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Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy

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Aims	Although pre-revascularization ischaemia testing is recommended, the interaction between the extent of ischaemia and myocardial scar with performance of revascularization on patient survival is unclear.
Methods and results	We identified 13 969 patients who underwent adenosine or exercise stress SPECT myocardial perfusion scintigraphy (MPS). The percent myocardium ischaemic (%I) and fixed (%F) were calculated using 5 point/20-segment MPS scoring. Patients lost to follow-up (2.8%) were excluded leaving 13 555 patients [35% with history (Hx) of known coronary artery disease (CAD), 65% exercise stress, 61% male, age 66 ± 12]. Follow-up was performed at 12–18 months for early revascularization and at >7 years for all-cause death (ACD) (mean follow-up 8.7 ± 3.3 years). All-cause death was modelled using Cox proportional hazards modelling adjusting for logistic-based propensity scores, MPS, revascularization, and baseline characteristics. During FU, 3893 ACD (29%, 3.3% /year) and 1226 early revascularization, and HxCAD, such that %I identified a survival benefit with early revascularization in patients without prior myocardial infarction (MI), whereas no such benefit was present in patients with prior MI (overall model χ^2 = 3932, <i>P</i> < 0.001; interaction <i>P</i> < 0.021). Further modelling revealed that after excluding patients with scar >10% total myocardium, %I identified a survival benefit in all patients.
Conclusion	In this large observational series with long-term follow-up, patients with significant ischaemia and without extensive scar were likely to realize a survival benefit from early revascularization. In contrast, the survival of patients with minimal ischaemia was superior with medical therapy without early revascularization.
Keywords	Myocardial perfusion SPECT • Prognosis • Revascularization • Medical therapy

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Introduction

The optimal strategy for the management of patients with known or suspected stable coronary artery disease (CAD) is a fundamental question that clinicians face daily. Early, small trials suggested that a strategy of initial revascularization was a superior approach to medical therapy for patients with extensive CAD.¹ More recently, the COURAGE trial found that a strategy of initial percutaneous intervention (PCI) with aggressive medical therapy had no survival advantage over aggressive medical therapy alone in patients with angiographically documented CAD.² The COURAGE nuclear cardiology substudy, however, performed in 314 of the COURAGE subjects, suggested that patients with significant ischaemia may have benefited from therapy to reduce ischaemia, which was more successfully achieved with PCI than optimal medical therapy alone.^{3,4} Although the guidelines regarding PCI in stable CAD patients currently recommend an ischaemia-based patient management strategy,⁵ this remains an unproven approach. Our previously reported observational data indicate that myocardial perfusion scintigraphy (MPS)-identified inducible ischaemia is associated with improved survival with revascularization in patients without prior myocardial infarction (MI) or revascularization,^{6,7} but whether this is the case in patients with known CAD is unclear.^{3,4} Thus, we sought to examine a large observational database to determine whether the results of stress ischaemia imaging can identify patient cohorts in whom survival is likely to be optimized with revascularization vs. medical therapy. Further, we sought to investigate the roles of prior CAD and extent of myocardial scar on the relationship between ischaemia, revascularization, and survival.

Methods

Study population

We identified 14 627 consecutive patients who underwent testing between January 1991 and June 1997 (inclusive) at Cedars-Sinai Medical Center using dual isotope Tc-99m/Tl-201 MPS with either adenosine or exercise stress with available social security data to permit use of the Social Security Death Index for all-cause death (ACD). Patients were excluded for missing or incomplete data (42; 0.3%), the presence of significant valvular heart disease (488; 3.4%), and non-ischaemic cardiomyopathy (106; 0.7%), leaving 13 969 patients for follow-up. Successful follow-up was completed in 97.2% of these patients, leaving a final study population of 13 555 patients who were followed-up for a mean of 8.7 \pm 3.3 years. Of these patients, 8791 were included in our previous study examining post-MPS therapy in patients without prior CAD on shortterm (2-year follow-up). 6,7 A total of 1226 patients underwent early revascularization [501 coronary artery bypass grafting (41%; 35% ACD rate) and 725 percutaneous coronary intervention (59%; 33% ACD rate)] and 12 329 did not (medical therapy; 28% ACD rate).

All patients were consented for enrolment in a predefined data registry at the time of testing. The study was approved by the Cedars-Sinai Medical Center Institutional Review Board. Prior MI was based on patient history. Patients without prior CAD were defined as those without prior revascularization or MI. The occurrence of a prior MI was based on either an initial report by the patient of a prior MI or chart documentation of a prior MI, with confirmation by the patients' physician. 'Anginal symptoms' were defined as the presence of either typical or atypical angina. Normal rest ECG was defined as the presence of no or limited abnormalities [sinus tachycardia, 1° A-V block, premature atrial or ventricular contractions, mild intraventricular conduction delay (≤ 0.12 s), or sinus bradycardia]. Peak stress heart rate was defined as the maximum heart rate value during stress for either exercise or adenosine stress.

Imaging and stress protocol

Patients were injected intravenously at rest with Tl-201 (111-166.5 MBq; dose variation based on patient weight) and MPS was initiated 10–15 min after radiopharmaceutical injection.⁸ The exercise MPS protocol employed symptom limited exercise treadmill test using the Bruce protocol. At near maximal exercise, a 925-1480 MBg dose of Tc-99m sestamibi was injected (actual patient dose varied with patient weight) and exercise was continued for one additional minute after injection. Tc-99m sestamibi SPECT imaging was begun 15-30 min later.⁸ For the adenosine MPS protocol, patients were instructed not to consume caffeine products for 24 h before MPS. Following rest imaging, Tc-99m sestamibi (925-1480 MBq) was injected at the end of the 2nd or 3rd minute of a 5 or 6 min adenosine infusion (140 μ g/kg/ min).⁸ Whenever possible, exercise was performed as an adjunct to adenosine infusion (0% grade and 1–1.7 m.p.h.). Both during exercise and adenosine testing, blood pressure was recorded at rest, at the end of each stress stage and at peak stress. Twelve-lead electrocardiographic recording was performed each minute of exercise, and leads AVF, V1, and V5 were continuously monitored. Maximal ST change 80 ms after the | point was assessed as horizontal, upsloping, or downsloping.

