Diagnostic and Prognostic Value of Stress CMR Imaging in Patients with Known or Suspected Coronary Artery Disease: a Twenty-Year Meta-Analysis

Running title: Stress CMR in Stable Chest Pain

Fabrizio Ricci MD, PhD, MSc[a,b,c], Mohammed Y Khanji MBBCh, PhD[c,d,e], Giandomenico Bisaccia MD[a], Alberto Cipriani, MD[f], Annamaria Di Cesare, MD[g], Laura Ceriello, MD[a], Cesare Mantini, MD, PhD[a], Marco Zimarino, MD, PhD[a], Artur Fedorowski, MD, PhD[b,h], Sabina Gallina MD, PhD[a], Steffen E Petersen MD, DPhil, MSc, MPH[d,e, i,j], Chiara Bucciarelli-Ducci MD, PhD[k,l*]

[a] Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy; giandomenico.bisaccia@unich.it; sabina.gallina@unich.it; lauraceriello@libero.it; cesare.mantini@gmail.com; m.zimarino@unich.it; fabrizio.ricci@unich.it

[b] Department of Clinical Sciences, Lund University, 214 28 Malmö, Sweden

[c] William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University London, Charterhouse Square, London, EC1M 6BQ, UK; m.khanji@qmul.ac.uk; s.e.petersen@qmul.ac.uk

[d] Newham University Hospital, Glen Road, Plaistow, Barts Health NHS Trust. London E13 8SL, UK

[e] Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, West Smithfield, EC1A 7BE, London, UK;

[f] Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padova, Italy; alberto.cipriani@unipd.it

[g] U.O. Cardiologia, Ospedale di Rimini, AUSL della Romagna, Italy; annamaria.dicesare@auslromagna.it

[g] Department of Clinical Sciences, Lund University, 214 28 Malmö, Sweden

[h] Department of Cardiology, Karolinska University Hospital, and Department of Medicine, Karolinska Institute, Stockholm, Sweden; artur.fedorowski@ki.se

[i] The Alan Turing Institute, London, UK

[j] Health Data Research UK, London, UK

[k] Royal Brompton and Harefield Hospitals, Guys and St Thomas NHS Trust London, United Kingdom of Great Britain & Northern Ireland; c.bucciarelli-ducci@rbht.nhs.uk

[l] School of Biomedical Engineering and Imaging Sciences, Faculty of Life Sciences and Medicine, Kings College London, United Kingdom

**** Corresponding author -*** Royal Brompton Hospital, Sydney Street, London, SW3 6NP, United Kingdom **-** E-mail address: c.bucciarelli-ducci@rbht.nhs.uk

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KEY POINTS

QUESTION

What is the diagnostic and prognostic value of stress CMR imaging for the evaluation of stable chest pain?

FINDINGS

In the largest contemporary meta-analysis pooling more than 65,000 patients and 381,357 person-years of follow-up, stress CMR yields high diagnostic accuracy and effective risk stratification in patients with known or suspected CAD, particularly with 3-Tesla imaging.

MEANING

Combined assessment of inducible myocardial ischemia and LGE by stress CMR imaging is a highly effective pathway to diagnose and risk stratify patients with stable chest pain. Normal stress CMR is associated with low risk of cardiovascular events for at least 3.5 years.

Abstract

Importance: Clinical utility of stress cardiovascular magnetic resonance (CMR) in stable chest pain is still debated and low-risk period for adverse events following a negative test is unknown.

Objective: To provide contemporary quantitative data synthesis of diagnostic accuracy and prognostic value of stress CMR in stable chest pain.

Data Sources: We searched PubMed, Embase, Cochrane and PROSPERO databases, and Clinical Trials Registry for potentially relevant articles.

Study Selection: CMR studies reporting estimates of diagnostic accuracy and/or raw data of adverse cardiovascular events for participants with either positive or negative stress CMR.

Data Extraction and Synthesis: This meta-analysis was planned, conducted, and reported in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Two reviewers extracted data and assessed the risk of bias.

Main Outcomes and Measures: Diagnostic odds ratio (DOR), sensitivity, specificity, area under the curve (AUC), odds ratios (ORs) and annualized event rates (AERs) for all-cause death, cardiovascular death, and major adverse cardiac events (MACE) defined as the composite of myocardial infarction and cardiovascular death.

Results: We identified 33 diagnostic studies pooling 7,815 individuals and 31 prognostic studies pooling 67,080 patients (mean follow-up: 3.5 years/381,357 person-years). Stress CMR yielded a DOR of 26.4 (95%CI:10.6-65.9), a sensitivity of 81% (95%CI:68-89%), a specificity of 86% (95%CI:75-93%), and an AUC of 0.84 (95%CI:0.77-0.89) for the detection of functionally obstructive CAD. In subgroup analysis, stress CMR yielded higher diagnostic accuracy in the setting of suspected CAD (DOR=53.4) or when using 3-Tesla

imaging (DOR=33.2). Presence of stress-inducible ischemia was associated with higher all-cause mortality (OR:2.0;95%CI:1.7-2.3), cardiovascular mortality (OR:6.4;95%CI:4.5-9.1), and increased risk of MACE (OR:5.3;95%CI:4.0-7.0). Presence of late gadolinium enhancement (LGE) was associated with higher all-cause mortality (OR 2.22; 95%CI:1.99-2.47), cardiovascular mortality (OR 6.03; 95%CI:2.76-13.13), and increased risk of MACE (5.42; 95%CI:3.42-8.6). After a negative test, pooled AERs for cardiovascular mortality and MACE remained <1%.

Conclusion and Relevance: Stress CMR yields high diagnostic accuracy and delivers robust prognostication, particularly with 3-Tesla scanners. While both inducible myocardial ischemia and LGE portend excess mortality and increased risk of MACE, normal stress CMR is associated with low risk of cardiovascular events for at least 3.5 years.

Keywords: stress CMR, ischemia, diagnostic accuracy, prognosis, chest pain, meta-analysis.

