

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

*Original*

Prevalence of Coronary Microvascular Disease and Coronary Vasospasm in Patients With Nonobstructive Coronary Artery Disease: Systematic Review and Meta-Analysis / Mileva, N., Nagumo, S., Mizukami, T., Sonck, J., Berry, C., Gallinoro, E., Monizzi, G., Candreva, A., Munhoz, D., Vassilev, D., Penicka, M., Barbato, E., De Bruyne, B., Collet, C.. - In: JOURNAL OF THE AMERICAN HEART ASSOCIATION. CARDIOVASCULAR AND CEREBROVASCULAR DISEASE. - ISSN 2047-9980. - ELETTRONICO. - 11:7(2022). [10.1161/JAHA.121.023207]

*Availability:*

This version is available at: 11583/2972250 since: 2022-10-12T10:57:50Z

*Publisher:*

WILEY

*Published*

DOI:10.1161/JAHA.121.023207

*Terms of use:*

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

*Publisher copyright*

(Article begins on next page)

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

Niya Mileva <sup>ID</sup>, MD; Sakura Nagumo, MD, PhD; Takuya Mizukami <sup>ID</sup>, MD, PhD; Jeroen Sonck, MD; Colin Berry <sup>ID</sup>, MD, PhD; Emanuele Gallinoro <sup>ID</sup>, MD; Giovanni Monizzi, MD; Alessandro Candreva, MD; Daniel Munhoz <sup>ID</sup>, MD, PhD; Dobrin Vassilev, MD, PhD; Martin Penicka, MD, PhD; Emanuele Barbato <sup>ID</sup>, MD, PhD; Bernard De Bruyne <sup>ID</sup>, MD, PhD; Carlos Collet <sup>ID</sup>, MD, PhD

**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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3–5</sup>

Correspondence to: Carlos Collet, MD, PhD, Cardiovascular Center Aalst, OLV-Hospital, Moorselbaan 164, 9300 Aalst, Belgium. E-mail. carloscollet@gmail.com

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023207>

For Sources of Funding and Disclosures, see page 11.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## 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

<b>CFR</b>	coronary flow reserve
<b>CMD</b>	coronary microvascular disease
<b>WISE</b>	Women's Ischemia Syndrome Evaluation

Recent guidelines reflect the wide spectrum of etio-pathogenesis of ischemic heart disease and chronic coronary syndromes.<sup>6</sup> 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).<sup>7</sup> Epicardial spasm, a separate clinical entity, can also lead to myocardial ischemia and myocardial infarction.<sup>8,9</sup> 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

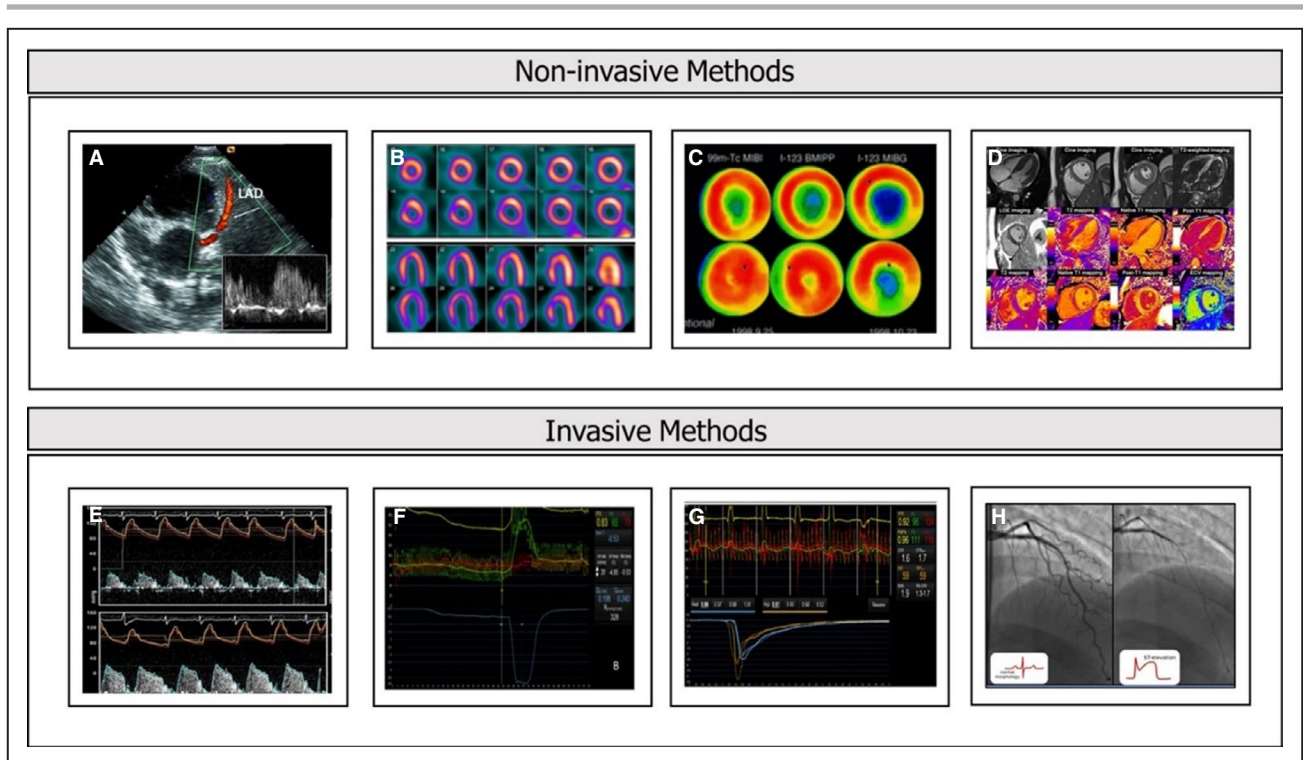
Studies describing prevalence of coronary microvascular disease and coronary spasm among patients with no obstructive CAD were reviewed. Two reviewers (N.M. and G.M.) systematically searched PubMed and Scopus. The search was conducted in August 2021, starting from inception, and was performed separately 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).<sup>10</sup> Quality of included studies was assessed by the Quality Assessment of Diagnostic Accuracy Studies tool.<sup>11</sup> 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.<sup>12</sup> 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

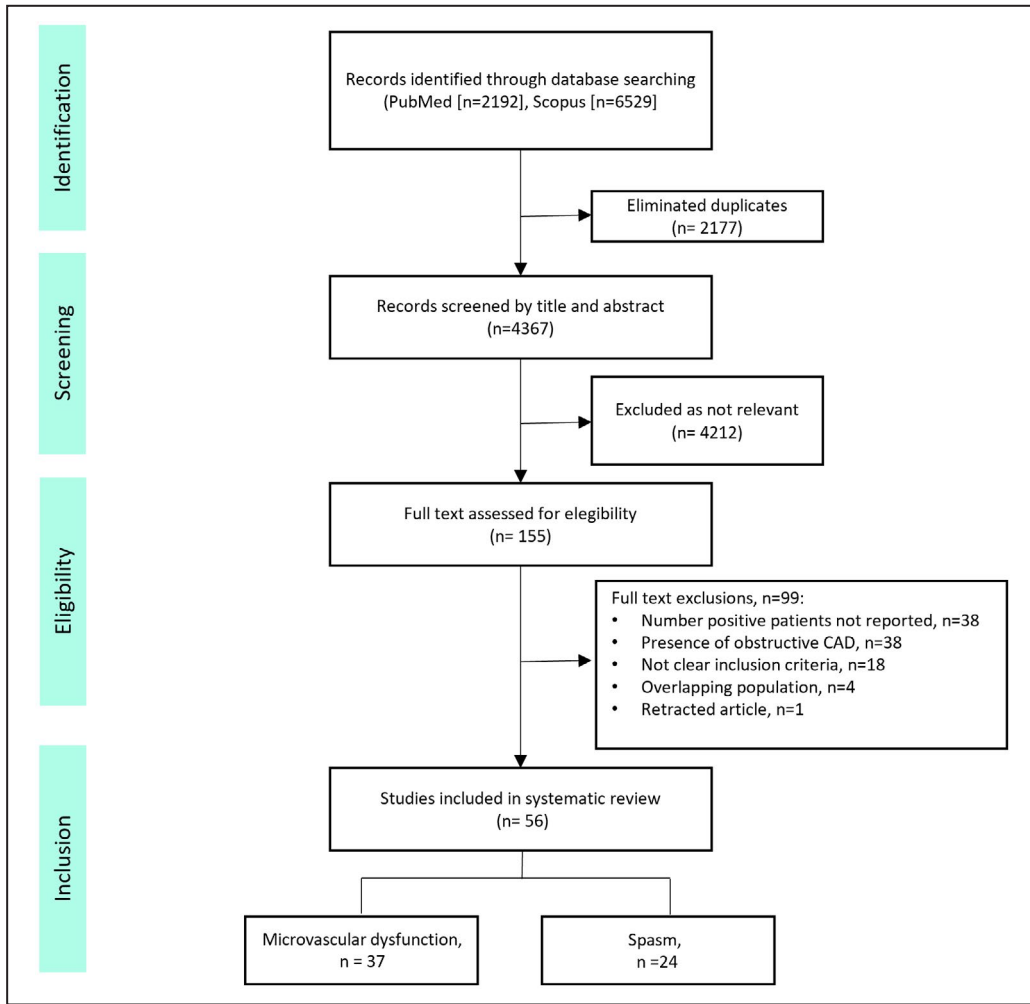
One hundred fifty-five articles received a complete review, and 56 studies met inclusion criteria and were included in the meta-analysis (Figure 2).<sup>13–67</sup> Overall, 14 427 patients were included. The mean age was 59±5 years, 65% were women, and 21% had diabetes. Most of the patients (75%) underwent 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



