openheart

Prognostic relevance of a false-positive stress echocardiography response: a systematic review and meta-analysis

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2025-003690).

To cite: Bennett S, Sattwika PD, Tafuro J, *et al*. Prognostic relevance of a false-positive stress echocardiography response: a systematic review and meta-analysis. *Open Heart* 2025;**12**:e003690. doi:10.1136/openhrt-2025-003690

Received 6 September 2025
Accepted 16 September 2025

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ABSTRACT

Background Stress echocardiography is a widely available and used imaging modality in the assessment of ischaemic heart disease (IHD) and preoperative risk stratification. Despite the higher rate of major adverse cardiovascular events (MACE) observed in positive stress echocardiography results, the prognostic relevance of a false-positive (FP) stress echocardiogram is unclear.

Methods The authors searched Medline, Embase, CINAHL, Web of Science, The Cochrane Central Register of Controlled Trials, EBSCO Open Dissertation and Clinicaltrials.gov from inception to 15 April 2024, for studies evaluating the prognostic relevance of a FP stress echocardiogram response in patients with suspected or known IHD. Primary outcomes included the occurrence of MACE within the studied follow-up duration. Random effects meta-analysis was performed to evaluate the direction of effect and allow comparisons between FP, true-positive and true-negative stress echocardiography results.

Results A total of five studies were included with 2426 patients (mean age 56–66 years, 60.2% males). In total, there were 737 (30.3%) FP stress echocardiogram results. MACE occurred in 274 participants, of which 79 (28.8%) occurred within the FP stress echocardiography group. Meta-analysis from three studies demonstrated more MACE outcomes in patients with a true positive in comparison to a FP stress echocardiography result (RR 1.64, 95% CI: 1.22 to 2.20). Two studies reported increased MACE outcomes in patients with a FP result when compared with a true negative result.

Conclusions An FP stress echocardiogram result is common and frequently associated with patients who have a low pre-test probability for IHD. FP results are not associated with increased incidence of MACE when compared with true positive results; however, there is insufficient evidence to establish whether FP results in dobutamine stress echocardiography identify a cohort of high-risk patients in comparison to true negative results.

PROSPERO registration number CRD 42024526741

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ False-positive stress echocardiography results are common and frequently related to patients with a low pre-test probability of ischaemic heart disease. The outcomes of patients who have false-positive stress echocardiography results are not well understood.

WHAT THIS STUDY ADDS

⇒ False-positive stress echocardiography results are associated with a lower risk of major adverse cardiovascular events compared with true-positive stress echocardiography results.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies should seek to establish whether false-positive results on dobutamine stress echocardiography identify a high risk of patients compared with true-negative results.

INTRODUCTION

Stress echocardiography is an established and widely used non-invasive functional imaging tool for the detection and risk stratification of patients with suspected or known ischaemic heart disease (IHD) or, for patients with high preoperative risk profiles.[1 2] Stress echocardiography can be undertaken using a number of stressors including exercise, dobutamine, dipyridamole or pacing.[3] Stress echocardiography has been shown to have high diagnostic accuracy,[4 5] reliable prognostic value in the management of patients[6] and is a cost-effective non-invasive imaging modality.[7]

Sensitivity and specificity rates for stress echocardiography have been reported as 85% and 75%, respectively, for exercise stress, 80% and 86% for dobutamine stress and 93% and 92% dipyridamole as a stressor.[8] For the detection of significant IHD on stress echocardiography, a positive response related to the stressor is required and involves the presence of new, or worsening left ventricular (LV) wall motion abnormality being present, compared with baseline echocardiography imaging.[3 9]

A recent systematic review and meta-analysis indicated that positive stress echocardiography results were associated with an

increased risk of all-cause mortality and major adverse cardiovascular events (MACE).[10] However, this review did not consider the impact of false-positive (FP) stress echocardiography results, whereby the stress echocardiogram result indicates the presence of IHD, which is not subsequently confirmed on coronary angiography.[11]

An FP stress echocardiography result has previously been associated with low risk patients cohorts,[12] chest wall deformities[13] and hypertensive response to exercise testing.[14] As such, an FP result has previously been considered as being benign.[15] However, there is also evidence to suggest that FP results are associated with a higher rate of MACE.[3 16 17] Therefore, this systematic review aims to evaluate and summarise the available evidence on the prognostic relevance of a FP stress echocardiogram for patients undergoing stress echocardiography for the assessment of IHD or preoperative risk stratification.

