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CLINICAL RESEARCH Clinical Trial

The Final 10-Year Follow-Up Results From the BARI Randomized Trial

The BARI Investigators*

Objectives We sought to compare 10-year clinical outcomes in the BARI (Bypass Angioplasty Revascularization Investigation) trial patients who were randomly assigned to percutaneous transluminal coronary balloon angioplasty (PTCA) versus coronary artery bypass grafting (CABG).

Background Angioplasty and bypass surgery have been compared in numerous studies, but long-term clinical outcomes are limited.

Methods Symptomatic patients with multivessel coronary artery disease (n = 1,829) were randomly assigned to initial treatment with PTCA or CABG and followed up for an average of 10.4 years. Analyses were conducted on an intention-to-treat basis.

Results The 10-year survival was 71.0% for PTCA and 73.5% for CABG (p = 0.18). At 10 years, the PTCA group had substantially higher subsequent revascularization rates than the CABG group (76.8% vs. 20.3%, p < 0.001), but angina rates for the 2 groups were similar. In the subgroup of patients with no treated diabetes, survival rates were nearly identical by randomization (PTCA 77.0% vs. CABG 77.3%, p = 0.59). In the subgroup with treated diabetes, the CABG assigned group had higher survival than the PTCA assigned group (PTCA 45.5% vs. CABG 57.8%, p = 0.025).

Conclusions There was no significant long-term disadvantage regarding mortality or myocardial infarction associated with an initial strategy of PTCA compared with CABG. Among patients with treated diabetes, CABG conferred long-term survival benefit, whereas the 2 initial strategies were equivalent regarding survival for patients without diabetes. (J Am Coll Cardiol 2007;49:1600–6) © 2007 by the American College of Cardiology Foundation

The BARI (Bypass Angioplasty Revascularization Investigation) randomized trial was designed to test whether percutaneous transluminal coronary balloon angioplasty (PTCA) compromised 5-year survival compared with coronary artery bypass grafting (CABG) in patients with multivessel coronary artery disease (CAD). After 5 years of follow-up, overall survival was similar for the 2 revascularization strategies (1); however, after 7 years of follow-up, CABG survival was statistically superior (2).

An unexpected finding of the BARI trial was that among patients without treated diabetes, survival rates for the PTCA and CABG randomized groups were almost identical throughout the 7 years of follow-up, whereas among patients with treated diabetes, the CABG group had significantly better survival. The survival difference was attributable to reduced cardiac mortality (3).

This report describes the final 10-year results from the BARI randomized trial for the entire study group as well as for subgroups defined by treated diabetes status.

Methods

The BARI trial enrolled patients with angiographically documented multivessel CAD and severe angina or objective evidence of ischemia requiring revascularization, as described previously (1,2). Between 1988 and 1991, BARI randomized 1,829 patients at 18 North American sites to receive initial revascularization with either CABG or PTCA.

The vital status of each patient was ascertained on March 31, 2000; patients who had not completed 10 years of follow-up by that date were followed up until they reached their 10-year visit. The BARI study ceased following up patients in 2002.

The primary end point was all-cause mortality, and secondary end points included death of cardiac cause, the composite end point of death or Q-wave myocardial infarction (MI), the composite end point of death of cardiac cause or any MI (Q-wave or non–Q-wave), subsequent revascularization procedures, and anginal status. All MI events were classified by the BARI central laboratory (St. Louis University) based on serial electrocardiographic analysis regardless of symptoms (4). The cause of death was classified by an independent review committee.

A priori subgroups specified by the BARI protocol included anginal status, number of diseased vessels, proxi-

*Please see the Appendix for a full list of the BARI Investigators. This study was supported by the following National Heart, Lung, and Blood Institute grants: HL38493, HL38504, HL38509, HL38512, HL38514-6, HL38518, HL38524-5, HL38529, HL38532, HL38556, HL38610, HL38642, and HL42145.

