Stress Cardiac Magnetic Resonance Imaging Provides Effective Cardiac Risk Reclassification in Patients With Known or Suspected Stable Coronary Artery Disease

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Background—A recent large-scale clinical trial found that an initial invasive strategy does not improve cardiac outcomes beyond optimized medical therapy in patients with stable coronary artery disease. Novel methods to stratify at-risk patients may refine therapeutic decisions to improve outcomes.

Methods and Results—In a cohort of 815 consecutive patients referred for evaluation of myocardial ischemia, we determined the net reclassification improvement of the risk of cardiac death or nonfatal myocardial infarction (major adverse cardiac events) incremental to clinical risk models, using guideline-based low (<1%), moderate (1% to 3%), and high (>3%) annual risk categories. In the whole cohort, inducible ischemia demonstrated a strong association with major adverse cardiac events (hazard ratio=14.66; P<0.0001) with low negative event rates of major adverse cardiac events and cardiac death (0.6% and 0.4%, respectively). This prognostic robustness was maintained in patients with previous coronary artery disease (hazard ratio=8.17; P<0.0001; 1.3% and 0.6%, respectively). Adding inducible ischemia to the multivariable clinical risk model (adjusted for age and previous coronary artery disease) improved discrimination of major adverse cardiac events (C statistic, 0.81–0.86; P=0.04; adjusted hazard ratio=7.37; P<0.0001) and reclassified 91.5% of patients at moderate pretest risk (65.7% to low risk; 25.8% to high risk) with corresponding changes in the observed event rates (0.3%/y and 4.9%/y for low and high risk posttest, respectively). Categorical net reclassification index was 0.229 (95% confidence interval, 0.063–0.391). Continuous net reclassification improvement was 1.11 (95% confidence interval, 0.81–1.39).

Conclusions—Stress cardiac magnetic resonance imaging effectively reclassifies patient risk beyond standard clinical variables, specifically in patients at moderate to high pretest clinical risk and in patients with previous coronary artery disease.

Clinical Trial Registration:—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01821924.

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Key Words: chronic ischemia ◼ magnetic resonance imaging

Clinical risk assessment is limited in patients with established stable coronary artery disease (CAD). The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial demonstrated that patients with stable CAD may be safely managed with an initial strategy of optimal medical therapy.1 However, patients with extensive ischemia may benefit from mechanical coronary revascularization.2-3 American College of Cardiology (ACC)/American Heart Association (AHA) practice guidelines also recommend that CAD patients deemed high risk for adverse events be...
Stress cardiac magnetic resonance imaging (CMR) offers a comprehensive assessment of the presence and extent of myocardial ischemia and viability. Although numerous studies have demonstrated an excellent diagnostic accuracy for CAD detection,7,8 the ability of stress CMR to influence clinical decision making by reclassification of patient risk has not been investigated. In this study, we sought to specifically test the hypothesis that stress CMR would effectively reclassify patients across ACC/AHA-recommended cardiac risk categories, the basis for management decisions in these patients.

Methods

Study Population

We performed vasodilator stress CMR in 815 patients referred for assessment of myocardial ischemia. Patients were consecutively enrolled between 2001 and 2011 from the Brigham and Women’s Hospital inpatient and outpatient cardiology and general medical service. Indication for referral was the assessment of suspected myocardial ischemia. Inclusion criteria included age ≥18 years and a clinical suspicion of myocardial ischemia at the discretion of the referring clinician. Exclusion criteria consisted of absolute contraindications to CMR (eg, metallic hazards, pregnancy, severe renal dysfunction) or contraindications to vasodilator stress testing. A physician obtained detailed medical history from the patient before CMR study. A history of previous CAD was defined by evidence of myocardial infarction (MI), previous percutaneous transluminal coronary angioplasty or coronary artery bypass graft, or angiographically significant coronary stenosis (>70% stenosis in any epicardial coronary artery or >50% of the left main coronary artery). Previous MI was confirmed by definite clinical evidence in the medical record or presence of pathological Q wave(s) by published criteria.7 The institutional review board approved patient follow-up with the use of a standardized questionnaire and telephone script. For the purpose of evaluating a clinical question different from the present study, 424 patients from our present study were used in a previous report.8 Patients with images adequate for CMR analysis and any clinical follow-up were included in the analysis (see Results below). The study is registered at http://www.clinicaltrials.gov (NCT01821924).