MATERIAL AND METHODS

Protocol registration

The protocol of the systematic review has been registered in PROSERO with the registration number CRD 42024526741. This protocol is available at:

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=526741. As this is a systematic review and meta-analysis, ethical approval was not required.

Search strategy and eligibility criteria

We searched Medline, Embase, CINAHL, Web of Science, The Cochrane Central Register of Controlled Trials, EBSCO Open Dissertation and Clinicaltrials.gov for all study types from inception until 15 April 2024. Electronic searches were complemented by manually searching all reference lists of identified studies and reviews for additional studies. We used subject headings and text words such as "stress echocardiogra*" OR "exercise echocardiogra*" OR "dobutamine echocardiogra*" OR dipyridamole echocardiogra*" combined with "diagnostic errors" OR "false positive" OR misdiagnos*, as well as their common synonyms. Restrictions involved non-English language, animal studies, conference abstracts, case reports/series, letters, editorials and reviews. The complete search strategy is shown within the Supplementary Data. Preferred Reporting Items for Systematic Reviews and Meta-Analysis[18] were applied to the search strategy; this can also be found in the supplemental material.

One reviewer (MS) conducted the initial search and removed duplications. Three reviewers (SB, PDS and JT) independently screened all articles by title and abstract. Three reviewers (SB, PDS and JT) then read the full text of potentially eligible items and decided on which studies to include. Discrepancies were resolved by discussion.

Study inclusion criteria included: original reports that reported MACE, all-cause and/or cardiovascular mortality outcomes on patients (aged ≥18 years of age) who had a FP stress echocardiogram for the assessment of IHD. MACE was defined as acute myocardial infarction, stroke and hospitalisation for unstable angina, revascularisation procedures or heart failure.[19 20] We excluded reports where patients underwent stress echocardiography for any other clinical reason, reports using CT or cardiac MRI to establish the diagnosis of IHD or where no outcome data was reported for MACE, all-cause and/or cardiovascular mortality.

Data extraction

Data extraction was undertaken by SB using a standardised data extraction form[21] and independently checked by PDS and JT. The following information was extracted from eligible studies: first author, year of publication, study registration, setting, study design, inclusion and exclusion criteria, participant numbers and characteristics, type of stress echocardiogram, follow-up duration, outcome definition, mean and SD for continuous data. Authors of the included studies were contacted if the required data could not be extracted from the published article. The completed data extraction table can be seen in the supplemental material.

Risk of Bias and quality of evidence assessment

The risk of bias was independently assessed by SB, PDS and JT using the Newcastle Ottawa Scale.[22] The tool uses a 'star system' whereby a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest. Discrepancies were resolved by discussion. The Newcastle Ottawa Scale that was used for this systematic review can be seen in the supplemental material. The standard Newcastle Ottawa Scale threshold for assessing study quality was used; this included studies being rated as 'poor quality', 'fair quality' and 'good quality'. These ratings were based on a study being awarded 0–2 stars, 5–7 stars or 6–9, respectively, for the categories of selection, comparability and outcome.[22]

Data synthesis and statistical analysis

We performed statistical analysis and created forest plots using R (V.4.3.1) and R Studio (V.2024.04.0+735). The rates of MACE as dichotomous outcomes were analysed using the risk ratio (RR) measure with 95% CIs. The Mantel-Haenszel random-effects model was used to estimate effect sizes. To understand the direction of effect and allow relative comparison between FP, true-positive and true-negative stress echocardiography groups, we presented forest plots summarising the MACE occurrence in both true-positive and true-negative relative to FP stress echocardiography group. The statistical heterogeneity among included studies was assessed by a χ^2 test on N-1 df with an alpha of 0.05 for statistical significance. The I^2 analysis was performed to detect the magnitude of variation attributable to heterogeneity rather than to chance with values of 25%, 50% and 75% corresponding to low, medium and high levels of heterogeneity.