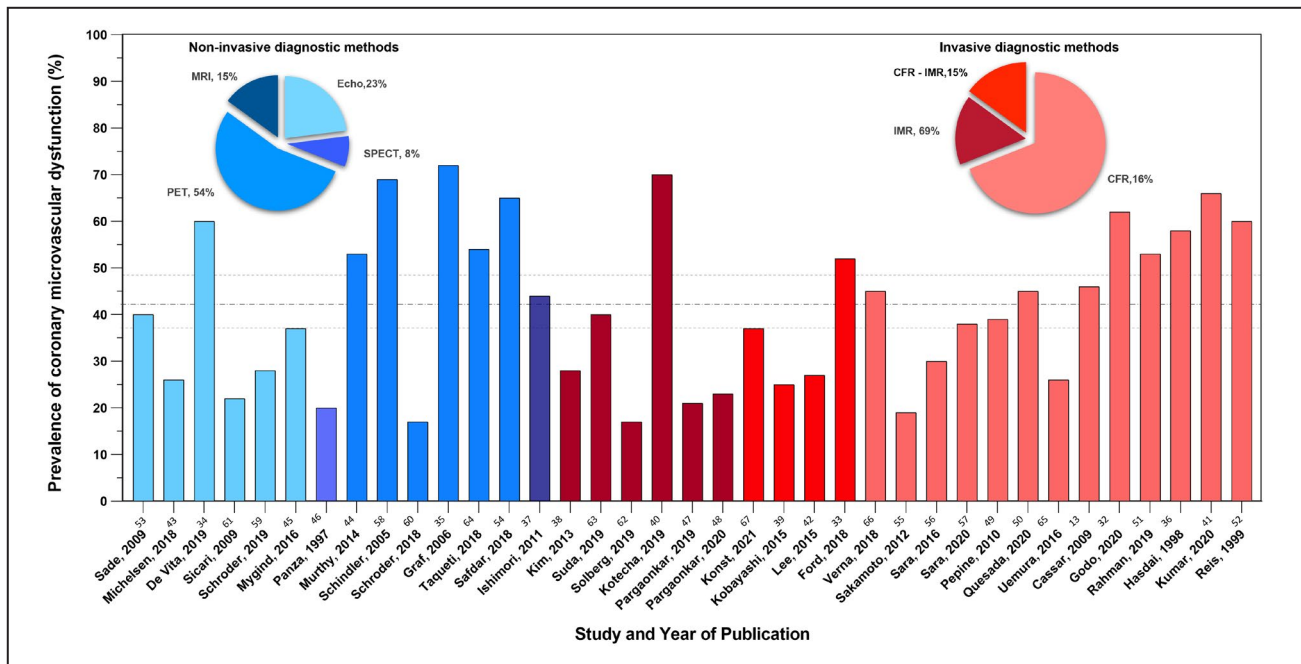
**Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.** CAD indicates coronary artery disease.

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  $\leq 2.5$  or  $\leq 2.0$ ) found no significant difference in rate of CMD (0.43 [95% CI, 0.35–0.51] for CFR  $\leq 2.5$  versus 0.46 [95% CI, 0.33–0.60] for CFR  $\leq 2.0$  ( $P=0.986$ ; 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  $60.5 \pm 8.0$  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%),<sup>14–17,19–23,31,63,66,68</sup> 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.<sup>30,34</sup> 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  $\geq 90\%$  or  $\geq 70\%$  coronary vasoconstriction), no significant difference in rate of spasm was detected: 0.47 (95% CI, 0.35–0.50) for  $\geq 90$  constriction versus 0.49 (95% CI, 0.42–0.55) for  $\geq 70\%$  constriction ( $P=0.133$ ).

### Combined Prevalence of CMD and Coronary Vasospasm

In 3 of the studies,<sup>33,36,63</sup> patients underwent evaluation for CMD and spasm. Overall, 541 patients, with a mean age of  $58\pm 10.2$  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.<sup>7,69</sup> 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.<sup>44,70</sup> 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**

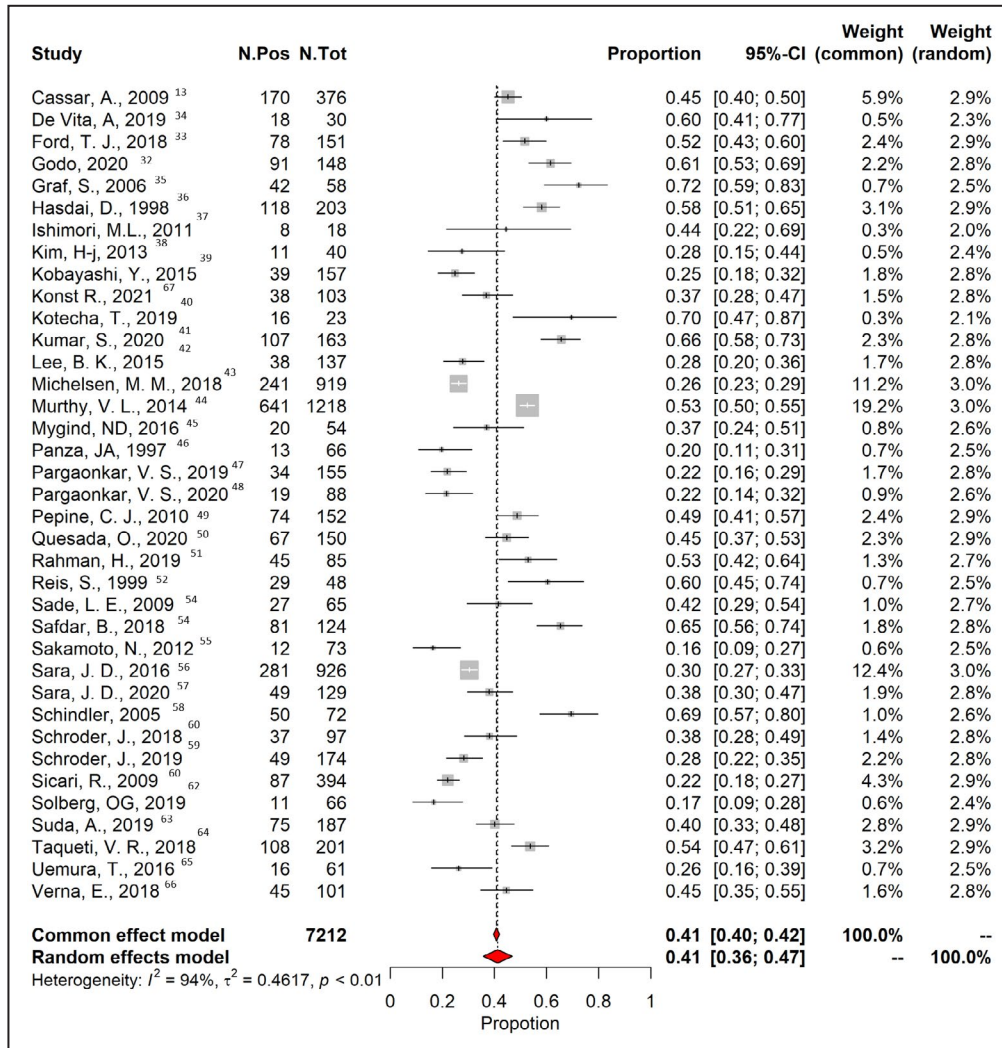
Study	Patients included	No. positive, n (%)	Age, y	Women, n (%)	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)	Current smoker, n (%)
Cassar, 2009 <sup>13</sup>	376	170 (45%)	49±11	254 (68%)	157 (42%)	36 (10%)	208 (55%)	NA
Godó, 2020 <sup>32</sup>	148	91 (62%)	44±9	111 (75%)	79 (53%)	11 (7%)	91 (62%)	60 (41%)
Ford, 2018 <sup>33</sup>	151	78 (52%)	61±10	111 (74%)	125 (81%)	29 (19.2%)	120 (79.5%)	24 (15.9%)
Graf, 2006 <sup>35</sup>	58	42 (72%)	58±10	39 (67%)	NA	8 (18%)	NA	17 (29%)
Hasdai, 1998 <sup>36</sup>	203	118 (58%)	51 (17–78)	158 (78%)	59 (29%)	8 (4%)	88 (43.3%)	28 (27%)
Kobayashi, 2015 <sup>39</sup>	157	39 (25%)	64±12	117 (29%)	77 (49%)	38 (24%)	91 (58%)	47 (30%)
Kotecha, 2019 <sup>40</sup>	23	16 (70%)	63±8	NA	6 (26%)	NA	NA	NA
Lee, 2015 <sup>42</sup>	137	38 (28%)	54±11	107 (77%)	74 (53%)	32 (23%)	87 (63%)	11 (8%)
Michelsen, 2018 <sup>43</sup>	919	241 (26%)	62±9	919 (100%)	467 (51%)	117 (13%)	580 (63%)	149 (16%)
Murthy, 2014 <sup>44</sup>	1218	641 (53%)	62 (53–69)	813 (67%)	894 (73%)	363 (30%)	663 (54%)	121 (10%)
Pargaonkar, 2019 <sup>47</sup>	155	34 (22%)	54±13	119 (77%)	68 (44%)	26 (17%)	90 (58%)	23 (15%)
Pargaonkar, 2020 <sup>48</sup>	88	32 (36%)	NA	53 (60%)	NA	NA	NA	NA
Pepine, 2010 <sup>49</sup>	152	74 (49%)	55±10	189 (100%)	57 (30%)	21 (11%)	50 (26%)	19 (10%)
Quesada, 2020 <sup>50</sup>	150	67 (45%)	54±12	36 (24%)	75 (50%)	25 (17%)	90 (60%)	22 (15%)
Sade, 2009 <sup>53</sup>	65	27 (40%)	55±8	68 (100%)	37 (54%)	NA	35 (52%)	16 (24%)
Safdar, 2020 <sup>54</sup>	124	81 (65%)	51±11	91 (73%)	81 (65%)	42 (34%)	53 (43%)	20 (16%)
Sakamoto, 2012 <sup>55</sup>	73	12 (16%)	65±8	36 (49%)	33 (45%)	6 (8%)	17 (23%)	11 (15%)
Sara, 2016 <sup>56</sup>	926	281 (30%)	52±13	567 (61%)	371 (40%)	59 (6%)	485 (52%)	111 (12%)
Schindler, 2005 <sup>58</sup>	72	50 (69%)	58 _ 8	28 (39%)	50 (69%)	3 (4%)	30 (42%)	18 (25%)
Sicari, 2009 <sup>61</sup>	394	87 (22%)	61±10	223 (57%)	238 (60%)	69 (18%)	NA	120 (31%)
Suda, 2019 <sup>63</sup>	187	75 (40%)	63±12	74 (40%)	100 (54%)	52 (28%)	66 (35%)	52 (28%)
Taqueti, 2018 <sup>64</sup>	201	108 (54%)	66 (57–79)	130 (65%)	152 (76%)	129 (64%)	66 (33%)	16 (8%)
Uemura, 2016 <sup>65</sup>	61	16 (26%)	59±15	18 (30%)	37 (61%)	15 (25%)	NA	37 (61%)
Verna, 2018 <sup>66</sup>	101	45 (45%)	60±11	48 (48%)	58 (57%)	9 (9%)	53 (53%)	21 (21%)
Solberg, 2019 <sup>62</sup>	66	11 (17%)	54±9	66 (100%)	15 (23%)	2 (3%)	8 (12%)	44 (67%)
Schroder, 2019 <sup>59</sup>	174	49 (28%)	64±10	NA	NA	NA	NA	NA
Sara, 2019 <sup>57</sup>	129	49 (38%)	50±12	61 (47%)	NA	NA	NA	NA
Kumar, 2020 <sup>41</sup>	163	107 (66%)	57±12	79 (48%)	118 (72%)	37 (23%)	122 (75%)	30 (18%)
De Vita, 2019 <sup>34</sup>	30	18 (60%)	67±10	19 (63%)	19 (63%)	4 (13%)	16 (53%)	15 (50%)
Mygind, 2016 <sup>45</sup>	54	20 (37%)	62±8	54 (100%)	29 (54%)	NA	34 (63%)	34 (63%)
Panza, 1997 <sup>46</sup>	66	13 (20%)	49±10	44 (67%)	NA	Na	NA	NA
Schroder, 2018 <sup>60</sup>	97	37 (38%)	62 (31–79)	97 (100%)	NA	NA	NA	NA
Reis, 1999 <sup>52</sup>	48	29 (60%)	54±10	48 (100%)	23 (48%)	6 (13%)	24 (49%)	NA
Kim, 2013 <sup>38</sup>	40	11 (28%)	53±11	NA	NA	NA	NA	NA
Ishimori, 2011 <sup>37</sup>	18	8 (44%)	41±11	18	NA	NA	NA	NA
Rahman, 2019 <sup>51</sup>	85	45 (53%)	57±10	66 (78%)	25 (29%)	11 (13%)	23 (27%)	12 (14%)
Konst, 2020 <sup>67</sup>	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.<sup>33,71</sup> 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.<sup>72</sup>

