Impact of Completeness of Revascularization on Long-Term Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus

Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)

Leonard Schwartz, MD; Marnie Bertolet, PhD; Frederick Feit, MD; Francisco Fuentes, MD; Edward Y. Sako, MD; Mehrdad S. Toosi, MD; Charles J. Davidson, MD; Fumiaki Ikeno, MD; Spencer B. King III, MD

Background—Patients with diabetes have more extensive coronary disease than those without diabetes, resulting in more challenging percutaneous coronary intervention or surgical (coronary artery bypass graft) revascularization and more residual jeopardized myocardium. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial provided an opportunity to examine the long-term clinical impact of completeness of revascularization in patients with diabetes.

Methods and Results—This is a post hoc, nonrandomized analysis of the completeness of revascularization in 751 patients who were randomly assigned to early revascularization, of whom 264 underwent coronary artery bypass graft surgery and 487 underwent percutaneous coronary intervention. The completeness of revascularization was determined by the residual postprocedure myocardial jeopardy index (RMJI). RMJI is a ratio of the number of myocardial territories supplied by a significantly diseased epicardial coronary artery or branch that was not successfully revascularized, divided by the total number of myocardial territories. Mean follow-up for mortality was 5.3 years. Complete revascularization (RMJI \(\leq 0\)) was achieved in 37.9% of patients, mildly incomplete revascularization (RMJI \(>0\leq 0.33\)) in 46.6%, and moderately to severely incomplete revascularization (RMJI \(>0.33\)) in 15.4%. Adjusted event-free survival was higher in patients with more complete revascularization (hazard ratio, 1.14; \(P = 0.0018\)).

Conclusions—Patients with type 2 diabetes mellitus and less complete revascularization had more long-term cardiovascular events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00006305.

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Key Words: coronary artery disease ■ type 2 diabetes mellitus ■ coronary artery bypass grafting ■ percutaneous coronary intervention

The number of Americans with diabetes has tripled from 1980 to 2007, reaching 17.4 million.\(^1\) Diabetes has become progressively disproportionately represented in patients undergoing coronary revascularization. In the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Percutaneous Coronary Intervention (PCI) Registry, the prevalence of diabetes increased from 23% in 1997 to 1999 to 31% in 2004.\(^2,3\) Similarly, in the Nationwide Inpatient Sample, the percentage of patients undergoing coronary artery bypass graft (CABG) having diabetes increased from 16.7% in 1988 to 1990 to 33.9% from 2003 to 2005.\(^4\) Patients with type 2 diabetes mellitus (T2DM), compared with those without diabetes, have a greater and more extensive atherosclerotic burden associated with impaired compensatory remodeling of the arterial wall.\(^5\) In addition, patients with diabetes have more diffuse coronary disease\(^6\) with a 2-fold higher rate of total occlusions and a tendency toward more distal disease.\(^7\) Thus revascularization is often more challenging in patients with diabetes and consequently may be less complete, whether by CABG or PCI.\(^8,9\) The effect of completeness of revascularization on long-term cardiovascular outcomes has not been studied in...
a large, prospective trial exclusively enrolling patients with T2DM. Such an opportunity was available in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, a large, multicenter, randomized study focusing on patients with T2DM and coronary artery disease (CAD) with stable symptoms.

**WHAT IS KNOWN**

- Patients with diabetes mellitus compared with those without diabetes have a more extensive atherosclerotic coronary burden and more diffuse disease.
- Complete revascularization is a greater challenge because coronary angiography may underestimate the disease proximally resulting in less than ideal angioplasty and distally limiting graftability.
- The BARI 2D design permitted investigators to choose the revascularization strategy that was thought to be the most suitable for the individual patient and therefore offered the best opportunity for completeness of revascularization.
- Despite this, incomplete revascularization occurred in 59% of patients undergoing PCI and 68% of those having CABG.