The dual isotope protocol employed for this study is associated with a moderately high radiation dose to the patient. Depending on the administered activities and method used for the calculations, the effective dose to the patient ranges from 21 to 40 mSv.^{9,10} These amounts are more than those of the more common rest/stress protocol based on Tc-99m single isotope studies (9–11 mSv).¹¹ Given the similar prognostic findings of Tc-99m protocols to dual isotope protocols with respect to risk stratification, the findings of this study are considered applicable to Tc-99m only studies.

SPECT acquisition protocol

Myocardial perfusion scintigraphy was performed as previously described using an elliptical 180 acquisition obtaining 60–64 projections over 180° for 35 (Tl-201) or 25 s (Tc-99m sestamibi) per projection.⁸ Filtered backprojection without attenuation or scatter correction was used. Transaxial images were reoriented into short-axis and vertical and horizontal long-axis slices using standard software (QPS, Cedars-Sinai Medical Center, Los Angeles, CA, USA).

Image interpretation and scintigraphic indices

Semi-quantitative visual interpretation was performed using 20 segments for each reoriented image set.⁸ Segments were scored by consensus of two experienced observers using a five-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction ofradioisotope uptake, and 4 = absence of detectable tracer uptake) as previously described. Summed stress and rest scores were obtained by adding the scores of the 20 segments of the stress and rest images, respectively.¹² The sum of the differences between each of the 20 segments on the stress and rest images was defined as the summed difference score, a variable representing the amount of ischaemia. Summed scores represented both extent and severity of perfusion defects. 'Fixed defects' defined by the summed rest scores were considered to represent the amount of prior MI ('scar'). These indices were converted to percent of the myocardium (%myocardium) having stress, ischaemic, or fixed defects by normalizing to the maximum potential score (4×20) .⁶ Normal studies were defined as those studies

having <5% myocardium abnormal (equivalent to a summed stress score <4). For the entire cohort, left ventricular (LV) size was assessed visually as normal, borderline, or enlarged.

Patient follow-up

Patient follow-up was initially performed at 12–18 months post-index test for resource utilization (referral to catheterization, revascularization). A subsequent follow-up was performed via the Social Security Death Index on 29 December 2004 for the occurrence of ACD. Death certificates were obtained for all patients who died in Los Angeles County. All-cause death was defined as any death during follow-up. Patients not confirmed to be deceased and without follow-up information (current questionnaire, current telephone interview, or at least 1 year of data in the hospital computer system) were considered lost to follow-up.

Statistical analysis

Baseline characteristics of patients undergoing medical therapy or revascularization were described in terms of median (25th, 75th percentiles) for continuous variables and frequencies for categorical variables. The former were compared using the Wilcoxon rank sum test and the latter using a χ^2 test; P < 0.050 was considered statistically significant.

Analysis design

Patients were categorized by revascularization status at 90 days and propensity analysis was used to take into account selection bias. 6,7,13

Multivariable modelling

A two-step process was used with initial development of a propensity score followed by multivariable survival analysis.

Propensity score

A propensity score was developed to adjust for potential biases introduced by the non-randomized referral patterns to revascularization in practice. This approach modelled a decision node (medical therapy vs. revascularization) using a logistic regression model to summarize measured covariates that were predictors of this decision into a single composite score that represents a probability of patient assignment to one therapy vs. another.^{14–16} Since the purpose of the propensity score was to represent these predictors as accurately as possible all measured factors known to influence this referral decision were considered for entry into a logistic regression model¹⁷ within the constraints of overfitting. By identifying those variables predictive of this referral, a single composite score representing the probability of patient assignment to a given therapy was derived and, this score was incorporated in the survival analysis to allow adjustment for the determinants of therapy.

Survival analysis

A Cox proportional hazards model (CPH) was used to determine the association of treatment with survival-time free of ACD after adjusting for baseline covariates and a propensity score, ^{14,18} thus permitting evaluation of treatment impact, *per* se. Whether specific baseline variables (e.g. inducible ischaemia) impact the survival benefit associated with revascularization was addressed formally with the Cox model by testing for treatment-covariate interactions.^{17,19} Additional survival modelling was performed in a subset limited to patients with <10% myocardium fixed. For all multivariable modelling, the thresholds for variable removal from the final models was *P* > 0.100. Care was given to examination of model assumptions including proportional hazards, linearity, and additivity.^{17,19} The survival impact of revascularization compare

with medical therapy was assessed at specific levels of ischaemia and was examined by multivariable hazard ratios based on CPH. Covariate selection for model entry was based on clinical experience and identification of covariates known to be multivariable predictors. The S-PLUS 2000 (Release 2) software package (Insightful Corp., Seattle, Washington, DC, USA) was used for all analyses.

Results

Patient characteristics

Table 1 compares the baseline characteristics of the 12 329 patients treated medically and the 1226 patients treated with early revascularization in the first 90 days after MPS. The patients undergoing early myocardial revascularization had more clinical risk factors (including greater age, more males, and more diabetes, hypertension, and hypercholesterolaemia according to history), more anginal symptoms, more frequent history of prior CAD, and a substantially greater frequency of abnormal MPS studies, with both more extensive and severe ischaemic and fixed perfusion abnormalities on MPS. Patients undergoing early revascularization were also more likely to be treated with beta-blockers, calcium channel blockers, and nitrates at the time of their index study.