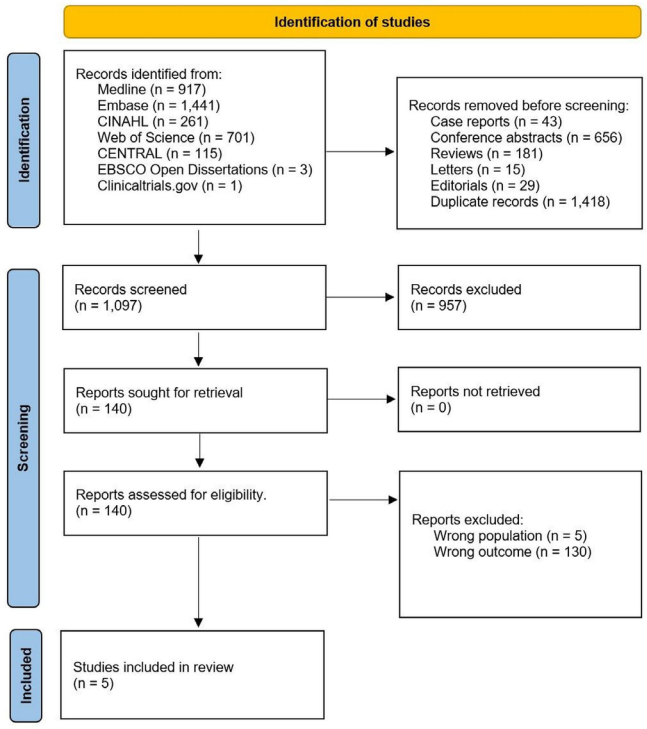

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of study selection.

Publication bias was assessed using Egger's regression test and visualised with funnel plot, as appropriate given the known limitations of these methods.

RESULTS

Characteristics of included studies

The search was conducted on 15 April 2024 and identified 1097 records from electronic databases. After full text screening (see figure 1), we included five eligible studies.[16 23–26] A description of the design of the studies, participant demographics, stress echocardiography protocols and participant inclusion criteria is shown in table 1. All of the included studies were observational in study design; three were retrospective[16 23 24] and two prospective in nature.[7 14] In total, 2426 participants were included. The range of mean age across the studies was 56–66 years, and the proportion of male patients was 60.2%. The mean follow-up duration varied between studies and ranged from 1.5 years to 7.1 years. Stress echocardiography positivity was reported as the onset of a new regional wall motion abnormality (RWMA). Only two studies defined this as a RWMA in ≥2 continuous LV segments.[24 26] In the remaining three studies,[16 23 25] no comment was made on the number of LV segments that needed to demonstrate a RWMA in order to confirm test positivity. Timeframes between the stress echocardiogram and coronary angiography were reported within 4 of the included studies and ranged from 15 days to 365 days.[16 23 24 26] In four studies, the definition of lesion on coronary angiography included: mild coronary artery disease defined as <50% stenosis and significant stenosis as ≥50% in ≥1 coronary arteries or major branches.[23–26] The remaining study defined a lesion on coronary angiography as non-obstructive where a lesion was visually assessed as being between 30% and 50% stenosed.[16]

Risk of bias

The study quality assessment is shown within the supplemental material (online supplemental table S1). All included studies were representative of the participants undergoing a stress echocardiogram. All included studies demonstrated reliable selection of control groups, reliable ascertainment of exposure (stress echocardiography), certainty that outcome was not present at the start of the study, reliable ascertainment of outcome (all-cause and cardiovascular related mortality) and adequate duration of follow-up. All studies had an adequate length of follow-up; only one study reported a 3% patient loss to follow-up, and[24] the remaining studies had no patients lost to follow-up. Only one study demonstrated the comparability of study groups on the basis of the design or analysis.[16] The average number of stars using the Ottawa-Newcastle scale was seven out of nine stars (range six to eight stars) indicating the quality rating of the included studies to be good (intermediate risk of bias) or high quality (low risk of bias) in accordance with the Newcastle Ottawa Scale.[22]

Stress echocardiography testing protocols and results

In three studies, medical therapy was discontinued at least 48 hours prior to a patient undergoing a stress echocardiogram.[23–25] In Sicari *et al*, medical therapy was discontinued at the discretion of the referring physician. This resulted in medical therapy being discontinued in 359/457 (78.6%) patients.[26] In Ciaroni *et al*, medical therapy was not discontinued prior to stress echocardiography.[16] The most common stressor used was dobutamine (44%) followed by exercise (37.1%), dipyridamole (18.8%) and finally transoesophageal pacing (0.04%).

