Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 44, No. 4, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.05.041

Native Coronary Disease Progression Exceeds Failed Revascularization as Cause of Angina After Five Years in the Bypass Angioplasty Revascularization Investigation (BARI)

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OBJECTIVES Coronary angiograms obtained five years following revascularization were examined to assess the extent of compromise in myocardial perfusion due to failure of revascularization versus progression of native disease.

BACKGROUND The Bypass Angioplasty Revascularization Investigation (BARI) randomized revascularization candidates between bypass surgery and angioplasty. Entry and five-year angiograms from 407 of 519 (78%) patients at four centers were analyzed.

METHODS Analysis of the distribution of coronary vessels and stenoses provided a measure of myocardial jeopardy that correlates with presence of angina. The extent to which initial benefits of revascularization were undone by failed revascularization versus native disease progression was assessed.

RESULTS Myocardial jeopardy fell following initial revascularization, from 60% to 17% for percutaneous coronary intervention (PCI)-treated patients compared with 60% to 7% for coronary artery bypass graft (CABG) surgery patients ($p < 0.001$), rebounding at five years to 25% for PCI and 20% for surgery patients ($p = 0.01$). Correspondingly, angina prevalence was higher at five years in PCI-treated patients than in surgery-treated patients (28% vs. 18%; $p = 0.03$). However, myocardial jeopardy at five years, and not initial treatment (PCI vs. surgery), was independently associated with late angina. Increased myocardial jeopardy from entry to five-year angiogram occurred in 42% of PCI-treated patients and 51% of CABG-treated patients ($p = 0.06$). Among the increases in myocardial jeopardy, two-thirds occurred in previously untreated arteries.

CONCLUSIONS Native coronary disease progression occurred more often than failed revascularization in both PCI- and CABG-treated patients as a cause of jeopardized myocardium and angina recurrence. These results support intensive postrevascularization risk-factor modification. (J Am Coll Cardiol 2004;44:766–74) © 2004 by the American College of Cardiology Foundation

The Bypass Angioplasty Revascularization Investigation (BARI) is a randomized study comparing a revascularization strategy of initial coronary angioplasty versus coronary surgery for management of patients with multivessel coronary disease. The primary BARI end point was five-year survival (1,2). To help understand the relationship of revascularization procedures to long-term angiographic and clinical outcome, four BARI clinical sites obtained repeat coronary angiography five years following study entry. The goals of the present analysis were to: 1) describe five-year angiographic history and outcome of BARI patients with multivessel coronary disease treated with initial percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) and 2) assess the relative impact of revascularization failure (e.g., restenosis or graft occlusion) versus native disease progression on the redevelopment of ischemic symptoms and myocardial jeopardy following revascularization by PCI or by surgery.

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METHODS

The BARI study protocol, including details regarding objectives, recruitment, inclusion, and exclusion criteria, data collection, procedural guidelines, angiographic definitions, and participating sites, has previously been published (3).

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Manuscript received June 30, 2003; revised manuscript received April 23, 2004, accepted May 4, 2004.

Abbreviations and Acronyms

BARI = Bypass Angioplasty Revascularization Investigation
CABG = coronary artery bypass graft surgery
CHC = Canadian Heart Classification
CI = confidence interval
LV = left ventricle/ventricular
OR = odds ratio
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction

Angiographic entry requirements included absence of severe left main disease and presence of multiterritory coronary disease. Patients were accepted as suitable candidates only if revascularization of clinically important stenoses were feasible by *both* angioplasty and surgery, as assessed by both cardiac surgeons and interventional cardiologists. There was no requirement for equivalent or complete revascularization. Balloon angioplasty was the only percutaneous technique utilized in BARI, although, at a few sites, stenting was available as a bailout device for threatened closure under a Food and Drug Administration-approved investigational protocol.

Patient population. Between August 1988 and July 1991, a total of 1,829 patients from 18 clinical centers were randomized in BARI. Four clinical sites volunteered to obtain five-year follow-up angiograms on all consenting five-year survivors out of the 572 randomized patients at their sites. Five-year angiography was accomplished in 407 of 519 surviving patients (78%). The sites were located at the Montreal Heart Institute (167 patients), Cleveland Clinic (107 patients), Duke University (79 patients), and Toronto General Hospital (54 patients). All patients completed five-year angiography within 12 months preceding or six months following their five-year anniversary. The mean follow-up interval was 5.0 years, with 94% of angiograms accomplished between 4.6 to 5.4 years. The presence of ischemic symptoms, use of hypolipidemic medications, and incremental hospitalizations were assessed from study entry to five-year follow-up by nurse-coordinator interviews at the clinical sites. A subset of 183 patients consented to one-year follow-up angiography in addition to five-year angiography (4).

