

Comparison of the Short-Term Survival Benefit Associated With Revascularization Compared With Medical Therapy in Patients With No Prior Coronary Artery Disease Undergoing Stress Myocardial Perfusion Single Photon Emission Computed Tomography

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Background—The relationship between the amount of inducible ischemia present on stress myocardial perfusion single photon emission computed tomography (myocardial perfusion stress [MPS]) and the presence of a short-term survival benefit with early revascularization versus medical therapy is not clearly defined.

Methods and Results—A total of 10 627 consecutive patients who underwent exercise or adenosine MPS and had no prior myocardial infarction or revascularization were followed up (90.6% complete; mean: 1.9 ± 0.6 years). Cardiac death occurred in 146 patients (1.4%). Treatment received within 60 days after MPS defined subgroups undergoing revascularization (671 patients, 2.8% mortality) or medical therapy (MT) (9956 patients, 1.3% mortality; $P=0.0004$). To adjust for nonrandomization of treatment, a propensity score was developed using logistic regression to model the decision to refer to revascularization. This model ($\chi^2=1822$, c index=0.94, $P<10^{-7}$) identified inducible ischemia and anginal symptoms as the most powerful predictors (83%, 6% of overall χ^2) and was incorporated into survival models. On the basis of the Cox proportional hazards model predicting cardiac death ($\chi^2=539$, $P<0.0001$), patients undergoing MT demonstrated a survival advantage over patients undergoing revascularization in the setting of no or mild ischemia, whereas patients undergoing revascularization had an increasing survival benefit over patients undergoing MT when moderate to severe ischemia was present. Furthermore, increasing survival benefit for revascularization over MT was noted in higher risk patients (elderly, adenosine stress, and women, especially those with diabetes).

Conclusions—Revascularization compared with MT had greater survival benefit (absolute and relative) in patients with moderate to large amounts of inducible ischemia. These findings have significant consequences for future approaches to post-single photon emission computed tomography patient management if confirmed by prospective evaluations. (*Circulation*. 2003;107:2900-2906.)

Key Words: coronary disease ■ prognosis ■ follow-up studies ■ revascularization ■ radioisotopes

Physicians commonly face the choice of recommending revascularization versus medical therapy in patients with stable coronary artery disease (CAD). On the basis of multiple, prospective randomized clinical trials comparing these alternatives, extensive evidence exists to support the selection of one therapy versus the other in a variety of clinical and angiographic patient subsets.¹⁻⁴

Although several studies using exercise treadmill test (ETT) have investigated the relative benefits of revascularization versus medical therapy in either randomized¹⁻³ or

registry data,^{5,6} they are limited by the age of most of the trials and the imprecision of estimating ischemic burden by ETT. Stress myocardial perfusion single photon emission computed tomography (SPECT) (myocardial perfusion stress [MPS]), a valuable prognostic test in CAD,^{7,8} is widely used to determine the need for catheterization^{9,10}; however, only limited, unadjusted studies compare survival with revascularization versus medical therapy after MPS.^{7,11}

We sought to compare the survival benefit associated with revascularization versus medical therapy on the basis of

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treatment assignment selected within the first 60 days after MPS using risk-adjusted techniques in an observational data series. We hypothesized that in patients undergoing MPS, increasing amounts of inducible ischemia will be associated with an increasing survival benefit with revascularization and, conversely, patients with no or small amounts of ischemia will have enhanced survival benefit from medical therapy compared with revascularization.

Methods

Study Population

We identified 15 474 consecutive unique patients who underwent exercise or adenosine stress MPS between January 1991 and March 1997 at Cedars-Sinai Medical Center. Patients with prior myocardial infarction (MI) or revascularization were excluded (4406), and 441 (3.98%) were lost to follow-up, leaving a final study population of 10 627 patients who were followed up for a mean of 1.9 ± 0.6 years. For purposes of this study, patients were separated into 2 groups, medical therapy (9956 patients) and early revascularization (671 patients), on the basis of the treatment received within 60 days after MPS.