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mal left anterior descending coronary artery disease, left ventricular function, and lesion complexity. The BARI central radiographic laboratory (Stanford University) interpreted baseline coronary angiograms (5). Based on a request from the study Data and Safety Monitoring Board in 1992, patients were classified by treated diabetes status defined as treatment with either oral hypoglycemic medication or insulin at study entry.

Statistical methods. Kaplan-Meier estimates and log rank tests were used to compare death, cardiac events, and subsequent revascularization rates according to the intention-to-treat principle. The mean restricted life expectancy was estimated by the area under the survival curve between 0 and 10 years. The significance of statistical interactions between randomized treatment and subgroup variables were assessed with Cox regression. Generalized estimation equations were used to analyze presence of angina over time, and Nelson-Aalen methods were used to estimate the number of subsequent procedures. A value of $p < 0.05$ was considered statistically significant except for the treatment comparisons within identified subgroups, in which $p < 0.01$ was used to control for multiple comparisons.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CAD = coronary artery disease

MI = myocardial infarction

PTCA = percutaneous transluminal coronary balloon angioplasty

Results

Baseline characteristics of CABG and PTCA groups were similar (Table 1). The average follow-up was 10.4 years.

Freedom from mortality and MI. At 10 years, mortality and MI event rates were not statistically different between randomized treatment groups (Table 2, Figs. 1 and 2). The mean restricted life expectancy after study enrollment was 8.86 years for CABG-assigned patients and 8.63 years for PTCA-assigned patients.

Table 1 BARI Randomized Trial Baseline Characteristics by Assigned Treatment and by Treated Diabetes Status

	All Patients			Patients Without Treated Diabetes			Patients With Treated Diabetes		
Baseline Characteristics	PTCA, % (n = 915)	CABG, % (n = 914)	p Value	PTCA, % (n = 742)	CABG, % (n = 734)	p Value	PTCA, % (n = 173)	CABG, % (n = 180)	p Value
Demographic variables									
Age >65 yrs	39	39	0.95	38	37	0.75	41	44	0.45
Female	27	26	0.64	23	22	0.702	44	42	0.67
Race			0.071			0.026			0.31
White	91	89		94	90		80	85	
Black	5	7		4	7		10	9	
Other race	4	3		2	3		10	6	
History of smoking	72	69	0.48	74	70	0.22	62	67	0.34
Body mass index >30 kg/m^2	28	30	0.25	24	26	0.55	43	49	0.25
Clinical history and status									
History of myocardial infarction	54	55	0.62	54	54	0.95	54	60	0.22
History of congestive heart failure	9	9	0.83	6	6	0.81	20	19	0.85
History of hypertension	49	49	0.94	45	45	0.78	65	66	0.79
History of peripheral vascular disease	17	16	0.69	16	15	0.54	23	24	0.86
History of renal dysfunction	3	2	0.28	2	1	0.15	6	6	0.92
Treated diabetes	19	20	0.67	0	0		100	100	0.78
Insulin use	9	9	0.56	0	0		45	47	0.69
Angina			0.26			0.51			0.45
Stable class 1 or 2	15	15		15	15		13	13	
Stable class 3 or 4	18	15		17	15		21	16	
Unstable	68	70		68	70		66	71	
Angina duration >1 yr	44	43	0.71	44	44	0.98	47	42	0.36
ECG characteristics									
Any major ECG abnormality	43	42	0.74	42	41	0.78	49	47	0.802
Q waves	18	17	0.64	17	17	0.86	21	18	0.47
ST-segment elevation	5	4	0.41	5	4	0.47	4	3	0.72
ST-segment depression	6	6	0.91	5	6	0.78	8	7	0.76
Angiographic profile									
Triple-vessel disease	41	41	0.99	41	40	0.67	44	48	0.44
Significant proximal LAD lesions	36	37	0.45	36	36	0.93	34	42	0.13
Class C lesions	38	41	0.26	38	41	0.26	40	41	0.78
Normal LV function	78	80	0.36	80	82	0.29	69	69	0.92

CABG = coronary artery bypass graft; ECG = electrocardiogram; LAD = left anterior descending coronary artery; LV = left ventricular; PTCA = percutaneous transluminal coronary balloon angioplasty.

