Circulation
Cardiovascular Imaging

The Prognostic Value of Normal Stress Cardiac Magnetic Resonance in Patients With Known or Suspected Coronary Artery Disease: A Meta-analysis

Paola Gargiulo, Santo Dellegrottaglie, Dario Bruzzese, Gianluigi Savarese, Oriana Scala, Donatella Ruggiero, Carmen D'Amore, Stefania Paolillo, Piergiuseppe Agostoni, Edoardo Bossone, Andrea Soricelli, Alberto Cuocolo, Bruno Trimarco and Pasquale Perrone Filardi

Circ Cardiovasc Imaging. 2013;6:574-582; originally published online June 14, 2013;
doi: 10.1161/CIRCIMAGING.113.000035
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080

The Prognostic Value of Normal Stress Cardiac Magnetic Resonance in Patients With Known or Suspected Coronary Artery Disease

A Meta-analysis

Paola Gargiulo, MD; Santo Dellegrottaglie, MD, PhD; Dario Bruzzese, PhD; Gianluigi Savarese, MD; Oriana Scala, MD; Donatella Ruggiero, MD; Carmen D'Amore, MD; Stefania Paolillo, MD; Piergiuseppe Agostoni, MD, PhD; Edoardo Bossone, MD; Andrea Soricelli, MD; Alberto Cuocolo, MD; Bruno Trimarco, MD; Pasquale Perrone Filardi, MD, PhD

Background—Ischemia detection with stress cardiac magnetic resonance (CMR) is typically based on induction of either myocardial perfusion defect or wall motion abnormality. Single-center studies have shown the high value of stress CMR for risk stratification. The aim of this study was to define the prognostic value of stress CMR for prediction of adverse cardiac events in patients with known or suspected coronary artery disease.

Methods and Results—Studies published between January 1985 and April 2012 were identified by database search. We included studies using stress CMR to evaluate subjects with known or suspected coronary artery disease and providing primary data on clinical outcomes of nonfatal myocardial infarction or cardiac death with a follow-up time ≥3 months. Total of 14 studies were finally included, recruiting 12 178 patients. The negative predictive value for nonfatal myocardial infarction and cardiac death of normal CMR was 98.12% (95% confidence interval, 97.26–98.83) during a weighted mean follow-up of 25.3 months, resulting in estimated event rate after a negative test equal to 1.88% (95% confidence interval, 1.17–2.74). The corresponding annualized event rate after a negative test was 1.03%. Comparable negative predictive values for major coronary events were obtained in studies considering the absence of inducible perfusion defect compared with those evaluating the absence of inducible wall motion abnormality (98.39% versus 97.31%, respectively; P=0.227 by meta-regression analysis).

Conclusions—Stress CMR has a high negative predictive value for adverse cardiac events, and the absence of inducible perfusion defect or wall motion abnormality shows a similar ability to identify low-risk patients with known or suspected coronary artery disease. **(*Circ Cardiovasc Imaging*. 2013;6:574-582.)**

Key Words: coronary artery disease ■ chronic ischemic heart disease ■ prognostic value ■ cardiac magnetic resonance imaging

Coronary artery disease (CAD) is a leading cause of death and disability in developed countries.[1] In patients with known or suspected CAD, stress single-photon emission computed tomography (SPECT) and stress echocardiography account for the vast majority of tests currently performed for ischemia detection. The diagnostic role of these 2 imaging modalities is well established, and a negative stress test with either SPECT or echocardiography is able to identify subjects at low risk of future cardiovascular events.[2,3] However, the use of stress SPECT may be hampered by soft-tissue attenuation artifacts and may expose patients to ionizing radiations, whereas disadvantages of stress echocardiography include suboptimal acoustic window in ≤25% of patients and frequent signal dropout in the anterior and lateral left ventricular walls.[2]

Clinical Perspective on p 582

Received January 15, 2013; accepted June 12, 2013.

From the SDN Foundation, Institute of Diagnostic and Nuclear Development, Naples, Italy (P.G., A.S.); Division of Cardiology, Ospedale Medico-Chirurgico Accreditato Villa dei Fiori, Acerra, Naples, Italy (S.D.); Z. and M.A. Wiener Cardiovascular Institute and M.-J. and H.R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, NY (S.D.); Departments of Public Health (D.B.) and Advanced Biomedical Sciences (G.S., O.S., D.R., C.D., S.P., A.C., B.T., P.P.F.), Federico II University, Naples, Italy; Centro Cardiologico Monzino, Institute for Treatment and Research, Milan, Italy (P.A.); Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy (P.A.); Cardiology Division, Cava de' Tirreni and Amalfi Coast Hospital, Heart Department, University of Salerno, Cava de' Tirreni, Salerno, Italy (E.B.); Cardiac Surgery Department, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy (E.B.); and Department of Studies of Institutions and Territorial Systems, University of Naples Parthenope, Naples, Italy (A.S.).

The online-only Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.113.000035/-/DC1.

Correspondence to Pasquale Perrone Filardi, MD, PhD, Division of Cardiology, Department of Advanced Medical Sciences, Federico II University, Via Pansini, 5 80131, Naples, Italy. E-mail fpperron@unina.it

Cardiac magnetic resonance (CMR) has recently undergone significant evolution in terms of imaging capabilities and feasibility.[4] It now represents a valuable alternative to other noninvasive imaging techniques with the possibility of overcoming some of their limitations in the evaluation of patients with CAD. The detection of myocardial ischemia with stress CMR is typically based on first-pass perfusion imaging, with the acquisition of high-spatial-resolution images during the injection of a bolus of a gadolinium-based contrast agent to search for inducible perfusion defects (PDs), or on wall motion abnormality (WMA) imaging, based on iterative collection of cine images allowing the identification of inducible impairment of regional systolic function. Previous reports on stress CMR showed good diagnostic accuracy for the detection of significant CAD.[5] Very recently, a few prospective studies and a meta-analysis reported higher diagnostic accuracy of stress CMR when compared with myocardial SPECT for the diagnosis of CAD.[6–8]

However, the prognostic value of CMR has only been evaluated in single-center studies of relatively limited sample size. Thus, we performed a meta-analysis of published studies, including patients with known or suspected CAD, to assess the predictive value for adverse cardiac ischemic events of normal stress CMR, defined as the absence of inducible PDs and the absence of inducible WMAs.

Methods

Data Sources and Study Selection

An English literature search was performed using the PubMed and Cochrane databases to identify articles published between January 1985 and April 2012. The search for studies was restricted to data obtained in humans and adults and was conducted using the following key words (alone and in different combinations): prognosis, prognostic value, stress, dipyridamole, adenosine, dobutamine, and CMR. The title and abstract of potentially relevant studies were screened for appropriateness before retrieval of the full article when relevant. Additional studies were identified by contacting authors working in the field and searching cited references of relevant articles. A study was included if all of the following criteria were met: (1) the study had prospective or retrospective analysis of subjects referred for suspected or known CAD who underwent pharmacological stress CMR for searching inducible ischemia; (2) the study included a negative test defined in the absence of inducible PDs and the absence of inducible WMAs during stress CMR; (3) the study provided the absolute number of patients with a negative test and primary data on clinical outcomes of nonfatal myocardial infarction (MI) and cardiac death; and (4) the follow-up time of the study was ≥3 months. Because only preliminary studies have been performed to evaluate the feasibility of exercise CMR, we excluded articles that used exercise as a stressor. In case of multiple studies reported from the same research group, potential cohort duplication was avoided by including the largest study only. Overall study quality was not used as a prespecified inclusion criterion.[9]

Data Extraction and Quality Assessment

To evaluate eligibility for the meta-analysis, as previously described,[10–12] each study was initially identified by considering journal, author, and year of publication. Additional extracted variables included study design (retrospective or prospective), MRI system, CMR sequence used for image acquisition, criterion used to classify a test as negative, type of pharmacological stressor used (dipyridamole, adenosine, or dobutamine), orientation and number of the obtained slices, and modality of data assessment (qualitative, semiquantitative, or quantitative). Data were also collected on age and on prevalence of female sex, traditional cardiovastily history of CAD, smoking), angina-like symptoms, history of CAD (including previous MI and previous myocardial revascularization), and prevalence of patients with late gadolinium enhancement (LGE) as detected by CMR. Mean and median follow-up time, number of events, or event rate based on negative tests, occurrence of primary outcomes (nonfatal MI or cardiac death), and secondary outcomes (coronary revascularization and admission for unstable angina [UA]) were recorded.

