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Long-term prognostic value of contemporary stress echocardiography in patients with suspected or known coronary artery disease: systematic review and meta-analysis

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ABSTRACT

Background Long-term outcome of contemporary stress echocardiography has not been systematically assessed.

Objective To evaluate the association between results of stress echocardiography and patients' outcomes with suspected coronary artery disease using randomised controlled trials.

Methods Multiple electronic databases were searched for studies evaluating long-term outcome (>12 months) of stress echocardiography in patients suspected of coronary artery disease since year 2000. A common-effect model was used to derive pooled estimates. The primary outcome was a composite of all-cause mortality or cardiovascular death and non-fatal myocardial infarction, depending on the definition applied in individual trials, termed as major adverse cardiovascular event (MACE). Secondary outcome was all-cause mortality. Positive stress echocardiography result was defined as inducible ischaemia in at least one of the 17 left ventricular segments and negative stress echocardiography with no inducible ischaemia.

Results Among a total of six trials, 16 581 subjects underwent either pharmacological or treadmill stress echocardiography, a median follow-up of 31 months (range 21–101). The annual event rate was 1.76% for the composite MACE and 1.35% for all-cause mortality. Compared with negative stress echocardiography, positive stress echocardiography was associated with an increased risk of the MACE and all-cause mortality with an annual event rate of 1.99% vs 1.54% (OR 2.04, 95% CI 1.79 to 2.33) and 1.68% vs 1.02% (OR 2.06, 95% CI 1.80 to 2.35), respectively.

Conclusion Positive stress echocardiography results were associated with poorer long-term MACE and all-cause mortality. Stress echocardiography results may provide a useful long-term guidance in intensifying preventative treatment in patients with suspected coronary artery disease.

PROSPERO registration number CRD42023416766.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The correlation of the outcome of stress echocardiography and the grade of angiographic coronary artery stenosis has been extensively reported. Anatomical coronary artery stenosis had been recently suggested not to be an appropriate comparator to stress echocardiography-induced ischaemia prediction. Worse short-term outcome had been reported in patients with inducible ischaemia during stress echocardiography.

WHAT THIS STUDY ADDS

⇒ Since the introduction of ultrasonic enhanced agents, the detection of wall motion abnormality has become more accurate during stress echocardiography. Poor long-term mortality has been shown to be associated with positive (abnormal) stress echocardiography results in this meta-analysis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Contemporary stress echocardiography practice may provide a useful long-term prediction and could facilitate guidance in delivering guideline-directed medical therapy in patients with suspected or known coronary artery disease.

INTRODUCTION

Coronary artery disease (CAD) is the leading cardiovascular cause of morbidity and mortality.[1 2] Stress echocardiography (SE) has been a cost-effective bedside test in the diagnosis of myocardial ischaemia for more than 50 years. Irrespective of the type of the stress modality, it relies on the detection of new regional wall motion abnormality (RWMA). The diagnostic accuracy of SE and the short-term (≤12 months) outcome of patients with normal and abnormal stress tests have been well documented in both chronic coronary syndrome and acute admission with presumed acute coronary syndrome.[3–5] Recent multisocietal guidelines suggest non-invasive functional tests (ie, SE) for patients with an intermediate risk of CAD.[2 6] Since the introduction of the ultrasound enhancing agents (UEA) in 2000, improved endocardial border detection has enhanced diagnostic accuracy and increased interpreter confidence during SE.[7 8] A current multicentre SE study in 31 UK hospitals showed nearly 70% usage of UEA with a 6-month negative predictive accuracy of 99% and positive accuracy of 83% for combined major adverse cardiovascular event (MACE).[9] Long-term outcome of SE with

contemporary imaging techniques in controlled trials has not been systematically investigated.

In this study, we explore the long-term (>12 months) clinical outcome of SE in a contemporary cardiology area with a literature review and data analysis.

METHODS

Search strategy and study inclusion

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for the planning, analysis and reporting of meta-analysed randomised controlled trials.[10] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023416766).

