Influence of the Bypass Angioplasty Revascularization Investigation National Heart, Lung, and Blood Institute Diabetic Clinical Alert on Practice Patterns
Results from the National Cardiovascular Network Database
Darren K. McGuire, MD, MHSc; Kevin J. Anstrom, PhD; Eric D. Peterson, MD, MPH

Background—In 1995, the Bypass Angioplasty Revascularization Investigation (BARI) found that patients with diabetes had a survival benefit when treated with surgical revascularization versus balloon angioplasty, prompting a National Heart Lung and Blood Institute (NHLBI) “Clinical Alert.” The influence of the BARI findings and of the Clinical Alert on practice patterns is unknown.

Methods and Results—The practice patterns of coronary revascularization among patients with diabetes and multivessel coronary artery disease (CAD) were analyzed using data collected in 1994 to 1997 from 13 centers participating in the National Cardiovascular Network. The study population included patients with diabetes and multivessel CAD who underwent elective coronary revascularization (n=9619). Over the 4 years of the study, the Clinical Alert had no significant impact on the proportion of diabetic patients undergoing percutaneous revascularization (28.6% before versus 26.8% after the Clinical Alert; P=0.06). Among individual hospitals, the probability of diabetic patients receiving percutaneous revascularization varied by >13-fold (4.3% to 56.6%). Adjusting for clinical factors and the BARI Clinical Alert did not alter this variability. Among the investigators surveyed, although 91% were aware of the Clinical Alert and 76% felt the findings were valid, >50% felt the Clinical Alert had limited or no impact on their personal or institution’s care patterns.

Conclusions—Limited consensus exists regarding the most appropriate method of revascularization for diabetic patients with multivessel CAD. The results from a large, randomized, clinical trial and subsequent Clinical Alert had no measurable impact on this practice variability. (Circulation. 2003;107:1864-1870.)

Key Words: diabetes mellitus ▪ coronary disease ▪ revascularization ▪ bypass ▪ angioplasty

The Bypass Angioplasty Revascularization Investigation (BARI) compared the effect of percutaneous transluminal coronary angioplasty (PTCA) with coronary artery bypass graft (CABG) surgery among patients with multivessel coronary artery disease (CAD).1 Funded by the National Heart, Lung, and Blood Institute (NHLBI) at a cost of >$35 million, the trial found that these 2 treatment strategies had similar long-term clinical outcomes. However, among patients with medically treated diabetes, CABG was associated with an almost 50% reduction in 5-year mortality compared with PTCA (18.4% versus 34.5%),1,2 a difference that has persisted through 7 years of follow-up.3 These findings prompted the NHLBI to release a “Clinical Alert” on September 21, 1995, recommending CABG over PTCA for patients with medically-treated diabetes and multivessel CAD requiring initial revascularization.4

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The primary purpose of the present study was to evaluate the influence of the BARI trial diabetic findings and the associated NHLBI Clinical Alert on practice patterns. Using data from the National Cardiovascular Network (NCN) Coronary Revascularization Database, we evaluated the rates of percutaneous versus surgical revascularization among diabetic patients meeting BARI clinical eligibility criteria before and after the Clinical Alert release. We also examined the major clinical predictors of percutaneous coronary intervention (PCI) versus CABG, compared revascularization strategies among individual centers, examined the rates of use of coronary stents, and surveyed the principal investigators about their impressions of revascularization issues in diabetic patients.

Methods

Study Population
The NCN project involves 28 US hospitals that provide data on all coronary revascularization procedures to a central coordinating center. The NCN centers, which range from community hospitals with modest cardiac volume to high-volume tertiary referral centers,
Baseline characteristics were compared using χ² tests for discrete variables and Kruskal-Wallis tests for continuous variables. A nonlinear mixed logistic regression model was used (SAS version 8.2) to test the association between the Clinical Alert and revascularization strategy. The response variable was PCI, and the hospitals were considered random effects. The fixed effects portion of the model was constructed using backward variable selection with significance set at 0.05, using univariate predictors (P<0.05) as candidate variables. Sensitivity analyses examined if either the date of the manuscript publication or the date of catheterization as a continuous variable coded as the number of days from beginning of the study interval (January 1, 1994) was statistically associated with PCI rates.

To adjust for possible confounding due to differences in patient mix before and after the alert, a propensity score model was developed based on patient and hospital characteristics to estimate each individual’s probability of undergoing revascularization before the Clinical Alert. Patients were categorized into 5 groups based on the estimated propensity score, and PCI rates were calculated using the method of direct adjustment. This method was also used to test possible associations between time period (ie, before or after the Clinical Alert) and revascularization strategy among individual hospitals and types of medical facilities. All statistical tests were 2-sided with a significance level of 0.05.

