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Long-term prognostic value of myocardial perfusion scintigraphy in patients with suspected coronary artery disease: systematic review and meta-analysis

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ABSTRACT

Background Long-term outcome of contemporary myocardial perfusion scintigraphy (MPS) has not been assessed systematically.

Objective To evaluate the association between results of MPS and long-term outcomes for patients with suspected coronary artery disease (CAD).

Methods Electronic databases were searched for Randomised controlled trials evaluating long-term outcome (≥12 months) of MPS in patients with suspected of CAD since year 2000. A meta-analysis adopting the random effects model was used to derive pooled estimates. The primary outcome was the composite of all-cause or cardiovascular mortality and non-fatal myocardial infarction as defined in individual trials, termed as major adverse cardiovascular event (MACE). Secondary outcome was all-cause or cardiovascular mortality. Positive MPS result was defined as reversible perfusion defect in any coronary artery territory.

Results Four trials fulfilled the search criteria. A total of 1764 patient had MPS with a median follow-up of 35.7 months (range 17–57). The mean age was 59 years and 50% were male. Fifty-three per cent had hypertension, 43% had dyslipidaemia, 15% were current smokers and 61% had diabetes mellitus. The overall annual event rate was 1.42% for the composite MACE and 0.22% for all-cause or cardiovascular mortality. Compared with negative MPS results, positive MPS was associated with an increased risk of the composite MACE and all-cause or cardiovascular mortality with an annual event rate of 2.16% versus 0.66%, OR 2.71 (1.38, 5.32) and 0.34% versus 0.10%, OR 3.41 (1.44, 8.11), respectively.

Conclusion In this meta-analysis, reversible perfusion defect on MPS was associated with higher risk of composite MACE, and that of all-cause or cardiovascular mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myocardial perfusion scintigraphy (MPS) has been the longest established functional imaging modality to diagnose obstructive coronary artery disease (CAD). Negative MPS results are associated with favourable long-term outcomes.

WHAT THIS STUDY ADDS

⇒ Contemporary single-photon emission CT imaging technology such as ECG-gating and attenuation-correction has led to more accurate diagnosis of inducible perfusion abnormality. This meta-analysis showed that positive (abnormal) MPS results are associated with worse long-term major adverse cardiovascular event.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Contemporary MPS practice may provide a long-term prediction and could facilitate the delivery of GDMT in patients with suspected or known CAD.

INTRODUCTION

The worldwide prevalence of coronary artery disease (CAD) as a primary cause of morbidity and mortality requires precise diagnostic and prognostic tools to direct clinical care. The assessment of chest pain to exclude CAD is a very common presentation to both primary and secondary care.[1–4] The European Society of Cardiology (ESC) recommends non-invasive cardiac stress imaging for patients with a pretest probability of 15%–85%.[5] The ISCHEMIA trial found that coronary intervention improves symptoms but not outcomes compared with optimal medical management in chronic coronary syndrome patients and moderate to severe ischaemia with functional testing (without left main disease).[6]

Myocardial perfusion scintigraphy (MPS) is the longest established non-invasive diagnostic tool that assesses blood flow within the heart muscle at rest and during stress to identify reversible perfusion defect and assess risk for patients with suspected or known CAD.[7] Normal MPS results correlate with low

cardiac event risk while abnormal MPS results indicate high cardiac risk.[7 8]

Single-photon emission CT (SPECT) to detect inducible perfusion defects underwent significant technical advancement since the late 1990s. Techniques such as ECG-gating and attenuation-correction have been implemented during MPS. ECG-gated SPECT reduces artefacts from heartbeats by synchronising image acquisition with ECG, hence it improves image quality. Attenuation correction addresses the impact of soft tissues on image intensity, enhancing the accuracy of perfusion measurements.[9–11]

Observational studies and a meta-analysis examined the prognostic significance of negative MPS results on cardiovascular or all-cause mortality and revascularisation.[7 8] Long-term outcome of negative and positive MPS using contemporary imaging techniques in controlled trials has not been investigated systematically. In this study, we use a literature review and meta-analysis to examine the long-term (≥12 months) clinical outcome following MPS in current cardiology practice.

