

The Bypass Angioplasty Revascularization Investigation 2 Diabetes Randomized Trial of Different Treatment Strategies in Type 2 Diabetes Mellitus With Stable Ischemic Heart Disease

Impact of Treatment Strategy on Cardiac Mortality and Myocardial Infarction

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Background—The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial in 2368 patients with stable ischemic heart disease assigned before randomization to percutaneous coronary intervention or coronary artery bypass grafting strata reported similar 5-year all-cause mortality rates with insulin sensitization versus insulin provision therapy and with a strategy of prompt initial coronary revascularization and intensive medical therapy or intensive medical therapy alone with revascularization reserved for clinical indication(s). In this report, we examine the predefined secondary end points of cardiac death and myocardial infarction (MI).

Methods and Results—Outcome data were analyzed by intention to treat; the Kaplan–Meier method was used to assess 5-year event rates. Nominal *P* values are presented. During an average 5.3-year follow-up, there were 316 deaths (43% were attributed to cardiac causes) and 279 first MI events. Five-year cardiac mortality did not differ between revascularization plus intensive medical therapy (5.9%) and intensive medical therapy alone groups (5.7%; *P*=0.38) or between insulin sensitization (5.7%) and insulin provision therapy (6%; *P*=0.76). In the coronary artery bypass grafting stratum (*n*=763), MI events were significantly less frequent in revascularization plus intensive medical therapy versus intensive medical therapy alone groups (10.0% versus 17.6%; *P*=0.003), and the composite end points of all-cause death or MI (21.1% versus 29.2%; *P*=0.010) and cardiac death or MI (*P*=0.03) were also less frequent. Reduction in MI (*P*=0.001) and cardiac death/MI (*P*=0.002) was significant only in the insulin sensitization group.

Conclusions—In many patients with type 2 diabetes mellitus and stable ischemic coronary disease in whom angina symptoms are controlled, similar to those enrolled in the percutaneous coronary intervention stratum, intensive medical therapy alone should be the first-line strategy. In patients with more extensive coronary disease, similar to those enrolled in the coronary artery bypass grafting stratum, prompt coronary artery bypass grafting, in the absence of contraindications, intensive medical therapy, and an insulin sensitization strategy appears to be a preferred therapeutic strategy to reduce the incidence of MI.

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

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Key Words: angioplasty ■ bypass ■ diabetes mellitus ■ myocardial infarction ■ prognosis

Patients with type 2 diabetes mellitus and coronary disease are at increased risk for death and myocardial infarction (MI) compared with nondiabetic patients.^{1–4} Interventions to

reduce cardiovascular risk include intensive medical therapy (IMT) to control atherosclerotic risk factors, prompt coronary revascularization, and optimization of glucose homeostasis

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through insulin sensitization (IS) or insulin provision (IP) therapies.^{5,6} In selected diabetic patients with stable ischemic coronary disease, revascularization with percutaneous coronary intervention (PCI) has not been shown to reduce the risk of all-cause death compared with IMT in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial after an average 5.3 years of follow-up.⁷ Similar results were reported by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial after a median 4.6-year follow-up.^{8,9} A history of diabetes mellitus was present in 34% of patients enrolled in the COURAGE trial, and the study was not designed to test an initial strategy of coronary artery bypass grafting (CABG).

Clinical Perspective on p 2540

The BARI 2D trial required that physicians determine which coronary revascularization strategy was preferred for individual patients considered for the study, and after the preferred type of revascularization was selected (either PCI or CABG), then patients were randomized to revascularization plus IMT (revascularization strategy) or IMT alone with revascularization reserved for clinical indication(s) (IMT strategy).^{10–12} The CABG population was different from the PCI population, with different anatomic characteristics and prognosis.^{7,11,12} The impact of an IS strategy compared with an IP strategy on cardiovascular outcomes was also tested with a 2×2 factorial design.⁶ The BARI 2D trial reported no significant differences in all-cause mortality, the primary end point of the trial, between the 4 main treatment strategies.⁷ However, nonfatal MI events were significantly reduced in revascularization patients who were in the CABG stratum.

Cardiac mortality, MI, and the composite of all-cause mortality/MI were prespecified secondary end points in BARI 2D.¹⁰ Comparison of treatment strategies designed to reduce cardiovascular morbidity and mortality requires that cardiac end points be analyzed specifically as well as all-cause mortality. The aim of this report is to examine whether an initial treatment strategy of revascularization versus IMT significantly influenced the secondary outcomes of cardiac death or MI, the composite end point of all-cause mortality/nonfatal MI, or the end point of cardiac death/MI. The impact of MI events on subsequent cardiac mortality was also examined.

Methods

Study Population and Treatment Strategies

A detailed description of the BARI 2D design, protocol, clinical patient characteristics, and consort diagram has been published previously.^{5–7,10–13} Briefly, the BARI 2D is a large international trial testing 2 major strategies in a 2×2 factorial design: (1) an early versus only if necessary revascularization strategy (revascularization versus IMT); and (2) a glycemic control strategy (IS versus IP therapy to a target glycohemoglobin A_{1c} [HbA_{1c}] of <7%). The trial randomized 2368 patients with angiographically defined coronary artery disease (CAD) between January 1, 2001, and March 31, 2005.^{7,13} The choice of revascularization (PCI or CABG) was determined after coronary angiography by the treating physician, and randomization was stratified by the type of intended revascularization procedure. Patients selected for CABG had more extensive disease, total occlusions, proximal left coronary disease, and greater myocardial jeopardy score than those selected by their physician for

PCI.¹¹ After randomization, all patients were treated according to current guidelines for lipid and blood pressure management, smoking cessation, physical activity, and weight loss.^{6,7,10} Medication use and achievement of risk factor–targeted therapeutic goals were measured at prespecified intervals during follow-up, and treatment was optimized.⁷ The baseline characteristics of the study population were similar across the 4 treatment strategies.^{7,12,13} The average age of the study population was 62.4 years, and 29.6% were women. The average duration of type 2 diabetes mellitus was 10.4 years. Patients were excluded if they required immediate revascularization or had revascularization within the prior 12 months, had left main coronary disease, class III or IV heart failure, creatinine >2 mg/dL, HbA_{1c} >13%, or significant hepatic dysfunction. The protocol was approved by the institutional review board at the University of Pittsburgh and at each participating site. All patients provided written informed consent. The trial was supported by the National Institutes of Health, with additional support from industry.

Outcome Evaluation

Myocardial Infarction

Reported myocardial ischemic events requiring hospitalization were classified at a Core Electrocardiography and Myocardial Infarction Classification Laboratory in St Louis.^{7,10} The adjudication was based on source documents such as emergency department records, admission history and physical, ECGs and biomarkers associated with the admission, discharge summary, and records of revascularization procedures when available. The BARI 2D criteria for MI were modified from the Universal MI definition criteria by requiring that an abnormal biomarker profile exceed at least twice the upper limits of normal for the local laboratory.¹⁴ When cardiac troponin and creatine kinase–MB were acquired simultaneously, cardiac troponin took precedence over creatine kinase–MB in establishing the diagnosis. MI was confirmed if abnormal cardiac biomarkers occurred and there was evidence of angina or angina-equivalent symptoms, ECG or imaging evidence of new myocardial ischemia, or autopsy evidence of recent MI.

All ECGs were interpreted at the core laboratory with the use of the Minnesota code with an adaptation of the NOVACODE for serial ECG comparisons.^{15,16} A Q-wave MI required the development of new pathological Q waves¹⁵ or the new occurrence of a left bundle-branch block in addition to abnormal biomarkers. Non-Q-wave MI required the aforementioned MI criteria without new pathological Q waves. Fatal MIs were defined as death occurring within 30 days after the event with a causal relationship to the death.

Cardiac biomarkers were not collected routinely within 96 hours of the index coronary revascularization procedure in patients assigned to the revascularization strategy. When biomarkers were collected, a 3-fold elevation in creatine kinase–MB after a PCI procedure and a 10-fold increase in creatine kinase–MB after CABG were used as the cut points to define periprocedural myocardial necrosis. The Universal MI definition subcategorizes MI into spontaneous (type 1) or PCI- or CABG-related (type 4 or 5) events.¹⁴ In this report, PCI- or CABG-related MIs are defined as occurring in the periprocedural phase or within 30 days of the procedure.

