Prognosis of unrecognised myocardial infarction determined by electrocardiography or cardiac magnetic resonance imaging: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To evaluate the prognosis of unrecognised myocardial infarction determined by electrocardiography (UMI-ECG) or cardiac magnetic resonance imaging (UMI-CMR).

DESIGN

Systematic review and meta-analysis of prospective studies.

DATA SOURCES

Electronic databases, including PubMed, Embase, and Google Scholar.

STUDY SELECTION

Prospective cohort studies were included if they reported adjusted relative risks, odds ratios, or hazard ratios and 95% confidence intervals for all cause mortality or cardiovascular outcomes in participants with unrecognised myocardial infarction compared with those without myocardial infarction.

DATA EXTRACTION AND SYNTHESIS

The primary outcomes were composite major adverse cardiac events, all cause mortality, and cardiovascular mortality associated with UMI-ECG and UMI-CMR. The secondary outcomes were the risks of recurrent coronary heart disease or myocardial infarction, stroke, heart failure, and atrial fibrillation. Pooled hazard ratios and 95% confidence intervals were reported. The heterogeneity of outcomes was compared in clinically recognised and unrecognised myocardial infarction.

RESULTS

The meta-analysis included 30 studies with 253 425 participants and 1 621 920 person years of follow-up. UMI-ECG was associated with increased risks of all cause mortality (hazard ratio 1.50, 95% confidence interval 1.30 to 1.73), cardiovascular mortality (2.33, 1.66 to 3.27), and major adverse cardiac events (1.61, 1.38 to 1.89) compared with the absence of myocardial infarction. UMI-CMR was also associated with increased risks of all cause mortality (3.21, 1.43 to 7.23), cardiovascular mortality (10.79, 4.09 to 28.42), and major adverse cardiac events (3.23, 2.10 to 4.95). No major heterogeneity was observed for any primary outcomes between recognised myocardial infarction and UMI-ECG or UMI-CMR. The absolute risk differences were 7.50 (95% confidence interval 4.50 to 10.95) per 1000 person years for all cause mortality, 11.04 (5.48 to 18.84) for cardiovascular mortality, and 27.45 (17.1 to 40.05) for major adverse cardiac events in participants with UMI-ECG compared with those without myocardial infarction. The corresponding data for UMI-CMR were 32.49 (6.32 to 91.58), 37.2 (11.7 to 104.20), and 51.96 (25.63 to 92.04), respectively.

CONCLUSIONS

UMI-ECG or UMI-CMR is associated with an adverse long term prognosis similar to that of recognised myocardial infarction. Screening for unrecognised myocardial infarction could be useful for risk stratification among patients with a high risk of cardiovascular disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Unrecognised myocardial infarction is highly prevalent, especially in patients with diabetes and those of older age

It remains unclear whether identification of unrecognised myocardial infarction offers any additional prognostic value over important traditional cardiovascular risk factors

Contemporary academic guidelines for cardiovascular disease prevention have raised concerns about screening for myocardial ischaemia in asymptomatic participants

WHAT THIS STUDY ADDS

Unrecognised myocardial infarction was associated with increased risks of all cause mortality and adverse cardiovascular outcomes compared with not having myocardial infarction

Electrocardiography and cardiac magnetic resonance can provide different information, and each modality has unique clinical value in the detection of unrecognised myocardial infarction

Screening for unrecognised myocardial infarction might be useful for risk stratification in the management of patients with a high risk of cardiovascular disease

Introduction

Unrecognised myocardial infarction is defined as myocardial infarction that was not detected during the acute phase because typical symptoms were lacking, but was later identified by pathological Q waves on an electrocardiogram, myocardial imaging evidence, or pathological findings on autopsy.[1 2] Previous studies have shown that unrecognised myocardial infarction accounts for one third to one half of all myocardial infarctions,[1-4] especially in patients with diabetes and those of older age.[5 6]

Some epidemiological studies have shown that unrecognised myocardial infarction detected by electrocardiography (UMI-ECG) is associated with subsequent increased risks of all cause mortality, recurrent cardiovascular disease, and heart failure,[7-9] although other studies found null associations.[10-12] Furthermore, it remains unclear whether UMI-ECG offers any additional prognostic value over important conventional cardiovascular risk factors.[10 11] Therefore,

contemporary academic guidelines for cardiovascular disease prevention have raised concerns about screening for myocardial ischaemia in asymptomatic people using electrocardiography, even in those with a high risk of cardiovascular disease.[13 14] In recent years, late gadolinium enhancement on cardiac magnetic resonance imaging has also been used to detect unrecognised myocardial infarction.[1 15] However, the diagnostic consistency between electrocardiography and cardiac magnetic resonance imaging has not been thoroughly explored. The high cost and time consuming nature of cardiac magnetic resonance imaging have so far limited its clinical application and use in large cohort studies. However, a handful of studies have shown that detection of unrecognised myocardial infarction by cardiac magnetic resonance imaging (UMI-CMR) is associated with an increased risk of mortality.[11 16]

To investigate these inconsistencies, we performed a systematic review and meta-analysis of prospective cohort studies by using available data on the prognostic value of UMI-ECG and UMI-CMR. Two key questions were addressed in our study. Is UMI-ECG or UMI-CMR associated with a poorer prognosis in terms of cardiovascular disease and mortality than the absence of myocardial infarction? Is the prognosis of unrecognised myocardial infarction different from that of clinically recognised myocardial infarction?

Methods

Search strategy and selection criteria

We followed the recommendations of the Meta-analysis of Observational Studies in Epidemiology group[17] and searched several electronic databases (PubMed, Embase, and Google Scholar) for prospective studies up to 30 June 2019. The search was restricted to human studies, but no restrictions were placed on language or publication form. Reference lists were manually checked to identify other potential studies. Online supplementary file 1 shows the detailed method used to search PubMed.

We included studies in the analysis if they met several criteria: prospective cohort studies with adult participants (age≥18 years); unrecognised myocardial infarction and other cardiovascular risk factors detected at baseline; and adjusted relative risks, odds ratios, or hazard ratios and 95% confidence intervals reported for all cause death or cardiovascular outcomes associated with unrecognised myocardial infarction versus those without myocardial infarction. Cardiovascular outcomes included cardiovascular mortality, composite major adverse cardiac events, new coronary heart disease or myocardial infarction, stroke, heart failure, and atrial fibrillation. Unrecognised myocardial infarction was defined as signs of myocardial infarction shown by electrocardiography or cardiac magnetic resonance imaging without a documented history of acute myocardial infarction. All reading mechanisms (computerised process, visual inspection, or combination of both) for interpreting UMI-ECG were considered. Recognised myocardial infarction was defined as a documented clinical history of myocardial infarction. Non-myocardial infarction was defined as not having recognised myocardial infarction, or electrocardiographic or cardiac magnetic resonance imaging positive findings of myocardial infarction.

