Prevalence of Coronary Microvascular Disease and Coronary Vasospasm in Patients With Nonobstructive Coronary Artery Disease: Systematic Review and Meta-Analysis

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SYSTEMATIC REVIEW AND META-ANALYSIS

Prevalence of Coronary Microvascular Disease and Coronary Vasospasm in Patients With Nonobstructive Coronary Artery Disease: Systematic Review and Meta-Analysis

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BACKGROUND: A relevant proportion of patients with suspected coronary artery disease undergo invasive coronary angiography showing normal or nonobstructive coronary arteries. However, the prevalence of coronary microvascular disease (CMD) and coronary spasm in patients with nonobstructive coronary artery disease remains to be determined. The objective of this study was to determine the prevalence of coronary CMD and coronary vasospastic angina in patients with no obstructive coronary artery disease.

METHODS AND RESULTS: A systematic review and meta-analysis of studies assessing the prevalence of CMD and vasospastic angina in patients with no obstructive coronary artery disease was performed. Random-effects models were used to determine the prevalence of these 2 disease entities. Fifty-six studies comprising 14 427 patients were included. The pooled prevalence of CMD was 0.41 (95% CI, 0.36–0.47), epicardial vasospasm 0.40 (95% CI, 0.34–0.46) and microvascular spasm 24% (95% CI, 0.21–0.28). The prevalence of combined CMD and vasospastic angina was 0.23 (95% CI, 0.17–0.31). Female patients had a higher risk of presenting with CMD compared with male patients (risk ratio, 1.45 [95% CI, 1.11–1.90]). CMD prevalence was similar when assessed using noninvasive or invasive diagnostic methods.

CONCLUSIONS: In patients with no obstructive coronary artery disease, approximately half of the cases were reported to have CMD and/or coronary spasm. CMD was more prevalent among female patients. Greater awareness among physicians of ischemia with no obstructive coronary arteries is urgently needed for accurate diagnosis and patient-tailored management.

Key Words: angina with nonobstructive coronary artery disease ■ ischemia with no obstructive coronary artery disease ■ vasospastic angina

Ischemic heart disease is the leading cause of mortality and morbidity globally.[1] However, in clinical practice, a relevant proportion of patients with suspected coronary artery disease (CAD) undergo invasive coronary angiography showing normal or nonobstructive coronary arteries.[2] Although many of these patients are considered as having normal coronary arteries, ischemia with no obstructive CAD has been associated with increased cardiovascular risk and higher rates of repeat coronary angiography.[3–5]

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CLINICAL PERSPECTIVE

What Is New?

- In patients with no obstructive coronary artery disease, approximately half of cases present with underlying disease, either coronary microvascular disease or coronary vasospasm.
- Coronary microvascular disease is more prevalent in female patients; nonetheless, male patients are affected in a significant proportion.
- Invasive and noninvasive diagnostic methods identified a similar proportion of patients with coronary microvascular disease.

What Are the Clinical Implications?

- The large variability of methods, definitions, and thresholds for diagnosing coronary microvascular disease and coronary vasospasm is a call to a refinement and standardization of diagnostic tools.
- Greater awareness among physicians of ischemia with no obstructive coronary arteries is urgently needed for proper diagnosis and patient-tailored management.

Nonstandard Abbreviations and Acronyms

CFR	coronary flow reserve
CMD	coronary microvascular disease
WISE	Women's Ischemia Syndrome Evaluation

Recent guidelines reflect the wide spectrum of etiopathogenesis of ischemic heart disease and chronic coronary syndromes.[6] Not only coronary atherosclerosis, but disorders of microcirculation and vasomotion may be part of the intricate process leading to myocardial ischemia. Coronary microvascular disease (CMD) is increasingly seen as an important contributor to the pathophysiology of ischemic heart disease. The diagnosis of CMD can be ascertained by means of invasive cardiac catheterization or noninvasive imaging techniques (Figure 1).[7] Epicardial spasm, a separate clinical entity, can also lead to myocardial ischemia and myocardial infarction.[8,9] The diagnosis of coronary spasm ideally relies on the results of provocation tests performed in the catheterization laboratory. However, the prevalence of CMD and coronary spasm in patients with nonobstructive CAD remains to be determined.

The aim of the present systematic review and meta-analysis was to determine the prevalence of CMD and coronary spasm assessed by invasive and noninvasive methods in patients with no obstructive CAD.

METHODS

The data that support the findings of this study are available from the first author upon reasonable request.

Search Strategy and Selection Criteria

Studies describing prevalence of coronary microvascular disease and coronary spasm among patients with no obstructive CAD were reviewed. Two reviewers (N.M. and G.M.) systematically searched PubMed and Scopus. The search was conducted in August 2021, starting from inception, and was performed separately for coronary microvascular dysfunction and coronary vasospasm (Table S1). No restrictions were applied for language. Additionally, reference lists of the eligible studies and recent systematic reviews were screened to identify relevant studies. In case of multiple publications with the same population, the latest report was used. The inclusion criteria were: (1) studies comprising patients with suspected CAD, (2) presenting with no obstructive coronary disease, and (3) undergoing a diagnostic test for CMD, spasm, or both with a report of the number of patients testing positive and the total number of patients evaluated. Studies were divided into 2 groups according to the pathophysiology assessed: CMD and coronary vasospasm, respectively. The definition of no obstructive coronary disease and the threshold of diagnostics tests used to define the presence of CMD were based on each individual study. The present systematic review and meta-analysis is presented in agreement with *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* reporting guidelines (Table S2).[10] Quality of included studies was assessed by the Quality Assessment of Diagnostic Accuracy Studies tool.[11] Risk of bias was evaluated across 4 domains: patient selection, index test, reference standard, and flow and timing. This systematic review and meta-analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews) (CRD42020220077).

Outcomes of Interest

The primary outcome of interest was the prevalence of CMD and/or coronary vasospasm among patients with no obstructive CAD. Patients' demographic and clinical characteristics, diagnostic methods performed, and number of positive patients were collected. In the present meta-analysis, definitions of CMD and vasospasm were used according to the ones defined in each study.

Statistical Analysis

Categorical variables are reported as percentages, and continuous variables are reported as mean±SD. To account for heterogeneity between studies, a

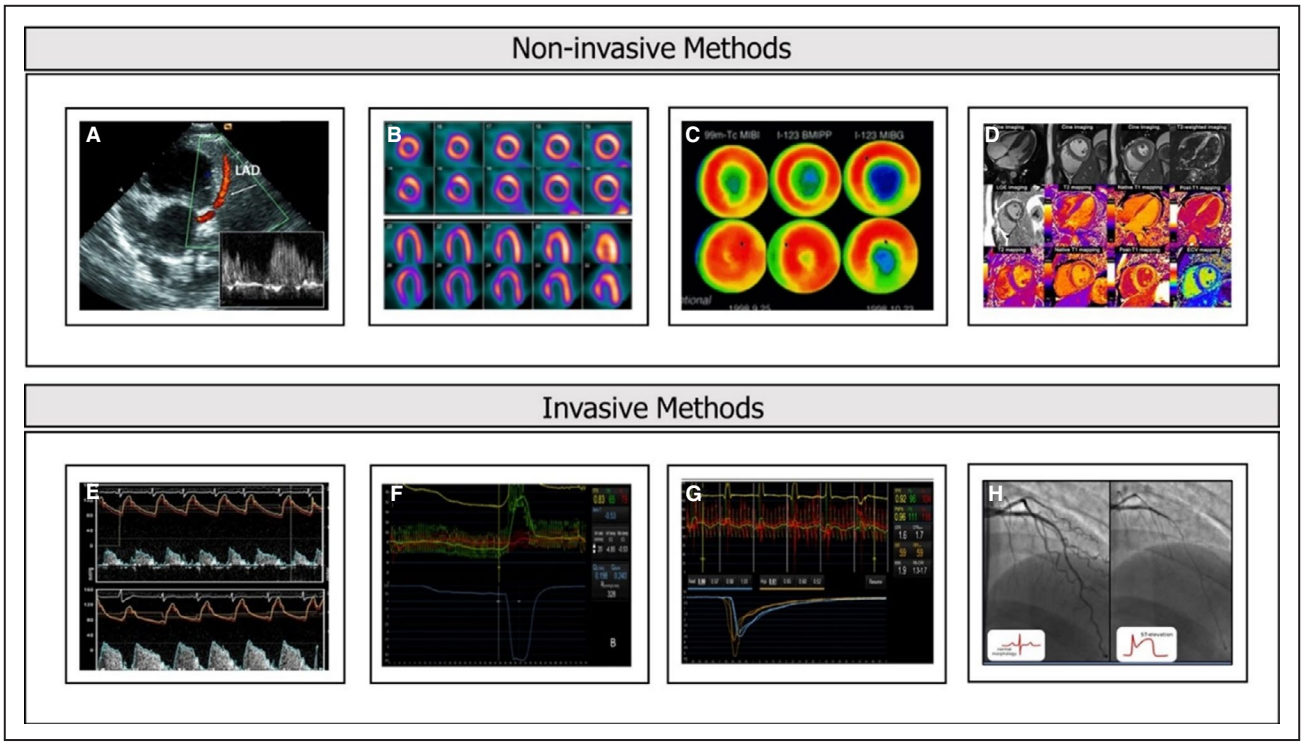

Figure 1. Methods used for evaluation of microvascular disease.
A, Transthoracic echocardiography with Doppler of LAD. **B**, PET. **C**, MIBI SPECT. **D**, CMR. **E,** Doppler CFR. **F**, Absolute coronary blood flow measured by thermodilution. **G**, Thermodilution, CFR and IMR. **H**, Acetylcholine testing. CFR indicates coronary flow reserve; CMR, cardiac magnetic resonance; IMR, index of microcirculatory resistance. LAD, left anterior descending artery; MIBI SPECT, myocardial perfusion imaging on single photon emission computed tomography; and PET, positron emission tomography.

random-effects model based on the Der Simonian-Laird method was used.[12] Weighted events are reported with 95% CIs. Heterogeneity was assessed using the I^2 value. I^2 values of 25%, 50%, and 75% represented mild, moderate, and severe inconsistency, respectively. Random-effects meta-regression analyses were used to explore the influence of sex, clinical characteristics, type of diagnostic method, different inclusion, and exclusion criteria on the outcome of interest. Linearity was assessed visually. Pairwise meta-analysis was performed to compare the risk of CMD between sexes. All analyses were performed using R version 4.0.2 meta and metafor packages (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

One hundred fifty-five articles received a complete review, and 56 studies met inclusion criteria and were included in the meta-analysis (Figure 2).[13–67] Overall, 14 427 patients were included. The mean age was 59±5 years, 65% were women, and 21% had diabetes. Most of the patients (75%) underwent invasive evaluation. Studies included in the systematic review, methods used, inclusion criteria, and definitions are described in Table S3.