Cardiac Mortality

Cause of death was classified by an independent Mortality and Morbidity Classification Committee as cardiac (direct or contributory), noncardiac but related to atherosclerotic disease, noncardiac medical cause (eg, cancer, pulmonary disease), trauma, suicide, accident, other, or unknown (Table I in the online-only Data Supplement). Cardiac death was defined as death within 1 hour to 30 days after a documented or probable MI, death from intractable congestive heart failure or cardiogenic shock, or other documented cardiac cause. Sudden cardiac death was defined as death occurring instantaneously or within 60 minutes after the onset of cardiac symptoms. Cardiac death was considered contributory if cardiac dysfunction contributed to the death but it was unclear if it was the direct cause of death. Classification was based on the report from the clinical center's principal investigator; death certificate; surgical and

Table 1. Five-Year Kaplan–Meier Estimates for Death, MI, and the Composite End Points of Death or MI or of Cardiac Death or MI According to Initial Treatment Strategy and According to PCI and CABG Strata

	n	Death			MI†, % (n)	Composite	
		All-Cause Death	Cardiac Death*	Sudden Cardiac Death*		Death or MI	Cardiac Death or MI
All patients	2368						
Revascularization	1176	11.7 (155)	5.9 (72)	4.0 (48)	11.5 (128)	21.1 (247)	15.9 (178)
IMT	1192	12.2 (161)	5.7 (64)	4.2 (46)	14.3 (151)	22.7 (266)	16.7 (179)
Nominal <i>P</i>		0.97	0.38	0.72	0.27	0.61	0.78
PCI stratum	1605						
Revascularization	798	10.8 (102)	5.0 (44)	3.8 (34)	12.3 (95)	21.1 (173)	16.0 (126)
IMT	807	10.2 (96)	4.2 (33)	3.4 (26)	12.6 (88)	19.6 (157)	14.2 (101)
Nominal <i>P</i>		0.48	0.16	0.25	0.42	0.19	0.045
CABG stratum	763						
Revascularization	378	13.6 (53)	8.0 (28)	4.3 (14)	10.0 (33)	21.1 (74)	15.8 (52)
IMT	385	16.4 (65)	9.0 (31)	6.0 (20)	17.6 (63)	29.2 (109)	21.9 (78)
Nominal <i>P</i>		0.33	0.79	0.35	0.003‡	0.010§	0.03§
IP therapy	1185	12.1 (160)	6.0 (70)	4.2 (47)	13.6 (149)	22.7 (265)	17.1 (189)
IS therapy	1183	11.8 (156)	5.7 (66)	4.0 (47)	12.2 (130)	21.2 (248)	15.6 (168)
Nominal <i>P</i>		0.89	0.76	0.97	0.21	0.29	0.21

Values are 5-year Kaplan–Meier estimates, expressed as percentages (n), unless otherwise specified.

*Cause of death determined by independent Mortality and Morbidity Committee.

†Includes documented MIs from the core ECG laboratory and/or fatal MIs as determined by death classification.

‡Significant after Bonferroni adjustment for multiple tests done in the table.

§Significant at nominal level.

catheterization laboratory reports within 30 days; ECG and biomarker data within 24 hours; patient's baseline, procedural, and hospital study data; and, if available, a coroner's report. Each case was reviewed by 2 classification committee members. Disagreements were resolved by consensus of the full committee.

Statistical Analysis

As of November 30, 2008, the vital status was known for 2283 patients (96%). The mean follow-up interval was 5.3 years (range, 3.4 to 7.8). The data were analyzed by intention to treat, and Kaplan–Meier analyses were used to assess 5-year cumulative event rates for all-cause death, cardiac death, MI, and the composite end point of cardiac death or MI.

MI rates include fatal and nonfatal events. The MI end point was censored at the last clinic follow-up visit, and the mortality end point was censored at the last patient contact. Noncardiac deaths were censored at time of death in the analysis of cardiac mortality. Kaplan–Meier estimates of event rate distributions were compared by the log-rank test. Cox regression analyses with a time-dependent variable to indicate presence of a follow-up MI were used to determine the hazard ratio (HR) between the randomization arms for death or cardiac death in the setting of an MI. An interaction term was added to the models to test the equality between the HR after the occurrence of an MI and the HR when no MI was suffered. If no MI event occurred, deaths were censored at the last known MI-free time. Cox regression was also used to estimate the HR for revascularization versus IMT in each of the glycemic treatment arms.

A *P* value of 0.05 was used to determine statistical significance. Nominal *P* values are presented. The tables also indicate significance after Bonferroni adjustment for multiple testing. Analysis was performed with the use of SAS 9.2 (SAS Institute Inc, Cary, NC), and figures were created with the use of R 2.8.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The 5-year Kaplan–Meier all-cause mortality rates did not differ significantly between revascularization (11.7%) and

IMT (12.2%; *P*=0.97) or between IS (11.8%) and IP strategies (12.1%; *P*=0.89), as reported previously⁷ (Table 1). Of the 316 deaths in BARI 2D, 136 (43%) were attributed to cardiac causes, and 94 of these (69.1%) were sudden deaths. The 5-year cardiac mortality did not differ significantly between revascularization (5.9%) and IMT (5.7%; *P*=0.38) or between IS (5.7%) and IP therapy (6%; *P*=0.76). Similar results were observed for the end point of death or MI and for the end point of cardiac death or MI (Table 1 and Figure 1).

When the 1605 patients in the PCI stratum were examined, there were no significant differences in the rates of cardiac death or MI between the treatment groups. When the 763 patients in the CABG stratum were examined, MI events were significantly less frequent in the revascularization group compared with the IMT group (10% versus 17.6%; *P*=0.003). The rate for the composite end point of all-cause death or MI was also significantly less in the revascularization CABG stratum group (21.1% versus 29.2%; *P*=0.010), and the composite end point of cardiac death or MI was also less frequent (*P*=0.03) (Figure 2). When procedure-related MI events were not counted, the difference in the composite end point of cardiac death or MI was 13.7% versus 21.4% (*P*<0.01) (Table II in the online-only Data Supplement). The HR of cardiac death for revascularization/IMT in the CABG stratum was significantly different (*P*=0.004) in the first 6 months after randomization (4.48; Kaplan–Meier rates, 3.4%/0.8%) compared with >6 months to the end of follow-up (0.55; 4.1%/7.5%). The data suggest that once the risk of CABG surgery is accounted for, there is a reduction in the subsequent hazard of cardiac death. This difference was not seen in the PCI stratum. The HR for cardiac death for