Coronary microvascular dysfunction has been deceptively recognized as a women’s disease.<sup>73</sup> 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.

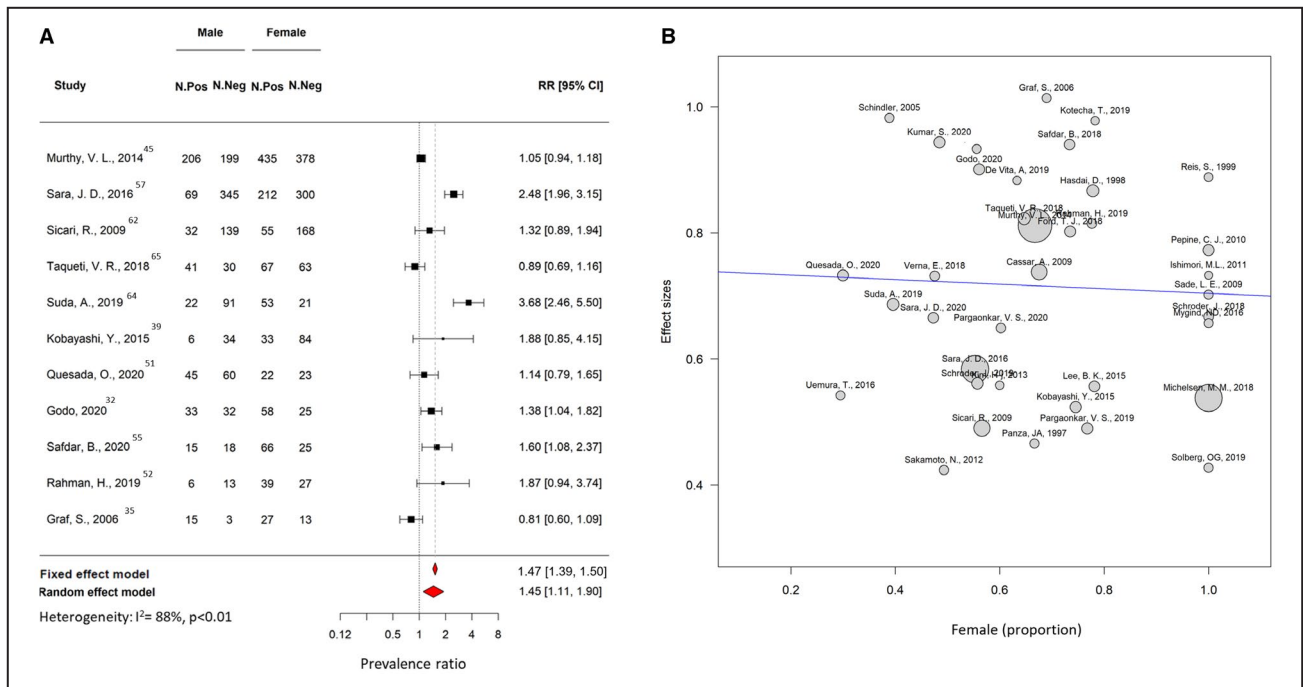
induced myocardial ischemia and coronary vasomotor dysfunction.<sup>49</sup> However, Murthy et al showed, using positron emission tomography, that CMD was highly prevalent in both sexes (51% in men versus 54% in women).<sup>44</sup> The present meta-analysis found that CMD is highly prevalent in both sexes; however, women are more likely to have CMD.<sup>44,49,74</sup> 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<sup>1</sup> or thermodilution technique.<sup>33,39,42,50</sup> In addition, some studies used a cutoff value of  $\leq 2.5$ ,<sup>13,36,50–52,55,56,66,75</sup> whereas others used  $\leq 2.0$ .<sup>32,33,39,41,42</sup> 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.<sup>76</sup> 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  $\leq 2.0$ , 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  $\geq 90\%$  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.<sup>76</sup>

Despite the increasing awareness of CMD as a cause of chest pain, diagnostic methods to assess its presence remain underused.<sup>77</sup> 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 non-invasive imaging.<sup>78,79</sup> 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 of coronary pathophysiology requires concepts beyond CFR, such as regional size–severity quantification versus global perfusion and subendocardial perfusion on relative tomographic images.<sup>80</sup>