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Table 2 Estimated 5- and 10-Year Survival for BARI Randomized Patients by Assigned Treatment and by Treated Diabetes Status

	All Patients				Patients Without Treated Diabetes				Patients With Treated Diabetes			
	PTCA, % (n = 915)	CABG, % (n = 914)	Relative Risk*	Log Rank p Value†	PTCA, % (n = 742)	CABG, % (n = 734)	Relative Risk*	Log Rank p Value†	PTCA, % (n = 173)	CABG, % (n = 180)	Relative Risk*	Log Rank p Value†
Survival												
5 yr	86.3	89.2	1.27		91.0	91.45	1.05		66.5	79.9	1.67	
10 yr	71.0	73.5	1.09	0.18	77.0	77.3	1.01	0.59	45.5	57.9	1.29	0.025
Survival and freedom from Q-wave MI												
5 yr	79.0	80.5	1.08		83.3	83.4	1.01		60.7	68.8	1.26	
10 yr	63.9	63.6	0.99	0.97	69.1	67.6	0.95	0.73	41.4	47.2	1.11	0.28
Cardiac survival												
5 yr	91.9	95.0	1.62		95.1	95.7	1.14		77.5	91.7	2.71	
10 yr	85.3	87.7	1.20	0.25	89.8	89.7	0.99	0.85	64.4	79.0	1.70	0.008
Cardiac survival and freedom from any MI												
5 yr	79.9	82.2	1.13		83.3	83.8	1.03		65.0	75.9	1.45	
10 yr	68.9	71.1	1.08	0.58	73.8	73.3	0.98	0.65	46.1	61.4	1.40	0.026

*Relative risk for PTCA versus CABG at 5 years and at 10 years. †p value for the log rank statistic comparing PTCA versus CABG based on 10-year follow-up data.
MI = myocardial infarction; other abbreviations as in Table 1.

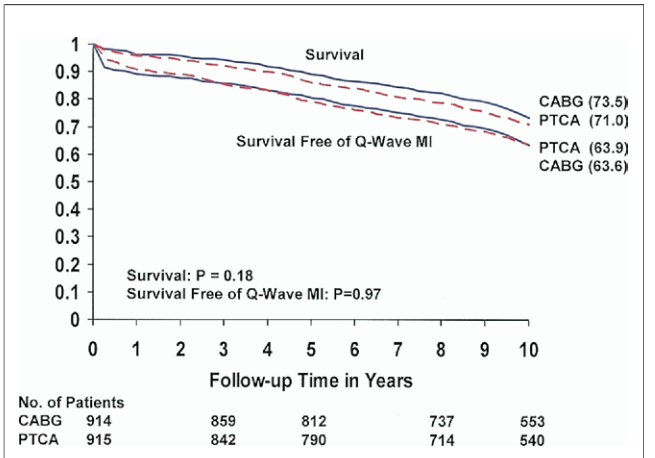

Figure 1 Overall Survival and Survival Free of Q-Wave MI by Randomized Treatment

The **blue solid lines** indicate coronary artery bypass grafting (CABG), and percutaneous transluminal coronary balloon angioplasty (PTCA) by **red dashed lines**. MI = myocardial infarction.