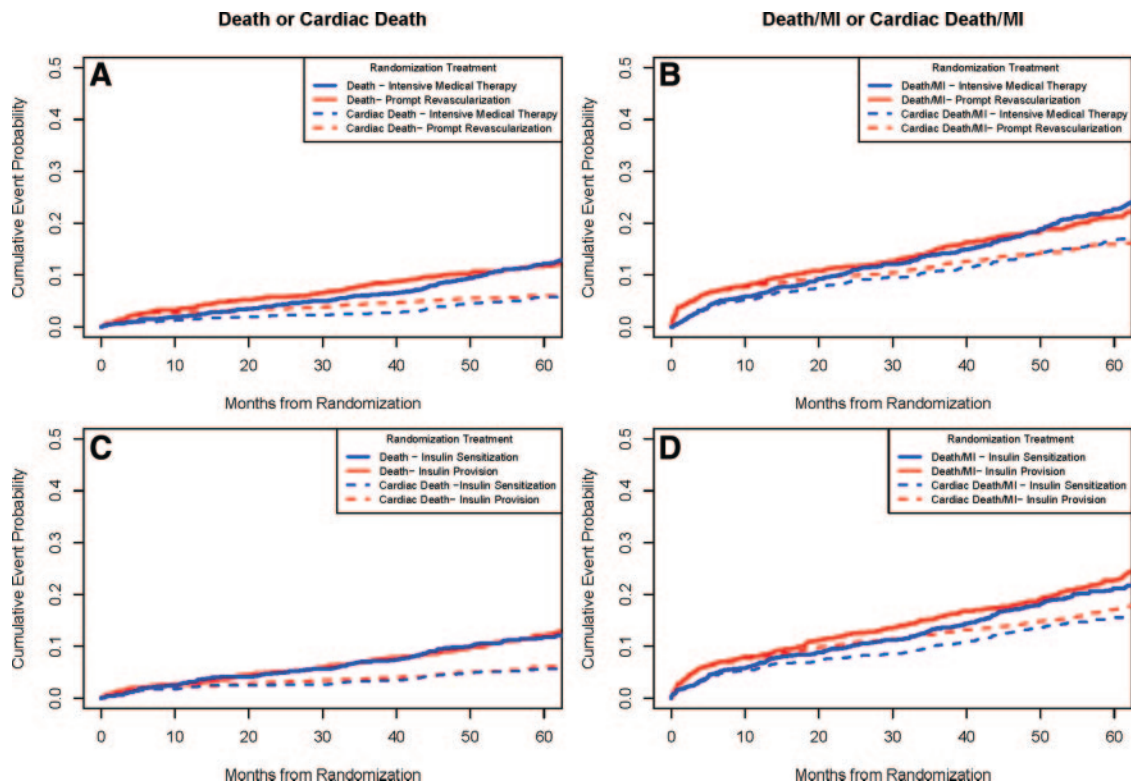


Figure 1. Rates of all-cause death or cardiac death and of death/MI or cardiac death/MI. There were no significant differences in the rates of death or cardiac death between the revascularization group and the IMT group (top left) or in the rates of the composite end point of all-cause death/MI or cardiac death/MI (top right). Similar results were seen between the IS group and the IP group (bottom).

revascularization/IMT in the PCI stratum was not significantly different ($P=0.70$) in the first 6 months after randomization (1.58; Kaplan–Meier rates, 1.8%/1.1%) compared with >6 months to the end of follow-up (1.30; 4.8%/3.0%).

Myocardial Infarction

Of the 2368 BARI 2D patients, 279 were diagnosed with a first postrandomization MI (Figure 3). In the PCI stratum, 5-year MI rates were 12.3% and 12.6% ($P=0.42$) for PCI versus IMT. The rates were 9.4% versus 11.4% ($P=0.69$) when procedure-related MI events were not counted (Table II in the online-only Data Supplement). In the CABG stratum, 5-year MI rates were 10% versus 17.6% ($P=0.003$) for CABG versus IMT; the rates were 5.9% and 14.8% ($P<0.001$) when procedure-related MI events were not counted. There were no overall differences in the rates of MI between IS and IP therapies (Table 1).

The HR of MI for revascularization/IMT in the CABG stratum was significantly different ($P=0.003$) in the first 6 months after randomization (1.13; Kaplan–Meier rates, 5.5%/5.0%) compared with >6 months to the end of follow-up (0.29; 3.9%/12.5%). A trend was seen in the HR of MI in the PCI stratum in the first 6 months after randomization ($P=0.03$) (1.81; 5.0%/2.8%) and >6 months to end of follow-up (0.90; 7.7%/8.8%).

At 5 years, 452 of 1192 (Kaplan–Meier estimate, 42.1%) patients in the IMT group (315 of 807 [Kaplan–Meier estimate, 43.3%]) in the PCI stratum and 137 of 385 [Kaplan–Meier estimate, 39.7%] in the CABG stratum) had crossed over and undergone clinically indicated revascularization. Of

the 452 patients in the IMT group that crossed over to the revascularization strategy, the procedure was precipitated by an MI event in 50 patients.

Impact of MI Events on Cardiac Mortality

In the overall BARI 2D cohort, the risk of death during the entire follow-up was 5.2 times higher after an MI compared with those with no MI. Thirty-six (12.9%) of the 279 first MI events were fatal. Among the remaining 243 nonfatal first MI events, 169 (69.5%) and 23 (9.4%) were type I symptomatic and silent MI events; 51 (21.0%) were procedure-related MI events. The 3-year cardiac mortality rates were 16.1% (HR, 8.2; $P<0.001$) and 10.7% (HR, 4.8; $P=0.03$) for type I symptomatic and silent MI events and 9.6% (HR, 3.4; $P=0.008$) for procedure-related MI events. The silent Q-wave MI events were detected during protocol ECG follow-up. The 3-year cardiac mortality rate for patients without a myocardial infarction during follow-up was 2.4%.

The 30-day cardiac mortality rate after an MI was 12.5% for patients initially assigned to revascularization versus 14.1% initially assigned to IMT. When these events were analyzed by the intended method of revascularization, the 30-day cardiac death rates were 9.5% and 11.6% for PCI versus IMT and 21.2% and 17.5% for CABG versus IMT. The difference in the 30-day cardiac mortality after MI was marginally greater after CABG ($P=0.09$). There were no significant long-term differences in the risk of all-cause death after an MI between the patients in the revascularization and IMT groups (Tables 2 and 3). However, for cardiac death, the relative risk for revascularization versus IMT was 0.58

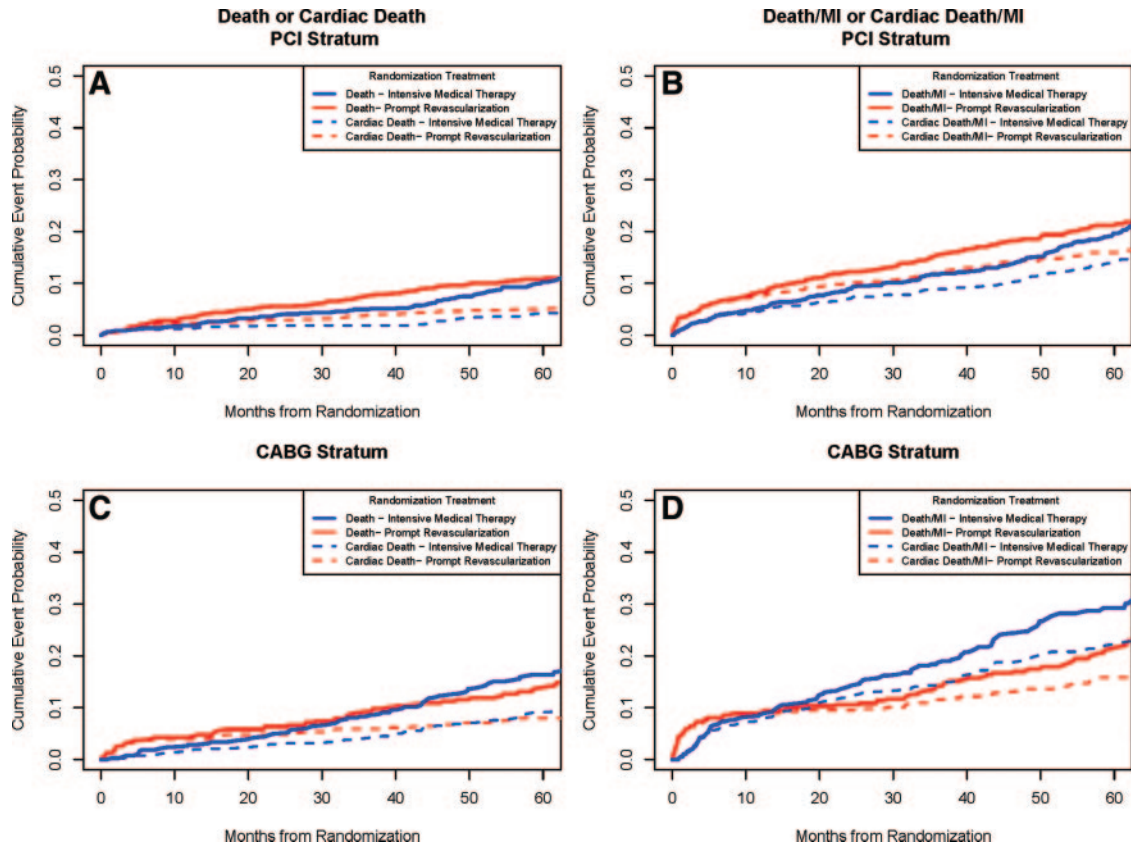


Figure 2. Rates of all-cause death or cardiac death and of death/MI or cardiac death/MI according to PCI and CABG strata. There were no significant differences in the rates of all-cause death or cardiac death between the revascularization group and the IMT group among patients who were selected for the PCI stratum (top left) or in the rates of the composite end point of all-cause death/MI or cardiac death/MI (top right). Among patients who were selected for the CABG stratum, the rates for all-cause or cardiac mortality were not significantly different (bottom left), but the rates for all-cause death free of MI ($P=0.009$) or cardiac death free of MI ($P=0.03$) were significantly better than in the IMT group (bottom right).