Physician Survey
All 29 principal investigators (cardiac surgeons and interventionalists) from the 13 NCN sites were asked to respond to a survey (Appendix 2) about the influence of the BARI diabetic finding on practice patterns at his or her institution.

Results
Patient Population
Between 1994 and 1997, 126,838 patients underwent either PCI or CABG at the 13 NCN centers; 31,896 (25.1%) of these patients had medically treated diabetes. Among these patients, 9,619 (30.2%) had multivessel CAD and were eligible for the BARI diabetic component; this subset was used for the present analyses.

Baseline Characteristics
Table 1 presents baseline demographic and clinical information by treatment strategy. Patients undergoing PCI versus CABG were younger, more often female, more often minority, less likely to require insulin, and more likely to have renal insufficiency and a prior myocardial infarction. PCI patients were less likely to have congestive heart failure, hypertension, chronic lung disease, and peripheral vascular disease. PCI patients also had better systolic function and less severe CAD severity, %

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCI (n=2644)</th>
<th>CABG (n=6975)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65 (56, 72)*</td>
<td>66 (59, 72)*</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>42.4</td>
<td>39.5</td>
</tr>
<tr>
<td>Race, %</td>
<td>White</td>
<td>84.8</td>
</tr>
<tr>
<td>Black</td>
<td>7.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Other</td>
<td>7.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>40.8</td>
<td>38.6</td>
</tr>
<tr>
<td>Prior CHF, %</td>
<td>14.9</td>
<td>23.8</td>
</tr>
<tr>
<td>Prior hypertension, %</td>
<td>67.0</td>
<td>69.9</td>
</tr>
<tr>
<td>Prior PVD, %</td>
<td>12.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Prior COPD, %</td>
<td>11.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Renal insufficiency, %</td>
<td>10.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Insulin treated, %</td>
<td>43.7</td>
<td>47.9</td>
</tr>
<tr>
<td>CAD severity, %</td>
<td>3-Vessel</td>
<td>31.2</td>
</tr>
<tr>
<td>2-Vessel with proximal LAD</td>
<td>26.2</td>
<td>16.3</td>
</tr>
<tr>
<td>LVEF, %*</td>
<td>47 (45, 50)</td>
<td>47 (40, 55)</td>
</tr>
<tr>
<td>CCS class 3 or 4 angina, %</td>
<td>82.4</td>
<td>84.3</td>
</tr>
<tr>
<td>Moderate or severe MR, %</td>
<td>3.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Values are percentage of patients or median (interquartile range). MI indicates myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society; and MR, mitral regurgitation.

Influence of the Clinical Alert on Practice Patterns
Overall, 27.5% of the population underwent PCI and 72.5% underwent CABG. Neither the release of the Clinical Alert on September 21, 1995 (28.6%) before versus 26.8% after; P=0.06), nor the publication of the main BARI article on July 25, 1996 (28.0% before versus 26.8% after, P=0.20), altered the proportion of diabetic patients undergoing PCI procedures compared with CABG (Figure 1). Although patients with 3-vessel CAD were less likely to have PCI than those with 2-vessel CAD throughout the study period, the Alert did not alter treatment patterns significantly in either patient subgroup (14.9% versus 13.6%, P=0.16; 49.8% versus 47.4%, P=0.16, respectively).

Table 2 displays the variables included in the regression model. The strongest predictor of treatment was CAD severity. Specifically, after controlling for other factors, patients...
with 3-vessel versus 2-vessel CAD were much less likely to undergo PCI versus CABG. Similarly, among patients with 2-vessel CAD, those with proximal left anterior descending artery stenosis were much less likely to undergo PCI. The presence of insulin treatment, chronic obstructive pulmonary disease, increased age, moderate or severe mitral regurgitation, Canadian Cardiovascular Society angina class 3 or 4, and history of congestive heart failure also decreased the likelihood of PCI. Other significant predictors of PCI included renal insufficiency and female sex. After multivariable adjustment, patients treated after the clinical alert were slightly more likely to receive PCI compared with those treated before the alert (odds ratio, 1.15; 95% confidence interval, 1.01 to 1.31; \(P = 0.04\)). When the date of revascularization was included as a continuous variable in the model, which also adjusted for clinical case-mix, use of PCI tended to increase over time (odds ratio, 1.06 per 365 days; 95% confidence interval, 1.00 to 1.12; \(P = 0.05\)).