We excluded studies if the diagnosis of unrecognised myocardial infarction was not based on electrocardiography or cardiac magnetic resonance imaging; when only unadjusted risks were reported for associated events; and when identical outcomes were derived from the same cohort. For multiple articles that reported identical outcomes from the same cohort, only the most recently published paper was included in the analysis.

Data extraction and quality assessment

Two reviewers (YY and WL) independently conducted the literature searches and screened the studies according to the predefined criteria. Quality assessment of the included studies was based on the Newcastle Ottawa quality assessment scale for cohort studies.[18] This scale assesses studies based on selection (four items, one point each), comparability (one item, up to two points), and exposure or outcome (three items, one point each). In our analysis, we graded the quality of all included studies as good (at least seven points), fair (four to six points), or poor (less than four points).[19 20]

We considered whether studies had been adequately adjusted for potential confounders (at least six of seven factors: sex, age, smoking, hypertension or blood pressure or antihypertensive treatment, diabetes mellitus or fasting plasma glucose or haemoglobin A_{1c}, body mass index or overweight or obesity, and serum cholesterol or hypercholesterolemia). We also assessed whether studies had been adjusted for risk scores for prediction of cardiovascular disease (eg, Framingham risk score), calculated from these metrics, with reference to previous studies.[21 22]

Statistical analysis

The primary outcomes were the risks of major adverse cardiac events, all cause mortality, and cardiovascular mortality associated with UMI-ECG and UMI-CMR compared with non-myocardial infarction. The secondary outcomes were the risks of recurrent coronary heart disease or myocardial infarction, stroke, heart failure, and atrial fibrillation. To examine whether the prognosis of unrecognised myocardial infarction differs from that of clinically recognised myocardial infarction, we also obtained the outcomes for recognised myocardial infarction compared with non-myocardial infarction.

We extracted the outcomes for multiple variables for the meta-analysis. If a study reported multiple results based on different numbers of covariates included in statistical adjustments, we extracted the results that adjusted for the most number of variables for the meta-analysis. We combined the natural logarithm of the hazard ratios and the corresponding standard errors by the inverse variance approach. When hazard

ratios were available for all studies, we used them directly in the meta-analysis to calculate the overall hazard ratio estimates. If outcomes were presented as odds ratios (ORs), data were converted to relative risks (RRs) for analysis by using the formula RR=OR/([1−pRef]+[pRef×OR]), where pRef is the prevalence of the outcome in the reference group.[23] The relative risk was considered an approximate hazard ratio for meta-analysis,[24 25] and all the combined estimated risks were presented as hazard ratios and 95% confidence intervals. We calculated the absolute risk difference for all cause mortality and cardiovascular outcomes associated with unrecognised myocardial infarction by multiplying the assumed comparator risk of each outcome of interest by the estimated hazard ratio minus one, according to the recommendation in the Cochrane guidelines.[26] The median risks of outcomes in the non-myocardial infarction participants across studies were regarded as the assumed comparator risks. Absolute risk differences were expressed in events per 1000 person years.

We used the I^2 statistic to test heterogeneity. An I^2 value of more than 50% was considered to indicate significant heterogeneity. However, even when no significant heterogeneity was found, we used the DerSimonian and Laird random effects model as the primary approach to pool results across studies rather than the fixed effects model because of underlying clinical and methodological heterogeneity (eg, baseline characteristics of the patients, adjustment for confounders, and follow-up duration). Subgroup analyses of the primary outcomes were conducted according to the following factors when appropriate: sex (men *v* women); ethnicity (Asian *v* non-Asian); age (average of <65 *v* ≥65 years); enrolment from a community based population (yes *v* no); presence of diabetes (yes *v* no); follow-up duration (<6 *v* ≥6 years); adjustment for confounders (adequate *v* inadequate); and study quality (good *v* fair). According to Cochrane guidelines,[27] we performed meta-regression analysis if data were reported in more than 10 studies to explore the potential impact of study characteristics on the associations between unrecognised myocardial infarction and outcomes. Study characteristics included sample size, average age, follow-up duration, prevalence of unrecognised myocardial infarction, study quality score, and absolute event rate in the original cohort. We evaluated publication bias by examining funnel plots for primary outcomes and performed further investigation by using Begg's test and Egger's test. A sensitivity analysis was conducted to assess the impact of individual studies on the estimated risk; the pooled hazard ratio was recalculated by omitting one study at a time. We also performed a sensitivity analysis by excluding the studies that presented the outcomes as odds ratios or relative risks because these metrics do not consider the time covariate in the statistical model.

We reviewed and summarised studies with data relating to improvement of risk prediction to assess whether screening with electrocardiography or cardiac magnetic resonance imaging can add additional predictive value on top of traditional cardiovascular risk factors (eg, change with area under the receiver operating characteristic curve, net reclassification improvement, or integrated discrimination improvement). The net reclassification improvement assesses changes in the estimated events prediction probabilities that imply a change from one category to another, while the integrated discrimination improvement assesses changes in the estimated events prediction probabilities as a continuous variable.[28]

We also compared the difference in diagnostic efficacy between electrocardiography and cardiac magnetic resonance imaging for detection of unrecognised myocardial infarction. Data were extracted from studies that used both of these methods to detect unrecognised myocardial infarction. With cardiac magnetic resonance imaging regarded as the gold standard, pooled sensitivity and specificity of electrocardiography for diagnosing unrecognised myocardial infarction was estimated by using a random effects model.[29]

Analyses were performed using Stata 12.0 (StataCorp LP, College Station, TX, USA), RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and Meta-Disc version 1.4 software programs.[30] All P values are two tailed and statistical significance was set at 0.05.

Patient and public involvement

Patients and the public were not involved in setting the research question, in the outcome measures, in the design, or in the implementation of the study. However, patients may be involved in future research, designed based on the results of the current study. No patients were asked to advise on interpretation or writing up of results.

Results

Studies retrieved and characteristics

Our initial search returned 17 687 articles. After we screened the titles and abstracts, 116 articles qualified for a full text review (fig 1). Finally, 30 published papers involving 253 425 participants were included in the analysis.[7 10-12 16 31-55] According to the Newcastle Ottawa quality assessment, only two studies were graded as fair quality; all other studies were graded as good quality. Online supplementary file 2 presents details of the quality assessment.