The risk of bias was low on the index test, reference standard, flow, and timing. Nevertheless, in 11% (6/56) of the studies, the risk of bias in the patient selection was considered high because of inclusion of women only (Figure S1). The assessment of the quality of the studies included in the meta-analysis is presented in (Table S4).

Coronary Microvascular Disease

Thirty-seven studies reporting rates of CMD in patients with no obstructive CAD were included. They comprised 7212 participants; the mean age was 59±5 years, 61% were women, 66% had hypertension, 22% had diabetes, and 19% were smokers. Twenty-four studies used invasive methods for diagnosing CMD, whereas 14 used noninvasive methods. Assessment of invasive coronary flow reserve (CFR), either by Doppler or thermodilution techniques, was the most used method (45%), followed by positron emission tomography in 32% of patients (Figure 3). Table 1 shows baseline clinical characteristics of patients undergoing CMD investigations.

The pooled prevalence of CMD was 0.41 (95% CI, 0.36–0.47; I^2=94%; Figure 4). In 18 studies, CMD prevalence were reported separately for men and women. In the meta-regression analysis, there was no association between the proportion of women included in

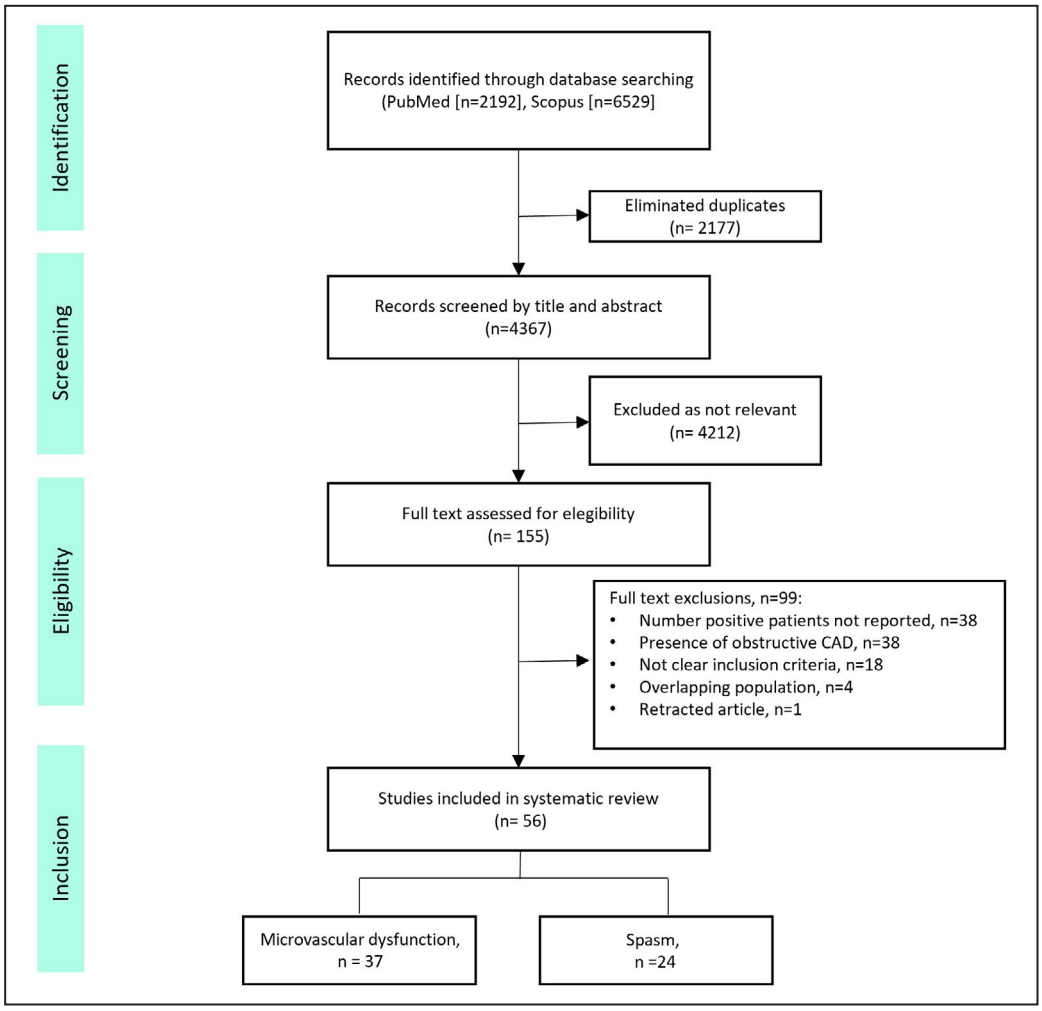

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.
CAD indicates coronary artery disease.

each study and prevalence of CMD. However, the risk of testing positive for CMD was 1.45 times greater than for men (Figure 5). The prevalence of CMD derived from invasive and noninvasive diagnostic methods was similar (0.43 [95% CI, 0.33–0.53] for invasive methods versus 0.42 [95% CI, 0.36–0.49] for noninvasive methods (P=0.993; Figure S2). Among noninvasive methods, a higher rate of CMD was found in patients who underwent positron emission tomography examination (0.46 [95% CI, 0.46–0.65]) compared with other noninvasive techniques (0.40 [95% CI, 0.30–0.55]; P=0.019).

Sensitivity analyses addressing definitions of CMD based on different CFR thresholds (eg, abnormal CFR considered ≤2.5 or ≤2.0) found no significant difference in rate of CMD (0.43 [95% CI, 0.35–0.51] for CFR ≤2.5 versus 0.46 [95% CI, 0.33–0.60] for CFR ≤2.0 (P=0.986; Figure S3). A separate analysis including only studies with at least 200 patients, performed to prevent overestimation bias seen in small studies, found similar prevalence of CMD (0.42 [95% CI, 0.36–0.49]).

Vasospastic Angina

Twenty-four studies investigating the presence of coronary vasospasm were included. They comprised 6553 patients; the mean age was 60.5±8.0 years, 39% were women, 21% had diabetes and 32% were smokers. Table 2 shows baseline and clinical characteristics of the patients undergoing coronary spasm investigations. Among studies investigating the presence of coronary vasospasm, 21 addressed epicardial spasm only, and 13 also reported the proportion of patients with microvascular spasm. The overall prevalence of coronary epicardial and microvascular spasm was 0.49 (95% CI, 0.43–0.56; I^2=96%; Figure 6). The prevalence of epicardial spasm was 0.40 (95% CI, 0.33–0.47; I^2=96%), whereas the prevalence of microvascular spasm was 0.24 (95% CI, 0.21–0.28; I^2=87%; Figure 7, Figure S4). For most of the patients, acetylcholine was used for the provocation test (98%),[14–17,19–23,31,63,66,68] and 2 studies

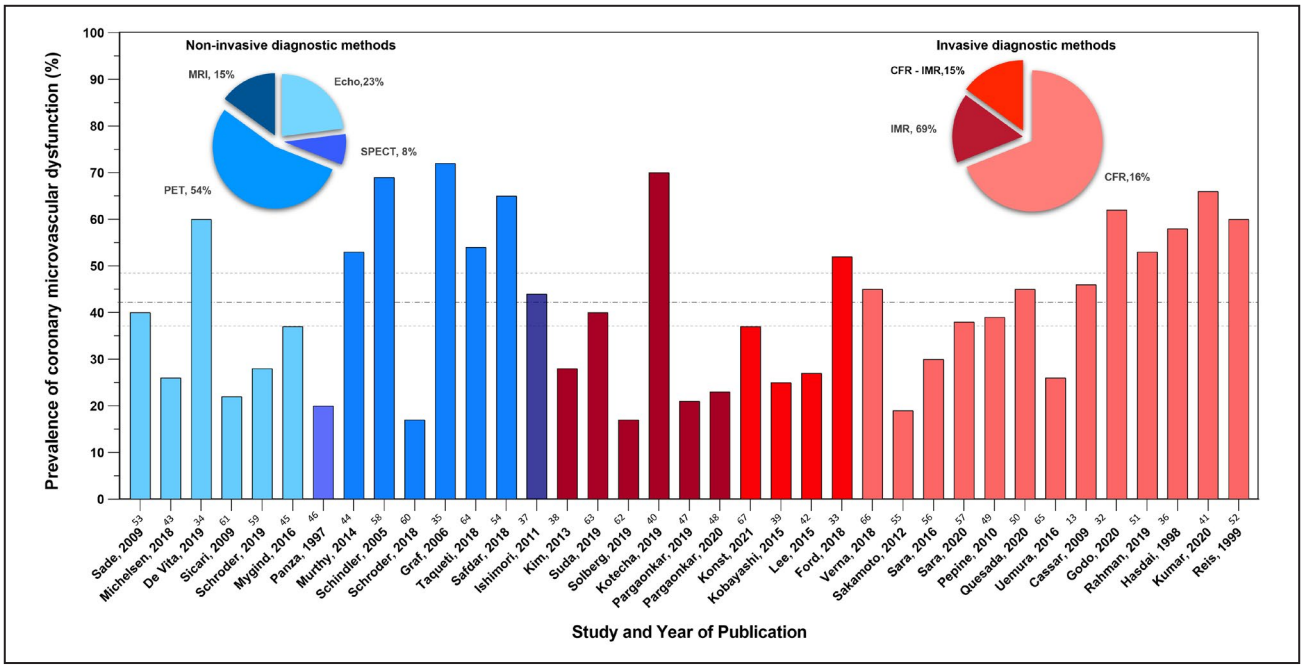

Figure 3. Bar plot chart with studies evaluating the prevalence of CMD assessed by invasive (different shades of red) and noninvasive (different shades of blue) methods.
Solid gray line illustrates the 42% pooled prevalence of CMD, and the dashed lines illustrate 95% CIs. CFR indicates invasive measurement of coronary flow reserve, Doppler, and thermodilution method; CMR, cardiac magnetic resonance; IMR, index of microcirculatory resistance; PET, positron emission tomography; and SPECT, myocardial perfusion imaging on single photon emission computed tomography.

used ergonovine.[30,34] No significant difference was found considering the type of provocation test and prevalence of spasm 0.49 (95% CI, 0.38–0.55) for acetylcholine versus 0.48 (95% CI, 0.39–0.57) for ergonovine (P=0.935). In 12 studies, coronary spasm prevalence was reported separately for men and woman. The prevalence of coronary spasm was similar between sexes 0.28 (95% CI, 0.22–0.53) in women versus 0.25 (95% CI, 0.18–0.35) in men (Figure 8). From subgroup analyses considering different definitions of epicardial spasm (ie, based on ≥90% or ≥70% coronary vasoconstriction), no significant difference in rate of spasm was detected: 0.47 (95% CI, 0.35–0.50) for ≥90 constriction versus 0.49 (95% CI, 0.42–0.55) for ≥70% constriction (P=0.133).