**WHAT THE STUDY ADDS**

- Over a 5-year follow-up, incomplete revascularization was shown to have an adverse effect on outcome, and this increased with the greater amount of residual jeopardized myocardium.

**Methods**

The BARI 2D protocol, the baseline angiographic findings, and the 5-year outcome data have been published. A total of 2368 patients with T2DM who were suitable for elective coronary revascularization were enrolled from 49 clinical sites. The protocol was approved by the institutional review boards of all participating sites, and all subjects provided informed consent. BARI 2D had a 2×2 factorial design with simultaneous randomization into a cardiac revascularization and a glycemic control strategy. For the cardiac treatment hypothesis, patients were randomly assigned to either early revascularization (placed in the CABG or PCI stratum by physician choice) plus aggressive medical therapy or aggressive medical therapy alone with the option of deferred revascularization if clinically warranted. For the glycemic control hypothesis, patients were randomly assigned to either an insulin-providing or insulin-sensitizing strategy for treatment of T2DM.

Before random assignment, all patients had undergone coronary angiography that was reviewed at the study site to confirm suitability for either CABG or PCI. The only angiographic exclusion was the presence of significant left main coronary disease defined as ≥50% diameter stenosis. In addition to angiographic evaluation at the site, baseline and postprocedure coronary angiograms were read centrally by the BARI 2D Angiographic Core Laboratory at Stanford University, using a standardized protocol (described below). This report focuses on the patients who were randomly assigned to early revascularization and who underwent an initial procedure (either CABG or PCI) within 3 months of the entry diagnostic coronary angiogram. Patients with prior revascularization were excluded from this analysis.

The angiographic definitions, creation of, rationale, and protocol for obtaining the myocardial jeopardy index (MJI) have been published. The MJI was originally used in the BARI and has been used in many subsequent publications. The data for this report are derived from the central laboratory reading. Significant lesions were defined as those with ≥50% diameter stenosis by caliper measurement. The territory score of each major epicardial coronary artery was determined by the size of the terminating vessel, the number and size of the branches, and the dominance or codominance. Each branch and distal terminating vessel was given a numeric score of 3, 2, or 1, corresponding to the size of territory supplied, large, medium, or small, respectively. In this way, the total number of myocardial territories and their size were determined for each patient. The MJI is the number of myocardial segments supplied by significantly diseased main coronary arteries or their branches divided by the total number of myocardial territories. All lesions (≥50% diameter stenosis) in main epicardial coronary arteries (left anterior descending [LAD], circumflex [CX], right coronary artery [RCA]) or their branches would contribute to the MJI, regardless of their location (ie, proximal, mid, or distal). However, proximal lesions would result in a higher MJI than more distal lesions because of the greater number of territories affected. This was determined in all patients, based on the diagnostic study before the procedure. For patients undergoing PCI, the residual MJI (RMJI) was remeasured postprocedure and reduced by the number of territories successfully revascularized. For patients undergoing CABG, the RMJI was recalculated based on the location of the distal anastomoses recorded by the surgeon and the segments served by the grafts. For further details on the calculation of the MJI, refer to the initial publication that describes and illustrates the methodology. As an example of MJI derivation, a patient with a significant proximal lesion in a dominant RCA supplying 7 posterolateral territories, a lesion in a second diagonal of the LAD supplying 2 of 10 anteroseptal LAD territories and no significant lesions in the CX supplying 7 anterolateral territories has a total of 24 territories, of which 9 are jeopardized, yielding an MJI of 9/24, or 0.375. Thus, before intervention, 37.5% of the myocardium is in jeopardy. The RCA lesion is treated successfully by PCI, and so the posterolateral territories are completely revascularized but the 2nd diagonal lesion is not treated. The residual post-MJI (RMJI) = 2/24 or 8.3%.

