Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 15, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.01.043

CME

Impact of Repeat Myocardial Revascularization on Outcome in Patients With Silent Ischemia After Previous Revascularization

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CME Editor Disclosure: *JACC* CME Editor Ajit Raisinghani, MD, FACC, reports that he has no financial relationships or interests to disclose.

Author Disclosures: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz)

CME Term of Approval:

Issue date: April 16, 2013
Expiration date: April 15, 2014

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Manuscript received September 15, 2012; revised manuscript received December 19, 2012, accepted January 8, 2013.

Impact of Repeat Myocardial Revascularization on Outcome in Patients With Silent Ischemia After Previous Revascularization

Objectives This study sought to compare the survival of asymptomatic patients with previous revascularization and ischemia, who subsequently underwent repeat revascularization or medical therapy (MT).

Background Coronary artery disease is progressive and recurring; thus, stress myocardial perfusion scintigraphy (MPS) is widely used to identify ischemia in patients with previous revascularization.

Methods Of 6,750 patients with previous revascularization undergoing MPS between January 1, 2005, and December 31, 2007, we identified 769 patients (age 67.7 ± 9.5 years; 85% men) who had ischemia and were asymptomatic. A propensity score was developed to express the associations of revascularization. Patients were followed up over a median of 5.7 years (interquartile range: 4.7 to 6.4 years) for all-cause death. A Cox proportional hazards model was used to identify the association of revascularization with all-cause death, with and without adjustment for the propensity score. The model was repeated in propensity-matched groups undergoing MT versus revascularization.

Results Among 769 patients, 115 (15%) underwent revascularization a median of 13 days (interquartile range: 6 to 31 days) after MPS. There were 142 deaths; mortality with MT and revascularization were 18.3% and 19.1% ($p = 0.84$). In a Cox proportional hazards model (chi-square test = 89.4) adjusting for baseline characteristics, type of previous revascularization, MPS data, and propensity scores, only age and hypercholesterolemia but not revascularization were associated with mortality. This result was confirmed in a propensity-matched group.

Conclusions Asymptomatic patients with previous revascularization and inducible ischemia on MPS realize no survival benefit from repeat revascularization. In this group of post-revascularization patients, an ischemia-based treatment strategy did not alter mortality. (J Am Coll Cardiol 2013;61:1616–23) © 2013 by the American College of Cardiology Foundation

Asymptomatic (silent) ischemia is common among patients with coronary artery disease (CAD) (1) and is associated with adverse outcomes (2). Patients with previous revascularization are prone to both recurrent ischemia and coronary events (due to progression of native coronary disease and/or graft closure and restenosis), which are often silent. Based on the ability of single-photon emission computed tomography (SPECT) to predict outcomes post-coronary artery bypass graft (CABG) (3,4), the appropriate-use criteria have deemed functional testing to be appropriate for asymptomatic patients >5 years after CABG but still uncertain for asymptomatic patients with previous percutaneous coronary intervention (PCI) or <5 years after CABG (5). Nonetheless, testing is often performed despite this uncertainty.

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Although the detection of silent ischemia identifies patients at risk, the more controversial aspect relates to whether this risk is responsive to treatment. Initial reports emphasized that the recognition of this entity was important because either medical therapy (MT) or revascularization have been linked to improved survival (6,7). Nonetheless, in the post-revascularization population, our recent work found no survival benefit from the use of such a strategy using stress echocardiography (8). These findings seemed consistent with the recent COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, which found that a strategy of initial PCI with aggressive MT has no survival benefit over aggressive MT alone in patients with angiographically documented CAD (9), irrespective of extent of baseline perfusion defect (10). These findings are discordant with observational data, which indicate that myocardial perfusion scintigraphy (MPS)-identified inducible ischemia is associated with improved survival with revascularization in patients without previous myocardial infarction or revascularization (11,12). Accordingly, because the usefulness of functional testing for symptomatic patients is well established (5), we hypothesized that repeat revascularization in asymptomatic post-revascularization patients who had MPS evidence of ischemia would improve their outcome. Thus, the aim of the current study was to define the benefit of repeat revascularization in this setting, after adjustment for baseline characteristics, type of previous revascularization, and size of inducible perfusion defects.