Among our 13 555 patients, there were 8797 patients (65%) without prior CAD, 1542 patients with prior revascularization but without prior MI (11%), and 3216 patients with prior MI (24%; patients with both prior MI and revascularization were included in this last group). Within these groups, the % myocardium abnormal was 4.6 ± 8.5 among those without CAD, 10.8 \pm 11.1 in those with prior revascularization, and 17.8 \pm 14.0 in those with prior MI, P < 0.001. These differences were due both to differences in % myocardium fixed (1.1 \pm 3.8 vs. 3.0 ± 5.9 vs. 9.6 ± 11.4 , respectively, P < 0.001) and differences in % myocardium ischaemic $(3.5 \pm 6.9 \text{ vs. } 7.8 \pm 9.0, \text{ vs. } 8.3 \pm 8.8,$ respectively, P < 0.001). Of patients referred to early revascularization, 5% had normal MPS results, 71% had significant ischaemia, and 24% had little or no ischaemia. Of patients with prior MI, 45% had no clinically meaningful scar (<5% myocardium with scar). However, considering scintigraphically defined scar as the presence of fixed defects of any severity (>0% myocardium with scar), 70% of patients with prior MI had scar present.

Outcome events

Over the follow-up interval, 3893 (28.7%) of our patients died, resulting in an annualized mortality rate of 3.3% per year. Mortality rates were lowest among patients without prior CAD, intermediate among patients with prior revascularization only, and were greatest among patients with prior MI (*Figure 1*).

Univariable predictors of all-cause mortality

Numerous factors were univariable predictors of all-cause mortality (*Table 2*). The most predictive of these included age, diabetes mellitus, digoxin use, dyspnoea, prior catheterization, MI or CABG, an abnormal rest ECG, peak stress heart rate, exercise stress, and several MPS variables including MPS ischaemia, fixed defects, and LV enlargement.

Table I Patient characteristics

	All (13 555)	Medical therapy (12 329)	Early revasc (1226)	
Clinical characteristics (%)				
Age	67 (57,75)	67 (57.75)	69 (61,76)	< 0.001
Male	61	59	73	< 0.001
Diabetes mellitus	18	17	25	< 0.001
Hypercholesterolaemia	45	45	50	< 0.001
Smoking	15	15	16	0.373
Family Hx CAD	25	25	27	0.133
Hypertension	48	48	53	< 0.001
Symptoms (%)				••••••
Typical angina	16	15	34	< 0.001
Atypical angina	28	27	29	0.142
Any anginal symptoms	44	42	63	< 0.001
Dyspnoea	5.6	5.5	6.8	0.069
Historical data (%)				••••••
Hx CAD	35	33	53	< 0.001
Prior catheterization	36	35	51	< 0.001
Prior MI	24	22	36	< 0.001
Prior CABG	15	15	19	< 0.001
Prior PCI	14	13	25	< 0.001
Medication use (%)				
Beta-blocker	9.9	9.5	13	< 0.001
Calcium channel blocker	14	14	19	< 0.001
Nitroglycerin	8.0	7.6	12	< 0.001
Digoxin	7.5	7.5	6.7	0.336
Rest ECG (%)				
Abnormal ECG	69	68	81	< 0.001
Stress test (%)				
Pharmacologic stress	35	35	40	< 0.001
lschaemic stress response	9.2	7.3	29	< 0.001
Ischaemic ECG response	17	15	32	< 0.001
MPS results (%)				••••••
%myocardium ischaemic	1 (0,8)	0 (0,5)	15 (8,24)	< 0.001
%myocardium fixed	0 (0,2)	0 (0,2)	3 (0,8)	< 0.001
>10% myo ischaemic	21	16	71	< 0.001
>10% myo fixed	11	10	19	< 0.001
Abnormal MPS	45	40	95	< 0.001
LV enlargement (any)	16	14	22	< 0.001

Continuous variables presented as median (25th, 75th %tiles); categorical variables presented as frequency (%).

Hx, history of; MI, myocardial infarction; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention; ECG, electrocardiogram; myo, myocardium; LV, left ventricular.

Multivariable modelling

A more detailed description of the results of multivariable modelling appears in the appendix.

Logistic regression-derived propensity score

Logistic regression identified multiple factors as predictive of referral to early referral to revascularization after MPS ($\chi^2 =$ 1770, *c* index = 0.88) (*Table 3*). The extent and severity of

ischaemia was the predominant factor driving this referral (χ^2 : 1204 of a model χ^2 : 1770). The predicted likelihood of referral to revascularization for each individual patient determined from this model was entered into the CPHs model as a propensity score to adjust for the lack of randomization.

Survival modelling

The final CPHs model (*Table 4*) was strongly associated with the occurrence of all-cause mortality (Wald χ^2 : 3932, P < 0.001).



Figure I Unadjusted Kaplan–Meier survival free of all-cause death in patients with no prior CAD, prior revascularization (revasc) but no prior MI, and prior MI. Difference between curves P < 0.001. MI, myocardial infarction; CAD, coronary artery disease.

Left ventricular enlargement, diabetes mellitus, %myocardium fixed, the use of digoxin, dyspnoea, abnormal rest ECG, and patient age were associated with the greatest risk (largest positive hazard ratios), and the use of exercise stress, higher peak stress heart rates, and anginal symptoms are associated with the lowest risk (most negative hazard ratio) (*Figure 2*). After risk-adjustment, compared with patients without prior CAD, patients with prior revascularization but without prior MI were at greater risk, but patients with prior MI were not [hazard ratio 1.28 (1.04,1.58) in the former, 0.97 (0.84,1.13) in the latter]. After excluding the covariate "prior MI" from this model, the three-way interaction (early revascularization x %myocardium ischaemic x prior MI) remained significant (P = 0.043).