Stress CMR Protocol

We performed stress CMR with a 1.5-T scanner before 2006 (n=381; 47%; Signa CV/i, General Electric, Milwaukee, WI; 8-element coil) or a 3.0-T scanner thereafter (n=434; 53%; TIM TRIO/VERIO, Siemens, Erlangen, Germany; 16-element coil). CMR protocol consisted of stress and rest myocardial perfusion, ventricular function, and late gadolinium enhancement (LGE). An ECG was obtained before and after CMR. Adenosine (n=396), regadenoson (n=389) (both from Astellas Pharma US, Deerfield, IL), or dipyridamole (n=30) (Boehringer Ingelheim, Germany) were prescribed as intravenous stress agents.9 Myocardial perfusion images were acquired during bolus injection of 0.1 mmol/kg intravenous gadolinium-DTPA (Magnevist, Bayer, Wayne, NJ). Stress CMR perfusion, when performed at 3 T, used a saturation-recovery prepared turbo fast low-angle single-shot gradient echo imaging sequence with the following specifications: repetition time/echo time=6 ms/2.3 ms; echo train length 4; SENSE 2; slice thickness 8 mm) in 3 parallel short-axis views of the left ventricle (LV) sampled every R-R interval. For perfusion images acquired on 3 T, a 4-chamber long-axis view was also obtained. Cine and LGE images (15–20 minutes after contrast) were acquired via similar protocols on 1.5 and 3 T, as published previously.10 All images were acquired at end-expiration with the use of ECG or pulse oximetry gating.

The presence and segmental extent of perfusion defects were confirmed by the consensus of 2 independent reviewers blinded to clinical and follow-up information. Perfusion defects were defined as hypoenhanced regions that persisted for at least 3 phases after peak contrast enhancement, were ≥1 pixel in thickness, and followed a coronary distribution. Following the ACC/AHA 16-segmental model, segments were graded as “1” if endocardial (<50% wall thickness) and “2” if transmural (>50% of wall thickness). Inducible ischemia was defined by the presence of a stress perfusion defect in any segment without matching LGE. Global extent of myocardial ischemia (ischemia score) was calculated as the sum of stress perfusion grades from all segments with inducible ischemia. In addition, we defined a binary variable stratified by the presence of >10% ischemia, estimated by the presence of inducible ischemia in ≥3 of 32 subsegments (endocardial and epicardial sectors for each of the 16 segments). This criterion of >10% ischemia has been observed as high risk in the nuclear substudy of the COURAGE trial.2 Infarct volume was defined as myocardial volume with signal intensity ≥2 SDs above remote normal myocardium. All CMR analyses used validated commercial software (Mass, Medis, Leiden, Netherlands).

Follow-Up of Cardiac Events

We first reviewed available electronic medical records across teaching hospitals of Partners HealthCare for notes from any physicians caring for the patient to assess for interval MI or mortality. Cardiac mortality was defined by any death preceded by an acute MI, decompensated heart failure, or ventricular arrhythmia. Nonfatal MI was defined by the presentation of an acute coronary syndrome and elevation of cardiac biomarkers (>99th percentile of the upper limit of normal) temporally consistent with an acute injury. In cases in which records were not found in the electronic medical records, we contacted treating physicians using a standardized institute-approved medical questionnaire to inquire about events and follow-up. Regardless of the results of the aforementioned follow-up procedures, annually we checked the mortality status from the Social Security Death Index of all patients and mailed a standardized institutional review board–approved medical questionnaire to all patients to inquire in detail about major adverse cardiac events (MACE). We confirmed cases of mortality by review of both medical records and the Social Security Death Index. If there remained inadequacy of follow-up information, we then telephoned to speak with the patient or a family member using the standardized medical questionnaire. Details of any outside hospitalization, including suspected acute MI, were checked by retrieving medical records from outside hospitals. Two cardiologists blinded to CMR results performed all standardized follow-up procedures. Our primary outcome included a composite of cardiac mortality or acute, nonfatal MI (MACE). All-cause mortality was a secondary outcome.

Statistical Analysis

Univariable associations with MACE were determined by Cox proportional hazards regression, and event-free survival stratified by inducible ischemia was estimated with Kaplan–Meier survival methods. A multivariable clinical risk model for MACE was constructed with the use of a backward elimination Cox regression strategy (P<0.10 for model retention). Previous CAD and age were forced into this clinical risk model given their prognostic importance in patients with suspected ischemia. To form this clinical risk model, all clinical, ECG, and CMR covariates, including LV/right ventricular volumes, mass, and ejection fraction, were considered in the model.
selection process. We also built another clinical risk model without CMR covariates considered. Time zero was defined as the day of the CMR study for all Cox regression analyses.

