Early Revascularization and Survival Benefit following Stress Testing among Patients with Normal versus Reduced LVEF

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Word Count: 4,889 words

Running title: Myocardial ischemia and benefit of revascularization

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ABSTRACT

Background. The utility of performing early myocardial revascularization among patients presenting with inducible myocardial ischemia and low left ventricular ejection fraction (LVEF) is currently unknown.

Objectives. To assess the relationship between stress-induced myocardial ischemia, revascularization, and all-cause mortality (ACM) among patients with normal versus low LVEF.

Methods. We evaluated 43,443 patients undergoing stress-rest SPECT myocardial perfusion imaging between 1998-2017. Median follow-up was 11.4 years. Myocardial ischemia was assessed for its interaction between early revascularization and mortality. A propensity score was used to adjust for nonrandomization to revascularization, followed by multivariable Cox modeling adjusted for the propensity score and clinical variables to predict ACM.

Results. The frequency of myocardial ischemia varied markedly according to LVEF and angina, ranging from 6.7% among patients with LVEF>55% and no typical angina to 64.0% among patients with LVEF<45% and typical angina (p<0.001). Among 39,883 patients with LVEF≥45%, early revascularization was associated with increased mortality risk among patients without ischemia and lower mortality risk among patients with severe (≥15%) ischemia (HR [95%CI] = 0.70 [0.52-0.95]). Among 3,560 patients with LVEF <45%, revascularization was not associated with mortality benefit among patients with no or mild ischemia, and with decreased mortality among patients with both moderate (10-14%) (HR [95%CI] = 0.67 [0.49-0.91]) and severe ischemia (HR [95%CI] = 0.55 [0.38-0.80]).

Conclusions. Within our cohort, early myocardial revascularization was associated with a significant reduction in mortality both among patients with normal LVEF and severe inducible

myocardial ischemia and patients with low LVEF and moderate or severe inducible myocardial ischemia.

CONDENSED ABSTRACT

We assessed the relationship between stress-induced myocardial ischemia, revascularization, and all-cause mortality among 43,443 patients undergoing stress-rest myocardial perfusion imaging, followed for 11.4 years. Among 39,883 patients with LVEF$\geq$45%, early revascularization was associated with increased mortality risk among patients without inducible ischemia and lower mortality risk among patients with severe ($\geq$15%) ischemia (HR [95%CI] = 0.70 [0.52-0.95]). Among 3,560 patients with LVEF <45%, revascularization was not associated with mortality benefit among patients with no or mild ischemia, and with decreased mortality among patients with both moderate (10-14%) (HR [95%CI] = 0.67 [0.49-0.91]) and severe ischemia (HR [95%CI] = 0.55 [0.38-0.80]).

ABBREVIATIONS

CAD: coronary artery disease

CABG: coronary artery bypass surgery

ACM: all-cause mortality

PCI: percutaneous coronary intervention

ISCHEMIA: International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

MPI: myocardial perfusion imaging

SPECT: stress-rest single photon emission computed tomography

CSMC: Cedars Sinai Medical Center

LV: left ventricular

LVEF: left ventricular ejection fraction

INTRODUCTION

The utility of performing early myocardial revascularization among patients with inducible myocardial ischemia has been the subject of both observational studies (1-6) and randomized clinical trials (7-9). Notably, most of these studies have been performed among patients with relatively normal left ventricular ejection fraction (LVEF) measurements. For instance, the median LVEF was 60% in the recently conducted International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, designed to assess the utility of myocardial revascularization among patients with moderate to severe ischemia (9). By contrast, studies regarding the utility of early myocardial revascularization among ischemic versus nonischemic patients with low LVEF are not only sparse, but they consist of conflicting results according to the analysis of such patients in two randomized clinical trials (10-11). Thus, there is a need to clarify the potential benefits of performing early myocardial revascularization among patients with low LVEF.