Methods

Study population. We identified 6,750 consecutive patients with a history of revascularization (CABG or PCI) who underwent exercise or adenosine stress MPS between

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
CPH = Cox proportional hazards
HR = heart rate
IQR = interquartile range
LVEF = left ventricular ejection fraction
MPS = myocardial perfusion scintigraphy
MT = medical therapy
PCI = percutaneous coronary intervention
SPECT = single-photon emission computed tomography

January 1, 2005, and December 31, 2007. Symptomatic patients and/or those without inducible ischemia on SPECT MPS were excluded, leaving a final study population of 769 patients (age 67.7 ± 9.5 years; 85% men) who were followed up over a median of 5.7 years (interquartile range [IQR]: 4.7 to 6.4 years) for all-cause death. The study was approved by the institutional review board of the Cleveland Clinic.

For the purpose of this study, patients were separated into those undergoing MT (n = 654) and those undergoing revascularization (n = 115). The median time to repeat revascularization after SPECT scan was 13 days (IQR: 6 to 31 days); the majority (n = 103) underwent revascularization within 60 days or less, another 11 had revascularization within 6 months, and 1 underwent revascularization within 1 year. These groups were compared by using a propensity score (as discussed in the Statistical Analysis section) to compensate for nonrandom referral to revascularization.

Stress testing. Exercise stress testing was performed in 323 patients (42%) who were able to exercise. Exercise capacity was estimated in metabolic equivalents, and heart rate (HR) and blood pressure responses were recorded. The chronotropic response index was calculated according to the formula using HR values: (peak HR − resting HR)/([220 − age] − resting HR), where HR is given in beats per min. A low chronotropic response index (<0.8) in a patient who is not receiving beta-blocker therapy is associated with an increased likelihood of CAD and a higher risk of death.

SPECT methods. Images were acquired in accordance with the American Society of Nuclear Cardiology guidelines for gated SPECT single- or 2-day technetium-99m tracer (tetrofosmin) protocols (13). We used a 17-segment model of the left ventricle to semiquantitatively score stress and rest perfusion images by using standard software (4D-MSPECT, University of Michigan Medical Center, Ann Arbor, Michigan) (14,15). Each segment was scored by consensus of 2 observers who used a 5-point scoring system. On the basis of the overall evaluation, including the number and severity of segmental scores, we identified the study as negative or positive for ischemia.

The summed stress and rest scores were obtained by adding the scores of the 17 segments of the respective images (14,15). The sum of the differences between each of the 17 segments was defined as the summed difference

Table 1 Baseline Characteristics of All Patients

Covariate	Medical Therapy (n = 654)	Revascularization (n = 115)	p Value
Age	68 ± 9.5	66 ± 9.7	0.07
Male (%)	551 (84)	102 (88)	0.34
Follow-up duration (yrs)	5.2 ± 1.6	5.3 ± 1.5	0.75
Risk factors			
Obesity	257 (39)	51 (44)	0.31
Diabetes mellitus	213 (33)	41 (36)	0.51
Current smoking of CAD	292 (45)	54 (47)	0.61
Hypertension	574 (88)	95 (83)	0.13
Hypercholesterolemia	607 (93)	103 (90)	0.23
Family history of CAD	47 (42)	317 (41)	0.97
SBP (mm Hg)	138 ± 19	137 ± 20	0.74
Hypothyroidism	39 (6)	8 (7)	0.68
Chronotropic response index	0.50 ± 0.38	0.60 ± 0.4	0.036
Aortic stenosis	16 (2)	6 (5)	0.1
Congestive heart failure	63 (10)	10 (9)	0.75
Transient ischemic attack	10 (1.5)	7 (6)	0.0022
Peripheral vascular disease	73 (11)	17 (15)	0.27
Atrial fibrillation	51 (8)	12 (10)	0.34
Ventricular fibrillation	22 (3.2)	7 (6.3)	0.90
Previous revascularizations	2 ± 1	2 ± 1	0.35
CABG	237 (36)	40 (35)	0.76
Time after last revascularization (yrs)	5.4 ± 5.4	5.0 ± 5.6	0.18
Stress results			
Exercise stress	265 (41)	58 (50)	0.047
Maximum heart rate	112.2 ± 33.5	120 ± 34	0.026
Percent predicted maximum HR	73 ± 21	77 ± 23	0.08
Maximum SBP	159 ± 29	165 ± 36	0.085
Rate-pressure product	18,486 ± 8,098	20,841 ± 9,463	0.023
Exercise capacity (METs)	9.2 ± 2	8.7 ± 2	0.15
SPECT results			
Summed stress score	10 ± 7	12 ± 8	0.004
Summed rest score	4 ± 6	4 ± 5	0.13
Summed difference score	6 ± 5	8 ± 6	<0.0001
Ejection fraction (%)	68 ± 2.7	57 ± 12	0.43