The presence of anginal symptoms was associated with reduced risk both in patients with and without prior CAD, as well as in the setting of extensive ischaemia. This seemingly paradoxical finding is accounted for by the characteristics of the patients without angina and extensive ischaemia—one-third of these patients had either dyspnoea as a presenting symptom or diabetes mellitus. Of patients with significant ischaemia but no angina, 47% of the events occurred in patients with diabetes mellitus and/or dyspnoea.

In this model, the relationship between post-MPS treatment and subsequent survival was dictated by the three-way interaction between the use of early revascularization, the %myocardium ischaemic, and history of prior CAD (*Table 4*). In the absence of prior CAD, increasing amounts of ischaemia were associated with lower hazard ratios with early revascularization (*Figure 3A*). In the setting of little or no ischaemia, early revascularization was associated with \sim 50% greater risk than medical therapy; whereas, with increasing ischaemia, a progressive improvement in risk with early revascularization compared with medical therapy was present. In the setting of extensive ischaemia (>20%)

myocardium), a 30% reduction in ACD risk was present with the use of early revascularization compared with medical therapy. Equipoise between strategies was present at ${\sim}10{-}15\%$ myocardium ischaemic.

In patients with prior revascularization but no prior MI (*Figure 3B*), as above, hazard ratios decreased across values of %myocardium ischaemic, indicating a progressive survival benefit with revascularization over medical therapy in the setting of extensive ischaemia, but increasing risk with revascularization in the presence of little or no ischaemia. Equipoise between strategies was present at 10% myocardium ischaemic. Compared with patients without prior CAD, the risk associated with performing early revascularization in the absence of ischaemia was not as great while the potential benefit in the setting of ischaemia was similar.

Finally, in patients with prior MI (*Figure 3C*), the relationship between ischaemia and the therapeutic hazard ratio was relatively flattened, suggesting that therapeutic benefit was relatively independent of the level of ischaemia. Although a survival benefit with revascularization compared with medical therapy was observed in the setting of extensive ischaemia, this benefit was attenuated at lower values of ischaemia with widening of the confidence intervals. Finally, the increased risk associated with the use of revascularization in patients without significant ischaemia described above was not observed in these patients.

Exclusion of patients with extensive scar

To more closely examine the impact of myocardial scar on the relationship between ischaemia and post-MPS patient management, we repeated the above modelling in a subset of patients with <10% myocardium fixed (myocardium ischaemic $8.5\% \pm 8.4$, myocardium fixed $20.3\% \pm 9.9$), hence excluding 1675 (12.4%) patients who had $\geq 10\%$ fixed myocardial defect. In the

Factor	χ²	Р	Hazard ratio
Clinical characteristics			
Age ^a	2260	<0.001	1.69 (1.59, 1.80)
Male	5	< 0.028	0.93 (0.87, 0.99)
Diabetes mellitus	259	< 0.001	1.58 (1.50, 1.68)
Hypercholesterolaemia	136	<0.001	0.68 (0.64, 0.72)
Smoking	5	0.029	1.10 (1.01, 1.20)
Family Hx CAD	38	<0.001	0.78 (0.73, 0.85)
Hypertension	112	<0.001	1.41 (1.32, 1.50)
Digoxin use	391	<0.001	2.49 (2.27, 2.72)
Use of early revascularization	23	<0.001	1.28 (1.16, 1.42)
Abnormal rest ECG	495	<0.001	2.67 (2.45, 2.91)
β-blocker use	1	0.331	0.95 (0.85, 1.06)
Symptoms			
Typical angina	0.3	0.601	1.02 (0.94, 1.11)
Any angina	0.5	0.476	0.98 (0.92,1.04)
Dyspnoea	368	< 0.001	2.49 (2.27,2.72)
Historical data			
Prior catheterization	189	<0.001	1.56 (1.46, 1.66)
Prior MI	282	< 0.001	1.77 (1.66, 1.89)
Prior CABG	310	<0.001	1.93 (1.80, 2.08)
Prior PCI	8	0.005	1.13 (1.04, 1.23)
Prior CAD (present vs. absent)	347	<0.001	1.94 (1,71, 1.94)
Prior CAD ^b	359	< 0.001	1.39 (1.35, 1.44)
Stress test			
Peak stress heart rate	1949	<0.001	0.981 (0.981, 0.982)
Rest heart rate	175	<0.001	1.02 (1.01, 1.02)
Exercise stress	1678	<0.001	0.28 (0.27, 0.30)
lschaemic stress response	7	0.006	0.85 (0.76, 0.96)
Ischaemic ECG response	161	< 0.001	0.51 (0.46, 0.57)
MPS results			
%myocardium ischaemic ^a (per 5%)	432	< 0.001	1.47 (1.41, 1.53)
%myocardium fixed ^a (per 5%)	886	< 0.001	1.51 (1.46, 1.57)
TID (any)	60	< 0.001	1.38 (1.27, 1.50)
LV enlargement (any)	506	<0.001	2.03 (1.91, 2.16)

Table 2 Single variable predictors of death (based on univariable Cox proportional hazards models)

CAD, coronary artery disease; ECG, electrocardiogram; LV, left ventricular; TID, transient ischaemic dilation.