Quality assessment was performed using a previously described methodology[13] and was on the basis of the presence of the following parameters: (1) complete follow-up in the majority of subjects (≥90% of the baseline cohort); (2) outcome data collected by investigators blinded to the test results; and (3) outcomes corroborated by hospital records and death certificates. Studies were defined as good quality if they fulfilled criterion 1 and ≥1 of the other 2 criteria, as fair quality if they fulfilled only the criterion 1, and as poor quality if they fulfilled none of the criteria.

Statistical Analysis

Demographical and clinical characteristics of all patients included in this meta-analysis were obtained as weighted averages of those reported in the single studies, the weights being the total sample size for each study. Statistical heterogeneity between studies was assessed using the Cochrane Q statistic (with a value of $P<0.1$ reflecting significant heterogeneity) and I^2 statistic,[14,15] which measures the percentage of total variability across studies not due to sampling error. Because of the large heterogeneity experienced, the pooled estimates of negative predictive value (NPV) for both hard and soft events and the pooled estimates of the event rate after negative tests (ERNT=1−NPV) were computed using the random-effects model of DerSimonian and Laird.[16] To correct for overdispersion, the raw proportions (NPV and ERNT) were initially converted using the Freeman-Tukey transformation and backtransformed after quantitative data synthesis.[17,18] For each study, the annualized ERNT was obtained as average during the lengths of follow-up. To investigate the potential sources of heterogeneity, subgroup analysis was a priori planned for the following categorical variables: criterion to define the test as negative (studies that considered the absence of PDs versus studies considering the absence of WMAs) and quality of studies (good versus fair). Univariate random-effects meta-regression analyses were used to examine the effects of other continuous variables.

Publication bias was visually checked by funnel plot and formally assessed using the Egger test.[19] All analyses were performed with R statistics (version 2.15.0), using the additional packages META e METAFOR.

Results

The initial database search identified 556 potentially eligible citations. After application of filters for human, English language, and adults (age >19 years), 202 studies were selected. Two couples of investigators (P.G. and S.D.; G.S. and E.B.) reviewed the titles and abstracts of these studies, discharging 171 citations because they were judged to be nonrelevant/nonpertinent. To determine eligibility, each couple of investigators reviewed the full text of the remaining 31 independently, and disagreements were resolved by the senior author (P.P.-F.). After revision, 18 articles were excluded. Thirteen articles were finally enrolled; in 1 of the studies,[20] a negative test was defined in case of coexisting absence of inducible PDs and WMAs, so each of the parameters was separately considered, and the study was included twice in all analyses. Accordingly, the final analysis considered 14 studies[20–32] including 12 178 patients. The complete literature search is presented in flow-chart form in Figure I in the online-only Data Supplement.

Demographical and clinical characteristics of patients included in the studies in the meta-analysis are detailed in Table 1. Study sample sizes ranged from 203 to 1722 patients enrolled, including a variable proportion of patients with previous CAD (0%–64%). The mean patient age ranged from 57 to 65 years, with the proportion of

Table 1. Demographical and Clinical Characteristics of Patients Included in the Studies Enrolled in Meta-analysis

Author	Bingham et al[21]	Bodi et al[20]	Bodi et al[20]	Coelho-Filho et al[22]	Gebker et al[23]	Hundley et al[24]
Year	2011	2012	2012	2011	2011	2002
Journal	*Circulation*	*Radiology*	*Radiology*	*JACC: Cardiovascular Imaging*	*Journal of Cardiovascular Magnetic Resonance*	*Circulation*
Imaging system	GE 1.5 T	Siemens 1.5 T	Siemens 1.5 T	Siemens 3 T	Philips 1.5 T	GE 1.5 T
CMR sequence	Notched saturation fast gradient echo	Notched saturation steady-state free precession	Cine steady-state free precession	Saturation-prepared fast gradient echo	Cine steady-state free precession	Single-slice gradient echo
CMR technique	Perfusion	Perfusion	Wall motion	Perfusion	Wall motion	Wall motion
Stressor	Adenosine	Dipyridamole	Dipyridamole	Adenosine or dipyridamole	Dobutamine	Dobutamine
Image number/ orientation	5–10 in SA	At least 4 in SA	3 in SA	4–5 in SA	3 in SA	3 in SA
		2 in 2-ch LA	2 in 2-ch LA		1 in 2-ch LA	1 in 2-ch LA
		2 in 4-ch LA	2 in 4-ch LA		1 in 3-ch LA	1 in 3-ch LA
					1 in 4-ch LA	1 in 4-ch LA
Image interpretation	Qualitative	Semiquantitative	Semiquantitative	Semiquantitative	Semiquantitative	Qualitative
Patients, n	932	1722	1722	405	1575	279
Mean age, y	65	64	64	57	63	63
Women, %	41	48	48	41	33	40
Hypertension, %	64	62	62	56	71	75
Dyslipidemia, %	NS	55	55	57	65	46
Diabetes mellitus, %	25	NS	NS	22	22	37
Family history of CAD, %	41	NS	NS	26	29	NS
Smokers, %	6	22	22	15	30	59
Symptoms, %	50	NS	NS	NS	100	NS
Personal history of CAD, %	50	NS	NS	NS	48	NS
Prior MI, %	35	23	23	20	30	41
Previous PCI, %	33	14	14	16	40	NS
Previous CABG, %	15	7	7	8	17	NS
Previous CABG/ PCI, %	NS	NS	NS	NS	NS	31
LGE, %	38	28	28	30	NP	NP
Mean follow-up, mo	31	13	13	30	25	20
ERNT for CD/MI, %	1.97	1.68	2.29	1.69	0.87	3.23
Annualized ERNT for CD/MI, %	0.76	1.55	2.11	0.68	0.42	1.94
NPV for CD/MI, %	98.03	98.32	97.71	98.31	99.13	96.77
Quality assessment	Fair	Fair	Fair	Fair	Fair	Good

2-ch Indicates 2-camber view; 3-ch, 3-chamber view; 4-ch, 4-chamber view; CABG, coronary artery bypass graft; CAD, coronary artery disease; CD, cardiac death; CMR, cardiac magnetic resonance; ERNT, event rate after negative test; LA, long-axis view; LGE, late gadolinium enhancement; MI, nonfatal myocardial infarction; NP, not performed; NPV, negative predictive value; NS, not specified; PCI, percutaneous coronary intervention; and SA, short-axis view.

*Quantitative analysis performed only in case of uncertainty in perfusion defect definition.

women ranging from 16% to 100%. The duration of follow-up after CMR ranged from 12 to 74 months; the primary ERNT (nonfatal MI and cardiac death) varied between 0% and 9.32%; and the primary annualized ERNT varied between 0% and 3.92%.