A systematic search in Medline, Embase, Cochrane Library for clinical trials, PubMed, Web of Science, ClinicalTrials.gov and PROSPERO database was performed for a period between 1 January 2000 and 1 January 2023 (to enhance the recruitment of contemporary SE trials; since the introduction of UEA by the American and European guidelines to improve diagnostic accuracy). Keywords including stress echocardiography, DSE, stress echo, dobutamine echocardiography, exercise stress echo or vasodilator stress echo were combined to explore the prognostic outcomes of SE. A reference list of identified articles was used, and relevant studies were included in the reviewed articles. A randomised controlled trial in the search criteria aimed the recruit studies with a highest research standard, hence, the lowest risk of bias irrespective of the design of the studies.

The screening of titles and abstracts, followed by the review of full-text articles, was independently conducted by two authors (JSC and NJ). Disagreements were resolved by a third author (UI) to reach a consensus. There was no process of blinding during the review process, this was to ensure included studies met predefined eligibility criteria. These criteria were: (1) clinical trials for investigating myocardial ischaemia in patients with suspected CAD using SE, (2) studies with longitudinal follow-up (≥12 months) recording events such as all-cause or cardiovascular mortality and MACE, or composite of these events, (3) enrolled a minimum of 50 patients aged 18 and above and (4) studies reported in the English language as full-text articles. The detailed characteristics of the trials are provided in tables 1 and 2.

Data extraction

Two of the investigators (NJ and JSC) independently extracted and crosschecked data from the included studies. Inconsistencies were resolved by discussion with the third investigator (UI). The risk of bias in the included randomised controlled trials was evaluated using the Cochrane Handbook. The quality of the included trials was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, using the GRADEpro tool pack to display this assessment.[11]

Table 1 Study characteristics

First author	Study outcome	SE modalities	Event endpoint	Study population, n	SE positive, n	SE negative, n	MACE for SE positive, n	MACE for SE negative, n
Cortigiani [18]	Risk score generated simple clinical variable may be able to optimise SE risk stratification. Retrospective analysis of prospectively recruited patients. UEA-NS	Dipyridamole, dobutamine, exercise	All-cause death	14279	3434	10855	359	587
Faglia [17]	Preclinical diagnosis of CAD reduces risk of MACE in patients with high-risk diabetes. UEA-NS	Dipyridamole, exercise	Non-fatal MI	71	15	56	0	1
Jeetley[13]	SE confers excellent prognosis in low-risk results. UEA	Dobutamine, exercise	Death (1) and non-fatal MI (1)	148	22	119	0	2
Laiq[14]	Addition of perfusion imaging enhances the predictive value of SE in men with no known CAD. UEA	Dobutamine, exercise	Non-fatal MI (5) or all-cause death (33)	857	123	729	10	28
Porter[15]	Predictive value of positive SE is significant for combined outcome of death and non-fatal MI. UEA	Dobutamine, exercise	All-cause death and non-fatal MI (not separate)	1035	226	803	17	34
Zacharias[16]	Exercise SE has demonstrated superior cost saving compared with exercise ECG. UEA	Exercise	Cardiovascular death (1)	191	9	181	0	1
Total				16581	3829	12743	386	653

CAD, coronary artery disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; NS, not stated; SE, stress echocardiography; UEA, ultrasound enhancing agent.

Table 2 Study characteristics

First author	Study population, n	Mean age (years)	Male, n (%)	Hypertension, n (%)	Hyperlipidaemia, n (%)	Current smoker, n (%)	Diabetes, n (%)	Prior MI, n (%)	Prior PCI, n (%)	Prior CABG, n (%)	Patient-years of follow-up
Cortigiani[18]	14279	63	8912 (62)	7943 (56)	6788 (48)	5241 (37)	2887 (20)	4487 (31)	2209 (16)	947 (7)	36887
Faglia[17]	71	59	42 (59)	32 (45)	29 (41)	46 (65)	71 (100)	0 (0)			309
Jeetley[13]	148	61	84 (57)	103 (70)	81 (55)	22 (15)	34 (23)	18 (12)	13 (9)	13 (9)	141
Laiq[14]	857	58	717 (44)	936 (57)	785 (48)	363 (22)	386 (23)	0 (0)	0 (0)	0 (0)	4260
Porter[15]	1035	60	994 (48)	1268 (61)	1112 (54)	469 (23)	533 (26)	192 (9)	241 (12)	162 (8)	5329
Zacharias[16]	191	55	134 (70)	76 (40)	67 (35)	27 (14)	27 (14)	0 (0)			334
Total	16581	59	10883 (59)	10358 (56)	8862 (48)	6168 (33)	3938 (21)	4697 (26)	2463 (13)	1122 (6)	47261

CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Outcomes

For the meta-analysis, we assessed the outcome of SE for inducible ischaemia (at least one of the 17 left ventricular segments showed worsening RWMA) and the long-term outcome on all-cause mortality or cardiovascular mortality and non-fatal myocardial infarction, depending on the definition applied in individual trials, defined as composite MACE as primary outcome. The secondary endpoint was all-cause mortality.

Statistical analysis

A common-effect meta-analytical model was specified to estimate a common effect of SE on composite MACE and all-cause mortality. Study-specific ORs were calculated based on the number of events and participants, then pooled using the Mantel-Haenszel method for each study outcome. A Wald-type statistical test for the hypothesis of no common effect of SE was conducted with reference to a standard normal distribution with a significance level of 5%. Statistical heterogeneity across studies was assessed using the Cochran Q statistic with the I^2 statistic and formally tested with reference to a χ^2 distribution. I^2 values of <25%, 25–50% or more than 50% were regarded as being indicative of low, moderate or high heterogeneity, respectively.[12] A forest plot, displaying the point estimate of the effect size and the corresponding 95% CI, was presented separately for MACE and all-cause mortality. A leave-one-out sensitivity analysis was conducted for each outcome to evaluate the impact of each study to the summary estimate of effect. Funnel plots in the online supplemental file 3 illustrate the potential for publication bias with the individual ORs for the endpoint of interest. A subgroup analysis was conducted to identify sources of heterogeneity, evaluating the effect of stressor agents and prevalence of previous CAD sample size. Annualised event rates for each study were calculated by dividing the number of events by the follow-up duration. A *negative test* was indicative of low risk and a *positive test* suggested a high risk of events. Statistical analysis was performed using Review Manager V.5 software (Review Manager (RevMan) (computer program) V.5.4 and The Cochrane Collaboration, 2020) and SPSS (V.18.0; IBM).

RESULTS

Study inclusion

A total of 542 records were identified through the search, as specified above. The title and abstracts were retrieved for evaluation. Out of these, 533 were excluded initially, and nine records were further reviewed as potential articles. Three out of the remaining nine were further excluded following a full-text assessment of eligibility. The remaining six, published between 1 January 2000 and 1 January 2023, were selected for the meta-analysis from the pool (online supplemental figure S1).[13–18] A total of 16581 patients underwent either pharmacological (dobutamine or dipyridamole) or treadmill SE with median follow-up of 31 months (range 21–101 months). Jeetley *et al* excluded seven participants (three tests were not performed and four deemed inconclusive[13]), Laiq *et al* and Porter *et al* excluded nine subjects each due to incomplete tests[14 15] and Zacharias *et al* excluded one subject with an inconclusive test.[16] The mean age was 59 years (range 55–63) and 59% (range 44–70) were male, 56% (range 40–70) had hypertension, 48% (range 35–55) had dyslipidaemia, 33% (range 14–65) were current smokers, 21% (range 14–100) had diabetes mellitus, 26% (range 0–31) had a history of myocardial infarction, 13% (range 0–16) had prior percutaneous coronary intervention and 6% (range 0–9) had prior coronary artery bypass graft surgery (tables 1 and 2).

