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Appropriate Revascularization in Stable Angina, Lessons from the BARI 2D Trial

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Abstract

Background—The 2012 Guidelines for Diagnosis and Management of Patients with Stable Ischemic Heart Disease recommend intensive antianginal and risk factor treatment (OMT) before considering revascularization to relieve symptoms. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) randomized patients with ischemic heart disease and anatomy suitable to revascularization to 1): initial OMT with revascularization if needed or 2): initial

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revascularization plus OMT, and found no difference in major cardiovascular events. Ultimately, however, 37.9% of the OMT group was revascularized (crossed over) during the 5 year follow-up period.

METHODS—Data from the 1192 patients randomized to OMT were analyzed to identify subgroups where the incidence of revascularization was so high that direct revascularization without a trial period could be justified. Multivariate logistic, Cox regression models of baseline data and a landmark analysis of participants not revascularized at six months were constructed.

RESULTS—The models using only data available at the time of study entry had limited predictive value for revascularization by 6 months or by 5 years; however, the model incorporating severity of angina during the first 6 months could better predict revascularization (C statistic = .789).

CONCLUSIONS—With the possible exception of patients with severe angina and proximal LAD disease, this analysis supports the recommendation of the 2012 GUIDELINES for a trial of OMT prior to revascularization. Patients could NOT be identified at the time of catheterization, but a short period of close follow-up during OMT identified the nearly 40% of patients who underwent revascularization.

Keywords

Diabetes mellitus; coronary revascularization; coronary artery disease

INTRODUCTION

Despite publication of several independent randomized studies showing intensive or optimal medical management (OMT) with revascularization *only if required clinically* provides results equal to OMT with revascularization performed promptly after angiography (R+OMT),^{2,3} many physicians and/or patients proceed with revascularization despite the lack of evidence that would support R+OMT over initial OMT only. A recent meta-analysis comparing 8 studies of R+OMT (stent) compared to OMT alone reached the conclusion: “initial stent implantation for stable coronary artery disease shows no evidence of benefit compared with initial medical therapy for prevention of death, nonfatal myocardial infarction, unplanned revascularization or angina.”⁴ These findings have been incorporated into the update of Appropriate Use Criteria for Coronary Revascularization where appropriateness was heavily dependent on symptoms, anatomy and response to medical treatment.⁵ However, incorporating these recommendations into practice remains problematic.^{6,7}

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial was designed to compare management strategies in persons with diabetes and stable coronary disease.³ Participants with documented ischemic disease were randomly assigned to receive OMT, with revascularization deferred until clinically indicated or to receive OMT and prompt revascularization (R+PMT). Despite similarities in outcome between the two arms, only 37.9% of participants assigned to OMT were revascularized during the 5 year follow-up.

Our goal was to identify patients assigned to OMT who would benefit from early revascularization obviating the need for a trial of therapy. We attempted to develop a model using baseline data to identify variables to predict a high likelihood for eventual revascularization. In effect, we reviewed these data to determine if the Appropriate Use Criteria⁵ were concordant with practice, and to produce a model creating subgroups within the BARI 2D OMT population so likely to be revascularized that a trial of anti-angina therapy was not needed. We were especially concerned in this diabetic population with a well described high incidence of silent ischemia,⁸ that clinical angina would not be a good indicator of the need for revascularization.⁹