^bCoded as 1, no prior CAD; 2, prior CAD but no prior MI; 3, prior MI.

remaining 11 880 patients (3009 ACDs), this second survival model revealed a strong overall association with ACD (Wald χ^2 : 2964, P < 0.001). After adjusting for potential confounders, the interactions that remained in the model were early revascularization × %myocardium ischaemic and male sex × prior CABG; the three-way interaction found in the initial model was no longer significant. Based on this model, a progressive decrease in hazard ratio with increasing ischaemia was noted, consistent with the presence of a survival benefit with revascularization over medical therapy in the setting of significant ischaemia (*Figure 3D*). Comparing early revascularization and medical

therapy, the risk associated with the latter increased as a function of %myocardium ischaemic, while the risk associated with the former decreased with increasing ischaemia (*Figure 4*).

Patients with extensive scar

We also examined predicted survival with medical therapy vs. revascularization in the 1675 patients with \geq 10% myocardium fixed (884 ACDs) excluded from the above analysis. This third model revealed a strong overall association with ACD (Wald χ^2 : 525, LR: 549.2 using 15 degrees of freedom, P < 0.001). In contrast to the models presented above, %myocardium ischaemic was of

^aNon-linear.

Table 3 Results of logistic regression modelling of early revascularization

Covariate	Beta coefficient	χ ²	Р
Intercept	- 4.290		< 0.001
Male sex	0.173	4.6	0.031
Hx prior PCI	0.472	31.6	0.003
Hx prior CABG	-0.653	51.6	< 0.001
Anginal symptoms	0.362	24.1	< 0.001
Clinical response to stress	0.792	71.7	< 0.001
ECG response to stress	0.335	15.2	< 0.001
Transient ischaemic dilation	0.184	6.3	< 0.001
%myocardium ischaemic ^a	0.012	1204	< 0.001
%myocardium fixed	0.0003	26.9	< 0.001
Use of exercise stress	-0.276	12.8	< 0.001

Global $\chi^2\!\!:$ 1770 using 18 degrees of freedom; Hx, history. ^aNon-linear.

borderline significance (P = 0.089) and the ischaemia-treatment interaction was not significant (P = 0.469).

Patients with extensive ischaemia

Finally, we also examined predicted survival with medical therapy vs. revascularization in the 2827 patients with \geq 10% myocardium ischaemic (1127 ACDs). After adjusting for potential confounders, both %myocardium ischaemic (P = 0.016), %myocardium fixed (P < 0.001), and use of early revascularization (P = 0.002) were all significant predictors of mortality (Wald χ^2 : 919, LR: 920 using 15 degrees of freedom, P < 0.001).

Discussion

Our study, which used a CPHs model that adjusted for potential confounding variables, found an interaction between MPS-detected ischaemia, post-MPS therapy, and history of CAD in the predicting of long-term all-cause mortality. Specifically, this interaction identified an increasing survival benefit with revascularization over medical therapy in the setting of extensive ischaemia both among patients without prior CAD as well as those with prior revascularization but no prior MI, but not among patients with prior MI. Of note, when patients with more extensive scar were excluded from the analysis (>10% total myocardium fixed), increasing amounts of ischaemia identified an increasing survival benefit among the remaining patients both with and without prior MI. This suggests that in the absence of extensive scar, there is a survival benefit associated with revascularization across the range of clinically meaningful ischaemia. The data also suggest possible harm with revascularization if ischaemia is not present and in patients with >10% total myocardium fixed, ischaemia had a reduced role in identifying optimal post-MPS therapy.

Previous studies

We have previously noted that MPS ischaemia identifies patients likely to accrue a survival benefit with revascularization compared

Table 4Cox proportional hazards model for all-causedeath: overall population

Factor	χ ²	β	Р
Age ^a	973	0.0213	<0.001
Diabetes mellitus	83	0.2728	< 0.001
Male sex	9	0.1168	0.008
Abnormal rest ECG	32	0.2657	< 0.001
Any anginal	7	-0.0937	0.010
Dyspnoea	27	0.2925	< 0.001
Digoxin use	55	0.3531	< 0.001
β-Blocker use	28	0.9197	0.002
Hx CAD ^b	8	0.0688	0.010
Hx myocardial infarction	8	-0.0047	0.018
Hx CABG	4	0.1511	0.066
Hx CABG \times Male sex	4	-0.1654	0.049
Peak stress heart rate	577	-0.0131	< 0.001
Rest heart rate	319	0.0222	< 0.001
Rest heart rate \times $\beta\text{-blocker}$ use	17	-0.0164	< 0.001
Use of early revascularization	22	0.6547	< 0.001
Propensity score	2	-0.3591	0.167
LV enlargement on MPS	53	0.3348	< 0.001
LV enlargement on MPS \times Hx MI	8	-0.1926	0.005
%myocardium fixed ^a	96	0.0643	< 0.001
%myocardium ischaemic	29	0.0255	< 0.001
Early revascularization \times %myocardium ischaemic \times Hx CAD ^b	5	0.0133	0.021
%myocardium ischaemic $ imes$ Hx CAD ^b	6	-0.0038	0.085
Early revascularization \times Hx CAD ^b	6	-0.2480	0.046
Early revascularization × %myocardium ischaemic	18	-0.0451	< 0.001
Total	3932		< 0.001

ECG, electrocardiogram; Hx, history of prior; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass surgery; MPS, myocardial perfusion scintigraphy.

^aModelled nonlinearly to satisfy Cox proportional hazards assumption of linearity in hazard. β shown for main term.