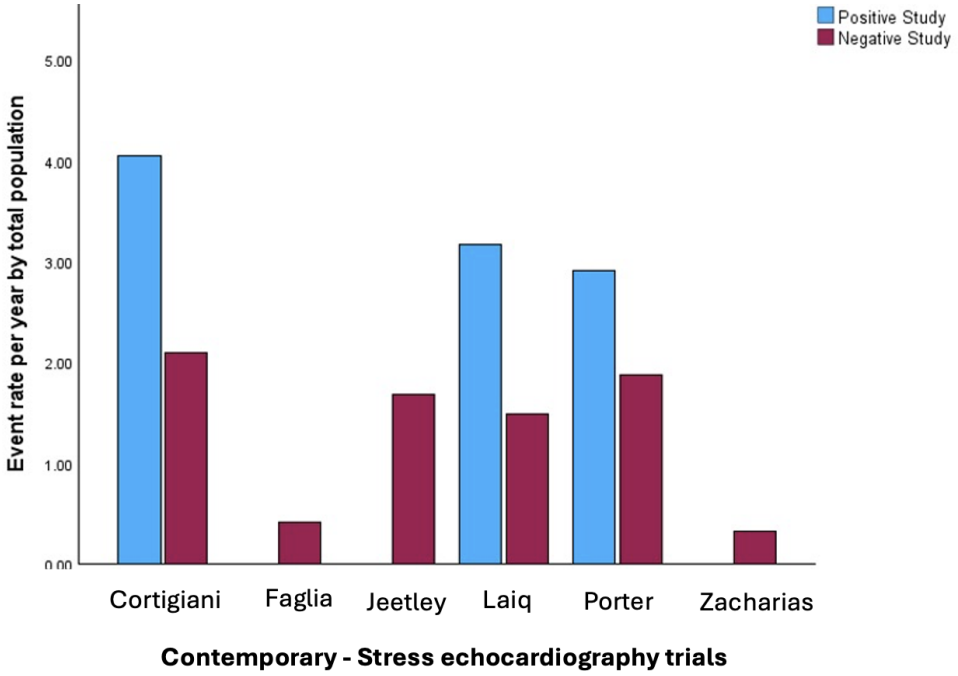

Figure 1 The effect of stress echocardiography outcome on the annual composite major adverse cardiovascular event (MACE) rate for the individual studies.

Meta-analysis of SE result on long-term outcome

Composite outcome: MACE

A total of 16565 patients from six studies with a median follow-up of 31 months (range 21–101 months) reported a composite MACE. Inducible ischaemia was found in 3829 individuals, while 12743 individuals had a negative test (table 1). The overall annual event rate was 1.76% for MACE (figure 1). Positive SE was associated with a MACE rate of 1.99% compared with 1.54% for a negative SE result (OR 2.04, 95% CI 1.79 to 2.33) (figure 2).

All-cause death

Five studies, pooling 15546 individuals, reported all-cause death or cardiovascular death. Inducible ischaemia was reported in 3603 patients, while 11940 had a negative SE. The overall annual event rate for death was 1.35%. The annual event rate for a positive SE was 1.68% compared with 1.02% for a negative SE result (OR 2.06, 95% CI 1.80 to 2.35) (figure 3).

Sensitivity and subgroup analysis

The *removal* of studies in which the stress agent was *dipyridamole* significantly reduced the total number of participants. However, positive dobutamine and exercise SE results remained prognostic indicators for both outcomes (OR 1.97 (95% CI 1.24 to 3.12) for the composite MACE and OR 2.61 (95% CI 1.26 to 5.38) for all-cause mortality). There was no indication of heterogeneity in this effect (χ^2=0.80 and 0.64, p=0.85 and 0.73, respectively).

Subgroup analysis of patients *with or without prior myocardial infarction* showed an association with positive SE and worse outcome; 2.03 (95% CI 1.77 to 2.32) and 2.04 (95% CI 1.78 to 2.34) for patients *with previous myocardial infarction* and 2.21 (95% CI 1.08 to 4.51) and 2.80 (95% CI 1.32 to 5.93) for patients with *no prior myocardial infarction* for all-cause mortality and MACE, respectively.