($P=0.048$) after an MI compared with relative risk of 1.95 ($P=0.006$) for patients who did not suffer an MI, and these relative risks differed significantly from each other ($P<0.001$). In the PCI stratum, the risk of death and cardiac death after an MI was lower among those assigned to revascularization than among those assigned to IMT; in contrast, in the CABG stratum, there was no significant treatment difference for cardiac mortality rates after MI.

Patients in the CABG stratum had more atherosclerotic lesions than in the PCI stratum (mean number of lesions, $>20\%$ [5.6 versus 4.3]). Analysis of 15 baseline angiographic descriptors analyzed by the core angiographic laboratory identified a greater number of atherosclerotic lesions ($P<0.001$) and greater myocardial jeopardy score ($P<0.001$) as predictors of MI in the IMT group. In the revascularization PCI strata, number of atherosclerotic lesions at baseline was a significant predictor of MI ($P<0.001$), whereas no significant angiographic descriptor differences were found in the revascularization CABG stratum.

Interaction of the 4 Treatment Strategies on Cardiac Death and MI End Points

The hazard ratios of revascularization/IMT for MI, cardiac death, and the composite of cardiac death/MI were not significantly different in the total population. This was also

true in the PCI stratum. However, when patients in the CABG stratum were examined, the hazard ratio of MI for revascularization/IMT was significantly different ($P=0.001$) in the IS group (0.32; Kaplan–Meier rates, 6.3%/19%), whereas the difference was not significant in the IP group (Table 4 and Figures 4 and 5). The P value for the overall 4-way comparison among the mutually exclusive treatment groups for first myocardial infarction in the CABG stratum was $P=0.007$. The P value for the difference in the revascularization group with insulin sensitization as compared with insulin provision therapy was $P=0.046$. The hazard ratio of cardiac death was 0.62 for revascularization/IMT ($P=0.21$) in the IS group and 1.4 in the IP group ($P=0.39$).

Discussion

The BARI 2D trial reported no significant differences in the primary end point of all-cause mortality or in the principal secondary end point of all-cause death/MI/stroke between patients with type 2 diabetes mellitus undergoing revascularization and those undergoing IMT or between strategies of IS and IP. However, in the CABG stratum, a significant reduction in major cardiovascular events (all-cause mortality/MI/stroke) was seen with CABG compared with IMT, largely because of a reduction in MI in patients within the IS strategy.⁷ In our original report, MI rates included only

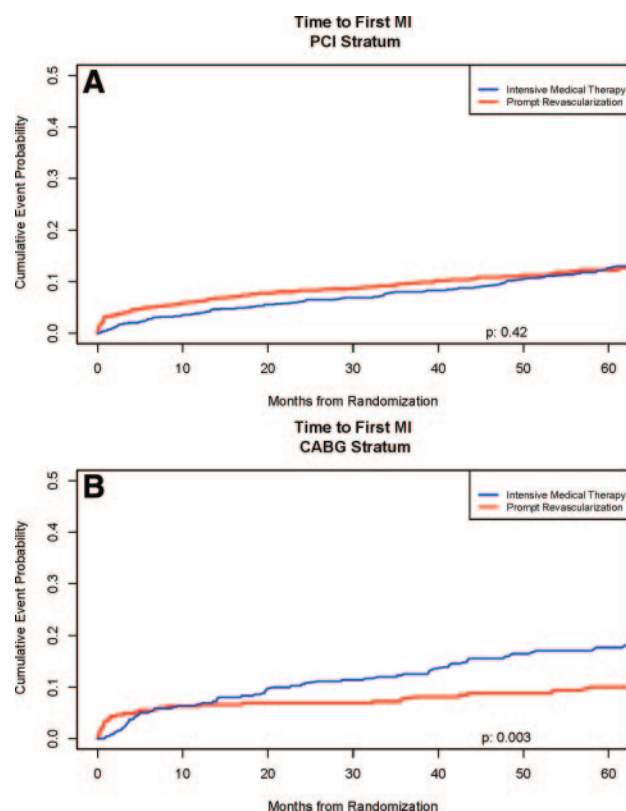


Figure 3. Time to first MI in the PCI stratum (top) and in the CABG stratum (bottom). The incremental risk of MI was continuous over time in the IMT groups. In the CABG stratum, the difference in MI rates between initial revascularization with CABG and an initial IMT strategy was significant ($P=0.003$).

nonfatal MI events; in this article, the MI rates reported include both fatal and nonfatal MI events.

In BARI 2D, 43% of the total mortality was attributed to cardiac causes over the average 5.3-year follow-up. Cardiovascular deaths accounted for 37% to 53% of all-cause mortality in the Action to Control Cardiovascular Risk in

Diabetes Study Group (ACCORD), Veterans Affairs Diabetes Trial (VADT), Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) T2D, and Randomized Intervention Treatment of Angina (RITA-2) trials.^{17–20} BARI 2D differs from the other diabetes trials in several respects, particularly by the protocol requirement that all patients needed to have angiographically documented coronary disease suitable for coronary revascularization (32%, severe enough to be considered for CABG). The cardiac mortality in BARI 2D was much lower than originally anticipated when it is considered that all patients had documented coronary disease and that other reports of type 2 diabetes mellitus estimate cardiac deaths to be 60% to 75% of all-cause death.^{1–4} We believe that the lower cardiac death rates in BARI 2D are a consequence of IMT that included frequent visits with aggressive implementation of IMT in all patients regardless of choice of revascularization procedure or randomization to IMT or revascularization. In BARI 2D at 3-year follow-up compared with baseline, the average reduction in low-density lipoprotein cholesterol was -16 mg/dL, triglycerides -20 mg/dL, systolic blood pressure -6 mm Hg, and HbA_{1c} -0.45% . The percentage of patients who smoked in the prior year was reduced from 22% to 11% after randomization with smoking cessation counseling.

Revascularization compared with IMT did not affect all-cause death rates,⁷ but comparisons of treatment effects on prevention of subsequent cardiovascular events such as cardiac death or MI (fatal and nonfatal) are diluted by noncardiac causes of death such as suicide, trauma, and sepsis, which would not be affected by the therapy received and thus confound the interpretation of potential therapeutic benefit. Therefore, the BARI 2D protocol prespecified that the secondary end points of cardiac death, MI, and all-cause death or MI be examined to determine whether there were significant treatment effects. In this

Table 2. HR of Death or Cardiac Death by Postrandomization MI Status

	No. of Deaths*		HR of Death* (95% CI), Revascularization/IMT	Nominal <i>P</i> for Equality Between HR	No. of Cardiac Deaths*		HR of Cardiac Death† (95% CI), Revascularization/IMT	Nominal <i>P</i> for Equality Between HR
	Revascularization	IMT			Revascularization	IMT		
All patients (<i>n</i> =2368)				0.22				<0.001‡
MI	36	46	0.82 (0.53–1.27)		22	36	0.58† (0.34–0.99)	
No MI	101	92	1.13 (0.86–1.50)		49	26	1.95† (1.21–3.14)	
PCI stratum (<i>n</i> =1605)				0.033†				<0.001‡
MI	24	27	0.65 (0.37–1.13)		13	20	0.44† (0.22–0.90)	
No MI	67	53	1.33 (0.93–1.91)		31	13	2.49† (1.30–4.75)	
CABG stratum (<i>n</i> =763)				0.35				0.48
MI	12	19	1.3 (0.63–2.71)		9	16	0.95 (0.41–2.17)	
No MI	34	39	0.86 (0.55–1.37)		18	13	1.41 (0.69–2.87)	

CI indicates confidence interval.

*Censored at last known MI follow-up.

†Significant at nominal level.

‡Significant after Bonferroni adjustment for multiple tests done in the table.

