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Long-term outcomes of ischaemia with no obstructive coronary artery disease (INOCA): a systematic review and meta-analysis

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ABSTRACT

Background The prognosis of myocardial ischaemia with no obstructive coronary artery disease (INOCA) and its underlying vasomotor disorders, vasospastic angina (VSA) and microvascular angina (MVA), is not well defined. The aim of this study was to perform a systematic review and meta-analysis of studies evaluating the long-term prognosis of patients with INOCA.

Methods We included studies evaluating the prognosis of patients with INOCA published between January 1984 and August 2023 in Medline, Embase, Web of Science and Cochrane databases. Studies were selected if they included patients who fulfilled the Coronary Vasomotor Disorders International Study Group (COVADIS) criteria for either possible or definitive VSA or MVA. The primary outcomes were composite of all-cause death and myocardial infarction (MI), and major adverse cardiovascular event (MACE) at annual intervals up to 5-year follow-up. The incidence of primary outcomes for INOCA, each INOCA endotype and by method used to determine the diagnosis was calculated using the random effects model.

Results Fifty-four studies (17 302 patients) meeting the eligibility criteria were selected. The rate of all-cause death and MI with VSA was 0.7 (95% CI 0.4 to 1.0)/100 patient-years and with MVA was 1.1 (95% CI 0.7 to 1.5)/100 patient-years (p>0.05). The rate of MACE with VSA was 1.1 (95% CI 0.5 to 1.9)/100 patient-years and with MVA was 2.5 (95% CI 1.6 to 3.6)/100 patient-years (p=0.025). Patients with reduced coronary flow reserve (CFR) had higher all-cause death and MI rates than patients whose diagnosis of MVA was established based on an abnormal exercise or imaging stress test (4.7 (95% CI 2.0 to 8.4) vs 0.5 (95% CI 0.1 to 1.1) vs 1.1 (95% CI 0.5 to 2.0)/100 patient-years, p=0.001).

Conclusions Overall, patients with INOCA have a low rate of MACEs, but patients with MVA, especially those with reduced CFR, have a significantly higher rate of MACE than other subgroups, although there is high heterogeneity among the included studies.

PROSPERO registration number CRD42021275070.

WHAT IS KNOWN ON THIS TOPIC

⇒ The population of patients suffering from ischaemia with no obstructive coronary artery disease (INOCA) is large and heterogeneous.
⇒ The prognosis of patients with INOCA is variable and may not be benign.

WHAT THE STUDY ADDS

⇒ Patients with confirmed vasospastic angina have a good long-term prognosis.
⇒ Patients with microvascular angina have a worse prognosis, especially if their diagnosis is based on reduced coronary flow reserve and not stress testing alone.
⇒ A focus on patient-centred outcomes is necessary both in clinical practice and in future research studies of INOCA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study will alert the medical community to the existence of poor and heterogeneous data on INOCA and especially INOCA endotypes and might stimulate researchers to study this area in a more rigorous manner.

INTRODUCTION

Rationale

Chest pain is one of the most common presenting complaints in outpatient visits and to the emergency department.[1 2] Of patients who are referred for invasive coronary angiography, with or without ischaemia on non-invasive stress testing, 30–50% are found to have ischaemia and no obstructive coronary artery disease (INOCA).[3–5] Despite the confirmed absence of epicardial coronary artery disease (CAD), many patients experience recurrent presentations for the evaluation of chest pain.[2 5] Physiological assessment of patients with INOCA has revealed endotypes, which include epicardial