Angiographic evaluation—BARI myocardial jeopardy index. Entry and subsequent procedure-related, intercurrent, and protocol-mandated one- and five-year angiograms were assessed by the Stanford angiography laboratory, blinded as to clinical outcomes. Angiographic data included identification of occluded and stenotic (≥50%) arteries and assessment of left ventricle (LV) myocardial jeopardy. The percentage of LV myocardium jeopardized by lesions ≥50% was based on the extent of distribution of the three main coronary arteries and all major branches. Each vessel was sized as small, medium, or large based on the vessel's length and extent of branching (Fig. 1) (5). Native coronary artery distribution was based on observer grading of the distal terminating arteries limited to those approximately ≥1.5 mm diameter. Terminating arteries for which size and territorial distribution were assigned potentially included 0-3 diagonal branches, 0-3 marginal branches, ramus intermedius, sub-branches for each of these, septal, posterolateral, posterior descending, and the distal terminations of the left anterior descending, circumflex, and right coronary arteries (Fig. 1).

A numerical score reflecting the size of LV territory supplied by each vessel was based on the ratio of the length of the terminating artery to the LV base to apex distance (and to a lesser extent the circumferential spread of smaller branches). A numerical LV score for each terminating artery was assigned based on extent of LV distribution: insignificant (ratio: <1/5; score: 0), small (ratio 1/5 to 1/3; score: 1); medium (ratio: 1/3 to 2/3; score: 2), and large (ratio: >2/3; score: 3;). The sum of scores for all terminal arteries reflects the coronary distribution to the entire LV myocardial territory. Regional myocardial jeopardy (anterior, inferior, and lateral) was computed as the ratio of units of anatomically relevant vessels containing a ≥50% stenosis to the sum of regional coronary territory scores.

The total units of myocardial territory per patient ranged from 8 to 38 (mean and median: 24), and the number of myocardial territory units jeopardized at study entry ranged from 3 to 27 (mean and median: 15). Entry myocardial jeopardy in this study ranged from 15% to 100% (mean and median: 60%). Coronary grafts not compromised by ≥ 50% stenosis were considered to relieve myocardial jeopardy in the grafted native vessel and its branches in both the anterograde and retrograde directions until encountering a ≥50% stenosis. Successful PCI (<50% residual stenosis and Thrombolysis In Myocardial Infarction [TIMI] flow grade 3), was considered to alleviate jeopardy distal to the treated stenosis.

An anatomically correct computer representation of native coronary vessel distribution combined with accurate placement of stenoses, graft insertions, and PCI results on a graphic "map" provided the basis for computer summation of global and regional myocardial jeopardies (5). Regions of prior myocardial infarction and wall-motion abnormalities were not excluded from the calculation of myocardial jeopardy so as to avoid assumptions of territory viability. Blinded recycling of 70 angiograms to assess reproducibility of myocardial jeopardy score yielded an intraclass correlation coefficient of 0.77 between duplicate readings (5), thereby indicating excellent reproducibility (6).

A caliper with electronic data output was used to measure stenosis minimum and reference diameters in a single-plane projection that adequately visualized maximum narrowing (7). Progression of preexisting disease and new disease required "visually unequivocal change." This definition was implemented in order to prevent minor numeric changes in caliper measurements that crossed a 50% stenosis threshold from having undue effects. Successful revascularization after

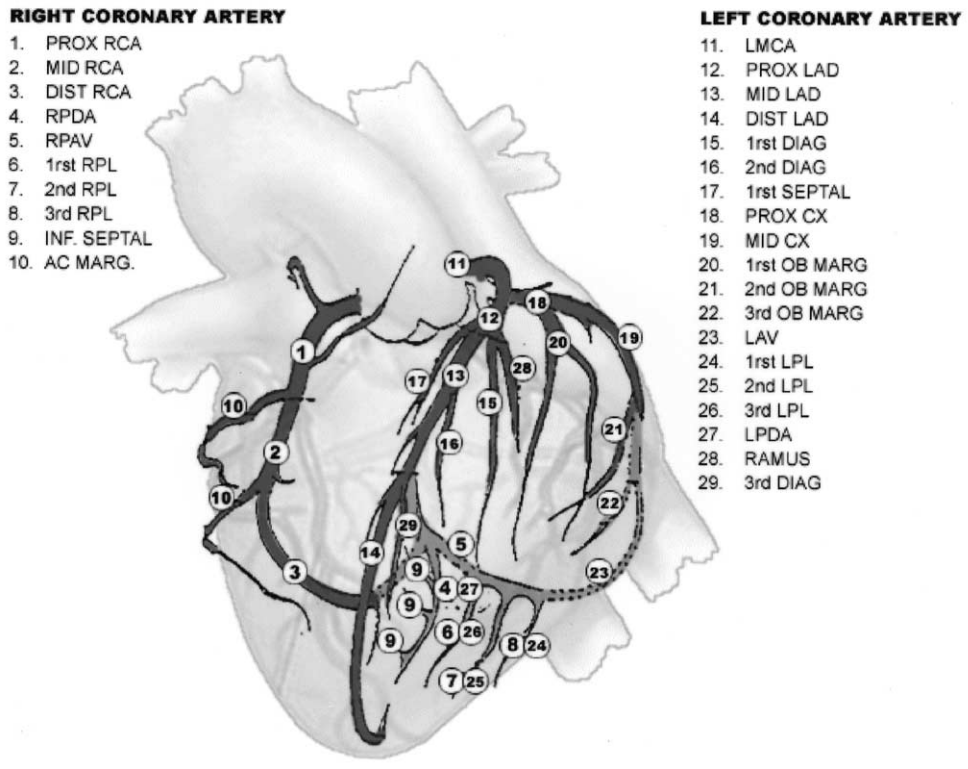

Figure 1. The coronary artery map used by Bypass Angioplasty Revascularization Investigations (BARI and BARI2D) is the basis for relative artery sizing, stenosis placement, and estimation of myocardial jeopardy. The map is a modification of the Coronary Artery Surgery Study (CASS) diagram with inclusion of additional branch segments.

an angioplasty required a residual stenosis of <50%, ≥20% change, and TIMI flow grade 3. At the five-year evaluation, success required <50% stenosis.