Imaging and Stress Protocol

Patients were injected intravenously at rest with Tl-201 (2.5 to 3.5 mCi; dose variation based on patient weight), and MPS was initiated 10 minutes after injection.¹²

Exercise MPS Protocol

After rest MPS, patients performed a symptom-limited ETT according standard protocols and previously described end points. At near maximal exercise, a 20- to 30-mCi dose of Tc-99 m sestamibi was injected (actual patient dose varied with patient weight), and exercise continued for 1 additional minute after injection. Stress MPS was begun 15 to 30 minutes later.¹²

Adenosine MPS Protocol

Patients were instructed not to consume caffeine products for 24 hours before MPS. Adenosine was infused (140 $\mu\text{g}/\text{kg}$ per min) for 6 minutes. Tc-99 m sestamibi (20 to 30 mCi) was injected at the end of the third minute of infusion, and MPS was initiated ≈ 60 minutes later.¹² For patients who underwent exercise as an adjunct to adenosine infusion, low-level ETT was performed at 0% grade and 1 to 1.7 mph.

During both stress types, 12-lead electrocardiographic recording was performed each minute with continuous monitoring of leads AVF, V₁, and V₅. Blood pressure was recorded at rest, after each stress stage, and at peak stress. Maximal ST segment change at 80 ms after the J point was assessed as horizontal, upsloping, or downsloping.

MPS Acquisition Protocol

Dual-isotope MPS was performed using 180-degree acquisition for 64 projections at 20 seconds per projection using standard energy windows for Tl-201 and Tc-99 m sestamibi.¹² No attenuation or scatter correction was used.

Image Interpretation

Semiquantitative 20-segment visual interpretation was performed by consensus of 2 experienced observers using a 5-point scoring system (0, normal; 1, equivocal; 2, moderate; 3, severe reduction of radioisotope uptake; and 4, absence of detectable tracer uptake).¹²

Scintigraphic Indices

The summed stress and rest scores were obtained by adding the scores of the 20 segments of the respective images.^{8,10} The sum of the differences between each of the 20 segments from these images was defined as the summed difference score, representing the amount of ischemia. Each of these variables incorporate the extent

and severity of perfusion defects, which independently add prognostic information.¹³ These indices were converted to percent of the total myocardium (% myocardium) involved with stress, ischemic, or fixed defects by dividing the summed scores by 80, the maximum potential score (4×20), and multiplying by 100.

Patient Follow-Up

Individuals blinded to MPS results performed follow-up by scripted telephone interview. The sole end point was cardiac death, defined as death attributable to any cardiovascular cause, confirmed by review of death certificate, hospital chart, or physician's records.^{7,8,10} Secondary analyses were performed using all-cause mortality.

Statistical Analysis

Baseline characteristics were described using median (25th and 75th percentiles) for continuous variables (compared using the Wilcoxon rank-sum test) and frequencies for categorical variables (using a χ^2 test for comparisons of discrete variables). $P < 0.05$ was considered statistically significant.

Analysis Design

We structured the present study's analysis of observational data to mimic a randomized clinical trial^{14,15}; ie, a patient's assignment to a treatment was based on the therapy selected in the first 60 days after MPS and nonrandomized treatment adjusted for via a propensity score. This time point was selected from previous work indicating that revascularization performed within this timeframe resulted from MPS results whereas referrals after 60 days tended to be attributable to worsening clinical status.¹⁶ Compared with 671 revascularizations performed within the first 60 days, 141 were performed within >1 year, 71 were performed within 6 to 12 months, and 116 were performed 60 days to 1 year after MPS.

To evaluate the impact of waiting-time bias, we considered 3 alternative approaches for assigning follow-up time: (1) Follow-up time began at the time of the index MPS; (2) patients undergoing revascularization had follow-up time counted as medical therapy until revascularization occurred, after which they were considered revascularization patients; or (3) all events occurring in the first 60 days after the index study were not considered in the analysis. The results obtained with each of these 3 approaches did not materially differ; thus, we used the results of the first approach.