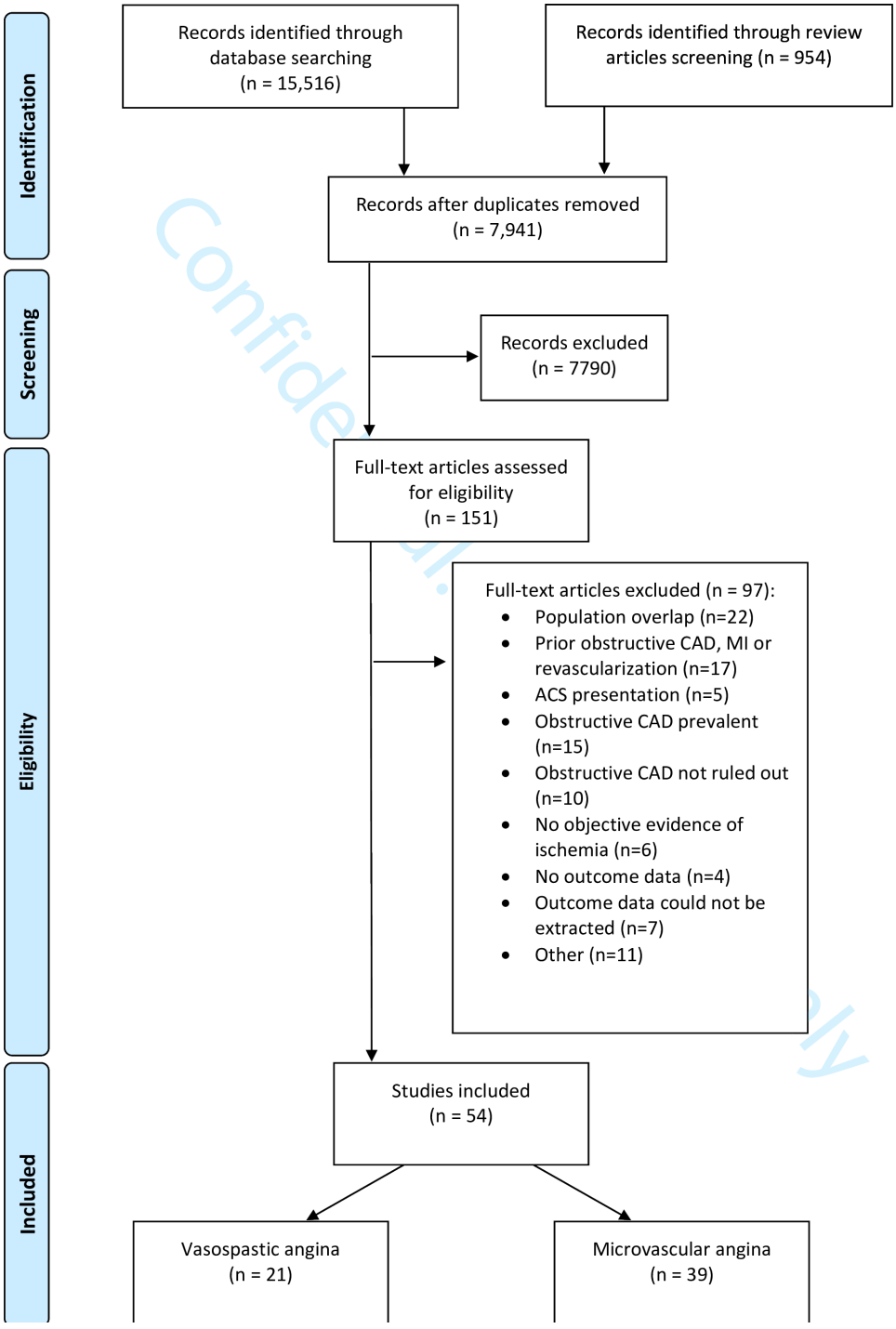

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram showing study selection process. ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction.

or microvascular vasospasm, coronary microvascular dysfunction or diffuse epicardial atherosclerosis in more than 75% of patients.[4]

While historically considered a benign syndrome, recent studies evaluating the long-term outcomes of patients with INOCA have reported a nearly four-fold increase in the incidence of mortality and major adverse cardiovascular events (MACEs) compared with patients without a diagnosis of INOCA.[6–8] Previous studies evaluating INOCA have included a heterogeneous population of patients with chest pain and no obstructive CAD, patients with a specific diagnosis based on non-invasive testing and patients with a diagnosis based on invasive functional testing.[9–14] Therefore, there are gaps in our understanding of INOCA and uncertainty regarding differences in the incidence of adverse events based on the underlying diagnosis (vasospastic angina (VSA) or microvascular angina (MVA)) or method of diagnosis (invasive or non-invasive).