After quality assessment, 7 studies were graded as good quality[24,25,27–29,31,32] and 7 studies as fair quality.[20–23,26,30] Of the 13 series of patients included for subanalysis using the criterion to define the test as negative, 7 used the absence of inducible PDs[20–22,27,29–31] as the criterion to define a negative test; of these studies, 1 used dipyridamole as the stressor, 4 used adenosine, and 2 used a stress protocol with both dipyridamole and adenosine. In the remaining 6 series of patients, the definition of a negative study was based on the absence of inducible

Table 1. Continued

Kelle et al[25]	Korosoglou et al[26]	Krittayaphong et al[27]	Kuijpers et al[28]	Lo et al[29]	Pilz et al[30]	Steel et al[31]	Wallace et al[32]
2011	2010	2011	2004	2011	2008	2009	2009
JACC: Cardiovascular Imaging	*Journal of the American College of Cardiology*	*International Journal of Cardiovascular Imaging*	*European Radiology*	*Quarterly Journal of Medicine*	*American Journal of Cardiology*	*Circulation*	*JACC: Cardiovascular Imaging*
Philips 1.5 T	Philips 1.5 T	Philips 1.5 T	Siemens 1 T	Siemens 1.5 T	GE 1.5 T	GE 1.5 T	GE 1.5 T
Cine fast gradient echo with parallel imaging	Cine steady-state free precession and hybrid gradient echo/ echo planar	Inversion recovery turbo gradient echo	Gradient echo pulse sequence	Fast steady-state free precession	Hybrid gradient echo/ echo-planar	Notched saturation fast gradient echo	Cine gradient echo
Wall motion	Wall motion and Perfusion	Perfusion	Wall motion	Perfusion	Perfusion	Perfusion	Wall motion
Dobutamine	Dobutamine	Adenosine	Dobutamine	Adenosine	Adenosine	Adenosine or Dipyridamole	Dobutamine
3 in SA	3 in SA	3 in SA	3 in SA	3 in SA	4–5 in SA	4–9 in SA	3 in SA
1 in 2-ch LA	1 in 2-ch LA			1 in 2-ch LA			1 in 2-ch LA
1 in 3-ch LA	1 in 3-ch LA			1 in 3-ch LA			1 in 3-ch LA
1 in 4-ch LA	1 in 4-ch LA			1 in 4-ch LA			1 in 4-ch LA
Semiquantitative	Semiquantitative*	Qualitative	Qualitative	Qualitative	Qualitative	Semiquantitative*	Semiquantitative
1463	1510	1232	299	203	229	254	266
61	65	65	63	62	63	58	63
33	36	52	16	41	44	41	100
73	71	63	28	69	68	57	73
70	53	62	30	46	37	61	57
17	19	35	16	30	9	25	38
35	22	NS	NS	4	43	29	52
44	18	15	NS	29	35	11	38
NS	NS	91	NS	NS	48	96	NS
52	55	16	64	16	0	NS	NS
25	NS	NS	34	10	0	22	28
NS	40	NS	NS	12	0	18	25
NS	12	NS	NS	3	0	11	19
43	NS	11	18	NS	0	NS	37
NP	NS	26	NP	13	0	28	28
44	24	35	24	38	12	17	74
3.08	0.42	1.24	1.87	1.25	0	5.56	9.32
0.84	0.21	0.42	0.93	0.39	0	3.92	1.51
96.92	99.58	98.76	98.13	98.75	100	94.44	90.68
Good	Fair	Good	Good	Good	Fair	Good	Good

WMAs[20,23–25,27,32]; of these, 1 used dipyridamole and 5 used dobutamine as the stressor. Data from 1 study were not considered for subanalysis because information related to PDs and WMAs could not be separated.[26] In this study, dobutamine was used as the stressor. Eight of the 14 included studies reported rates of myocardial revascularization and UA in addition to major coronary events.

Predictive Value of Stress CMR for Cardiac Death and Nonfatal MI

Figure 1 shows the forest plot of NPV and ERNT for nonfatal MI and cardiac death for each study, as well as the pooled estimates yielded by the random-effect model. In the individual studies, NPV ranged from 90.68% to 100%. During a weighted mean follow-up of 25.3 months, the summary NPV

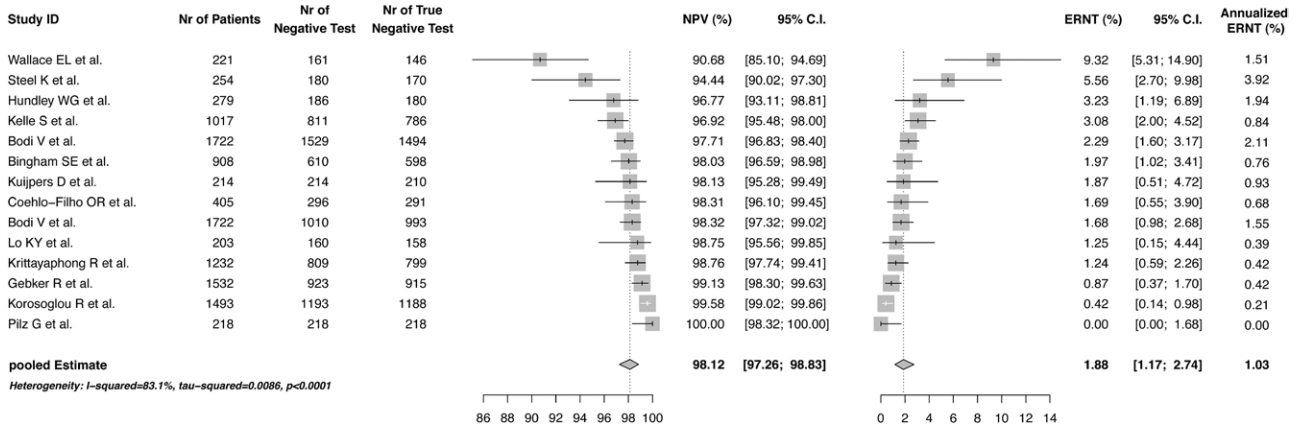


Figure 1. Negative predictive value (NPV) and event rate after negative test (ERNT) for cardiac death and nonfatal myocardial infarction. CI indicates confidence interval.

was 98.12% (95% confidence interval [CI], 97.26–98.83), resulting in a pooled ERNT of 1.88% (95% CI, 1.17–2.74). The corresponding annualized ERNT was 1.03%.

A high level of heterogeneity was observed between studies (I^2=83.1%; P<0.0001), and in univariate random-effects meta-regression analysis, it showed a significant association with the prevalence of patients with previous coronary artery bypass graft and percutaneous coronary intervention (β=–0.09%; 95% CI, –0.14 to –0.04; P=0.001) and the prevalence of LGE (β=–0.06%; 95% CI, –0.09 to –0.02; P=0.001; Table 2).

Comparable NPVs for the prediction of major coronary events during follow-up were obtained in studies considering the absence of inducible PDs to define a negative test compared with those evaluating the absence of inducible WMAs (98.39% versus 97.31%, respectively; P=0.263 by meta-regression analysis). However, the level of heterogeneity was higher in the group of studies evaluating WMAs (I^2=84.3%) compared with studies assessing PDs (I^2=67.9%; Figure 2).

In subgroup analysis by study quality, fair-quality studies resulted in a higher pooled NPV compared with that observed in high-quality studies (98.85% versus 96.89%, respectively; P=0.031 by meta-regression analysis), although the annualized ERNT was similar between them (1.05% versus 1.03%). The heterogeneity remained high in both good quality (I^2=79.7%) and fair-quality (I^2=80.1%; Figure 3) studies.