Complete revascularization (CR) was defined as a RMJI=0, mildly incomplete revascularization (MICR) as an RMJI >0 and ≤33 (to generally correspond to a single vessel residual diseased region), and moderately to severely incomplete revascularization (MISCR) as an RMJI of >33 (to generally correspond to multivessel residual diseased regions). The example above had mildly incomplete revascularization.

The degree of completeness of revascularization was at the discretion of the surgeon or PCI operator at the time of the procedure. The protocol did not mandate complete revascularization. The reason(s) for not revascularizing an artery was stated by the surgeon or PCI operator.

**End Points**

The primary end point of BARI 2D was mortality, and the principal secondary end point was the composite of death/myocardial infarction (MI)/stroke. For this analysis, we also considered MI and subsequent procedure individually. The death end point was assessed on all patients by final contact if possible and if necessary by death index and obituary searches. The other end points were assessed on each patient as long as they were followed; the mean follow-up was 5.3 years.

**Statistical Analysis**

This report compares nonrandomized groups from the BARI 2D trial. Continuous variables were compared with Student t test or Wilcoxon nonparametric statistics and categorical variables with \( \chi^2 \) statistics. For the time-to-event analysis, time zero was defined as the date of the initial procedure. If specified as a staged PCI procedure before the procedure started, then the time zero was defined as the date of the final stage. Cox proportional hazards regression models that included adjustment covariates were used to determine the effect of completeness of revascularization (ie, RMJI, whether modeled as...
a continuous or a categorical variable) on the outcomes. Adjustment covariates included the following baseline measures: glycemic randomization assignment, sex, age, race, ethnicity, hypertension status, smoking status, serum creatinine, insulin use, HbA1c, duration of diabetes, history of congestive heart failure (CHF), body mass index, left ventricular ejection fraction, high-density lipoprotein, triglycerides, and low-density lipoprotein. The statistical interactions between the initial revascularization procedure (CABG or PCI) and RMJI for the outcomes were tested within a Cox proportional hazards model. The analysis was performed on the entire group, in addition to stratifying on initial revascularization procedure (CABG or PCI). These analyses only included events that occurred after the initial procedure. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

### Results

Of 2368 patients enrolled in BARI 2D, 763 were selected for the CABG stratum, of whom 378 were randomly assigned to early revascularization and 1605 were selected for the PCI stratum, of whom 798 were randomly assigned to early revascularization. Of the 378 patients assigned to CABG, 339 actually underwent an initial CABG and 7 underwent an initial PCI. Of the 798 patients assigned to PCI, 758 actually underwent an initial PCI and 8 underwent an initial CABG. This yields 1112 patients (347 CABG and 765 PCI) available for this analysis. An additional 256 patients were excluded because of a prior revascularization procedure; 3 patients were excluded because of incomplete angiographic information; and 28 patients were excluded because the MJI procedure was zero. Finally, 41 CABG patients and 33 PCI patients were excluded because the interval between the diagnostic angiogram and the revascularization procedure exceeded 3 months. This leaves 751 patients for this analysis, of whom 264 underwent CABG and 487 underwent PCI.

Of the 751 patients, there were 531 men and 220 women, with mean age of 62.3 ± 9.0 years, ranging from 33.9 to 85.5 years, and 31%, 37%, and 31% had 1, 2, and 3 diseased regions, respectively (Table 1). The mean and SD of the preprocedure MJI was 40.1 ± 21.0 (P < 0.0001). The crude percentages of patients' completeness of revascularization categories are shown in Table 1 overall and by initial procedure (ie, PCI or CABG). Overall, 37.9% of patients had complete revascularization, 46.6% had mildly incomplete revascularization, and 15.4% had moderately to severely incomplete revascularization. There were significant differences in categorical completeness of revascularization by mode of therapy: patients undergoing CABG were less likely to have a complete revascularization (32.2% versus 41.1%) but also less likely to have moderately to severely incomplete revascularization than those undergoing PCI (12.5% versus 17.0%). Postprocedure mean RMJI was no different for patients undergoing CABG (14.9 ± 15.0) and PCI (15.6 ± 18.8) (P = 0.59). The mean number of stents in the PCI procedures was 1.40, and the mean number of grafts in the CABG procedures was 3.11.