The importance of examining this question is highlighted by two factors. First, there is a proportional increase in cardiac events and all-cause mortality (ACM) with declining levels of resting LVEF (2,12). Second, recent data indicate a markedly higher rate of inducible myocardial ischemia among patients with low LVEF (13-14). Accordingly, in this study we assess the relationship between myocardial ischemia, mortality, and patients' mode of therapy (medical therapy versus early revascularization) among a large cohort of patients undergoing stress-rest single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) between 1998-2017, with stratification of patients according to normal versus low LVEF.

METHODS

Patient population.

We identified 52,853 consecutive patients who underwent stress/rest SPECT MPI at Cedars Sinai Medical Center (CSMC) between January 1, 1998, and December 31, 2017. From this group, we excluded 1,586 patients with known valvular heart disease, cardiomyopathy, or history of cardiac transplantation; 6,555 patients missing essential data (LVEF or early revascularization status); and 1,269 patients who were lost to follow-up. For patients undergoing more than one test during the study period, only the first test was included. Overall, 43,443 patients were included in the final patient population. All patients were prospectively enrolled in a research database at the time of testing and were followed for the occurrence of mortality. The study was approved by the CSMC Institutional Review Board and complied with the Declaration of Helsinki.

Data regarding early revascularization was prospectively collected and included patients who underwent percutaneous coronary interventions (PCI) or coronary bypass graft surgery (CABG) within the first 90 days after SPECT MPI. Hereafter, these patients are referred as the "early revascularization" group and the patients who did not undergo early revascularization are referred to as the "medical" group. Late revascularization was not considered as either an intervention or outcome.

Historical variables.

Demographic information was obtained at the time of testing including age, gender, chest pain symptoms, cardiac risk factors, body mass index, medication use, and prior CAD status. Four chest pain categories (asymptomatic, non-anginal chest pain, atypical and typical angina) were identified according to the method of Diamond and Forrester (15). Asymptomatic patients presenting with symptoms of dyspnea were considered as a separate symptom group (16). Patient risk factors included hypertension, dyslipidemia, diabetes, smoking status, and family history of premature CAD. Patients were considered to have prior CAD if they had previous MI or had undergone prior myocardial revascularization (17).

<u>Imaging and stress protocol.</u>

Patients underwent either Bruce protocol treadmill exercise or pharmacological testing using adenosine, regadenoson, or dobutamine. Exercise testing was symptom-limited and patients who began exercise but who could not achieve 85% of their maximal predicted heart rate were routinely re-assessed using pharmacologic stress testing after resting heart rate and blood pressure returned to baseline.

Stress/rest SPECT MPI was performed in accordance with standard protocols (18). Patients were imaged using a dual isotope ^{201}thallium/^{99m}technetium sestamibi protocol until 2007, and then a stress/rest ^{99m}Tc-sestamibi protocol thereafter. Semi-quantitative visual interpretation of SPECT MPI images was performed by experienced observers according to a five-point score (0 = normal to 4 = absence of tracer uptake) for each myocardial segment, with division of images into 20 myocardial segments before February 2005 and 17 myocardial segments thereafter (19). Summed stress scores, summed rest scores (SRS), and summed difference scores (SDS) were generated and converted to percent abnormal and ischemic myocardium by dividing summed scores by 80 for studies involving 20-segment analysis or by 68 for studies involving 17-segment analysis, and then multiplying by 100. Reversible perfusion defects were classified using percent ischemic myocardium (based on SDS) and fixed perfusion defects were classified using percent myocardial defect at rest (based on SRS). Percent myocardial ischemia <5% was considered as no ischemia, and those of 5-9%, 10-14% and

≥15%, defined the presence of mild, moderate, and severe myocardial ischemia, respectively. Percent fixed perfusion defect was considered as presence of myocardial scar.

Left ventricular (LV) enlargement and transient ischemic dilation of the LV (classified as either none, equivocal, or present) were assessed at the time of SPECT MPI reporting. LV ejection fraction (LVEF) was measured with 8-frame gating using Quantitative Gated SPECT (QGS) software (CSMC, Los Angeles, CAC).

Follow-up.