METHODS

Study Population and Treatment Strategies

The BARI 2D methods and exclusion criteria have been described in detail.³ BARI 2D was a multi-center international randomized clinical trial testing two major strategies. Eligible subjects had Type 2 diabetes mellitus and documented ischemia and angiographically defined coronary artery disease (CAD); at least one lesion $\geq 50\%$ stenosis, or symptoms of angina and a lesion of $\geq 70\%$. Participants were assigned to either a glycemic control strategy of “insulin sensitization” or a glycemic control strategy of “insulin provision” therapy to a target HbA1c of $<7.0\%$ AND a strategy of OMT and up-front revascularization (R+OMT) or OMT with revascularization only if necessary. Randomization was stratified according to the intended method of revascularization: percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The method of revascularization was chosen by the treating physician after coronary angiography, but before randomization. CABG stratum participants had more extensive disease, total occlusions, proximal left coronary disease, and a greater myocardial jeopardy index¹⁰ than those selected for PCI.¹ Between January 1, 2001 and March 31, 2005, participants were enrolled at 49 clinical sites in the United States, Canada, Brazil, Mexico, the Czech Republic, and Austria. Overall, 2,368 participants were enrolled in the study; of these, 1192 participants were randomized to OMT with revascularization only if needed clinically. Of these, 385 (32.3%) were in the CABG stratum and 807 (67.7%) were in the PCI stratum. All participants were treated with OMT according to current guidelines for risk factor control: lipid, glucose and blood pressure management, smoking cessation, physical activity, and weight loss.¹¹ “Target levels for risk factors were adjusted throughout the trial to comply with changes in recommended clinical practice guidelines. The goals for low-density lipoprotein cholesterol <2.59 mmol/L (<100 mg/dL) with an optional goal of <1.81 mmol/L (<70 mg/dL); plasma triglyceride level <1.70 mmol/L (<150 mg/dL); blood pressure level <130 mm Hg systolic and <80 mm Hg diastolic; and smoking cessation treatment for all active smokers. Algorithms were developed for the pharmacologic management of dyslipidemia and hypertension. Dietary prescriptions for the management of glycemia, plasma lipid profiles, and blood pressure levels were adapted from existing clinical practice guidelines. Patients with a body mass index >25 were prescribed moderate caloric restriction; after the trial was under way, a lifestyle weight-management program was instituted. All patients were formally prescribed both endurance and resistance/flexibility exercises, individually adapted to their level of disability and fitness. Pedometers were distributed as a biofeedback strategy.

Strategies to achieve the goals for risk factors were designed by BARI 2D working groups (lipid, cardiovascular and hypertension, and nonpharmacologic intervention) and the ongoing implementation of the strategies is monitored by lipid, hypertension, and lifestyle intervention management centers.”¹¹

For participants assigned to OMT, revascularization was to be used only when clinically indicated. A manual plus training sessions provided definitions for symptoms, and atypical angina/angina equivalents.¹² By protocol, subsequent revascularization could be performed if severity of angina progressed to unacceptable levels despite medical therapy, acute coronary syndrome with hemodynamic instability developed or recurred, or anatomic disease had sufficiently advanced and noninvasive testing demonstrated severe ischemia.¹³ Participants were seen monthly by a cardiologist and diabetologist for the first 6 months and then every 3 months. The mean follow-up interval was 5.3 years (range, 3.4-7.8 years). A Mortality and Morbidity Committee adjudicated all acute coronary syndrome events. The institutional review board at the University of Pittsburgh and at each participating site approved the protocol. All participants provided written consent.

Statistical Analysis—We evaluated participants randomized to OMT to establish rates of revascularization within six months of randomization and within the five-year follow-up period, respectively, and also to identify predictors of revascularization. Baseline demographic, clinical and angiographic characteristics were compared between participants who did not require revascularization during the study to those who underwent revascularization by six months and by five years, respectively. Distributions of baseline variables were compared using chi-square tests to analyze differences between those groups.

A logistic regression model was developed to identify clinical and angiographic variables which predicted the need for revascularization within six months of randomization, using only information available at study entry. We repeated this analysis using the worst recorded angina status within the first six months to determine if early angina was the main driver of revascularization. This model was created using a forward selection algorithm with age, sex, race, and geographic region forced to enter the model at onset. The primary outcome is revascularization within six months of randomization. Using the same forward selection algorithm, we developed a Cox proportional-hazards model to determine which clinical and angiographic variables predicted a need for revascularization within the entire follow up period. A landmarked Cox analysis, using only participants who survived six months without a revascularization, was performed to evaluate the effects of severity of angina at the six month visit on the likelihood of revascularization for the duration of the study. The primary outcome measure for these analyses is the occurrence of revascularization by any means after six months, but before the end of the five-year follow up period. P-values < 0.05 were considered statistically significant for all analyses reported here. No statistical adjustment was made for multiple comparisons.