To address the incremental prognostic value of inducible ischemia on MACE, we added inducible ischemia to the multivariable clinical risk model to obtain an adjusted hazard ratio (HR) for ischemia. In addition, we assessed for significant incremental changes in model C statistic before and after addition of inducible ischemia. To assess whether early revascularization performed in response to the extent of inducible ischemia modified the association between ischemia and outcome, we included an interaction term between early coronary revascularization (<90 days after CMR) and ischemia score as a covariate in Cox models for prediction of MACE. For all multivariable models, proportional hazards assumptions were validated and calibrated as described previously.10

To evaluate the ability of inducible ischemia to reclassify patients, we performed net reclassification improvement (NRI) analyses11 using categories of <1%, 1% to 3%, and >3% per year event rates (per ACC/AHA guidelines) to define low-, moderate-, and high-risk categories, respectively.12 NRI calculations were performed with the use of 3-year event data because this time point is between the median and 75th percentile for follow-up and optimizes the tradeoff between loss of power for earlier time points and potential bias for later time points. Three-year event rates were then annualized to facilitate comparison with previous studies. Pretest risk was defined by the annualized probability of MACE estimated by the multivariable clinical risk model. Posttest risk was defined by the annualized probability of MACE estimated by a model combining the multivariable clinical model and inducible ischemia. NRI was computed by pooling all upward reclassified subjects, calculating their Kaplan–Meier event rate, and performing the same calculation for all downward reclassified subjects.

All statistical analyses were performed with the use of SAS (SAS Institutes, version 9.2, Cary, NC). A 2-tailed P value <0.05 was considered significant.

### Results

#### Patient Characteristics

Indications for stress CMR referral included chest pain or dyspnea (n=700), palpitations or arrhythmias (n=57), syncope (n=20), and abnormality on ECG (n=38). Of the 815 patients, 13 (2%) could not undergo or complete stress CMR because of severe claustrophobia (n=8), adverse or intolerable reaction to adenosine (n=4), or inadequate gating (n=1). Of the remaining 802 patients, 8 patients (1%) had nondiagnostic perfusion quality. Clinical follow-up was successful in all but 2 patients (99%). The remaining 792 patients formed the cohort for analysis (273 with previous CAD; 34%). Baseline patient and stress CMR characteristics stratified by presence or absence of previous CAD are shown in Table 1.

### Univariable Associations With MACE and Event-Free Survival

Univariable associations of selected clinical and stress CMR parameters with MACE were measured (Table 2). Among clinical, ECG, or stress CMR markers considered, presence and extent of inducible ischemia (>10% ischemia) demonstrated the highest association with MACE in the whole cohort (presence of ischemia: HR=14.66; P<0.0001) and in patients with previous CAD (presence of ischemia: HR=8.17; P=0.0001). In Kaplan–Meier analysis, patients with inducible ischemia experienced a substantial reduction in MACE-free survival compared with patients without inducible ischemia in the whole cohort (Figure 1; P<0.0001) and in patients with