Follow-up for all-cause mortality was conducted using internal hospital records as well as the Social Security Death Index, California Non-comprehensive Death File, and National Death Index. The last date of access for the Social Security Death Index was April 9, 2012; the last date of access for California Non-comprehensive Death File was July 22, 2020; the last date of access for the National Death Index was February 12, 2018. The median follow-up was 11.4 (7.8-14.2) years.

Statistical Analyses.

All data were analyzed using STATA version 14 (StataCorp LP, College Station, Texas, USA). Continuous variables were compared using either t-test or Wilcoxon rank-sum test for two groups, and Cuzick's test for trend across ordered groups. Categorical variables were compared using the Pearson Chi-square test across ordered groups. Mortality rates were expressed as event rates per-100 person years and visualized using Kaplan-Meier curves and compared using the log-rank test.

To adjust for potential biases associated with the non-randomization of patients to early revascularization, a propensity score was developed using logistic regression in a two-step process. A total of 19 covariates that could potentially be associated with the decision to pursue revascularization were entered in the propensity score model, along with interactions: Age, gender, body mass index, chest pain syndrome, hypertension, dyslipidemia, smoking, diabetes, family history, history of CAD, peripheral vascular disease (with an indicator variable for missing data for earlier years), in-patient, out-patient or ED status, pharm stress test, abnormal resting ECG, atrial fibrillation, LVEF at stress, LV enlargement, TID (yes, no, or equivocal) and % summed rest score (SRS). The continuous variables (age, BMI, LVEF at stress, and % SRS) were entered as restricted cubic splines with the number of knots chosen based on Akaike information criteria (AIC) for best fit, and parsimony, and absence of numerical issues. Absolute mean standardized differences between groups were assessed before and after propensity score adjustment to assess the adequacy of adjustment, with differences >0.100 considered significant (20).

Cox regression analysis was used to assess the associations between early revascularization, ischemia (modeled as a categorical variable) and ACM both without and with the use of propensity scores (21). We assessed unadjusted models, multivariable models (adjusted for age, gender, patient symptoms, CAD risk factors, mode of stress, and history of CAD status), propensity score adjusted multivariable models, and inverse probability of treatment weighting (IPTW). In the propensity-score adjusted model, the propensity score was included in the multivariable model along with matching factors with residual absolute mean standardized differences >0.100. In the IPTW analysis, the propensity score was used to establish weights in the Cox models along with variables with residual absolute mean standardized differences >0.100 (22). Cox models were also used to assess the relationship between ACM risk in the form of log-hazards with percent myocardial ischemia to estimate thresholds for ischemia at which patients may benefit from revascularization. These models included early revascularization, ischemia %, the two-way interaction term between them, the propensity score, and any matching factors with standardized differences ≥0.100. We performed pre-specified analyses according to LVEF groups (LVEF < 45% vs LVEF ≥ 45%). Cox modeling assumptions were tested, including proportional hazards, linearity, collinearity, and additivity. The interaction between therapeutic mode (early revascularization vs. medical) and ischemia was assessed in all models. We also performed an analysis assessing the interaction between therapeutic mode (early revascularization vs. medical) and percent fixed myocardial defect. Two-tailed P-values of <0.05 were considered statistically significant.

RESULTS

In total, 43,443 patients (55.8% male, mean age 62.0 $\pm$ 13.4 years) were included. The clinical characteristics of our patient population are shown in Table 1. Compared to the medical therapy patients, the early revascularization patients were older, had more male patients, and a higher percentage of patients with known CAD, typical angina, hypertension, hypercholesterolemia, and diabetes. The early revascularization patients also had a higher frequency of patients with myocardial ischemia and myocardial scar in all abnormal categories, transient ischemic dilation, and low LVEF values.