**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 <sup>14</sup>	1379	813 (59%)	62±11.9	799 (58%)	970 (70%)	237 (17%)	841 (61%)	502 (36%)
Ford, 2018 <sup>33</sup>	151	56 (37%)	61 (53–68)	111 (74%)	NA	29 (19%)	120 (80%)	24 (16%)
Hoshino, 2016 <sup>15</sup>	292	90 (30%)	64±11	156 (51.7%)	114 (39%)	33 (11%)	98 (34%)	130 (45%)
Kim, 2018 <sup>16</sup>	328	128 (39%)	58±10.4	233 (71%)	128 (39%)	31 (9.4%)	72 (22%)	39 (12%)
Mohri, 1998 <sup>17</sup>	117	81 (74%)	63 (54–68)	59 (50%)	56 (48%)	26 (22%)	49 (42%)	50 (43%)
Montone, 2018 <sup>18</sup>	80	37 (46%)	63±11	40 (50%)	32 (40%)	8 (10%)	19 (24%)	17 (21%)
Montone, 2020 <sup>19</sup>	210	118 (56%)	62±11	82 (39%)	79 (38%)	13 (6%)	54 (26%)	27 (13%)
Oh, 2019 <sup>20</sup>	464	156 (34%)	57±11	164 (35%)	60 (13%)	23 (5%)	94 (20%)	48 (10%)
Ohba, 2012 <sup>21</sup>	370	264 (71%)	63±11	211 (57%)	197 (53%)	73 (20%)	193 (52%)	107 (29%)
Ong, 2014 <sup>23</sup>	847	488 (58%)	62±12	485 (57%)	609 (72%)	142 (17%)	460 (54%)	307 (36%)
Ong, 2012 <sup>22</sup>	124	77 (53%)	64±10	100 (%)	102 (71%)	31 (22%)	83 (58%)	22 (15%)
Ong, 2014 <sup>24</sup>	137	69 (50%)	63±11	93 (68%)	105 (77%)	27 (20%)	73 (53%)	38 (28%)
Pirozzolo, 2020 <sup>25</sup>	96	56 (58%)	65±12	49 (51%)	84 (88%)	15 (16%)	84 (88%)	25 (26%)
Quyumi, 1992 <sup>26</sup>	51	5 (10%)	51±11	31 (61%)	20 (39%)	NA	NA	NA
Suda, 2019 <sup>63</sup>	187	126 (67%)	63±12	74 (40%)	100 (54%)	52 (28%)	66 (35%)	52 (28%)
Sun, 2002 <sup>29</sup>	55	14 (26%)	60±10	23 (42%)	26 (47%)	9 (16%)	26 (47%)	30 (55%)
Sun, 2005 <sup>28</sup>	131	101 (79%)	59±11	69 (53%)	59 (45%)	30 (13%)	50 (38%)	36 (27%)
Tsuchida, 2005 <sup>30</sup>	102	74 (77%)	57±11	15 (15%)	43 (42%)	31 (30%)	NA	82 (80%)
Uemura, 2016 <sup>65</sup>	61	15 (28%)	59±15	18 (30%)	37 (61%)	15 (25%)	NA	37 (61%)
Verna, 2018 <sup>66</sup>	101	57 (57%)	60±11	48 (48%)	58 (57%)	9 (9%)	53 (52%)	21 (20%)
Seitz, 2020 <sup>27</sup>	847	283 (33%)	64±11	529 (63%)	533 (63%)	129 (15%)	411 (49%)	260 (31%)
Yamanaga, 2015 <sup>31</sup>	50	29 (58%)	62±13	24 (48%)	28 (56%)	10 (20%)	29 (58%)	10 (20%)
Quesada, 2020 <sup>50</sup>	150	83 (55%)	54±12	36 (24%)	75 (50%)	25 (17%)	90 (60%)	22 (15%)
Hasdai, 1998 <sup>36</sup>	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.

**Sources of Funding**

None.

**ARTICLE INFORMATION**

Received July 11, 2021; accepted October 19, 2021.

**Affiliations**

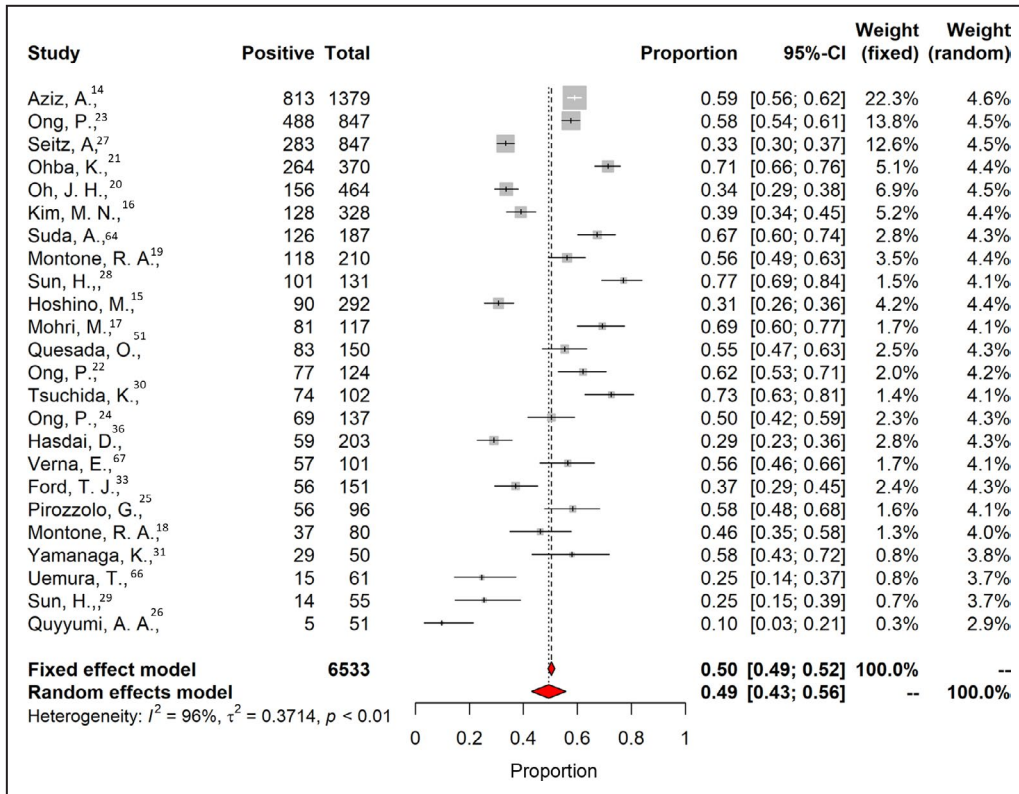
Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium (N.M., S.N., J.S., E.G., G.M., A.C., D.M., M.P., E.B., B.D.B., C.C.); Cardiology Clinic, Alexandrovska University Hospital, Sofia, Bulgaria (N.M., D.V.); Division of Cardiology, Department of Internal Medicine, Showa University, Fujigaoka Hospital, Kanagawa, Japan (S.N., T.M.); British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (C.B.); Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy (E.G.); Department of Clinical Medicine, Discipline of Cardiology, University of Campinas UNICAMP, Campinas, Brazil (D.M.); Department of Advanced Biomedical Sciences, University of Naples,

Federico II, Naples, Italy (J.S., D.M., E.B.); and Department of Cardiology, Lausanne University Hospital, Lausanne, Switzerland (B.D.B.).

**Disclosures**

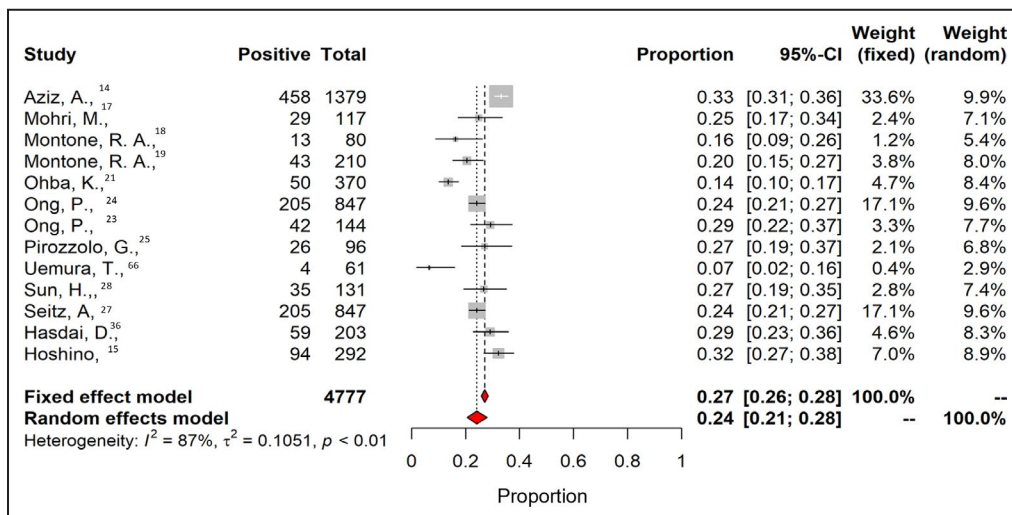
Dr Sonck reports research grants provided by the Cardiopath PhD program. Dr Berry is employed by the University of Glasgow, which holds research and/or consultancy agreements with AstraZeneca, Abbott Vascular, Boehringer Ingelheim, GSK, HeartFlow, Opsons, and Novartis. Dr Berry received research funding from the British Heart Foundation (RE/18/6134217). Dr De Bruyne has a consulting relationship with Boston Scientific, Abbott Vascular, CathWorks, Siemens, and Coroventis Research; receives research grants from Abbott Vascular, Coroventis Research, CathWorks, and Boston Scientific; and holds minor equities in Philips, Siemens, GE Healthcare, Edwards Life Sciences, HeartFlow, Opsons, and Celyad. Dr Collet reports receiving research grants from Biosensor, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, CathWorks, Boston Scientific, Siemens, HeartFlow, and Abbott Vascular; and consultancy fees from HeartFlow, Opsons, Abbott Vascular, and Philips. The remaining authors have no disclosures to report.