Non-standard Abbreviations and Acronyms

AER	Annualized event rate
AUC	Area under the receiver operating characteristic curve
CMR	Cardiovascular magnetic resonance
DAN-NICAD	Danish Study of Non-Invasive Diagnostic Testing in Coronary Artery Disease
DOR	Diagnostic odds ratio
FFR	Fractional flow reserve
ICA	Invasive coronary angiography
LGE	Late gadolinium enhancement
MACE	Major adverse cardiovascular events
MR-IMPACT II	The Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease
MR-INFORM	The Myocardial Perfusion CMR versus Angiography and FFR to Guide the Management of Patients with Stable Coronary Artery Disease
nLR	Negative likelihood ratio
pLR	Positive likelihood ratio
SPINS	Stress CMR Perfusion Imaging in the United States)

Introduction

Coronary artery disease (CAD) is the leading cause of cardiovascular morbidity and mortality worldwide. Non-invasive imaging plays a central role in the recent 2019 European Society of Cardiology guidelines on chronic coronary syndromes and in the 2021 AHA/ACC guidelines on chest pain. Evaluation of inducible myocardial ischemia by assessment of perfusion reserve or regional wall motion abnormalities is a key element in the diagnostic work-up of patients with stable chest pain and an intermediate-to-high pre-test probability of CAD[1,2].

New recommendations for the use of non-invasive imaging in coronary syndromes developed by a transatlantic intersociety task force endorse the use of stress cardiovascular magnetic resonance (CMR) to detect ischemia and guide clinical decision-making in patients with high intermediate pre-test clinical likelihood of CAD[3]. Consistently, the 2021 American College of Cardiology and American Heart Association guidelines for the evaluation and diagnosis of chest pain delivered Class I and IIa recommendations for stress CMR as a first-line functional investigation for evaluation of chest pain in intermediate-risk patients with known or suspected CAD[4].

CAD is one of the primary indications for CMR[5,6] and utilization of stress CMR has been steadily growing worldwide[6]. However, contemporary data on the diagnostic accuracy and prognostic value of stress CMR in patients with known or suspected CAD is currently lacking. After twenty years of clinical use and the recent completion of large multicenter observational studies[7,8] and randomized clinical trials[9,10], which were not included in previous systematic reviews and meta-analyses[11-14], we have appraised the best available contemporary evidence to deliver the most updated quantitative synthesis on diagnostic accuracy and prognostic value of stress CMR for the assessment of chest pain.

Methods

This systematic review and meta-analysis was planned, conducted, and reported according to the PRISMA statement for design, analysis, and reporting of meta-analyses of randomized and observational studies[15] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[16]. A review protocol was prospectively registered on PROSPERO (CRD42022299275).

Systematic review

We searched PubMed and Embase databases, the Cochrane Database of Systematic Reviews, PROSPERO database (www.crd.york.ac.uk/prospero), and Clinical Trials Registry (www.clinicaltrials.gov) from January 2000 through December 2021 (**Figure 1**). We used two pre-specified combinations of keywords related to diagnostic accuracy and prognostic significance of stress CMR (**eMethods**). We also searched reference lists of all identified articles for additional relevant studies, including hand-searching reviews and published meta-analyses. Two authors (G.B., A.D.C.) performed the screening of titles and abstracts, reviewed full-text articles, and determined their eligibility. Discrepancies were resolved by consensus with other reviewers (F.R., M.Y.K., A.C.). The review process was not blinded to study results. Studies were eligible if they met the following criteria: (i) published as full-length article; (ii) English language; (iii) prospective or retrospective study design; (iv) enrolling ≥100 patients aged ≥18 years; (v) reporting estimates of diagnostic accuracy of stress CMR compared with invasive coronary angiography (ICA) or fractional flow reserve (FFR) as reference test, and/or raw data about all-cause death, CV death, and major adverse cardiovascular events (MACE, defined as composite of CV death and myocardial infarction) for study participants with either positive or negative stress CMR scans. Studies were eligible regardless of whether they were referred for suspected or known CAD and regardless of the

technique used for evaluation of inducible ischemia: wall motion analysis, perfusion (qualitative, semiquantitative, fully quantitative). Two investigators (G.B., A.D.C.) abstracted relevant data of patient populations, study-level characteristics, and outcomes from original eligible sources. The ascertainment of clinical events was accepted as reported. The quality of eligible studies was evaluated by QUADAS-2 tool[17] and Newcastle-Ottawa Scale[18] for diagnostic and prognostic studies, respectively.

Statistical analysis

Categorical variables were reported as percentages, and continuous variables as means and standard deviation or medians and interquartile range, as appropriate. We used the inverse variance heterogeneity model for the meta-analysis of diagnostic studies, which proved superior to the standard bivariate model[19]. For each study, raw data of true positives, true negatives, false positives, and false negatives were either extracted from the study or generated from reported diagnostic estimates. Diagnostic odds ratio (DOR), area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, negative (nLR) and positive likelihood ratios (pLR) were calculated. A ROC plot was used to summarize study-level findings. Pooled estimates of sensitivity and specificity for stress CMR derived from the meta-analysis were used to generate a leaf plot illustrating the relationship between pre-test and post-test probability of CAD. In the prognostic meta-analysis, summary effect sizes for all-cause death, CV death, and myocardial infarction have been calculated primarily for presence or absence of inducible ischemia, and additionally for late gadolinium enhancement (LGE). A random-effects model was used, and study-specific odds ratios (ORs) were pooled using the Mantel–Haenszel method for each study outcome. The Hartung-Knapp adjustment[20] was applied to all analyses except for those with ≤3 studies per group. Average effects were not calculated for outcomes reported by less than 3 studies. Inter-study

