0.001             | <0.001                      | <0.001                 |
| 0                             | 39 (25.2)       | 0 (0.0)    | 0 (0.0)   | <0.001             | 0.001                       | 0.008                  |
| 1                             | 47 (30.3)       | 6 (12.5)   | 14 (50.0) |                       |                             |                       |
| 2                             | 36 (23.2)       | 17 (35.4)  | 11 (39.3) |                       |                             |                       |
| 3                             | 33 (21.3)       | 25 (52.1)  | 3 (10.7)  | <0.001             | 0.001                       | 0.008                  |
| Left main, n (%)              | 9 (5.8)         | 10 (20.8)  | 0 (0.0)   | <0.001             | 0.001                       | 0.008                  |
| Proximal LAD, n (%)           | 41 (39.1)       | 23 (47.9)  | 10 (47.6) | 0.02 (0.006)        | 0.18                        |                       |

Medical therapy, n (%)  

| Aspirin                      | 194 (26.9)      | 13 (28.9)  | 8 (29.6)  | 0.92 (0.78)         | 0.95                        |                       |
| ACE inhibitor                | 235 (31.9)      | 17 (35.4)  | 11 (40.7) | 0.57 (0.62)         | 0.65                        |                       |
| \(\beta\)-Blocker            | 111 (14.8)      | 9 (18.8)   | 3 (10.7)  | 0.62 (0.46)         | 0.35                        |                       |

ACE indicates angiotensin converting enzyme; BMI, body-mass index; Gly-Hgb, glycosylated hemoglobin; LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease.
Evidence based (level of evidence C). The present investigation focused on asymptomatic diabetics with abnormal SPECT myocardial perfusion and demonstrated that CABG was associated with improved survival among patients with high-risk perfusion abnormalities but not among those with less-severe SPECT imaging results. Our findings parallel those of Hachamovitch et al.\textsuperscript{21} in a study of combined nondiabetic and diabetic patients with a high prevalence of angina, they reported greater survival with revascularization for patients with large ischemic territories (i.e., involving $>20\%$ of the left ventricle) but not for patients with smaller amounts of ischemia. However, given the unique nature of atherosclerosis, differences in the subjective perception of ischemia, and other comorbidities in diabetics, it is difficult to extrapolate the conclusions of that study and others to asymptomatic diabetic patients.\textsuperscript{2,3,13,21} Our study, therefore, provides important new information regarding the management of asymptomatic diabetic patients with abnormal SPECT.

The mode of revascularization in diabetics has been the subject of intense debate. The BARI trial reported a highly significant difference in survival for predominantly symptomatic diabetics with multivessel disease who were randomized to CABG compared with PCI.\textsuperscript{4} This improved survival was not evident among diabetics in the BARI registry, in which patients with multivessel, proximal LAD disease and multiple lesions ($\geq 4$) were more likely to undergo CABG.\textsuperscript{22,23} Among the patients with high-risk SPECT imaging in the current study, the benefit of revascularization on survival was present for CABG but not PCI. Although our results parallel those of the randomized BARI study, precise comparisons are difficult, because asymptomatic patients comprised only $2\%$ of randomized BARI patients and only $7\%$ of diabetics in the BARI registry.

The paucity of data on the impact of revascularization in asymptomatic diabetic patients is likely responsible for the conservative approach to these patients observed in the current study. Despite the presence of abnormal myocardial perfusion, only $28\%$ of these patients subsequently underwent coronary angiography, including only $53\%$ of those with high-risk SPECT studies. Moreover, among the patients found to have CAD involving the left main, proximal left anterior descending artery, or 3-vessel disease, $55\%$ did not undergo revascularization and were treated with medical therapy alone.
Despite our results, the incremental benefit of revascularization has not been definitely proven because of the nonrandomized nature of this study. Presently, the potential benefit of early revascularization in diabetics is the subject of 2 ongoing National Heart, Lung and Blood Institute-sponsored randomized trials.3 Of note, enrollment criteria for BARI 2 Diabetes trial include objective evidence of ischemia and coronary anatomy suitable for revascularization, but patients with or without cardiovascular symptoms may participate. Clearly, such randomized, controlled trials are needed. Hopefully, enough asymptomatic patients will be included to analyze this subset. However, the statistical power for this subset is not clear at this stage, and the results of this study will not be available for several years.

Although the present investigation suggests improved survival after early revascularization in asymptomatic diabetics with high-risk SPECT scans, the mortality of revascularized patients remained high (3.8% per year for all revascularized patients; 3.0% per year for patients who had CABG). Moreover, whereas revascularization was not associated with greater survival in the absence of a high-risk scan, the 5-year survival of patients with less-severe abnormalities was 83%. Thus, mild SPECT abnormalities are associated with adverse outcomes as has been demonstrated in prior investigations.24,25 Several mechanisms have been postulated to account for the poorer outcome of diabetics after revascularization, including greater endothelial dysfunction, a prothrombotic state, adverse remodeling, increased protein glycosylation, intimal hyperplasia, and vascular matrix deposition.2 Of note, glycemic control in the current study population was relatively poor at the time of SPECT imaging (mean glycosylated hemoglobin, 9.9% for revascularized patients). Improved glycemic control predicts cardiovascular events and should be a principal target in the management of these patients.

**Study Limitations**

The major limitation consists of a retrospective, nonrandomized study and selection of therapy at the discretion of the individual physicians caring for these patients. The observed association between CABG and improved survival is strengthened by adjustment for confounding variables but, nonetheless, cannot substitute for a randomized trial. Whereas the current investigation suggests an association between early CABG and improved survival for patients with high-risk perfusion abnormalities, these conclusions were derived from nonrandomized data. Furthermore, the number of patients who underwent revascularization was relatively small with respect to the number of patients initially screened. Whereas the sizes of these subgroups may reflect a broad application of CAD screening, the diabetic patients in this study may represent the more extreme spectrum of “sicker” asymptomatic diabetic patients. This possibility has been discussed in prior publications.11,12 In the Detection of Ischemia in Asymptomatic Diabetics study, the yield of stress SPECT imaging was not as high as in the present study.8 The true prevalence of CAD was not established in the entire study population, although prior studies have observed similar rates of referral for coronary angiography among asymptomatic diabetic patients26 and in symptomatic populations of diabetics and nondiabetics.27 Information on therapy, including diabetes control and risk-factor reduction, during the follow-up period was not available. Finally, therapy in this study population predated the clinical use of drug-eluting stents and off-pump bypass surgery, both of which have been associated with improved outcomes.

**Clinical Implications**

The present investigation suggests improved survival with CABG for asymptomatic diabetics with high-risk perfusion abnormalities. These data, although nonrandomized, add support for the broader implementation of CAD screening, as advocated by the current American Diabetes Association guidelines, for the purposes of improving the cardiovascular outcomes in patients with diabetes.

**References**


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