Incomplete revascularization occurred in 59% of patients undergoing PCI; in 53%, this was intentional (ie, part of the pre-PCI strategy and usually due to inaccessible lesions or chronic total occlusions), whereas in 6% it was unintentional
and due to a variety of reasons, the most common being inability to cross the lesion with a wire or inability to advance the device into the lesion. Incomplete revascularization occurred in 68% of patients undergoing CABG; in 58%, this was the intended pre-CABG strategy (usually nongraftable territories), whereas in 10% it resulted from either small caliber and/or diseased distal vessels found at surgery.

In Table 2, the baseline data are shown for the entire cohort and across the 3 categories of RMJI. Those with higher RMJI were older, but there were no other baseline risk factor differences. The number of lesions at baseline was significantly higher for the higher categories of RMJI.

Hazard ratios for cardiovascular outcomes for both categorical degrees of completeness of revascularization, compared with a reference of complete revascularization, and for 10-point increments of incompleteness, as measured by RMJI, are displayed in Table 3. This analysis is adjusted for baseline covariates. The end point of death was significantly more likely with higher degrees of incomplete revascularization by continuous analysis but not by categorical analysis. Subsequent revascularization procedures occurred with greater frequency, with higher degrees of incomplete revascularization by either method of analysis. MI outcome was not significantly more likely with higher degrees of incomplete revascularization by either mode of analysis. The composite end point of death/MI/stroke was significantly more likely with higher degrees of incomplete revascularization whether analyzed categorically or continuously.

Table 4 shows the end points by initial revascularization procedure. Subsequent revascularization is significantly more likely with less complete revascularization but only in patients undergoing PCI by continuous analysis. Death, MI, and the composite end points are unaffected by completeness for either revascularization procedure.

Discussion
This analysis demonstrates that incomplete revascularization has an adverse effect on long-term cardiovascular outcomes in diabetic patients undergoing elective myocardial revascularization. The outcome of death was significantly more likely with higher degrees of incomplete revascularization when analyzed as a continuous variable but not by categorical analysis. The fact that there is more power in continuous analysis may explain this discrepancy. Except for MI in patients receiving CABG, end points were more likely with less complete revascularization with the continuous analysis. When analyzed by mode of revascularization, only repeat procedures for patients undergoing PCI were more likely with higher degrees of incomplete revascularization.

There is prior evidence supporting the negative impact of residual nonrevascularized myocardium after a revascularization procedure both in the general population and in the diabetic cohort. A single-center, multivariate retrospective analysis of 1034 patients, undergoing an initial CABG (of whom 32% had diabetes) demonstrated that incomplete revascularization was an independent risk factor for cardiac and all-cause mortality at 3.3±1.6 years of follow-up.17 In this study, 13.1% of the patients with diabetes had incomplete revascularization compared with 7.6% of those without diabetes. In a single-center study of >500 patients with multivessel CAD who underwent PCI, the incidence of cardiac death and need for any repeat revascularization was significantly lower in patients with complete versus incomplete revascularization. In the subgroup of patients with diabetes, complete revascularization was associated with better rates of the primary composite end point of cardiac death, MI, and revascularization.18 In the New York State’s PCI registry of multivessel diseased patients during the bare metal stent era (1997–2000), incomplete revascularization occurred more commonly in patients with than in those without DM (71.9% versus 67.8% [P<0.001]),19 and in the DES era (2003–2004) this had actually increased to 72.9% compared with 67.1%, respectively (P<0.001).20 In each era and overall, incomplete revascularization had an adverse impact on the adjusted rate of long-term survival. In the latter era,20 the composite end point of mortality/MI over 18-month follow-up in diabetic patients was 11.9% with incomplete revascularization versus 8.5% with complete revascularization (adjusted hazard ratio, 1.29; 95% CI, 1.01–1.65; P=0.04). A study of patients with multivessel CAD and diabetes undergoing PCI in Israel confirmed that completeness of revascularization had an independent, positive impact on 5-year survival and survival free of MI.21