Based on 10-year survival, there were no statistically significant interactions between treatment and the subgroup variables analyzed (Fig. 3). Clinical outcomes were influenced by treated diabetes status (Table 2, Fig. 4). Among patients without treated diabetes, survival was comparable for the randomized treatment groups throughout the 10 years of follow-up. In the treated diabetes subgroup, patients assigned to CABG had significantly higher cardiac survival ($p < 0.01$) and trends for better survival and greater freedom from cardiac death or any MI ($p < 0.05$); note that the interaction between diabetes and treatment for freedom from cardiac death was significant ($p = 0.032$). The mean restricted life expectancy was 9.05 years for CABG-assigned

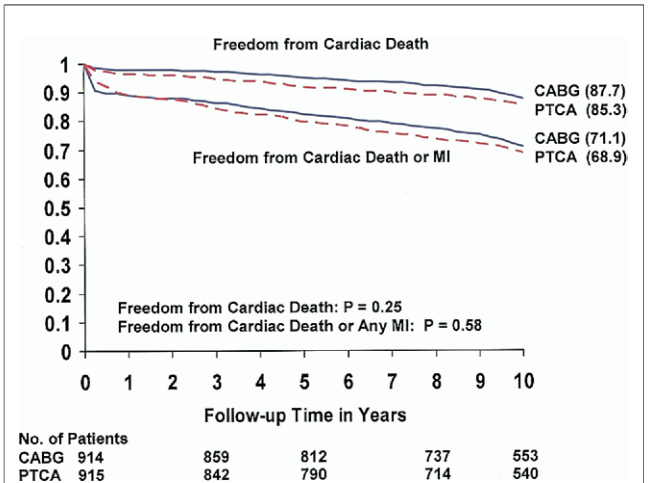

Figure 2 Freedom From Cardiac Death and Freedom From Cardiac Death or Any MI by Randomized Treatment

The **blue solid lines** indicate CABG, and PTCA by **red dashed lines**. Abbreviations as in Figure 1.

patients and 9.02 years for PTCA-assigned patients without treated diabetes and 8.07 years for CABG-assigned patients and 6.93 years for PTCA-assigned patients with treated diabetes.

Among patients with treated diabetes who received their assigned revascularization procedure, CABG patients receiving at least 1 arterial graft (n = 145) had 64.3% 10-year survival, compared with 39.4% in CABG patients receiving only vein grafts (n = 33) and 45.5% in PTCA patients (n = 63). Among patients without treated diabetes, there was no difference in 10-year survival between CABG patients with an arterial graft (n = 602, 75.3%) and those with only vein grafts (n = 134, 77.8%).

Repeat revascularization. A significantly smaller proportion of patients assigned to CABG received subsequent revascularization (Table 3), and they had substantially fewer revascularization procedures over the 10 years of follow-up (Fig. 5).

Angina. At 10 years, the prevalence of angina was similar in the randomized treatment groups (Fig. 6). At 6 months, angina was less frequent in CABG patients, but the odds of having angina increased 8% per year for CABG patients ($p < 0.001$) and decreased 6% per year for PTCA patients ($p < 0.001$). Among surviving patients without diabetes, 10-year angina rates were 15.0% for each treatment group, and among those with diabetes, rates were 25.7% in the PTCA group and 23.1% in the CABG group.

Medications. A majority of patients received beta-blockers, calcium antagonists, or long-acting nitrates (75% PTCA and 66% CABG at 8 years) and antiplatelet therapy, almost entirely aspirin (84% PTCA and 86% CABG at 8 years). Rates of lipid-lowering therapy increased steadily from 29% PTCA and 21% CABG at 1 year to 65% PTCA and 63% CABG by 10 years.