RESULTS

The 1192 participants assigned to OMT alone had an average age of 62.4 ± 9.0 years with average diabetes duration of 10.7 ± 8.8 years. Of these, 24.2% had prior revascularization,

30.4% triple vessel disease, and 13.3% proximal LAD disease: In the six weeks preceding study entry, 41% had no angina, 44% Canadian Cardiovascular Society (CCS) class I/II angina, 7% CCS class III/IV and 8% unstable angina.

Overall, 452 (37.9%) participants randomized to initially only OMT were revascularized within five years of follow up. Baseline characteristics by the status of the subsequent revascularization are displayed in Table 1. Severity of baseline angina status, low systolic blood pressure, geographic region/country, and proximal LAD disease were associated with increased likelihood of revascularization. Specifically, 35% of participants with no or CCS Class I or II angina at baseline and 51% of the participants with more severe angina -CCS Class III or IV or unstable angina - were ultimately revascularized during the 5 year follow-up. No significant differences were observed in other baseline variables by revascularization status including extent of disease such as intended revascularization stratum, number of significant lesions, myocardial jeopardy index, and the presence of total occlusion, or baseline HgA1c.

The percentage of participants who had eventual revascularization in the PCI intended stratum was similar to that in the CABG intended stratum (35.6% vs. 39.0%, $p=0.36$, Figure 1). Severe angina symptoms was the most common reason for revascularization, accounting for 47% of revascularizations, with acute coronary syndrome accounting for 23%, thus sum, 70% of revascularizations were for continuing ongoing severe angina or acute coronary syndrome. Worsened ischemia accounted for 18% of the revascularizations, disease progression in 6% and other reasons in 6%.

Risk factors for revascularization within 6 months were evaluated using a multivariate logistic regression model (Table 2). The strongest risk factors for early revascularization were baseline angina symptoms, low systolic blood pressure (<100 mm Hg), and proximal LAD disease. However, the predictive quality of this model was relatively weak (Harrell's C-statistic = 0.677). Replacing baseline angina status with the worst recorded angina status within the first six months markedly improved the model-- C statistic = .789 (Table 3). "Baseline HbA1C" did not improve the overall model so we did not include it in Table 3.

In the subset of 21 participants with a proximal LAD lesion and severe clinical symptoms, 15 (71.4%) were revascularized. There was no significant difference in mortality rate or the rate of cardiovascular events between those that were revascularized and those that were not. Participants with unstable angina at baseline and proximal LAD disease (1.7% of the BARI-2D population) were more than twice as likely to be revascularized as participants with unstable angina but no LAD disease. However, the numbers of patients that fit this category are so small that no definitive comments can be made.

Risk factors for revascularization during the 5 year BARI 2D follow-up were evaluated using a Cox proportional-hazards regression model. The severity of angina in the first 6 months, low systolic blood pressure, elevated triglycerides, proximal LAD disease, and the number of diseased myocardial regions at baseline were significantly associated with an increased risk of long-term revascularization after adjusting for age, sex, race, and country. Participants with ≥ 2 diseased myocardial regions were more likely to be revascularized than

participants with one diseased region, but this effect emerged after several months. Overall, the model demonstrated reasonably good discrimination (C-Index =.701) but the predictive value for the individual patient was not sufficient to identify individual participants to a high enough level of certainty to permit *a priori* revascularization.

In the six months after randomization, 151 participants were revascularized, 16 died and 32 were lost to follow-up. The landmark analysis restricted to the 993 participants that survived and were procedure-free at six months showed that the number of diseased myocardial regions at baseline, angina status at the six-month visit and triglyceride levels > 150mg/dL were predictive of subsequent revascularization, but again with a fairly low level of certainty (C-Index =.677. (Table 4, Figure 2). The HgA1c level at 6 months, a measure of diabetic control was not quite associated with revascularization and improved the C statistic .001 (Table 4) Over 50% of participants with severe angina at the six-month visit were revascularized within the next six months, and over 70% within the next 4 years. However, the number of participants with class III or IV angina category was low, (71 or 6% of the patients randomized to OMT with revascularization if needed), so that even though certain subgroups of participants had a very high likelihood of revascularization, the model itself had only a modest ability to discriminate between those who received and those who did not receive revascularization.