Frequency of inducible myocardial ischemia

The frequency of inducible myocardial ischemia varied substantially according to resting LVEF and presence or absence of typical angina. Among the 34,438 patients with LVEF >55%, 7.5% had an ischemic study. The frequency of ischemia increased to 22.9% among the 5,445 patients with an LVEF of 45-54%, and 42.2% among the 3,560 patients with an LVEF <45% (p<0.001 among groups). Among 2,310 patients with typical angina, 814 (35.2%) had inducible ischemia, compared to 4,505 patients (11.0%) having inducible myocardial ischemia among 41,133 patients without typical angina (P<0.001). Among each LVEF subgroup, those patients with typical angina had a higher frequency of inducible myocardial ischemia (Figure 1).

Mode of therapy, magnitude of ischemia, and mortality

During median follow-up of 11.4 years (interquartile range 7.8 - 14.2), 12,510 patients (28.8%) died. Annualized mortality was 3.0% per year. Figure 2 shows the Kaplan Meier survival curves and Table 1 shows the mortality rates per 100 years among patients divided according to ischemia and revascularization status. Among the medically treated patients, there was a stepwise decrease in survival with increasing myocardial ischemia (log-rank p<0.001).

Among the revascularized patients, there was no stepwise decrease in survival with increasing baseline ischemia (log-rank p=0.04).

<u>Impact of revascularization upon mortality according to the magnitude of ischemia</u>

The components of the propensity score are shown in Supplemental Table 1. The absolute standardized mean differences, between medical therapy and revascularization groups, for covariates before and after adjusting for the propensity score are shown in Supplemental Figure 1. Absolute standardized mean differences remained >0.100 for age, hypertension, prior CAD, pharmacologic stress testing, abnormal resting ECG, LV enlargement, in-patient status, and SRS %. The multivariable Cox proportional hazard model was thus adjusted for those variables with standardized mean differences >0.100 and propensity score.

The association between myocardial ischemia modeled as a continuous variable, early revascularization, and ACM is shown in Figure 3. There was a significant interaction between the percent ischemic myocardium and ACM (interaction p value <0.001). Early revascularization was associated with a progressively greater reduction in mortality risk with increasing magnitude of myocardial ischemia. The reduction in mortality risk with early revascularization became significant (i.e., upper bounds of the 95% confidence intervals crossing unity) among patients with >8.1% ischemic myocardium. Figure 4 shows the association between myocardial ischemia as a continuous variable and early revascularization in patients divided into those with LVEF≥45% versus LVEF<45%. Within both LVEF groups, the level of ischemia at which early revascularization was associated with reduced mortality risk was similar. By contrast, the interaction between fixed myocardial perfusion defect, early myocardial revascularization, and ACM was not significant among patients with preserved or reduced LVEF (Supplemental Figure

2). This suggests that the potential therapeutic benefit from early revascularization does not vary according to fixed perfusion defect size.

Impact of revascularization with ischemia assessed as a categorical variable

Table 2 shows the unadjusted, risk-adjusted, propensity score-adjusted and propensity-weighted hazard ratios for ACM according to revascularization status and the presence and magnitude of inducible myocardial ischemia, assessed as a categorical variable. Early revascularization was associated with no reduction in the propensity-adjusted and fully adjusted hazard ratios for ACM among patients with either none or only mildly inducible ischemia. Among patients who had moderate and severe ischemia, early revascularization was associated with a significant reduction in mortality compared to medically treated patients.

Results of the categorical analysis stratified by LVEF are shown in Table 3. Among patients with LVEF≥45%, early revascularization was associated with a reduced risk of ACM in patients with severe myocardial ischemia. Among patients with LVEF < 45%, early revascularization was associated with a reduced risk of ACM in patients with either moderate or severe myocardial ischemia.

Temporal assessment of revascularization, myocardial ischemia, and mortality

To assess whether the impact of myocardial revascularization upon mortality in relationship to myocardial ischemia changed over time, we divided our patients into three temporal groups: patients studied between 1998-2002, 2003-2008, and 2009-2017. The clinical characteristics of these groups are shown in Supplemental Table 2. From the first to third temporal period, there was a substantial increase in the use of statin therapy, various classes of anti-hypertensive medications, and aspirin. As shown in Figure 5, the association of myocardial revascularization with a proportional decline in mortality risk with increasing myocardial ischemia was maintained between the first and third temporal periods.