Combined Prevalence of CMD and Coronary Vasospasm

In 3 of the studies,[33,36,63] patients underwent evaluation for CMD and spasm. Overall, 541 patients, with a mean age of 58±10.2 years and comprising 63% women, were included. The prevalence of CMD alone was 0.23 (95% CI, 0.10–0.45), coronary spasm alone (either epicardial or microvascular) 0.19 (95% CI, 0.10–0.33), and coexistent CMD and coronary vasospasm in 0.23 (95% CI, 0.17–0.31).

DISCUSSION

The main findings of the present systematic review and meta-analysis can be summarized as follows: (1) The proportion of patients with no obstructive coronary arteries presenting with CMD was 41%, whereas coronary spasm (epicardial and/or microvascular) was present in 49% of the cases. (2) Women are more likely than men to be affected by CMD. (3) Invasive and noninvasive diagnostic methods identified similar proportions of patients with CMD. (4) There was high heterogeneity between studies in the observed prevalence of CMD and vasospastic angina.

There is an increasing awareness among clinicians of the importance of microvascular function testing in patients with nonobstructive coronary arteries.[7,69] Murthy et al reported that even in the absence of obstructive coronary atherosclerosis, 53% of patients who present with chest pain have evidence of inducible myocardial ischemia. Moreover, it was shown that the presence of CMD identifies patients at increased risk of death and myocardial infarction.[44,70] The present meta-analysis found that almost half of patients with no obstructive coronary arteries undergoing evaluation of the coronary microcirculation have CMD. Coronary

Table 1. Number of Positive Patients and Baseline Clinical Characteristics of the Patients Included in the Studies Investigating the Prevalence of Coronary Microvascular Disease

Study	Patients included	No. positive, n (%)	Age, y	Women, n (%)	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)	Current smoker, n (%)
Cassar, 2009[13]	376	170 (45%)	49±11	254 (68%)	157 (42%)	36 (10%)	208 (55%)	NA
Godo, 2020[32]	148	91 (62%)	44±9	111 (75%)	79 (53%)	11 (7%)	91 (62%)	60 (41%)
Ford, 2018[33]	151	78 (52%)	61±10	111 (74%)	125 (81%)	29 (19.2%)	120 (79.5%)	24 (15.9%)
Graf, 2006[35]	58	42 (72%)	58±10	39 (67%)	NA	8 (18%)	NA	17 (29%)
Hasdai, 1998[36]	203	118 (58%)	51 (17–78)	158 (78%)	59 (29%)	8 (4%)	88 (43.3%)	28 (27%)
Kobayashi, 2015[39]	157	39 (25%)	64±12	117 (29%)	77 (49%)	38 (24%)	91 (58%)	47 (30%)
Kotecha, 2019[40]	23	16 (70%)	63±8	NA	6 (26%)	NA	NA	NA
Lee, 2015[42]	137	38 (28%)	54±11	107 (77%)	74 (53%)	32 (23%)	87 (63%)	11 (8%)
Michelsen, 2018[43]	919	241 (26%)	62±9	919 (100%)	467 (51%)	117 (13%)	580 (63%)	149 (16%)
Murthy, 2014[44]	1218	641 (53%)	62 (53–69)	813 (67%)	894 (73%)	363 (30%)	663 (54%)	121 (10%)
Pargaonkar, 2019[47]	155	34 (22%)	54±13	119 (77%)	68 (44%)	26 (17%)	90 (58%)	23 (15%)
Pargaonkar, 2020[48]	88	32 (36%)	NA	53 (60%%)	NA	NA	NA	NA
Pepine, 2010[49]	152	74 (49%)	55±10	189 (100%)	57 (30%)	21 (11%)	50 (26%)	19 (10%)
Quesada, 2020[50]	150	67 (45%)	54±12	36 (24%)	75 (50%)	25 (17%)	90 (60%)	22 (15%)
Sade, 2009[53]	65	27 (40%)	55±8	68 (100%)	37 (54%)	NA	35 (52%)	16 (24%)
Safdar, 2020[54]	124	81 (65%)	51±11	91 (73%)	81 (65%)	42 (34%)	53 (43%)	20 (16%)
Sakamoto, 2012[55]	73	12 (16%)	65±8	36 (49%)	33 (45%)	6 (8%)	17 (23%)	11 (15%)
Sara, 2016[56]	926	281 (30%)	52±13	567 (61%)	371 (40%)	59 (6%)	485 (52%)	111 (12%)
Schindler, 2005[58]	72	50 (69%)	58 _ 8	28 (39%)	50 (69%)	3 (4%)	30 (42%)	18 (25%)
Sicari, 2009[61]	394	87 (22%)	61±10	223 (57%)	238 (60%)	69 (18%)	NA	120 (31%)
Suda, 2019[63]	187	75 (40%)	63±12	74 (40%)	100 (54%)	52 (28%)	66 (35%)	52 (28%)
Taqueti, 2018[64]	201	108 (54%)	66 (57–79)	130 (65%)	152 (76%)	129 (64%)	66 (33%)	16 (8%)
Uemura, 2016[65]	61	16 (26%)	59±15	18 (30%)	37 (61%)	15 (25%)	NA	37 (61%)
Verna, 2018[66]	101	45 (45%)	60±11	48 (48%)	58 (57%)	9 (9%)	53 (53%)	21 (21%)
Solberg, 2019[62]	66	11 (17%)	54±9	66 (100%)	15 (23%)	2 (3%)	8 (12%)	44 (67%)
Schroder, 2019[59]	174	49 (28%)	64±10	NA	NA	NA	NA	NA
Sara, 2019[57]	129	49 (38%)	50±12	61 (47%)	NA	NA	NA	NA
Kumar, 2020[41]	163	107 (66%)	57±12	79 (48%)	118 (72%)	37 (23%)	122 (75%)	30 (18%)
De Vita, 2019[34]	30	18 (60%)	67±10	19 (63%)	19 (63%)	4 (13%)	16 (53%)	15 (50%1)
Mygind, 2016[45]	54	20 (37%)	62±8	54 (100%)	29 (54%)	NA	34 (63%)	34 (63%)
Panza, 1997[46]	66	13 (20%)	49±10	44 (67%)	NA	Na	NA	NA
Schroder, 2018[60]	97	37 (38%)	62 (31–79)	97 (100%)	NA	NA	NA	NA
Reis, 1999[52]	48	29 (60%)	54±10	48 (100%)	23 (48%)	6 (13%)	24 (49%)	NA
Kim, 2013[38]	40	11 (28%)	53±11	NA	NA	NA	NA	NA
Ishimori, 2011[37]	18	8 (44%)	41±11	18	NA	NA	NA	NA
Rahman, 2019[51]	85	45 (53%)	57±10	66 (78%)	25 (29%)	11 (13%)	23 (27%)	12 (14%)
Konst, 2020[67]	103	38 (37%)	62±9	NA	NA	NA	NA	NA

NA indicates information is not available.

function testing enables stratifying management of patients from different endotypes of ischemia with no obstructive CAD. Individualized treatment strategies are required, given the different pathophysiological mechanisms underlying these distinct disease endotypes. Objective evidence of the cause of chest pain and stratified therapy positively influence the quality of life of these patients.[33,71] Furthermore, identification of CMD or coronary spasm as the cause of symptoms prevents patients from undergoing repeated invasive diagnostic evaluations, which may reduce health care costs and allows for medical therapy optimization according to a specific diagnosis.[72]

Coronary microvascular dysfunction has been deceivingly recognized as a women's disease.[73] The WISE (Women's Ischemia Syndrome Evaluation) study demonstrated that 39% of women who present with chest pain and no obstructive CAD have evidence of