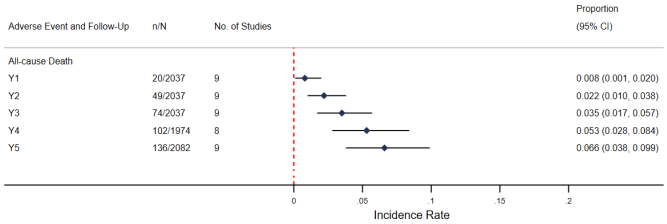

Figure 2 Annual event rates for up to 5 years of follow-up. Forest plot showing overall estimated annual event rates with 95% CI for all-cause death. Blue diamonds with horizontal lines represent weighted point estimates of cumulative incidence rate per year with 95% CI for each outcome.

Objectives

In this meta-analysis, we sought to determine the long-term prognosis of patients with INOCA stratified by both the underlying diagnosis and the method of diagnosis.

METHODS

Search strategy

We conducted a systematic review and meta-analysis of published studies using a predefined protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021275070).

We searched Medline, Embase, Web of Science and Cochrane databases using a Boolean search strategy consisting of both keywords and controlled vocabulary combining terms for INOCA including 'microvascular disease', 'coronary vasospasm', 'no obstructive coronary artery disease', 'microcirculatory' *and* 'coronary' with 'outcomes', 'major adverse events' and 'mortality'. The search was restricted to studies published in English language from January 1984 to August 2023. The complete search strategy is provided in online supplemental appendix table 1.

Study selection criteria

Studies were selected if they reported prespecified outcomes in patients with INOCA. Only studies that reported non-obstructive CAD (<70% narrowing) using anatomical evaluation (coronary CT angiography (CTA) or invasive angiography) were selected. Additionally, studies had to meet the inclusion criteria based on the Coronary Vasomotor Disorders International Study Group (COVADIS) guidelines (online supplemental appendix tables 2, 3).[15 16]

Studies were excluded if (1) more than 10% of study participants had CAD or prior or current acute coronary syndrome (ACS) presentations; (2) patients were diagnosed with less defined coronary abnormalities, such as diffuse (but non-obstructive) atherosclerosis, endothelial dysfunction, elevated resting flow and myocardial bridging; (3) the study included uncharacterised endotypes such as 'angiographic slow flow' that do not meet contemporary criteria for a disorder of coronary vasomotion and non-coronary surrogate testing (such as brachial artery flow mediated vasodilation, cold pressor test, handgrip test, etc).

Two investigators (NO and SSK) independently screened titles and abstracts generated by database search for eligibility criteria (figure 1). Additionally, two investigators (NO and AS) screened review records and selected relevant review articles whose bibliographies were screened for potentially relevant studies. If a study was considered potentially relevant, a full-text article was reviewed by NO and AS.

Data abstraction

Two investigators (NO and AS) independently extracted the data into a Microsoft Excel spreadsheet and cross-checked for accuracy. The following fields were collected: first author first name and last name, year of publication, number of subjects, years of enrolment, study population baseline demographics including gender and cardiovascular risk factors, modality used to rule out obstructive CAD and method and modality of diagnosing specific INOCA subtype (invasive or non-invasive, specific type of test). Outcome measures were extracted with annual event rates for up to 5 years of follow-up.

Prespecified outcomes

We investigated two composite outcomes: (1) all cause-death and myocardial infarction (MI); (2) MACEs, defined as a composite of cardiovascular death, MI, stroke, hospitalisation for cardiovascular causes or coronary revascularisation.

Statistical analysis

Statistical analysis was performed by ZZ and HP. The results for each outcome were presented as incidence rates with 95% CIs.

Incidence rates from eligible studies were pooled using the DerSimonian-Laird random effects model. Freeman-Tukey double arcsine transformation was used to handle low incidence rates and to stabilise the variance. Degree of heterogeneity was estimated using I^2 statistics with the criteria: none '<25%', low '25–49%', moderate '50–74%', and high '75+%'. Publication bias and small study effect were assessed by degree of funnel plot asymmetry and Egger's regression test. The estimated missing studies were imputed by trim-and-fill method. Sensitivity analysis was conducted by sequentially excluding individual studies and the influence of each study on the overall incidence rate was examined. To examine sources of between-study variability, we performed subgroup analysis and random-effects meta-regression. All statistical analyses were performed using Stata V.17.0 (Stata Corp, College Station, Texas, USA).