Table 3. HR of Death or Cardiac Death by Postrandomization MI Status for IP and IS

	No. of Deaths*		HR of Death* (95% CI), IP/IS	Nominal <i>P</i> for Equality Between HR	No. of Cardiac Deaths*		HR of Cardiac Death (95% CI), IP/IS	Nominal <i>P</i> for Equality Between HR
	IP	IS			IP	IS		
All patients (n=2368)				0.54				0.34
MI	44	38	0.87 (0.57–1.35)		30	28	0.79 (0.47–1.32)	
No MI	97	96	1.03 (0.77–1.36)		39	36	1.10 (0.70–1.73)	

CI indicates confidence interval.

*Censored at last known MI follow-up.

report, we present nominal *P* values. This should be taken into account when the results are interpreted. A number of tests have retained significance after Bonferroni adjustment for multiple comparisons; this is noted in the tables. An important aspect of the BARI 2D trial design was that the revascularization arm was stratified according to the intended type of revascularization procedure.⁵ Thus, as expected, CABG patients compared with those selected for PCI, on average, had more 3-vessel disease (52% versus 20%; *P*<0.001), more total occlusions (61% versus 32%; *P*<0.001), more proximal left anterior descending stenosis ≥50% (19% versus 10%; *P*<0.001), a greater number of nonobstructive and obstructive atherosclerotic and class C lesions (*P*<0.001), and, as shown in this report, an increased cardiac death rate. We did not observe a treatment benefit in terms of prevention of all-cause death, cardiac death, MI, or the composite end point of cardiac

death or MI in the PCI stratum. Our data from patients with stable ischemic coronary disease are consistent with the findings from the COURAGE, RITA-2, and other randomized trials showing no survival benefit with prompt PCI compared with state-of-the-art initial IMT with revascularization reserved for worsening symptoms or clinical indications after ≈5 years of follow-up.^{8,20,21}

This was not the case in the patients with more severe and extensive coronary disease in the CABG stratum. Compared with IMT patients in the CABG stratum, there were significantly fewer MI events during follow-up in the CABG group and a significant reduction in the composite end point of all-cause death or MI (driven by the MI end point) and the cardiac death or MI end point in which both components contributed to the reduction in event rates. MI events were associated with a significantly increased risk of subsequent cardiac death regardless of MI type and regardless of initial

Table 4. HR of Revascularization/IMT for MI, Cardiac Death, and Cardiac Death or MI Within Glycemic Randomization Arm

	MI			Cardiac Death			Cardiac Death/MI		
	5-Year Kaplan–Meier Estimate	HR Revascularization/IMT (95% CI)	Nominal <i>P</i> for HR	5-Year Kaplan–Meier Estimate	HR Revascularization/IMT (95% CI)	Nominal <i>P</i> for HR	5-Year Kaplan–Meier Estimate	HR Revascularization/IMT (95% CI)	Nominal <i>P</i> for HR
All patients (n=2368)									
IS		0.78 (0.55–1.10)	0.16		1.11 (0.68–1.80)	0.68		0.92 (0.68–1.24)	0.57
Revascularization (n=584)	10.3 (56)			5.5 (34)			14.2 (79)		
IMT (n=599)	14.1 (74)			5.8 (32)			16.9 (89)		
IP		0.97 (0.70–1.34)	0.85		1.21 (0.76–1.94)	0.42		1.15 (0.86–1.52)	0.35
Revascularization (n=592)	12.7 (72)			6.4 (38)			17.6 (99)		
IMT (n=593)	14.4 (77)			5.7 (32)			16.5 (90)		
PCI stratum (n=1605)									
IS		1.18 (0.77–1.80)	0.45		1.74 (0.89–3.38)	0.10		1.39 (0.95–2.03)	0.09
Revascularization (n=396)	12.1 (45)			5.0 (23)			15.7 (61)		
IMT (n=408)	11.7 (41)			3.7 (14)			13.3 (47)		
IP		1.08 (0.73–1.62)	0.69		1.12 (0.60–2.07)	0.73		1.23 (0.86–1.76)	0.26
Revascularization (n=402)	12.4 (50)			5.0 (21)			16.3 (65)		
IMT (n=399)	13.5 (47)			4.8 (19)			15.2 (54)		
CABG stratum (n=763)									
IS		0.32 (0.16–0.64)	0.001*		0.62 (0.29–1.32)	0.21		0.41 (0.24–0.72)	0.002*
Revascularization (n=188)	6.3 (11)			6.6 (11)			11.0 (18)		
IMT (n=191)	19.0 (33)			10.5 (18)			24.6 (42)		
IP		0.79 (0.45–1.37)	0.40		1.37 (0.67–2.83)	0.39		1.03 (0.64–1.64)	0.91
Revascularization (n=190)	13.5 (22)			9.4 (17)			20.5 (34)		
IMT (n=194)	16.2 (30)			7.6 (13)			19.3 (36)		

Kaplan–Meier values are expressed as percentage (n). CI indicates confidence interval.

*Significant after Bonferroni adjustment for multiple tests done in the table.

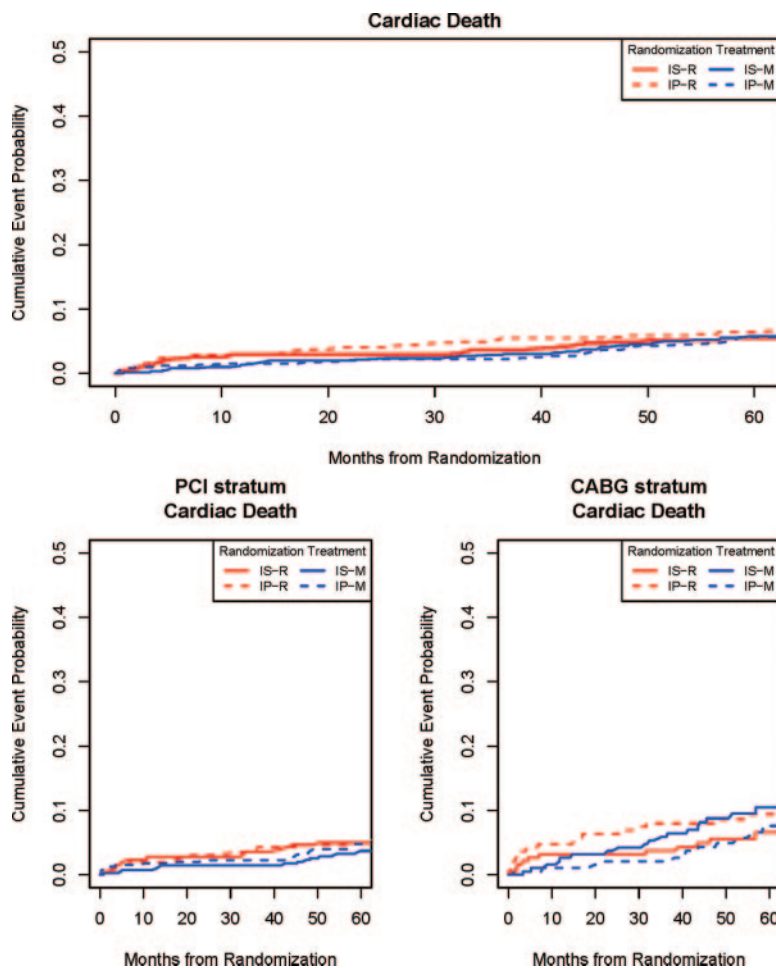


Figure 4. Time to cardiac death according to the 4 initial treatment strategies (top) and in the PCI stratum (bottom left) or CABG stratum (bottom right). IS-R indicates revascularization IS group; IP-R, revascularization IP group; IS-M, IMT IS group; and IP-M, IMT IP group.