heterogeneity was assessed by I^2 statistic and represented as Baujat plot[21]. Significant heterogeneity was considered for $I^2 \geq 50\%$. The z-statistic was computed for each endpoint of interest, and the results were considered statistically significant at a $p<0.05$. Meta-analysis results were presented by classic forest plots with point estimates of the effect size and 95%CIs, with square area indicating study weight. A Jackknife sensitivity analysis was performed for each outcome to evaluate the robustness of the results and the impact of every single study on the summary estimate of effect. The likelihood of publication bias was assessed using funnel plots by displaying individual study OR with 95%CIs for the endpoints of interest, with the addition of the non-parametric 'trim-and-fill' procedure to adjust for funnel plot asymmetry by generating hypothetical missing studies; for all models including more than 10 studies, funnel plot asymmetry was also evaluated by tests proposed by Deeks[22] and Egger[23] for diagnostic and prognostic studies, respectively ($p<0.10$ indicative of significant publication bias). Subgroup analyses were performed to investigate possible sources of heterogeneity and to assess the effect of selected variables, including sample size, sex, CAD prevalence, thresholds of diameter stenosis, year of publication, magnetic field strength, and stressor agent. Annualized event rates (AERs) for studies were calculated by dividing the number of events by the follow-up duration. The low-risk period was defined as the mean time interval the patient group with a negative test remained below the threshold of 1% cumulative MACE rate[24]. All statistical analyses were performed using R version 4.1.0. (R packages and functions are detailed in **eMethods**).

Results

Of 3,144 citations identified and retrieved for title and abstract evaluation, we reviewed full-text of 237 potentially relevant articles and finally included 33 diagnostic studies and 31 prognostic studies, published between 2002 and 2021 (**Figure 1**). Study-level prevalence of CAD ranged between 11% and 83% in diagnostic studies. Mean follow-up was 3.5 years (range 0.9 to 8.8) for a total of 381,357 person-years. The overall quality of included studies was high (**eFigure 1, eTable 3**). Main characteristics of studies included in the diagnostic and prognostic meta-analyses are summarized in **eTable 1** and **eTable 2**.

Diagnostic Meta-Analysis

Stress CMR vs ICA

Diagnostic accuracy of stress CMR compared with ICA as the reference test was reported in 30 studies[8,10,25-52], pooling 7,496 symptomatic patients with known (n=537) or suspected CAD (n=2825).

On a per-patient analysis, stress CMR yielded a pooled DOR of 19.1 (95%CI:12.6-29.1), a sensitivity of 84% (95%CI:79-88%), a specificity of 79% (95%CI:73-84%), a pLR of 4.0 (95%CI:3.0-5.3), a nLR of 0.21 (95%CI:0.2-0.3), and AUC of 0.81 (95%CI:0.78-0.84) for the detection of anatomically obstructive CAD (**Figure 2**).

On a per-vessel analysis, stress CMR yielded pooled DOR of 21.0 (95%CI:10.2-43.4), sensitivity of 72% (95%CI:61-81%), specificity of 89% (95%CI:82-94%), pLR of 6.7 (95%CI:3.8-11.8), nLR of 0.3 (95%CI:0.2-0.5), and AUC of 0.82 (95%CI:0.76-0.87).

Stress CMR vs invasive FFR

Diagnostic accuracy of stress CMR compared with invasive FFR as the reference test was reported in 8 studies[10,27,37,44,45,53-55], pooling 1,196 symptomatic patients with known (n=354)

or suspected (n=593) CAD. On per-patient analysis, stress CMR yielded pooled DOR of 26.4 (95%CI:10.6-65.9), sensitivity of 81% (95%CI:68-89), specificity of 86% (95%CI:75-93%), a pLR of 5.8 (95%CI:3.0-11.4), nLR of 0.2 (95%CI:0.1-0.4), and AUC of 0.84 (0.77-0.89) for detection of functionally obstructive CAD (**Figure 2**). On per-vessel analysis, stress CMR yielded pooled DOR of 24.1 (95%CI:5.5-105.4), sensitivity of 70% (95%CI:46-86%), specificity of 91% (95%CI:74-97%), pLR of 8.0 (95%CI:2.4-26.5), nLR of 0.3 (95%CI:0.1-0.8), and AUC of 0.83 (95%CI:0.70-0.91).

Prognostic Meta-Analysis

All-cause mortality

A total of 11 studies[56-66] pooling 51,166 individuals reported all-cause mortality. Presence of inducible ischemia was associated with two-fold increased mortality (OR 2.0; 95%CI:1.7-2.3, p<0.005; **Figure 3A**). Presence of LGE was associated with two-fold increased mortality (OR 2.22; 95%CI:1.99-2.47, p<0.001; **Figure 4A**). Pooled AERs for all-cause mortality in patients with and without inducible ischemia were respectively 3.0% and 1.4% (p<0.0001; **Figure 5A**). Pooled AERs for all-cause mortality in patients with and without LGE were respectively 4.5% and 2.3% (p<0.0001; **Figure 5A**).

Cardiovascular mortality

A total of 14 studies[62,64,66-77] pooling 12,252 individuals reported CV mortality data Presence of inducible ischemia detected by stress CMR was associated with six-fold increased CV mortality (OR 6.4 95%CI:4.5-9.1, p<0.0001; **Figure 3B**). Presence of LGE was associated with six-fold increased CV mortality (OR 6.03; 95%CI:2.76-13.13, p<0.001; **Figure 4B**). Pooled AERs for CV death in patients with and without inducible ischemia were respectively 2.5% and 0.6% (p<0.0001; **Figure 5A**). Pooled AERs for CV mortality in patients with and

245 without LGE were respectively 2.51% and 0.71% (p<0.0001; **Figure 5A**).

246

247 ***MACE***

248 A total of 22 studies[7,25,59,60,64,66-69,72-84] pooling 17,084 individuals reported MACE data.
249 Presence of inducible ischemia was associated with five-fold increased risk of incident
250 MACE (OR 5.3 95%CI:4.0-7.0, p<0.000; **Figure 3C**). Presence of LGE was associated with
251 five-fold increased risk of MACE (OR 5.42; 95%CI:3.42-8.6, p<0.001; **Figure 4C**). Pooled
252 AERs for MACE in patients with and without ischemia were respectively 4.3% and 1.0%
253 (p<0.0001; **Figure 5A**). Pooled AERs for MACE in patients with and without LGE were
254 respectively 2.9% and 0.78%, p<0.0001; **Figure 5A**). Combining ischemia and LGE
255 information, we documented the highest AER when both present and the lowest AER when
256 both absent (**Figure 5B**). At mean follow-up of 3.5 years, normal stress CMR, featuring
257 absence of inducible ischemia and no LGE, was associated with a pooled AER of 0.58%,
258 whilst the presence of ischemia and LGE yielded a pooled AER of 4.24%.