Multivariable Modeling

A two-step process was used, initial development of a propensity score followed by covariate adjustment via multivariable survival analysis incorporating the propensity score as well. A propensity score was developed using a logistic regression model to summarize predictors of the decision to refer patients to revascularization versus medical therapy.^{17,18} This yielded a single composite score representing the probability of assignment to one therapy versus another. In principal, adjusting survival analysis for this score reduces or eliminates the bias introduced by nonrandomized referral patterns to revascularization in clinical practice. Because the purpose of the propensity score was to represent these predictors as accurately as possible, all factors known to influence this referral decision were considered for entry into a logistic regression model.^{19–21}

A Cox proportional hazards model was used to assess the association of treatment with survival time free of cardiac death.²² This approach was used to control for or "subtract out" the effect of baseline patient differences and the impact of nonrandomized treatment assignment (propensity score) on survival, thus permitting evaluation of the treatment effect per se. The question of whether specific baseline variables impacted the survival benefit associated with revascularization was addressed formally with the Cox model by testing for interactions between treatment and these covariates.^{19,21} Secondary analyses were performed modeling all-cause mortality using the Cox proportional hazards model. S plus 2000 was used for all analyses.

The threshold for variable entry into models was $P < 0.05$ and for variable removal was $P > 0.10$. Particular care was given to exami-

TABLE 1. Patient Characteristics

	Medical Therapy	Early Revascularization	P
No.	9956	671	
Exercise stress, % (No.)	71 (7065)	64 (430)	<0.001
Male, % (No.)	53 (5323)	72 (480)	<0.001
History of cardiac catheterization, % (No.)	10 (987)	14 (92)	<0.001
Digoxin use, % (No.)	5 (544)	4 (29)	NS
Hypertension, % (No.)	46 (4538)	55 (371)	<0.001
Diabetes mellitus, % (No.)	12 (1240)	21 (140)	<0.001
Hypercholesterolemia, % (No.)	41 (4102)	48 (319)	<0.001
Smoking, % (No.)	13 (1310)	14 (97)	NS
Family history coronary artery disease, % (No.)	22 (2189)	22 (148)	NS
Anginal symptoms, % (No.)	38 (3788)	65 (435)	<0.001
Abnormal rest ECG, % (No.)	58 (5743)	70 (471)	<0.001
Age, y	65 (55 to 73)	69 (61 to 76)	<0.001
Prescan likelihood coronary artery disease	0.19 (0.05 to 0.57)	0.74 (0.31 to 0.97)	<0.001
Stress defect, % myocardium	0 (0 to 3.8)	17.5 (11.3 to 27.5)	<0.001
Ischemia, % myocardium	0 (0 to 2.5)	16.3 (10.0 to 25.0%)	<0.001
Fixed defect, % myocardium	0 (0 to 0)	0 (0 to 0)	NS

nation of the assumptions of proportional hazards, linearity, and additivity, as appropriate.^{19–21,23} The predicted lives saved per 100 patients treated with revascularization versus medical therapy was defined as (predicted cardiac death rate_{medical therapy})–(predicted cardiac death rate_{revascularization}).

Results

Patient Characteristics

Baseline characteristics of the medical therapy and revascularization cohorts differed significantly, with a higher frequency of exercise stress in the medical therapy group but more frequent male sex, prior catheterization, hypertension, diabetes mellitus, cholesterol, anginal symptoms, and abnormal rest ECG in the revascularization group (Table 1). The latter also had greater age and greater total defect size and total ischemic defect size. Fixed defects involving >5% of the myocardium were present in 365 patients (3.7%) undergoing medical therapy and 71 patients (10.6%) undergoing revascularization ($P<0.001$).

With regard to the type of revascularization performed, 325 patients underwent coronary artery bypass surgery (CABG), and 346 underwent percutaneous coronary interventions. CABG accounted for 44%, 39%, 38%, 44%, and 60% of revascularizations in the setting of 0%, 1% to 5%, 6% to 10%, 11% to 20%, and >20% myocardium ischemic.