UMI-ECG and health outcomes

Twenty studies reported outcome data for participants with UMI-ECG.[7 10-12 31-46] Online supplementary file 3 presents the key characteristics of the included studies. The studies comprised 250 407 participants with a mean follow-up duration of 6.4 years (range 2.3-17 years). Fifteen studies included participants from the general population, two studies included patients with chronic kidney disease, two studies included patients with diabetes, and one study included patients with suspected stable coronary artery disease. Online

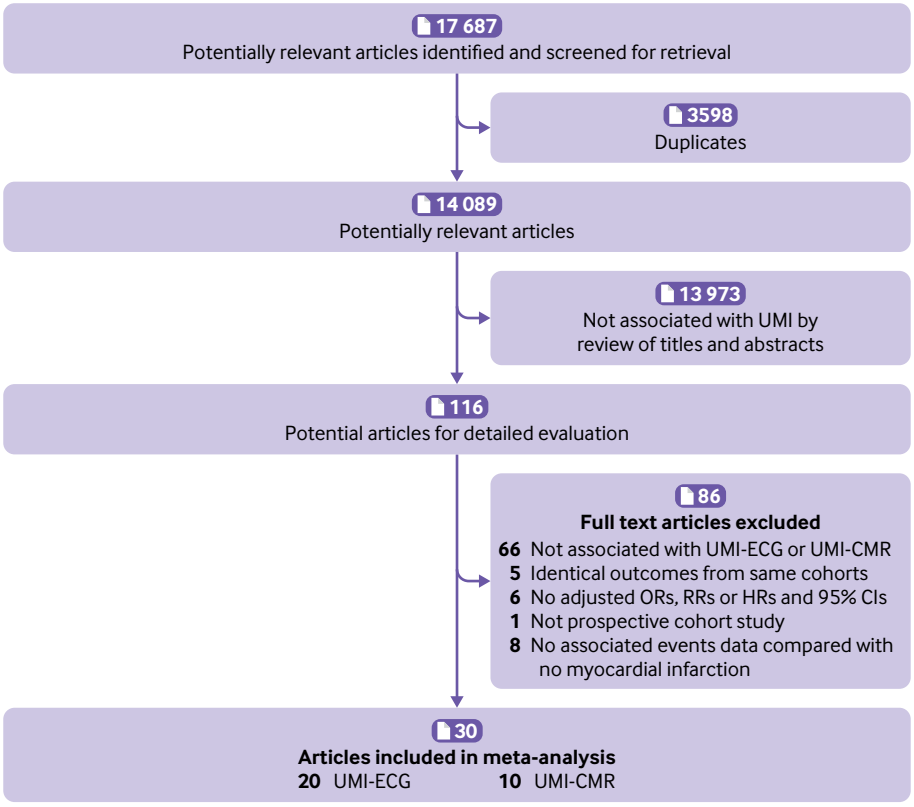

Fig 1 | Flow of papers through review. CI=confidence interval; HR=hazard ratio; OR=odds ratio; RR=relative risk; UMI=unrecognised myocardial infarction; UMI-ECG=unrecognised myocardial infarction detected by electrocardiography; UMI-CMR=unrecognised myocardial infarction detected by cardiac magnetic resonance imaging

supplementary file 3 presents interpretation methods for electrocardiograms (computerised process, visual inspection, or combination of both). All studies defined unrecognised myocardial infarction based on a major Q wave abnormality that met Minnesota code criteria, with different modifications across studies. The prevalence of UMI-ECG in the cohorts ranged from 0.3% to 36.0% (median 5.4%) and constituted 22.9-61.7% of all myocardial infarctions. In general population studies, the median prevalence of UMI-ECG was 5.0%. According to the predefined criteria, seven studies were not adequately adjusted for potential confounders, while all others were adequately adjusted (online supplementary file 4).

One included study reported adjusted odds ratios for all cause mortality associated with UMI-ECG,[34] which were converted to relative risks, and then considered as approximate hazard ratios for meta-analysis. All other studies reported hazard ratios for all evaluated events. Random effects model analyses showed that UMI-ECG was associated with increased risks of all cause mortality (hazard ratio 1.50, 95% confidence interval 1.30 to 1.73), cardiovascular mortality (2.33, 1.66 to 3.27), and major adverse cardiac events (1.61, 1.38 to 1.89) compared with non-myocardial infarction (fig 2). Furthermore, UMI-ECG was associated with increased risks of new coronary heart disease or myocardial infarction (hazard ratio 1.66, 95% confidence interval 1.25 to 2.20) and heart failure (1.50, 1.22 to 1.85), but not stroke (1.55, 0.75 to 3.19) or atrial fibrillation (1.44, 0.61 to 3.39; fig 3). We did not detect any publication bias based on the funnel plot (online supplementary file 5), or Begg's test and Egger's test (both P>0.05).

Online supplementary file 6 presents the absolute risks of primary outcomes in non-myocardial infarction and UMI-ECG. The absolute risk difference in UMI-ECG is 7.50 (95% confidence interval 4.50 to 10.95) per 1000 person years for all cause mortality, 11.04 (5.48 to 18.84) for cardiovascular mortality, and 27.45 (17.1 to 40.05) for major adverse cardiac events compared with non-myocardial infarction.

UMI-CMR and health outcomes

Ten studies among 3018 participants reported the prognostic outcomes of UMI-CMR.[16 47-55] Online supplementary file 7 presents the key characteristics of the included studies. The mean follow-up duration was 6.4 years (range 1.3-11 years). Two studies included participants from the general population, two studies included patients with acute myocardial infarction, three studies included patients with diabetes or impaired fasting glucose, and three studies included patients with suspected stable coronary artery disease and without history of myocardial infarction. All studies determined the presence of hyperenhancement in the late gadolinium enhancement of cardiac magnetic resonance imaging by visual inspection. Four