Both global and regional myocardial jeopardy were assessed on all entry, intercurrent, or postangioplasty and five-year angiograms. Immediate post-CABG myocardial jeopardy was assessed, assuming that all grafts placed during surgery are initially patent. Comparisons with preceding angiograms were performed using dual projectors to identify new stenoses exceeding 50% and to note changes in previously observed lesions.

Myocardial jeopardy observed on the final five-year angiogram was attributed to the most proximate cause. Thus, myocardium, jeopardized by a stenosis initially relieved by a successful PCI procedure, but jeopardized by restenosis at five-year angiography, is considered a revascularization failure. A graft occlusion or stenosis ≥50% in a graft is considered a revascularization failure. A new stenosis appearing distal to a graft insertion, or a new ≥50% native vessel stenosis observed on the five-year angiogram, each adds to myocardial jeopardy depending upon the amount of territory involved.

Statistical analysis. Baseline clinical and angiographic characteristics were compared between patients who had five-year angiography and both surviving and nonsurviving subsets of patients without five-year angiography by use of chi-square tests for categorical variables and Wilcoxon tests for continuous variables. Five-year rates of repeat revascularization were calculated, irrespective of whether or not PCI or CABG was performed as the first repeat procedure, and whether or not the first repeat procedure occurred within the initial six months of follow-up. These analyses were restricted to the 402 five-year angiography patients (PCI = 202; CABG = 200) who underwent their randomly assigned treatment (per protocol analysis). Risk-factor status (smoking history, aspirin use, lipid-lowering drug use) was also assessed at baseline and at five-year follow-up owing to its potential influence on long-term disease progression.

Logistic regression analysis was used for two purposes: 1) estimate risk of angina at five years in relation to baseline clinical and angiographic characteristics, including myocardial jeopardy; and 2) estimate impact of use of lipid-lowering drugs at study entry and during the first two years of follow-up on risk of increased jeopardized myocardium at the five-year angiographic assessment. Comparisons of myocardial jeopardy (at study entry, postinitial revascularization, and at five-year follow-up) overall, and within individual myocardial territories, were made between PCI- and CABG-treated patients by use of Student *t* tests. Within treatments, paired *t* tests were used to compare myocardial jeopardy at entry and five-year follow-up. Comparisons of causes of increased jeopardy at five years (i.e., revascularization failure vs. disease progression) and specific vessels (initially treated vs. untreated) with increased jeopardy were compared be-

Table 1. Comparison of Clinical and Angiographic Characteristics of 5-Year Angiography Patients and Other BARI Patients

Patient Characteristics	5-Yr Survivors at Protocol Angiography Sites		All Other BARI Patients	
	Patients With 5-Yr Angiography (n = 407)	Patients Without 5-Yr Angiography (n = 112)	5-Yr Surviving Patients (n = 1,087)	Patients Not Surviving to 5 Yrs (n = 223)
Entry features—clinical				
Age (mean ± SD)	59 (9)	61 (10)	62 (9)	65 (9)
Women	25%	43%	25%	28%
Aspirin use	71%	73%	77%	73%
Lipid-lowering drug	9%	13%	12%	10%
Current smoker	26%	39%	24%	22%
Prior MI	50%	60%	55%	58%
History of CHF	2%	8%	8%	26%
Severe angina at study entry*	75%	76%	80%	82%
Treated diabetes	12%	18%	18%	42%
Entry features—angiographic				
Three-vessel disease	34%	42%	43%	46%
Lesions ≥50% (mean ± SD)	3.3 (1.4)	3.5 (1.4)	3.5 (1.3)	3.8 (1.6)
One or more 100% lesions	28%	31%	40%	41%
Ejection fraction <50%	15%	28%	22%	37%
Percent myocardium jeopardized (mean ± SD)	60 (16)	61 (16)	62 (17)	63 (17)
Randomly assigned to PCI (vs. CABG)	50%	50%	49%	56%
Risk factor control at 5 yrs				
Aspirin use	87%	88%	84%	—
Lipid-lowering drug	44%	36%	36%	—
Current smoker	22%	14%	11%	—

*Canadian Heart Classification, (CHC) 3, 4, or unstable angina. Missing cases: lesions ≥50% stenosis (n = 3); 1 or more 100% lesions (n = 3); percentage myocardium jeopardized (n = 4); lipid-lowering drug (n = 2); history of myocardial infarction (MI) (n = 18); history of congestive heart failure (CHF) (n = 10); vessel disease (n = 3); ejection fraction (n = 475).