RESULTS

The literature search resulted in 15516 records through database searching and 954 records through review article screening (figure 1). After removing duplicate publications, 7941 records were screened for eligibility criteria.

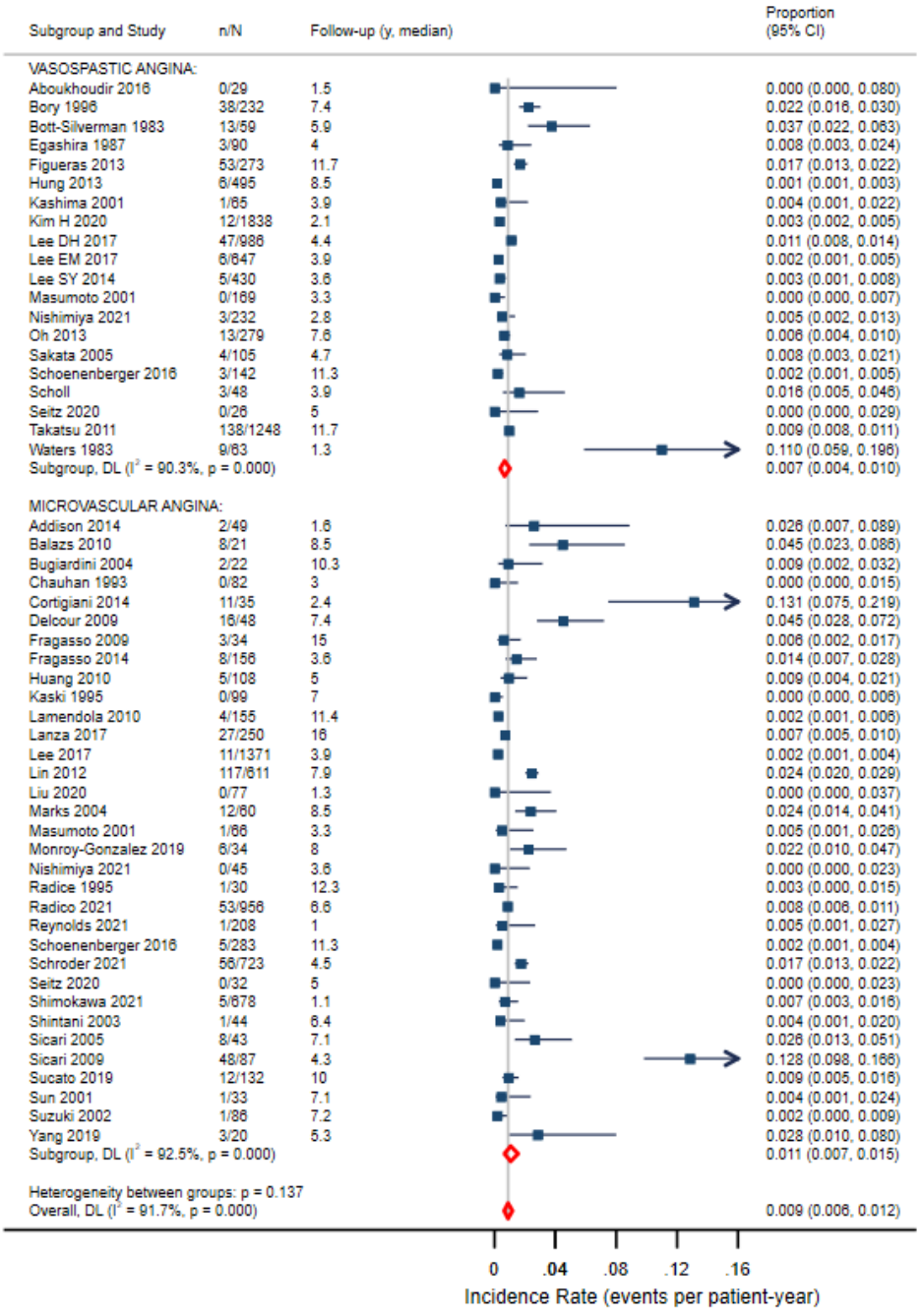

Figure 3 Combined incidence of all-cause death and myocardial infarction (MI). Forest plot showing individual and overall estimated incidence with 95% CI for the combined outcome of all-cause death and MI. The vertical line represents the pooled incidence rate estimate for the entire INOCA cohort. The red diamonds represent the overall estimated incidence for vasospastic angina (VSA) subgroup, microvascular angina (MVA) subgroup and the overall INOCA group with 95% CI in a DerSimonian-Laird random effects model. Blue squares with horizontal lines represent weighted point estimates of incidence for each single study with 95% CI. I^2, Higgins' index of heterogeneity; INOCA, ischaemia with no obstructive coronary artery disease.