DISCUSSION

The utility of performing early myocardial revascularization among patients with low resting LVEF is currently uncertain. Accordingly, we examined the relationship between early myocardial revascularization, myocardial ischemia, and mortality risk among a large cohort of patients undergoing stress/rest myocardial perfusion imaging, with specific comparison of patients presenting with normal versus low LVEF. Of note in this regard, the REFINE registry indicates that the frequency of inducible myocardial ischemia varies most strongly in accordance with the presence of and magnitude of pre-existing scar and LVEF reduction across each of the medical cohorts that comprise this registry (14). In our study, the frequency of inducible myocardial ischemia increased in stepwise manner with decreasing LVEF and was present in over two-fifths of patients with an LVEF <45%. In part, this ischemia-LVEF relationship may be explained by the increasing concentration of CAD risk factors among patients with low LVEF values and the likelihood that such patients have more extensive CAD (13-14). At each LVEF level, the frequency of ischemia was increased if typical angina was also present.

Early revascularization and mortality

Among our medically treated patients, there was a stepwise increase in mortality with increasing myocardial ischemia, ranging from 2.6%/year among medically treated patients without inducible myocardial ischemia to 7.3%/year among patients with severe ischemia. By contrast, no difference in mortality rates emerged upon stratifying patients who underwent early revascularization according to their baseline magnitude of ischemia prior to intervention.

Early myocardial revascularization was associated with a proportional decline in mortality risk with increasing myocardial ischemia. In the overall patient population, early revascularization was associated with a reduced risk of ACM in patients with >8.1% myocardial ischemia. The level of ischemia at which early myocardial revascularization was associated with reduced ACM remained relatively similar upon division of patients into those with LVEF ≥45% versus <45%.

In addition to assessing myocardial ischemia as a continuous variable, we also assessed the relationship between early myocardial revascularization and mortality after dividing patients according to a categorical classification of myocardial ischemia. This analysis revealed that among patients with LVEF ≥45%, early revascularization was associated with decreased risk for those patients with severe ischemia. Among the patients with LVEF <45%, early revascularization was associated with decreased mortality risk for patients with either moderate or severe ischemia. Our findings were consistent among each of the statistical techniques we applied for assessing hazard ratios.

To assess the generalizability of our findings, we also evaluated the relationship between myocardial revascularization and mortality as a function of ischemic magnitude following the subdivision of our patients into three temporal periods. Despite the increasing use of lipid lowering medications, blood pressure medications, and aspirin use that occurred between our first and third temporal periods, the association between revascularization and progressive lowering of mortality risk that occurred with increasing baseline ischemia remained similar over time. As a complementary observation, Sharir et al used electronic medical records to track optimal versus suboptimal statin therapy in their observational analysis of 47,894 patients undergoing stress/rest SPECT MPI (3). Optimal statin use did not diminish the favorable association between myocardial revascularization and reduced mortality among patients with moderate to severe ischemia within their cohort.

<u>Prior studies</u>

After the introduction of radionuclide stress testing in the late 1970s, the modality become readily used to guide which patients may benefit from early myocardial revascularization, based on evidence of an exponential relationship between inducible myocardial ischemia and cardiac events (23). Since revascularization reduces ischemia, an assumption was made that its performance would also reduce clinical events. This assumption was supported by an observational study by Hachamovitch et al which evaluated 10,627 patients undergoing stress-rest MPI at between 1991 and 1997 at CSMC (1). This study found that early revascularization was associated with reduced mortality among patients with moderate to severe ischemia. Subsequently, however, no difference in outcomes was observed among stable CAD patients who were prospectively randomized to early revascularization versus medical therapy in two clinical trials, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (7,24) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (8,25). These findings led to the recently conducted ISCHEMIA trial which found no difference in therapeutic benefit with myocardial revascularization versus medical therapy among a large cohort of patients with moderate to severe inducible myocardial ischemia.