^bCoded as 1, no prior CAD; 2, prior CAD but no prior MI; 3, prior MI.

with medical therapy among patients without prior known CAD.^{6,7} In such patients, the absence of inducible myocardial ischaemia identifies patients likely to have superior survival with medical therapy alone. In subsequent work, we found that inducible ischaemia, but not scar, LV volumes, or LV ejection fraction (LVEF), identifies the occurrence of a survival benefit.⁷ The current study extends these previous findings in two ways. First, we now report that the previous findings identifying the association of MPS results and therapeutic benefit can be extended to patients with prior revascularization as well as to those patients with prior MI who have limited extent of myocardial scar. Second, the absence of an interaction of prior CAD with ischaemia and post-MPS therapy after exclusion of patients with extensive scar suggests that the magnitude of scar, not the history of MI per se, attenuates the utility of the presence of ischaemia to identify therapeutic benefit in all study patients. Hence, the presence of scar attenuates





the ischaemia-identified benefit otherwise associated with revascularization. Notably, our prior studies were limited only to the prediction of short-term cardiac outcome, whereas our present study extends our findings to the prediction of long-term outcome, as assessed by rates of all-cause mortality at a median follow-up of 8.7 years.

Of note, in this regard, is the consistency between our findings and that of the COURAGE Nuclear Substudy³ (involving 314 of the 2287 trial patients). In that sub-study, revascularization combined with optimal medical therapy yielded greater ischaemia reduction than optimal medical therapy alone (-2.7% vs. -0.5%, P < 0.001). The patients with ischaemia reduction had lower unadjusted risk for death or MI [P = 0.037 (risk-adjusted P < 0.26)], particularly in the setting of moderate to severe baseline ischaemia [P < 0.001 (risk-adjusted P = 0.08)]. While these results are concordant with those observed in our study, the COURAGE Nuclear Substudy was underpowered to assess the findings regarding benefit as a function of inducible ischaemia.

Our results differ from the results of the COURAGE trial, however, in that we observed an overall survival benefit with the use of revascularization in multiple patient subsets. This difference may be due to several possibilities. First, it is possible that the extent and severity of ischaemia in COURAGE, and hence the %myocardium ischaemic, did not reach the minimum threshold necessary to have accrued survival benefit following revascularization.² Second, revascularization was performed by PCI or CABG in the present study, vs. only PCI in COURAGE. Finally, participation in the COURAGE trial mandated a rigorous schedule of medical therapy and prevention in both study arms, the impact of which

may have negated the impact of revascularization. It is likely that this medical therapy regimen was more extensive and superior to that used in the patients followed in the current study, thus resulting in a greater observed beneficial impact of revascularization in our study. However, even the rigorous optimal medical therapy in COURAGE did not by itself significantly reduce ischaemia (in contrast to PCI).²

Our results also help elucidate prior observations reported by Tarakji *et al.*⁴ Using a propensity-matched approach, they reported that results of cardiac stress PET and viability imaging did not identify which patients accrue a survival benefit from revascularization vs. medical therapy. The cohort examined by these authors consisted of patients with severe LV dysfunction (<35%). The patients included in their matched comparison had extensive infarct (median 30%), little ischaemia (median 4%), and severely reduced LVEF (median 25%). These findings are consistent with our observation that imaging did not identify therapeutic benefit in the setting of historical prior MI or observed extensive scar.

The results of the current study pose the question of why the presence of extensive scar may preclude a survival benefit with revascularization despite the presence of significant ischaemia. This finding may be related, in part, to a higher procedural risk of PCI and CABG in patients with large infarcts, compounded by LV dilation and dysfunction that is observed in such patients.²⁰ Potentially, this elevated risk may be sufficient to obviate any downstream benefit that such patients may accrue from revascularization. Alternatively, MPS may be less accurate in defining ischaemia in patients with large scar than in patients with no or small prior MI. Finally, it is possible that more routine use of



Figure 3 Hazard ratio associated with early revascularization compared with medical therapy at specific values of %myocardium ischaemic. (A) patients with no prior coronary artery disease, (B) patients with prior revascularization but no prior myocardial infarction, (C) patients with prior MI, and (D) patients with <10% fixed defect. P-values as per Cox proportional hazards model.

viability imaging with identification of viable myocardium may have enhanced the ability of MPS to identify revascularization candidates as well as altered our results with respect to patients with extensive scar.

The current manuscript differs from our previous publication⁶ in several respects. The results of the current study are considerably more robust, due to a longer follow-up (8.7 ± 3.3 vs. 1.9 ± 0.6 years), a different endpoint (all cause vs. cardiac death), greater power (3893 vs. 146 events), and a larger revascularization patient group (1226 vs. 671 patients). Further, these studies differ with respect to their goals and generalizability. The prior manuscript was limited to patients without prior CAD in the belief that LV scar, reduced LVEF, and other sequelae of chronic CAD would potentially confound the relationship between ischaemia, patient management, and subsequent patient survival. The current study utilizes a broader population permitting examination of this relationship while patients without prior CAD serve strictly

as a control group. Thus, the results of the prior study would not be generalizable across the types of patients referred for nuclear stress testing. The findings of the current study extend those of the previous study both with respect to the cohort examined but also with respect to implicating myocardial scar as a 'brake' on the potential survival benefit associated with revascularization over medical therapy in the setting of ischaemia. Through this finding, we broaden substantially the applicability of the findings, while at the same time providing insight into the limitations of ischaemia in predicting a survival benefit from revascularization in patients with prior MI.

Limitations

Owing to the single-site, observational design, the generalizability of this study is limited. As with many other facets of an observational study, trade-offs are made in study design. It is possible that the clinical message of the current study could have been





further honed if certain patient subsets within our cohort of consecutive patients would, on clinical grounds, be excluded. However, this approach serves to introduce bias and undermines both the internal and external validity of the study. In this trade-off, we chose to protect validity at the cost of potentially obfuscating the clinical message and possibly introducing statistical noise into our comparison.