### TABLE 2. Major Predictors of Percutaneous vs Surgical Revascularization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2)-Vessel CAD without proximal LAD*†</td>
<td>35.1</td>
</tr>
<tr>
<td>(2)-Vessel CAD with proximal LAD*†</td>
<td>20.6</td>
</tr>
<tr>
<td>CCS angina class 1/2†</td>
<td>13.6</td>
</tr>
<tr>
<td>No history of COPD</td>
<td>6.2</td>
</tr>
<tr>
<td>Mitral regurgitation (none/mild)‡</td>
<td>5.8</td>
</tr>
<tr>
<td>Diabetes not requiring insulin</td>
<td>5.6</td>
</tr>
<tr>
<td>Female sex</td>
<td>4.8</td>
</tr>
<tr>
<td>Decreasing age (per decade)</td>
<td>3.8</td>
</tr>
<tr>
<td>No history of heart failure</td>
<td>3.4</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.8</td>
</tr>
<tr>
<td>After clinical alert</td>
<td>2.3</td>
</tr>
</tbody>
</table>

\(2\)-Vessel CAD indicates coronary artery disease; LAD, left anterior descending artery; CCS, Canadian Cardiovascular Society; renal insufficiency, serum creatinine \(\geq 2\) mg/dL; and COPD, chronic obstructive pulmonary disease.

\(\dagger\)Compared with patients with 3-vessel CAD. Fixed effects estimates from the nonlinear mixed model.

\(\ddagger\)Compared with CCS angina class 3/4.

\(\dagger\dagger\)Compared with moderate/severe mitral regurgitation.

**Figure 1.** Revascularization trends among BARI-eligible diabetic patients at 13 NCN centers, relative to the release of the BARI Clinical Alert and article publication.

**Figure 2.** Influence of the BARI Clinical Alert on revascularization strategies among BARI-eligible diabetic patients at each of the 13 NCN sites after direct adjustment for differences in patient mix. Each line depicts an NCN site reflecting the revascularization strategy before and after the BARI Clinical Alert. ○ indicates sites with no significant change in PCI rates after the BARI Clinical Alert relative to before; ● sites that significantly increased the rate of PCI.

#### Interhospital Variability in Revascularization Strategies

Overall, the use of PCI varied markedly among NCN sites (4.3% to 56.6%). Similar results were observed after stratification by number of diseased vessels, ranging from 25% to 84% among patients with 2-vessel CAD and from 1% to 46% among patients with 3-vessel CAD. After adjusting for clinical variables, there remained significant variability in the PCI rates, and significant changes in PCI likelihood after the Clinical Alert were observed in only 2 of 13 sites, both of which increased use of PCI (Figure 2).

#### Effect of Hospital Type on Treatment Selection

Overall, academic medical centers were more likely to use PCI compared with those not affiliated with a university (30.0% versus 23.3%; \(P = 0.001\)). After adjusting for case mix, the rate of PCI did not change after the Alert among academic centers (30.1% versus 32.4%; \(P = 0.07\)) or among centers not affiliated with a medical school (22.1% versus 23.4%; \(P = 0.39\)) (Figure 3). Centers that had participated in BARI were less likely to use PCI than non-BARI affiliated centers (24.6% versus 27.0%; \(P = 0.31\)) and among centers not affiliated with the BARI study (28.7% versus 29.5%; \(P = 0.46\)) were not statistically different.

#### Changes in PCI Strategy

During the study period, the use of intracoronary stents was emerging as an adjunct to conventional balloon angioplasty and may have contributed to the lack of effect of the Clinical Alert on practice. As expected, patients undergoing PCI after versus before the Clinical Alert were more likely to be treated with a coronary stent (50.8% versus 11.7%; \(P = 0.001\); Figure 4) However, we found no significant correlation between frequency of stent use among PCI cases and overall rate of PCI among centers (\(R^2 = 0.01\); Figure 5).

#### Physician Survey

We obtained survey responses from 21 of the 29 (72%) principal investigators at the 13 NCN sites, of whom 11 were
interventional cardiologists and 10 were cardiac surgeons. Among respondents, 19 (91%) were aware of the BARI diabetic findings, 16 (76%) felt the diabetic findings were valid, and 14 (67%) believed they were generalizable to current practice at their institution. However, 10 (48%) felt that the BARI findings had limited or no influence on their institution’s overall treatment decisions, and 11 (52%) felt the findings had limited or no impact on their personal practice patterns. The most common reasons offered for why practice patterns did not change markedly in the wake of BARI are presented in Figure 6; these included technological advances in revascularization care that made the BARI results obsolete (67%) and treatment preferences of the patient or referring physician (57%). Although 50% of cardiac surgeons viewed the BARI diabetic findings as “still relevant,” only 20% of interventional cardiologists felt the study applied to current practice due to therapeutic advances.