By contrast, there has been only sparse and contradictory findings emanating from the sub-analyses from two randomized trials: the Surgical Treatment for IsChemic Heart Failure (STICH) trial (26), which evaluated CAD patients with LVEF <35%, and the ISCHEMIA trial. No significant difference in clinical outcomes were observed with myocardial revascularization versus medical therapy among the STICH patients who had inducible myocardial ischemia at baseline (10,27). However, among ISCHEMIA trial patients with a history of heart failure or left ventricular dysfunction, a higher survival and less clinical events were noted among patients randomized to revascularization versus medical therapy (11). Recent observational studies have not assessed the association between myocardial revascularization and clinical outcomes among patients with low LVEF (3-5), but in support of our findings, a sub-analysis of the CSMC patients undergoing stress-rest MPI between 1991-1997 also found that myocardial revascularization was associated with reduced cardiac events both among patients with normal and low LVEF (2).

Discordance between observational studies versus clinical trials

The Central Illustration emphasizes a striking contradiction between the clinical trials that have randomized patients to revascularization versus medical therapy and the results of five large recent observational studies, including the results of our present study. This contradiction raises the need to resolve the two sets of evidence. A potential clue comes from the observation of no stepwise increase in mortality with increasing ischemia among the medically treated patients within the ISCHEMIA trial (9). At least two possibilities are raised by this observation. One possibility is that optimal guideline-based medical therapy, as employed within the ISCHEMIA trial, is now as effective as myocardial revascularization in reducing the clinical risk of patients with moderate or severe myocardial ischemia. Under such conditions, no observable differences would be expected in outcomes among ischemic patients randomized to medical therapy versus revascularization. This very possibility has been previously illustrated by the Adenosine Sestamibi Post-Infarction Evaluation (INSPIRE) trial (28). That trial observed no difference in clinical outcomes among post-MI patients with inducible ischemia following their randomization to medical therapy versus revascularization precisely, but both patient groups experienced a comparable and marked decrease in inducible myocardial ischemia. In contrast to the optimized medical treatment that can be achieved in clinical trials, optimal therapy of ischemic patients is often not achieved in clinical practice (29). Under such conditions, myocardial revascularization may be more effective than medical therapy for patients who present with moderate to severe ischemia.

Alternatively, the ability to apply the findings of the ISCHEMIA trial to clinical settings depends on whether the trial operated according to clinical equipoise. Clinical equipoise in this setting would mean that physicians consenting to patient enrollment were generally willing to accept comparable risk for managing moderate to severe ischemia with medical therapy or revascularization. If equipoise were lacking, it is possible that the patients recruited into the ISCHEMIA trial could have been biased toward the selection of ischemic patients of low clinical risk who do not adequately reflect the true level of clinical risk associated with moderate to severe myocardial ischemia within routine medical practice.

Clinical Implications

The strong discordance between the data emanating from recent large observational registries, such as our own, and the ISCHEMIA trial, emphasize a need for continued study as to the benefits or early myocardial revascularization versus medical therapy among patients who manifest moderate to severe inducible myocardial ischemia during cardiac stress testing. Additional randomized trials in this regard are unlikely due to their high cost. However, further observational studies, with more comprehensive data for adjusting for confounders should be conducted with data searches of electronic medical records not previously available. In the interim, our findings underscore the general lack of benefit to performing myocardial revascularization procedures among stable patients who do not manifest inducible myocardial ischemia, even when LVEF is reduced.

Our observation regarding the very low frequency of inducible myocardial ischemia among patients with low LVEF and high frequency of inducible ischemia among patients with normal LVEF may also have important implications for optimizing the future applications of cardiac stress tests. With respect to increasing interest in using anatomic tests (i.e., CAC scanning or CCTA) as a first line test among diagnostic patients (30-33), our findings suggest that this approach may have its greatest effectiveness among patients with normal LVEF due to the low frequency of inducible ischemia among such patients. Rather, stress-rest MPI may have greater effectiveness when applied to patients with a high pre-test likelihood of inducible myocardial ischemia, such as patients with low LVEF, known CAD, or pre-determined evidence of significant atherosclerosis (13-14, 32-33).