In total, there were 1204 (49.6%) true-positive results, 737 (30.4%) FP results and 485 (20%) true-negative results. In patients who had a FP result, the most common stressor was exercise (50.3%) followed by dobutamine (43.8%) and dipyridamole (5.8%). The number of ischaemia segments at peak stress was reported in three of the included studies.[23–25] In From *et al*, 40.8% of patients with a FP result had four or less ischaemic segments, the remaining patients (59.1%) had five or more ischaemic segments.[23] In Rachwan *et al*, the FP group had severe RWMAs (defined as two or more ischaemic segments) in 47% of patients.[24] Finally, Aboukhoudir *et al*. reported 79.3% of patients with a FP result had less than four segments of ischaemia.[25]

FP responses and patient characteristics

Patient characteristics that were associated with a FP result were reported in all five studies. In From *et al*, increasing age was associated with a significant reduction in a FP stress echocardiogram (every 10 year increase

Table 1 Study design and participant characteristics

Study ID	Study design; country; year	Number of analysed participants	Mean age	Percentage male	Stress echo protocol	Participant inclusion criteria
Aboukhoudir *et al*	Prospective single centre study; France; 2010–2012	93	60	59	DSE	Patients who had a coronary angiogram with 12 months of stress test.
Ciaroni *et al*	Prospective single centre cohort study; Switzerland; 1993–2000	94	63	58.5	DSE	Patients with suspected or known IHD, who were assessed with DSE and who had >30% and <50% stenosis of at least one major epicardial vessel on coronary angiography within 27 days of DSE.
From *et al*	Retrospective single centre cohort study; USA; 2003–2006	1477	66	61	Treadmill stress, transoesophageal pacing or DSE	Patients with (1) normal LVSF (no RWMAs at rest), a markedly abnormal LV response to stress and had coronary angiogram within 30 days of stress test. Angiographically mild CAD was defined by the presence of <50% stenoses and angiographically significant CAD by the presence of ≥50% stenoses in ≥1 of the coronary arteries or major branches. Patients with ≥70% stenoses were also identified.
Rachwan *et al*	Prospective single centre cohort study; USA; 2013–2017	305	60	59	DSE or treadmill stress	Patients with a history of chest pain, stress echo and who underwent coronary angiography within 15 days of the stress echo and coronary angiogram. Coronary angiogram showing either absent or non-significant (<50% visually) stenosis in any major vessel or secondary branch.
Sicari *et al*	Retrospective single centre cohort study; Italy; 1983–2002	457	56	54	DSE or dipyridamole	Patients suspected of IHD for DSE.

CAD, coronary artery disease; DSE, Dobutamine stress echocardiography; IHD, ischemic heart disease; LV, left ventricle; LVSF, left ventricular systolic function; RWMA, regional wall motion abnormality.

in age, OR 0.75, 95% CI 0.62 to 0.89, p=0.001), while female gender (OR 3.98 (95% CI 2.61 to 6.12, p<0.001), absence of diabetes mellitus (OR 2.45, 95% CI 1.43 to 4.33, p<0.001), no history of IHD (OR 7.52, 95% CI 4.33 to 13.9, p<0.001) and negative results on stress electrocardiogram (OR 2.61, 95% CI 1.71 to 4.01, p<0.001) were all associated with an increased risk of a FP stress echocardiogram. In Rachwan *et al*, patient characteristics associated with a significant reduction in the odds of a FP stress echocardiogram included female gender (OR 0.48, 95% CI 0.28 to 0.83, p=<0.001), absence of diabetes mellitus (OR 0.54, 95% CI 0.31 to 0.93, p=0.027), no history of IHD (OR 0.41, 95% CI 0.22 to 0.75, p=0.004) and a lower stress wall motion score index (OR 0.26, 95% CI 0.07 to 0.87, p=0.029).[23] Aboukhoudir *et al.* reported hypercholesterolaemia (HR 21.3, 95% CI 3.45 to 131.7, p=0.001) and less than four segments of ischaemia at peak stress (HR 4.3, 95% CI 1.14 to 16.23, p=0.034) to be associated with an increased odds of having a FP result.[25] In Sicari *et al*, compared with patients with a true negative result, a FP result was associated with a higher incidence of family IHD (59% vs 41%, p=0.003) and a higher proportion of smokers (53% vs 35.4%, p=0.002).[27] Finally, Ciaroni *et al.* highlighted that patients with a FP result, compared with a true negative result, were more likely to present with a family history of IHD (65% vs 13%, p<0.01), hypertension (74% vs 7%, p<0.01) and hypercholesterolaemia (61% vs 15%, p<0.01).[16] In Rachwan *et al*, females and non-diabetics were associated with FP results.[24]

Primary outcomes

MACE occurred in 274 patients (11.3% of overall participants), of which 79 (10.7%) occurred in patients who had a FP result, 166 (13.8%) occurred in patients who had a true positive result and 49 (10.1%) occurred in patients with a true negative result. Tables 2–4 highlight the number of FP, false-negative and true-negative results along with patient outcomes.