Predictive Value of Stress CMR for Myocardial Revascularization and UA

Rates of coronary revascularization and admission for UA were provided in 8 of the 14 series of patients.[20,26–30] Figure 4 shows the forest plot of the NPV and ERNT for each study, as well as the pooled estimates yielded by the random-effect model (I^2=94.7%; P<0.001). The individual NPVs ranged from 75.27% to 100%. The summary NPV, during a weighted mean follow-up of 20.4 months, was equal to 97.17% (95% CI, 94.70–98.91), resulting in a pooled ERNT of 2.83% (95% CI, 1.09–5.30). The corresponding annualized ERNT in patients with a negative test was 1.73%. Because of the small number of studies reporting information on secondary events, neither subgroup analysis nor meta-regression was conducted.

Publication Bias

There was no evidence of significant publication bias for studies enrolled in this meta-analysis using the Egger test[19] (α=–2.21, P=0.219 for cardiac death and nonfatal MI; α=–3.99, P=0.341 for myocardial revascularization and UA). These findings were consistent with the funnel plots shown in Figures 2 and 3 in the online-only Data Supplement, respectively.

Discussion

Although the diagnostic accuracy of stress CMR has been repeatedly reported in single studies and in meta-analyses,[5–7] the prognostic value of stress CMR for predicting major adverse cardiac events is less defined. This systematic review and meta-analysis are the first comprehensive analysis of available literature reporting the prognostic value of cardiac stress MRI in subjects with known or suspected CAD. Our

Table 2. Meta-regression Analysis for Cardiac Death and Nonfatal MI for All Studies

	Cardiac Death/Nonfatal MI			
			95% CI	
Moderators	Coefficient	*P* Value	Lower Bound	Upper Bound
Mean age, y	0.20	0.172	–0.09	0.48
Women, %	–0.05	0.054	–0.11	0.00
Hypertension, %	0.01	0.817	–0.05	0.07
Dyslipidemia, %	–0.04	0.212	–0.1	0.02
Diabetes mellitus, %	–0.08	0.053	–0.16	0.00
Family history of CAD, %	–0.05	0.257	–0.13	0.03
Smoking, %	–0.02	0.457	–0.08	0.03
Symptoms, %	–0.02	0.492	–0.06	0.03
History of CAD, %	–0.02	0.275	–0.05	0.02
Prior MI, %	–0.06	0.076	–0.12	0.01
Previous PCI, %	0.00	0.976	–0.06	0.06
Previous CABG, %	–0.10	0.165	–0.24	0.04
Previous CABG/PCI, %	–0.09	0.001	–0.14	–0.04
LGE, %	–0.06	0.001	–0.09	–0.02

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; LGE, late gadolinium enhancement; MI, myocardial infarct; and PCI, percutaneous coronary intervention.

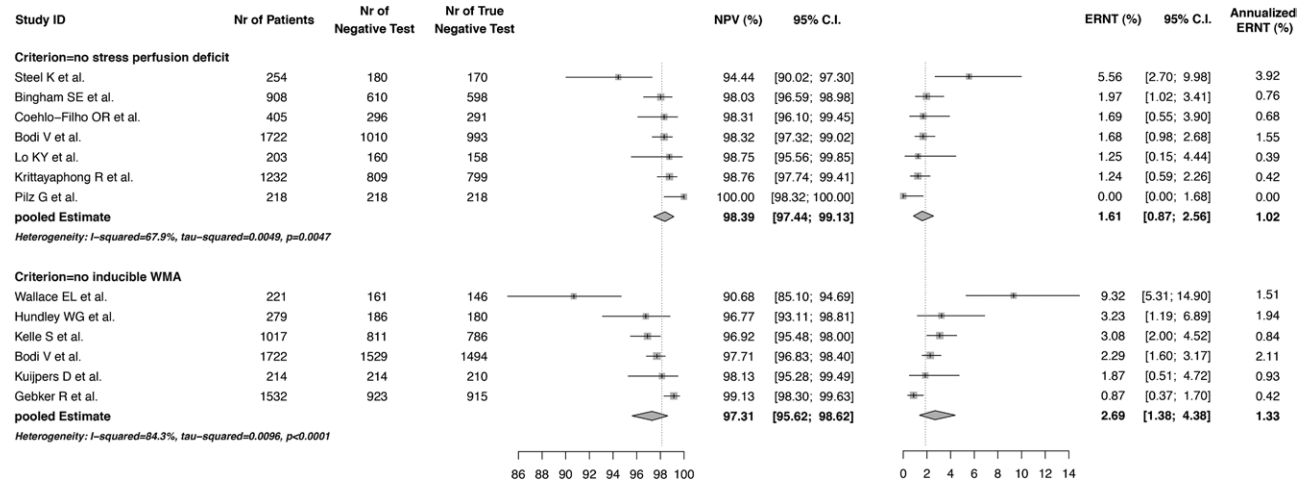


Figure 2. Negative predictive value (NPV) and event rate after negative test (ERNT) for cardiac death and nonfatal myocardial infarction for criterion used to define negative cardiac magnetic resonance. CI indicates confidence interval.

analysis revealed that in subjects evaluated for known or suspected CAD, the absence of inducible ischemia on stress CMR predicts a low risk of cardiovascular events during a short-term to midterm follow-up. The calculated annualized major event rate after a normal stress CMR was ≈1%; this is only slightly higher than the background event rate observed in healthy low-risk individuals (<1%).[33]

In a previous meta-analysis considering stress SPECT and stress echocardiography for noninvasive risk stratification, very low (<1%) annualized event rates have been reported in subjects with a normal imaging stress test.[3] However, this analysis considered only studies using physical exercise stress, which may have introduced a bias toward a relatively more healthy population. In fact, subjects undergoing pharmacological stress tests generally have a worse prognosis.[34] A different meta-analysis, comparing risk stratification with pharmacological and exercise stress SPECT in patients with known or suspected CAD, reported that annualized ERNT (for cardiac death and nonfatal MI) after normal pharmacological SPECT was significantly higher than after normal exercise SPECT (1.78% versus 0.65%; $P<0.001$), and at meta-regression analysis, exercise capacity was the single most important predictor of cardiac events.[35] Stress CMR is almost exclusively performed with pharmacological stress because standard equipment for exercise is generally not compatible with MRI, CMR image acquisition may be difficult under postexercise conditions for high heart rate and rapid breathing, and ECG signal is adversely affected by the system used for CMR imaging. However, exercise stress may offer information about functional capacity, blood pressure, and heart rate response to physical activity, arrhythmias, and the link between symptom reproducibility and the presence of ischemia.[36] Recently, Raman et al,[37] using a modified treadmill constructed to be located in the scanner room, studied with exercise stress CMR 43 patients undergoing exercise stress SPECT because of known or suspected CAD. Agreement between SPECT and CMR was moderate (κ=0.58) without significant difference in CAD diagnosis (P=0.625). Interestingly, at the 6-month follow-up, cardiac death and nonfatal MI did not occur in any of the 29 patients with normal exercise CMR (NPV=100%) and in 33 of 34 patients with normal exercise SPECT (NPV=99%). Unfortunately, exercise CMR might not have been easy to