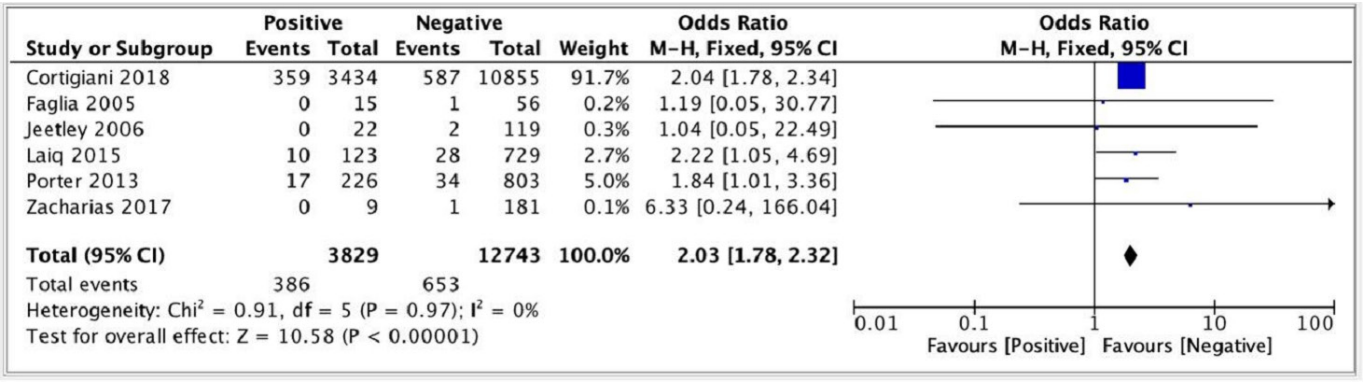

Figure 2 Meta-analysis of composite major adverse cardiovascular event (MACE) of patients undergoing stress echocardiography.

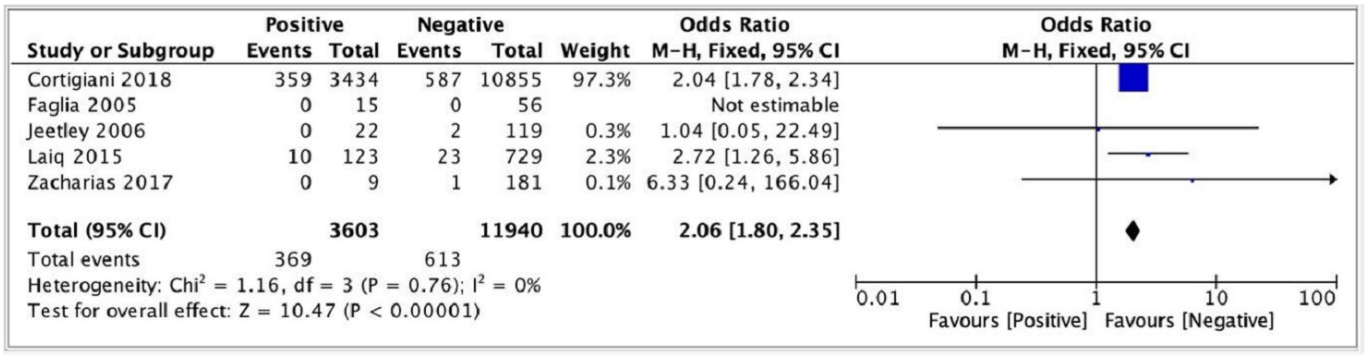

Figure 3 Meta-analysis of all-cause or cardiovascular death of patients undergoing stress echocardiography.

Risk of bias

The Risk-of-Bias Visualization tool was used to construct a table to visualise the risk of bias inherent in each study.[10 12] An independent reviewer evaluated each piece of literature against the guidelines outlined in the Cochrane Handbook, encompassing five major domains which we listed as an online supplemental file 3.In addition, we used the GRADEpro analysis tool to analyse the certainty of our assessments by rating the quality of our retrieved evidence (online supplemental table S1). Using the tools provided in the Cochrane Handbook to assess the risk of bias, the major limitations of the studies were a high level of uncertainty around the blinding of participants and personnel, with a high risk of bias in this domain assessed in four of the six papers included as part of this meta-analysis (figure 4).[10 12] However, due to the generally favourable assessment of the other six domains, and the overall low to unclear risk of bias, the authors do not believe this should warrant downgrading of the quality of evidence based on study design or execution. In addition, the funnel plot shows that publication bias is not a significant contributor to this study (online supplemental figure S2).