Outcome Events

During follow-up, 146 cardiac deaths (1.4%) and 492 all-cause mortality deaths (4.6%) occurred. As a function of treatment, revascularization and medical therapy were associated with 2.8% and 1.3% cardiac death rates, respectively (Figure 1; log-rank $P=0.0004$). Observed (unadjusted) mortality rates as a function of the % myocardium ischemic (Figure 2) reveal that in the absence of inducible ischemia, patients treated medically were at very low risk; patients

undergoing revascularization were very few in number and had a single event, making the interpretation of the event rate limited. With increasing amounts of inducible ischemia, mortality rates progressively increased in patients undergoing medical therapy ($P<0.0001$) but not in patients referred for revascularization. Furthermore, in patients with >20% myocardium ischemic, revascularization had a lower cardiac mortality compared with medical therapy ($P<0.02$).

Propensity Score

Logistic regression revealed that the best predictors of referral to revascularization included % myocardium ischemic, anginal symptoms, percent myocardium fixed, ischemic ST segment changes, elevated cholesterol, and prior catheterization (C index 0.94, $\chi^2=2119$, $P<10^{-7}$). A significant interaction was present between % myocardium ischemic and anginal symptoms, and percent myocardium was modeled nonlinearly. The most important of these variables were %

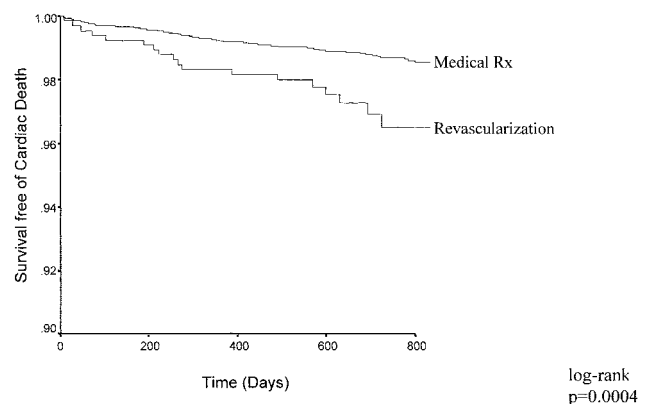


Figure 1. Unadjusted Kaplan-Meier survival in patients undergoing revascularization vs medical therapy (Medical Rx).

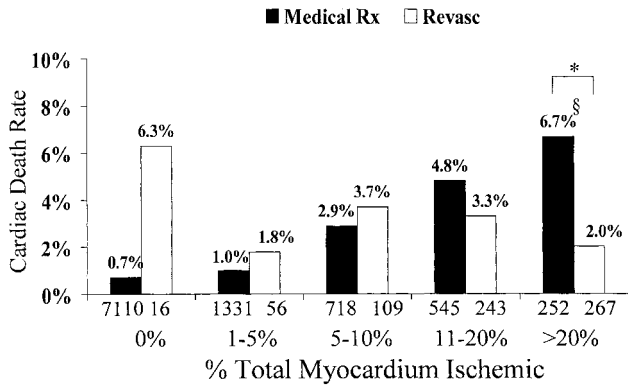


Figure 2. Observed cardiac death rates over the follow-up period in patients undergoing revascularization (Revasc) vs medical therapy (Medical Rx) as a function of the amount of inducible ischemia. Increase in cardiac death frequency as a function of inducible ischemia, $P < 0.0001$.

myocardium ischemic and anginal symptoms (providing 83% and 6% of information, respectively). Increasing amounts of inducible ischemia were associated with increasing likelihood of revascularization, with very sharp increases between 0 to $\approx 10\%$ to 12.5% myocardium ischemic, with a relative plateau in this likelihood with additional increases in inducible ischemia (Figure 3). The increase in this likelihood was greatest in the setting of typical angina pectoris, with lesser increases with atypical angina and asymptomatic presentations.