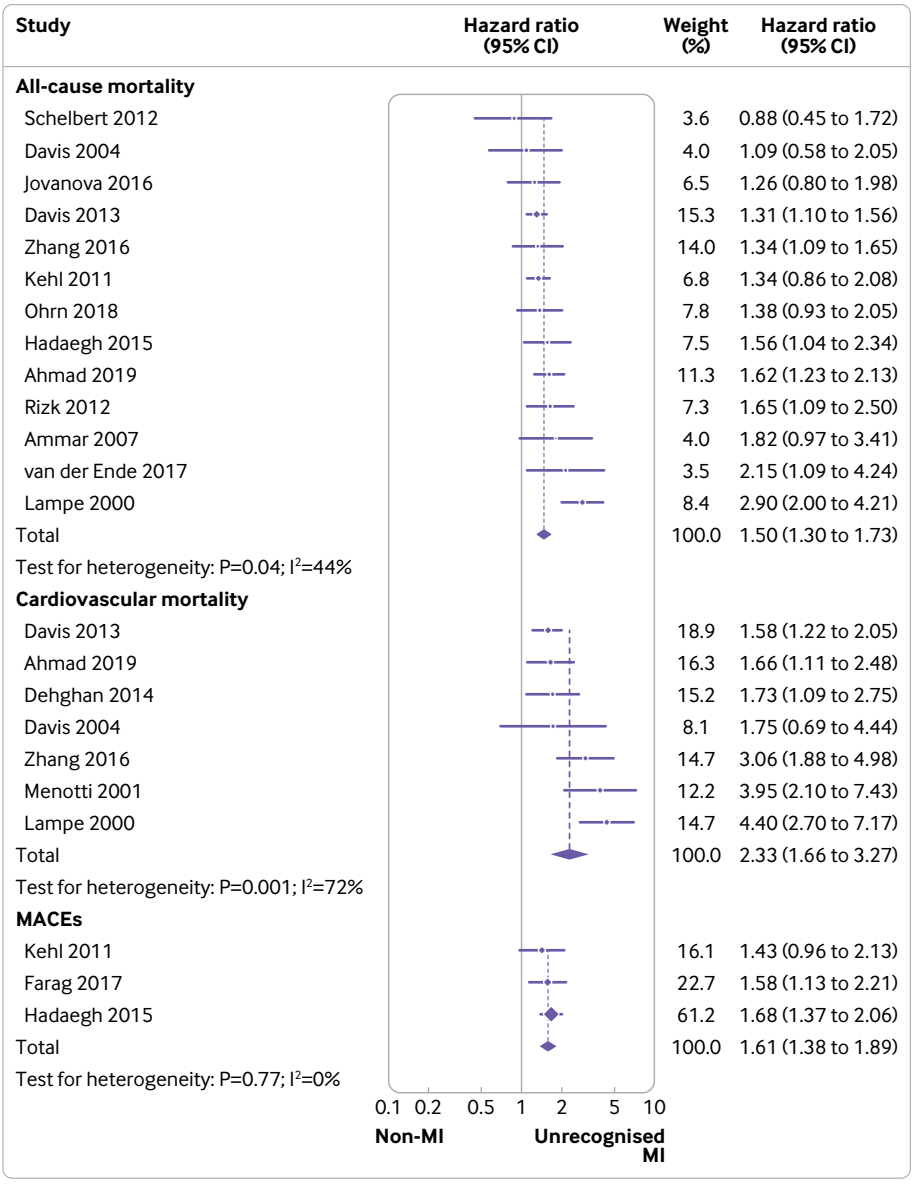

Fig 2 | Forest plot of estimates for risks of primary outcomes associated with unrecognised myocardial infarction detected by electrocardiography. CI=confidence interval; MACE=major adverse cardiac event; MI= myocardial infarction

studies further calculated the myocardial mass of late gadolinium enhancement, two by manual inspection and two by using a semiautomatic detection method. Two studies categorised late gadolinium enhancement as either typical myocardial infarction (involving the subendocardium) or atypical (subepicardial, patchy midwall, or diffuse circumferential subendocardial pattern); six studies defined unrecognised myocardial infarction when subendocardial late gadolinium enhancement was present. In two studies that included patients with acute myocardial infarction, unrecognised myocardial infarction was defined as the presence of subendocardial late gadolinium enhancement in the non-acute infarcted area other than the acute infarcted area. The prevalence of UMI-CMR in the cohorts ranged from 8.2% to 31.0% (median 22.5%) and constituted 51-83.3% of all myocardial infarctions. In general population studies, the median prevalence was 10.8%. Three studies were not adequately adjusted for potential confounders, while all other studies were adequately adjusted (online supplementary file 4).

Random effects model analyses showed that UMI-CMR was associated with increased risks of all cause mortality (hazard ratio 3.21, 95% confidence interval 1.43 to 7.23), cardiovascular mortality (10.79, 4.09 to 28.42), and major adverse cardiac events (3.23, 2.10 to 4.95) compared with non-myocardial infarction. Each 1% and 10% increase in left ventricular mass of late gadolinium enhancement was associated with a 9% and 77% increase in major adverse cardiac events, respectively (fig 4). One study showed that UMI-CMR was associated with increased risks of future myocardial infarction (hazard ratio 1.87, 95%

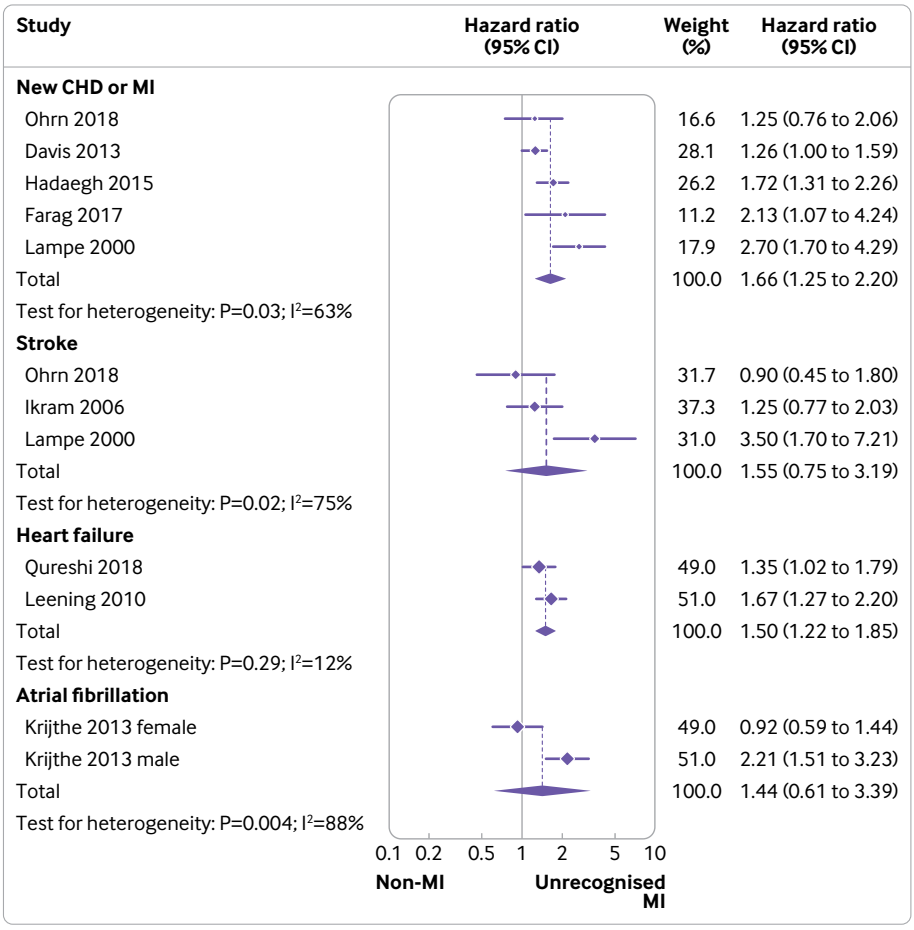

Fig 3 | Forest plot of estimates for risks of secondary outcomes associated with unrecognised myocardial infarction detected by electrocardiography. CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction

confidence interval 1.28 to 2.73) and heart failure (1.40, CI 1.00 to 2.00) compared with non-myocardial infarction after adjusting for multiple risk factors.[47] We could not exclude possible publication bias as detected by the funnel plot for the major adverse cardiac events (online supplementary file 8) and as shown by Begg's test (P=0.01) and Egger's test (P=0.03). However, when we applied the trim and fill adjustment method, no change in the overall effect estimate was produced for major adverse cardiac events associated with UMI-CMR.