One major advantage of the BARI 2D design is that it permitted investigators to select the mode of revascularization that was considered to be best suited for each patient. This undoubtedly resulted in a lower likelihood of incomplete revascularization in the patients undergoing PCI. In all studies with head-to-head comparisons of PCI and CABG, more complete revascularization is generally found in the latter even when “complete revascularization” is mandated for both procedures. In the current analysis of patients in BARI 2D randomly assigned to early revascularization, the preprocedure MJI and the extent of coronary disease (ie, number of disease regions) were higher in patients undergoing CABG than those undergoing PCI. This is not unexpected, given the general tendency to select a strategy of CABG in patients with DM and a greater degree of CAD. The mean postprocedure MJI was the same. More PCI patients had complete revascularization, which probably is because 43% had single-vessel disease compared with 9% in the CABG stratum, but more PCI patients than CABG patients had moderately to severely incomplete revascularization.

The current analysis has several limitations and provisos. First, this was a post hoc, nonrandomized analysis. BARI 2D was not a comparison of CABG versus PCI. Our analysis is not a comparison of CABG versus PCI. The patients in this analysis were randomly assigned to an early revascularization treatment but the decision as to which mode of revascularization was chosen was a clinical one, based on the extent and complexity of the coronary disease. The CABG patients in our analysis had more diseased regions, more lesions, and a higher baseline MJI than the PCI patients. The PCI patients had fewer lesions requiring treatment, fewer lesions treated than the CABG patients, and, not surprisingly, more often had complete revascularization. However, because of the inherent limitations of PCI compared with CABG in revascularizing certain disease territories (eg, chronic total occlusions), more
Table 2. Baseline Table