Limitations

Our study has important limitations which characterize observational studies in general. Most notably, we did not collect information regarding the intensity and optimization of medical therapies following cardiac testing. We also did not collect information regarding other key variables that could influence clinical outcomes, including the completeness of myocardial revascularization, changes in ischemic burden following stress testing, and patients' anatomic extent of CAD. The latter was not available since most patients did not undergo invasive coronary angiography. In addition, we did not collect information regarding cardiac-specific outcomes, but other recent observational studies have shown that myocardial revascularization is associated with both reduction in adverse cardiac outcomes and all-cause mortality among patients with moderate to severe ischemia (3-5). In addition, it is possible and even probable that unmeasured confounders influenced our findings.

Conclusions

Within this large observational study, the overall benefit of early myocardial revascularization was similar among patients with normal and low LVEF. Within both LVEF groups, early myocardial revascularization was not associated with survival benefit among patients with either no or only mild inducible myocardial ischemia. By contrast, early revascularization was associated with a significant survival benefit among patients with normal LVEF and severe inducible myocardial ischemia and among patients with low LVEF and moderate to severe inducible myocardial ischemia.

PERSPECTIVES

Competency in Medical Knowledge 1: Our study provides robust new evidence for an association between early myocardial revascularization following stress testing and reduced subsequent mortality among patients found to have moderate to severe inducible myocardial ischemia during stress testing.

Competency in Medical Knowledge 2: While the frequency of inducible myocardial ischemia increases with decreasing LVEF, the benefit between early myocardial revascularization and reduced mortality is similar among patients presenting with normal or reduced LVEF.

Translational Outlook: Further resolution of the discordance between observational studies and randomized trials could be obtained by expanding the breadth of registry data obtained at the time of cardiac stress testing, coupled with recording changes in medical therapies that are initiated during patient follow-up.

Key words: coronary artery disease; myocardial ischemia; stress testing; myocardial revascularization; myocardial perfusion imaging.

ACKNOWLEDGEMENTS

Funding: The work was supported in part by the Dr Miriam and Sheldon G Adelson Medical Research Foundation and by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award numbers R01HL089765. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of interest: Dr. Daniel Berman participates in software royalties for QPS software at Cedars-Sinai Medical Center. The remaining authors have nothing to disclose.

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LEGENDS

Figure 1. Frequency of myocardial ischemia according to LVEF and typical angina. The frequency of inducible myocardial ischemia is shown according to presence or absence of typical angina among patients with left ventricular ejection fraction (LVEF) ≥55%, 45-54%, and <45%.

Figure 2. Survival according to magnitude of inducible ischemia and revascularization status. Survival free of all-cause mortality among the patients undergoing early myocardial revascularization (Revasc) versus no early revascularization, stratified according to the presence of inducible myocardial ischemia. Medical patients without inducible ischemia had the highest survival and medical patients with inducible ischemia had the lowest survival. (SDS = summed difference score).

Figure 3. Myocardial ischemia, early revascularization, and survival in all patients. All-cause mortality with early myocardial revascularization across levels of percent myocardial ischemia, analyzed as a continuous variable. The solid curve represents the relative hazard estimate for revascularization compared to medical therapy with dashed curves representing the 95% confidence intervals.

Figure 4. Myocardial ischemia, early revascularization, and survival according to LVEF. Association between early revascularization versus medical therapy with ischemia and all-cause mortality among patients with LVEF≥45% (left) and LVEF <45% (right). Solid curve represents the relative hazard estimate for revascularization compared to medical therapy with dashed curves representing the 95% confidence intervals.

Figure 5. Temporal association between ischemia, early revascularization, and all-cause mortality. The association between early revascularization versus medical therapy with ischemia

and all-cause mortality is shown for three temporal periods: 1998-2002, 2003-2008, and 2009-2017.

Figure 6. Central illustration. Divergent findings emanating from observational studies versus prospective clinical trials regarding the relationship between inducible myocardial ischemia, early myocardial revascularization versus medical therapy, and mortality risk.