It is possible that not all patients with chest pain referred to testing and later found not to have CAD (e.g. valve disease, cardiomyopathy) were identified and excluded. However, as these patients are less likely to manifest ischaemia, and are likely to be treated medically, we would anticipate that their presence in any significant numbers would inflate the medical therapy mortality rate in patients without ischaemia. This would serve to decrease the survival advantage of medical therapy over revascularization in the setting of little or no ischaemia.

Although the impact of selection biases, spurious observations, and unmeasured covariates cannot be ignored, patients in observational studies better represent those seen in practice and, unlike randomized clinical trials (RCTs), can account for changes in therapy over time. However, the results of this and all other observational studies constitute hypothesis generating findings that, ideally, may spur on further investigations, preferably with randomized methodologies. Whether a survival benefit definitively exists at any level of ischaemia can only be answered by an RCT. Further, limitations associated with multivariable techniques (including propensity scores) applied to observational data to adjust for potential confounding have been characterized.¹⁹

The current study was designed as an effectiveness study in that the treatment received by patients was dictated by the clinical practice of their physicians. Thus, 'medical therapy' after MPS was defined as that treatment received in the absence of referral to revascularization but the nature of medical therapy was unknown. Both medical therapy and the type of revascularization used are likely to be 'under-treatment' relative to today's recommendations, as these patients were tested in an era prior to the development of many therapeutics used routinely today. That said, the current use of post-imaging therapeutics-catheterization referral and medical therapy—is far less than expected, and 30-45% of patients are not on guideline indicated medications after the finding of extensive abnormalities on imaging.^{21,22} Nonetheless, whether such medications were given and to whom is not known in our data. Also, we did not differentiate in the current analysis between revascularizations performed with CABG vs. PCI. Recent studies suggest that the efficacy of these two approaches may differ in select patient subgroups, hence, the addition of this component to our analysis may have identified inter-treatment differences.²³

The current study is limited by the use of all-cause mortality as the primary endpoint. Although this approach limits potential misclassification bias associated with the assignment of cause of death, it is also limited in that the interventions we assess impact cardiac death far more than all-cause mortality. The US Social Security Death Index was used to identify deaths occurring on long-term follow-up. It is possible that we 'missed' events due to deaths occurring outside of the US or to the 'lag period' between time of death and its appearance in the death index. Hence, it is possible that a misclassification bias exists in 'missing' deaths that occurred very late in the follow-up period. However, we believe the number of deaths missed is relatively few.

The current study utilized a 20-segment scoring model and the summed defect scores converted to %myocardium. Compared with the 17-segment system, this approach is hampered by overweighting of the apical segments. Hypothetically, this may result

in a difference in risk estimation. However, we have previously compared the results of 20-segment and 17-segment scoring,²⁴ finding very close agreement (r = 0.982; kappa = 0.866) between the %myocardium determined by 17- and 20-segment scoring.

The current study does not include data regarding measured LV volumes and EF since these patient studies in large part pre-dated the routine used of gated SPECT techniques at our institution. Finally, the use of a dual isotope protocol using Tl-201 for the rest images may have resulted in underestimation of ischaemia and overestimation of scar due the greater frequency of attenuation artefacts associated with Tl-201.

Clinical implications and conclusions

Our findings indicate that the presence of substantial MPS-identified inducible ischaemia is associated with enhanced survival in patients undergoing revascularization compared with medical therapy, whereas the lack of inducible ischaemia is associated with superior survival with medical therapy compared with revascularization among patients without prior CAD, prior revascularization, and prior non-extensive MI. The therapeutic benefit of revascularization is attenuated among patients with evidence of large prior MI by MPS. These findings provide support for current guidelines concerning the use of ischaemia testing in stable patients prior to revascularization and strengthen those guidelines that recommend a medical approach among patients with overt evidence of CAD but minimal ischaemia. Nonetheless, due to the limitations of a observational data, there is a need for an adequately powered prospective study that will attempt to definitively demonstrate a survival benefit among patients undergoing revascularization, and ideally to define the cutoff value for the level of ischaemia that must be present for such a benefit. In the interim, our results imply that both the absence of significant ischaemia and the presence of extensive MI identify patients who are unlikely to benefit from referral to revascularization. Conversely, patients with >10% inducible ischaemia appear to have a survival advantage from early revascularization in the absence of extensive scar.

Conflict of interest: D.S.B. has grants from Lantheus Medical Imaging, Inc. and is on the speaker bureau for Astellas Pharma, Inc. D.S.B. and G.G. participate in royalties to Cedars-Sinai Medical Center for licensure of software used in this study. R.H. has grants from Astellas Pharma, Inc., GE Healthcare, Siemens Medical Solutions, and Bracco and consultants for Lantheus Medical Imaging. The other authors report no conflicts.

Appendix: Results of Multivariable Modelling

Logistic regression-derived propensity score

(*Table 3*) Logistic regression identified patient sex, prior PCI, prior CABG, anginal symptoms, clinical response to stress, ECG response to stress, the presence of transient ischaemic dilation, the type of stress performed, and the amount of ischaemia and fixed defect as the model best associated with early referral to

revascularization after MPS ($\chi^2 = 1770$, *c* index = 0.88). Patients undergoing exercise stress and patients with a prior history of bypass surgery were less likely to be referred to revascularization. Conversely, the other model covariates were all associated with increased referral rates to revascularization.

Indices of ischaemia accounted for 69% of the information used for the decision to refer to revascularization (based on χ^2 , covariate χ^2 : 1204 vs. a model global χ^2 : 1770).

The predicted likelihood of referral to revascularization for each individual patient was entered into the Cox proportional hazards model as a propensity score.