### Table 1. Baseline Characteristics of the Cohort and Patients With Previous CAD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=792)</th>
<th>Patients With Previous CAD (n=273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±14</td>
<td>61±12</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>319 (40)</td>
<td>73 (27)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28±6</td>
<td>29±6</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±15</td>
<td>69±14</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>131±21</td>
<td>131±22</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72±12</td>
<td>71±13</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>185 (24)</td>
<td>115 (43)</td>
</tr>
<tr>
<td>History of heart failure, n (%)</td>
<td>141 (18)</td>
<td>67 (25)</td>
</tr>
<tr>
<td>Cardiac risk factors, n (%)</td>
<td>386 (49)</td>
<td>196 (73)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>143 (18)</td>
<td>75 (27)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>411 (52)</td>
<td>179 (66)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>162 (22)</td>
<td>61 (24)</td>
</tr>
<tr>
<td>Smoking</td>
<td>128 (16)</td>
<td>61 (23)</td>
</tr>
<tr>
<td>≥3 risk factors</td>
<td>182 (23)</td>
<td>98 (36)</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td>404 (52)</td>
<td>220 (81)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>412 (52)</td>
<td>204 (75)</td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
<td>390 (50)</td>
<td>202 (75)</td>
</tr>
<tr>
<td>Statin</td>
<td>115 (15)</td>
<td>42 (16)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>103 (13)</td>
<td>82 (30)</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>346 (44)</td>
<td>158 (59)</td>
</tr>
<tr>
<td>ECG abnormalities, n (%)</td>
<td>53 (7)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>68 (9)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>116 (15)</td>
<td>60 (22)</td>
</tr>
<tr>
<td>Resting ST-segment changes</td>
<td>110 (14)</td>
<td>60 (41)</td>
</tr>
<tr>
<td>Pathological Q wave sample</td>
<td>196 (25)</td>
<td>140 (51)</td>
</tr>
<tr>
<td>Ischemic ECG abnormalities (Q waves, ST abnormality)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress CMR</td>
<td>56±15</td>
<td>51±16</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>89±31</td>
<td>96±35</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>42±31</td>
<td>51±35</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>61±19</td>
<td>65±19</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>54±9</td>
<td>54±10</td>
</tr>
<tr>
<td>RV ejection fraction, %</td>
<td>34±15</td>
<td>34±16</td>
</tr>
<tr>
<td>Resting wall motion abnormality, n (%)</td>
<td>206 (26)</td>
<td>137 (51)</td>
</tr>
<tr>
<td>LGE, n (%)</td>
<td>275 (35)</td>
<td>175 (65)</td>
</tr>
<tr>
<td>LGE mass, g</td>
<td>5±12</td>
<td>11±16</td>
</tr>
<tr>
<td>Inducible ischemia, n (%)</td>
<td>210 (27)</td>
<td>150 (55)</td>
</tr>
<tr>
<td>&gt;10% ischemia, n (%)</td>
<td>136 (17)</td>
<td>106 (39)</td>
</tr>
</tbody>
</table>

Data are listed where available (n=792 for categorical variables; n=273 for continuous variables). ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; RV, right ventricular; and RVESVI, right ventricular end-systolic volume index.

*Inducible ischemia score was calculated in patients with ischemia.
Annual Rates of MACE and Mortality

Over a median follow-up of 1.9 years (range, 1–8.5 years), 68 deaths (8.6%) and 24 nonfatal acute MIs (3%) occurred. There were 29 cardiac deaths, attributed to fatal acute MI (n=4), congestive heart failure (n=20), or lethal ventricular arrhythmia (n=5). Annual event rates by inducible ischemia for the whole cohort and stratified by the presence or absence of previous CAD are shown in Figure 3. The annual rate of MACE for the whole cohort was 3.1%. Patients with absence of inducible ischemia experienced low annual rates of MACE (0.6%, 1.3%, and 0.4% in the whole cohort, group with previous CAD, and group with no previous CAD, respectively). On the other hand, patients with inducible ischemia had a higher annual rate of MACE (9.4%, 11%, and 5.5% in the whole cohort, group with previous CAD, and group with no previous CAD, respectively). Annual rates of cardiac death and all-cause mortality were significantly lower in patients who did not have inducible ischemia.

Improvement of Risk Discrimination and NET

The multivariable clinical risk model consisted of age, history of CAD, hypertension, significant smoking, resting ST-segment abnormalities on ECG, and LV ejection fraction (Table 3). Neither presence nor extent of LGE was selected to enter this clinical multivariable model. This model was well calibrated to observed MACE (model 1, calibration $\chi^2=13.95; P=0.12$). When inducible ischemia was added to this clinical risk model, it improved the model discrimination (C statistic increased from 0.81 of model 1 to 0.86 of model 2; $P=0.04$; adjusted HR=7.37; $P<0.0001$) and goodness of fit (global $\chi^2=68.67$ without ischemia increased to 98.28 with ischemia; $P<0.0001$; Table 3). Model 2 was well calibrated (Figure I in the online-only Data Supplement; calibration $\chi^2=6.53; P=0.69$). Inducible ischemia also improved discrimination of MACE by C statistic in multivariable models for cardiac and all-cause mortality. Although both LGE presence and LGE mass (in grams) demonstrated significant univariable association with MACE, neither provided incremental association with MACE above inducible ischemia in the whole cohort. Neither LGE presence nor LGE mass provided additional model risk discrimination when added to a model that combined the clinical risk model and inducible ischemia.