A total of 54 studies met the criteria and were included in the meta-analysis. Of these, 21 studies reported outcomes for VSA and 39 for MVA. Study and patient characteristics are presented in online supplemental appendix tables 4, 5. Overall, the mean age was 56 years for VSA and 59 years for MVA; 30% of patients with VSA were female compared with 61% of patients with MVA. The mean duration of follow-up was 5.3 years for VSA and 6.6 years for MVA.

The average rate of the composite outcome of all-cause death and MI in the entire INOCA cohort was 0.9 (95%

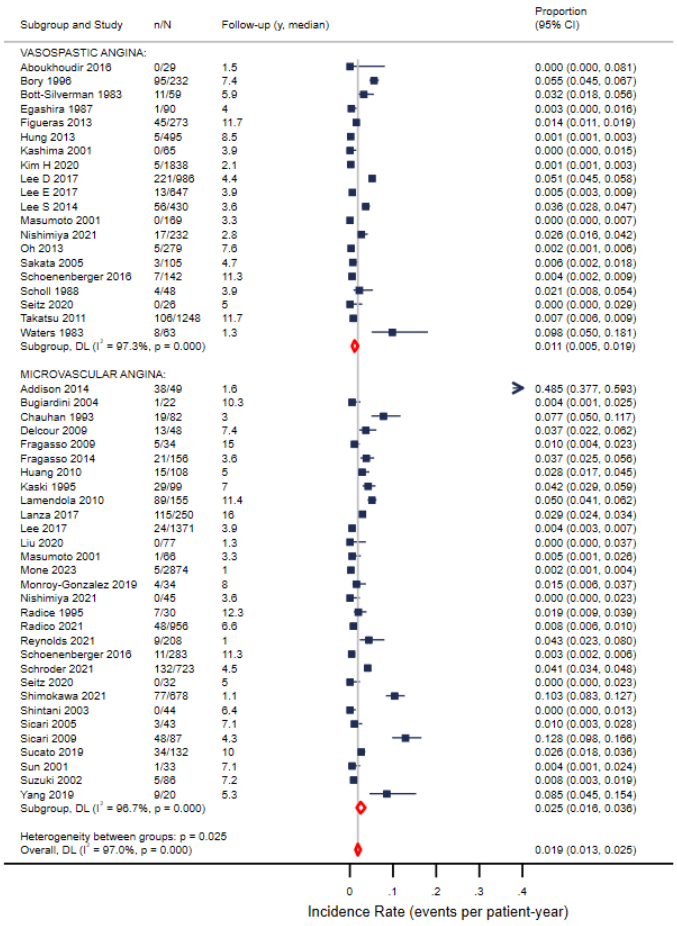

Figure 4 Combined incidence of major adverse cardiovascular event (MACE). Forest plot showing individual and overall estimated incidence with 95% CI for the combined outcome of MACE consisting of cardiovascular death, myocardial infarction, stroke, hospitalisation for cardiovascular causes and coronary revascularisation. The vertical line represents the pooled incidence rate estimate. The red diamonds represent the overall estimated incidence for vasospastic angina (VSA) subgroup, microvascular angina (MVA) subgroup and the overall INOCA group with 95% CI in a DerSimonian-Laird random effects model. Blue squares with horizontal lines represent weighted point estimates of incidence for each single study with 95% CI. I^2, Higgins' index of heterogeneity; INOCA, ischaemia with no obstructive coronary artery disease.

CI 0.6 to 1.2)/100 patient-years (I^2=91.7%, p<0.01). The average rate of the composite outcome of MACE was 1.9 (95% CI 1.3 to 2.5)/100 patient-years (I^2=97.0%, p<0.01). Annual rates up to 5 years of all-cause death are shown in figure 2.