259

260 ***Assessment of study quality and publication bias***

261 According to QUADAS-2 tool, risk of bias was low in 29 of 33 diagnostic studies **(eFigure**
262 **3**). Of 31 prognostic studies, 15 studies scored 9 stars, and 16 studies scored 8 stars according
263 to the Newcastle-Ottawa Scale (**eTable 3**). In ICA studies, Deeks' test ruled-out small-study
264 bias and publication bias (p=0.34) (**eFigure 2**). Deeks' test was not performed in FFR studies
265 since the number of studies was insufficient. With regards to prognostic studies, we ruled-out
266 publication bias by visual inspection of funnel plots and Egger's test of intercept that was
267 non-significant for each outcome (**eFigure 3**).

Subgroup analysis

Results are summarized in **eTables 4, 5**. Stress CMR demonstrated higher diagnostic performance for detection of anatomically and functionally obstructive CAD in two scenarios: suspected CAD and 3-Tesla. In FFR studies, higher diagnostic accuracy was observed in women or when lowering FFR cut point to 0.75. In ICA studies, quantitative assessment yielded higher DOR and specificity compared with visual assessment, and dipyridamole achieved overall higher accuracy compared with adenosine.

Sensitivity analysis

Two diagnostic studies[10,85] were visually and quantitatively identified as outliers in the ICA analysis (**eFigure 2**). Removal of the two outliers increased diagnostic accuracy with a pooled DOR of 25.2 (**eFigure 4**). In the FFR analysis, removal of the single outlier[10] improved diagnostic summary estimates, attaining a pooled DOR of 41.3 (**eFigure 5**). No single prognostic study affected the pooled OR for each endpoint of interest.

Discussion

The current analysis covers the last 20 years of clinical research in the field of stress CMR imaging using state-of-the-art statistical methods for quantitative data synthesis. We provide the largest summary evidence available by pooling more than 65,000 patients and 381,357 person-years of follow-up and reaffirming that stress CMR imaging yields high diagnostic accuracy, robust cardiac prognostication, and effective risk stratification in patients with stable chest pain and known or suspected CAD. Our analysis was focused on symptomatic patients, in line with current international guidelines indications on deferring or eliminating unnecessary testing when the diagnostic yield is low or in asymptomatic individuals[1,86].

Stress CMR delivers high diagnostic accuracy consistently across multiple clinical scenarios and time trend analysis. This is even more evident for detecting functionally obstructive lesions assessed by FFR, which has been shown to provide optimum balance between myocardial revascularization and medical treatment in the FAME trials[87,88]. In addition to previous meta-analyses[89,90], our findings build on supporting better diagnostic performance of stress CMR in the setting of suspected CAD, or when using 3-Tesla imaging, due to improved contrast resolution[91-93], and quantitative perfusion assessment, which can be advantageous to better identify disease extent or peri-infarct ischemia than visual assessment alone in multivessel CAD, detect microvascular disease and verify stress adequacy[94]. The signal of dipyridamole outperforming adenosine studies is intriguing and possibly reflecting the incremental diagnostic value of combined perfusion and wall motion assessment[76]. This requires careful interpretation and prospective verification in regadenoson studies and needs to be weighed against the cost, potential tolerability, and effectiveness of the stressor agents[95].

In our diagnostic meta-analysis, two studies were identified as outliers that

showed a lower-than-average diagnostic yield of stress CMR. The Dan-NICAD randomized clinical trial[10] enrolled patients with low-to-intermediate pre-test probability of CAD and an abnormal CCTA scan prior to CMR testing and found low sensitivity for second-line perfusion investigations. However, the specific study design could have led to selection bias and potentially impacted diagnostic estimates[96]. The MR-IMPACT II study[85] compared stress CMR and SPECT in a population with intermediate CAD prevalence (49%), but also a fairly high number of patients with prior MI (27%), in whom it can be more difficult to discriminate myocardial scarring and residual ischemia, and with expected higher prevalence of microvascular disease inflating the number of false positive findings. This multicenter study enrolling from 33 different institutions aimed to frame a realistic clinical environment not restricted to high-volume leading centers. In both studies, measurements were performed by an independent core laboratory with readers fully blinded to additional patient information and results, limiting the bias of the clinical context when reporting stress CMR studies.

When interpreting these findings, we should remember that myocardial ischemia exists as a continuum and binary categorizations have inherent limitations. Furthermore, shortcomings in the accuracy of established invasive gold standards must be carefully considered. Notably, FFR was firstly calibrated against non-invasive tests[97], including bicycle exercise testing, thallium scintigraphy, stress echocardiography with dobutamine, which were, themselves, validated against ICA as the reference test, falling into a challenging circular thinking[98,99]. An FFR threshold of ≤0.80 has been adopted into clinical practice guidelines as an actionable value to guide revascularization, despite robust evidence supporting larger treatment benefit at lower FFR values[100,101] and our findings indicating better agreement with an FFR threshold of 0.75.

More recently, the MR-INFORM trial randomized 918 symptomatic patients at high pre-test probability of CAD to undergo ICA plus FFR versus stress CMR-guided

care[9]. MACE rate and percentage of patients free from angina were similar for both strategies at 1-year, yet the use of stress CMR was associated with a noticeably lower incidence of downstream ICA and coronary revascularization than was the use of FFR. Similar findings have been reported in the setting of low-risk acute coronary syndromes by a network meta-analysis of diagnostic randomized controlled trials demonstrating how stress CMR was associated with fewer referrals to downstream ICA than coronary CT angiography or other non-invasive imaging modalities, and without obvious impact on subsequent risk of myocardial infarction[102].