treatment or revascularization stratum compared with patients without an MI during follow-up. One possible explanation as to why patients in the CABG stratum had fewer MIs during follow-up, as compared with the IMT group and in contrast to patients in the PCI stratum, may be that patients in the CABG stratum had more severe and extensive CAD at baseline.¹² The initial selection process of patients for the CABG stratum resulted in a population of patients with a much greater atherosclerotic burden and more lesions than in the PCI stratum, and the rates of subsequent MI and cardiac death in the IMT group were greater in the CABG stratum than in the PCI stratum. An increased number of atherosclerotic lesions at baseline was associated with an increased number of MI events during follow-up. The more comprehensive revascularization required for patients in the CABG stratum resulted in more vessels bypassed (average of 3.0 ± 1.0 compared with 1.5 ± 0.8 for PCI-treated patients),⁷ thus offering greater protection against plaque rupture (if it occurred proximal to a patent graft insertion) compared with the IMT patients in the CABG stratum. Furthermore, the difference in MI rates was affected dramatically by the type of initially assigned glyce-mic strategy. IP compared with IS in the CABG stratum was associated with a higher rate of MI, whereas initial IS and CABG therapy significantly reduced MI rates compared with the IS and IMT groups. A reduction in MI rates with IS therapy has been reported previously in observational stud-

ies.^{22,23} It is not clear why IS was specifically beneficial in those receiving CABG but not in those receiving PCI, a question that remains to be determined. One factor that was entertained in the design and implementation of the BARI 2D trial was the development of insulin-sensitizing drugs in part because they appeared to retard vasculopathy and the evolution of atherosclerotic plaques vulnerable to rupture.^{24–28} One mechanism implicated in conferring such benefits was the impact of these drugs in attenuating the increased expression of plasminogen activator inhibitor type 1²⁸ in blood and vessel walls associated with insulin resistance, thereby potentially enhancing endogenous thrombolysis and facilitating formation of biologically stable atherosclerotic plaques as opposed to plaques vulnerable to rupture.²⁹ In view of these observations, results in the present study that show a significant reduction of MI in those receiving CABG are particularly cogent and consistent with laboratory observations demonstrating vascular protective effects of insulin sensitizers in the context of insulin resistance. Although we did not observe a significant difference in cardiac death rates in patients initially assigned to IMT or to CABG, prevention of MI events is an important goal of revascularization therapy to reduce morbidity and potentially to reduce long-term cardiac death. The Coronary Drug Project enrolled 8341 men aged <65 years with a prior MI and reported a significant 17% reduction in MI

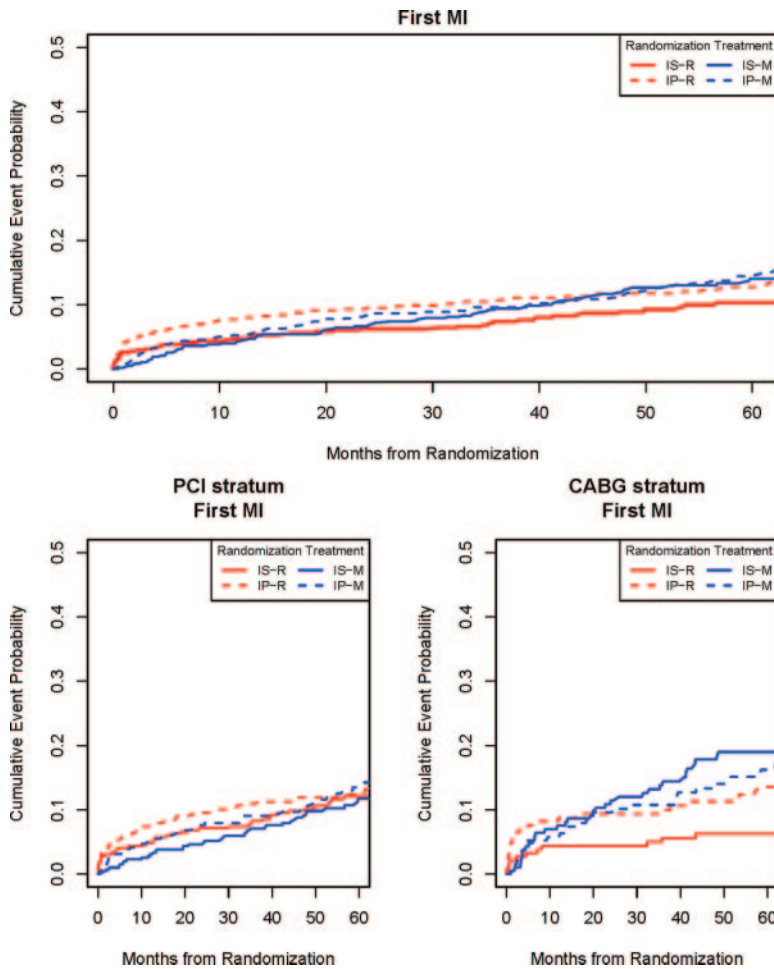


Figure 5. Time to first MI (top) according to initial treatment strategy and in the PCI stratum (bottom left) and CABG stratum (bottom right). A marked reduction in MI incidence is seen in the revascularization IS group. The relative risk of MI for revascularization/IMT was significantly different ($P=0.001$) in the IS group, whereas the difference was not significant in the IP group. IS-R indicates revascularization IS group; IP-R, revascularization IP group; IS-M, IMT IS group; and IP-M, IMT IP group.

events after 5 years of follow-up without a mortality difference between treatments.³⁰ It was only 9 years after termination of the trial that a significant mortality difference was observed with treatment (niacin) compared with placebo. Differential treatment trends in outcome that become statistically significant only after a more prolonged follow-up are well known and have been reported with trials in type 2 diabetes mellitus as well as trials comparing revascularization with medical therapy.^{31–33} The average duration of follow-up in the patients who had a nonfatal MI in BARI 2D was 3.2 years, a relatively limited amount of time for nonfatal MI events to increase mortality risk that could significantly affect longer-term treatment differences in cardiac death rates. In the BARI 2D CABG stratum, revascularization was associated with a small nonsignificant reduction in total mortality and cardiac mortality. The data support the notion that evaluation of treatment strategies in chronic disease states such as diabetes mellitus and associated coronary disease may require >5 years to determine the impact of nonfatal events known to reduce long-term survival, such as MI.

In the PCI stratum, we did not observe a significant difference in the rate of MI or cardiac mortality compared with IMT, although the relative risk of later cardiac death after sustaining a nonfatal MI was significantly less in patients in the PCI group compared with IMT alone. This

difference was not seen in the CABG stratum even though MI events were reduced. Insertion of bypass conduits distal to significant obstructive disease in the native circulation can result in competitive flow and may result in proximal occlusion of the bypassed vessel.³⁴ If graft occlusion later developed in this type of graft-dependent patient with more extensive and diffuse disease at baseline, the resultant MI may be larger and of greater consequence over time if the area of myocardium at risk was substantial.

The increased 30-day cardiac mortality rates seen after MI in the CABG compared with the PCI group are explained, in part, by the fact that the selection process for the intended revascularization at baseline resulted in the CABG stratum being at greater prognostic risk to start with as demonstrated by increased 5.3-year cardiac mortality rates in the CABG IMT group (9%) compared with the PCI IMT group (4.2%). Other explanations that might explain this observation include the fact that the upper reference limit to define periprocedure-related MI after CABG was 10 times compared with 3 times the upper limits of normal after PCI, thus restricting the diagnosis to larger MI events in the CABG compared with the PCI group, in which a lower biomarker threshold was used.

We did not observe any significant treatment differences overall between IS and IP therapy in prevention of death, cardiac death, death or MI, and cardiac death or MI. How-

ever, because BARI 2D was a 2×2 factorial design, we were able to examine interactions between the 4 treatment strategies. In the CABG stratum, the relative risk of MI for revascularization/IMT was significant ($P=0.001$) in the IS group but not in the IP group, and the interaction term was significant. The explanation for this observation requires additional research. The glycemic strategies used in BARI 2D tested IS versus IP therapy, and, within each strategy, various doses and combinations of drugs were used. Because the benefit in terms of MI reduction in the CABG stratum was only seen in patients initially assigned to the IS therapy, and IS therapy is cardioprotective against late MI events in patients with more severe and extensive coronary disease referred for CABG, this should be considered the initial therapeutic approach in this type of patient when there is no clinical contraindication(s).

Limitations

The BARI 2D trial design did not require collection of cardiac biomarkers immediately after the index revascularization procedure. Abnormal cardiac troponin or creatine kinase-MB elevations are common after a PCI or CABG procedure, and the greater the magnitude of biomarker release, the greater is the increase in mortality.^{35–39} Most patients do not have a marked increase in these biomarkers, and therefore the impact of these smaller procedural MI events on the treatment outcome mortality comparisons should be relatively small over the follow-up period in this study. In BARI 2D, total and cardiac death rates were similar between treatment strategies after 5.3 years of follow-up, although there was a nonsignificant reduction in total and cardiac mortality in the CABG stratum, and MI events were significantly reduced compared with IMT alone.