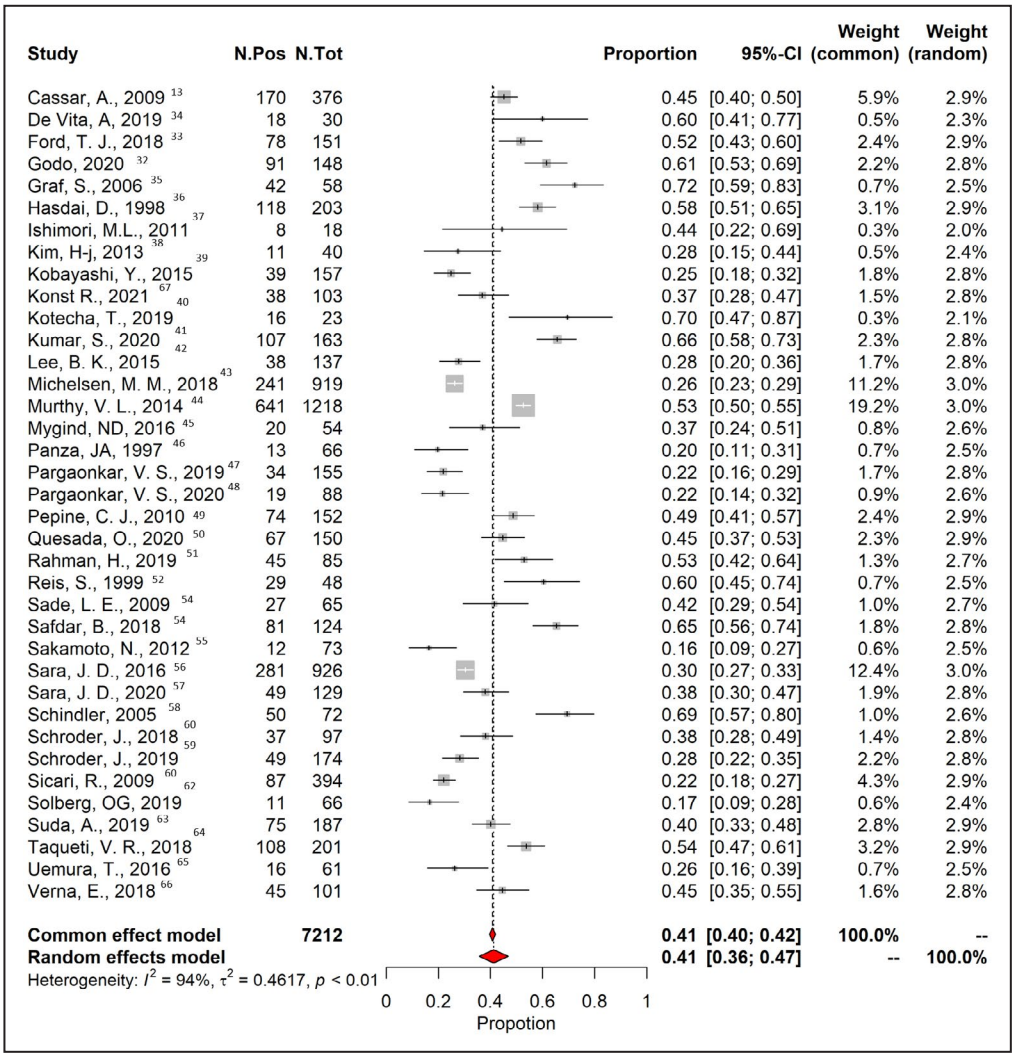

Figure 4. Prevalence of coronary microvascular dysfunction.
The vertical black line indicates the pooled averaged prevalence rate estimate, and the red diamond represents the overall estimated prevalence with 95% CI in a random-effects model. Gray squares indicate weighted-point estimates of incidence for each single study, with gray horizontal lines indicating 95% CI. I^2 indicates Higgins index of heterogeneity. Pos indicates positive; and Tot, total.

induced myocardial ischemia and coronary vasomotor dysfunction.[49] However, Murthy et al showed, using positron emission tomography, that CMD was highly prevalent in both sexes (51% in men versus 54% in women).[44] The present meta-analysis found that CMD is highly prevalent in both sexes; however, women are more likely to have CMD.[44,49,74] An important fact to consider is that a substantial number of the studies did not evaluate men in a similar proportion to women.

Stratified Approach

The prevalence of CMD in patients with angina and no obstructive CAD undergoing invasive angiography depends on the methods and cutoffs applied. Assessment of invasive CFR was found to be the most-used method for detecting CMD. However, it was derived mainly using a Doppler[1] or thermodilution technique.[33,39,42,50] In addition, some studies used a cutoff value of ≤2.5,[13,36,50–52,55,56,66,75] whereas others used ≤2.0.[32,33,39,41,42] The different methods and cutoffs may partially explain the high between-study heterogeneity. However, we found that the prevalence of CMD was similar between methods and cutoffs. The recently published consensus document on diagnosis of CMD defined specific thresholds for identification of distinct endotypes of ischemia with no obstructive CAD.[76] Here, CMD is defined as the presence of symptoms of myocardial ischemia, unobstructed coronary arteries (ie, diameter stenosis <50% or fractional flow reserve >0.80), and any of the following: index of microcirculatory resistance >25, CFR ≤2.0, and hyperemic

*References 13, 32, 36, 41, 49, 51, 52, 55, 56, 66, 75.

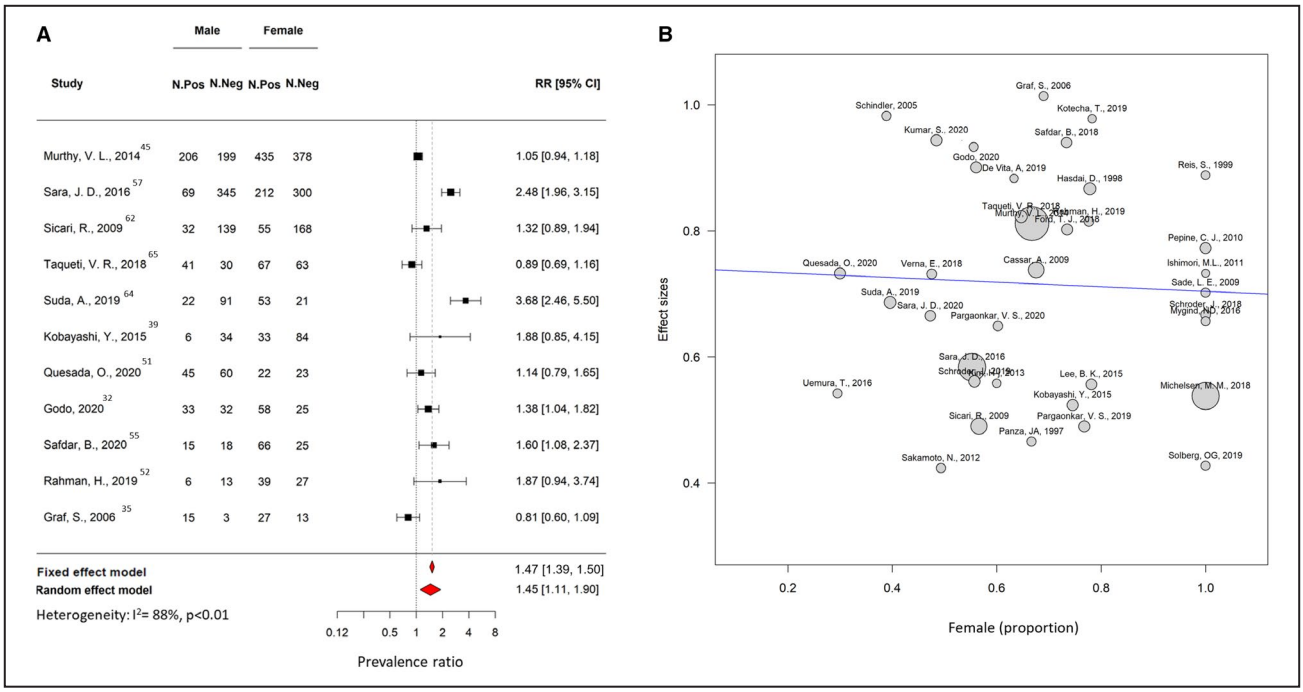

Figure 5. Sensitivity analysis of prevalence of microvascular disease according to sex.
A, Forest plot illustrating the risk ratio (RR) and 95% CI of prevalence of coronary microvascular disease according to sex. **B**, Metaregression plot showing association between the prevalence of coronary microvascular resistance (*y*-axis) and the proportion of women included in each study. The size of the bubble represents the number of patients included in each study. Neg indicates negative; and Pos, positive.

microvascular resistance >1.9. Vasospastic angina, assessed with an acetylcholine provocation test, is considered positive for epicardial spasm when ≥90% diameter stenosis (compared with the angiography performed after nitrate administration) occurs with angina and ischemic ECG changes, whereas microvascular spasm is defined as the presence of angina and ischemic ECG changes without severe epicardial narrowing.[76]

Despite the increasing awareness of CMD as a cause of chest pain, diagnostic methods to assess its presence remain underused.[77] There are 2 main barriers to the widespread adoption of these methods in clinical practice. One refers to the limited availability of methods to diagnose CMD, such as positron emission tomography and invasive measurements. The second arises from the lack of effective medical therapies to treat CMD. Therefore, future research should focus on the evaluation of therapies to improve quality of life in patients with CMD. A breakthrough in this field would potentially facilitate the widespread adoption of CMD and vaso-function testing in clinical practice.

Limitations

The main limitation of the present meta-analysis is the lack of data on individual patients, which would have allowed for a standardization of CMD and coronary spasm definitions. Moreover, we observed a high level of heterogeneity between studies. The possibility of publication bias cannot be excluded (Figure S5). We were unable to identify specific variables leading to heterogeneity; however, this is most likely related to the inclusion criteria of each individual study and the difference between definitions of CMD and spasm that were used across the studies (Table S2). Another fact that should be accounted for is the possibility of false-positive cases, especially in the studies with noninvasive imaging.[78,79] During the past years, more attention has been drawn to the fact that CFR is unable to define the pathophysiologic substrate for all cases of angina with no obstructive coronary arteries. It has been suggested that assessing the full range coronary pathophysiology requires concepts beyond CFR, such as regional size–severity quantification versus global perfusion and subendocardial perfusion on relative tomographic images.[80]

CONCLUSIONS

In patients with no obstructive CAD, approximately half of the cases present with underlying disease, either CMD or coronary vasospasm. CMD is more prevalent in women; nonetheless, men are affected in

Table 2. Number of Positive Patients and Baseline Clinical Characteristics of the Patients Included in the Studies Investigating the Prevalence of Vasospasm