This evidence translates into the uniquely favorable cost-effective profile of stress CMR imaging compared to its relevant comparators[103]. According to a cost-effectiveness analysis comparing different first-line diagnostic pathways for stable chest pain and a decision-analytic model to estimate lifetime health care costs and quality-adjusted life-years derived from the multicenter SPINS study, stress CMR strongly dominated SPECT and coronary CT angiography strategies either when considering all MACE or hard events alone[104]. Thus, having access to CMR is a win situation for patients and can lead to significant cost savings by reducing the need for additional, unnecessary tests and revascularization procedures[105,106].

The prognostic value of non-invasive cardiac investigations has been the objective of a previous meta-analysis raising the possibility of clinical equipoise for prediction of CV death and myocardial infarction [13]. While the message that any negative test conveys excellent prognosis is reassuring and challenges need for further downstream testing, post-test probability of disease needs adjustment for baseline population event risk and should always be carefully interpreted in the context of pre-test probability, prevalence of disease and according to the clinical scenario. In our analysis, the presence of inducible ischemia by stress CMR was a robust predictor of increased mortality and risk of MACE, further

heightened by the presence of LGE. Conversely, normal stress CMR was associated with very low incidence of adverse cardiovascular events, yielding a low-risk post-test period of at least 3.5 years. Our data echoes the results of previous meta-analyses[107,108] and of the Euro-CMR registry[5], where patients with suspected CAD and a negative stress CMR experienced an AER for hard cardiovascular endpoints of less than 1%.

Ultimately, the prognostic value of stress CMR, either performed with vasodilators or dobutamine, is incremental to traditional risk factors[66,81]. Further studies are needed to establish the optimal CMR method for absolute quantification of myocardial blood flow and the optimal ischemic threshold associated with larger treatment effect, as a tipping point useful to identify patients who would most benefit from myocardial revascularization versus safe deferral.

Strengths and limitations

We summarized the largest evidence available making use of the best methods for quantitative synthesis and provided robust estimates on the diagnostic and prognostic value of stress CMR. We provide new information on the duration of low-risk period for MACE following a normal stress CMR. This knowledge has the potential to inform future clinical guidelines about ideal time intervals for repeat imaging and to provide useful guidance to subsequent management of symptomatic patients with initial normal imaging results or subclinical disease[109]. Results of subgroup analyses also suggest better diagnostic performance of stress CMR in the setting of suspected CAD, especially when using 3-Tesla imaging and fully quantitative approaches. We acknowledge a few limitations. Firstly, we did not compare the yield of stress CMR to other imaging modalities as it was beyond the scope of the current work, and literature specifically addressing these topics already exist [110-112]. Secondly, our results are mostly derived from observational studies reflecting different

guideline recommendations across two decades of practice. Within this timespan, thresholds for coronary stenosis have changed[113], methods for estimation of pre-test probabilities of obstructive CAD have been updated and recalibrated[1,86], and CMR protocols have been implemented with quantitative perfusion assessment[61], new tools for evaluation of stress adequacy[114-116], more widespread use of regadenoson[117], and other disruptive technical innovations[118-120]. Finally, we recognize lack of information about medical therapy, completeness of myocardial revascularization, extent of inducible ischemia, degree of myocardial fibrosis, and prevalence of microvascular dysfunction. Despite intrinsic challenges and limitations of study-level meta-analysis, including limited adjustment for confounding factors and ecological fallacy, we attempted to synthesize the results in a robust manner addressing potential bias.

Conclusions

In patients with stable chest pain and known or suspected CAD, stress CMR yields high diagnostic accuracy to detect both anatomically and functionally significant CAD, with 3-Tesla and quantitative perfusion approaches delivering higher diagnostic performance. Stress CMR provides also robust prognostic information and effective risk stratification. While presence of ischemia and LGE portend higher CV risk and mortality, normal stress CMR is associated with very low risk of MACE for at least 3.5 years.

401 **Contributors**

402 FR, GB, MYK, CBD had full access to all the data in the study and take responsibility of the
403 data and accuracy of the data analysis. FR, AC, LC, ADC, AF contributed to the study concept
404 and design. FR, GBD, LC, AC, ADC contributed to the acquisition of data. All authors
405 analyzed and interpreted the data. SG was the study supervisor. GBD and FR did the statistical
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407 from all co-authors. FR, GB, MYK, AF, SEP and CBD contributed to the revision process with
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417