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=751)</th>
<th>0–RMJI (n=285)</th>
<th>0&lt;RMJI≤33 (n=350)</th>
<th>33&lt;RMJI≤100 (n=116)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin providing</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Randomization group, %</td>
<td>48.9</td>
<td>42.5</td>
<td>53.7</td>
<td>50</td>
<td>0.018*</td>
</tr>
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<td><strong>Strata, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCI</td>
<td>65.1</td>
<td>70.5</td>
<td>58.3</td>
<td>72.4</td>
<td>0.0011*</td>
</tr>
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<td>CABG</td>
<td>34.9</td>
<td>29.5</td>
<td>41.7</td>
<td>27.6</td>
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<tr>
<td><strong>Male sex, mean, median</strong></td>
<td>1.29, 1</td>
<td>1.32, 1</td>
<td>1.27, 1</td>
<td>1.28, 1</td>
<td>0.36</td>
</tr>
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<td><strong>Age at study entry, y, mean, median</strong></td>
<td>62.28, 62</td>
<td>61.21, 61</td>
<td>62.87, 63</td>
<td>63.12, 64</td>
<td>0.035*</td>
</tr>
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<td><strong>BMI, mean, median</strong></td>
<td>31.47, 31</td>
<td>31.93, 31</td>
<td>31.29, 31</td>
<td>30.87, 30</td>
<td>0.22</td>
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<td><strong>Region of world, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>United States</td>
<td>60.2</td>
<td>61.4</td>
<td>60.9</td>
<td>55.2</td>
<td>0.30</td>
</tr>
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<td>Canada</td>
<td>15.2</td>
<td>14.7</td>
<td>13.7</td>
<td>20.7</td>
<td></td>
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<tr>
<td>Mexico</td>
<td>4.7</td>
<td>4.6</td>
<td>4.3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>16.1</td>
<td>14</td>
<td>18.6</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Czech Republic/Austria</td>
<td>3.9</td>
<td>5.3</td>
<td>2.6</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td><strong>Race/ethnicity, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White non-Hispanic</td>
<td>64.8</td>
<td>61.4</td>
<td>68.6</td>
<td>62.1</td>
<td>0.35</td>
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<td>17.4</td>
<td>17.9</td>
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<td>Hispanic</td>
<td>14.1</td>
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<td>14.7</td>
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<td>Asian non-Hispanic</td>
<td>3.2</td>
<td>4.6</td>
<td>2.9</td>
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<tr>
<td>Other non-Hispanic</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
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<tr>
<td><strong>Current smoker, %</strong></td>
<td>12.6</td>
<td>14.1</td>
<td>11.4</td>
<td>12.2</td>
<td>0.60</td>
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<tr>
<td><strong>Currently taking insulin, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>72.6</td>
<td>71.9</td>
<td>73.1</td>
<td>73</td>
<td>0.94</td>
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<td>Yes</td>
<td>27.4</td>
<td>28</td>
<td>26.9</td>
<td>27</td>
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<td><strong>Duration of DM, mean, median</strong></td>
<td>10.01, 9</td>
<td>9.44, 7</td>
<td>10.26, 9</td>
<td>10.62, 10</td>
<td>0.32</td>
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<tr>
<td><strong>Core: HbA1c, %, mean, median</strong></td>
<td>7.43, 7</td>
<td>7.46, 7</td>
<td>7.38, 7</td>
<td>7.54, 7</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>History of hypoglycemic episode, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>79.2</td>
<td>76.2</td>
<td>79.6</td>
<td>85.2</td>
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<tr>
<td>Yes</td>
<td>20.8</td>
<td>23.8</td>
<td>20.4</td>
<td>14.8</td>
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<tr>
<td><strong>Core: HDL, mg/dL, mean, median</strong></td>
<td>37.09, 36</td>
<td>37.30, 36</td>
<td>37.28, 36</td>
<td>35.98, 37</td>
<td>0.53</td>
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<td><strong>Core: Triglyceride, mg/dL, mean, median</strong></td>
<td>165.03, 139</td>
<td>174.24, 144</td>
<td>163.12, 134</td>
<td>148.16, 136</td>
<td>0.12</td>
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<td><strong>Core: LDL, mg/dL, mean, median</strong></td>
<td>89.88, 89</td>
<td>88.60, 90</td>
<td>90.21, 89</td>
<td>92.03, 91</td>
<td>0.71</td>
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<td><strong>Serum creatinine, mg/dL, mean, median</strong></td>
<td>1.05, 1</td>
<td>1.02, 1</td>
<td>1.06, 1</td>
<td>1.08, 1</td>
<td>0.050</td>
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<td><strong>Site LVEF, mean, median</strong></td>
<td>54.98, 60</td>
<td>55.94, 60</td>
<td>54.53, 60</td>
<td>54.00, 60</td>
<td>0.41</td>
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<td><strong>History of CHF req tx, %</strong></td>
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<td>No</td>
<td>94.7</td>
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<td>5.3</td>
<td>5.3</td>
<td>4.3</td>
<td>8.6</td>
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<tr>
<td><strong>Sitting BP &gt;140/90, %</strong></td>
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<td>No</td>
<td>72</td>
<td>76.4</td>
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<td>28</td>
<td>23.6</td>
<td>31.8</td>
<td>27.4</td>
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<td><strong>No. of lesions ≥20%, mean, median</strong></td>
<td>4.63, 4</td>
<td>3.24, 3</td>
<td>5.24, 5</td>
<td>6.20, 6</td>
<td>&lt;0.0001*</td>
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<td><strong>Lesions ≥50% stenosis, mean, median</strong></td>
<td>2.68, 2</td>
<td>1.62, 1</td>
<td>3.12, 3</td>
<td>3.97, 4</td>
<td>&lt;0.0001*</td>
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<td><strong>Lesions ≥70% stenosis, mean, median</strong></td>
<td>1.11, 1</td>
<td>0.63, 0</td>
<td>1.29, 1</td>
<td>1.76, 1</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Computed No. of vessels with lesions ≥50%, %</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>4.1</td>
<td>9.5</td>
<td>0.6</td>
<td>1.7</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>1</td>
<td>33.3</td>
<td>56.5</td>
<td>22</td>
<td>10.3</td>
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<td>2</td>
<td>37.8</td>
<td>26.7</td>
<td>46.6</td>
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<tr>
<td>3</td>
<td>24.8</td>
<td>7.4</td>
<td>30.9</td>
<td>49.1</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial jeopardy, mean, median</strong></td>
<td>47.96, 46</td>
<td>36.28, 33</td>
<td>50.89, 50</td>
<td>67.80, 68</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