Study	Patients included	No. positive, n (%)	Age, y	Women, n (%)	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)	Current smoker, n (%)
Aziz, 2017[14]	1379	813 (59%)	62±11.9	799 (58%)	970 (70%)	237 (17%)	841 (61%)	502 (36%)
Ford, 2018[33]	151	56 (37%)	61 (53–68)	111 (74%)	NA	29 (19%)	120 (80%)	24 (16%)
Hoshino, 2016[15]	292	90 (30%)	64±11	156 (51.7%)	114 (39%)	33 (11%)	98 (34%)	130 (45%)
Kim, 2018[16]	328	128 (39%)	58±10.4	233 (71%)	128 (39%)	31 (9.4%)	72 (22%)	39 (12%)
Mohri, 1998[17]	117	81 (74%)	63 (54–68)	59 (50%)	56 (48%)	26 (22%)	49 (42%)	50 (43%)
Montone, 2018[18]	80	37 (46%)	63±11	40 (50%)	32 (40%)	8 (10%)	19 (24%)	17 (21%)
Montone, 2020[19]	210	118 (56%)	62±11	82 (39%)	79 (38%)	13 (6%)	54 (26%)	27 (13%)
Oh, 2019[20]	464	156 (34%)	57±11	164 (35%)	60 (13%)	23 (5%)	94 (20%)	48 (10%)
Ohba, 2012[21]	370	264 (71%)	63±11	211 (57%)	197 (53%)	73 (20%)	193 (52%)	107 (29%)
Ong, 2014[23]	847	488 (58%)	62±12	485 (57%)	609 (72%)	142 (17%)	460 (54%)	307 (36%)
Ong, 2012[22]	124	77 (53%)	64±10	100 (%)	102 (71%)	31 (22%)	83 (58%)	22 (15%)
Ong, 2014[24]	137	69 (50%)	63±11	93 (68%)	105 (77%)	27 (20%)	73 (53%)	38 (28%)
Pirozzolo, 2020[25]	96	56 (58%)	65±12	49 (51%)	84 (88%)	15 (16%)	84 (88%)	25 (26%)
Quyyumi, 1992[26]	51	5 (10%)	51±11	31 (61%)	20 (39%)	NA	NA	NA
Suda, 2019[63]	187	126 (67%)	63±12	74 (40%)	100 (54%)	52 (28%)	66 (35%)	52 (28%)
Sun, 2002[29]	55	14 (26%)	60±10	23 (42%)	26 (47%)	9 (16%)	26 (47%)	30 (55%)
Sun, 2005[28]	131	101 (79%)	59±11	69 (53%)	59 (45%)	30 (13%)	50 (38%)	36 (27%)
Tsuchida, 2005[30]	102	74 (77%)	57±11	15 (15%)	43 (42%)	31 (30%)	NA	82 (80%)
Uemura, 2016[65]	61	15 (28%)	59±15	18 (30%)	37 (61%)	15 (25%)	NA	37 (61%)
Verna, 2018[66]	101	57 (57%)	60±11	48 (48%)	58 (57%)	9 (9%)	53 (52%)	21 (20%)
Seitz, 2020[27]	847	283 (33%)	64±11	529 (63%)	533 (63%)	129 (15%)	411 (49%)	260 (31%)
Yamanaga, 2015[31]	50	29 (58%)	62±13	24 (48%)	28 (56%)	10 (20%)	29 (58%)	10 (20%)
Quesada, 2020[50]	150	83 (55%)	54±12	36 (24%)	75 (50%)	25 (17%)	90 (60%)	22 (15%)
Hasdai, 1998[36]	203	59 (29%)	51 [17–78]	158 (78%)	59 (29%)	8 (4%)	88 (43%)	28 (14%)

NA indicates information is not available.

a significant proportion. The large variability of methods, definitions, and thresholds for diagnosing these conditions is a call to a refinement and standardization of diagnostic tools. Greater awareness among physicians of ischemia with no obstructive coronary arteries is urgently needed for accurate diagnosis and patient-tailored management.

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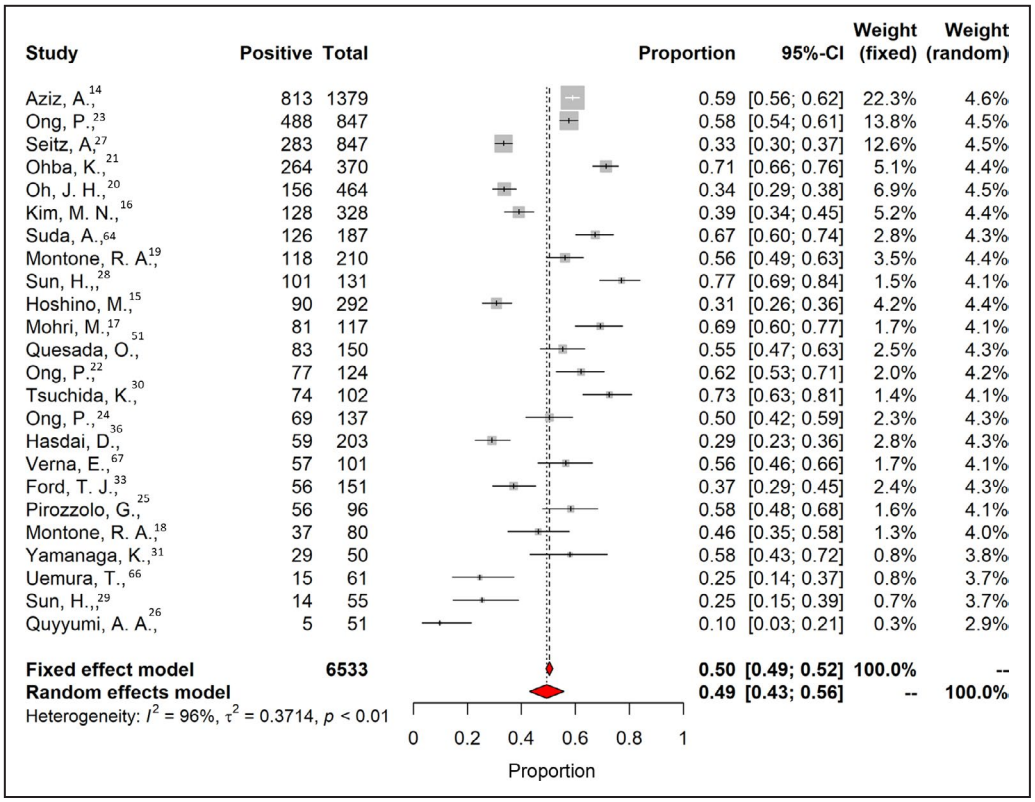

Figure 6. Prevalence of coronary vasospasm.
The vertical black line indicates the pooled averaged prevalence rate estimate, and the red diamond represents the overall estimated prevalence with 95% CI in a random-effects model. Gray squares indicate weighted-point estimates of incidence for each single study, with gray horizontal lines indicating 95% CI. I^2 indicates Higgins index of heterogeneity.

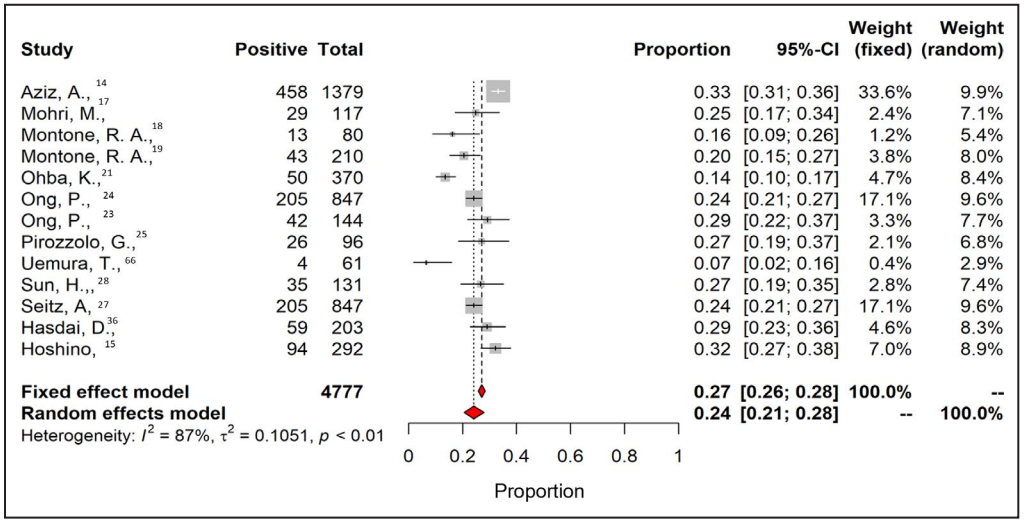

Figure 7. Prevalence of coronary microvascular spasm.

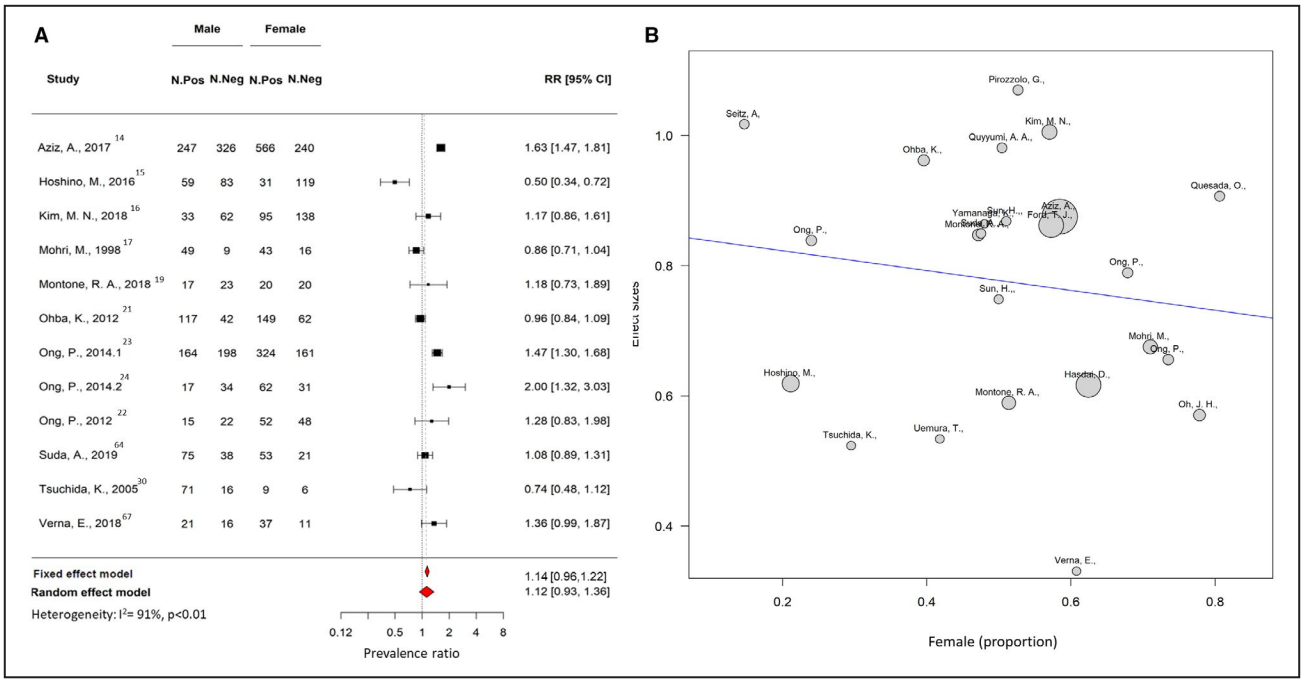

Figure 8. Sensitivity analysis of prevalence of coronary vasospasm according to sex.
A, Forest plot illustrating the risk ratio (RR) and 95% CI of the prevalence of coronary vasospasm according to sex. **B**, Metaregression plot showing association between the prevalence of coronary vasospasm (*y*-axis) and the proportion of women included in each study. The size of the bubble represents the number of patients included in each study. Neg indicates negative; and Pos, positive.