418 **Supplemental Materials**

419 eMethods
420 eFigures 1-5
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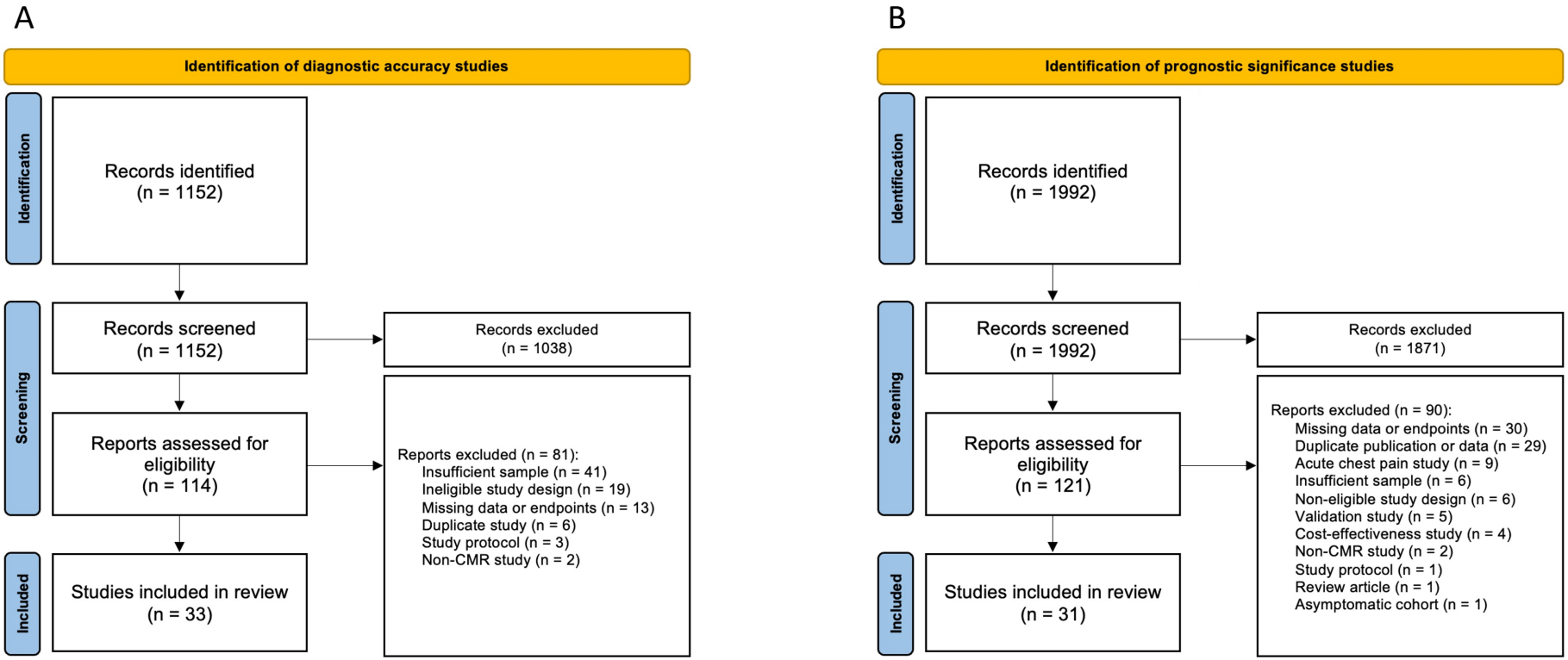
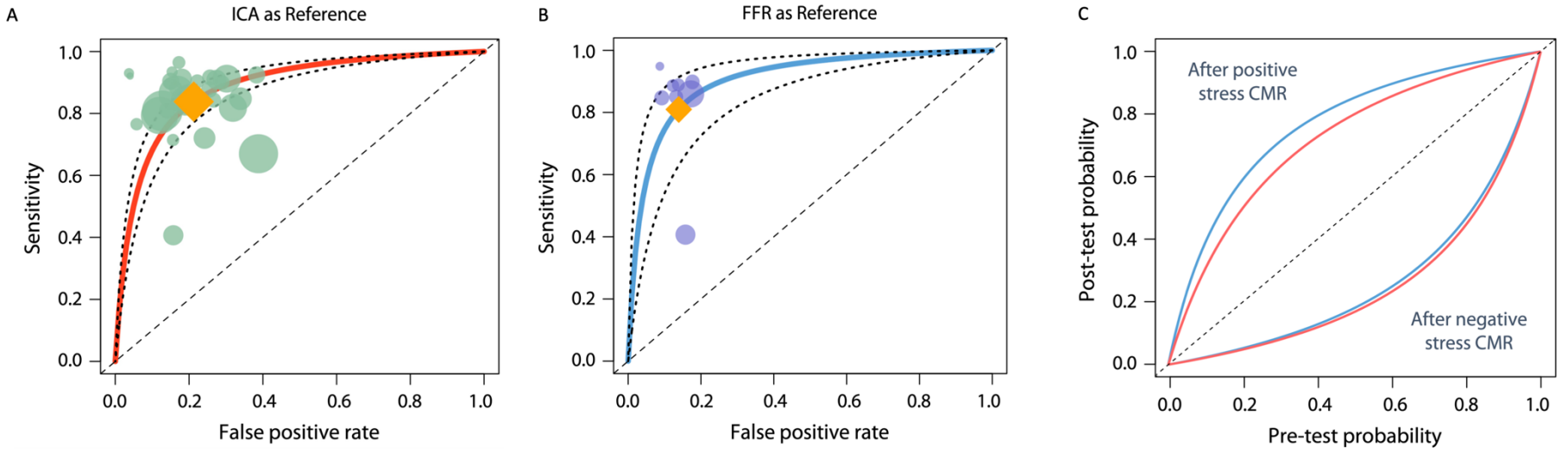
Figure 1 - PRISMA 2020 diagrams of search results.