RMJI indicates residual postprocedure myocardial jeopardy index; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; and BP, blood pressure.

*Statistically significant, P<0.05.
PCI patients than CABG patients after the procedure had moderately severe myocardial jeopardy.

Second, jeopardized myocardium is not necessarily equivalent to residual ischemic myocardium and may not always be viable. Neither preoperative nuclear imaging nor viability testing was required for entry into the study.

Third, only 1 coronary score, the MJI, and 1 index of extent of revascularization, the RMJI, were used. Newer scores, for example, SYNTAX, have become available since the inception of BARI 2D. SYNTAX is a reflection of the severity of disease and may have an impact on outcome not only in patients randomly assigned to early revascularization but also assigned to optimal medical treatment alone. The distribution of SYNTAX scores is currently being examined in the entire BARI 2D cohort but was not available for this substudy.

Another measurement often used today to determine the need to treat individual lesions particularly with PCI is the fractional flow reserve, but this was not a requirement for BARI 2D enrollment and was not routinely performed during the entry diagnostic coronary angiogram. Therefore, it could not be used for this analysis. The MJI score defines a significant lesion as $\geq 50\%$ diameter stenosis. This has been the definition used for all BARI trials and has been consistently reliable from a prognostic standpoint. Contemporary studies evaluating new imaging techniques and validating new markers such as gene expression levels in CAD detection have used a $50\%$ diameter stenosis threshold, and the early experimental studies by Gould et al showed that at this threshold during stress regional flow distribution abnormalities appeared. The heretofore referred to score of the SYNTAX trial defined a significant lesion as $50\%$ reduction in luminal diameter by visual assessment and the actual percent diameter above that is not considered in the algorithm. Nonetheless, other studies use a different definition of a flow limiting lesion. For

### Table 3. End Point Table

<table>
<thead>
<tr>
<th>End Point</th>
<th>Categorical RMJI, CR (n=285)</th>
<th>MICR (n=350)</th>
<th>MSICR (n=116)</th>
<th>P Value</th>
<th>Continuous RMJI, HR for 10 Unit Change (n=751)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.0</td>
<td>1.54 (0.93, 2.64)</td>
<td>2.02 (1.07, 3.76)</td>
<td>0.08</td>
<td>1.13 (1.01, 1.25)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Subsequent procedure</td>
<td>1.0</td>
<td>1.41 (0.92, 2.18)</td>
<td>2.42 (1.47, 3.95)</td>
<td>0.002†</td>
<td>1.24 (1.13, 1.36)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>MI</td>
<td>1.0</td>
<td>2.28 (1.21, 4.52)</td>
<td>2.34 (1.05, 5.18)</td>
<td>0.03*</td>
<td>1.14 (1.00, 1.29)</td>
<td>0.047*</td>
</tr>
<tr>
<td>Death or MI or stroke</td>
<td>1.0</td>
<td>1.87 (1.25, 2.86)</td>
<td>2.21 (1.34, 3.61)</td>
<td>0.002†</td>
<td>1.14 (1.05, 1.23)</td>
<td>0.0018†</td>
</tr>
</tbody>
</table>

RMJI indicates residual postprocedure myocardial jeopardy index; HR, hazard ratio; CI, confidence interval; and MI, myocardial infarction.