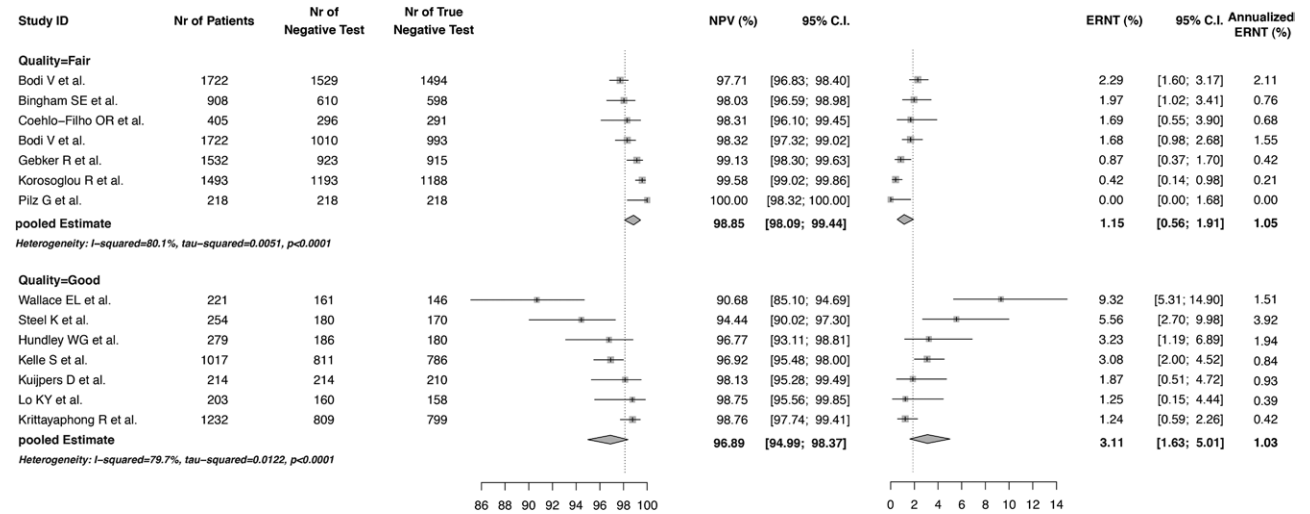


Figure 3. Negative predictive value (NPV) and event rate after negative test (ERNT) for cardiac death and nonfatal myocardial infarction for quality of studies. CI indicates confidence interval.

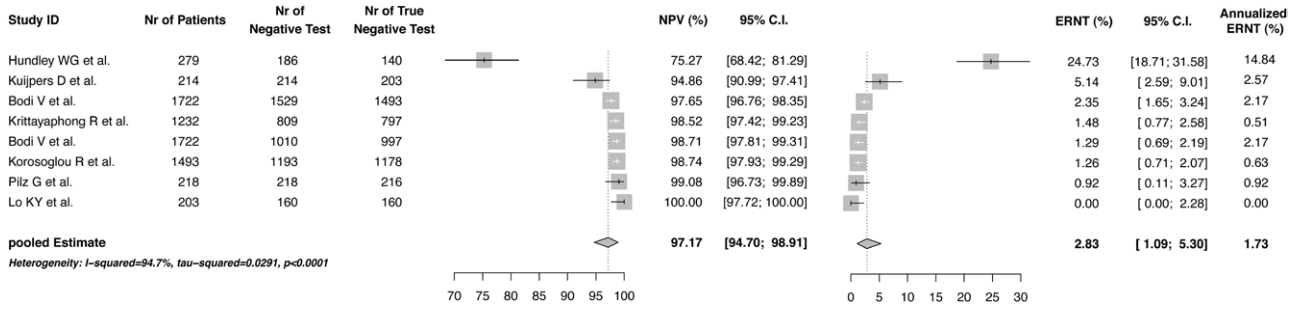


Figure 4. Negative predictive value (NPV) and event rate after negative test (ERNT) for coronary revascularization and admission for unstable angina. CI indicates confidence interval.

implement, especially outside research centers, because of the requirement for expensive dedicated exercise equipment and difficulties in obtaining adequate images owing to technical limitations such as frequent occurrence of motion artifacts.

With stress CMR, both myocardial perfusion and systolic function can be accurately assessed. Our results highlighted that the NPV of stress CMR in predicting adverse events is similar for studies considering PDs and those based on the evaluation of WMAs to define a negative examination. Because the occurrence of PDs precedes the development of WMAs on the basis of ischemic cascade, perfusion CMR could be more sensitive in ischemia detection, although the induction of WMAs at CMR should be associated with more severe ischemic burden. Actually, the assessment of myocardial PDs and WMAs during a single stress session with stress CMR appeared to enhance the sensitivity for ischemia detection.[38] In a large cohort of patients, Korosoglou et al[26] showed a very low risk of major cardiac events (0.4%) after negative CMR with concurrent evaluation of PDs and WMAs, suggesting that myocardial wall motion and perfusion assessment could yield complementary prognostic information.

Evaluation of LGE in the left ventricular myocardium to detect previous myocardial necrosis is part of standard CMR protocols applied to the characterization of patients with CAD. A growing body of evidence is pointing to the prognostic value of LGE in several clinical scenarios and suggests the potential for combining this information with that provided by myocardial perfusion and wall motion assessment during a stress CMR study.[39,40] In this regard, using CMR, Steel et al[31] reported the lowest annual event rates (<2%) for cardiac death or nonfatal MI in the group of patients with neither reversible PDs nor LGE. More recently, Bingham et al[21] found a very low annual cardiac mortality rate (≤0.4%) in patients contemporaneously showing normal perfusion, no LGE, normal aortic flow, and left ventricular function evaluated at CMR, emphasizing the great potential of this modality for assessing within a single examination complementary prognostic parameters. Our results are consistent with this previous evidence of an additional value of LGE for prognostic stratification, as demonstrated by the observed interaction of the prevalence of patients with LGE and the capacity of CMR-detected ischemia to predict the risk of hard cardiac events.

In our meta-analysis, we did not include analyses of positive predictive values. These values are particularly subject to bias because of differing patient risk profiles, as well as to the effect of positive tests on subsequent revascularization and medical management. Variation in test performance among subjects at very high or very low risk of disease (spectrum bias) may also affect the results of prognostic studies and the assessment of NPV.[41] Our systematic review includes studies of cohorts with supposedly varying pretest risk of disease, as manifested by a broad range of percentages of subjects with major cardiovascular risk factor, history of CAD, prior MI, history of previous coronary revascularization procedures, or anginal symptoms (Table 1). The assessment of pretest risk is relevant for evaluating the clinical impact of cardiovascular imaging,[42] but the availability of incomplete clinical data in many of the included studies prevents the possibility of performing further subgroup analyses and consequently evaluating more carefully the NPV in relation to pretest risk. However, meta-regression analysis showed that the percentage of patients with previous revascularization (coronary artery bypass graft and percutaneous coronary intervention) was a significant predictor of major cardiac events, increasing the risk of cardiac death/nonfatal MI after normal CMR. In addition, our meta-analysis excluded patients at the highest risk of cardiac events such as those hospitalized for acute chest pain syndrome[43] or with recent MI.[44] Thus, even though our study showed a low annualized event rate associated with the absence of inducible ischemia at stress CMR, it should be cautioned that the negative predictive power of the test might be lower in patient populations at very high cardiovascular risk.

Limitations

As previously reported for other meta-analyses reporting the diagnostic and prognostic value of noninvasive imaging modalities in patients with CAD, our results were obtained from a relatively limited number of studies with a moderate to high level of heterogeneity. In addition, not all studies provided data on risk factors, presence of symptoms, prevalence of known CAD, and previous revascularization procedures; therefore, we could not perform additional subgroup analyses. Compared with more traditional imaging modalities, stress CMR reached a less advanced level of standardization on the applied methodology for both image acquisition and interpretation, including the number and orientation of acquired slices, rate and concentration of contrast infusion, and methods for image interpretation. These aspects may have represented additional sources of heterogeneity among studies included in this meta-analysis.

Furthermore, we know that double-counting of the study of Bodi et al[20] in the main analysis might be debatable from

a methodological standpoint because of potential incorrect increase of population. The authors reported a separate analysis for wall motion and perfusion in the same patients. Therefore, we treated these 2 analyses as 2 different studies. Although this allowed us to add wall motion and perfusion results to the respective subgroup analyses in our study, it slightly increased the true number of patients collected in the main analysis. However, the consistency of the results of this study with the results of other included studies makes a substantial impact on the main findings of the analysis unlikely.