Values are mean ± SD or n (%).
CABG = coronary artery bypass graft; CAD = coronary artery disease; HR = heart rate; METs = metabolic equivalents; SBP = systolic blood pressure; SPECT = single-photon emission computed tomography.

Table 2 Features Associated With Revascularization

Covariate	Beta Coefficient	Wald	p Value
Maximum rate-pressure product (per 1,000)	0.168	8.148	0.004
Transient ischemic attack	−3.611	8.060	0.005
Summed difference score	0.097	6.690	0.010
Diabetes mellitus	0.976	4.231	0.040
Atrial fibrillation	−1.588	4.029	0.045
Hypothyroidism	−1.838	3.581	0.058
Ventricular fibrillation	−3.137	3.555	0.059
Congestive heart failure	2.297	3.084	0.079
Male	1.585	2.930	0.087

Nonsignificant associations with revascularization included age, non–diabetes mellitus risk factors, comorbidities (chronic renal failure, cancer, chronic lung disease), exercise capacity, previous CABG and number of previous revascularizations, left ventricular function (ejection fraction, severe left ventricular dysfunction and ischemic cardiomyopathy), sum rest score, valve disease, vascular disease (peripheral, cerebrovascular, aortic), and arrhythmias.

Table 3 Characteristics of the Matched Patients From Medical Therapy Versus Revascularization