DISCUSSION

The 2012 Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease¹⁴ and the 2012 Appropriate Use Criteria for Coronary Revascularization⁵ have emphasized that a trial of medical therapy prior to revascularization for the majority of patients with stable coronary disease will limit procedures without an increase in adverse clinical events. We evaluated this strategy in a post hoc analysis of the BARI 2D database to attempt to identify clinical features which could predict early revascularization to obviate the need for such a trial. Relatively few risk factors were independently associated with revascularization. Unfortunately, the model did not permit identifying patients who would undergo intervention with a high enough level of certainty that interventions could be done promptly or *ad hoc*, at the time of the diagnostic cath. While there were more interventions in patients presenting with more severe angina (Table 1),¹⁵ this variable alone did not predict intervention (crossover). However, if we included the most severe angina over first six months, that model was fairly robust. (Table 3). Monitoring symptoms of angina for the first 6 months seemed to be the most consistent technique to identify participants who could not be managed without intervention. Seventy percent of revascularizations were for severe angina, while 24% of revascularizations were for increased ischemia or progression of coronary disease-presumably the result of stress testing, which was not mandated. The rate of revascularization in all participants within 6 months of randomization was only about 20 percent.

This conclusion is similar to that of an analysis of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial which showed that patients who were randomized to OMT and crossed over to revascularization did not have a higher incidence of irreversible ischemic events or impaired 12 month health status. The

authors concluded that an initial trial of medical therapy was supported since only 1/3 of patients were ultimately revascularized.¹⁶ Several other analyses of the BARI 2D database have been done to attempt to go beyond the important finding that the major outcomes of the group as a whole were similar for both the R+OMT group and the OMT group. Dagenais et al. showed that early revascularization limited the progression of symptoms during the study, but primarily in the patients with high risk anatomy in the CABG strata,¹⁵ and Brooks et al. noted that while all patients' health status improved during the study, improvement in R+OMT patients, especially those in the CABG strata, was slightly but statistically significantly better than OMT,¹⁷ and was most evident in the high risk fraction.¹ In the remaining patients there was no benefit to early revascularization in these endpoints

Patients with diabetes have an increased incidence of silent ischemia ranging from 12% to 33%.^{8,18} There has been a concern that clinical management, which relies heavily on symptoms, would be inferior to aggressive "upfront" revascularization.⁹ However, monitoring symptoms was successful in the BARI 2D.

These findings have important implications when considering the current fashion for *ad hoc* PCI in patients with stable angina.¹⁹ We have found that in the BARI 2D study, with the possible exception of patients with significant proximal LAD disease and severe angina symptoms, it was not possible to identify patients who would go on to intervention with a high enough degree of certainty that preemptive intervention could be justified.

Limitations

This post-hoc analysis acknowledges the complex interplay of numerous factors that inform clinical decisions made by scores of physicians and can only be hypothesis generating. Risk factors were all well managed, but other clinical features that might impact the decision were either not measured, such as frailty, bleeding risk, compliance with meds, patient preference, or developed during the trial. The trial established guidelines for performing revascularization, but the decision to revascularize was left to the individual physicians and participants.

CONCLUSION

Using the data available at the time of the initial diagnostic angiogram, models could not be constructed to identify patients who would undergo revascularization either in the first 6 months or during the entire course of the study with enough confidence for preemptive revascularization. Closely following patients on OMT during the first six months, reserving intervention for those with continuing severe angina or worsening ischemia, revascularization was recommended in less than 40% of patients. The outcome over 5 years was similar compared to patients who were revascularized on study entry. These findings support the appropriate use criteria for revascularization as published and should give pause to performing *ad hoc* PCI in suboptimally treated diabetic patients with stable coronary disease.