Downloaded from <http://ahajournals.org> by on April 3, 2022

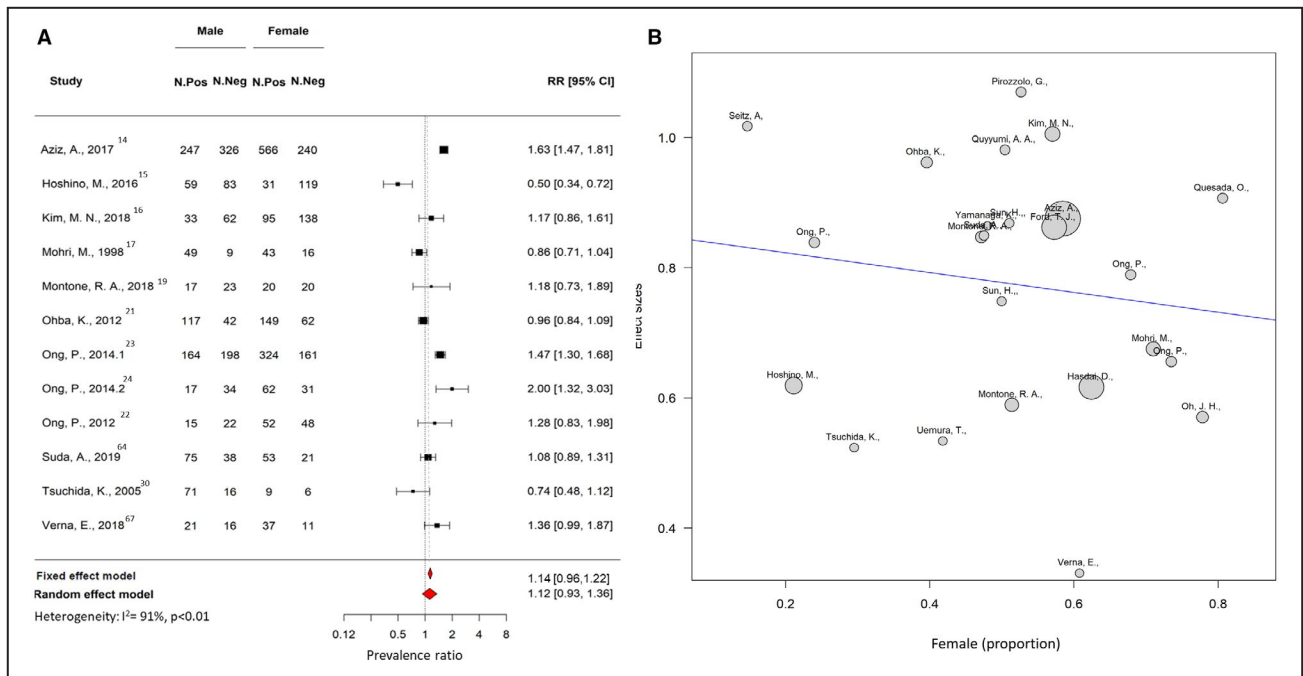


**Figure 6. Prevalence of coronary vasospasm.**

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

**REFERENCES**

- Khan MAB, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R, Alblooshi FMK, Almatrooshi MEAH, Alzaabi MEH, Al Darmaki RS, et al. Global epidemiology of ischemic heart disease: results from the Global Burden of Disease Study. *Cureus*. 2020;12:e9349. doi: 10.7759/cureus.9349
- Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895. doi: 10.1056/NEJMo a0907272
- Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, Jørgensen E, Kelbæk H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–744. doi: 10.1093/eurheartj/ehr331
- Da Costa A, Isaaq K, Faure E, Mourot S, Cerisier A, Lamaud M. Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram; a 3-year follow-up study of 91 patients. *Eur Heart J*. 2001;22:1459–1465. doi: 10.1053/ehuj.2000.2553
- Radico F, Zimarino M, Fulgenzi F, Ricci F, Di Nicola M, Jespersen L, Chang SM, Humphries KH, Marzilli M, De Caterina R. Determinants of long-term clinical outcomes in patients with angina but without obstructive coronary artery disease: a systematic review and meta-analysis. *Eur Heart J*. 2018;39:2135–2146. doi: 10.1093/eurheartj/ehy185
- Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477. doi: 10.1093/eurheartj/ehz425
- Masi S, Rizzoni D, Taddei S, Widmer RJ, Montezano AC, Lüscher TF, Schiffrin EL, Touyz RM, Paneni F, Lerman A, et al. Assessment and pathophysiology of microvascular disease: recent progress and clinical

implications. *Eur Heart J*. 2021;42:2590–2604. doi: 10.1093/eurheartj/ehaa857

- Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J*. 2015;36:475–481. doi: 10.1093/eurheartj/ehu469
- Thygesen K, Alpert JS, Jaffe AS, Chaitman BF, Bax JJ, Morrow DA, White HD; Group ESD. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2018;40:237–269. doi: 10.1093/eurheartj/ehy462
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62:e1–e34. doi: 10.1016/j.jclinepi.2009.06.006
- Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155:529–536. doi: 10.7326/0003-4819-155-8-201110180-00009
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188. doi: 10.1016/0197-2456(86)90046-2
- Cassar A, Chareonthaitawee P, Rihal CS, Prasad A, Lennon RJ, Lerman LO, Lerman A. Lack of correlation between noninvasive stress tests and invasive coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease. *Circ Cardiovasc Interv*. 2009;2:237–244. doi: 10.1161/CIRCINTERVENTIONS.108.841056
- Aziz A, Hansen HS, Sechtem U, Prescott E, Ong P. Sex-related differences in vasomotor function in patients with angina and unobstructed coronary arteries. *J Am Coll Cardiol*. 2017;70:2349–2358. doi: 10.1016/j.jacc.2017.09.016
- Hoshino M, Yonetsu T, Mizukami A, Matsuda Y, Yoshioka K, Sudo Y, Ninomiya R, Soeda M, Kuroda S, Ono M, et al. Moderate vasomotor response to acetylcholine provocation test as an indicator of long-term prognosis. *Heart Vessels*. 2016;31:1943–1949. doi: 10.1007/s00380-016-0827-9
- Kim MN, Kim HL, Park SM, Shin MS, Yu CW, Kim MA, Hong KS, Shim WJ. Association of epicardial adipose tissue with coronary spasm and coronary atherosclerosis in patients with chest pain: analysis of data collated by the KoRean wOmen’S chest pain rEgistry (koROSE). *Heart Vessels*. 2018;33:17–24. doi: 10.1007/s00380-017-1029-9