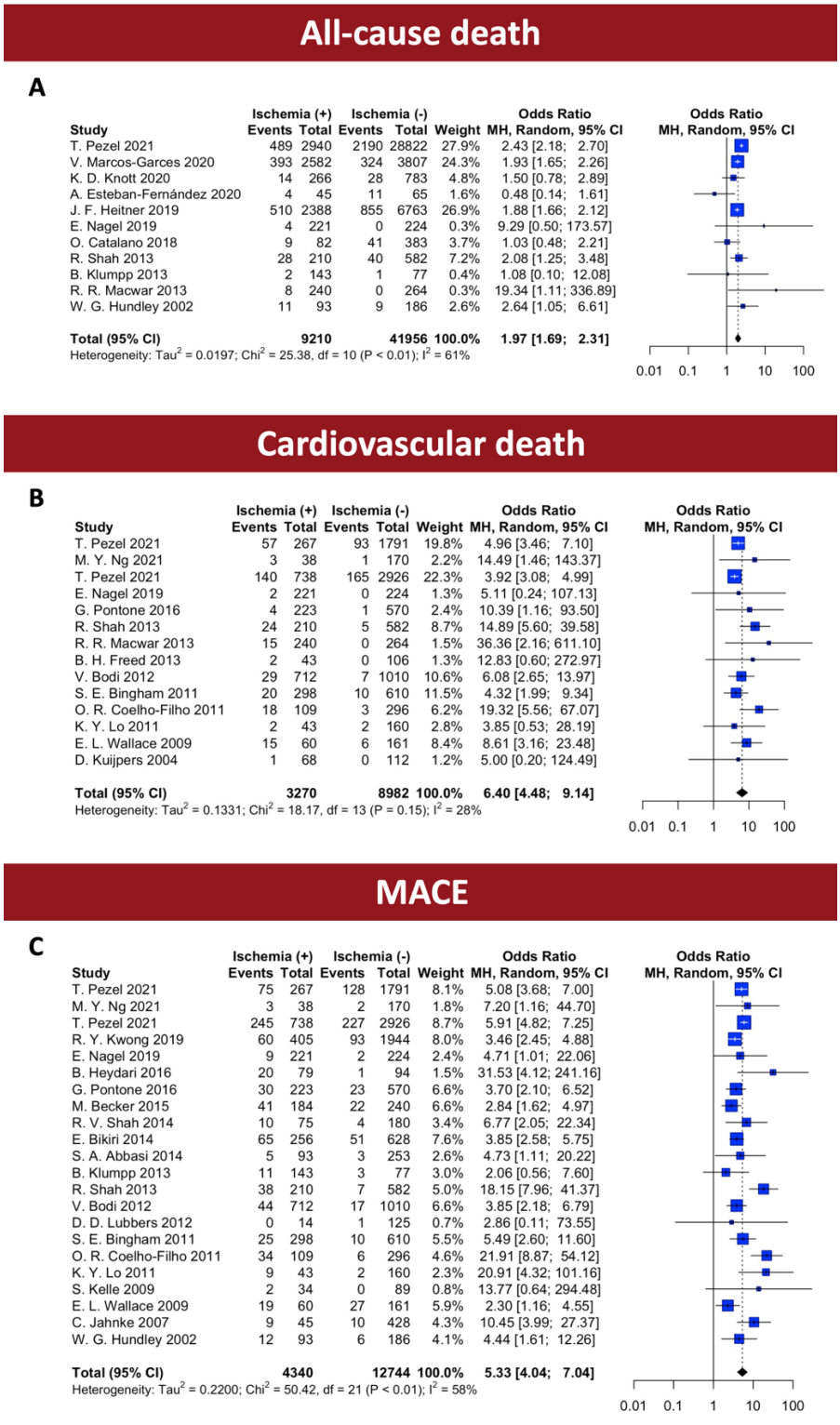
Flow chart of search results for (A) diagnostic and (B) prognostic studies.

Figure 2 - Diagnostic yield of stress CMR in stable chest pain.



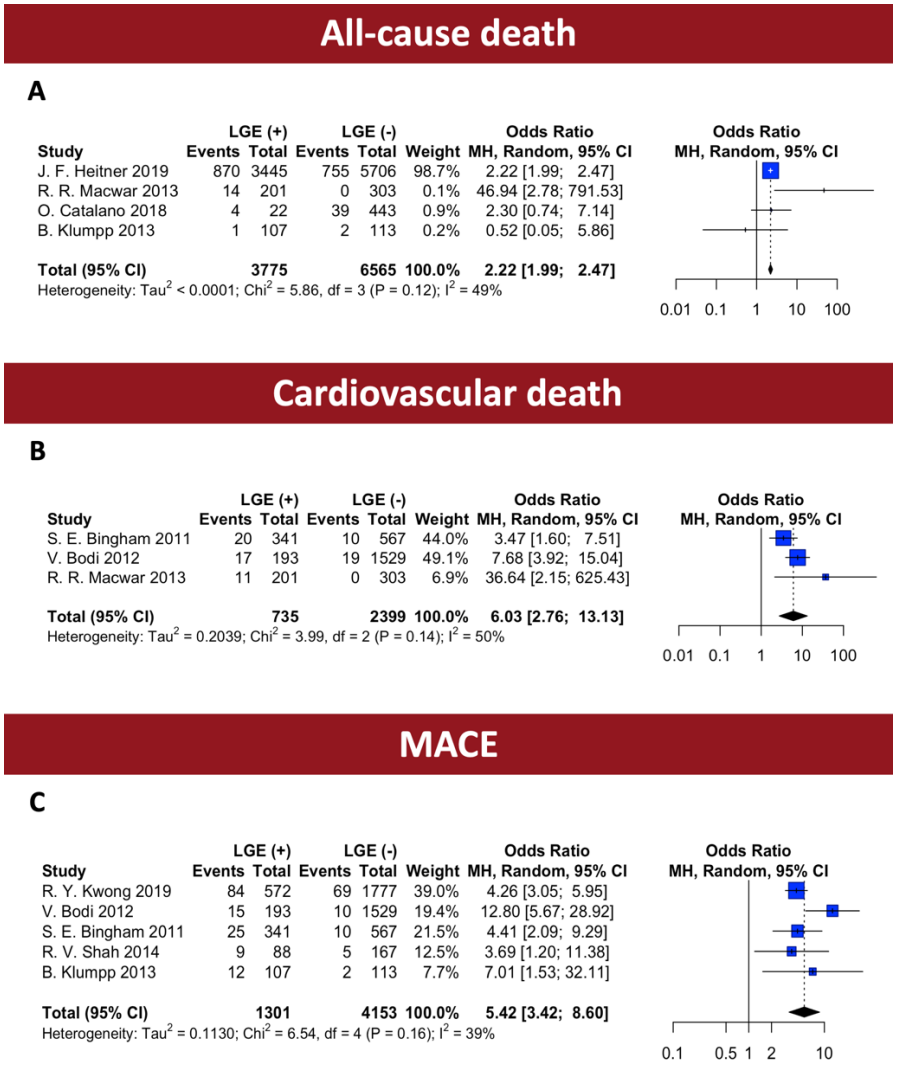
Plot of summary receiver operating curve characteristic of stress CMR compared with ICA (A) or FFR (B) as reference. The receiver operator characteristic curve provides a graphical display of diagnostic accuracy by plotting false positive rate (or 1-specificity) in the horizontal axis and sensitivity in the vertical axis. (C) Leaf plot illustrating the relationship between pre-test and post-test probability of CAD based on pooled estimates of sensitivity and specificity for stress CMR with ICA (red) or FFR (blue) as reference. CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; FFR, fractional flow reserve; ICA, invasive coronary angiography.