A meta-analysis from three studies which compared FP results versus true-positive results[23–25] demonstrated

Table 2 Number of participants with false-positive, true-positive or true-negative stress echocardiography results

Study ID	Number of analysed participants	False-positive result (% of analysed participants)	True-positive result (% of analysed participants)	True-negative result (%)
Aboukhoudir *et al*	93	29 (31.2%)	64 (68.8%)	N/A
Ciaroni *et al*	94	23 (24.5%)	N/A	71 (75.5%)
From *et al*	1477	480 (32.5%)	997 (67.5%)	N/A
Rachwan *et al*	305	162 (53.1%)	143 (46.9%)	N/A
Sicari *et al*	457	43 (9.4%)	N/A	414 (90.6%)

more MACE outcomes in patients with a true positive in comparison to a FP stress echocardiography result (1204 patients with true positive and 671 patients with FP, RR 1.64, 95% CI 1.22 to 2.20) with no significant heterogeneity demonstrated among the studies (I^2=29%, p=0.24), as displayed in figure 2.

In the two studies that compared patients with a true-negative stress echocardiogram result to patients with a FP stress echocardiogram result, Ciaroni *et al*. reported that patients with a FP result had a significantly higher annual rate of MACE (7.9% vs 0.2%, p<0.001).[16] In Sicari *et al*, patients with a true-negative result had significantly fewer MACE outcomes over a follow-up duration of 7.1 years compared with patients with a FP result (18% vs 7.2%, p=0.018).

DISCUSSION

This systematic review and meta-analysis highlight the following key findings: (1) An FP stress echocardiogram result is common, is most likely to occur with exercise stress protocols and occurs more commonly in patients with fewer comorbidities for IHD. (2) Patients with a FP result have lower MACE in comparison to patients who have a true-positive stress echocardiography result. (3) There is insufficient evidence to confirm whether patients with an FP result on dobutamine stress echocardiography, in comparison to a true negative result, are at a higher risk of future MACE.

This systematic review indicates that FP stress echocardiography results are common, occurring in approximately 30% of patients undergoing stress echocardiography. Furthermore, exercise was the most common protocol in patients who had a FP result subsequently followed by the use of dobutamine. These findings are on the higher side of previously published literature whereby FP results have been reported to range from rates of 6%[28] to 28%.[23] Exercise protocols have previously been reported as being commonly associated with FP results due to hypertensive response to exercise,[15] worsening of non-ischaemic RWMAs including abnormal septal motion secondary to left bundle branch block,[29] a decrease in contractile response[30] and poor image quality resulting in the misinterpretation of wall motion changes.[31] However, literature on this is mixed, with some studies highlighting exercise stress echocardiography protocols as being most commonly associated with FP results,[13] whereas other studies suggest there to be similar rates of FP results among exercise, dobutamine and dipyridamole protocols.[12]

This review highlights that true-positive results have a higher incidence of combined mortality (all-cause or cardiovascular related) and MACE in comparison to FP results. These findings are not surprising given previous literature indicating true positives to be associated with higher MACE.[3 10 32] Furthermore, this finding supports recent arguments whereby FP results may be due to an overestimation of the pre-test probability of IHD,[13 33] particularly as patient characteristics that are associated with FP results generally included low-risk patients cohorts, including young patients, female gender and those with an absence of IHD risk factors including diabetes mellitus, hypertension and a history of IHD.[29 34 35] As it is known that the prevalence of FP results is determined by disease prevalence among the studied population,[36] there is an argument for stress echocardiography being unnecessarily used within low cardiovascular

Table 3 Overall number of participants with mortality (all-cause or cardiovascular) and major adverse cardiovascular events reported for false-positive, true-positive or true-negative stress echocardiography results