Covariate	Medical Therapy (n = 115)	Revascularization (n = 115)	p Value
Ejection fraction	0.57 ± 0.12	0.57 ± 0.12	0.87
Follow-up time (yrs)	5.1 ± 1.7	5.3 ± 1.5	0.56
Interval between last revascularization and stress test (yrs)	5.3 ± 4.8	5.0 ± 5.6	0.14
Male	91 (79)	101 (88)	0.08
Age (yrs)	69 ± 7.5	66 ± 10	0.062
Exercise test (%)	42 (37)	58 (50)	0.03
Obesity	49 (43)	51 (44)	0.8
Maximum heart rate	109 ± 34	120 ± 35	0.03
Maximum SBP (mm Hg)	158 ± 30	165 ± 36	0.12
Maximum DBP (mm Hg)	83 ± 12	86 ± 13	0.15
Maximum rate-pressure product	17,975 ± 8,393	20,842 ± 9,464	0.03
Exercise time (min)	6.6 ± 0.3	6.9 ± 1.9	0.29
Exercise capacity (METs)	9 ± 2	9 ± 2	0.36
HR recovery	8 ± 11	10 ± 10	0.12
Percent predicted maximum HR (%)	71 ± 22	77 ± 23	0.07
Resting SBP	138 ± 20	137 ± 20	0.78
Resting DBP	81 ± 11	81 ± 11	0.92
Chronotropic response index	0.47 ± 0.39	0.59 ± 0.4	0.05
Diabetes mellitus	37 (32)	41 (36)	0.54
Current smoking	48 (42)	54 (47)	0.39
Hypertension	105 (91)	95 (83)	0.05
Hypercholesterolemia	107 (93)	103 (90)	0.35
Family history of CAD	38 (33)	47 (41)	0.18
Arrhythmia	0	3 (3)	0.25
Atrial fibrillation	9 (8)	12 (10)	0.35
Atrial flutter	0	1 (0.9)	0.95
Nonsustained VT	2 (2)	0	0.16
SVT	1 (0.9)	2 (2)	1
V-FIB	0	5 (4)	0.06
VT	3 (3)	2 (2)	0.95
Aortic aneurysm	6 (5)	3 (3)	0.5
Aortic insufficiency	8 (7)	4 (3)	0.37
Aortic stenosis	2 (2)	6 (5)	0.28
Mitral regurgitation	20 (17)	12 (10)	0.13
Mitral valve prolapse	2 (2)	0	0.5
Tricuspid regurgitation	5 (4)	3 (3)	0.72
Nonrheumatic valve disease	1 (0.9)	4 (3)	0.37
Asthma	4 (3)	5 (4)	0.95
Cancer	11 (10)	15 (13)	0.4
Cardiac arrest	1 (0.9)	4 (3)	0.37
Cardiomyopathy	3 (3)	2 (2)	0.95
Carotid atherosclerosis	27 (23)	21 (18)	0.33
CVA	9 (8)	4 (3)	0.25
TIA	2 (2)	7 (6)	0.17
Heart failure	14 (12)	10 (9)	0.39
Ischemic cardiomyopathy	3 (3)	1 (0.9)	0.62
Severe LV dysfunction	1 (0.9)	1 (0.9)	0.95
Complete heart block	1 (0.9)	0	0.95
Chronic pulmonary disease	6 (5)	5 (4)	0.76
Chronotropic response index	1 (0.9)	2 (2)	0.95
End-stage renal disease	4 (3)	3 (3)	0.95
Hyperlipidemia	106 (92)	103 (90)	0.47
Hyperthyroidism	1 (0.9)	1 (0.9)	0.95
Hypothyroidism	9 (8)	8 (7)	0.06
Peripheral vascular disease	16 (14)	17 (15)	0.85
Sleep apnea	6 (5)	3 (3)	0.72
Syncope/near-syncope	5 (4)	6 (5)	0.76
No. of previous revascularizations	2 ± 1.5	2 ± 1.2	0.13
Previous CABG	52 (45)	40 (35)	0.11
Summed stress score	10 ± 7	12 ± 8	0.06
Summed rest score	5 ± 6	4 ± 5	0.13
SDS	5 ± 4	8 ± 6	<0.0001
Time between catheterization and last stress test (days)	303 ± 143	233 ± 151	0.06

Continued in the next column

Table 3 Continued

Values are mean ± SD or n (%).

CAD = coronary artery disease; CVA = cardiovascular accident; DBP = diastolic blood pressure; LV = left ventricular; SDS = summed difference score; SVT = supraventricular tachycardia; TIA = transient ischemic attack; V-FIB = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

score (SDS), representing the amount of ischemia. Each of these variables incorporate the extent and severity of perfusion defects, which independently add prognostic information (16).

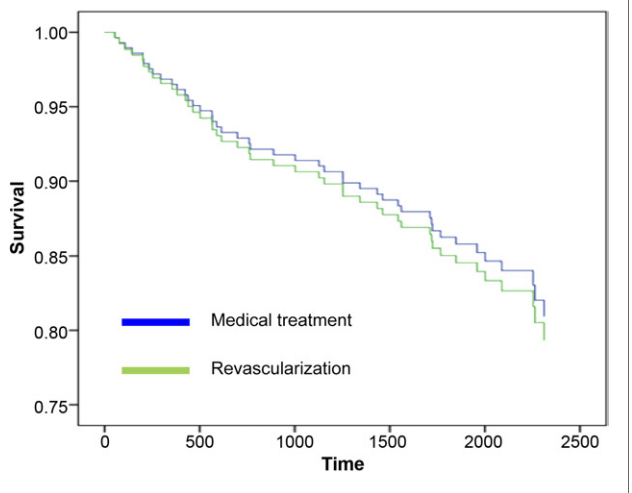

Figure 1 Survival of Propensity-Matched Subjects Undergoing Medical Therapy or Revascularization, Adjusted for Age, Sex, and Ejection Fraction