METHODS

Search strategy and study inclusion

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines for the planning analysis and reporting of meta-analysed randomised controlled trials (RCTs). The detailed methods and protocol were also registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023416766).[12]

A 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 MPS trials; since the introduction of quality improvement techniques such as ECG-gated SPECT and attenuation-corrected SPECT to advance diagnostic accuracy in the late 1990s). Keywords including MPS, MPI, myocardial perfusion scintigraphy, SPECT, myocardial perfusion scanning were used to investigate the prognostic outcomes of MPS and identify a reference list of articles. The relevant studies were included in the reviewed articles. See also PICOS criteria in online supplemental document.

A protocol following the PRISMA guidelines was constructed. The screening of titles and abstracts was performed and subsequent review of full-text articles was performed by two authors independently (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 and all included studies met predefined eligibility criteria. RCT in the search criteria aimed to identify and include studies with the highest research standard, hence the lowest risk of bias irrespective of the design of the studies.

These criteria were:

1. Prospective randomised control trial for different trials investigating myocardial ischaemia in patients with suspected CAD, using MPS.
2. Studies with longitudinal follow-up (≥12 months) recording events such as all-cause or cardiovascular mortality and major adverse cardiovascular events (MACE) or composite of these events.
3. Enrolled a minimum of 50 patients aged 18 and above.
4. Studies reported in the English language as full-text articles.

Data extraction

Two researchers (NJ and JSC) independently extracted and cross-checked data from the included studies. Inconsistencies were resolved by discussion with the third investigator (UI). The included randomised control trials' risk of bias was assessed through the Cochrane Handbook. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system and the GRADE pro tool pack assessed the trial quality and displayed the evaluation results.[13]

Risk of bias

The four RCTs included in the meta-analysis were analysed for bias and quality of evidence using the GRADE framework.[13] This meta-analysis focused on two sets of pooled outcomes. The primary outcome was a pooled analysis of all-cause or cardiovascular mortality (as defined in individual trials) and non-fatal myocardial infarction. The secondary outcome was all-cause or cardiovascular mortality. The risk of bias for each study was analysed by an independent reviewer and covered the five domains as outlined in the Cochrane Handbook.

The risk of bias in each domain is summarised in the Risk-Of-Bias Visualisation tool (figure 1). Overall risk of bias has been deemed not serious. None of the included studies showed bias in allocation concealment, incomplete outcome data or selective reporting. One study was deemed to have a high risk of bias for blinding of participants and personnel; however, this study contained the smallest number of participants, and, therefore, it was deemed the overall risk of bias to be non-serious with regards to the pooled outcome. This was the same across both outcomes represented in the GRADE analysis (online supplemental table S1). In addition, the funnel plot shows that publication bias is not a significant contributor to this study (online supplemental figure S1).

Outcome

For the meta-analysis, we assessed the outcome of MPS for reversible perfusion defect as positive (abnormal perfusion) or negative (normal perfusion) and the long-term outcome on all-cause or cardiovascular mortality (as defined in individual trials) and non-fatal myocardial infarction, defined as composite MACE as primary outcome. The secondary endpoint was all-cause or cardiovascular mortality.