Study ID	Overall number of outcomes (%)	False-positive outcomes (%)	True-positive outcomes (%)	True-negative outcomes (%)
Aboukhoudir *et al*	21 (22.6%)	2 (6.9%)	19 (29.7%)	N/A
Ciaroni *et al*	13 (13.8%)	11 (47.8%)	N/A	2 (2.8%)
From *et al*	140 (13.8%)	35 (7.3%)	125 (12.5%)	N/A
Rachwan *et al*	42 (13.8%)	20 (6.6%)	22 (7.2%)	N/A
Sicari *et al*	58 (12.7%)	11 (25.6%)	N/A	47 (11.4%)

Table 4 Breakdown of participants with mortality (all-cause or cardiovascular) and major adverse cardiovascular events reported for false-positive, true-positive or true-negative stress echocardiography results

Study ID	Overall number of outcomes (%)	False-positive outcomes (%)	True-positive outcomes (%)	True-negative outcomes (%)
Aboukhoudir *et al* *(MACE: unstable angina)*	21 (22.6%)	Mortality (not defined): 0 (0%) MACE: 2 (6.9%)	Mortality (not defined): 0 (0%) MACE: 19 (29.7%)	N/A
Ciaroni *et al* *(MACE: myocardial infarction, unstable angina, revascularisation)*	Cardiovascular mortality: 1 (1.1%) MACE: 12 (12.7%)	Cardiovascular mortality: 1 (4.3%) MACE: 10 (43.5)	N/A	Cardiovascular mortality: 0 (0%) MACE: 2 (2.8)
From *et al*	All-cause mortality: 42 (13.8%)	All-cause mortality: 20 (6.6%)	All-cause mortality: (7.2%)	N/A
Rachwan *et al*	All-cause mortality: 42 (13.8%)	All-cause mortality: 20 (6.6%)	All-cause mortality: 22 (7.2%)	N/A
Sicari *et al* *(MACE: myocardial infarction)*	All-cause mortality: 38 (8.3%) Cardiovascular mortality: 14 (3.1%) MACE: 6 (1.3%)	All-cause mortality: 8 (18.6%) Cardiovascular mortality: 3 (7.0%) MACE: 0 (0%)	N/A	All-cause mortality: 30 (7.2%) Cardiovascular mortality: 11 (2.7%) Non-fatal MI: 6 (1.5%)

risk populations.[33] Future studies may wish to investigate the impact of incorporating these known, low-risk patient characteristics into the analysis of stress echocardiography results to identify whether this could highlight the cohort of patients who have a FP result, reducing the need for additional diagnostic testing and/or coronary angiography without detrimentally impacting on patient prognosis.

Only two of the eligible studies compared patients with a true negative result to a FP result.[16 27] The findings of these studies suggest that patients with a FP result have a higher incidence of combined mortality (all-cause and cardiovascular related) and MACE. Interestingly, both of these studies used dobutamine protocols; medical therapy was stopped in all patients within one study[27] and 78.6% of patients in the other study.[16] In both of these studies, patient characteristics that were associated with a FP result included patients with hypertension, smokers, family history of IHD, hypertension and high cholesterol. In the two studies that compared patients with a false-negative result to a FP result, anti-anginal medication was continued in all patients in Ciaroni *et al*[16] and stopped at the discretion of the referring physician in 79% in Sicari *et al*.[26] In both studies, mortality (all-cause and cardiovascular related) and MACE occurred in 2.8% and 11.4% of patients, respectively. However, these outcomes may be underestimated due to the lower test sensitivity which can occur when stress echocardiography is conducted on patients who continue anti-anginal medication therapy.[3]

This review highlights the need for further clarification regarding the incidence of mortality, MACE and prognostic outlook for patients with risk factors for IHD who have a FP result during dobutamine stress echocardiography. This may be particularly important for future treatment options, as previously this patient group would have been considered low risk and benign with anti-anginal medication being considered unnecessary.[15] However, this group may potentially reveal an important subset of patients who are at a higher risk of MACE who may benefit from aggressive medical therapy,[37] particularly as FP results using some protocols, for example, vasodilators such as dipyridamole, are less likely to be

Figure 2 Meta-analysis of composite major adverse cardiovascular event (MACE) in patients undergoing stress echocardiography. Figure 2 Legend: Meta-analysis of composite mortality (all-cause or not defined) and major adverse cardiovascular event (MACE) in patients undergoing stress echocardiography. The forest plot represents the composite outcomes risk ratio of true-positive relative to false-positive stress echocardiography group.