DISCUSSION

In this systematic review and meta-analysis recruiting 16 581 patients from six studies who underwent SE since 2000 over a 23-year period for suspected or known CAD, we found that inducible ischaemia was associated with worse long-term outcomes. Both composite MACE and all-cause mortality fared worse in patients with a positive SE (figure 5). The novelty of our study stems from the selected search criteria that guaranteed the recruitment of the highest quality studies with the longest follow-up analysing both the impact of positive as well as negative SE results on MACE and all-cause mortality. The selection of the publication dates after 2000 also assured the recruitment of the SE studies using the most contemporary echocardiographic equipment, and most of the studies used UEA to improve visualisation of the left ventricle endocardial border for wall motion analysis.

Individual observational and clinical trials using randomised design have shown a strong association between the SE outcome, based on inducible ischaemia due to development of new RWMA during SE, and MACE. Most of these trials had short-term follow-up.[9] Our review encompasses the most contemporary

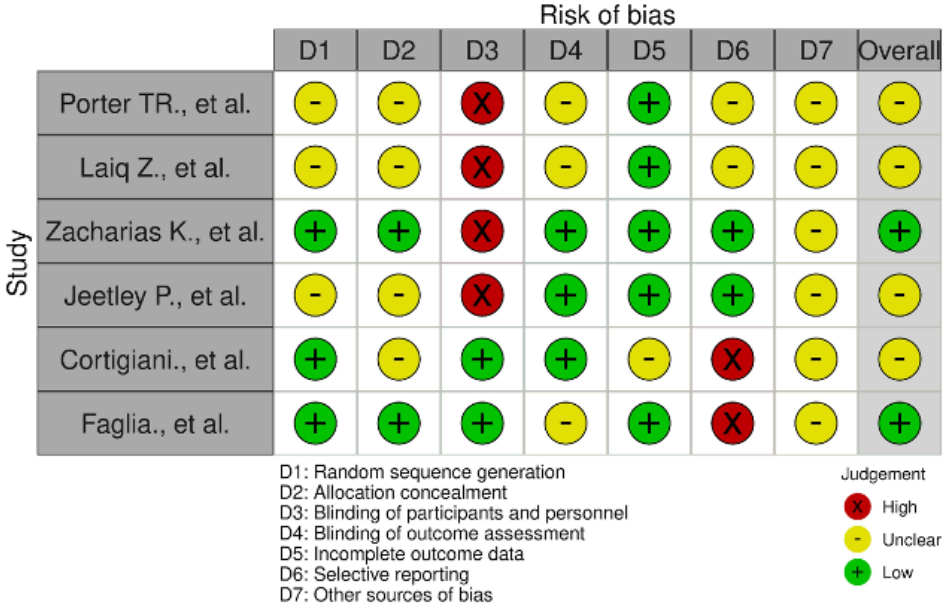

Figure 4 Risk of bias analysis.