17. Mohri M, Koyanagi M, Egashira K, Tagawa H, Ichiki T, Shimokawa H, Takeshita A. Angina pectoris caused by coronary microvascular spasm. *Lancet*. 1998;351:1165–1169. doi: 10.1016/S0140-6736(97)07329-7
18. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Cammà G, Lanza GA, Crea F. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J*. 2018;39:91–98. doi: 10.1093/eurheartj/ehx667
19. Montone RA, Niccoli G, Russo M, Giaccari M, Del Buono MG, Meucci MC, Gurgoglione F, Vergallo R, D'Amario D, Buffon A, et al. Clinical, angiographic and echocardiographic correlates of epicardial and microvascular spasm in patients with myocardial ischaemia and non-obstructive coronary arteries. *Clin Res Cardiol*. 2020;109:435–443. doi: 10.1007/s00392-019-01523-w
20. Oh JH, Song S, Kim C, Ahn S, Park JS, Lee HW, Choi JH, Lee HC, Cha KS, Hong TJ. Effect of intracoronary adenosine on ergonovine-induced vasoconstricted coronary arteries. *Cardiol J*. 2019;26:653–660. doi: 10.5603/CJ.a2018.0072
21. Ohba K, Sugiyama S, Sumida H, Nozaki T, Matsubara J, Matsuzawa Y, Konishi M, Akiyama E, Kurokawa H, Maeda H, et al. Microvascular coronary artery spasm presents distinctive clinical features with endothelial dysfunction as nonobstructive coronary artery disease. *J Am Heart Assoc*. 2012;1:e002485. doi: 10.1161/JAHA.112.002485
22. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. the ACOVA study (abnormal coronary vasomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol*. 2012;59:655–662. doi: 10.1016/j.jacc.2011.11.015
23. Ong P, Athanasiadis A, Borgulya G, Vokshi I, Bastiaenen R, Kubik S, Hill S, Schäufole T, Mahrholdt H, Kaski JC, et al. Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries. *Circulation*. 2014;129:1723–1730. doi: 10.1161/CIRCULATIONAHA.113.004096
24. Ong P, Athanasiadis A, Hill S, Schäufole T, Mahrholdt H, Sechtem U. Coronary microvascular dysfunction assessed by intracoronary acetylcholine provocation testing is a frequent cause of ischemia and angina in patients with exercise-induced electrocardiographic changes and unobstructed coronary arteries. *Clin Cardiol*. 2014;37:462–467. doi: 10.1002/clc.22282
25. Pirozzolo G, Seitz A, Athanasiadis A, Bekeredjian R, Sechtem U, Ong P. Microvascular spasm in non-ST-segment elevation myocardial infarction without culprit lesion (MINOCA). *Clin Res Cardiol*. 2020;109:246–254. doi: 10.1007/s00392-019-01507-w
26. Quyyumi AA, Cannon RO III, Panza JA, Diodati JG, Epstein SE. Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation*. 1992;86:1864–1871. doi: 10.1161/01.CIR.86.6.1864
27. Seitz A, Gardezy J, Pirozzolo G, Probst S, Athanasiadis A, Hill S, Mahrholdt H, Bekeredjian R, Sechtem U, Ong P. Long-term follow-up in patients with stable angina and unobstructed coronary arteries undergoing intracoronary acetylcholine testing. *JACC Cardiovasc Interv*. 2020;13:1865–1876. doi: 10.1016/j.jcin.2020.05.009
28. Sun H, Fukumoto Y, Ito A, Shimokawa H, Sunagawa K. Coronary microvascular dysfunction in patients with microvascular angina: analysis by TIMI frame count. *J Cardiovasc Pharmacol*. 2005;46:622–626. doi: 10.1097/01.fjc.0000181291.96086.ae
29. Sun H, Mohri M, Shimokawa H, Usui M, Urakami L, Takeshita A. Coronary microvascular spasm causes myocardial ischemia in patients with vasospastic angina. *J Am Coll Cardiol*. 2002;39:847–851. doi: 10.1016/S0735-1097(02)01690-X
30. Tsuchida K, Hori T, Tanabe N, Makiyama Y, Ozawa T, Saigawa T, Watanabe R, Tanaka T, Nasuno A, Fukunaga H, et al. Relationship between serum lipoprotein(a) concentrations and coronary vasomotion in coronary spastic angina. *Circ J*. 2005;69:521–525. doi: 10.1253/circj.69.521
31. Yamanaga K, Tsujita K, Komura N, Kaikita K, Sakamoto K, Miyazaki T, Saito M, Ishii M, Tabata N, Akasaka T, et al. Single-wire pressure and flow velocity measurement for quantifying microvascular dysfunction in patients with coronary vasospastic angina. *Am J Physiol Heart Circ Physiol*. 2015;308:H478–H484. doi: 10.1152/ajpheart.00593.2014
32. Godo S, Corban MT, Toya T, Gulati R, Lerman LO, Lerman A. Association of coronary microvascular endothelial dysfunction with vulnerable plaque characteristics in early coronary atherosclerosis. *EuroIntervention*. 2020;16:387–394. doi: 10.4244/EIJ-D-19-00265
33. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, Eteiba H, Shaukat A, Lindsay M, Robertson K, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol*. 2018;72:2841–2855. doi: 10.1016/j.jacc.2018.09.006
34. De Vita A, Manfredonia L, Lamendola P, Villano A, Ravenna SE, Bisignani A, Niccoli G, Lanza GA, Crea F. Coronary microvascular dysfunction in patients with acute coronary syndrome and no obstructive coronary artery disease. *Clin Res Cardiol*. 2019;108:1364–1370. doi: 10.1007/s00392-019-01472-4
35. Graf S, Khorsand A, Gwechenberger M, Schutz M, Kletter K, Sochor H, Dudczak R, Maurer G, Pirich C, Porenta G, et al. Myocardial perfusion in patients with typical chest pain and normal angiogram. *Eur J Clin Invest*. 2006;36:326–332. doi: 10.1111/j.1365-2362.2006.01635.x
36. Hasdai D, Holmes DR Jr, Higano ST, Burnett JC Jr, Lerman A. Prevalence of coronary blood flow reserve abnormalities among patients with nonobstructive coronary artery disease and chest pain. *Mayo Clin Proc*. 1998;73:1133–1140. doi: 10.4065/73.12.1133
37. Ishimori ML, Martin R, Berman DS, Goykhman P, Shaw LJ, Shufelt C, Slomka PJ, Thomson LEJ, Schapira J, Yang Y, et al. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. *JACC Cardiovasc Imaging*. 2011;4:27–33. doi: 10.1016/j.jcmg.2010.09.019
38. Kim HJ, Hong MK, Kim SH, Chung SM, Chung EJ, Han SW, Ryu KH. Evaluation of microvascular angina with timi frame count using nitroprusside induced hyperemia. *Microvasc Res*. 2013;87:95–99. doi: 10.1016/j.mvr.2013.02.003
39. Kobayashi Y, Fearon WF, Honda Y, Tanaka S, Pargaonkar V, Fitzgerald PJ, Lee DP, Stefanick M, Yeung AC, Tremmel JA. Effect of sex differences on invasive measures of coronary microvascular dysfunction in patients with angina in the absence of obstructive coronary artery disease. *JACC Cardiovasc Interv*. 2015;8:1433–1441. doi: 10.1016/j.jcin.2015.03.045
40. Kotecha T, Martinez-Naharro A, Boldrini M, Knight D, Hawkins P, Kalra S, Patel D, Coghlan G, Moon J, Plein S, et al. Automated pixel-wise quantitative myocardial perfusion mapping by CMR to detect obstructive coronary artery disease and coronary microvascular dysfunction: validation against invasive coronary physiology. *JACC Cardiovasc Imaging*. 2019;12:1958–1969. doi: 10.1016/j.jcmg.2018.12.022
41. Kumar S, Mehta PK, Eshtehardi P, Hung OY, Koh J-S, Kumar A, Al-Badri A, Rabah R, D'Souza M, Gupta S, et al. Functional coronary angiography in symptomatic patients with no obstructive coronary artery disease. *Catheter Cardiovasc Interv*. 2020 Sep 9. [pub ahead of print]. doi: 10.1002/ccd.29237
42. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, Lee DP, Yeung AC, Tremmel JA. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation*. 2015;131:1054–1060. doi: 10.1161/CIRCULATIONAHA.114.012636
43. Michelsen MM, Pena A, Mygind ND, Bech J, Gustafsson I, Kastrop J, Hansen HS, Høst N, Hansen PR, Prescott E. Coronary microvascular dysfunction and myocardial contractile reserve in women with angina and no obstructive coronary artery disease. *Echocardiography*. 2018;35:196–203. doi: 10.1111/echo.13767
44. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation*. 2014;129:2518–2527. doi: 10.1161/CIRCULATIONAHA.113.008507
45. Mygind ND, Michelsen MM, Pena A, Frestad D, Dose N, Aziz A, Faber R, Høst N, Gustafsson I, Hansen PR, et al. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study. *J Am Heart Assoc*. 2016;5:e003064. doi: 10.1161/JAHA.115.003064
46. Panza JA, Laurienzo JM, Curiel RV, Unger EF, Quyyumi AA, Dilisjian V, Cannon RO III. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol*. 1997;29:293–301. doi: 10.1016/S0735-1097(96)00481-0
47. Pargaonkar VS, Kobayashi Y, Kimura T, Schnitger I, Chow EKH, Froelicher VF, Rogers IS, Lee DP, Fearon WF, Yeung AC, et al. Accuracy of non-invasive stress testing in women and men with angina in the absence of obstructive coronary artery disease. *Int J Cardiol*. 2019;282:7–15. doi: 10.1016/j.ijcard.2018.10.073