Supplemental Material

Figures S1–S5

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Supplemental Material

Table of contents

Table S1. Search strategy

Database	Investigator 1
Pubmed	Coronary microvascular disease: (non-obstructive OR "non obstructive" OR "non occlusive" OR normal angio* OR epicardial) AND (ischemia OR angina OR "chest pain" OR myocardial ischemia OR coronary artery disease OR "coronary artery disease") Spasm: (non-obstructive OR "non obstructive" OR "non occlusive" OR epicardial) AND (ischemia OR angina OR "chest pain" OR myocardial ischemia OR coronary artery disease OR "coronary artery disease") AND (spasm OR vasospasm OR vasospastic) AND (Microci* OR Microva* OR Microvessels OR spasm OR vasospasm OR vasospastic)

Database	Investigator 2
Pubmed	Coronary microvascular disease: : (non*) AND (obs* OR "obstructive" OR "occlusive" OR epicardial) AND (angina OR ischemia OR "chest pain" OR myocardial ischemia OR coronary artery disease OR "coronary artery disease") AND ("ANOCA" OR "INOCA") Spasm: (non*) AND (obs* OR "obstructive" OR "occlusive" OR epicardial) AND (angina OR ischemia OR "chest pain" OR myocardial ischemia OR coronary artery disease OR "coronary artery disease") AND (spasm OR vasospasm OR vasospastic) AND (Microci* OR Microva* OR Microvessels OR spasm OR vasospasm OR vasospastic) AND ("ANOCA" OR "INOCA")

Table S2: PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	20, 21
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7, 8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6, 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Table S3. Studies included in the systematic review – method used for evaluation of CMD and inclusion criteria. CMD indicates coronary microvascular disease; ES, epicardial vasospasm; MVS, microvascular spasm; ECG, electrocardiogram; CFR, coronary flow reserve; IMR, index of microcirculatory resistance; Ach, Acetylcholine.

Study	Year	Method	Definition	Inclusion Criteria
Quyumi	1992	ACh test	ES : Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction >50%	Patients with angina and epicardial coronary stenoses <10%
Panza	1997	MIBI	CMD - Thallium perfusion defect on stress images	Patients with angina and epicardial coronary stenoses <30%
Hasdai	1998	CFR doppler	CMD - CFR ≤2.5	Patients with recurrent chest pain with no obstructive CAD <40% and no previous MI
Mohri	1998	ACh test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥70% 2. MVS: ischemic ECG changes and symptoms	Chest pain and <50% coronary organic stenosis.
Reis	1999	CFR	CMD - CFR<2.5	Women with chest pain and normal coronary arteries ≤50%
Sun	2002	ACh test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75%	Patients with chest pain and no coronary stenosis >50%

			2. MVS: ischemic ECG changes and symptoms	
Sun	2005	Ach test TIMI frame count	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75% 2. MVS: ischemic ECG changes and symptoms CMD - TIMI frame count as 60 counts or more in LAD and 45 or more in LCX.	Patients with chest pain and normal coronary arteriograms (no stenosis >50%)
Schindler	2005	PET	CMD – MBF ≤40%	Patients with angina and no coronary stenosis (“smooth coronary vessels without evidence of luminal wall irregularities or diffuse caliber reduction and stenosis”).
Tsuchid	2005	Ergonovine test	ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% spasm	Patients with angina and no organic stenosis (>50%)
Graf	2006	PET	CMD - CFR <2.5	Patients with angina, positive stress test and normal angiogram not older than 3 months
Cassar	2009	CFR Doppler	CMD - CFR ratio of ≤ 2.5 during infusion of adenosine.	Patients with positive stress test and non-obstructive CAD (≤ 40% luminal diameter stenosis)
Sicari	2009	TTE CFR Doppler LAD	CMD - CFR ≤ 2.0	Patients with history of chest pain, coronary angiography with stenosis <50%
Sade	2009	TTE CFR LAD	CMD - CFR<2.0	Women who underwent angiography and had no obstructive coronary artery disease
Pepine	2010	CFR Doppler	CFR <2.32	Women undergoing clinically indicated coronary

				angiography and no CAD (<50%)
Ishimori	2011	CMR	1. Any stress perfusion defect size ≥5%	Consecutive female patients presenting with typical and atypical anginal and no angiographically documented CAD (≥70% stenosis)
Ohba	2012	ACh test	2. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 3. MVS: ischemic ECG changes and symptoms	Patients with angina and nonobstructive CAD (<50%) undergoing ACh test.
Ong	2012	ACh test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75% 2. MVS: ischemic ECG changes and symptoms	Patients with exercise-related angina and no coronary stenosis > 20%
Sakamoto	2012	CFR doppler	CMD - CFR <2.8	Patient with chest pain. No CAD and no vasospasm.
Ong	2014	ACh test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75% 2. MVS: ischemic ECG changes and symptoms	Patients with suspected myocardial ischemia and unobstructed coronary arteries (stenosis<50%)
Murthy	2014	PET	CMD - CFR < 2.0	Women referred for evaluation of suspected CAD with no previous history of CAD and no visual evidence

				of CAD on rest/stress positron emission tomography (PET) myocardial perfusion imaging.
Ong	2014	ACh test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75% 2. MVS: ischemic ECG changes and symptoms	Unobstructed coronary arteries (stenosis <50%) and exertional angina with performed bicycle stress test
Yamanaga	2015	ACH test	ES - Vasoconstriction >90% with angina and/or ECG changes	Pts with angina and no obstructive CAD undergoing Ach test, stenosis <50% and EF >50%
Kobayashi	2015	CFR cont thermodilution IMR	CMD: CFR<2 or IMR >25	Patients with angina in the absence of obstructive CAD (>50% stenosis; FFR -<0.8).
Lee	2015	CFR cont thermodilution IMR ACHtest	CFR<2 IMR>25 Endothelial dysfunction – vasoconstriction <20%	Angina with or without stress test in the absence of obstructive CAD (stenosis >50%)
Sara	2016	CFR Doppler	CMD - CFR≤2.5	Patients with chest and/or abnormal functional stress test and coronary stenosis <40%
Uemura	2016	CMR Ach test	CMD - CFR <2.5 1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 2. MVS: ischemic ECG changes and symptoms	Patients without coronary artery disease (stenosis >50%)
Hoshino	2016	ACh test	ES: vasoconstriction >=75%	Consecutive patients with coronary stenosis (>50%) who underwent ACH test

Mygind,	2016	TTE LAD PET	CFVR <2.0 MBFR<2.5	Patients with clinically indicated coronary angiography and no stenosis >50%
Kim	2017	ACh test	1. ES: vasoconstriction >=90%	Patients with chest pain, who underwent coronary angiography without CAS (>50%)
Aziz	2017	ACh test	ES 1. Reproduction of typical symptoms; 2. ECG changes; 3. diffuse or focal vasoconstriction >75% 2. MVS – 1. Reproduction of typical symptoms; 2. ECG changes	Consecutive patients with angina pectoris who underwent ACH test and unobstructed coronary arteries (no stenosis > 50%)

Ford	2018	CFR cont thermodilution IMR ACh test	3. CMD - CFR<2.0 or IMR>-25 4. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction >=90% MVS: ischemic ECG changes and symptoms	Patients with angina and no obstructive CAD (stenosis >50% and FFR ≤0.80)
Michelsen	2018	TTE LAD - CFR	CMD = CFVR<2.0	Women with angina, left ventricular ejection fraction (LVEF) >45%, and an invasive coronary angiogram without significant stenosis (>50%).
Safdar	2018	PET	CMD - CFR<2.5	Patients with chest pain that underwent PET with no regional perfusion defect or calcification
Montone	2018	ACh test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 2. MVS: ischemic ECG changes and symptoms	MI without obstructive coronary artery disease (stenosis<50% at coronary angiography)
Taqueti	2018	PET	CMD - CFR <-2.0	Patients without prior history of CAD, undergoing evaluation for suspected CAD with PET an no evidence of flow limiting CAD (semi-quantitative perfusion summed stress score >2)
Scroder	2018	PET	CMD - MBFR <2.5	Women with no significant obstructive coronary artery disease (<50%

				stenosis
Verna	2018	CFR doppler	CMD - CFVR <2.5.	Patients with suspected SIHD and NOCAD (absence of >50% stenosis and FFR <0.8)
Montone	2019	ACh test	ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% MVS: ischemic ECG changes and symptoms	Coronary angiography for suspected myocardial ischemia with evidence of non-obstructive CAD (angiographically normal coronary arteries or diffuse atherosclerosis with stenosis < 50%) and undergoing an intracoronary provocative test
Rahman	2019	CFR	CMD - CFR ≤2.5	Patients with chest pain, LV EF >50% and unobstructed coronary arteries (stenosis <30% and or FFR>0.8)
Oh	2019	Erogonovine test	ES: Vasoconstriction > 90% alone or vasoconstriction > 70% + symptoms and ECG changes	Angina patients with variant angina undergoing provocative test
Kotecha	2019	IMR	IMR > 25	Patients with stable angina who underwent CMR and absence of obstructive CAD (FFR<-0.8
Pirozzolo	2019	ACH test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 2. MVS: ischemic ECG changes and symptoms	Patients with NSTEMI and non-obstructive CAD (stenosis <50%)
Pargaonkar	2019	IMR	CMD - IMR >25	Angina and no-obstructive CAD (stenosis <50%)
Suda,	2019	ACh test IMR CFR	CMD - IMR >18 or CFR<2.0 ES - vasoconstriction > 90%	Angina and normal coronaries (stenosis<70%, FFR >0.80) that underwent invasive stress test.