We also assessed NRI by inducible ischemia above the multivariable clinical risk model for MACE across ACC/AHA practice guideline–recommended annualized risk categories (low, <1%; moderate, 1% to 3%; high, >3%; Figure 4). Categorical NRI was 0.229 (95% confidence interval [CI], 0.063–0.391; 0.037 for patients with events; 0.193 for patients without events). Continuous NRI was 1.11 (95% CI, 0.81–1.39). As shown in Figure 4, risk reclassification by inducible ischemia was most effective in patients at moderate pretest risk with reclassification of 65.7% (140/213) of patients to low risk and 25.8% (55/213) of patients to high risk by inducible ischemia, with a low (0.3%/y) and a high (4.9%/y) annual rate of MACE, respectively. For patients at high pretest risk, inducible ischemia reclassified 31.6% (60/190) and 5.8% (11/190) into moderate and low risk, with low annual rates of MACE (2.1% and 0%, respectively), which were in contrast to previous CAD ($P<0.0001$). Cumulative hazard function (log-survival) plots of the first 5 years of follow-up after stress CMR illustrated that the rate of MACE was steady and markedly higher in patients with inducible ischemia than in those without ischemia (Figure 1). CAD patients without inducible ischemia qualitatively had an initially low accumulation of MACE in the 2 years after index CMR; after that, the rate of events started to increase. In the whole cohort and in patients with previous CAD, having inducible ischemia was associated with substantially higher mortality by Kaplan–Meier analysis than in those without ischemia (Figure 2).
to a high annual rate of MACE (14.3%) among patients who remained at high posttest risk (Table 4).

We also built the multivariable clinical model without inclusion of any CMR parameters such as LV function, LV sizes, or LGE. This model consisted of age, history of CAD, diabetes mellitus, significant smoking, and resting ST-segment changes. Adding inducible ischemia to the clinical model substantially improved the model discrimination of MACE (C statistic=0.79–0.85; P=0.01; adjusted HR=7.36; P<0.0001) and model goodness of fit (global $\chi^2=67.95$ without ischemia to 97.49 with ischemia; from 6–7 df, respectively; P<0.0001). Inducible ischemia also provided effective and robust risk reclassification to this multivariable clinical model: Categorical NRI was 0.28

Figure 1. Kaplan–Meier major adverse cardiac event–free survival curves for the whole cohort (top left) and patients with previous coronary artery disease (CAD; top right). Follow-up period was truncated to 8 years. Bottom, Corresponding cumulative hazard function for illustration of rates of major adverse cardiac event accumulation in these respective patient groups during the first 5 years after stress cardiac magnetic resonance imaging assessment. P value was derived with the log-rank test. ISCH indicates inducible ischemia by stress cardiac magnetic resonance imaging.

Figure 2. Kaplan–Meier all-cause mortality–free survival curves for the whole cohort (A) and patients with previous coronary artery disease (CAD; B). Follow-up period was truncated to 8 years. P value was derived with the use of the log-rank test. ISCH indicates inducible ischemia by stress cardiac magnetic resonance imaging.
Similarly, inducible ischemia provided effective risk reclassification in patients with previous CAD. Absence of inducible ischemia reclassified 43.5% (30/69) of patients at moderate pretest risk to low risk, and these patients experienced low observed posttest annual rates of MACE (1.2%). In addition, absence of inducible ischemia reclassified 32.5% of high pretest risk patients with previous CAD to moderate risk, and these patients also experienced a low observed annual rate of MACE (1.4%). In contrast, patients at high risk pretest who remained high risk posttest experienced a 13.4% annual rate of MACE.