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The contributions of all the investigators in the BARI 2D study have been enumerated in the past³

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BRIEF SUMMARY

BARI-2D patients in the optimal medical therapy cohort were analyzed to identify subgroups where crossover revascularization was so high that a trial of medical therapy was not needed. A model was developed after 6 months follow-up which identified a group with such a likelihood of crossover but this could not be done at baseline. With this paradigm, only 40% of patients were revascularized but with an outcome similar to those with upfront revascularization.

Figure 1.
Time to first procedure among BARI 2D participants assigned to medical therapy, stratified by Intended Revascularization Strata, CABG or PCI
Abbreviations: CABG = Coronary Artery Bypass Grafting
PCI=Percutaneous Coronary Intervention

Figure 2.

Landmark analysis: Estimate of subsequent procedure rate, by Baseline Angina and Angina at 6 Months. The curves are reset at 6 months using the angina status at 6 months.

Angina 1 = No Angina

Angina 2 = Stable Angina CCS Class I/II

Angina 3 = Stable Angina CCS Class III/IV

Angina 4 = Unstable Angina

The ability of the model to classify patients (i.e. its predictive performance) was evaluated using the C statistic, a term equivalent to the area under a receiver operating characteristic curve for dichotomous outcomes.

Table 1

Relationship of Demographics to Time to First Revascularization Procedure*

		Time to First Procedure			P-Value
		(<6 months)	6mo-5 years	None	
Demographics					
Sex					0.394
Male	838	99 (11.8%)	214 (25.5%)	525 (62.7%)	
Female	354	52 (14.7%)	87 (24.6%)	215 (60.7%)	
Race					0.132
White	794	100 (12.6%)	189 (23.8%)	505 (63.6%)	
Black	194	29 (14.9%)	55 (28.3%)	110 (56.7%)	
Hispanic	147	18 (12.2%)	39 (26.5%)	90 (61.2%)	
Other	57	4 (7.0%)	18 (31.5%)	35 (61.4%)	
Countries					<0.001
United States of America	756	107 (14.2%)	212 (28.0%)	437 (57.8%)	
Canada	178	25 (14%)	56 (31.5%)	97 (54.5%)	
Brazil	178	8 (4.5%)	19 (10.7%)	151 (84.8%)	
Mexico	43	5 (11.6%)	6 (14.0%)	32 (74.4%)	
Czech Republic/Austria	37	6 (16.2%)	8 (21.6%)	23 (62.3%)	
Clinical Characteristics					
Blood Pressure					0.017
<130/80	536	78 (14.6%)	149 (27.8%)	309 (57.7%)	
130/80	636	69 (10.9%)	150 (23.6%)	417 (65.6%)	
Total cholesterol, mg/dl					0.161
<200	925	109 (11.8%)	230 (24.9%)	586 (63.4%)	
200	237	36 (15.2%)	66 (27.9%)	135 (57.0%)	
HbA1c					0.361
<7.0%	451	56 (12.4%)	103 (22.8%)	292 (64.8%)	
7.0-8.0%	305	36 (11.8%)	89 (29.2%)	180 (59.0%)	
>8.0%	409	55 (13.5%)	105 (25.7%)	249 (60.9%)	
History of Disease					
History of Myocardial Infarction					0.177
Yes	378	49 (13.0%)	82 (1.7%)	247 (65.3%)	
No	790	99 (12.5%)	211 (26.7%)	480 (60.8%)	
History of Classic Angina					0.186
Yes	863	117 (13.6%)	223 (25.8%)	523 (60.6%)	
No	328	34 (10.4%)	78 (23.8%)	216 (65.9%)	
Recent Angina (within 6 weeks of randomization)					<0.001
No Angina	489	44 (9.0%)	119 (24.3%)	326 (66.7%)	
Stable, CCS Class I/II	526	70 (13.3%)	129 (24.5%)	327 (62.2%)	