BARI = Bypass Angioplasty Revascularization Investigation; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

tween PCI- and CABG-treated patients by use of the Fisher's exact test. Any p values below 0.05 were considered statistically significant. Owing to the descriptive nature of this analysis (rather than hypothesis-confirming), no corrections were made for the multiple statistical tests performed.

RESULTS

Patient features of full BARI cohort. The 407 patients who had five-year angiography presented with a different and overall less severe clinical profile at study entry than the other five-year surviving and nonsurviving BARI patients (Table 1). Specifically, among survivors at the four protocol angiography sites, those who had angiographic evaluation at five years were younger (59 ± 9 vs. 61 ± 10 years; p = 0.01), and less likely to be female (25% vs. 43%; p = 0.0004), a current smoker (26% vs. 39%; p = 0.006), have a history of congestive heart failure (2% vs. 8%; p = 0.006), and have an ejection fraction <50% (15% vs. 28%; p = 0.009) than were patients without five-year angiography. Similar differences were observed comparing the 407 patients who had five-year angiography and the five-year surviving patients at nonprotocol angiography sites. Comparing the five-year angiography patients with nonsurvivors at all sites indicated younger age (59 ± 9 vs. 65 ± 9 years), less frequent history of congestive heart failure (2% vs. 26%), less treated diabetes (12% vs. 42%), fewer stenoses ≥50% at study entry (3.3 ± 1.4 vs. 3.8 ± 1.6), and less prevalent ejection fraction <50% (15% vs. 37%) (p < 0.0001 for all comparisons). Thus, the five-year angiography patients had the least severe clinical profile at study entry, the other BARI-surviving patients were intermediate in terms of risk, and patients who did not survive to five years had the most severe clinical and angiographic presentation.

At study entry, aspirin use was frequent among the four patient groups (71% to 77%); the prevalence of current smoking was modest (22% to 39%), and use of lipid-lowering drugs was infrequent (9% to 13%). Among the five-year survivors, aspirin use increased (used in 84% to 88% of all patients), and the use of lipid-lowering drugs increased by approximately 4-fold, yet remained below 50% (36% to 44% of all patients). The prevalence of smoking was essentially unchanged from study entry to five years among patients who underwent five-year angiography (26% vs. 22%). In contrast, smoking decreased markedly from study entry to five years in the other surviving patients at both protocol (39% to 14%) and nonprotocol (24% to 11%) angiography sites.

Initial and intercurrent revascularization of patients who underwent five-year angiography. The 202 PCI-treated patients who subsequently underwent five-year angiography had a mean of 3.2 lesions of ≥50% severity at study entry, of which, 2.6 lesions were attempted on the initial PCI (total 522 lesions) (Table 2). At the initial procedure, 65%

Table 2. Initial and Intercurrent Revascularization by Randomization Assignment

	Assigned to PCI (n = 202)	Assigned to CABG (n = 200)
Initial revascularization		
Vein grafts (CABG)	—	334
LIMA grafts (CABG)	—	198
Stenoses attempted (PCI)	522	—
Stenoses ≥50% attempted (PCI)	485	—
Stenoses ≥50% successfully treated	412 (85%)	—
LAD revascularization*	77%	90%
LCx/RCA revascularization*	86%	99%
Mean % of myocardium remaining jeopardized after initial revascularization*	17 ± 19	7 ± 11
Mean % of initial myocardial jeopardy remaining uncorrected*	28 ± 30	11 ± 16
Intercurrent revascularization		
No repeat revascularization*†	47%	92%
PCI without CABG	33%	7%
PCI within 6 months of randomization	18%	1%
PCI beyond 6 months of randomization	14%	6%
PCI first with subsequent CABG	6%	0%
CABG as first repeat revascularization	14%	0%
CABG at any time	20%	0%

*$p < 0.001$ for comparison of PCI- and CABG-assigned patients. †The incidence of any type of repeat revascularization was statistically different ($p < 0.001$) between PCI and CABG patients irrespective of whether or not they participated in the five-year angiography study.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LIMA = left internal mammary artery; RCA = right coronary artery; other abbreviations as in Table 1.

of PCI patients had all attempted lesions successfully dilated (<50% residual stenosis and TIMI flow grade 3), an additional 29% had ≥1 attempted lesion successfully dilated, and the remaining 6% had no lesions successfully dilated. On a lesion level, 412 of 485 attempted lesions (85%) with initial stenosis ≥50% were successfully dilated (Table 2). The 200 coronary surgery patients had a mean of 3.3 stenoses, with an average of 2.9 distal graft anastomoses per patient. A total of 198 internal mammary artery grafts and 334 saphenous vein grafts were placed at the initial surgery.

The higher mean number of stenoses treated in surgery patients than in PCI-treated patients was reflected in more frequent initial revascularization in both the left anterior descending artery (90% vs. 77%; $p = 0.0005$) and left circumflex and/or right coronary artery (99% vs. 86%; $p < 0.0001$) (Table 2). Similarly, separate consideration of the anterior, lateral, and inferior territories showed that the initial CABG procedure was significantly better than the initial PCI procedure for immediate improvement of jeopardy in all three territories (data not shown). Thus, the mean percentage of remaining myocardium jeopardized after initial revascularization was lower in surgery than in PCI patients (7% vs. 17%; $p < 0.0001$), as was the mean percentage of initial myocardial jeopardy remaining uncorrected (11% vs. 28%; $p < 0.0001$).