Online supplementary file 9 presents the absolute risks of primary outcomes in non-myocardial infarction and UMI-CMR across studies. The absolute risk difference in UMI-CMR is 32.49 (95% confidence interval 6.32 to 91.58) per 1000 person years for all cause mortality, 37.2 (11.7 to 104.20) for cardiovascular mortality, and 51.96 (25.63 to 92.04) for major adverse cardiac events compared with non-myocardial infarction.

Comparison of prognosis between unrecognised and clinically recognised myocardial infarction

When cardiovascular outcomes or mortality associated with unrecognised myocardial infarction and clinically recognised myocardial infarction were reported in the same study, data were pooled to determine whether the prognosis differed between unrecognised and recognised myocardial infarction. We did not observe any significant heterogeneity between UMI-ECK and recognised myocardial infarction compared with non-myocardial infarction for the risks of all cause mortality, cardiovascular mortality, major adverse cardiac events, or stroke. However, the risks of recurrent coronary heart disease or myocardial infarction and heart failure were higher in recognised myocardial infarction (fig 5, top panel). We did not observe any significant heterogeneity for health outcomes (including all cause mortality, major adverse cardiac events, recurrent coronary heart disease or myocardial infarction, and heart failure) between recognised myocardial infarction and UMI-CMR compared with non-myocardial infarction (fig 5, bottom panel).

Subgroup analyses, meta-regression analyses, and sensitivity analyses

The predefined subgroup analyses showed that UMI-ECG was associated with increased risks of all cause mortality and cardiovascular mortality compared with non-myocardial infarction among all subgroup comparisons, except in female patients (hazard ratio 1.19, 95% confidence interval 0.91 to 1.56 for all

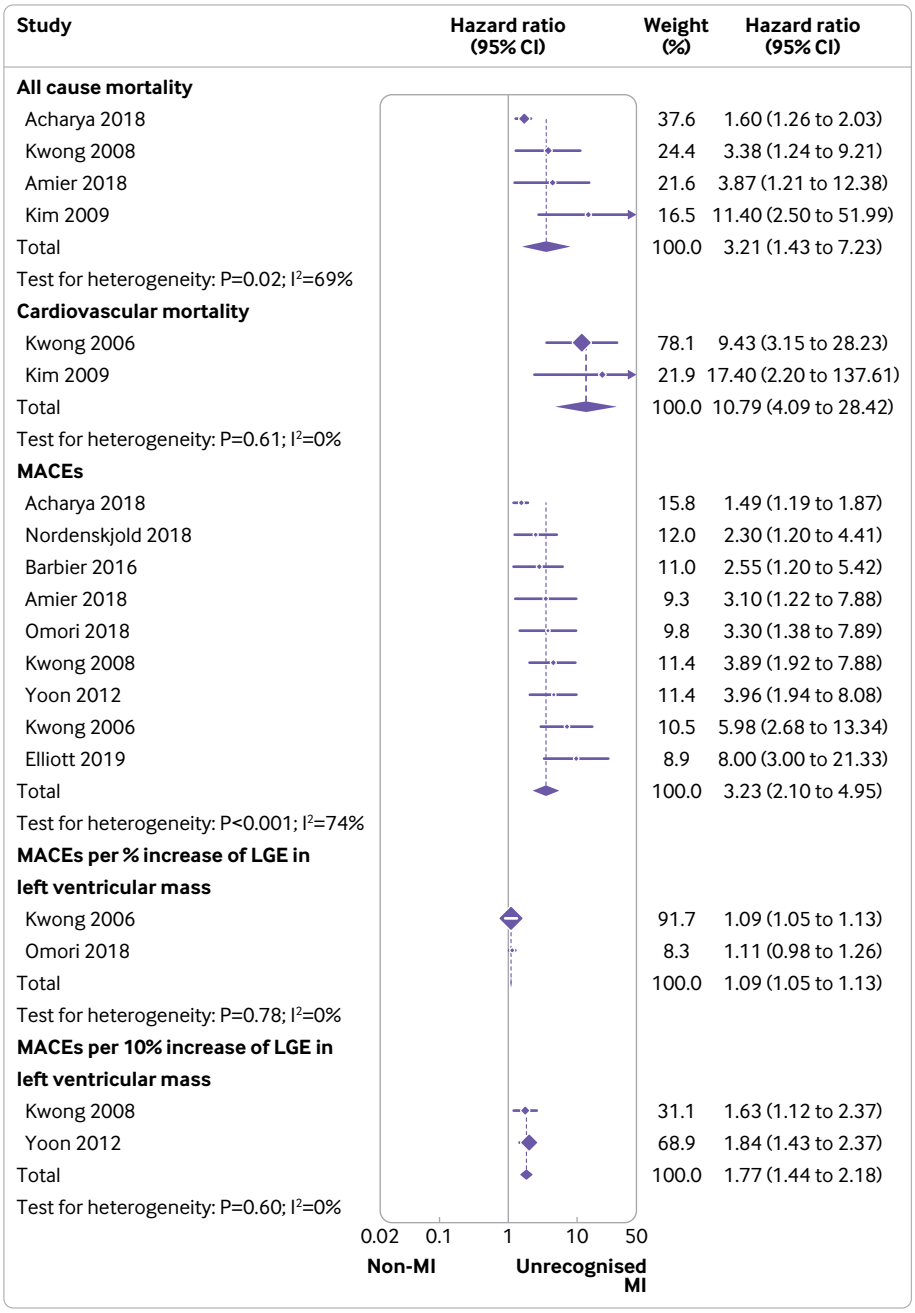

Fig 4 | Forest plot of estimates for risks of primary outcomes associated with unrecognised myocardial infarction detected by cardiac magnetic resonance imaging. CI=confidence interval; LGE=late gadolinium enhancement; MACE=major adverse cardiac event; MI=myocardial infarction

cause mortality; 2.10, 0.78 to 5.56 for cardiovascular mortality; online supplementary file 10). However, no significant heterogeneity was observed between male and female groups on all primary outcomes (all P>0.10). UMI-CMR was associated with increased risks of all primary outcomes among all subgroup comparisons (online supplementary file 11). We did not perform subgroup analyses for the other cardiac outcomes because available studies were limited. In 13 studies that reported the risk of all cause mortality associated with UMI-ECG, meta-regression analysis showed no significant associations among study characteristics and risk of all cause mortality (all P>0.05; online supplementary file 12). The sensitivity analyses confirmed that the association between primary endpoint events and UMI-ECG or UMI-CMR did not change with the use of random effects models or fixed effects models for the meta-analysis. Additionally this association did not change when we recalculated hazard ratios by omitting one study at a time. Furthermore, after excluding the study by van der Ende and colleagues,[34] which reported adjusted odds ratios for all cause mortality associated with UMI-ECG, the hazard ratio for all cause mortality was 1.48