Neither therapy (hazard ratio [HR]: 0.91 [95% confidence interval (CI): 0.50 to 1.66]; p = 0.77) nor male (HR: 1.30 [95% CI: 0.62 to 2.73]; p = 0.48) showed an association with survival. Survival was associated with age (HR: 1.06 [95% CI: 1.02 to 1.11]; p = 0.002) and ejection fraction (HR: 0.98 [95% CI: 0.95 to 0.99]; p = 0.04).

Follow-up. Patients were followed up over a median of 5.7 years (IQR: 4.7 to 6.4 years) for the primary endpoint (all-cause mortality). All-cause death was defined as any death during the follow-up period, and the deaths were confirmed by review of death certificate and hospital chart or physician records. Of 769 patients, 2 were lost during follow-up because they were followed up by others rather than by the Cleveland Clinic healthcare system (99.7% follow-up rate). The survival status of all patients, including the 2 patients lost to follow-up, was confirmed by using the Social Security Death Index at the end of follow-up.

Statistical analysis. Continuous variables are described as mean ± SD. Between-group comparisons were performed by using the Student *t* test for continuous variables and a chi-square test for categorical variables. Analyses were performed by using standard statistical software (SPSS version 18.0 [IBM, Chicago, Illinois] and SAS version 9.3 [SAS Institute, Cary, North Carolina]; S-plus Release 2, Insightful Corporation, Seattle, Washington).

The first step in the analysis was based on developing a propensity model, using a nonparsimonious logistic regression to summarize factors associated with the decision to refer patients to revascularization versus MT (17,18); all factors known to influence this referral decision were used in the analysis (19–21). This score was used to reduce the bias introduced by nonrandomized referral patterns to revascularization in clinical practice in 2 ways. This score was used as the basis for a propensity-matched survival analysis. In addition, to ensure that these results were not due to loss of study power by this selection process, we analyzed the full cohort with the incorporation of this score into a Cox proportional hazards (CPH) model as a covariate (22).

Survival analyses were performed by using CPH modeling to examine the association of post-MPS treatment and event-free survival time after adjustment for baseline patient characteristics and potential confounders. Our primary study hypothesis was directly addressed in these CPH models by examining the following: 1) whether post-MPS revascularization was associated with improved survival time; and 2) whether an interaction was present between post-MPS revascularization and several predefined imaging metrics, including percent myocardium ischemic, percent myocardium fixed, and left ventricular ejection fraction (LVEF). To avoid model overfitting, we developed an initial CPH model incorporating baseline clinical, historical, and demographic data into a single composite score summarizing baseline patient risk. We pre-specified this model to include end-stage renal disease, diabetes mellitus, history of previous revascularization, age, smoking history, sex, appropriateness score, history of cancer, history of anemia, and aortic stenosis. Predicted probability of death for each subject was extracted from the model and used to represent the medical risk in subsequent models.

Based on the previous report that compared the effect of revascularization versus MT in asymptomatic patients (23), the expected hazard ratio was 0.34. In the setting of a 2-tailed alpha of 0.05 and power of 0.90, the required sample size was 117.

Results

Patient characteristics. Table 1 shows the comparison of baseline characteristics between the 654 patients who underwent MT and the 115 who underwent revascularization. There were few differences in baseline characteristics between these 2 groups. Patients who underwent revascularization had a higher maximum HR and rate-pressure product during stress testing, probably because of a higher frequency of exercise testing in this group. In addition, patients who had post-MPS revascularization were more likely to have a history of transient ischemic attack, ventricular fibrillation, pulmonary embolism, and lower exercise capacity (metabolic equivalents), as well as a greater total ischemic burden as determined by a higher SDS.