Survival Analysis

The final Cox proportional hazards model predicting cardiac death (Table 2) included type of stress performed, male sex, diabetes mellitus, age, digoxin use, early revascularization (treatment), percent myocardium fixed, and % myocardium ischemic. Propensity score remained in the model with borderline significance. Significant interactions were present between treatment given and % myocardium ischemic as well as between sex and diabetes mellitus.

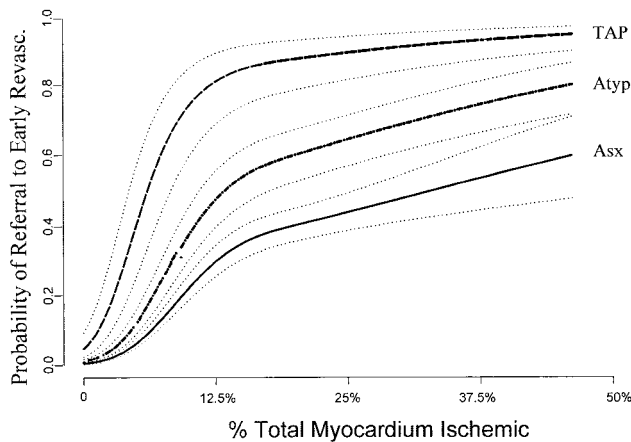


Figure 3. Likelihood of referral to revascularization as a function of % myocardium ischemic based on logistic regression analysis. TAP indicates typical angina; Atyp, atypical angina pectoris; and Asx, asymptomatic.

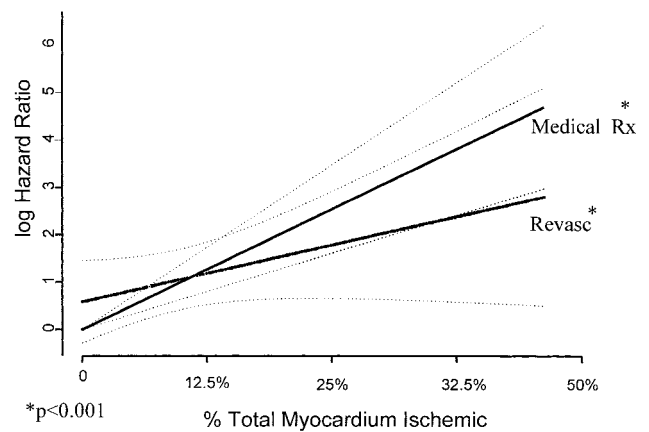
TABLE 2. Cox Proportional Hazards Model Predicting Cardiac Death

Factor	χ^2	Degrees of Freedom	P
Male sex*	8.62	2	0.0134
Interactions	8.00	1	0.0047
Diabetes mellitus*	13.80	2	0.0010
Interactions	8.00	1	0.0047
Age	66.51	2	<0.0001
Nonlinear	18.63	1	<0.0001
Exercise stress	22.53	1	<0.0001
Digoxin use	8.95	1	0.0028
% Myocardium fixed	91.42	1	<0.0001
Early revascularization*	5.28	2	0.0712
Interactions	4.68	1	0.0305
% Myocardium ischemic*	32.79	2	<0.0001
Interactions	4.68	1	0.0305
Propensity score	2.80	1	0.0944
Male sex \times diabetes mellitus*	8.00	1	0.0047
Early revascularization \times % myocardium ischemic*	4.68	1	0.0305
Total interaction	13.09	2	0.0014
Total nonlinear + interaction	32.55	3	<0.0001
Total	396.41	12	<0.0001

*Factor + higher order factors.

The relationship between % myocardium ischemic and the log of the hazard ratio for revascularization versus medical therapy based on this Cox model (Figure 4) revealed that in the setting of no or mild amounts of inducible ischemia, patients undergoing medical therapy had a survival advantage over patients undergoing revascularization. These 2 lines intersect at a value of $\approx 10\%$ to 12.5% myocardium ischemic, above which the survival benefit for revascularization over medical therapy increases as a function of increasing amounts of inducible ischemia.