Fifty-three percent of PCI-treated patients had repeat revascularization within five years compared to only 8% of surgery-treated patients (Table 2). Among initial PCI-treated patients, 20% had bypass surgery during follow-up.

Angiographic evaluation at five years. Five-year angiography showed that of 412 successfully treated significant lesions, 61% had no interval restenosis, an additional 23% remained successful after interval retreatment, and the remaining 16% remained stenotic as a result of no retreatment or failed retreatment (Table 3). Of 334 vein grafts placed during the initial surgery, 16% had a ≥50% stenosis at five years and 13% were totally occluded (Table 3). Of 198 internal mammary artery grafts placed during the initial procedure, 11% had a stenosis or vessel kink ≥50%, and 5% were totally occluded at five years. The 223 distal anastomoses to the left anterior descending artery (left internal mammary artery: 198; vein grafts: 25) were more likely to be patent and free of significant stenoses at five years (91%) than were the 320 distal anastomoses to other vessels (82%).

On a patient level, myocardial jeopardy remained lower at five years for patients initially having surgery compared with those treated with PCI (surgery: 20% vs. PCI: 25%; $p = 0.01$) despite 53% of PCI-treated patients having additional revascularization procedures versus 8% of CABG-treated patients (Table 3). However, taking into account the more extensive initial revascularization performed in surgery patients, the mean change in myocardial jeopardy from post-initial revascularization to five-year assessment was actually higher in patients initially treated with surgery than in PCI-treated patients (13% vs. 8%; $p = 0.03$). This reflected a mix of graft failures, new disease, and few incremental procedures in surgery-treated patients. At five years, only

Table 3. Angiographic Evaluation at 5 Years by Randomization Assignment

Angiographic Measurements	Assigned to PCI (n = 202)	Assigned to CABG (n = 200)
Revascularization: lesion-level analysis		
PCI—no interval stenosis ≥ 50% (n = 412)*	61%	—
PCI—interval stenosis successfully treated	23%	—
PCI—interval stenosis not treated or failed retreatment	16%	—
Vein graft ≥ 50% stenosis (n = 334)	—	16%
Vein graft 100% stenosis	—	13%
LIMA graft ≥ 50% stenosis (n = 198)	—	11%
LIMA graft 100% stenosis		5%
Myocardial jeopardy: patient-level analysis		
Mean % of myocardium jeopardized		
Global—all territories†	25 ± 22	20 ± 20
Anterior territory‡	23 ± 33	14 ± 22
Lateral territory	22 ± 33	21 ± 30
Inferior territory	33 ± 44	29 ± 40
Change in % myocardium jeopardized between post-initial revascularization and 5-yr assessment†	8 ± 25	13 ± 17

*Includes the 412 of 485 significant lesions (≥ 50% stenosis) that were attempted and successfully treated (≤ 50% stenosis, Thrombolysis In Myocardial Infarction 3) at the initial PCI. †$p < 0.05$. ‡$p < 0.01$.
Abbreviations as in Tables 1 and 2.

the anterior territory retained a significantly lower jeopardy after CABG compared with PCI (Table 3).

Among the subset of 183 patients who underwent both one- and five-year angiography, the majority of angiographic benefit achieved (reduced jeopardized myocardium) was retained between years one and five of follow-up (Fig. 2A). Importantly, the relationship between angina and myocardial jeopardy is evident in the subset of 183 BARI patients who had baseline and both protocol-directed one-year and five-year angiography (Fig. 2B).

Angina at five-year follow-up and relationship to myocardial jeopardy. The proportion of five-year angiography patients with any angina, including unstable angina, fell from 96% at entry to 23% at five-year clinical follow-up. At five years, 28% of the 202 patients initially treated with PCI had angina compared with 18% of the 200 surgery-treated patients ($p = 0.03$). For PCI-treated patients, the prevalence of angina at five years was 21% for patients who had a subsequent coronary surgery, 22% for patients who had no incremental revascularization procedures, and 38% for patients who had intercurrent PCI without additional coronary surgery.

By logistic regression analysis, factors independently predictive of angina at five years included five-year myocardial jeopardy (odds ratio [OR], 1.22 per 10% increase, 95% confidence interval [CI], 1.09 to 1.36), severe angina at entry (OR, 2.20, 95% CI, 1.17 to 4.14), and ever a smoker at study entry (OR, 1.91, 95% CI, 1.09 to 3.35; Table 4). Thus, for each 10% increase in myocardial jeopardy at follow-up, the estimated odds of having angina increased by 22%. The heightened risk of angina at five years associated with greater myocardial jeopardy was similar between PCI- and surgery-treated patients.

Causes of increased myocardial jeopardy over time. Figure 3 shows the proximate cause of any increase in myocardial jeopardy from that assessed after completion of the initial revascularization procedure (PCI or CABG) to the five-year angiogram. This analysis considers only myocardial jeopardy present on the five-year angiogram that had not been mitigated by additional intercurrent revascularization procedures, and it identifies whether disease progression or revascularization failure most immediately preceded the final angiogram. Thus, individual patients could have disease progression and/or revascularization failure contributing to five-year myocardial jeopardy.