The time between the previous revascularization and the index MPS in patients who received MT was similar to patients referred for revascularization (5.4 ± 5.4 years vs.

Table 4 Cox Proportional Hazards Model for Aggregate Clinical Risk Score

Variable	β	p Value	Hazard Ratio	Lower 0.95 Confidence Interval	Upper 0.95 Confidence Interval
End-stage renal disease	1.4299	0.0026	4.1782	1.646	10.604
Diabetes mellitus	0.1832	0.32	1.2011	0.837	1.724
Appropriateness score	0.0978	0.11	1.1028	0.979	1.243
History of previous revascularization	−0.1237	0.097	0.8836	0.764	1.023
Female	−4.8052	0.0041	0.0082	0.001	0.218
Age	0.0206	0.32	1.0208	0.980	1.063
Age × sex	0.0597	0.011	1.0615	1.014	1.111
Smoking	0.4968	0.0057	1.6435	1.156	2.337
Aortic stenosis	−0.8266	0.14	0.4375	0.147	1.302
Cancer	0.6821	0.0036	1.9780	1.250	3.131
Anemia	0.6255	0.047	1.8692	1.008	3.467
Overall model: Wald chi-square test = 88; $p < 0.0001$; Score test = 94; $p < 0.0001$					

5.0 ± 5.6 years; p = 0.18), and the type of previous revascularization was similar (p = 0.76).

Outcome events. Over the 5.7-year follow-up period, 142 patients died. Mortality with MT was 18.3% compared with 19.1% with revascularization (p = 0.84).

Propensity-matched analysis. Multiple factors (Table 2) associated with referral to revascularization after MPS were included in the propensity model (chi-square test = 79.6; c index = 0.842; p = 0.008). Propensity-matched groups undergoing MT compared with revascularization (Table 3) showed no difference in survival (chi-square test = 13.603; p = 0.767) (Fig. 1).

A clinical risk score was developed by using a CPH model (global chi-square test = 88; p < 0.0001) (Table 4). The major predictors in this model included a history of cancer, anemia, end-stage renal disease, and smoking as well as patient age and sex. The latter 2 variables also interacted in the model. Predicted probabilities of death for each subject from this model were used in subsequent CPH models as a clinical risk score.

Unadjusted comparison of all patients (chi-square test = 80.1; p = 0.69) showed no association of revascularization with mortality (Fig. 2A). Mortality was associated with age (hazard ratio: 1.07 [95% confidence interval (CI): 1.04 to 1.09]; p ≤ 0.0001) and hypercholesterolemia (hazard ratio: 2.34 [95% CI: 1.44 to 3.80]; p = 0.001).

Multivariable modeling. A CPH model was used to identify the association of revascularization with all-cause death, with adjustment for the clinical risk score and the propensity score. In the final CPH model adjusted for propensity score (Wald chi-square test = 89.6; p ≤ 0.0001) (Table 5), clinical risk score and the use of pharmacological stress were the most important predictors of outcome. None of the imaging variables were significant predictors of all-cause death. Percent myocardium ischemic, percent myocardium fixed, and LVEF did not significantly interact with post-MPS revascularization in the final CPH model. Adjusted comparison of all patients showed no association of revascularization with mortality (p = 0.53) (Fig. 2B).

Finally, we examined limited CPH models to explore the association of combinations of 4 covariates with cardiac death as the endpoint (42 total cardiac deaths). After adjusting for clinical risk score and the use of pharmacological stress, neither percent myocardium abnormal nor LVEF were significant predictors in the CPH model (p = 0.35 and p = 0.36, respectively; global chi-square test = 36.7).