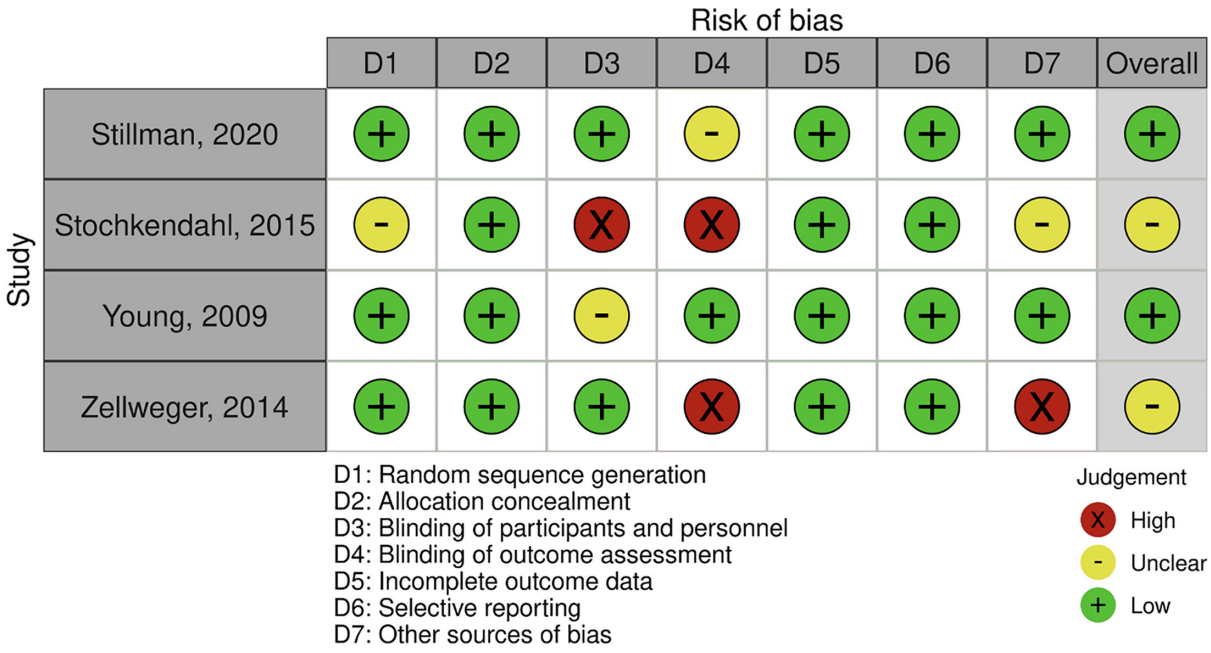

Figure 1 Risk of bias analysis.

Statistical analysis

A random-effects meta-analytical model was specified to estimate association of MPS outcome with composite MACE and all-cause or cardiovascular mortality. Study-specific OR 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 fixed effect of MPS 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 >50% were regarded as being indicative of low, moderate or high heterogeneity, respectively.[14] A forest plot, displaying the point estimate of the effect size and the corresponding 95% CI, was presented separately for MACE and all-cause or cardiovascular 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 supplementary material illustrate the potential for publication bias with the individual ORs for the endpoint of interest. The subgroup analysis investigated sources of heterogeneity through an evaluation of previous CAD prevalence or population with a history of diabetes mellitus in the 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) V.5.4) and The Cochrane Collaboration, 2020 and SPSS (V.18.0; IBM, Armonk, New York).

RESULTS

Study inclusion

A total of 961 records were identified through the search, as specified above. The title and abstracts were retrieved for evaluation. Out of these, 950 were excluded initially and 11 records were further reviewed as potential articles. One was excluded due to a small percent of SPECT, and a preponderance of participants had exercise ECG with no individual breakdown. One study had only rest images, one myocardial perfusion assessed by contrast echocardiography and the last four excluded studies were an undifferentiated combination of functional imaging modalities. The remaining four,[15–18] published between 1 January 2000 and 1 January 2023, were selected for the meta-analysis (table 1) (online supplemental data, figure S2).

Included studies involved a total of 1764 subjects who underwent either pharmacological (Adenosine) or exercise Tc-99m-sestamibi MPS with a median follow-up of 35.7 months (range 16.8–57.6 months). The mean age was 59 years, and 50% were male. Fifty-three percent had a history of hypertension, 43% had dyslipidaemia, 15% were current smokers, 61% had diabetes mellitus and 3% had a prior history of CAD (table 2).

Meta-analysis of stress echocardiography result on long-term outcome

Primary outcome: composite outcome—MACE

Four studies, with 1764 individuals, reported a composite MACE (all-cause mortality[15 16] or cardiovascular death[17 18] and non-fatal myocardial infarction[15–18]). There were 153 inconclusive results across the studies. Reversible perfusion defect was found in 230 individuals, while 1381 had a negative MPS. The overall annual event rate was