		Time to First Procedure			P-Value
		(<6 months)	6mo-5 years	None	
Stable CCS Class III/IV	84	17 (20.2%)	25 (29.8%)	42 (50.0%)	
Unstable Angina	92	20 (21.7%)	28 (30.4%)	44 (47.8%)	
Insulin at study entry					0.114
Yes	341	51 (15.0%)	93 (27.3%)	534 (63.9%)	
No	836	97 (11.6%)	205 (24.5%)	197 (57.8%)	
Extent of Disease					
# Significant Lesions (> 50% stenosis)					0.184
0	82	8 (9.8%)	20 (24.4%)	54 (65.9%)	
1-2	546	66 (12.1%)	124 (22.7%)	356 (65.2%)	
3+	562	76 (13.5%)	157 (27.9%)	329 (58.5%)	
Myocardial Jeopardy Index (MJI)					0.296
<25%	312	37 (11.9%)	71 (22.8%)	204 (65.4%)	
26-50%	429	54 (12.6%)	109 (25.4%)	266 (62.0%)	
51-75%	312	36 (11.5%)	79 (25.3%)	197 (63.1%)	
>75%	137	23 (16.8%)	42 (30.7%)	72 (52.3%)	
Presence of Total Occlusion					0.166
Yes	490	60 (12.2%)	111 (22.7%)	319 (65.1%)	
No	700	90 (12.9%)	190 (27.1%)	420 (60.0%)	
Proximal LAD Disease					0.064
Yes	158	28 (17.7%)	43 (27.2%)	87 (55.1%)	
No	1032	122 (11.8%)	258 (25.0%)	652 (63.2%)	

Table 2

Multivariate Logistic Regression Model for Early Revascularization (< 6 months)

	OR	95% CI	P-Value
Baseline Angina (vs. No Angina)			<.001
CCS Stable I/II	1.50	0.98-2.29	
CCS Stable III/IV	2.79	1.47-5.31	
Unstable Angina	2.34	1.26-4.36	
Systolic Blood Pressure (vs. >120)			0.006
101-120	1.30	0.86-1.96	
100	3.64	1.60-8.30	
Proximal LAD Disease			0.021
Yes	1.75	1.09-2.82	

*Adjusted for age, sex, race, and geographic region

C-Statistic = 0.677

All explanatory variables are obtained at baseline.

CCS = Canadian Cardiovascular Society Angina score

LAD = Left Anterior Descending coronary artery

OR = Odds Ratio

95% CI = 95% Confidence Intervals

Table 3

Multivariate Logistic Regression Model for Revascularization < 6 months

	OR	95% CI	P-Value
Worst 6-Month (vs. No Angina)			<.001
CCS Stable I/II	2.08	1.23-3.53	
CCS Stable III/IV	9.97	4.51-21.99	
Unstable	18.91	9.82-36.39	
Systolic Blood Pressure (vs. >120)			0.006
101-120	1.29	0.78-2.11	
100	4.62	1.80-11.84	
Proximal LAD Disease			0.034
Yes	1.89	1.05-3.40	

* Multivariate logistic regression model adjusted for age, sex, race, and geographic region

C-Statistic = 0.789

Angina CCS score is worst level in the first 6 monthly visits.

Blood pressure and LAD disease are at baseline.

Abbreviations

OR = Odds Ratio

95% CI = 95% Confidence intervals

Table 4

Landmark Cox Proportional-Hazards Model predicting Long-term Subsequent Revascularization among Patients free of revascularization at 6 months

	Adjusted HR	95% CI	P-Value
Worst 6-Month (vs. No Angina)			<.001
Stable CCS I or II	1.73	1.25-2.41	
Stable CCS III or IV	4.53	2.40-8.54	
Unstable Angina	6.21	3.76-10.53	
Systolic Blood Pressure (vs. >120)			0.045
101-120	0.91	0.66-1.25	
100	1.77	1.01-3.08	
Triglycerides (vs. <150)			
150	1.42	1.05-1.90	0.021
# Diseased Regions			<.001
2	1.59	1.10-2.30	
3	1.77	1.22-2.59	
6-month HbA1c	1.12	1.00-1.26	0.054

*Adjusted for age, sex, race, and country

C-Statistic = 0.678

This analysis takes all persons at 6 months not yet revascularized and models long term subsequent revascularizations during the remainder of the study.

Abbreviations

HR Hazard Ratio