Myocardial jeopardy increases at five years were frequent and modestly more likely to occur in surgery- than in PCI-treated patients (51% vs. 42%; $p = 0.06$) (Fig. 3). This modest difference was principally due to more disease progression in surgery patients (40% vs. 30%; $p = 0.05$), as rates of increased jeopardy due to revascularization failure were similar by initial mode of revascularization (22% vs. 20%; $p = 0.62$, respectively). Overall, 9% of all patients who underwent five-year angiography showed evidence of increased jeopardy due to both revascularization failure and disease progression.

Figure 4 shows the distribution of sources of increased jeopardized myocardium among the subset of 158 patients who showed evidence of new or progressive disease on the five-year angiogram. Among PCI-treated patients, new or progressive disease was most likely to occur in untreated vessels only (65%) compared to initial treated vessels only (20%) and both treated and untreated vessels (14%). Similar results were observed among surgery patients (55% vs. 27% vs. 18%, respectively). Thus, coronary disease progression was more commonly seen in artery locations that, at study entry, had not been the target of the initial interventions.

Relation of lipid control and disease progression during follow-up. Use of lipid-lowering drugs increased sharply from baseline to five-year follow-up (from 9% to 44%), yet they

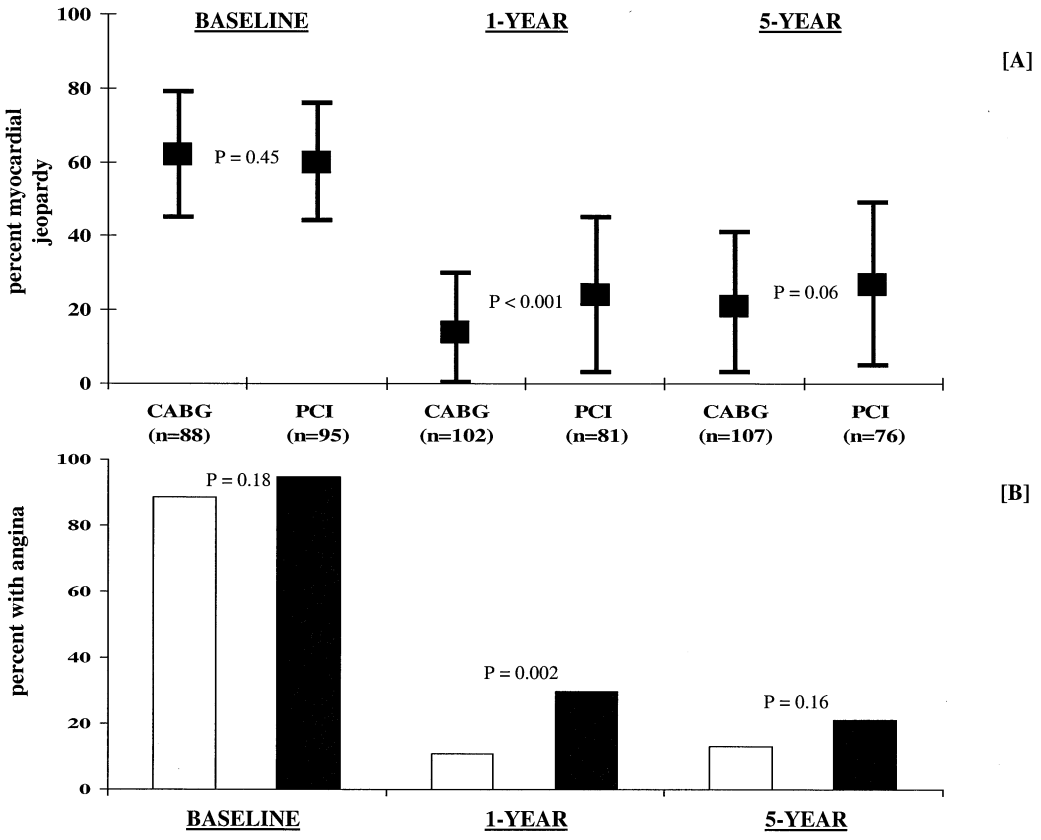

Figure 2. (A) The distribution of myocardial jeopardy scores at baseline, one-year, and five-year angiography among the subset of 183 patients with all three assessments. The **center block** on each vertical line depicts the mean myocardial jeopardy; the **horizontal hash marks** at each end of the vertical line represent myocardial jeopardy scores at ± 1 SD from the mean. The "n's" for the percutaneous coronary intervention (PCI) group reflect not having undergone prior coronary artery bypass graft surgery (CABG) at each follow-up assessment. **(B)** Histogram of the percentage of patients with angina at baseline, one-year, and five-year angiography by assigned mode of initial revascularization (CABG or PCI).