Table 1 Study characteristics

First author, trial	Study outcome. Rate of revascularisation	Study design Data collection (year)	MPS modality criteria of perfusion abnormality	Event endpoint	Study population N	MPS positive N	MPS negative N	MACE for MPS positive N (%)	MACE for MPS negative N (%)
Young,[15] DIAD	Low cardiac event rates and not significantly reduced by MPS screening for myocardial ischaemia over 4.8 years. 10% in MPS positive and 3.9% in MPS negative cases	Prospective, multicentre, RCT of asymptomatic DM patients MPS vs no MPS guided management on outcome. 2000–2002.	Adenosine Tc-99m-sestamibi MPS. ≥10% of LV myocardium.	All cause death or non-fatal MI	561†	83 (492)‡	409 (492)‡	7 (8.4)	16 (3.9)
Stochkendahl,[16] Danish Registry	MPS improved prediction of incident CAD in non-specific chest pain patients. 7.1% in MPS positive and 0.4% in MPS negative cases	Single-centre, RCT. Prognostic role of stress SPECT MPI in predicting cardiac events in patients with acute, non-specific chest pain. 2006–2008.	Adenosine or symptom-limited exercise stress Tc-99m-sestamibi MPS. SSS≥4 with at least one segment having a score≥2.	All cause death or non-fatal MI	272	42	230	1 (2.3)	6 (2.6)
Stillman,[17] RESCUE	No difference in outcomes between MPS and CCTA in patient with stable angina. 30% in MPS positive and 2.7% in MPS negative cases	Multicentre, RCT to compare CCTA vs MPS guided imaging to guide optimal medical therapy in stable angina. 2011–2013.	Adenosine Tc-99m-sestamibi MPS. ≥10% of LV myocardium.	*Cardiac death or non-fatal MI	531	23	436	1 (4.3)	2 (0.5)
Zellweger,[18] BARDOT	High-risk asymptomatic patients with DM and normal MPS have a low rate of CAD. Combined invasive and medical strategy for silent CAD may reduce scintigraphy but not symptomatic CAD progression vs medical therapy alone. 34% of positive MPS and 0% in MPS negative cases	Prospective, multicentre outcome study with pilot RCT treatment substudy in asymptomatic DM patients—medical vs medical and invasive strategy based on MPS outcome. 2004–2010.	Adenosine Tc-99m-sestamibi MPS. SSS≥4 (≥5% myocardium); SDS≥2 (≥3% ischaemia)	*Cardiac death or non-fatal MI	400	82	306	5 (6.0)	5 (1.6)
Total					1764	230	1381	14 (6.0)	29 (2.0)

*Cardiac death defined as: fatal myocardial infarction (within 30 days); death due to heart failure or arrhythmia; or sudden cardiac death.
†39 out of the 561 did not undergo MPS for the following reasons: 22 refused, 16 were unable to schedule their MPS within the required 3-month time window, and the screening MPI of one participant was poor quality and not interpretable. They were excluded from the analysis.
‡MPS abnormality beyond inducible myocardial perfusion defect included transient left ventricular dilatation and ECG changes during MPS in 30 patients, these patients had been excluded from the analysis.
CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DM, Diabetes Mellitus; LV, left ventricle; MACE, major adverse cardiovascular event; MI, myocardial infarction; MPI, myocardial perfusion imaging; MPS, myocardial perfusion scintigraphy; RCT, randomised controlled trial; SDS, summed difference score; SPECT, single photon emission computed tomography; SSS, summed stress score.

Table 2 Patient characteristics

First author	Study population N	Mean age (years)	Male N (%)	Hypertension N (%)	Hyperlipidaemia N (%)	Current smoker N (%)	Diabetes N (%)	Prior MI N (%)	Patient years follow-up
Young[15]	561	60.7	290 (51.6)	315 (56.5)	255 (45)	57 (10)	561 (100)	0.00	2361.6
Stochkendahl[16]	272	54.3	157 (57.7)	86 (31.6)	85 (31.3)	70 (25.7)	14 (5.15)	0.00	1013.2
Stillman[17]	531	58	287 (54.0)	317 (59.7)	313 (58.9)	87 (16.4)	114 (21.5)	55 (10)*	619.7
Zellweger[18]	400	63.4	149 (37.3)	N/A	121 (30.3)	50 (12.5)	400 (100)	0.00	785.7
Total	1764	59	883 (50)	718 (53)	774 (43)	264 (15)	1089 (61)	55 (3)	4780.2

*Indicates prior coronary artery disease with no specific reference to MI.
MI, myocardial infarction; NA, not available.