Conclusions

Stress CMR provides a high NPV for adverse cardiac events in subjects with known or suspected CAD. The ability to identify low-risk subjects with stress CMR does not differ whether the absence of inducible PDs or the absence of inducible WMAs is used to define a negative test.

Combining perfusion and wall motion assessment with LGE may further increase the prognostic power of stress CMR and deserves further evaluation in prospective clinical trials.

Acknowledgments

We would like to thank Rungroj Krittayaphong, MD, David K.Y. Lo, MD, Oliver Husser, MD, Raymond Kwong, MD, and Grigorios Korosoglou, MD, for clarification or provision of data.

Disclosures

None.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361:13–20.
2. Gibbons RJ. Noninvasive diagnosis and prognosis assessment in chronic coronary artery disease: stress testing with and without imaging perspective. *Circ Cardiovasc Imaging*. 2008;1:257–269.
3. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol*. 2007;49:227–237.
4. Pennell DJ. Cardiovascular magnetic resonance. *Circulation*. 2010;121:692–705.
5. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. *J Am Coll Cardiol*. 2007;50:1343–1353.
6. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, Bijsterveld P, Ridgway JP, Radjenovic A, Dickinson CJ, Ball SG, Plein S. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet*. 2012;379:453–460.
7. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, Nelemans PJ, Schalla S. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol*. 2012;59:1719–1728.
8. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K, Schonberg SO, Luchner A, Strohm O, Ahlstrom H, Dill T, Hoebel N, Simor T. MR-impact II: magnetic resonance imaging for myocardial perfusion assessment in coronary artery disease trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J*. 2012; 34:775–81.
9. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med*. 2006;144:427–437.
10. Costanzo P, Perrone-Filardi P, Petretta M, Marciano C, Vassallo E, Gargiulo P, Paolillo S, Petretta A, Chiariello M. Calcium channel blockers and cardiovascular outcomes: a meta-analysis of 175,634 patients. *J Hypertens*. 2009;27:1136–1151.
11. Costanzo P, Savarese G, Rosano G, Musella F, Casaretti L, Vassallo E, Paolillo S, Marsico F, Rengo G, Leosco D, Perrone-Filardi P. Left ventricular hypertrophy reduction and clinical events: a meta-regression analysis of 14 studies in 12,809 hypertensive patients. *Int J Cardiol*. July 20, 2012.
12. Gargiulo P, Petretta M, Bruzzese D, Cuocolo A, Prastaro M, D'Amore C, Vassallo E, Savarese G, Marciano C, Paolillo S, Filardi PP. Myocardial perfusion scintigraphy and echocardiography for detecting coronary artery disease in hypertensive patients: a meta-analysis. *Eur J Nucl Med Mol Imaging*. 2011;38:2040–2049.
13. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ*. 2001;323:42–46.
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
17. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann. Math. Statist*. 1950; 21:607–611.
18. Miller JJ. The inverse of the freeman-tuckey double arcsine transformation. *American Statistician*. 1978; 32:138.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
20. Bodi V, Husser O, Sanchis J, Núñez J, Monmeneu JV, López-Lereu MP, Bosch MJ, Rumiz E, Miñana G, García C, Diago JL, Chaustre F, Moratal D, Gómez C, Aguilar J, Chorro FJ, Llacer A. Prognostic implications of dipyridamole cardiac MR imaging: a prospective multicenter registry. *Radiology*. 2012;262:91–100.
21. Bingham SE, Hachamovitch R. Incremental prognostic significance of combined cardiac magnetic resonance imaging, adenosine stress perfusion, delayed enhancement, and left ventricular function over preimaging information for the prediction of adverse events. *Circulation*. 2011;123:1509–1518.
22. Coelho-Filho OR, Seabra LF, Mongeon FP, Abdullah SM, Francis SA, Blankstein R, Di Carli MF, Jerosch-Herold M, Kwong RY. Stress myocardial perfusion imaging by CMR provides strong prognostic value to cardiac events regardless of patient's sex. *JACC Cardiovasc Imaging*. 2011;4:850–861.
23. Gebker R, Jahnke C, Manka R, Hucko T, Schnackenburg B, Kelle S, Klein C, Fleck E, Paetsch I. The role of dobutamine stress cardiovascular magnetic resonance in the clinical management of patients with suspected and known coronary artery disease. *J Cardiovasc Magn Reson*. 2011;13:46.
24. Hundley WG, Morgan TM, Neagle CM, Hamilton CA, Rerkpattanapipat P, Link KM. Magnetic resonance imaging determination of cardiac prognosis. *Circulation*. 2002;106:2328–2333.
25. Kelle S, Chiribiri A, Vierecke J, Egnell C, Hamdan A, Jahnke C, Paetsch I, Wellnhofer E, Fleck E, Klein C, Gebker R. Long-term prognostic value of dobutamine stress CMR. *JACC Cardiovasc Imaging*. 2011;4:161–172.
26. Korosoglou G, Elhmidi Y, Steen H, Schellberg D, Riedle N, Ahrens J, Lehrke S, Merten C, Lossnitzer D, Radeleff J, Zugck C, Giannitsis E, Katus HA. Prognostic value of high-dose dobutamine stress magnetic resonance imaging in 1,493 consecutive patients: assessment of myocardial wall motion and perfusion. *J Am Coll Cardiol*. 2010;56:1225–1234.
27. Krittayaphong R, Chaithiraphan V, Maneesai A, Udompanturak S. Prognostic value of combined magnetic resonance myocardial perfusion imaging and late gadolinium enhancement. *Int J Cardiovasc Imaging*. 2011;27:705–714.
28. Kuijpers D, van Dijkman PR, Janssen CH, Vliegenthart R, Zijlstra F, Oudkerk M. Dobutamine stress MRI, part II: risk stratification with dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. *Eur Radiol*. 2004;14:2046–2052.
29. Lo KY, Leung KF, Chu CM, Loke KL, Chan CK, Yue CS. Prognostic value of adenosine stress myocardial perfusion by cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease. *QJM*. 2011;104:425–432.
30. Pilz G, Jeske A, Klos M, Ali E, Hoefling B, Scheck R, Bernhardt P. Prognostic value of normal adenosine-stress cardiac magnetic resonance imaging. *Am J Cardiol*. 2008;101:1408–1412.
31. Steel K, Broderick R, Gandla V, Larose E, Resnic F, Jerosch-Herold M, Brown KA, Kwong RY. Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac

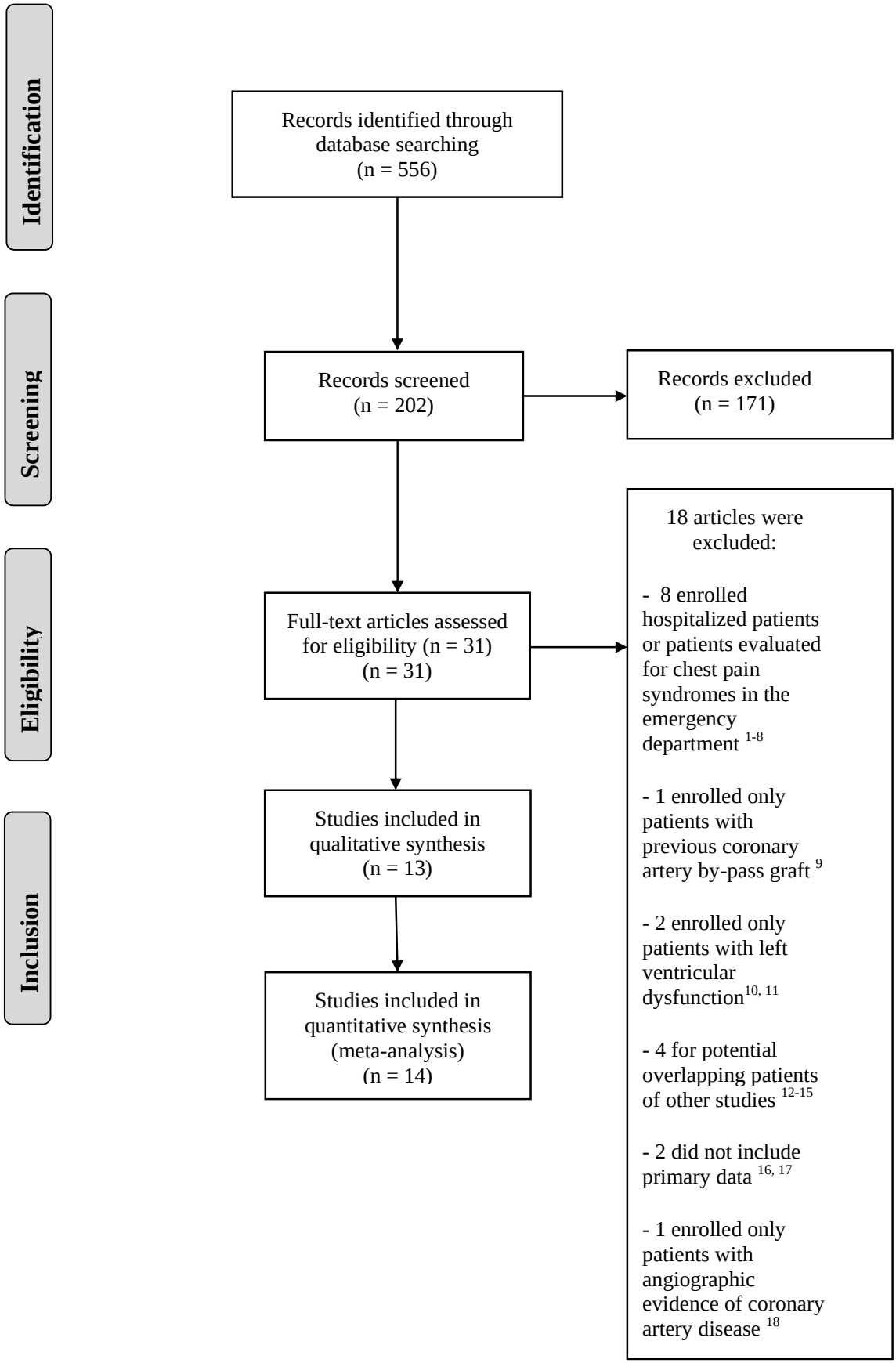
magnetic resonance in patients with known or suspected coronary artery disease. *Circulation*. 2009;120:1390–1400.
32. Wallace EL, Morgan TM, Walsh TF, Dall'Armellina E, Ntim W, Hamilton CA, Hundley WG. Dobutamine cardiac magnetic resonance results predict cardiac prognosis in women with known or suspected ischemic heart disease. *JACC Cardiovasc Imaging*. 2009;2:299–307.
33. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
34. Calnon DA, McGrath PD, Doss AL, Harrell FE Jr, Watson DD, Beller GA. Prognostic value of dobutamine stress technetium-99m-sestamibi single-photon emission computed tomography myocardial perfusion imaging: stratification of a high-risk population. *J Am Coll Cardiol*. 2001;38:1511–1517.
35. Navare SM, Mather JF, Shaw LJ, Fowler MS, Heller GV. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: a meta-analysis. *J Nucl Cardiol*. 2004;11:551–561.
36. Tavel ME. Stress testing in cardiac evaluation: current concepts with emphasis on the ECG. *Chest*. 2001;119:907–925.
37. Raman SV, Dickerson JA, Jekic M, Foster EL, Pennell ML, McCarthy B, Simonetti OP. Real-time cine and myocardial perfusion with treadmill exercise stress cardiovascular magnetic resonance in patients referred for stress SPECT. *J Cardiovasc Magn Reson*. 2010;12:41.
38. Gebker R, Jahnke C, Manka R, Hamdan A, Schnackenburg B, Fleck E, Paetsch I. Additional value of myocardial perfusion imaging during dobutamine stress magnetic resonance for the assessment of coronary artery disease. *Circ Cardiovasc Imaging*. 2008;1:122–130.
39. Flett AS, Westwood MA, Davies LC, Mathur A, Moon JC. The prognostic implications of cardiovascular magnetic resonance. *Circ Cardiovasc Imaging*. 2009;2:243–250.
40. Zemrak F, Petersen SE. Late gadolinium enhancement CMR predicts adverse cardiovascular outcomes and mortality in patients with coronary artery disease: systematic review and meta-analysis. *Prog Cardiovasc Dis*. 2011;54:215–229.
41. Mulherin SA, Miller WC. Spectrum bias or spectrum effect? Subgroup variation in diagnostic test evaluation. *Ann Intern Med*. 2002;137:598–602.
42. Schoenhagen P, Hachamovitch R. Evaluating the clinical impact of cardiovascular imaging: is a risk-based stratification paradigm relevant? *J Am Coll Cardiol*. 2013;61:185–186.
43. Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. *J Am Coll Cardiol*. 2006;47:1427–1432.
44. Prunier F, Brette S, Delépine S, Geslin P, Le Jeune JJ, Furber AP. Three-dimensional MRI assessment of regional wall stress after acute myocardial infarction predicts postdischarge cardiac events. *J Magn Reson Imaging*. 2008;27:516–521.

CLINICAL PERSPECTIVE

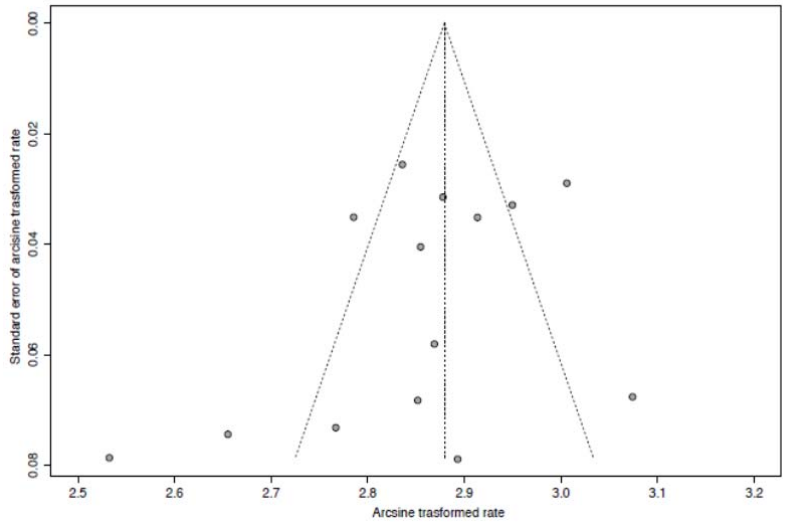
Prospective studies and meta-analyses have shown that cardiac magnetic resonance (CMR) stress testing has high diagnostic accuracy for the detection of coronary artery disease. However, the prognostic value of CMR has been evaluated only in single-center studies of relatively limited sample size. Our meta-analysis demonstrates that in subjects evaluated for known or suspected coronary artery disease, the absence of inducible ischemia on stress CMR predicts a low risk of cardiovascular events, only slightly higher than the background event rate observed in healthy low-risk individuals. Risk stratification is not influenced by the criterion used to define inducible ischemia with CMR (inducible perfusion defects versus inducible wall motion abnormalities). Furthermore, our findings indicate that late gadolinium enhancement provides additional prognostic stratification, suggesting the need for routine evaluation in combination with myocardial perfusion and wall motion during a stress CMR study. The results of our study reveal that stress CMR is a useful modality for prognostic evaluation in patients with known or suspected coronary artery disease. It is conceivable that the combination of perfusion and wall motion assessment together with late gadolinium enhancement might further increase the prognostic power, but this deserves further evaluation in large, prospective clinical trials.