Cox proportional hazards modelling

The final Cox proportional hazards model, as shown in *Table 4*, was strongly associated with the occurrence of all-cause mortality (Wald χ^2 : 3932, LR: 4135, 27 degrees of freedom, P < 0.001). The variable 'type of stress performed' violated the proportional hazards assumption, hence, was included as a stratification factor. The hazard ratios for the variables in this model—except for the variables affected by the ischaemia-therapy-Hx CAD interaction (discussed below)—are graphically depicted in *Figure 2*. Of the variables in the model, LV enlargement, diabetes mellitus, %myocardium fixed, the use of digoxin, dyspnoea, abnormal rest ECG, and patient age are associated with the greatest risk (largest positive hazard ratios), and the use of exercise stress, higher peak stress heart rates, and anginal symptoms are associated with the lowest risk (most negative hazard ratio).

In this model, the relationship between post-MPS treatment and subsequent survival was dictated by the three-way interaction between the use of early revascularization, %myocardium ischaemic, and history of prior CAD (Table 4; P = 0.021). This interaction reveals several important results. First, in the absence of prior CAD (Hx CAD = 0), only the interaction between early revascularization and %myocardium ischaemic remains (interaction P <0.001, $\beta = -0.0451$). This negative β coefficient (lower risk) indicates that in the setting of early revascularization, as compared with medical therapy, risk (as expressed by a hazard ratio) decreases with increasing ischaemia, thus offsetting the risk of the revascularization procedure (positive β coefficient). For patients with prior CAD (Hx CAD >0), the overall effect of these interactions blunted the prognostic effect of revascularization across values of ischaemia. These relationships between early revascularization, Hx CAD, and ischaemia are best examined graphically, as depicted in Figures 3A-C in the form of hazard ratios associated with the use of early revascularization compared with medical therapy across values of %myocardium ischaemic.

In patients without prior CAD (*Figure 3A*), there was a downsloping relationship such that increasing amounts of ischaemia were associated with lower hazard ratios. In the setting of little or no ischaemia, early revascularization was associated with \sim 50% greater risk than medical therapy; whereas, with increasing ischaemia, a progressive improvement in risk with early revascularization compared with medical therapy was present. In the setting of extensive ischaemia (>20% myocardium), a 30% reduction in all-cause death risk was present with the use of early revascularization compared with medical therapy. Equipoise between strategies was present at $\sim 10-15\%$ myocardium ischaemic.

In patients with prior revascularization but no prior MI (*Figure 3B*), there was a significant decrease in hazard ratios across values of %myocardium ischaemic, indicating, as above, a progressive survival benefit with revascularization over medical therapy in the setting of extensive ischaemia, but increasing risk with revascularization in the presence of little or no ischaemia. Equipoise between strategies was present at 10% myocardium ischaemic. Compared with patients without prior CAD, the risk associated with performing early revascularization in the absence of ischaemia was not as great (hazard ratio 1.18 vs. 1.51), while the potential benefit in the setting of ischaemia was similar (0.68 vs. 0.74).

In patients with prior MI (*Figure 3C*), on the other hand, a relatively flattened relationship between ischaemia and the therapeutic hazard ratio was present, suggesting that therapeutic benefit was relatively independent of the level of ischaemia. While a survival benefit with revascularization was observed in the setting of extensive ischaemia, this benefit was attenuated at lower values of ischaemia with widening of the confidence intervals. Finally, the increased risk associated with the use of revascularization in patients without significant ischaemia described above was not observed in these patients.

Exclusion of patients with extensive scar

To more closely examine the impact of myocardial scar on the ability of ischaemia to identify patients with a potential survival benefit, we repeated the above modelling in a subset of patients with <10% myocardium fixed, hence excluding 1675 (52%) patients who had >10% fixed myocardial defect (myocardium ischaemic $8.5\% \pm 8.4$, myocardium fixed $20.3\% \pm 9.9$). In the remaining 11 880 patients (3009 all-cause deaths), this second survival model revealed a strong overall association with all-cause death (Wald χ^2 : 2964, LR: 3104.43 using 19 degrees of freedom, P < 0.0001). Compared with the Cox model presented above, after adjusting for potential confounders, the interactions that remained in the model were early revascularization \times %myocardium ischaemic and male sex \times prior CABG; the three-way interaction found in the initial model was no longer significant. The exclusion of patients with extensive scar also resulted in reduced prognostic value for %myocardium fixed (χ^2 : 97–40) and LV enlargement (χ^2 : 54–27), a smaller increase in %myocardium ischaemic $(\chi^2: 29-36)$, and prior MI was no longer in the model (P > 0.10). Based on this second Cox proportional hazards model, a progressive decrease in hazard ratio with increasing ischaemia was noted, consistent with the presence of a survival benefit with revascularization over medical therapy in the setting of significant ischaemia (Figure 3D).

Patients with extensive scar

We also examined predicted survival with medical therapy vs. revascularization in the 1675 patients with \geq 10% myocardium fixed (884 all-cause deaths) excluded from the above analysis. This third model revealed a strong overall association with all-cause death (Wald χ^2 : 525, LR: 549.2 using 15 degrees of

freedom, P < 0.0001). In contrast to the models presented above, %myocardium ischaemic was of borderline significance (P = 0.089) and the ischaemia-treatment interaction was not significant (P = 0.469).

Patients with extensive ischaemia

Finally, we also examined predicted survival with medical therapy vs. revascularization in the 2827 patients with \geq 10% myocardium ischaemic (1127 all-cause deaths), thus excluding all patients without extensive ischaemia. After adjusting for potential confounders, both %myocardium ischaemic (P = 0.016), %myocardium fixed (P < 0.0001), and use of early revascularization (P = 0.002) were all significant predictors of mortality (Wald χ^2 : 919, LR: 920 using 15 degrees of freedom, P < 0.001). Hence, in patients with extensive ischaemia, the use of early revascularization was associated with enhanced survival compared with medical therapy alone.

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