1.42% for the composite outcome (table 1, figure 2). Positive MPS was associated with an MACE rate of 2.16% compared with 0.66% for a negative MPS result OR: 2.71 (1.38, 5.32) (figure 3).

Secondary outcome: all-cause or cardiovascular mortality

The overall annual event rate for all-cause or cardiovascular mortality was 0.22%. The annual mortality rate for a positive MPS was 0.34% compared with 0.10% for a negative MPS result, OR: 3.41 (1.44, 8.11) (figure 4).

Sensitivity and subgroup analysis

Sensitivity analysis among studies without previous cardiac event shows that a positive MPS result, when compared with a negative MPS result, had an OR 2.43 (1.2, 4.91) and 3.41 (1.44, 8.11) for the combined MACE and all-cause or cardiovascular death, respectively. There was no heterogeneity in this effect (χ^2 values of 1.38 and 1.56, I^2=0, p=0.46 and 0.43), for combined MACE and all-cause or cardiovascular death, respectively.

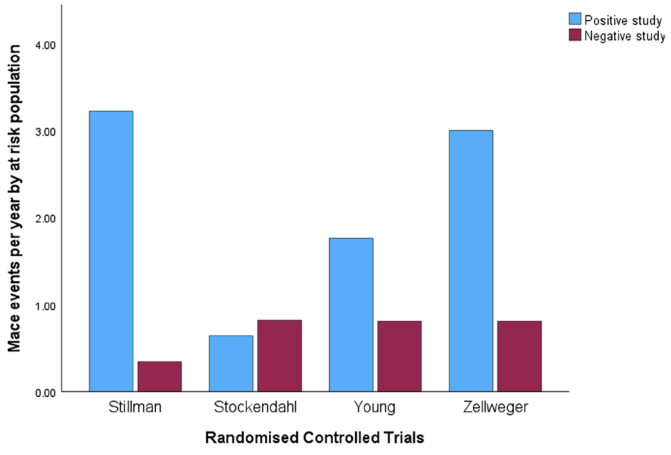

Figure 2 The effect of myocardial perfusion scintigraphy outcome on the annual composite MACE rate for the individual studies. MACE, major adverse cardiovascular event.

Subgroup analysis including studies *only recruiting diabetic patients* revealed that, compared with a negative MPS result, a positive MPS showed an OR 2.73 (1.30, 5.76) and 4.03 (1.63, 9.96) for the combined MACE and all-cause or cardiovascular death, respectively. In studies with minority of diabetic patients (5% and 21%), the OR was 2.8 (0.24, 32.32) and 0.59 (0.03, 11.20), for the combined MACE and all-cause or cardiovascular death, respectively.

DISCUSSION

In this systematic review and meta-analysis recruiting 1764 patients from four studies who underwent MPS since 2000 for suspected or known CAD, we found that reversible perfusion defect was associated with worse long-term outcome. Both composite MACE and all-cause or cardiovascular mortality were higher in patients with a positive MPS. The novelty of these findings stems from the selected search criteria that guaranteed the recruitment of the highest quality studies with the longest follow-up, analysing the impact of positive as well as negative MPS results on MACE and all-cause or cardiovascular mortality. The selection of the publication dates after 2000 also assured the recruitment of the MPS studies using most contemporary SPECT imaging technology such as ECG-gating and attenuation-correction to improve diagnostic accuracy of myocardial perfusion detection that were widely introduced in the late 1990s.