**Effects of Early Coronary Revascularization**

Early coronary revascularization (within 90 days after stress CMR) occurred in 76 patients (9.6%) and was performed in patients with a greater extent of ischemia by CMR (ischemia score of 4.9±4.2 and 0.8±2.3 in whose who did and did not receive early revascularization, respectively; \( P<0.0001 \)). The interaction term between early revascularization and ischemia score was significant \( (P=0.02) \) when included in the multivariable clinical model for MACE, indicating effect modification by early revascularization on the association between ischemia score and MACE. Seventeen patients underwent early revascularization and experienced MACE. A greater extent of ischemia was strongly associated with increased hazard of MACE in patients who did not undergo early revascularization (32 patients with MACE; HR=1.18; 95% CI, 1.13–1.24; \( P<0.0001 \)), but this association was not significant in patients who received early revascularization (HR=1.06; 95% CI, 0.95–1.18; \( P=0.30 \)). Similarly, among patients with previous CAD, a greater extent of ischemia score demonstrated increased hazards for MACE for those who did not receive early revascularization (n=211; 24 patients with MACE; HR=1.11; 95% CI, 1.05–1.18; \( P=0.0007 \)), but such association was not significant in patients who received revascularization (n=62; 14 patients with MACE; HR=1.04; 95% CI, 0.92–1.18; \( P=0.51 \)). Similarly, among patients with previous CAD, a greater extent of ischemia score demonstrated increased hazards for MACE for those who did not receive early revascularization (n=211; 24 patients with MACE; HR=1.11; 95% CI, 1.05–1.18; \( P=0.0007 \)), but such association was not significant in patients who received revascularization (n=62; 14 patients with MACE; HR=1.04; 95% CI, 0.92–1.18; \( P=0.51 \)).

When patients who underwent early coronary revascularization were censored on the day of the procedure, inducible ischemia, inducible ischemia score, and >10% ischemic myocardium reclassified risk above a multivariable clinical risk model for MACE across guideline-based annual risk categories (categorical NRI, 0.16; continuous NRI, 0.82 in the whole cohort). Among 213 patients at moderate pretest risk, >10% ischemic myocardium reclassified 84 (39%) and 39 (18%) as low and high risk, respectively. A low 0.5% and a high 6% annual rate of MACE were observed in these groups, respectively.
the multivariable clinical model (which consisted of age, previous CAD, ST-segment change, and LV ejection fraction) (C statistic=0.82–0.87; \( P = 0.04 \); adjusted HR=7.16; \( P < 0.0001 \)) and improved the model goodness of fit (global \( \chi^2 = 51.96 \) without ischemia to 76.88 with ischemia; from 4–5 df, respectively; \( P < 0.0001 \)). For patients with moderate pretest clinical risk, addition of inducible ischemia reclassified 89% of patients (57% to low risk; 32% to high risk) with corresponding changes in the observed event rates (0.4%/y and 5.4%/y for low and high risk posttest, respectively). Categorical and continuous NRI values were 0.208 (95% CI, 0.001–0.414) and 1.21 (95% CI, 0.87–1.57), respectively.

**Discussion**

We found that stress CMR provides highly effective patient risk reclassification for cardiac death and nonfatal MI beyond clinical covariates in patients with both suspected and established CAD. The overall rate of MACE in our population was...
3.1%/y, which is comparable to large registry data from the nuclear scintigraphy literature. Inducible ischemia by stress CMR was the strongest univariable and multivariable predictor of cardiac death and MI. An absence of inducible ischemia identified a subgroup of patients with excellent cardiac prognosis (<1% risk of cardiac death) even in patients with known CAD who are at high risk. Most importantly, we found that stress CMR improved risk reclassification for the vast majority of patients at intermediate pretest risk both in the whole cohort and in patients with known CAD. These results were supported by a low observed rate of MACE (0.3%/y) in those patients at intermediate pretest risk reclassified to low risk by the absence of inducible ischemia. On the other hand, patients at intermediate pretest risk reclassified to high risk by the presence of inducible ischemia had very high rates of MACE (≈5%/y), substantially higher than the ACC/AHA-proposed high-risk category. Patients without inducible ischemia had a very low rate of accumulation of cardiac events for 2 years after stress CMR. With 98% of studies achieving diagnostic quality, stress CMR is a practical and robust method that can discriminate and reclassify patient cardiac risk and potentially guide clinical decision making for further invasive investigation.

Current clinical risk algorithms and stress testing in patients with previous CAD remain challenging. Despite excellent long-term prognosis with a negative nuclear stress test in an overall referral population (<1% annual rate of MACE), there remains significant heterogeneity of risk ascribed to patient-specific cardiac risk factors and the presence and extent of CAD. In a registry study of 7376 patients, Hachamovitch et al demonstrated higher rates of MACE in patients with previous CAD versus those without in the setting of normal nuclear perfusion imaging in both groups (1.4%/y versus 0.4%/y, respectively). Whereas non-CAD patients with a normal test had a stable hazard of MACE over time, the hazard of MACE increased for every 6 months after index testing in patients with previous CAD. Furthermore, Rozanski et al and others showed that patients who were unable to perform exercise stress testing and had to undergo vasodilator stress testing experienced higher rates of MACE (approaching 3.9%/y) despite a normal nuclear perfusion imaging. These large, well-designed studies reaffirmed the inherent Bayesian limitations in further risk stratifying patients already at moderate to high pretest clinical risk. Our study results showed that stress CMR is a promising tool for risk stratification in these common clinical settings.