De Vita	2019	TTE LAD	CMD - CBF velocity reduction ≥ 20%	Patients with NSTE-ACS, who were found to have NO-CAD (i.e., normal coronary arteries or < 50% coronary stenosis in major epicardial coronary arteries) at angiography
Solberg	2019	IMR	Microvascular dysfunction defined as IMR >20.8 mmHg	Women with angina pectoris and normal or near-normal coronary angiograms with FFR >0.80.
Schroder	2019	Echo doppler LAD CFR	CMD - CFR<2.0	Pts with angina and no obstructive CAD, stenosis <50%
Pargaonkar	2020	Ach test	CMD – IMR >25	Angina and no-obstructive CAD (stenosis <50%)
Pirozzolo	2020	Ach test	1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 2. MVS: ischemic ECG changes and symptoms	Patients with NSTEMI and non- obstructive CAD (stenosis <50%)
Quesada	2020	CFR bolus thermodilution	CMD - CFR <2.5	Typical angina pectoris with no relevant CAD <50%
Sara	2020	CFR Doppler	CMD = CFR ≤ 2.5	Patients with chest pain and normal coronaries (stenosis < 40%)
Kumar	2020	CFR	CMD - CFR < 2.0, HMR ≥2.0	Symptomatic patients with No obstructive CAD on coronary angiography (defined as <50% luminal obstruction in one or more epicardial coronary arteries) and normal fractional flow reserve (FFR > 0.8)
Seitz	2020	ACh testing	1. ES – Reproduction of typical symptoms; ECG changes and epicardial	Patients with symptoms of myocardial ischemia but NOCA (<50% epicardial stenosis as determined by quantitative coronary angiography

			vasoconstriction ≥75% 2. MVS: ischemic ECG changes and symptoms	
Godo	2020	CFR doppler	CMD - CFR<2.0	Patients with angina and angiographically normal coronary arteries (<40% stenosis)
Pargaonkar	2020	IMR	IMR >25	Patients with persistent (>3 months) typical/atypical angina and a suspected MB based on CCTA and excluded obstructive CAD (stenosis>50%)
Konst	2021	IMR, CFR – bolus thermodilution	CMD – CFR <2.0 IMR >25	Patients with angina and no obstructive CAD (<50% stenosis)

Table S4. Quality assessment, risk of bias and generalizability of the studies included in the systematic review.

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Aziz, 2017	☺	☺	☺	☺	☺	☺	☺
Cassar, 2009	☹	☺	☺	☺	☹	☺	☺
De Vita, 2019	☺	☺	☺	☺	☺	☺	☺
Ford, 2018	☹	☺	☺	☺	☹	☺	☺
Good, 2020	☺	☺	☺	☺	☺	☺	☺
Graf, 2006	☺	☺	☺	☺	☺	☺	☺
Hasdai, 1998	☹	☺	☹	☹	☹	☺	☺
Hoshino, 2016	☺	☺	☺	☺	☺	☺	☺
Ishimori, 2011	☹	☺	☹	☺	☹	☺	☺
Kim, 2013	☹	☺	☺	☺	☹	☺	☺
Kim, MN, 2017	☺	☺	☺	☺	☺	☺	☺
Kobayashi, 2015	☺	☺	☺	☺	☺	☺	☺
Kotecha, 2019	☹	☺	☺	?	☹	☺	☺
Kumar, 2020	☹	☺	☺	☹	☹	☺	☺
Lee, 2015	☹	☺	☺	?	☹	☺	☺
Michelsen, 2019	☹	☺	☺	☺	☺	☺	☺
Mohri, 1998	☹	☺	☹	?	☹	☺	☺
Montone, 2018	☹	☺	☺	☹	☹	☺	☺
Montone, 2019	☹	☺	☺	?	☹	☺	☺
Murthy, 2014	☹	☺	☺	☹	☹	☺	☺
Mygind, 2016	☺	☺	☺	☺	☺	☺	☺
Oh, 2019	☺	☺	☺	?	☹	☺	☺
Ohba, 2012	☺	☺	☺	☹	☹	☺	☺
Ong, 2012	☹	☺	☺	?	☹	☺	☺
Ong, 2014	☹	☺	☺	☹	☹	☺	☺
Ong, 2014	☺	☺	☺	☺	☺	☺	☺
Pirozzolo, 2019	☹	☺	☺	?	☹	☺	☺
Pargaonkar, 2019	☹	☺	☺	☹	☹	☺	☺
Pargaonkar, 2020	☹	☺	☺	?	☹	☺	☺
Pepine, 2010	☹	☺	☺	☹	☹	☺	☺
Quesada, 2020	☺	☺	☺	☺	☺	☺	☺
Quyyumi, 1992	☹	☺	☹	?	☹	☺	☺
Rahman, 2019	☹	☺	☺	☹	☹	☺	☺
Reis, 1999	☹	☺	☺	?	☹	☺	☺
Sade, 2009	☹	☺	☺	☹	☹	☺	☺
Safdar, 2018	☹	☺	☺	☺	☹	☺	☺
Sakamoto, 2012	☺	☺	☺	☺	☺	☺	☺
Sara, 2016	☺	☺	☺	☺	☺	☺	☺
Sara, 2020	☹	☺	☺	☺	☹	☺	☺
Schindler, 2005	☹	☺	☺	☺	☹	☺	☺
Seitz, 2020	☺	☺	☺	☺	☺	☺	☺
Schroder, 2018	☺	☺	☺	☺	☺	☺	☺
Schroder, 2019	☹	☺	☺	☺	☹	☺	☺

Sicari, 2009	☹	☺	☺	?	☹	☺	☺
Solberg, 2019	☹	☺	☺	☺	☺	☺	☺
Suda, 2019	☺	☺	☺	☺	☺	☺	☺
Sun, 2005	☹	☺	☺	☺	☹	☺	☺
Sun, 2002	☹	☺	☺	?	☹	☺	☺
Taqueti, 2018	☹	☺	☺	☺	☹	☺	☺
Tsuchida, 2005	☺	☺	☺	?	☺	☺	☺
Uemura, 2016	☹	☺	☺	☺	☹	☺	☺
Verna, 2018	☹	☺	☺	☺	☹	☺	☺
Yamanaga, 2015	☺	☺	☺	☺	☺	☺	☺
Prasada, 2014	☺	☺	☺	☺	☺	☺	☺

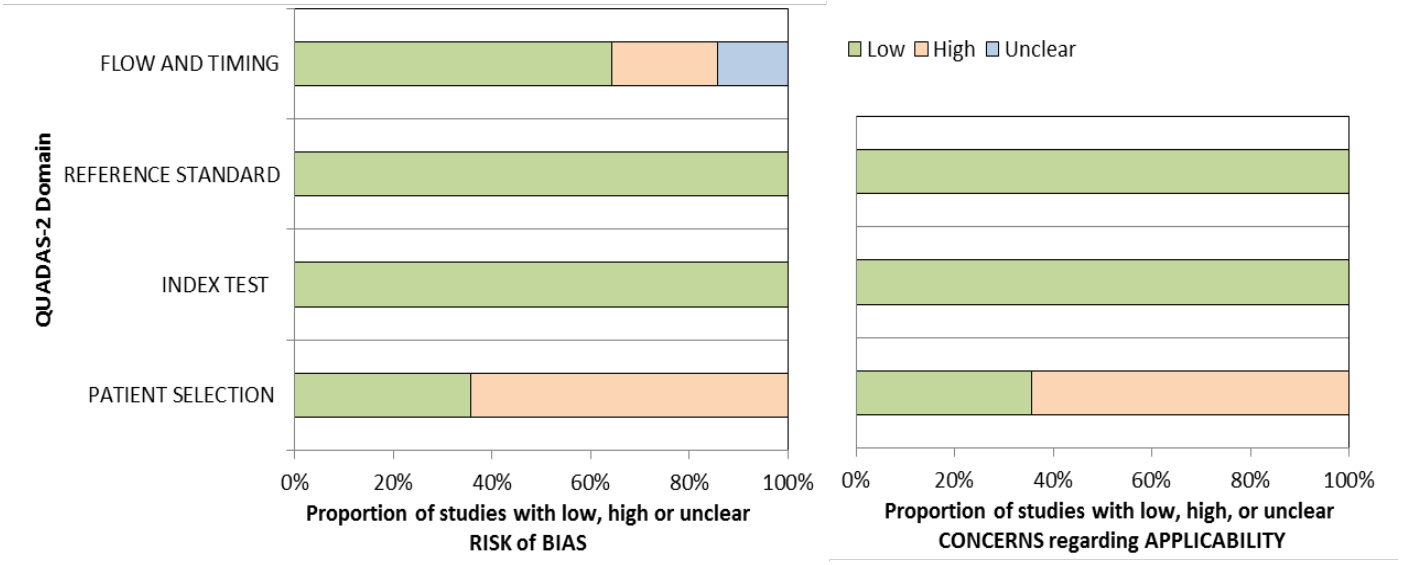


Figure S1. Prevalence of coronary microvascular disease after exclusion of six studies with high risk of bias due to inclusion of female patients only.