The significance of negative MPS on outcome

Smulders *et al* in their systematic review and meta-analyses comparing the prognostic value of negative non-invasive functional and anatomical cardiac tests (such as stress echocardiography (SE), Cardiac MRI, MPS, Positron Emission Tomography and Coronary CT Angiography (CCTA) showed that a negative MPS was associated with an excellent prognosis for patient with suspected or known CAD.[8] The corrected annualised combined

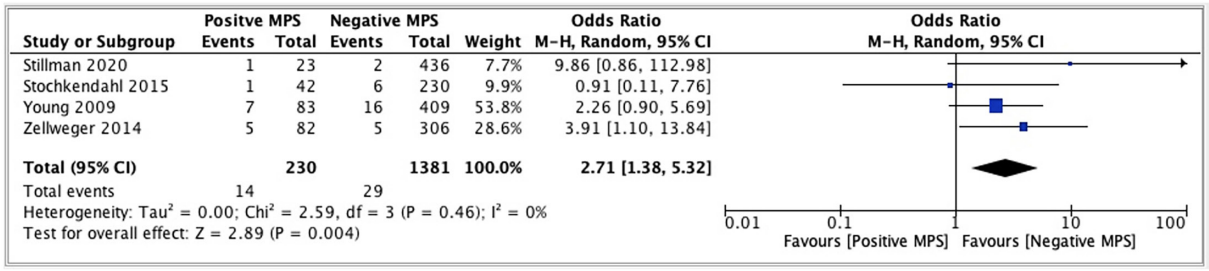

Figure 3 Forest plot of composite MACE of patients undergoing MPS. MACE, major adverse cardiovascular event; MPS, myocardial perfusion scintigraphy. M-H, Mantel-Haenszel.

MACE rates for negative MPS in that meta-analysis were 1.07% compared with the recent analysis of 0.66%. The earlier study[8] recruited studies between January 1990 and April 2015; of the 55 MPS studies, 22% were published prior 2000. 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 SPECT-MPS technology and hence lower diagnostic accuracy.

Negative MPS results enable the identification of low-risk patients that in turn may reduce the need for invasive procedures and downstream testing, hence could save healthcare expenses. Observational longitudinal follow-up registries have indicated a warranty period for a negative MPS and SE of 5 years for patient without known CAD.[19 20]

The effect of MPS in patient with no prior CAD

Studies in this meta-analysis had a limited number of patients with prior CAD, 55 (3%) of the total population with angina or myocardial infarction with or without revascularisation (table 2). Sensitivity analysis of the effect of MPS result on the primary and secondary outcome exclusively on patient with no prior CAD showed a very similar results to the main outcome measures with low heterogeneity.

The effect of MPS in patients with diabetes mellitus

The two studies[15 18] that recruited only diabetic patients showed higher rate of mortality (OR: 4.03 vs 3.41) but similar MACE rate (OR: 2.73 vs 2.71) compared with the entire cohort associated with positive MPS results. This could emphasise the significance of diabetes mellitus in predicting outcome in patients with suspected CAD.[21] Indeed, Mäenpää *et al* in a retrospective analysis of their registry data showed that the prevalence of haemodynamically significant CAD (ie, positive results) by MPS was almost twofold in type 2 diabetes compared with non-diabetic patients.[21] This was reinforced by our observation that the studies recruited only diabetic patients had 18% abnormal MPS results compared with the studies with low proportion of diabetic patients where the MPS-positive results were only 10%. Similarly, they also showed that combination of haemodynamically significant CAD and type 2 diabetes was associated with the highest adverse event rate during long-term follow-up.[21] The effect of diabetes mellitus on coronary atherosclerotic plaque burden and outcome has been validated in the recent SCOT-Heart substudy showing that diabetes mellitus was an independent predictor of quantitatively assessed plaque burden, particularly calcified plaque, and was associated with an increased risk of myocardial infarction.[22]

Comparative value of MPS and other non-invasive imaging

This review suggests that MPS is effective in forecasting long-term adverse outcome for CAD patients by detecting inducible ischaemia. Positive MPS results correlate with higher rates of all-cause as well as cardiovascular mortality and non-fatal myocardial infarction in keeping with prior observations.[23–25] The prognostic utility of MPS has been compared with other non-invasive tests, such as SE and CCTA, with similar predictive capabilities.[23] Combination of anatomical and functional assessment provides more comprehensive strategy to detect coronary atherosclerosis and its functional significance, as shown by prior landmark studies like the PROMISE trial and ISCHEMIA trial.[6 23] The observations in the current meta-analysis are comparable to the meta-analysis of long-term outcome of