Figure 3. Prognostic significance of inducible ischemia in stable chest pain.



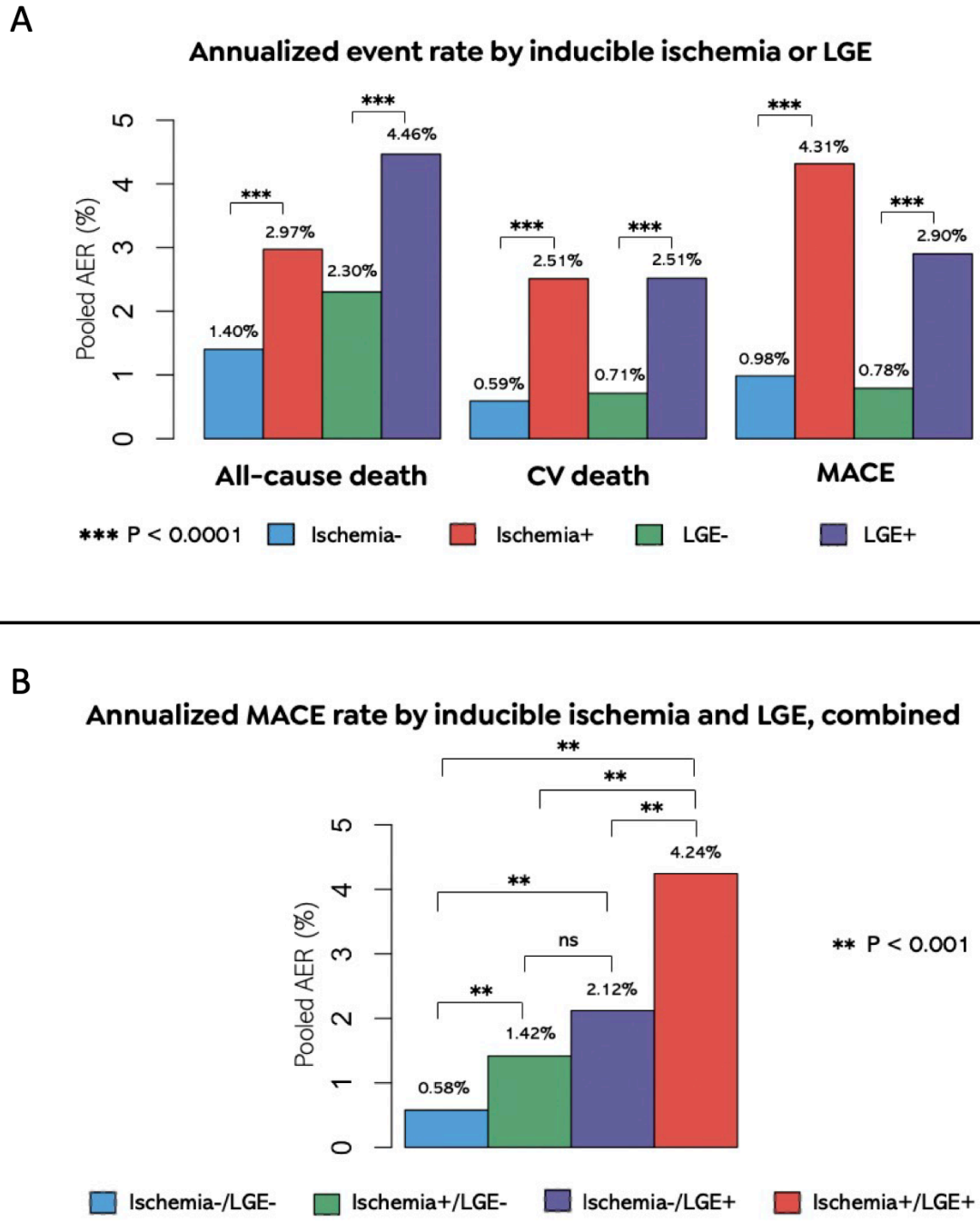
Forest plots with individual and overall odds ratio estimates for all-cause death, cardiovascular death and MACE by presence or absence of inducible ischemia (A, B, C). The solid vertical line at the centre of the graph is the 'line of no effect', that is, an odds ratio of 1.0 represented. An odds ratio >1.0 favors individuals without inducible ischemia, whereas an odds ratio <1.0 favors individuals with inducible ischemia. The interrupted vertical line indicates the pooled effect estimate. The diamond size is proportional to the overall weight in this random-effects model. Blue squares indicate weighted point estimates of the effect of each single study. CI, confidence interval; MACE, major adverse cardiovascular events; MH, Mantel-Haenszel.

Figure 4. Prognostic significance of LGE in stable chest pain.



Forest plots with individual and overall odds ratio estimates for all-cause death, cardiovascular death and MACE by presence or absence of or LGE (A, B, C). The solid vertical line at the centre of the graph is the 'line of no effect', that is, an odds ratio of 1.0 represented. An odds ratio >1.0 favors individuals without LGE, whereas an odds ratio <1.0 favors individuals with LGE. The interrupted vertical line indicates the pooled effect estimate. The diamond size is proportional to the overall weight in this random-effects model. Blue squares indicate weighted point estimates of the effect of each single study. CI, confidence interval; MACE, major adverse cardiovascular events; MH, Mantel-Haenszel; LGE, late gadolinium enhancement.

Figure 5. Pooled annualized event rate by stress CMR imaging findings in stable chest pain.



Grouped bar charts plotting (A) pooled annualized event rate for all-cause death, CV death and MACE by inducible ischemia or LGE with colors indicating the secondary category level for each analysis; (B) pooled annualized event rate for MACE by combination of inducible ischemia and LGE information. LGE, late gadolinium enhancement; MACE, major adverse cardiovascular events.