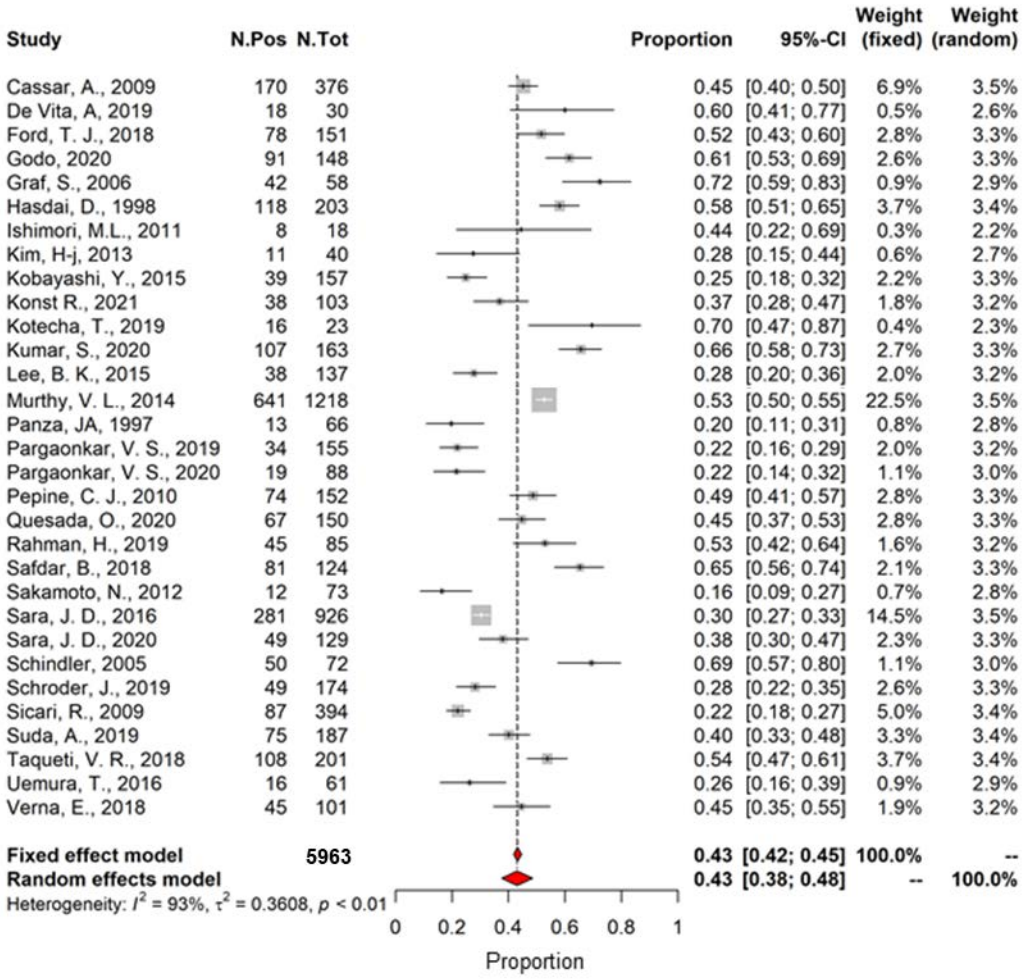


Figure S2. Prevalence of coronary microvascular disease in subgroups of invasive and non-invasive methods.

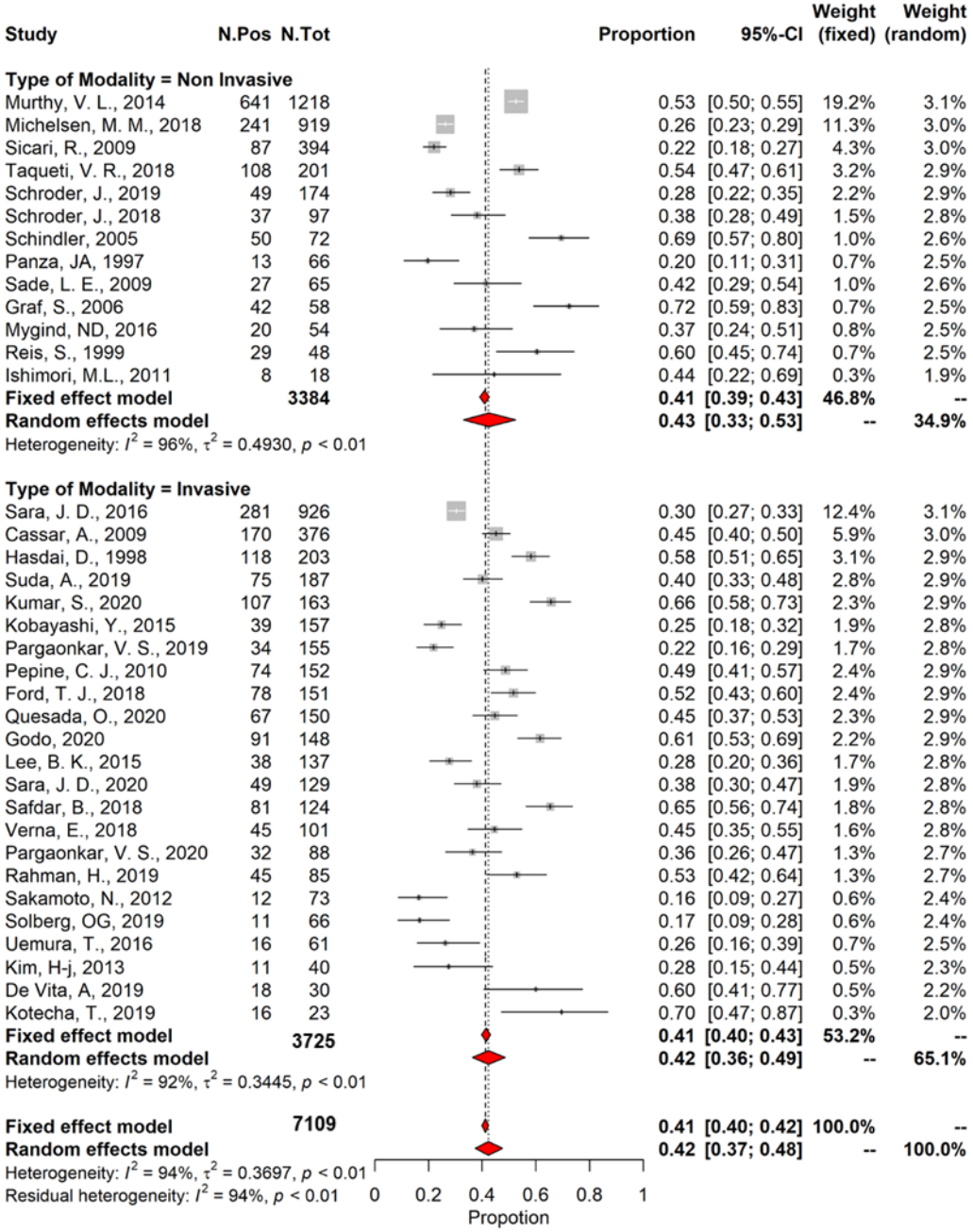


Figure S3. Prevalence of coronary microvascular disease in subgroups, based on definitions of CMD using different CFR thresholds (e.g., abnormal CFR considered ≤2.5 or ≤2.0).

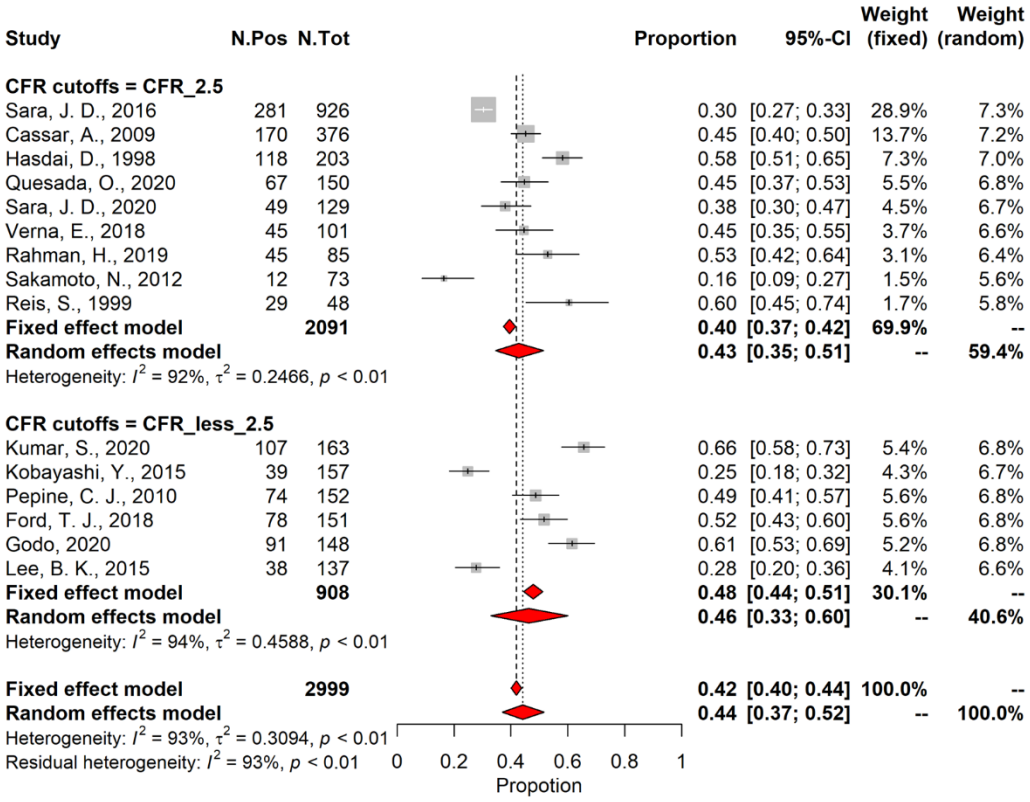
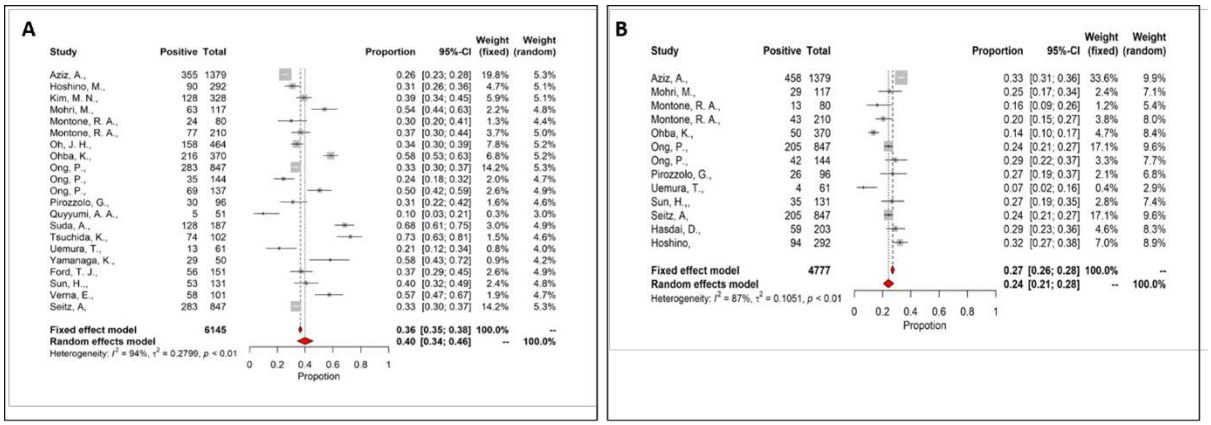


Figure S4. Prevalence of epicardial coronary spasm and microvascular spasm



Epicardial spasm | Microvascular spasm

Figure S5. Funnel plots with Egger's test for funnel plot asymmetry. A) Studies included in the coronary microvascular analysis, z = 2.08, p = 0.04. B) Studies included in coronary spasm analysis, z = 3.47, p=0.005.