On the basis of this Cox model, in patients undergoing medical therapy, predicted mortality increased significantly



* $p < 0.001$

Figure 4. Log hazard ratio for revascularization (Revasc) vs medical therapy (Medical Rx) as a function of % myocardium ischemic based on final Cox proportional hazards model. Model, $P < 0.0001$; interaction, $P = 0.0305$.

TABLE 3. Predicted Mortality Rates in Patients Treated With Revascularization Versus Medical Therapy Based on Final Cox Proportional Hazards Model

	% Myocardium Ischemic		
	Small (5% to 10%)	Moderate (10% to 20%)	Large (>20%)
Nondiabetic			
Men			
Medical therapy, %	2.5	3.4	5.1
Revascularization, %	2.3	1.8	1.9
Lives saved per 100 patients treated	0.2	1.6	3.2
Women			
Medical therapy, %	2.7	4.9	10.0
Revascularization, %	3.9	3.7	2.5
Lives saved per 100 patients treated	-1.2	1.2	7.5
Diabetic			
Men			
Medical therapy, %	1.2	5.1	5.0
Revascularization, %	1.0	2.1	1.9
Lives saved per 100 patients treated	0.2	-3.0	3.1
Women			
Medical therapy, %	4.7	10.0	17.1
Revascularization, %	6.6	5.5	4.4
Lives saved per 100 patients treated	-1.9	-4.5	12.7
Age			
<60 years			
Medical therapy, %	0.8	1.8	2.7
Revascularization, %	0.7	0.7	0.7
Lives saved per 100 patients treated	0.1	1.1	2.0
60 to 80 years			
Medical therapy, %	1.7	2.8	4.8
Revascularization, %	1.3	2.1	1.4
Lives saved per 100 patients treated	0.4	0.7	3.4
>80 years			
Medical therapy, %	5.6	8.8	12.4
Revascularization, %	6.3	4.9	4.9
Lives saved per 100 patients treated	-0.7	3.9	7.5
Stress type			
Exercise			
Medical therapy, %	1.1	1.6	3.3
Revascularization, %	1.7	1.2	1.1
Lives saved per 100 patients treated	-0.6	0.4	2.2
Adenosine			
Medical therapy, %	5.0	8.1	12.8
Revascularization, %	4.5	4.8	4.9
Lives saved per 100 patients treated	0.5	3.3	7.9

as a function of % myocardium ischemic (Table 3), but in revascularized patients, mortality rates did not increase. In both treatment groups, mortality rates and lives saved per 100 patients treated were greater in women (particularly diabetic women), the elderly, and patients undergoing adenosine stress. In all patient groups, a significant increase was noted with greater increases in women, particularly diabetic

women. Patients with small amounts of inducible ischemia (5% to 10% myocardium ischemic) had a marginal survival advantage for medical therapy in women and no difference between therapies in men. Small survival advantages for revascularization over medical therapy in both men and women were noted with moderate amounts of inducible ischemia (10% to 20% myocardium ischemic), more so in

diabetic patients. With large amounts of inducible ischemia (>20% myocardium ischemic), the survival benefit for revascularization increased more in women compared with men, such that it was more than 2-fold greater in women compared with men, more so in diabetic patients.

Patients with >10% myocardium ischemic Cox analysis in the subgroup of patients with >10% myocardium ischemic revealed that the model above (excluding % myocardium ischemic-early revascularization interaction) was associated with cardiac death ($P < 0.00001$). Early revascularization had a hazard ratio of 0.49, indicating >50% reduction of cardiac death with revascularization in this patient subset.

All-Cause Mortality

Secondary analysis modeling all-cause mortality identified the same covariates listed above as the model most predictive of this outcome, although the interaction between patient sex and diabetes mellitus was no longer present (Wald χ^2 589, $P < 0.000001$). In both the model of cardiac death and that for all-cause death, the β coefficient for the % myocardium ischemic-early revascularization interaction almost entirely offset that of ischemia (cardiac death: ischemia β 0.0594, interaction β -0.0479; all-cause death: ischemia β 0.0594, interaction β -0.0488), suggesting that revascularization in large part neutralizes the prognostic impact of ischemia.