The low cardiac mortality in patients with type 2 diabetes mellitus and anatomically defined coronary disease in BARI 2D and other recently published trials in which coronary anatomy definition was not a prerequisite to enrollment is less than had been expected on the basis of natural history studies in this population, in which the majority of deaths are cardiovascular.^{1–4,40} The reasons for this finding might be the beneficial results of IMT or the duration of follow-up in the natural history studies, which allows a longer exposure time for cardiovascular events to occur and is longer than the average 5.3-year follow-up in BARI 2D. Fewer cardiac deaths in BARI 2D would result in less power to detect differences between revascularization and IMT, and a longer duration of follow-up might be required to demonstrate longer-term treatment differences. BARI 2D patients had their coronary anatomy defined before randomization, and a preselection entry bias that excluded patients with even more severe and extensive CAD than those enrolled in BARI 2D cannot be excluded. The number of patients lost to follow-up was small (4%) and not significantly different between treatment strategies.

The BARI 2D has several design advantages; it allowed clinician to assess patient revascularization needs and choose PCI or CABG accordingly, thus simulating real-practice

scenarios and challenges. By the nature of this choice, it permitted recruitment of a wider spectrum of patients with coronary disease, allowing for a broader application of our results to patients with type 2 diabetes mellitus and CAD. In the glycemic trial strategy, clinicians were allowed to maximize IS and IP therapy drugs, as in clinical practice, if the HbA_{1c} could not be lowered satisfactorily with drugs in the randomly assigned therapy group alone.

Conclusions

Our data show that for many patients with type 2 diabetes mellitus and stable but less severe and extensive CAD, intensive medical therapy is an excellent first-line strategy and does not require immediate PCI to prevent cardiac death or MI. Revascularization can be applied later if drug therapy does not adequately control symptoms without incurring an increased risk of MI or cardiac death by waiting until symptoms worsen. This is consistent with recently conducted trials in patients with stable CAD.^{8,17} However, prompt revascularization in the absence of clinical contraindications, IMT, and an IS strategy is appropriate in patients with type 2 diabetes mellitus with more severe and extensive CAD, similar to those enrolled in BARI 2D, to prevent MI. Longer-term follow-up will determine whether the reduction in MI rates seen with CABG compared with IMT translates into a treatment reduction in cardiac mortality.

BARI 2D was not designed to address whether PCI may produce outcome results similar to those of CABG in patients with more extensive disease, a question that is being addressed in the ongoing Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial.⁴¹

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Disclosures

Dr Chaitman reports receiving consulting/advisory board fees from Eli Lilly and lecture fees from Gilead. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

In this report from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, we comment on the secondary end points of cardiac death and myocardial infarction. Cardiac death accounted for 43% of all-cause mortality during an average 5.3-year follow-up, emphasizing the critical importance of intensive medical therapy to reduce death rates from cardiovascular disease in patients with type 2 diabetes mellitus and obstructive coronary artery disease. The low cardiac mortality rate is even more impressive when one considers that the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials reported that 50% to 53% of deaths were cardiovascular and only 32% to 35% of the population entered had a prior history of known coronary artery disease. The BARI 2D trial enrolled 2368 patients with stable ischemic heart disease assigned before randomization to percutaneous coronary intervention or coronary artery bypass grafting strata, and we found similar 5-year all-cause and cardiac mortality rates with insulin sensitization versus insulin provision therapy and with a strategy of prompt initial coronary revascularization plus intensive medical therapy or intensive medical therapy alone with revascularization reserved for clinical indication(s). We did not find any difference in the percutaneous coronary intervention stratum compared with intensive medical therapy in all-cause death, cardiac death, or myocardial infarction. Thus, for many patients with type 2 diabetes mellitus and stable but less severe and extensive coronary artery disease, intensive medical therapy is an excellent first-line strategy and does not require immediate prophylactic percutaneous coronary intervention to prevent cardiac death or myocardial infarction. In contrast, prompt coronary artery bypass grafting with an intensive medical therapy and insulin sensitization strategy is superior to a strategy of “watchful waiting” and intensive medical therapy alone in patients with more severe and extensive coronary artery disease to prevent nonprocedural myocardial infarctions that are associated with an increased cardiac mortality risk.

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The Bypass Angioplasty Revascularization Investigation 2 Diabetes Randomized Trial of Different Treatment Strategies in Type 2 Diabetes Mellitus With Stable Ischemic Heart Disease: Impact of Treatment Strategy on Cardiac Mortality and Myocardial Infarction

Bernard R. Chaitman, Regina M. Hardison, Dale Adler, Suzanne Gebhart, Mary Grogan, Salvador Ocampo, George Sopko, Jose A. Ramires, David Schneider, Robert L. Frye and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study Group

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Correction

In the article “The Bypass Angioplasty Revascularization Investigation 2 Diabetes Randomized Trial of Different Treatment Strategies in Type 2 Diabetes Mellitus With Stable Ischemic Heart Disease: Impact of Treatment Strategy on Cardiac Mortality and Myocardial Infarction” by Chaitman et al, which appeared in the December 22/29, 2009 of the journal (*Circulation*. 2009;120;2529–2540), an acknowledgment statement was omitted.

The acknowledgment was added on page 2538 and should read, “The authors thank Burton E. Sobel, MD, Maria M. Brooks, PhD and Sheryl F. Kelsey, PhD, for their support of this study.”

The online version of the article has been corrected. The authors regret the error.

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Supplement Table 1. Definitions for Causes of Death

3. Cause of Death: To record the primary cause of death. Record only one answer. Classify cause of death as one of the following:

3.1 Cardiac: Death originating from heart malfunction. Examples include cardiogenic shock, MI and primary cardiac arrest.

Cardiac cause of death: Specific definition provided below (check all that apply):

Sudden cardiac death (SCD): Death that occurs instantaneously or within 60 minutes after the onset of cardiac symptoms. Classification as sudden cardiac death will be made on the basis of time from onset of cardiac symptoms until death, regardless of subsequent pathologic findings. Patients who are resuscitated from cardiac arrest but die within 60 minutes after arrest will be classified as sudden death.

Probable sudden cardiac death: Death that is a consequence of SCD. For example, if the patient is resuscitated from SCD and survives 60 minutes or more, but does not recover function and dies. This would be classified as probable SCD. Also, an unwitnessed death where evidence clearly indicates SCD, could also be classified as probable SCD.

Definite myocardial infarction (MI): Death when the patient had an infarction with documentation that patient met the criteria for confirmed Q-wave or non-Q-wave MI.

Probable MI: Check if there was evidence highly suggestive of necrosis, but no physical documentation (no testing was performed or testing was incomplete).

Congestive heart failure: Verification by a physician's statement in the medical record is required. In general, CHF is clinically manifested by one or more features including: dyspnea on exertion (shortness of breath on exertion), bilateral pedal edema, fatigue, orthopnea (sleeping on two or more pillows to facilitate breathing), paroxysmal nocturnal dyspnea (shortness of breath that awakens the patient from sleep). Other findings supporting the clinical manifestations include but are not restricted to: presence of S3 gallop by auscultation, elevated jugular venous pressure >8 cm H₂O by physical exam or radiographic evidence of pulmonary congestion.

Cardiac procedure: Death within 30 days or within the same hospitalization of a cardiac procedure such as PCI, CABG, or diagnostic angiogram, when death can be reasonably attributed to the procedure (i.e. death would not have been likely to occur had the procedure not been performed).

Cardiogenic shock: Defined as a systolic blood pressure < 80 mmHg, which either persists for more than one hour or requires specific treatment for at least one hour. In general, shock is associated with a low urine output, decreased mental acuity or coma, and compensatory

vasoconstriction (decrease in blood vessel caliber). Hypotension without these associated manifestations of low cardiac output will NOT be considered shock.

Unwitnessed: Death which occurs more than 60 minutes after last observation of patient.

Other: A death for which there is evidence of a primary cardiac cause but has not been or cannot be classified as any of the above. Specify if this is the case.