**Discussion**

The present study is the first to examine the influence of the BARI NHLBI Clinical Alert on revascularization treatment patterns in diabetic patients with multivessel CAD. On a positive note, patients with diabetes and multivessel CAD undergoing revascularization tended to be treated with CABG that most often included an internal mammary artery graft, a strategy consistent with the BARI findings. Also, the use of CABG versus PCI increased with increasing CAD severity, consistent with evidence of benefit from prior studies. However, substantial variability exists in practice patterns among individual hospitals, suggesting a lack of clinical consensus. Most importantly, we found that neither the Clinical Alert based on the BARI diabetic findings nor the subsequent publication of the BARI results measurably influenced practice patterns.

**National Institutes of Health Clinical Alerts**

The National Institutes of Health (NIH) adopted a policy in 1991 of publicizing results from NIH trials when the findings were felt to warrant an immediate change in clinical practice. These announcements are released as Clinical Alerts and Advisories on the National Library of Medicine website. To date, 23 Clinical Alerts and 5 Clinical Advisories have been released. The impact of the NIH Clinical Alert program on practice patterns is unclear. One recent study found that carotid endarterectomy use increased almost immediately after each of 2 NIH Clinical Alerts were released. In contrast, we found no change in practice patterns over an extended period after the BARI Clinical Alert. These discordant observations...
provide an opportunity to review some of the challenges associated with incorporating clinical trial evidence into practice.

**Dissemination of Information**
To affect practice, clinical trial findings must be disseminated. The BARI results were summarized in the Clinical Alert, presented at scientific meetings, reported in the media, and summarized in the scientific press. The Alert was distributed to physicians, other healthcare providers, medical societies, government agencies, medical school libraries, and the press, and it is archived on the National Library of Medicine website. The primary BARI article, along with several reports exploring the diabetes findings, have been published and widely discussed. As a result, >90% of the clinicians in our survey were aware of the BARI findings. Therefore, limited dissemination of the BARI results does not explain the lack of effect on clinical practice patterns.

**Study Validity and Generalizability**
Physicians must determine whether new study results are valid and applicable to their patients. The BARI study was a multicenter, randomized trial with complete follow-up that used “intention-to-treat” analysis, thereby meeting all of the major criteria for trial validity. Although the validity of the overall BARI results is not questioned, the appropriateness of the BARI diabetic substudy analysis has been debated. Specifically, the BARI diabetic findings are subject to all of the potential limitations of post hoc subgroup analyses.

The validity of subgroup analyses can be strengthened by results from other studies. Similar to BARI, other randomized trials have reported improved survival among diabetic patients with multivessel CAD treated with CABG versus PCI. Analyses from observational registries, however, have produced conflicting results. Despite these discrepancies, 76% of physicians surveyed thought the diabetic findings from BARI were valid, suggesting that these concerns do not account for their lack of influence on clinical practice.

**Technological Advances**
Another important challenge in the application of trial results involves the rapid advancement of healthcare technology, cited by 67% of the survey respondents as the major factor explaining the lack of influence of the Clinical Alert. Since BARI was initiated in 1988, coronary revascularization has changed markedly; it now includes the widespread use of coronary stents, glycoprotein IIb/IIIa receptor antagonists, and arterial bypass conduits. In the present study, we observed a 10-fold increase in the rate of stent use over the relatively short 4-year period. However, we observed no correlation between the rate of PCI and the respective institutional rate of stent use among PCI cases, suggesting that increasing use of intracoronary stents does not explain lack of influence of the Clinical Alert.

Whether these therapeutic advances will translate into improved outcomes compared with CABG among patients with diabetes and multivessel CAD undergoing PCI remains to be determined. Meta-analyses of glycoprotein IIb/IIIa trials suggest a mortality benefit associated with this class of drugs among the diabetic cohort, but their relative effects compared with CABG remain undefined. Further confounding these considerations is the emergence of drug-coated stents. The absence of a clinical consensus demonstrated by the present data and therapeutic advances in revascularization warrant continued clinical investigation.