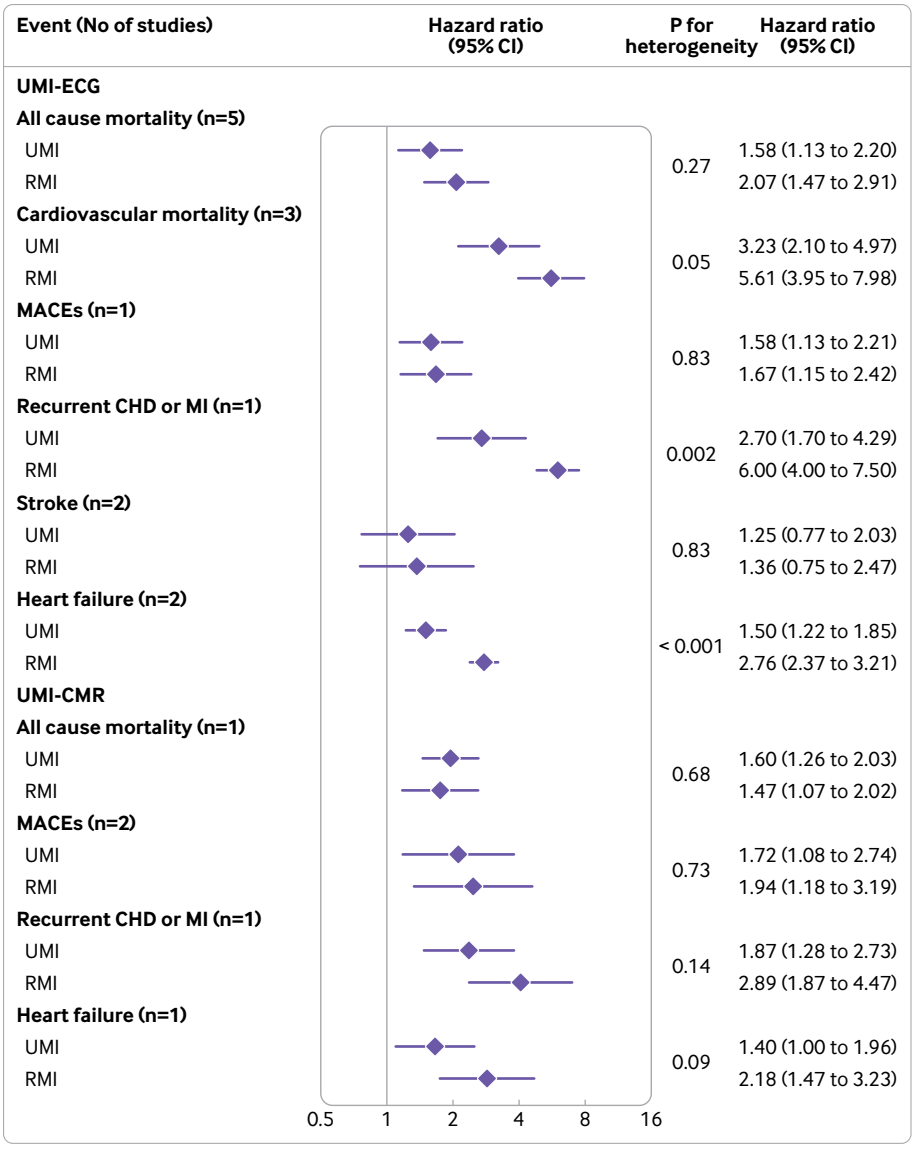

Fig 5 | Heterogeneity of all cause mortality and cardiac outcomes between unrecognised myocardial infarction and clinically recognised myocardial infarction compared with non-myocardial infarction. CHD=coronary heart disease; MACE=major adverse cardiovascular event; MI=myocardial infarction; RMI=clinically recognised myocardial infarction; UMI=unrecognised myocardial infarction; UMI-ECG=unrecognised myocardial infarction detected by electrocardiography; UMI-CMR=unrecognised myocardial infarction detected by cardiac magnetic resonance imaging

(95% confidence interval 1.28 to 1.71). These results are similar to those reported when all studies were included in the analysis (1.50, 1.30 to 1.73).

Additional predictive effects for health outcomes of unrecognised myocardial infarction

Few studies reported the additional predictive effects of UMI-ECG.[11 16 38] The United Kingdom prospective diabetes study showed that in patients with type 2 diabetes, UMI-ECG was associated with small but statistically significant improvement in all cause mortality (integrated discrimination improvement 0.0025, 95% confidence interval 0.001 to 0.0039) and fatal myocardial infarction risk stratification (0.0043, 0.0016 to 0.007) in a multivariable adjusted model.[38] However, other studies showed that the addition of UMI-ECG did not improve the risk prediction for future recurrent myocardial infarction or mortality by using the Framingham risk score.[10 11] Three studies consistently showed that UMI-CMR can improve the risk prediction for all cause mortality or major adverse cardiac events (table 1).[11 16 51]

Difference in diagnostic efficacy between UMI-ECG and UMI-CMR

Five studies reported the diagnostic efficacy of electrocardiography and cardiac magnetic resonance imaging for unrecognised myocardial infarction detection.[11 16 49 53 55] Pooled data from 1731 participants showed that when cardiac magnetic resonance imaging was used as the gold standard, diagnosing unrecognised myocardial infarction by using

Table 1 | Risk classification comparing models with and without unrecognised myocardial infarction for mortality and cardiovascular outcomes