Discussion

Although the appropriateness of MPS as a surveillance tool to assess for residual or recurrent ischemia post-revascularization is uncertain, it is often used routinely for this purpose (5). The underlying assumption is that the identification of post-revascularization ischemia would be an adverse prognostic finding, and the corollary belief is that repeat revascularization would be of benefit in reducing subsequent clinical events such as myocardial infarction or death. In this study, asymptomatic patients with MPS-proven ischemia after previous revascularization (PCI or CABG) who underwent repeat revascularization realized no survival benefit over those who received MT either in

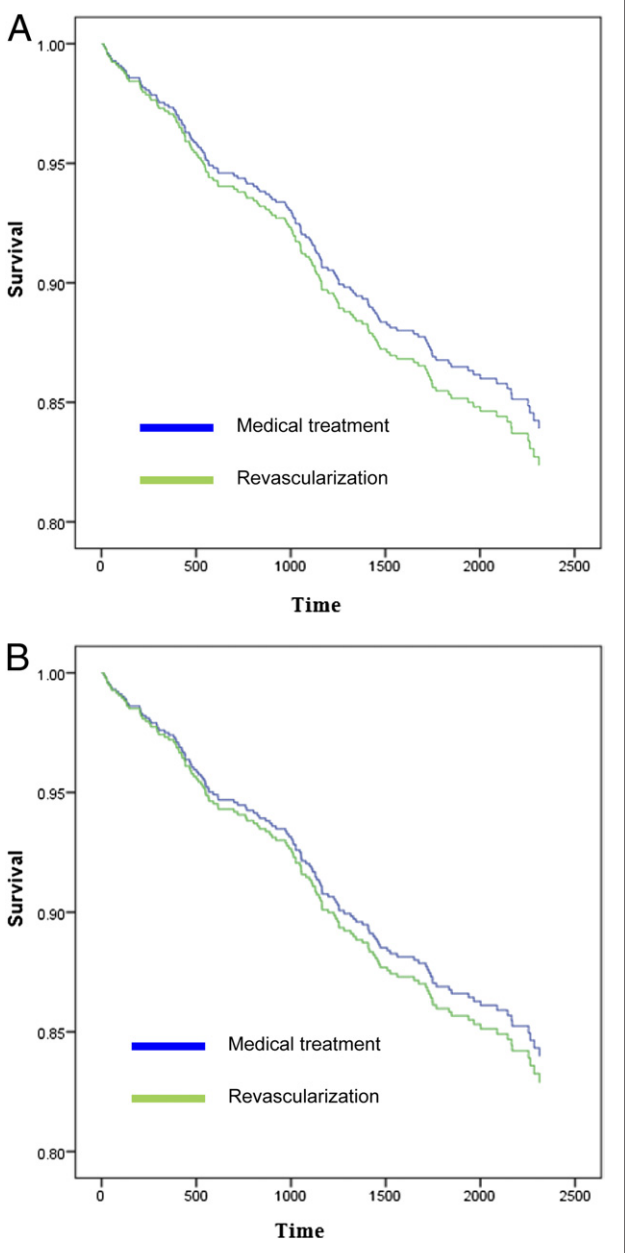

Figure 2 Survival of All Patients Undergoing Medical Therapy or Revascularization

(A) Unadjusted survival. There was no association of revascularization with mortality (HR: 0.90 [95% CI: 0.55 to 1.48]; p = 0.69). **(B)** Adjusted survival. There was no association of revascularization with mortality (HR: 1.18 [95% CI: 0.70 to 2.00]; p = 0.53). Abbreviations as in Figure 1.

Table 5 Cox Proportional Hazards Model: Aggregate Clinical Risk Score With Imaging Data

Variable	β	p Value	Hazard Ratio	Lower 0.95 Confidence Interval	Upper 0.95 Confidence Interval
Percent myocardium ischemic	0.0005	0.9875	1.001	0.962	1.040
History of previous revascularization	−0.1387	0.0702	1.059	0.749	1.010
Use of post-MPS revascularization	−0.1688	0.5293	1.184	0.700	2.00
Percent myocardium fixed	0.0114	0.5220	1.011	0.977	1.050
Left ventricular ejection fraction	−0.3556	0.1238	0.701	0.446	1.100
Use of pharmacological stress	1.4521	<0.0001	4.272	2.555	7.140
Clinical risk score	0.6363	<0.0001	1.889	1.549	2.310
Propensity score	0.5172	0.5928	1.6787	0.252	11.16
Overall model: Wald chi-square test = 89.6; $p \leq 0.0001$; Score test = 99; $p < 0.0001$					

MPS = myocardial perfusion scintigraphy.

propensity-matched groups or unadjusted and adjusted analyses. In contrast, age and hypercholesterolemia were strongly associated with all-cause mortality.