48. Pargaonkar VS, Lee JH, Chow EKH, Nishi T, Ball RL, Kobayashi Y, Kimura T, Lee DP, Stefanick ML, Fearon WF, et al. Dose-response relationship between intracoronary acetylcholine and minimal lumen diameter in coronary endothelial function testing of women and men with angina and no obstructive coronary artery disease. *Circ Cardiovasc Interv.* 2020;13:e008587. doi: 10.1161/CIRCINTERVENTIO NS.119.008587
49. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, Johnson BD, Sopko G, Bairey Merz CN. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia. Results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol.* 2010;55:2825–2832. doi: 10.1016/j.jacc.2010.01.054
50. Quesada O, AlBadri A, Wei J, Shufelt C, Mehta PK, Maughan J, Suppogun N, Aldiwani H, Cook-Wiens G, Nelson MD, et al. Design, methodology and baseline characteristics of the Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction (WISE-CVD). *Am Heart J.* 2020;220:224–236. doi: 10.1016/j.ahj.2019.11.017
51. Rahman H, Ryan M, Lumley M, Modi B, McConkey H, Ellis H, Scannell C, Clapp B, Marber M, Webb A, et al. Coronary microvascular dysfunction is associated with myocardial ischemia and abnormal coronary perfusion during exercise. *Circulation.* 2019;140:1805–1816. doi: 10.1161/CIRCULATIONAHA.119.041595
52. Reis SE, Holubkov R, Lee JS, Sharaf B, Reichel N, Rogers WJ, Walsh EG, Fuisz AR, Kerensky R, Detre KM, et al. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol.* 1999;33:1469–1475. doi: 10.1016/S0735-1097(99)00072-8
53. Sade LE, Eroglu S, Bozbaş H, Özbiçer S, Hayran M, Haberal A, Müderrisoğlu H. Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. *Atherosclerosis.* 2009;204:580–585. doi: 10.1016/j.atherosclerosis.2008.09.038
54. Safdar B, D'Onofrio G, Dziura J, Russell RR, Johnson C, Sinusas AJ. Prevalence and characteristics of coronary microvascular dysfunction among chest pain patients in the emergency department. *Eur Heart J Acute Cardiovasc Care.* 2020;9:5–13. doi: 10.1177/2048872618764418
55. Sakamoto N, Iwaya S, Owada T, Nakamura Y, Yamauchi H, Hoshino Y, Mizukami H, Sugimoto K, Yamaki T, Kunii H, et al. A reduction of coronary flow reserve is associated with chronic kidney disease and long-term cardio-cerebrovascular events in patients with non-obstructive coronary artery disease and vasospasm. *Fukushima J Med Sci.* 2012;58:136–143. doi: 10.5387/fms.58.136
56. Sara JD, Lennon RJ, Ackerman MJ, Friedman PA, Noseworthy PA, Lerman A. Coronary microvascular dysfunction is associated with baseline qtc prolongation amongst patients with chest pain and non-obstructive coronary artery disease. *J Electrocardiol.* 2016;49:87–93. doi: 10.1016/j.jelectrocard.2015.10.006
57. Sara JD, Taher R, Kolluri N, Vella A, Lerman LO, Lerman A. Coronary microvascular dysfunction is associated with poor glycemic control amongst female diabetics with chest pain and non-obstructive coronary artery disease. *Cardiovasc Diabetol.* 2019;18:22. doi: 10.1186/s12933-019-0833-1
58. Schindler TH, Nitzsche EU, Schelbert HR, Olschewski M, Sayre J, Mix M, Brink I, Zhang X-L, Kreissi M, Magosaki N, et al. Positron emission tomography-measured abnormal responses of myocardial blood flow to sympathetic stimulation are associated with the risk of developing cardiovascular events. *J Am Coll Cardiol.* 2005;45:1505–1512. doi: 10.1016/j.jacc.2005.01.040
59. Schroder J, Mygind ND, Frestad D, Michelsen M, Suhrs HE, Bove KB, Gustafsson I, Kastrup J, Prescott E. Pro-inflammatory biomarkers in women with non-obstructive angina pectoris and coronary microvascular dysfunction. *Int J Cardiol Heart Vasc.* 2019;24:100370. doi: 10.1016/j.ijcha.2019.100370
60. Schroder J, Zethner-Moller R, Bové KB, Mygind ND, Hasbak P, Michelsen MM, Gustafsson I, Kastrup J, Prescott E. Protein biomarkers and coronary microvascular dilatation assessed by rubidium-82 PET in women with angina pectoris and no obstructive coronary artery disease. *Atherosclerosis.* 2018;275:319–327. doi: 10.1016/j.atherosclerosis.2018.06.864
61. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. *Am J Cardiol.* 2009;103:626–631. doi: 10.1016/j.amjcard.2008.10.033
62. Solberg OG, Stavem K, Ragnarsson A, Beitnes JO, Skårðal R, Seljeflot I, Ueland T, Aukrust P, Gullestad L, Aaberge L. Index of microvascular resistance to assess the effect of rosuvastatin on microvascular function in women with chest pain and no obstructive coronary artery disease: a double-blind randomized study. *Catheter Cardiovasc Interv.* 2019;94:660–668. doi: 10.1002/ccd.28157
63. Suda A, Takahashi J, Hao K, Kikuchi Y, Shindo T, Ikeda S, Sato K, Sugisawa J, Matsumoto Y, Miyata S, et al. Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease. *J Am Coll Cardiol.* 2019;74:2350–2360. doi: 10.1016/j.jacc.2019.08.1056
64. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, Hainer J, Bibbo CF, Dorbala S, Blankstein R, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J.* 2018;39:840–849. doi: 10.1093/eurheartj/ehx721
65. Uemura T, Yamamuro M, Kaikita K, Takashio S, Utsunomiya D, Hirakawa K, Nakayama M, Sakamoto K, Yamamoto E, Tsujita K, et al. Late gadolinium enhancement on cardiac magnetic resonance predicts coronary vasomotor abnormality and myocardial lactate production in patients with chronic heart failure. *Heart Vessels.* 2016;31:1969–1979. doi: 10.1007/s00380-016-0816-z
66. Verna E, Ghiringhelli S, Provasoli S, Scotti S, Salerno-Uriarte J. Epicardial and microvascular coronary vasomotor dysfunction and its relation to myocardial ischemic burden in patients with non-obstructive coronary artery disease. *J Nucl Cardiol.* 2018;25:1760–1769. doi: 10.1007/s12350-017-0871-6
67. Konst RE, Meeder JG, Wittekoek ME, Maas A, Appelman Y, Piek JJ, van de Hoef TP, Damman P, Elias-Smale SE. Ischaemia with no obstructive coronary arteries. *Neth Heart J.* 2020;28:66–72. doi: 10.1007/s12471-020-01451-9
68. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Camma G, Lanza GA, Crea F. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J.* 2018;39:91–98. doi: 10.1093/eurheartj/ehx667
69. Pries AR, Reglin B. Coronary microcirculatory pathophysiology: can we afford it to remain a black box? *Eur Heart J.* 2017;38:478–488. doi: 10.1093/eurheartj/ehv760
70. Gdowski MA, Murthy VL, Doering M, Monroy-Gonzalez AG, Slart R, Brown DL. Association of isolated coronary microvascular dysfunction with mortality and major adverse cardiac events: a systematic review and meta-analysis of aggregate data. *J Am Heart Assoc.* 2020;9:e014954. doi: 10.1161/JAHA.119.014954
71. Olson MB, Kelsey SF, Matthews K, Shaw LJ, Sharaf BL, Pohost GM, Cornell CE, McGorray SP, Vido D, Bairey Merz CN. Symptoms, myocardial ischaemia and quality of life in women: results from the NHLBI-sponsored WISE study. *Eur Heart J.* 2003;24:1506–1514. doi: 10.1016/S0195-668X(03)00279-3
72. Rutledge T, Vaccarino V, Johnson BD, Bittner V, Olson MB, Linke SE, Cornell CE, Eteiba W, Sheps DS, Francis J, et al. Depression and cardiovascular health care costs among women with suspected myocardial ischemia: prospective results from the WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol.* 2009;53:176–183. doi: 10.1016/j.jacc.2008.09.032
73. Anderson RD, Petersen JW, Mehta PK, Wei J, Johnson BD, Handberg EM, Kar S, Samuels B, Azarbal B, Kothawade K, et al. Prevalence of coronary endothelial and microvascular dysfunction in women with symptoms of ischemia and no obstructive coronary artery disease is confirmed by a new cohort: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD). *J Interv Cardiol.* 2019;2019:7169275. doi: 10.1155/2019/7169275
74. Corban MT, Prasad A, Gulati R, Lerman LO, Lerman A. Sex-specific differences in coronary blood flow and flow velocity reserve in symptomatic patients with non-obstructive disease. *EuroIntervention.* 2019;16:1079–1084.
75. Sara JDS, Corban MT, Prasad M, Prasad A, Gulati R, Lerman LO, Lerman A. Prevalence of myocardial bridging associated with coronary endothelial dysfunction in patients with chest pain and non-obstructive coronary artery disease. *EuroIntervention.* 2020;15:1262–1268. doi: 10.4244/EIJ-D-18-00920
76. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas A, Prescott E, Karam N, Appelman Y, Fraccaro C, et al. An EAPCI

- 
- expert consensus document on ischaemia with non-obstructive coronary arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J*. 2020;41:3504–3520. doi: 10.1093/eurheartj/ehaa503
77. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas A, Prescott E, Karam N, Appelman Y, Fraccaro C, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *EuroIntervention*. 2021;16:1049–1069. doi: 10.4244/EIJY20M07\_01
78. Djaïleb L, Riou L, Piliro N, Carabelli A, Vautrin E, Broisat A, Leenhardt J, Machecourt J, Fagret D, Vanzetto G, et al. spect myocardial ischemia in the absence of obstructive CAD: contribution of the invasive assessment of microvascular dysfunction. *J Nucl Cardiol*. 2018;25:1017–1022. doi: 10.1007/s12350-017-1135-1
79. Zimarino M, Marano R, Radico F, Curione D, De Caterina R. Coronary computed tomography angiography, ECG stress test and nuclear imaging as sources of false-positive results in the detection of coronary artery disease. *J Cardiovasc Med (Hagerstown)*. 2018;19(suppl 1):e133–e138. doi: 10.2459/JCM.0000000000000591
80. Gould KL, Johnson NP. Coronary physiology beyond coronary flow reserve in microvascular angina: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:2642–2662. doi: 10.1016/j.jacc.2018.07.106

# Supplemental Material

## Table of contents

Table S1 Search strategy.

Table S2. PRISMA checklist.

Table S3. Baseline clinical and angiographic characteristics of the studies included in the meta-analysis.

Table S4. Quality assessment, risk of bias and generalizability.

Figure S1. Forest plot revealing subgroup analysis of prevalence of CMD after exclusion six studies with high-risk of bias due to inclusion of female patients only.

Figure S2. Forest plot revealing subgroup analysis of prevalence of CMD between non-invasive and invasive tests.