Study and endpoint	ROC AUC	NRI (95%CI)	IDI (95%CI)
UMI-ECG			
Schelbert 2012 (all cause mortality)			
Base model*	—	Reference	Reference
Baseline model+UMI	—	−0.05 (−0.17 to 0.05)	0.000 (−0.004 to 0.001)
P value	—	0.35	0.71
Davis 2013 (all cause mortality)			
Base model†	0.699	—	Reference
Baseline model+UMI	0.701	—	0.0025 (0.001 to 0.0039)
P value	0.07	—	0.001
Davis 2013 (fatal myocardial infarction)			
Base model*	0.713	—	Reference
Baseline model+UMI	0.718	—	0.0043 (0.0016 to 0.007)
P value	0.16	—	0.002
Ohrn 2018 (future myocardial infarction)			
Base model‡	0.681	—	—
Baseline model+UMI	0.682	—	—
P value	0.96	—	—
UMI-CMR			
Schelbert 2012 (all cause mortality)			
Base model*	—	Reference	Reference
Baseline model+UMI	—	0.16 (0.01 to 0.31)	0.008 (0.004 to 0.013)
P value	—	0.04	0.001
Barbier 2016 (MACEs)			
Base model§	0.68	Reference	Reference
Baseline model+UMI	0.75	0.67 (0.28 to 1.06)	0.068 (0.025 to 0.111)
P value	0.04	0.0007	0.002
Elliott 2019 (MACEs)			
Base model§	—	—	Reference
Baseline model+UMI	—	—	0.156 (0.063 to 0.249)
P value	—	—	0.001

IDI=integrated discrimination improvement; MACE=major adverse cardiac event; NRI=net reclassification improvement; ROC AUC=area under the curves of receiver operating characteristic curve; UMI=unrecognised myocardial infarction; UMI-CMR=unrecognised myocardial infarction detected by cardiac magnetic resonance imaging; UMI-ECG=unrecognised myocardial infarction detected by electrocardiography.
The NRI assesses changes in the estimated events prediction probabilities that imply a change from one category to another, while the IDI assesses changes in the estimated events prediction probabilities as a continuous variable.
*Adjusted for age, sex, diabetes, and recognised myocardial infarction.
†Adjusted for age, sex, ethnicity, smoking, haemoglobin A1c, systolic blood pressure, total cholesterol or high density lipoprotein cholesterol ratio.
‡Adjusted for age, sex, hypertension, diabetes, smoking, total cholesterol or high density lipoprotein cholesterol, cholesterol lowering medication, and family history of premature myocardial infarction.
§Adjusted for Framingham risk score.

electrocardiography had low sensitivity (13.2%, 95% confidence interval 9.7% to 17.5%) and high specificity (95.7%, 94.5% to 96.7%; fig 6). The pooled positive likelihood ratio was 2.78 (95% confidence interval 1.47 to 5.25), which indicated that the probability of a patient with unrecognised myocardial infarction and a positive finding on the electrocardiogram was about 2.8-fold compared with the probability of a healthy person with positive testing (online supplementary file 13).

Discussion

Principal findings

This is a comprehensive systematic review and meta-analysis that examined the mortality and cardiovascular outcomes associated with unrecognised myocardial infarction, stratified by detection with electrocardiography or cardiac magnetic resonance imaging. Three key findings were reported in our study. Firstly, UMI-ECG or UMI-CMR was associated with increased risks of all cause mortality and multiple cardiovascular outcomes compared with the absence of myocardial infarction. Secondly, the risks of all cause mortality, cardiovascular mortality, and major adverse cardiac events were similar in unrecognised myocardial infarction and clinically recognised myocardial infarction. Finally, electrocardiographic screening for unrecognised myocardial infarction is of low sensitivity but high specificity, and might add additional predictive values for mortality and new myocardial infarction; however, the results are inconsistent. In contrast, screening with cardiac magnetic resonance imaging can increase the predictive values for mortality and cardiovascular disease.

Meaning of the study and future research

Our results provide robust evidence that although patients are asymptomatic, unrecognised myocardial infarction is associated with a poorer long term prognosis compared with non-myocardial infarction, and a similar prognosis to clinically recognised myocardial infarction. The median prevalence of UMI-ECG was 5.4% in all included studies and 5.0% in general population cohorts. The corresponding prevalence for UMI-CMR was 22.5% in all included studies and 10.8% in general population cohorts.

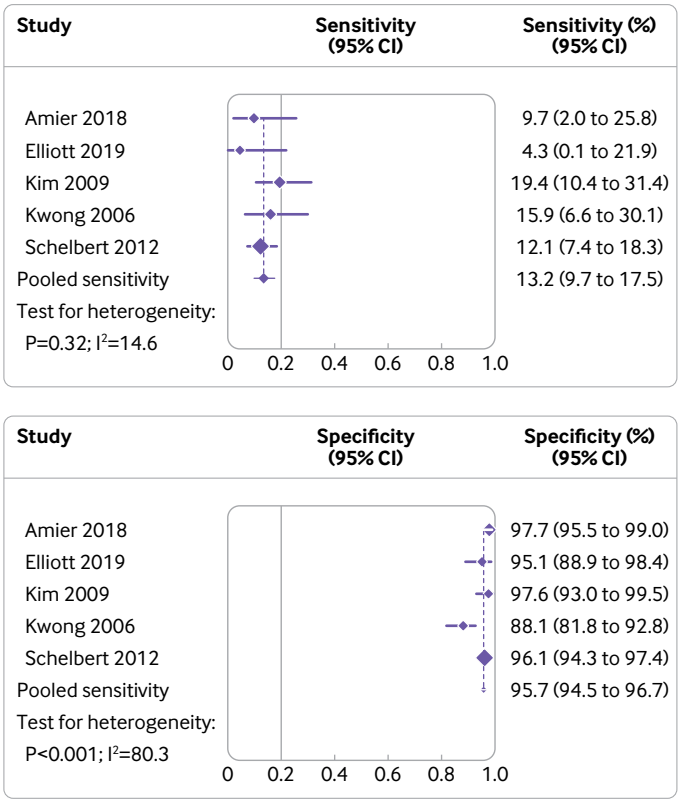

Fig 6 | Sensitivity and specificity of electrocardiography for detecting unrecognised myocardial infarction. Cardiac magnetic resonance was regarding as gold standard in this analysis. CI=confidence interval

Furthermore, UMI-ECG and UMI-CMR constituted 22.9-61.7% and 51-83.3% of all myocardial infarctions, respectively. Considering the high prevalence and important adverse long term prognosis associated with unrecognised myocardial infarction, it is important to screen and properly manage these patients.