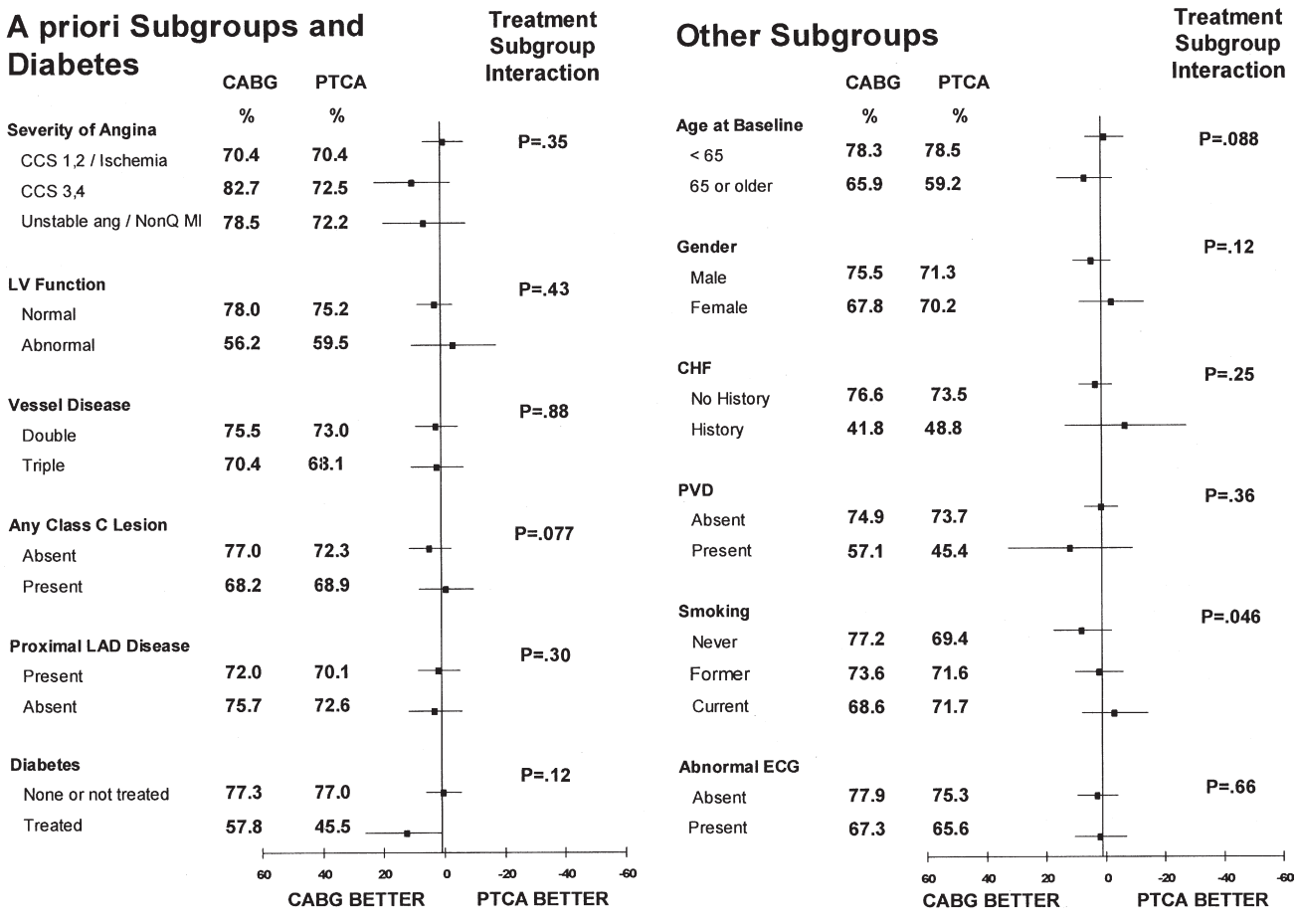

Figure 3 10-Year Survival Rates for Patients According to Subgroups Based on Characteristics at Study Entry

Ninety-nine percent confidence intervals of the absolute treatment difference between 10-year survival rates are shown for each subgroup. The test of the interaction between treatment effect and subgroup is based on proportional hazards models. CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society classification of angina; CHF = congestive heart failure; ECG = electrocardiogram; LAD = left anterior descending coronary artery; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary balloon angioplasty; PVD = peripheral vascular disease.