Discussion

In the present study, we sought to determine the threshold of inducible ischemia at which a short-term survival benefit was associated with early revascularization versus medical therapy in patients with no prior MI or revascularization by using multivariable modeling in a large observational data series. Unadjusted analysis revealed that patients undergoing revascularization early after MPS had significantly greater mortality compared with patients undergoing medical therapy. As stratifying by % myocardium ischemic, mortality rates increased significantly in patients undergoing medical therapy but not in patients referred for revascularization. The propensity score adjusting for nonrandomized therapy assignment identified inducible ischemia and anginal symptoms as the best predictors of referral to early revascularization. Cox proportional hazards models revealed a significant interaction between treatment and % myocardium ischemic. An increasing survival benefit for revascularization over medical therapy was present with increasing amounts of inducible ischemia. Revascularization seemed to nearly neutralize the prognostic impact of ischemia. On the basis of the Cox model, the predicted lives saved with revascularization versus medical therapy increased with increasing patient risk (increasing % myocardium ischemic, age, adenosine stress, female patients, and especially diabetic patients). In patients with >10% myocardium ischemic, revascularization was associated with a 50% risk-adjusted reduction in cardiac death. Similar results were found when using all-cause mortality as the end point.

Previous Studies

A large body of evidence, based on multiple prospective randomized clinical trials (RCTs), supports the survival

benefit of revascularization over medical therapy in several patient subsets.¹⁻⁴ Less extensive data are available from RCTs regarding the survival benefit of revascularization in relation to baseline stress testing data. Data from 2 major RCTs^{2,24} and the CASS registry^{5,6} describe a reduced mortality associated with revascularization versus medical therapy in patients with abnormal ETT that was confirmed in a study pooling RCT data.⁴

Regarding MPS, we previously reported enhanced unadjusted survival with revascularization over medical therapy in the setting of severely abnormal scans.⁷ O'Keefe et al¹¹ compared unadjusted survival in patients with mild to moderate amounts of ischemia, finding that patients undergoing medical therapy had superior outcomes compared with revascularization.

Comparison of the Present Study With Previous Studies

The results of the present study do not conflict with those of previous RCTs, which demonstrated that patients with extensive CAD preferentially benefited from revascularization whereas patients with small amounts of disease did not.^{2-4,25} The strength of the present study is the finding that one does not need to know the extent of angiographic CAD to predict benefit, only the extent of ischemia, a marker available noninvasively and earlier.

Our study extends prior information regarding the management of patients with suspected CAD in several ways. This is the first large study evaluating survival as a function of therapy given and the results of stress imaging using advanced statistical techniques. Contrary to previous results obtained with ETT,⁶ we found that both women and men who may potentially benefit from revascularization can be identified by MPS, especially diabetic women. Finally, the present study is the first concerning MPS to use a propensity score, an accepted means to adjust for the lack of randomization of therapy assignment. A byproduct of this score is a rigorous model evaluating physician resource utilization after noninvasive testing, revealing a potentially important relationship between presenting symptoms, inducible ischemia, and referral to revascularization.

Measurement of Incremental Prognostic Value of Noninvasive Testing

To date, assessments of the incremental prognostic value of noninvasive testing have been limited to patients undergoing medical therapy after testing, because patients undergoing early revascularization are censored from analyses because ischemia on noninvasive testing prompts patient referral to early revascularization.^{16,26} This posttest referral bias may result in underestimating the prognostic value of noninvasive testing because of the removal of the highest risk patients.^{27,28} The analytic methodology used in the present study provides an alternative definition of a test's clinical incremental prognostic value—the ability to identify patients who for a given test result will benefit from a particular therapeutic approach as opposed to another. The advantages of this approach are 2-fold. It is less subject to posttest referral bias because it incorporates all patients. Furthermore, it is defined

in a more clinically applicable manner than estimation of risk with medical therapy alone by providing prediction of benefit associated with each therapeutic option.