attributed to hypertensive responses, as is the case with exercise protocols, and instead are associated with true myocardial ischaemia.[38] Furthermore, FP results on stress echocardiography have previously been attributed to endothelial dysfunction, vasomotor changes and coronary microvascular dysfunction, the latter of which, being linked to a fivefold increase in MACE and nearly fourfold increase in mortality,[39] highlighting a potential spectrum of FP responses ranging from physiological responses to macro and microvascular disease. Additionally, FP results have previously been reported to be associated with high downstream costs secondary to increased non-elective cardiac-related hospital admissions in comparison to true-negative responses (£1445.74±600.52 vs £226.68±270.54).[40]

The definition of a positive result on stress echocardiography was inconsistent across the studies included within this review. Current guidance suggests proceeding to coronary angiography when moderate to severe forms of ischaemia are present on stress echocardiography.[41] However, while guidelines provide much needed structure to stress echocardiography reports enabling consistency,[9] there is a lack of consensus regarding what constitutes a 'moderate or severe' burden of ischaemia on stress echocardiography.[9 42] Inconsistency was also seen within the included studies between the number of ischaemic segments present in patients who had a FP result, with studies indicating less than four segments[25] of ischaemia and five or more segments[23] of ischaemia both being associated with FP result. Patients who have an FP result with five or more segments of ischaemia have previously been associated with a forme fruste of apical ballooning,[28] whereas patients with a FP result less than four ischaemic segments have been associated with coronary spasm[25] or misinterpretation of wall tethering, as can be noted in basal inferior regions of the LV.[13] Regardless of these findings, clearer definitions of what constitutes 'moderate to severe ischaemic burden' on stress echocardiography, in addition to what constitutes a FP result, have been advocated previously.[37] This may also limit the number of FP results which occur due to discrete abnormalities typically involved in one or two LV segments which are often associated with off-axis imaging planes, left bundle branch block, ventricular pacing, chest deformities and basal inferior and basal inferolateral LV abnormalities.[13 14 29 43] Furthermore, the definition of true positive and FP stress echocardiography results depends on the comparison with coronary angiography. However, only a small proportion of patients, typically those with higher clinical suspicion of significant IHD, will undergo coronary angiography.

The included studies were generally of good to high quality and were generalisable to the wider population of patients undergoing stress echocardiography, therefore minimising the risk of bias. However, this review has several limitations. First, there were a limited number of studies exploring our primary outcomes in patients with a FP stress echocardiography result, and there was also a clear lack of direct comparison to both patients who had a true-positive and true-negative study. Of the two studies that did explore this, patient cohorts and outcome event rates were small. Future studies should report on all stress echocardiography results and pertinent patient outcomes to ensure transparency of findings. Second, stress echocardiography protocols varied across the included studies in terms of the discontinuation of medication prior to the stress echocardiogram and in reporting the presence of ischaemia. Third, all studies included a patient group who had had a FP result which may overestimate the true incidence of FP results and associated outcomes. Finally, due to the limited number of included studies, small participant numbers and varying definitions of outcomes within this review, we elected to combine mortality (all-cause and cardiovascular) with MACE. However, it has been noted that the use of composite outcomes such as MACE can inflate event rates, whereas hard endpoints like mortality are of greater clinical significance. This is because composite outcomes are often driven by more frequent but less clinically meaningful events (eg, repeat revascularisation or rehospitalisation), leading to statistically significant findings that may not accurately reflect true clinical benefit.[44]

CONCLUSION

This systematic review and meta-analysis highlight that FP stress echocardiogram results are common, frequently associated with patients who have a low pre-test probability. An FP result is not associated with increased incidence of MACE when compared with true-positive results. There is insufficient evidence to establish whether FP results on dobutamine stress echocardiography identify a cohort of high-risk patients in comparison to true-negative results.

Acknowledgements SB is an ICA Pre-doctoral Clinical and Practitioner Academic Fellow supported by the National Institute for Health and Care Research.

Contributors PL and SB were involved in the conception of the review. MS developed the search strategy and performed the systematic search. SB, PDS and JT undertook the titles/abstracts screening, data extraction and risk of bias assessment. SB and PDS analysed the data. SB wrote the manuscript and is the guarantor. All authors critically revised the manuscript and approved the final version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; internally peer-reviewed.

Data availability statement Data are available upon reasonable request.

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