were used by less than half of all five-year angiography patients (Table 1). Eight percent of patients (32 of 398) reported use of hypolipid medications at both study entry and during two-year follow-up; 29% (115 of 398 patients) reported being nonusers at study entry while becoming first users during the initial two years of follow-up; and the remaining 63% (251 of 398 patients) reported being nonusers both at entry and during two-year follow-up. Compared to consistent nonusers of hypolipid medications, logistic regression analyses (with adjustment for age, gender, entry myocardial jeopardy, type of revascularization, and smoking status) showed that hypolipid medication users at study entry, but not those who became first users during two-year follow-up, had a significantly lower adjusted odds of increased myocardial jeopardy during follow-up (OR, 0.38, 95% CI, 0.16 to 0.89; OR, 1.11, 95% CI, 0.70 to 1.75, respectively). When the cause of increased myocardial jeopardy was limited to revascularization failure, there was a nonsignificant suggestion that use of hypolipid

Table 4. Logistic Regression Analysis of Entry Clinical and Angiographic Features Associated With Angina at 5 Years (n = 401 Patients Who Underwent Their Randomly Assigned Treatment)

Entry Feature	Odds Ratio	95% Confidence Interval	p Value
Angiographic (continuous variable)			
Myocardial jeopardy at 5 yrs (per 10% increase)	1.22	1.09–1.36	0.0003
Clinical (discrete variable)			
Severe angina at entry (CHC 3, 4, or unstable angina)	2.20	1.17–4.14	0.01
Current or former smoker at baseline	1.91	1.09–3.35	0.02

Other variables considered include age, gender, initial mode of revascularization (PCI or CABG), totally occluded lesion, diffuse lesion, number of significant lesions, history of diabetes, MI, or CHF, regular exercise at baseline, percentage of new disease at five years, percentage of disease progression at five years. In a separate model that included initial mode of revascularization (PCI or CABG), the interaction effect between mode of revascularization and percentage jeopardized myocardium at five years was not statistically significant (p = 0.51).

Abbreviations as in Table 1.

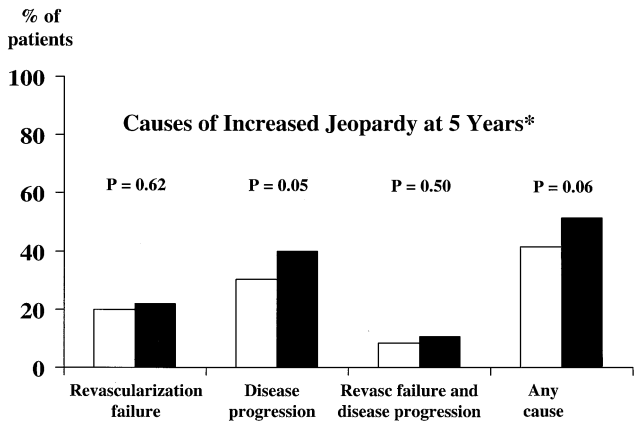

Figure 3. Percentage of patients with increased jeopardized myocardium at five years, including cause of increased jeopardy and assigned mode of initial revascularization. Some patients have multiple causes of increased myocardial jeopardy, and thus are included in multiple categories. **Open bars** = percutaneous coronary intervention patients (202); **solid bars** = coronary artery bypass graft surgery patients (200). *Defined as increased jeopardy that occurs after initial revascularization and is not mitigated by subsequent revascularization procedures.

medications at baseline, as well as first use during follow-up, conferred preferential benefit (baseline use: OR, 0.43, 95% CI, 0.14 to 1.30; follow-up use: OR, 0.61, 95% CI, 0.34 to 1.09).

DISCUSSION

Relationship of angina to myocardial jeopardy. The goal of this study was to evaluate the extent to which failure of revascularization or disease progression accounted for myocardial jeopardy and associated angina five years after a patient's initial revascularization procedure. The index of LV myocardial jeopardy that was used as a correlate of ischemic symptoms is supported by the strong association between five-year angiographic assessment of global myocardial jeopardy and the prevalence of angina that was observed for both PCI- and CABG-treated patients (Table 4). Moreover, a close temporal relationship existed between myocardial jeopardy score and angina in the subset of study patients who had one-year angiography despite not factoring in the viability of the perfused myocardium (Fig. 2).

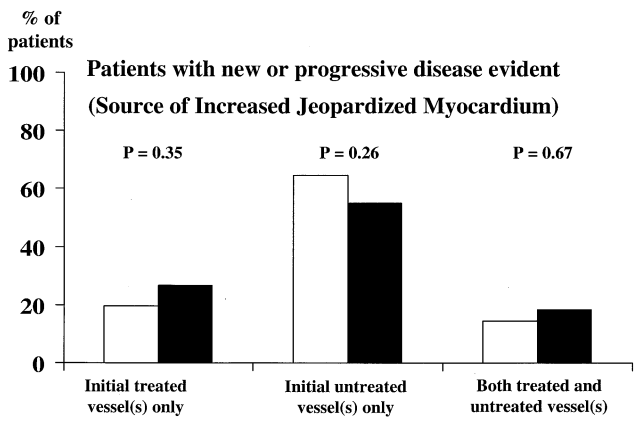

Figure 4. Among patients with new or progressive disease evident at five years, histogram shows the percentage of all patients who experienced increased myocardial jeopardy attributable to vessels treated and/or untreated at the initial revascularization procedure. **Open bars** = percutaneous coronary intervention patients (76); **solid bars** = coronary artery bypass graft surgery patients (82).