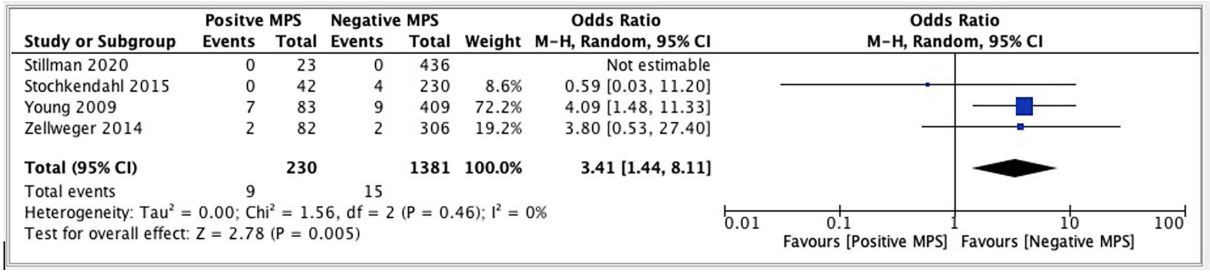

Figure 4 Forest plot of all cause or cardiovascular death of patients undergoing myocardial perfusion scintigraphy (MPS).

SE in similar population.[26] Notably, positive test results of SE and MPS irrespective of the extent of ischaemia increase the composite MACE by 2 and 2.7-fold and the mortality by 2 and 3.4-fold, respectively (online supplemental table S2). This supports the ESC recommendation that either functional test can be applied for diagnosing flow-limiting CAD (or high-risk coronary microvascular disease) and to predict long-term outcome of patients with suspected CAD.[5]

Coronary revascularisation on outcome in MPS positive patients

Although a positive MPS is linked to poor outcomes, observational studies and RCTs have shown that coronary revascularisation offers no improvement.[6 27] In a recent opinion paper, Zaman *et al* aired the concept of assessing degree of atherosclerotic CAD and timely initiation of therapy at an early stage of the disease.[28] Although the degree of coronary artery obstruction is the only predictor that can be influenced by revascularisation in patient with stable CAD functional test like MPS is essential to investigate patients' effort symptoms to understand its cardiac origin.[6 20] Stress testing will continue to help clinicians and patients define whether ischaemic heart disease is the cause of their symptoms.

The OR 2.43 for composite MACE and 3.07 for mortality highlights the significance of positive MPS outcome, beyond the severity of epicardial coronary artery obstruction. Nevertheless, in addition to conventional clinical variables additional risk factors such as polygenetic risk scores (derived from the genome-wide association studies) and risk estimates using AI technology that identifies changes not recognisable to the human eye, as well as novel blood-borne and electrical biomarkers will enhance early risk prediction to allow developments of timely intervention to prevent unfavourable events and improve healthy ageing.[29]

Limitation

There are several limitations of this study. First, the generalisability of these findings to wider healthcare applications is limited since the small size of the study. However, we selected studies with high research rigour (containing RCT in the text) and contemporary SPECT-MPS techniques. ECG-gated SPECT-reducing artefacts by synchronising image acquisition, attenuation correction by addressing the impact of soft tissues on image intensity and enhancing the accuracy of perfusion measurements[9–11] were introduced in the late 1990s, hence, we have chosen the literature search from 2000. These selection criteria are the warranty of the quality of this meta-analysis that as future trials relevant to MPS long-term outcome are reporting this can provide the ground for further extended analysis. Second, this meta-analysis does not provide information on the extent of inducible perfusion abnormality that could influence more precise risk assessment and treatment choices. These results were not readily available for the selected trials, and decision was made to simplify the assessment in a binary fashion. Third, we did not analyse the effect of fixed perfusion abnormality in patients with prior myocardial infarction on outcome, however, it has been shown to have prognostic value.

Conclusion

This meta-analysis demonstrates that positive MPS by diagnosing reversible perfusion abnormalities acts as a valuable long-term prognostic tool in patients with suspected CAD including a composite MACE as well as mortality. We also confirmed prior results that negative MPS has a good long-term prognosis. In summary, MPS provides a useful long-term prediction and could facilitate guidance in delivering guideline-directed medical therapy in patients with suspected CAD.

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

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Competing interests None declared.

Patient consent for publication Not applicable.

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

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