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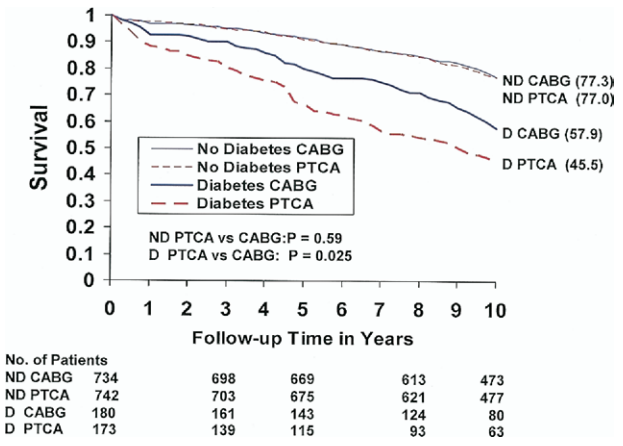

Figure 4 Overall Survival by Randomized Treatment Stratified by Diabetes Status

Patients who were being treated for diabetes at baseline are shown with **heavy lines**, and all other patients are shown with **light lines**. The **blue solid lines** indicate CABG, and the **red dashed lines** indicate PTCA. D = treated diabetes; ND = no treated diabetes; other abbreviations as in Figure 1.

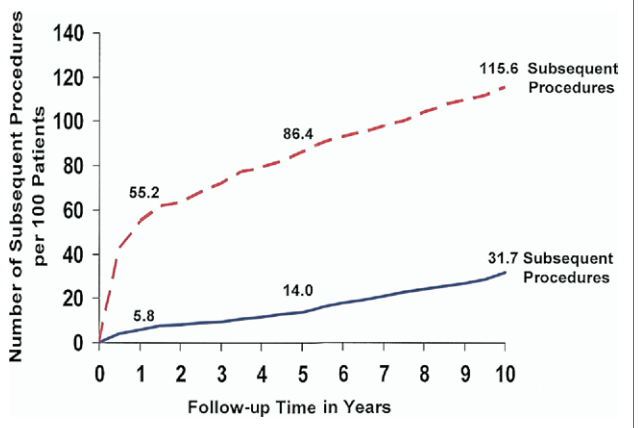

Figure 5 Cumulative Number of Subsequent Revascularization Procedures per 100 Patients by Randomization

The **blue solid lines** indicate CABG, and the **red dashed lines** indicate PTCA. Abbreviations as in Figure 1.

Discussion

The long-term follow-up of this large cohort of selected patients with multivessel CAD randomized to receive either balloon angioplasty or coronary bypass surgery shows similar rates of survival and freedom from MI over 10 years. The initial cardiac revascularization procedures in BARI were performed between 1988 and 1991, before the introduction of coronary stents and other technical refinements in angioplasty and surgery. Although some might argue that these procedural refinements make the results of the BARI trial obsolete, we believe that our observations with respect to death and MI remain applicable to contemporary practice. Overviews of the randomized trials of bare metal stents (6,7) and drug-eluting stents (8,9) show that these devices have no significant advantage regarding mortality or MI compared with balloon angioplasty despite striking reductions in rates of restenosis and repeat revascularization procedures. Furthermore, observational studies of patients undergoing angioplasty indicate that restenosis does not confer a worse prognosis concerning survival (10).

A comprehensive review of trials and registries comparing percutaneous coronary intervention with CABG is presented elsewhere (11). The BARI trial results are consistent with those of recent clinical trials such as ARTS (Arterial Revascularization Therapies Study) (12), which reported comparable 5-year mortality for coronary bare-metal stenting and CABG (8.0% stents vs. 7.6% CABG), but more subsequent revascularization (30.3% vs. 8.8%) and more angina (21.2% vs. 15.5%) in the stenting group. Meta-analyses (13) and registries (14) based on larger and more diverse populations have shown small but statistically significant survival advantages with CABG at 3 to 5 years. In the New York cardiac registry, 37,212 multivessel CAD patients undergoing CABG had better risk-adjusted survival than 22,102 undergoing stenting (14). Given the observed 10-year mortality rate in BARI, more than 7,200 patients would be required to have sufficient power to detect a 3% absolute difference in mortality, thus reflecting the challenge of conducting clinical trials.