Although a growing number of clinical studies have demonstrated strong prognostic association of stress CMR findings with major cardiovascular events, the ability of CMR to affect clinical management via risk reclassification is unknown. We show that stress CMR improved risk reclassification in the majority of patients at intermediate to high pretest risk, regardless of status of previous CAD, across ACC/AHA practice guideline–recommended strata that guide current clinical management decisions. Our study also provided observational supportive evidence that knowledge of extent of ischemia provided to clinicians guiding their decisions to perform early coronary revascularization may have altered patient outlook. In the context of current guideline recommendations for coronary revascularization in patients at high risk for cardiac events, our results suggest that stress CMR effectively defines and reclassifies those patients who may benefit from these invasive investigations.

Our study has several limitations. The sample size and number of adverse events allowed assessment of the prognostic value of ischemia by CMR with adjustments to only a limited number of clinical covariates. We included CMR-based LV functional parameters and used a backward elimination strategy to build a robust clinical model against which inducible ischemia by CMR still emerged to provide incremental patient risk reclassification. Whether CMR can guide
decision making in utilizing an invasive approach in addition to medical therapy requires prospective evaluation. Third, we assessed the NRI of inducible ischemia for MACE (composite cardiac death and acute MI) because of the limited sample size and number of cases of cardiac death in our cohort; whether these results are applicable to risk reclassification for cardiac mortality alone requires further evaluation.

In conclusion, stress CMR provides effective risk reclassification across ACC/AHA guideline–recommended categories, most notably in patients with intermediate pretest risk. Future investigations involving stress CMR as part of a comprehensive strategy to guide clinical decision making for invasive angiography and mechanical revascularization in addition to medical therapy merits prospective evaluation.

Sources of Funding
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References


**CLINICAL PERSPECTIVE**

Recent results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial suggest that an initial strategy of mechanical reperfusion may not improve cardiac outcomes beyond optimized medical therapy in patients with stable coronary artery disease (CAD). Nevertheless, a subgroup of patients with significant myocardial ischemia may still benefit from coronary revascularization, and current practice guidelines recommend that CAD patients at high risk for adverse events be considered for revascularization. Given increasing concern over effective resource utilization in cardiac imaging, establishing evidence indicating how cardiac imaging successfully influences clinical decision making is imperative. We studied 815 consecutive patients referred for evaluation of myocardial ischemia by stress cardiac magnetic resonance imaging, finding that inducible ischemia had the strongest association with major adverse cardiovascular events that include cardiac death or myocardial infarction after adjustment for clinical predictors, previous CAD, and left ventricular ejection fraction. Absence of inducible ischemia by cardiac magnetic resonance imaging was associated with low annual rate of events in the entire population and in a subgroup with CAD. Adding inducible ischemia to a clinical risk model reclassified $>90\%$ of patients at moderate pretest risk, with corresponding observed event rates of 0.3%/y and 4.9%/y for low- and high-risk posttest groups, respectively. These results demonstrate that cardiac magnetic resonance imaging effectively reclassifies risk beyond clinical risk predictors, specifically in the moderate pretest risk subgroup and in patients with previous CAD. Stress cardiac magnetic resonance imaging offers an effective strategy to safely manage some patients without the need for invasive angiography.
Stress Cardiac Magnetic Resonance Imaging Provides Effective Cardiac Risk Reclassification in Patients With Known or Suspected Stable Coronary Artery Disease


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SUPPLEMENTAL MATERIAL
Supplemental Figure 1. Calibration plot for Model 2. We computed observed and expected event rates at 3 years and then annualized them. Subjects were grouped into deciles of predicted event rates. Kaplan-Meier observed event rates across deciles of predicted rates were well calibrated (Nam-D'Agostino modification of Hosmer-Lemeshow Calibration adjusted chi-squared: 6.53, p=0.69, Model 2 of Table 3) with a slope which did not vary significantly from unity and an intercept which did not vary significantly from zero.
Observed = 0.95 * (Predicted) + 0.0003
R^2 = 0.955
H0 (slope = 0): P < 0.0001
H0 (slope = 1): P = 0.75
H0 (intercept = 0): P = 0.92