The BARI myocardial jeopardy index used in this study (5) was developed to correlate with ischemic symptoms by including smaller LV myocardial subdivisions than prior algorithms (based on coronary branch vessel distribution) and choice of a 50% rather than a 70% threshold, which is somewhat better correlated with survival (8). The threshold used in this study to define myocardial jeopardy reflects current practice patterns that use a 50% threshold to identify ischemia-provoking revascularization targets. However, this threshold of a 50% reduction in lumen diameter does not account for the effects of arterial remodeling and disease progression in adjacent comparator vessel segments.

In addition to myocardial jeopardy, severe angina and prior smoking history at study entry were independently associated with angina at five years. Although initial or subsequent bypass surgery was suggestive of lower myocardial jeopardy at five years compared to treatment with PCI alone, only myocardial jeopardy was independently associated with angina at five years. These data support use of myocardial jeopardy as a surrogate of ischemia, irrespective of whether PCI and/or bypass surgery was performed.

In our study, diabetes was not predictive of increased myocardial jeopardy, a finding that may reflect early mortality reducing representation of diabetic patients. Patients having protocol-directed angiography in this five-year follow-up study had less adverse clinical and angiographic profiles than all other surviving and nonsurviving BARI patients. Despite this limitation, this cohort of subjects represents a consecutive series of randomized patients (survivors) at four participating clinical centers. During five years of follow-up post-PCI, angiographic restenosis was observed in 39% of initial successfully treated lesions, of which the majority were successfully retreated by angioplasty alone. Slightly more then half of all angioplasty patients required additional revascularization within five years, and 20% of these patients underwent bypass surgery.

Limitations of serial angiography to assess the role of disease progression versus revascularization failure on ischemic outcomes. A five-year angiogram alone cannot identify on a lesion-by-lesion basis the final cause of LV jeopardy without considering the intervening sequence of revascularization successes and failures, additional revascularization procedures, and native vessel changes revealed by clinically indicated angiograms. This study, therefore, uses a vessel-by-vessel analysis that accepts intercurrent revascularizations and their failures as normal clinical practice, and attributes causes of incremental five-year jeopardy to changes revealed on the most immediately relevant angiograms. Revascularization events and coronary disease progression occur at different times and in different vascular locations, which combine to yield a net measurement of five-year myocardial jeopardy and its causes.

Our results are based on five-year survivors who, follow-

ing initial coronary revascularization, had late follow-up angiographic assessment. The net effect of these selection criteria is not clear. Presumably, the overall less severe clinical and angiographic profile at study entry in the five-year angiography patients may have restricted the range of native vessel disease progression and revascularization failure that truly occurred in the BARI cohort at large. This uncertainty should be kept in mind when interpreting the results of this study.

The rates of additional procedures in this BARI study are similar to historical rates reported for multivessel disease patients having bypass surgery or angioplasty. However, failure rates for coronary surgery and PCI procedures have dropped substantially since 1988–1991 when BARI patients received their initial revascularization, reflecting multiple procedural and pharmacologic advances (stents, arterial grafts, and coagulation inhibitors). In past angiographic follow-up studies, progression of disease in coronary vessels not requiring revascularization was observed in up to 32% of vessels and 65% of patients (9).

Coronary disease progression can undo the benefits of revascularization. Five-year angiography in the Coronary Artery Surgery Study (CASS) (10,11) reported disease progression in 4.3% of normal segments and 18.6% of previously diseased segments with diabetes noted as predictive of disease progression. Risk-factor modification has demonstrable clinical and angiographic benefit from currently prescribed intensive low density lipoprotein cholesterol-lowering strategy. The post-CABG study's aggressive lipid-lowering strategy reduced the number of patients with graft occlusion from 19% to 12% ($p < 0.001$) compared with moderate hypolipidemic treatment at 4.3 years mean angiographic follow-up (12).

The extent to which new or progressing native vessel disease exceeds that of failed revascularization as the cause of increasing myocardial jeopardy in this comparison of PCI- and surgery-treated patients is not easily extrapolated to current revascularization strategies. Initial PCI and operative procedures in BARI (1988 to 1991) antedate current benefits of drug and nondrug-eluting stents, use of platelet IIb/IIIa inhibitors, and placement of single or multiple arterial grafts, all of which improve procedural outcomes. Current guidelines for lifestyle change and use of hypolipidemic drugs are more aggressive than in the BARI study, during which time less than half of all patients were taking hypolipidemic medication. Intensive risk-factor modification and hypolipid medication use slows atherosclerosis progression within native coronary arteries of both PCI- and CABG-treated patients and may to a lesser extent improve long-term patency of both PCI-treated segments and surgical conduits. The potential for disease progression to undo the benefits of revascularization is evident in this study and supports vigorous risk-factor reduction for patients having revascularization procedures.

Acknowledgments

The assistance of Brooke Hollak, Angiography Core Laboratory, is gratefully appreciated. Graphic data acquisition and myocardial jeopardy computer programs were developed by Mr. William Sanders (Sanders Data Systems).

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