*Nominally significant but not significant after multiple testing.
†Significant after adjusting for multiple testing.

Death adjusted for continuous and categorical outcomes 0.05/2 = 0.025. All other end points adjusted for 3 end points, each continuous and categorical 0.05/6 = 0.008.

### Table 4. End Point Table Stratified by Initial Procedure Received

<table>
<thead>
<tr>
<th>End Point</th>
<th>Categorical RMJI, PCI (n=200)</th>
<th>CABG (n=85)</th>
<th>P Value</th>
<th>Continuous RMJI, HR for 10 Unit Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>PCI</td>
<td>1.0 (n=204)</td>
<td>0.52</td>
<td>1.09 (0.96, 1.22)</td>
<td>0.18</td>
</tr>
<tr>
<td>Subs. Proc.</td>
<td>CABG</td>
<td>1.0 (n=146)</td>
<td>0.054</td>
<td>1.25 (1.02, 1.51)</td>
<td>0.050*</td>
</tr>
<tr>
<td>MI</td>
<td>PCI</td>
<td>1.0 (n=83)</td>
<td>0.02*</td>
<td>1.28 (1.17, 1.40)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Death or MI or stroke</td>
<td>CABG</td>
<td>1.0 (n=33)</td>
<td>0.75</td>
<td>0.77 (0.47, 1.12)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

RMJI indicates residual postprocedure myocardial jeopardy index; HR, hazard ratio; CI, confidence interval; CR, complete revascularization; MICR, mildly incomplete revascularization; MSICR, moderately to severely incomplete revascularization; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; and MI, myocardial infarction.

*Nominally significant but not significant after multiple testing.
†Significant after adjusting for multiple testing.

Death adjusted for continuous and categorical outcomes 0.05/2 = 0.025. All other end points adjusted for 3 end points, each continuous and categorical 0.05/6 = 0.008.
example, the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation (COURAGE)27 used a ≥70% diameter stenosis.

Fourth, there was an unavoidable delay between the diagnostic entry angiogram and the revascularization procedure. The BARI protocol mandated a maximum of 1 month between random assignment and treatment, but the delay between angiography and treatment could be longer. For this analysis, patients with CABG or PCI longer than 3 months from the diagnostic angiogram were excluded. Still, it is possible that significant disease progression may have occurred during this interval with previously not significant lesions reaching significance and not being recognized as such and therefore not treated. This would have potentially resulted in a greater baseline and postprocedure myocardial jeopardy score than calculated from the diagnostic angiogram.

Finally, although BARI 2D was a randomized trial, patients were not randomly assigned to complete versus incomplete revascularization. Such studies are difficult to execute and to interpret because of restricted inclusion criteria and high rates of crossover. It is possible that the inability to achieve complete revascularization especially with CABG may be a marker of, for example, more diffuse disease and portend a less favorable outcome in itself.

Nonetheless, this represents the largest cohort of patients with T2DM enrolled in a prospective, randomized trial in which detailed adjudicated data were gathered and interpreted in Core Laboratories. Our major finding is that patients with T2DM and CAD who have incomplete revascularization are more likely to have adverse long-term clinical outcomes regardless of the revascularization strategy. This has important implications for the care of such patients.

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References


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Impact of Completeness of Revascularization on Long-Term Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus: Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)

Leonard Schwartz, Marnie Bertolet, Frederick Feit, Francisco Fuentes, Edward Y. Sako, Mehrdad S. Toosi, Charles J. Davidson, Fumiaki Ikeno and Spencer B. King III

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