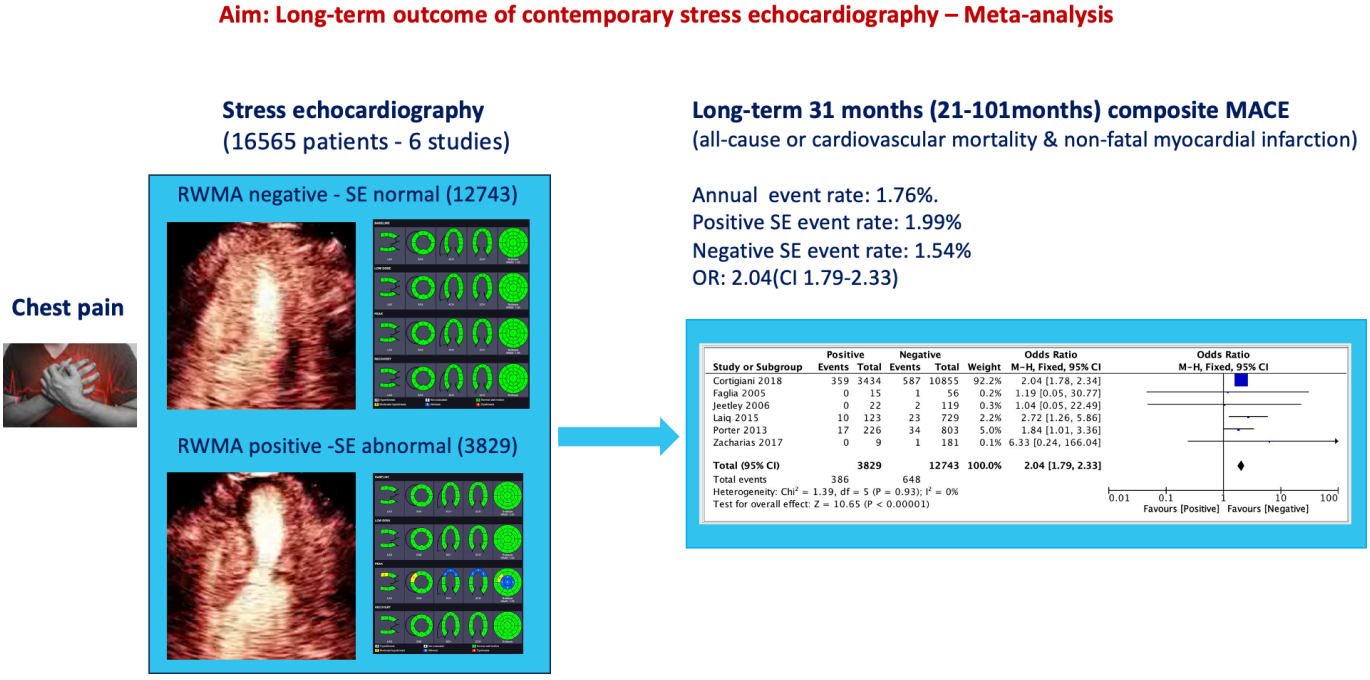

Figure 5 Graphical abstract. MACE, major adverse cardiovascular event; RWMA, regional wall motion abnormality; SE, stress echocardiography.

and longest SE follow-up analysis. Positive SE studies are associated with strong prognostic prediction irrespective of the degree of angiographic coronary artery stenosis especially when dobutamine was used.[19] Patient with non-occlusive CAD and positive SE are at high risk of cardiovascular events especially when reduced Doppler-based coronary flow velocity reserve (CFVR) in the distal left anterior descending (LAD) artery is considered.[20 21] Multiparametric SE is a promising proposition in diagnosing all phenotypes of CAD.[22] Validation studies of SE in the past relied on correlating SE outcome to predict degree of coronary artery stenosis.[2 23] A recent opinion paper by Shah and Senior eloquently proposed the usage of 'anatomical–functional imaging mismatch' to overcome the discrepancies and acknowledge the prognostic value of positive SE also in patients with non-occlusive CAD.[24] Addressing these parameters is outside the scope of this meta-analysis.

We have chosen the literature search from 2000 as it coincided with the introduction of UEA by the international societies[7 8] for left ventricular endocardial border delineation and hence more accurate wall motion analysis. In addition, there was a significant improvement in ultrasound technology to support image acquisition on all echocardiographic platforms. This gave us the possibility to assess contemporary SE practices. For example, the EVAREST multicentre trial in 31 UK hospitals confirmed a 73% usage of UEA with an excellent negative and positive predictive accuracy.[9]

The sensitivity analysis showed that our results were consistent across the spectrum of stressors including dobutamine, dipyridamole or exercise SE and was similar in patients with and without prior known CAD. Similar observations were reported for perfusion cardiac MRI (pCMR) despite guideline-directed medical therapy (GDMT) patients with inducible perfusion abnormality having poorer outcome.[25] However, a retrospective cohort study on >31 000 patients and 6-year follow-up showed that pCMR-guided revascularisation improved all-cause death but only in those with ≥6 segment inducible perfusion abnormality during vasodilator stress.[26]