In patients with type 2 diabetes, CABG conferred a consistent, clinically relevant, absolute survival benefit over balloon angioplasty that diminished somewhat over extended follow-up because patients in both groups had

Table 3 Estimated Cumulative Rates of Subsequent Revascularization Procedures* at 10 Years by Assigned Treatment and by Treated Diabetes Status

	All Patients		Patients Without Treated Diabetes		Patients With Treated Diabetes	
	PTCA (n = 915)	CABG (n = 914)	PTCA (n = 742)	CABG (n = 734)	PTCA (n = 173)	CABG (n = 180)
No subsequent revascularization	33.2	79.7	35.6	79.3	20.3	81.7
No subsequent revascularization or at most 1 subsequent PTCA†	43.4	89.8	46.7	90.0	25.8	88.8
Two or more subsequent PTCAs	27.2	6.8	24.3	6.6	45.4	7.9
Subsequent CABG	41.2	3.7	38.3	3.6	57.7	4.1

*The percent of patients with subsequent procedures, subsequent CABG, or subsequent PTCA are based on Kaplan-Meier estimates at 10 years. †At most 1 subsequent PTCA procedure (i.e., no second subsequent PTCA procedure and no subsequent CABG).

Abbreviations as in Table 1.

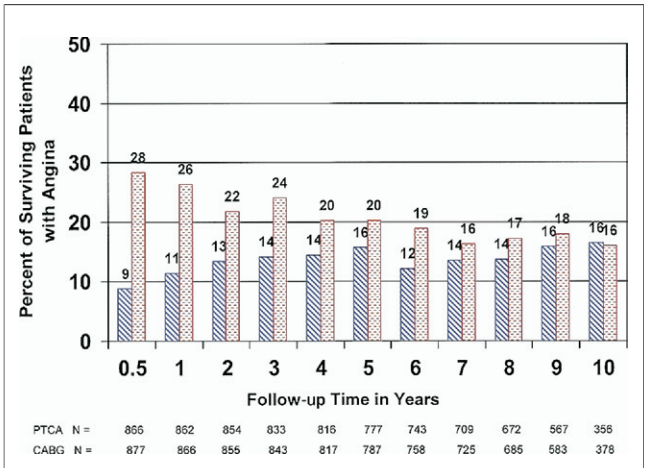

Figure 6 **Percent of Surviving Patients With Stable or Unstable Angina at Each Follow-Up by Randomization**

The **blue diagonally-striped bars** indicate CABG, and the **red horizontally-dashed bars** indicate PTCA. Abbreviations as in Figure 1.

higher event rates. Five-year mortality results from ARTS (diabetes: 13.4% stents vs. 8.3% CABG, relative risk = 1.61, p = 0.27; no diabetes: 6.8% stents vs. 7.5% CABG, relative risk = 0.91, p = 0.71) (15) support the finding that CABG may have particular advantages for patients with diabetes. It remains to be seen whether advances in percutaneous procedures and medical management over the past decade will make contemporary angioplasty a reasonable option in this cohort.

The steady incidence of cardiac events over the 10 years of follow-up in both treatment groups emphasizes that coronary revascularization does not reverse the underlying pathophysiology of coronary disease. Underuse of evidence-based medical therapies is unfortunately common among patients with coronary disease. Clinical outcomes for all patients may be improved further by providing long-term aggressive medical management after revascularization.

Acknowledgment

The entire BARI team acknowledges the unfortunate death of our esteemed colleague and friend Dr. Katherine Detre. This analysis of the 10-year results of the original BARI trial is dedicated to her. Dr. Detre led the BARI investigation with distinction and a commitment to enhance the care of patients by way of rigorous analysis of clinical evidence.

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APPENDIX

A complete list of the BARI Investigators is published in reference 3.

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