Prognostic Implications of Inducible Ischemia Versus Stress Perfusion Defect

Previous studies have shown that the summed stress score, the overall extent and severity of stress defects, is the most powerful predictor of adverse outcomes.^{7,8,10} Despite this, the present study demonstrates that predicting treatment benefit is limited to % myocardium ischemic, because no interaction could be found between treatment and percent myocardium abnormal with stress. The present findings also imply that even in a patient population without prior MI, the percent myocardium with fixed defect impacts risk of cardiac death but not the potential benefit from revascularization.

Expressing Perfusion Results as a Percent of Total Myocardium

This manuscript represents the first time we have converted our semiquantitative summed scores into percent myocardium. The benefits of this approach include that the percent myocardium abnormal provides a measure with intuitive implications not possible with the unitless summed scores, that it can be applied easily with scoring systems using varying numbers of segments (eg, 20, 17, and 13), and that it is applicable to quantitative methods that directly measure these abnormalities as percent myocardium.

Limitations

Statistical and Clinical

The limitations of multivariable techniques applied to observational data to adjust for baseline characteristics are well described.^{14,18,19,21,28} However, the analyses used here and by others^{14,15} provide results similar to those of RCTs in similar populations.²⁹ Nonetheless, this remains an observational study with the flaws inherent in its design. Although the impact of selection biases, spurious observations, and missing covariates cannot be ignored, patients in observational studies better represent those seen in practice and, unlike RCTs, can account for changes in therapy over time. However, whether a survival benefit definitively exists at any level of ischemia can only be answered by an RCT.

Although most patients in our study had normal scans, we also included a subset analysis of those patients with >10% myocardium ischemic, the results of which were identical to the overall results. Whether and in how many patients revascularization was not performed because of significant comorbidities is unknown. It is possible, if not probable, that patients with unmeasured comorbidities were preferentially treated medically, thus contributing to the early survival benefit found with revascularization. However, our results, despite limited follow-up, indicate the strength of MPS for identifying revascularization candidates.

Study Design

We used a 60-day window in which therapy selection is assigned to allow the structure of the present study to mimic that of an RCT. An alternative approach would be to change

the patient's treatment category at the time of any revascularization and count the time before revascularization toward medical therapy time and subsequent time as revascularization time. This would not have lent itself to incorporation into a clinical strategy (eg, selection of therapy in patients after MPS) and would have resulted in underestimating revascularization's efficacy because of the relatively short follow-up after later revascularizations. Most importantly, it would have prevented the use of a propensity score.

The thresholds in the present study hold true for the patients from our center; whether they will vary when populations from other centers with other interpreters and practice patterns are examined is unclear. Our cohort was drawn from patients referred for MPS, thus limiting generalizability of the results. We additionally limited generalizability by selecting a cohort without prior CAD at the expense of study power. Our study design assumed that medical therapy patients were given usual care rather than standardized, maximal medical therapy and was, therefore, that of an efficacy study. Whether the use of maximal medical therapy would yield the same results is beyond the scope of this manuscript. No comparison of CABG and percutaneous coronary intervention as therapies was made because of the lack of angiographic data and insufficient power. Because both procedures potentially reduce the amount of inducible ischemia, we believe that combining these two does not compromise the present results.

Technical

MPS was interpreted by experienced observers using a standardized, semiquantitative approach to visual interpretation documented to be highly reproducible.³⁰ This forms the basis for existing quantitative analysis programs that have been shown to correlate strongly with those of quantitative analysis.³⁰

Conclusion

In this observational study, revascularization reduced the absolute and relative risk of cardiac death more than medical therapy in patients with moderate to large amounts of inducible ischemia by stress MPS. This study, if confirmed by prospective evaluation, has significant consequences for the approach to post-MPS patient management in the future.

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