The observational CLARIFY registry of 20 000 participants suggests an 8% 5-year risk of cardiovascular death or myocardial infarction with the current management of chronic coronary syndrome.[27] This was, however, in a population with documented myocardial infarction, coronary artery stenosis of at least 50%, chest pain with evidence of myocardial ischaemia during SE or coronary artery bypass grafting percutaneous coronary intervention in the last 3 months. Interestingly, 58.2% of individuals had a combined outcome of cardiovascular death or myocardial infarction without angina or ischaemia. Indeed, only 17.3% of the combined outcome was observed in patients with both angina and ischaemia, with 12.2% in patients with angina alone and 12.4% in patients with ischaemia alone. This may suggest that ischaemia assessed by inducible RWMA may well not be the final arbiter for the likelihood of future hard events accepting that the extent of ischaemia is prognostically important and influences plan for revascularisation. In addition, maybe RWMA may be just part of the imaging biomarkers, and other parameters such as CFVR in the distal LAD can add to the diagnostic and prognostic accuracy.[20 21]

In their systematic review and meta-analyses comparing the prognostic value of negative non-invasive functional and anatomical cardiac tests (such as SE, CMR, myocardial perfusion scintigraphy, positron emission tomography (PET) and coronary CT angiography), Smulders *et al* showed that a negative SE had an excellent prognosis for patients with suspected or known CAD.[5] The annualised combined MACE rates for SE in that meta-analysis were 1.66% compared with the recent analysis of 1.54%. This study has recruited studies between January 1990 and April 2015. Of the 36 SE studies, 50% were published prior 2000, and nine of the remaining 18 studies from later than 2000 had studied special populations only, such as women only, elderly patients and Afro-Americans only, and one study used ergonovine stress test. The slightly higher composite MACE rate may be due to the difference in the selected studies that were 10 years earlier with the inherent problem of older ultrasound technology and the lack of UEA approval at that time, hence,

less accurate RWMA detection. The alteration in management of CAD over that period as well as the studied special population in some of the studies may also contribute to the difference.

Limitation

We have recruited solely clinical trials using randomised design in the hope of maximising the quality of the acquired data, hence, our observed lower risk of bias in our data collection. We selected trials with limited proportion of patients with prior myocardial infarction to reduce confounders of test results and associated prognosis. We did not have detailed information regarding medical therapy and frequency and type of revascularisation for patients with a positive SE result. Nevertheless, those patients would have been prescribed and received GDMT that would have improved their long-term outcome.

A binary result of either a positive or negative SE was assessed; however, the extent of a positive result defined as the number of ischaemic segments in the left ventricle could have an impact on the outcome. Nevertheless, a positive SE result yielded a worse outcome compared with a negative SE result. Investigating the population event risk would be interesting as an important factor affecting the annualised event rate; however, due to the insufficient number of studies and necessary information needed for such analysis this was not possible. Additional information to provide the estimate of the overall annual event risk can be found in the online supplemental table.

Finally, although the study by Cortigiani *et al* provided the preponderance of the data,[18] the OR in the remaining studies remained statistically significant.

CONCLUSION

This meta-analysis established a correlation between positive SE results and an increased risk of adverse long-term outcomes, including a composite MACE as well as all-cause death in isolation. We also confirmed prior results that negative SE has a good long-term prognosis. In summary, SE results may provide a useful long-term prediction and could facilitate guidance in delivering GDMT in patients with suspected or known CAD.

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Contributors AK conceived the research idea, assisted with literature review, meta-analysis and data analysis, contributed to drafting and finalising of the paper, performed literature review, data analysis and statistical analysis, drafted the initial manuscript, gave critical appraisal of the final draft, served as the corresponding author and acted as the guarantor. UI assisted in finalising of the research protocol, performed literature review, meta-analysis and statistical analysis, and contributed to drafting and finalising of the paper. NJ and JSC assisted with literature review, meta-analysis and data analysis, contributed to drafting of the manuscript and gave critical appraisal of the final draft. GS and NO provided with their expertise in advising the method of meta-analysis, helped with drafting of the manuscript and gave critical appraisal of the final draft. JK and IS helped with drafting of the manuscript and gave critical appraisal of the final draft.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study adhered to the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent revisions.

Provenance and peer review Not commissioned; externally peer reviewed.

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