Vasospastic angina

Twenty-one studies (7523 patients) were included for VSA (online supplemental appendix table 4). All studies ruled out obstructive CAD with coronary angiography. One study used the clinical diagnosis of VSA, 16 studies established the diagnosis of VSA invasively and 4 studies used either clinical or invasive criteria for subject inclusion. Among studies using invasive criteria, 6 used acetylcholine only, 12 used ergonovine or methylergonovine only, and 2 used either. Six studies used a cut-off ≥90% lumen reduction by visual assessments to define spasm and the remaining 15 studies used a cut-off that was lower than that or multiple cutoffs. Definitive VSA based on the COVADIS criteria was diagnosed in 5 studies and possible in the remaining 16 studies. The combined incidence of all-cause death and MI was 0.7 (95% CI 0.4 to 1.0)/100 patient-years (I^2=90.3%, p<0.01) (figure 3) and a combined incidence of MACE was 1.1 (95% CI 0.5 to 1.9)/100 patient-years (I^2=97.3%, p<0.01) (figure 4). There was no difference in either of the two composite outcomes when we compared studies defining spasm as ≥90% lumen reduction versus studies using lower a cut-off or when we compared studies with definitive versus possible VSA by the COVADIS criteria (p>0.05) (online supplemental appendix tables 7, 8).

Coronary microvascular angina

Thirty-nine studies (9779 patients) met the inclusion criteria for coronary MVA (online supplemental appendix table 5). One study used CTA, two studies used either CTA or angiography, and the remaining studies relied exclusively on coronary angiography to rule

out obstructive CAD. The diagnosis of suspected MVA was present based on positive stress tests in 20 studies, while 17 studies had evidence of impaired coronary microvascular function: 11 had impaired coronary flow reserve (CFR), 5 had microvascular spasm and 1 study had an abnormal index of microcirculatory resistance. Two studies included participants meeting both criteria for suspected and definitive MVA but did not provide outcomes separately for the groups. The combined incidence of all-cause death and MI was 1.0 (95% CI 0.6 to 1.4)/100 patient-years (I^2=92.2%, p<0.01) (figure 3) and a combined incidence of MACE was 2.5 (95% CI 1.6 to 3.6)/100 patient-years (I^2=96.7%, p<0.01) (figure 4).

Patients whose diagnosis was established based on a positive stress test of any type had 5.7 times lower rates of all-cause death and MI (0.5 (95% CI 0.1 to 1.1) and 1.1 (95% CI 0.5 to 2.0) for exercise and imaging, respectively) than patients who had an abnormal CFR (4.7 (95% CI 2.0 to 8.4), p<0.01). When the outcomes were expanded to MACE, this trend persisted, but without statistical significance. The incidence of MACE was higher in the MVA cohort compared with the incidence in patients with VSA (2.5 (95% CI 1.6 to 3.6) vs 1.1 (95% CI 0.5 to 1.9), p=0.025) (online supplemental appendix tables 7, 8).

Publication bias

We observed no funnel plot asymmetry for all-cause death and MI (online supplemental appendix figure 1, Egger's test: p=0.154), but the presence of funnel plot asymmetry for MACE (online supplemental appendix figure 2, Egger's test: p=0.022) indicated the presence of publication bias. A sensitivity analysis was performed with the leave-one-out method. There were no studies that substantially influenced the overall incidence estimate (online supplemental appendix figures 3, 4).

Additional analyses

We included continuous variables hypertension, hyperlipidaemia and diabetes in the meta-regression to further characterise between-study variance. On average, patients with hypertension, hyperlipidaemia or diabetes had higher MACE rates (p<0.01). For the incidence of all-cause death and MI, the between-study variance can be explained by hypertension (20.2%), hyperlipidaemia (16.1%) and diabetes (28.2%); for the incidence of MACE, the between-study variance can be explained by hypertension (38.6%) and diabetes (18.4%) via the R^2 statistics. However, high residual variation due to between-study heterogeneity remained (I^2>90%), which may be due to other covariates or uncharacterised factors (online supplemental appendix tables 9,10).