SUPPLEMENTAL MATERIAL

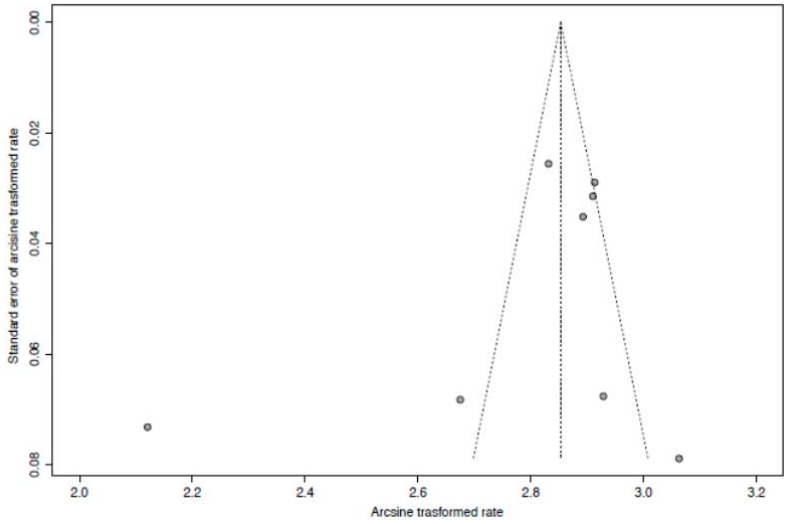
Supplemental Figure 1.



Supplemental Figure 2.



Supplemental Figure 3.



Supplemental Figure Legends

Supplemental Figure 1. Flow-chart of literature search.

Supplemental Figure 2. Funnel plot to assess publication bias for cardiac death and/or non-fatal myocardial infarction.

Supplemental Figure 3. Funnel plot to assess publication bias for coronary revascularization and/or admission for unstable angina.

Supplemental References

1. Bodi V, Sanchis J, Nunez J, Mainar L, Lopez-Lereu MP, Monmeneu JV, Rumiz E, Chaustre F, Trapero I, Husser O, Forteza MJ, Chorro FJ, Llacer A. Prognostic value of a comprehensive cardiac magnetic resonance assessment soon after a first st-segment elevation myocardial infarction. *JACC Cardiovasc Imaging*. 2009;2:835-842.
2. Eitel I, Desch S, de Waha S, Fuernau G, Gutberlet M, Schuler G, Thiele H. Long-term prognostic value of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *Heart*. 2011;97:2038-2045.
3. Hall ME, Miller CD, Hundley WG. Adenosine stress cardiovascular magnetic resonance-observation unit management of patients at intermediate risk for acute coronary syndrome: A possible strategy for reducing healthcare-related costs. *Curr Treat Options Cardiovasc Med*. 2012;14:117-125.
4. Hartlage G, Janik M, Anadiotis A, Veledar E, Oshinski J, Kremastinos D, Stillman A, Lerakis S. Prognostic value of adenosine stress cardiovascular magnetic resonance and dobutamine stress echocardiography in patients with low-risk chest pain. *Int J Cardiovasc Imaging*. 2011;28:803-812.
5. Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. *J Am Coll Cardiol*. 2006;47:1427-1432.
6. Lerakis S, McLean DS, Anadiotis AV, Janik M, Oshinski JN, Alexopoulos N, Zaragoza-Macias E, Veledar E, Stillman AE. Prognostic value of adenosine stress cardiovascular magnetic resonance in patients with low-risk chest pain. *J Cardiovasc Magn Reson*. 2009;11:37.
7. Miller CD, Hwang W, Case D, Hoekstra JW, Lefebvre C, Blumstein H, Hamilton CA, Harper EN, Hundley WG. Stress cmr imaging observation unit in the emergency department reduces 1-year medical care costs in patients with acute chest pain: A randomized study for comparison with inpatient care. *JACC Cardiovasc Imaging*. 2011;4:862-870.
8. Prunier F, Brette S, Delepine S, Geslin P, Le Jeune JJ, Furber AP. Three-dimensional mri assessment of regional wall stress after acute myocardial infarction predicts postdischarge cardiac events. *J Magn Reson Imaging*. 2008;27:516-521.
9. Klein C, Nagel E, Gebker R, Kelle S, Schnackenburg B, Graf K, Dreysse S, Fleck E. Magnetic resonance adenosine perfusion imaging in patients after coronary artery bypass graft surgery. *JACC Cardiovasc Imaging*. 2009;2:437-445.
10. Dall'Armellina E, Morgan TM, Mandapaka S, Ntim W, Carr JJ, Hamilton CA, Hoyle J, Clark H, Clark P, Link KM, Case D, Hundley WG. Prediction of cardiac events in patients with reduced left ventricular ejection fraction with dobutamine cardiovascular

magnetic resonance assessment of wall motion score index. *J Am Coll Cardiol*. 2008;52:279-286.
11. Tsukiji M, Nguyen P, Narayan G, Hellinger J, Chan F, Herfkens R, Pauly JM, McConnell MV, Yang PC. Peri-infarct ischemia determined by cardiovascular magnetic resonance evaluation of myocardial viability and stress perfusion predicts future cardiovascular events in patients with severe ischemic cardiomyopathy. *J Cardiovasc Magn Reson*. 2006;8:773-779.
12. Bodi V, Sanchis J, Lopez-Lereu MP, Nunez J, Mainar L, Monmeneu JV, Husser O, Dominguez E, Chorro FJ, Llacer A. Prognostic value of dipyridamole stress cardiovascular magnetic resonance imaging in patients with known or suspected coronary artery disease. *J Am Coll Cardiol*. 2007;50:1174-1179.
13. Bodi V, Sanchis J, Lopez-Lereu MP, Nunez J, Mainar L, Monmeneu JV, Ruiz V, Rumiz E, Husser O, Moratal D, Millet J, Chorro FJ, Llacer A. Prognostic and therapeutic implications of dipyridamole stress cardiovascular magnetic resonance on the basis of the ischaemic cascade. *Heart*. 2009;95:49-55.
14. Kelle S, Egnell C, Vierecke J, Chiribiri A, Vogel S, Fleck E, Nagel E. Prognostic value of negative dobutamine-stress cardiac magnetic resonance imaging. *Med Sci Monit*. 2009;15:MT131-136.
15. Korosoglou G, Gitsioudis G, Voss A, Lehrke S, Riedle N, Buss SJ, Zugck C, Giannitsis E, Osman NF, Katus HA. Strain-encoded cardiac magnetic resonance during high-dose dobutamine stress testing for the estimation of cardiac outcomes: Comparison to clinical parameters and conventional wall motion readings. *J Am Coll Cardiol*. 2011;58:1140-1149.
16. Jahnke C, Furundzija V, Gebker R, Manka R, Frick M, Schnackenburg B, Marx N, Paetsch I. Gender-based prognostic value of pharmacological cardiac magnetic resonance stress testing: Head-to-head comparison of adenosine perfusion and dobutamine wall motion imaging. *Int J Cardiovasc Imaging*. 2011;28:1087-1098.
17. Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: Adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation*. 2007;115:1769-1776.
18. Doesch C, Seeger A, Doering J, Herdeg C, Burgstahler C, Claussen CD, Gawaz M, Miller S, May AE. Risk stratification by adenosine stress cardiac magnetic resonance in patients with coronary artery stenoses of intermediate angiographic severity. *JACC Cardiovasc Imaging*. 2009;2:424-433.