3.2 Stroke: Stroke is defined as the rapid onset of persistent neurologic deficit attributed to an obstruction or rupture of the brain arterial system. The deficit is not known to be secondary to brain trauma, tumor, infection or other cause. The deficit must last more than 24 hours unless death supervenes or there is demonstrable lesion on CT or MRI compatible with an acute stroke.

Type of stroke (check one):

Cerebral infarction (CI): The acute onset (minutes to hours) of a focal neurological deficit persisting for longer than 24 hours, with or without CT or MRI documentation, and due to altered circulation to a limited region of the cerebral hemispheres, brainstem or cerebellum. CT or MRI will not show evidence of an intracerebral hemorrhage. Hemorrhagic infarction found on CT or MRI will be classified as infarction. Infarction of the retina, cochlea or labyrinth will be excluded.

Intracerebral hemorrhage (ICH): The acute onset of a focal neurological deficit associated with some or all of the following: headache, vomiting, altered level of consciousness, signs of meningeal irritation or blood stained cerebrospinal fluid. CT or MRI or autopsy will demonstrate a parenchymal hemorrhage. The rupture of either an arteriovenous malformation (AVM) or aneurysm resulting in a parenchymal hemorrhage which is noted associated with hemorrhage in the subarachnoid space will be classified as an ICH. Traumatic ICH will be excluded. ICH into an area of brain affected by another disease process such as tumor (primary or secondary) or encephalitis will be excluded.

Primary subarachnoid hemorrhage (SAH): The abrupt onset of headache, with or without altered consciousness, with signs of meningeal irritation. A focal neurological deficit may develop acutely or with a delay of hours or days after the other criteria were known to have been present. CT or MRI will show blood in the subarachnoid space. If performed, cerebrospinal fluid examination will show increased red blood cell count or xanthochromia. The imaging studies may show an intraparenchymal hemorrhage which occurred either at or after the onset of the primary subarachnoid hemorrhage. Parenchyma hemorrhage that extends into the subarachnoid space will be classified as an Intracerebral hemorrhage. SAH due to trauma will be excluded.

Indeterminant cerebrovascular event (stroke of uncertain type): Clinical evidence of a stroke but insufficient information to establish a pathologic diagnosis.

3.3 Non-cardiovascular – atherosclerotic disease other than stroke: Death related to atherosclerotic vascular disease other than stroke but clearly not to cardiac death. Examples include aneurysm and atherosclerotic renal failure.

3.4 Non-cardiovascular – medical: Death clearly not related to cardiac disease or atherosclerotic vascular disease, although heart disease may be present. This category includes neoplasm, liver disease and septic shock.

3.5 Non-cardiovascular – related to surgery or procedure: Patient died as a direct result of a complication occurring during or within 24 hours after an elective procedure. An example of such elective procedures would be surgery for hernia repair and GI bleeding post procedure.

3.6 Diabetes complication other than cardiovascular disease: Disease complication cause of death (check all that apply):

Hypoglycemia: (1.) Sudden death within 30 minutes of a known blood glucose < 40 mg/dL. (2.) Death resulting from MVA, drowning, fall, injury, accident within 30 minutes of a known blood glucose < 50 mg/dL.

Diabetic ketoacidosis (DKA): Death from metabolic cause within 24 hours of documented DKA defined by absolute insulin deficiency with hyperglycemia (glucose level >300 mg/dL) with increased lipolysis, increased ketone production (ketone levels positive at 1:4 dilution of serum or greater OR beta hydroxybutyrate > 2 mmol/L), and acidosis (pH<7.30 or HCO₃ <15 mEq/L).

Hyperosmolar hyperglycemic nonketotic coma: Death within 48 or 72 hours of documented blood glucose >600 mg/dL and no other cause (e.g. MI, pancreatitis, sepsis, etc.)

Other: If diabetes cause of death is other than one of the above categories, specify cause of death.

Specify: Self-explanatory.

3.7 Diabetes-related renal failure: Death with BUN >100, serum creatinine >5.0, serum potassium >6.0, urine protein >300 mg/DL or on dialysis with nephropathy or biopsy proven glomerulosclerosis, or no evidence of renal disease other than diabetic nephropathy.

3.8 Diabetes-related amputation: Non-traumatic amputation required for gangrene, foot ulcer and intractable infection leading to death.

3.9 Accident and trauma: Refers to violent death due to accident, such as automobile accident, drowning, or gunshot wound.

3.10 Suicide: Patient deliberately brings about own death.

3.11 Unknown: If primary cause cannot be determined, record “unknown.”

Supplement Table 2. Five Year Kaplan-Meier Estimates for Non-Procedural MI Events, According to Type of Myocardial Infarction (Q-wave and non-Q-wave), and Cardiac Cath or Non-Procedural Myocardial Infarction, According to Initial Treatment Strategy, and According to PCI and CABG Stratum

5 year KM estimate (n)	N	Non-Procedural MI			Cardiac Death or Nonprocedural MI
		Documented		All Non-procedural MI (includes Fatal)	
		Q-wave	Non-Q		
All Patients	2368				
Prompt Coronary Revascularization	1176	2.5% (25)	5.5% (61)	8.8% (96)	13.4% (149)
Intensive Medical Therapy	1192	2.9% (32)	9.0% (92)	13.3% (138)	15.8% (167)
Nominal P-Value		0.41	0.017*	0.009*	0.40
PCI Stratum	1605				
Prompt Coronary Revascularization	798	2.3% (17)	6.6% (51)	9.4% (72)	13.3% (105)
Intensive Medical Therapy	807	2.6% (18)	8.0% (54)	11.4% (79)	13.2% (93)
Nominal P-Value		0.93	0.87	0.69	0.29
CABG Stratum	763				
Prompt Coronary Revascularization	378	3.0% (8)	2.9% (10)	7.6% (24)	13.7% (44)
Intensive Medical Therapy	385	3.6% (14)	11.2% (38)	17.1% (59)	21.4% (74)
Nominal P-Value		0.23	<0.001**	0.0001**	0.006*
Insulin Provision Therapy	1185	2.1% (22)	8.2% (89)	11.4% (122)	15.0% (164)
Insulin Sensitization Therapy	1183	3.3% (35)	6.3% (64)	10.7% (112)	14.2% (152)
Nominal P-value		0.08	0.03*	0.47	0.45

[†]Cause of Death determined by independent Mortality and Morbidity committee; ^{††}Includes documented MI's from the Core ECG lab and/or Fatal MI's as determined by death classification

*significant at nominal level

** significant after Bonferroni adjustment for multiple tests done in the table

Supplement Table 3. Hazard Ratio of Death or Cardiac Death by Post Randomization Non-procedural MI Status

	Number of Deaths†		HR of Death† (95% CI)	Nominal p-value for equality between HR	Number of Cardiac Deaths†		HR of Cardiac Death* (95% CI)	Nominal p-value for equality between HR
	Rev	IMT	Rev/IMT		Rev	IMT	Rev/IMT	
All Patients (n = 2368)								
MI	30	45	0.96 (0.61- 1.53)	0.48	19	35	0.78 (0.44 – 1.36)	0.013*
No MI	107	93	1.17 (0.89– 1.54)		52	27	1.96* (1.23 – 3.12)	
PCI Stratum (n = 1605)								
MI	19	26	0.66 (0.37 – 1.20)	0.04*	11	19	0.54 (0.26 – 1.15)	0.003*
No MI	72	54	1.37 (0.97 – 1.96)		33	14	2.41* (1.28- 4.50)	
CABG Stratum (n = 763)								
MI	11	19	2.1 (1.01– 4.52)	0.05	8	16	1.50 (0.63 – 3.54)	0.97
No MI	35	39	0.88 (0.56 – 1.39)		19	13	1.47 (0.72 – 2.97)	
	IP	IS	IP/IS		IP	IS	IP/IS	
All Patients (n = 2368)								
MI	41	34	0.98 (0.62-1.55)	0.93	28	26	0.88 (0.52 – 1.51)	0.56
No MI	100	100	1.01 (0.76 – 1.33)		41	38	1.09 (0.70-1.69)	

†censored at last known MI follow-up

*significant at nominal level

CABG = coronary artery bypass grafting; IP/IS = insulin provision/insulin sensitization; MI = myocardial infarction; PCI = percutaneous coronary intervention; Rev/Med = revascularization/medicine