DISCUSSION

In this meta-analysis, we examined the incidence of clinical outcomes in patients with INOCA using contemporary criteria to define different INOCA endotypes. We found that the aggregate incidence of adverse events was low, but patients with MVA had a worse long-term prognosis than those with VSA. This was especially true for patients with a reduced CFR, who had a worse prognosis than those with an empiric diagnosis based on stress testing.

Prior studies and meta-analyses of long-term outcomes in patients without obstructive CAD included clinical presentations such as ACS (myocardial infarction with non-obstructive coronary arteries (MINOCA)) and stable angina but also possibly a large portion of relatively healthy subjects.[17 18] A more recent meta-analysis attempted to limit study inclusion to those enrolling only symptomatic stable patients.[9] Our meta-analysis of patients with INOCA is the first to limit study inclusion based on contemporary COVADIS criteria and to compare outcomes of VSA and coronary MVA. Our results for the overall cohort are concordant with Radico *et al*[9] (pooled incidence of all-cause death and MI for the entire INOCA cohort in our meta-analysis of 0.9 (95% CI 0.6 to 1.2)/100 patient-years vs 0.98 (95% CI 0.77 to 1.19)/100 patient-years in their meta-analysis).

A meta-analysis of 11 studies by Gdowski *et al* found a HR of 3.62 for mortality in patients with reduced CFR compared with patients without reduced CFR.[6] Although we were able to include only 2 of the 11 studies from that meta-analysis based on the COVADIS inclusion criteria, we also concluded that a reduced CFR carries 5.7 times higher risk of all-cause death and MI compared with positive stress test alone. This is in concordance with the existing literature showing that abnormal CFR leads to worse outcomes in patients with non-obstructive coronary artery disease.[19 20]

In a subgroup analysis done by Radico *et al*, the presence or absence of myocardial ischaemia on stress testing did not affect the rates of all-cause death and MI. However, once stratified by type of stress test, Radico *et al* found that those with ischaemia on plain exercise treadmill tests had significantly lower incidences of adverse events compared with those with ischaemia on imaging stress tests (0.56 (95% CI 0.23 to 0.88) vs 1.52 (95% CI 0.45 to 2.58), p=0.02). By contrast, in our analysis the incidence of all-cause death and MI in studies with positive exercise stress test versus stress tests with imaging was not significantly different (0.5 (95% CI 0.1 to 1.1) vs 1.1 (95% CI 0.5 to 2.0) (p>0.05).

While the overall rates of MACE are low for both MVA and VSA, affected patients have a high burden of symptoms, impaired quality of life and increased healthcare costs.[21] Patient-reported outcomes have been seldom studied in detail in the trials of INOCA. Future prospective studies of outcomes in patients with INOCA should include patient reported outcomes as well as 'hard' endpoints with standardised definitions of endotypes to further characterise the long-term prognosis of coronary vasomotor disorders. To address current gaps in our knowledge, the DISCOVER INOCA prospective multicentre registry (NCT05288361) is currently ongoing, which will include standardised assessments of patient-reported outcomes, angiography, physiology and intravascular imaging.

Limitations

Our meta-analysis has limitations including high heterogeneity among the included studies, many of which were single centre studies. The overall quality of data is poor and few studies fulfil the criteria for 'definitive', while most can only be classified as 'possible' VSA or MVA. Additionally, it is likely that an unknown burden of atherosclerotic coronary artery disease beyond angiographic assessment existed; therefore, the contribution of coronary artery disease to the reported associations remains incompletely characterised.

CONCLUSIONS

Overall, patients with INOCA have a low rate of MACE, although there is heterogeneity in outcomes based on the underlying phenotype. Patients with VSA have a relatively benign long-term prognosis, whereas patients with MVA have a significantly higher rate of MACE at long-term follow-up. Among patients with MVA, those with reduced CFR had higher rates of all-cause death and MI.

Contributors NO: Conceptualisation, investigation, writing—original draft. ANS: Investigation. ZZ: Statistical analysis. SSK: Investigation. SJK: Investigation. HP: Statistical analysis. DT: Conceptualisation, writing—review and editing. II: Writing—review and editing. AJL: Conceptualisation, writing—review and editing. CGP: Writing—review and editing. SMS: Conceptualisation, investigation, writing—original draft, supervision. NO and SMS are the guarantors.

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