Academic guideline recommendations on electrocardiographic screening

The use of electrocardiography to screen asymptomatic adults for cardiovascular disease is controversial. Although electrocardiographic screening is safe, it could "lead to higher downstream cardiac testing use, more specialist consultations, and potentially higher rates of adverse events, including excess radiation exposure and procedural complications of angiography."[56] Therefore, the United States Preventive Services Task Force suggests not to use electrocardiographic screening in patients at low risk of cardiovascular disease (10 year event risk of less than 10%). In patients with increased risk of cardiovascular disease, the Task Force cited that the current evidence is insufficient to assess the balance of benefits and harms of electrocardiographic screening.[13] However, the American College of Cardiology/American Heart Association guideline considered electrocardiographic screening to be "reasonable" in asymptomatic people with hypertension or diabetes and that it "may be considered" in those without hypertension or diabetes.[57] The 2019 European Society of Cardiology guidelines on diabetes, prediabetes, and cardiovascular diseases stated that "resting ECG is recommended in patients with diabetes mellitus with hypertension or suspected cardiovascular disease."[58] However, both these guidelines acknowledged the lack of data to support this expert consensus (level of evidence C). Therefore, the robust evidence in the current study, which showed that UMI-ECG was associated with adverse outcomes, supports developing strategies for screening and preventing cardiovascular disease in high risk patients. However, limited data showed that electrocardiography can add additional predictive values for mortality and new myocardial infarction, and the results were inconsistent. These inconsistencies could arise from the fact that most of the studies included patients with a low risk of cardiovascular disease. In this context, further studies are needed to evaluate the impact of electrocardiography on incremental improvements in risk stratification in high risk patients.

A large scale registry study from Spain showed that although the positive predictive value of asymptomatic Q waves for diagnosing unrecognised myocardial infarction was 29.2% overall, it was much higher (75%) in participants with a 10 year coronary heart disease risk of at least 10% than in lower risk participants.[3] Therefore, we agree with the proposal in the Canadian diabetes guideline that electrocardiographic screening should be performed in patients with a high risk of cardiovascular disease. This screening gives information on baseline cardiac ischaemia and can also provide information for comparison with future electrocardiographic data.[59] A repeat resting electrocardiogram might detect changes that result from unrecognised myocardial infarction, leading to earlier detection of critical cardiovascular disease.

How to screen for unrecognised myocardial infarction

Although electrocardiography is the most widely used non-invasive technique for cardiovascular assessment, its limited sensitivity for screening unrecognised myocardial infarction has been questioned. It is known that Q waves can resolve with time, and patients with non-ST segment elevation myocardial infarction do not have characteristic Q waves on the electrocardiogram.[60] Our study also showed that the use of electrocardiography to detect unrecognised myocardial infarction has a low sensitivity (13.2%) but a high specificity (95.7%). Therefore, it is important to develop more precise, sensitive, and sophisticated models based on electrocardiography to estimate unrecognised myocardial infarction. This is possible given the availability of digital data, which provide hundreds of waveform measurements and development of machine learning technology.[61]

Not surprisingly, cardiac magnetic resonance imaging can detect more people with unrecognised myocardial infarction than electrocardiography.

However, the high cost and time consuming nature of cardiac magnetic resonance imaging limit its application in clinical practice. Furthermore, the intravenous gadolinium used in cardiac magnetic resonance imaging could pose a risk of nephrogenic systemic fibrosis in patients with kidney disease.[62] Therefore, we should note that both of these methods can provide different information, and each modality has unique clinical value in the detection of unrecognised myocardial infarction. Further studies are needed to explore how to integrate electrocardiography and cardiac magnetic resonance imaging rather than replace one with the other to screen and manage patients with a risk of myocardial ischaemia. We also propose that if unrecognised myocardial infarction is identified by electrocardiography in routine clinical care, cardiac magnetic resonance imaging could be performed to identify the presence and extent of actual myocardial damage and guide treatment decisions.[63]

How to manage patients with unrecognised myocardial infarction

Two randomised trials showed that screening for silent ischaemia with a stress test does not improve the prognosis in patients with diabetes compared with simply controlling cardiovascular risk factors.[64 65] Although these studies had limited samples and were underpowered, they emphasised the importance of controlling cardiovascular risk factors in the treatment of asymptomatic coronary artery disease. In real clinical practice, however, many patients with unrecognised myocardial infarction are undertreated. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, the proportions of patients with unrecognised myocardial infarction who received treatment with aspirin, β blockers, and statins were only 44.4%, 25.8%, and 33.9%, respectively, which were much lower than the proportions of patients with clinically recognised myocardial infarction.[66] Similar results were observed in the Iceland MI study, which were attributed to the high mortality of patients with unrecognised myocardial infarction.[11]

Further efforts should be made to increase the adherence to guideline recommendations for prevention of cardiovascular disease in patients with unrecognised myocardial infarction. However, evidence seems to be lacking to show that therapeutic strategies would change after identification of unrecognised myocardial infarction. Further studies are needed to fill this gap in the research. In selected patients, adjunctive coronary revascularisation is worthy of prospective testing. A recent cohort study of 9897 patients with silent ischaemia showed that coronary revascularisation was associated with a 19% and 42% reduction of death and myocardial infarction, respectively, compared with medical treatment during a median follow-up of 4.6 years.[67]

Strengths and limitations of study

Our study has several major strengths. Firstly, we included and stratified studies of electrocardiography or cardiac magnetic resonance imaging, which are the most prevalent methods for screening unrecognised myocardial infarction. Secondly, only prospective cohort studies with adjusted risks were included. Most of the included studies were of high quality and adequately adjusted for confounders. Thirdly, the sample size was large and the follow-up duration was long (more than 1.6 million person years).

However, some limitations of the study should be noted. Firstly, significant heterogeneity of the populations existed in the included studies and we had no access to the data of individual participants. However, consistent results were found in the comprehensive subgroup analyses and sensitivity analyses, and meta-regression showed that the risk of all cause mortality in UMI-ECG was not affected by the study characteristics. These characteristics could mitigate the possibility of influencing the association between unrecognised myocardial infarction and outcomes by confounding factors. Secondly, most studies that used cardiac magnetic resonance imaging involved patients with conditions such as diabetes or chronic kidney disease. These patients had higher risks than those included in electrocardiographic screening; thus, direct comparison of cardiovascular disease risks between the two screening methods was unavailable. Thirdly, UMI-ECG was defined using different criteria in included studies (as described in online supplementary file 3), which was an underlying factor for the heterogeneity among the studies.

Conclusions

Our study has shown that unrecognised myocardial infarction is highly prevalent and associated with an adverse long term prognosis, which is similar to that of clinically recognised myocardial infarction. Screening for unrecognised myocardial infarction might be useful for risk stratification among patients with a high risk of cardiovascular disease. Further studies are needed to develop standard methods for screening and treating unrecognised myocardial infarction.

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and had full access to all of the data, including statistical reports and tables, and take full responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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The lead author (YulH) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results from the present study will be disseminated to appropriate audiences such as academia, clinicians, policy makers, and the general public through various channels, including press release, social media, e-newsletter, websites of collaborators' universities, and monthly bulletins.

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Web appendix: Supplementary material