**Clinical Receptivity and Economic Challenges**
The influence of data from randomized trials on clinical practice may also be affected by the receptiveness of the medical community to change and on the economic impact of these changes. For example, the 2 carotid endarterectomy Clinical Alerts promoted a strategy for stroke prevention beyond medical therapy that had been the mainstay of care and supported increases in diagnostic studies and surgical case volume. In contrast, the BARI results challenged the rapidly evolving clinical application of PCI as an alternative to CABG for the diabetic cohort. With diabetes affecting as many as 30% of patients undergoing PCI, surgical referral represents a significant decrease in caseload for interventional cardiologists. As such, it is not surprising that although 80% of the interventional cardiologists felt technological changes have made BARI “nonapplicable to current practice,” the majority of cardiac surgeons believe that the results are still relevant.

**Practice Variability**
Perhaps the most remarkable finding in our study was the marked variability in revascularization strategies among 13 US centers. Even after accounting for CAD severity and other clinical factors, the rate of PCI varied widely from one center to another. Similarly, the use of stents during the study period varied considerably among the participating centers. These observations underscore the need to develop clinical consensus as therapeutic strategies emerge.

**Limitations**
We used the BARI clinical inclusion criteria; we were unable to review coronary angiograms as was done in BARI and, therefore, our study population approximates the BARI population. The 13 NCN centers may not accurately reflect national practice patterns. However, these sites represent a diverse geographic area and a balanced mix of academic and nonacademic centers. Our database did not have detailed anatomic information that may influence treatment, nor did we have data on the use of glycoprotein IIb/IIIa antagonists. Finally, it was not our intent to compare the long-term clinical outcome data of these revascularization strategies.

**Conclusions**
At 13 clinical centers participating in the NCN, a remarkable degree of variability was observed in the rate of PCI versus CABG among diabetic patients with multivessel CAD, demonstrating a lack of clinical consensus regarding revascularization in this high-risk population. Among these centers, the BARI diabetes findings and the resulting Clinical Alert had
no measurable impact on overall clinical practice patterns or on intersite variability. The inability of the Clinical Alert, which was based on a multimillion dollar large-scale randomized trial, to modify clinical practice highlights a number of the challenges associated with implementing evidence-based medicine. These observations underscore the need for clinical trials to be planned, executed, analyzed, and reported in a timely fashion so that the findings are not obsolete before the results are known, and for clinicians to consistently apply the results of clinical trials to practice.

Appendix 1

NCN Sites Included in the Current Analyses
Abbott Northwestern Hospital, Minneapolis, Minn; Albany Medical Center, Albany, NY; Duke University Medical Center, Durham, NC; Jewish Hospital, Louisville, Ky; William Beaumont Hospital, Royal Oak, Mich; St John’s Hospital, Springfield, Ill; UPMC Shadyside Hospital, Pittsburgh, Pa; Indiana Heart Institute, Indianapolis, Ind; Bryan LGH Medical Center, Lincoln, Neb; Maine Medical Center, Portland, Maine; Good Samaritan Hospital, Naperville, Ill; Hillcrest Medical Center, Tulsa, Okla; Emory University System Health Care, Atlanta, Ga.

Appendix 2

NCN BARI Survey
Specialty (circle one):
Cardiology
Cardio-thoracic Surgery
(1) Are you familiar with the 1995–1996 BARI randomized trial analysis comparing treatment outcomes among diabetic patients with multivessel coronary disease?
Yes
No
(2) If yes, what is your understanding of the findings?
Diabetic patients with multivessel coronary disease undergoing initial revascularization:
A. have significantly improved survival if initially randomized to PTCA (versus CABG).
B. have equivalent survival outcomes regardless of initial randomized treatment.
C. have significantly improved survival if initially randomized to CABG (versus PTCA).

(3) Do you feel that the diabetic analysis of the BARI study is correct (ie, true, valid)?
A. Strongly believe that the findings are correct.
B. Tend to believe that the findings are correct.
C. Neutral with regard to the “correctness” of the findings.
D. Tend to believe that the findings are incorrect.
E. Strongly believe that the findings are incorrect.

(4) Do you feel that these findings are generalizable to the current practice at your hospital?
A. Strongly believe that the findings apply to the current practice at my hospital.
B. Tend to believe that the findings apply to the current practice at my hospital.
C. Neutral with regard to the generalizability of the findings to current practice at my hospital.
D. Tend to believe that the findings do NOT apply to the current practice at my hospital.
E. Strongly believe that the findings do NOT apply to the current practice at my hospital.

(5) Have the BARI randomized trial results influenced your personal treatment choices regarding revascularization in diabetic patients with multivessel coronary disease undergoing initial revascularization?
A. The results have had no impact on my treatment choices.

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