Many studies have examined the clinical outcomes derived from myocardial revascularization in patients undergoing MPS. Generally, these studies have examined patients without CAD (11,12), or patients with a history of CAD with or without previous revascularization (4), but they have not discriminated symptomatic from asymptomatic patients. This distinction is important because revascularization can be readily defended in symptomatic patients. The discordant findings between these observations and our current result may very likely reflect differences in the study populations.

In the recently published baseline nuclear substudy of the COURAGE trial (10), patients with extensive inducible ischemia at baseline (of whom >85% were symptomatic) did not seem to have a greater event rate with optimal MT alone compared with revascularization. In contrast, Hachamovitch et al. (24) reported that post-MPS treatment and subsequent survival were dictated by the interaction between the use of early revascularization, percentage of ischemic myocardium, and history of previous CAD. In the absence of previous CAD, a greater extent of ischemia was associated with greater improvement in all-cause mortality risk with early revascularization compared with MT; in the presence of little or no ischemia, early revascularization was associated with approximately 50% greater risk than MT. These findings are concordant with studies showing revascularization to be an effective treatment for patients with extensive coronary disease burden (25–27). The novelty of our current work is that it focused on application in asymptomatic post-revascularization patients with ischemia, a group that would be a subpopulation in the previous studies.

In asymptomatic patients, such a decision would have to be justified prognostically, and the evidence to support this action seems controversial. In the SWISSI II (Swiss Interventional Study on Silent Ischemia Type II) trial (28), PCI improved survival from cardiac death, as a secondary endpoint, in patients with silent ischemia after a recent myocardial infarction. However, in another substudy of 283 asymptomatic patients from the COURAGE trial (23), of whom 13% to 14% of patients were post-revascularization and 76% had ≥5% ischemic myocardium, the addition of PCI to optimal MT did not significantly decrease composite outcomes or mortality. Our current study, limited to asymptomatic post-revascularization patients, is in agreement with this finding.

Study limitations. This study was a single-site, observational trial and as such has inherent flaws relating to selection bias, spurious observations, unmeasured covariates, and nonrandom allocation to treatment (19,21,29–31). We sought to avoid these problems by using standardized templates in the electronic medical record and incorporating a propensity model with the multivariable analysis.

In this study of 769 patients, 115 (15%) underwent revascularization, and there were 142 deaths, 22 of whom were in the revascularized group. As a result, the study was only adequately powered for relatively large effects, especially in relation to interactions. By using all-cause mortality as the primary endpoint, we may have diluted a potential benefit of intervention on cardiovascular outcome, although in this population, we would expect cardiovascular causes of death to predominate, and the avoidance of death certificate diagnosis avoided misclassification bias. We did not differentiate between revascularization performed with CABG versus PCI; the efficacy of these 2 approaches may differ in select patient subgroups (32).

Conclusions

Routine MPS in asymptomatic patients late after revascularization is deemed to be of indeterminate appropriateness. Our recent work has shown no survival benefit from this approach (8) when using stress echocardiography, but this observation is tempered by the limited number of abnormal stress test results. In this MPS-based study, our data found no evidence that repeat revascularization provides a survival benefit, even in patients with inducible ischemia. If invasive downstream therapeutic responses do not alter survival even when ischemia is present, it is difficult to justify using MPS to investigate asymptomatic patients post-revascularization.

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Key Words: ischemia ■ outcome ■ revascularization ■ SPECT.