Figure S3. Forest plot revealing subgroup analysis of prevalence of CMD between studies using CFR threshold  $\leq 2.0$  or threshold CFR  $\leq 2.5$

Figure S4. Forests plot revealing prevalence of A) microvascular spasm and B) epicardial spasm


Figure S5. Funnel plots and Egger's test assessing the studies included in the analysis of A) coronary microvascular disease and B) coronary spasm

**Table S1. Search strategy**

Database	Investigator 1
<b>Pubmed</b>	<p>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”)</p> <p>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)</p>

Database	Investigator 2
<b>Pubmed</b>	<p>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”)</p> <p>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”)</p>

**Table S2: PRISMA checklist**

 <b>PRISMA 2009 Checklist</b>			
Section/topic	#	Checklist item	Reported on page(s)
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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
<b>RESULTS</b>			
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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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 $\leq 2.5$	Patients with recurrent chest pain with no obstructive CAD <40% and no previous MI
Mohri	1998	ACh test	<ol style="list-style-type: none"> <li>ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction <math>\geq 70\%</math></li> <li>MVS: ischemic ECG changes and symptoms</li> </ol>	Chest pain and <50% coronary organic stenosis.
Reis	1999	CFR	CMD - CFR <2.5	Women with chest pain and normal coronary arteries $\leq 50\%$
Sun	2002	ACh test	<ol style="list-style-type: none"> <li>ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction <math>\geq 75\%</math></li> </ol>	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 $\geq 75\%$ 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 $\leq 40\%$	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 $\geq 90\%$ 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 $\leq 2.5$ during infusion of adenosine.	Patients with positive stress test and non-obstructive CAD ( $\leq 40\%$ luminal diameter stenosis)
Sicari	2009	TTE CFR Doppler LAD	CMD - CFR $\leq 2.0$	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 $\geq 5\%$	Consecutive female patients presenting with typical and atypical anginal and no angiographically documented CAD ( $\geq 70\%$ stenosis)
Ohba	2012	ACh test	2. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction $\geq 90\%$ 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 $\geq 75\%$ 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 $\geq 75\%$ 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	<ol style="list-style-type: none"> <li>ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction <math>\geq 75\%</math></li> <li>MVS: ischemic ECG changes and symptoms</li> </ol>	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 $\leq 2.5$	Patients with chest and/or abnormal functional stress test and coronary stenosis $< 40\%$
Uemura	2016	CMR Ach test	<p>CMD - CFR <math>&lt; 2.5</math></p> <ol style="list-style-type: none"> <li>ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction <math>\geq 90\%</math></li> <li>MVS: ischemic ECG changes and symptoms</li> </ol>	Patients without coronary artery disease (stenosis $> 50\%$ )
Hoshino	2016	ACh test	ES: vasoconstriction $\geq 75\%$	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 $\geq 20\%$	Patients with NSTEMI-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	<ol style="list-style-type: none"> <li>ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction <math>\geq 90\%</math></li> <li>MVS: ischemic ECG changes and symptoms</li> </ol>	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 $\leq 2.5$	Patients with chest pain and normal coronaries (stenosis $< 40\%$ )
Kumar	2020	CFR	CMD - CFR $< 2.0$ , HMR $\geq 2.0$	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	<ol style="list-style-type: none"> <li>ES – Reproduction of typical symptoms; ECG changes and epicardial</li> </ol>	Patients with symptoms of myocardial ischemia but NOCA ( $<50\%$ epicardial stenosis as determined by quantitative coronary angiography)

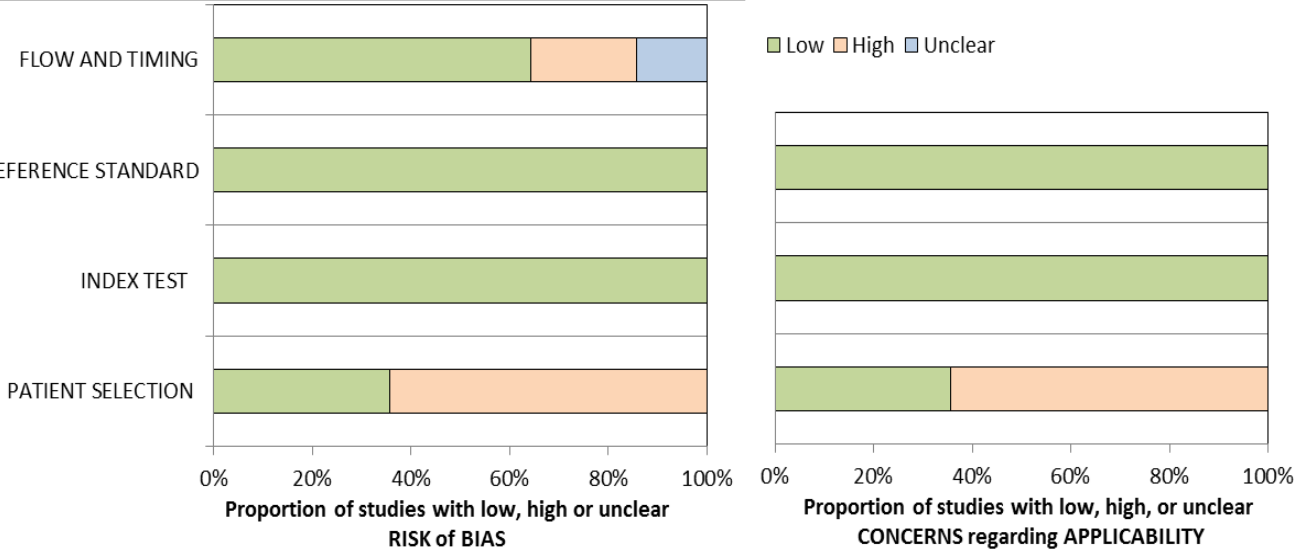
			vasoconstriction $\geq 75\%$ 2. MVS: ischemic ECG changes and symptoms	
Godo	2020	CFR doppler	CMD - CFR < 2.0	Patients with angina and angiographically normal coronary arteries (<40% stenosis)
Pargaonkar	2020	IMR	IMR > 25	Patients with persistent (>3 months) typical/atypical angina and a suspected MB 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.**

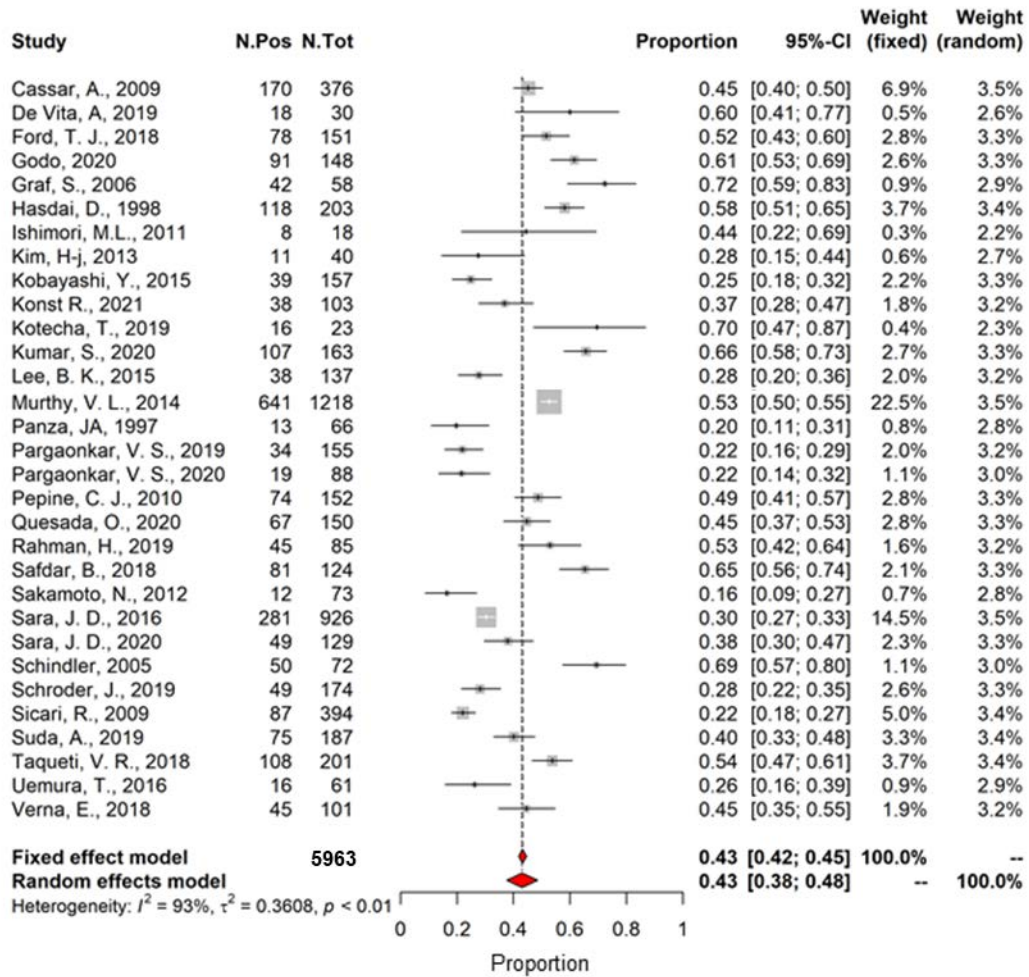
Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Aziz, 2017	😊	😊	😊	😊	😊	😊	😊
Cassar, 2009	😞	😊	😊	😊	😞	😊	😊
De Vita, 2019	😊	😊	😊	😊	😊	😊	😊
Ford, 2018	😞	😊	😊	😊	😞	😊	😊
Good, 2020	😊	😊	😊	😊	😊	😊	😊
Graf, 2006	😊	😊	😊	😊	😊	😊	😊
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	😊	😊	😊	😊	😊	😊	😊
Quyumi, 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	😊	😊	😊	😊	😊	😊	😊

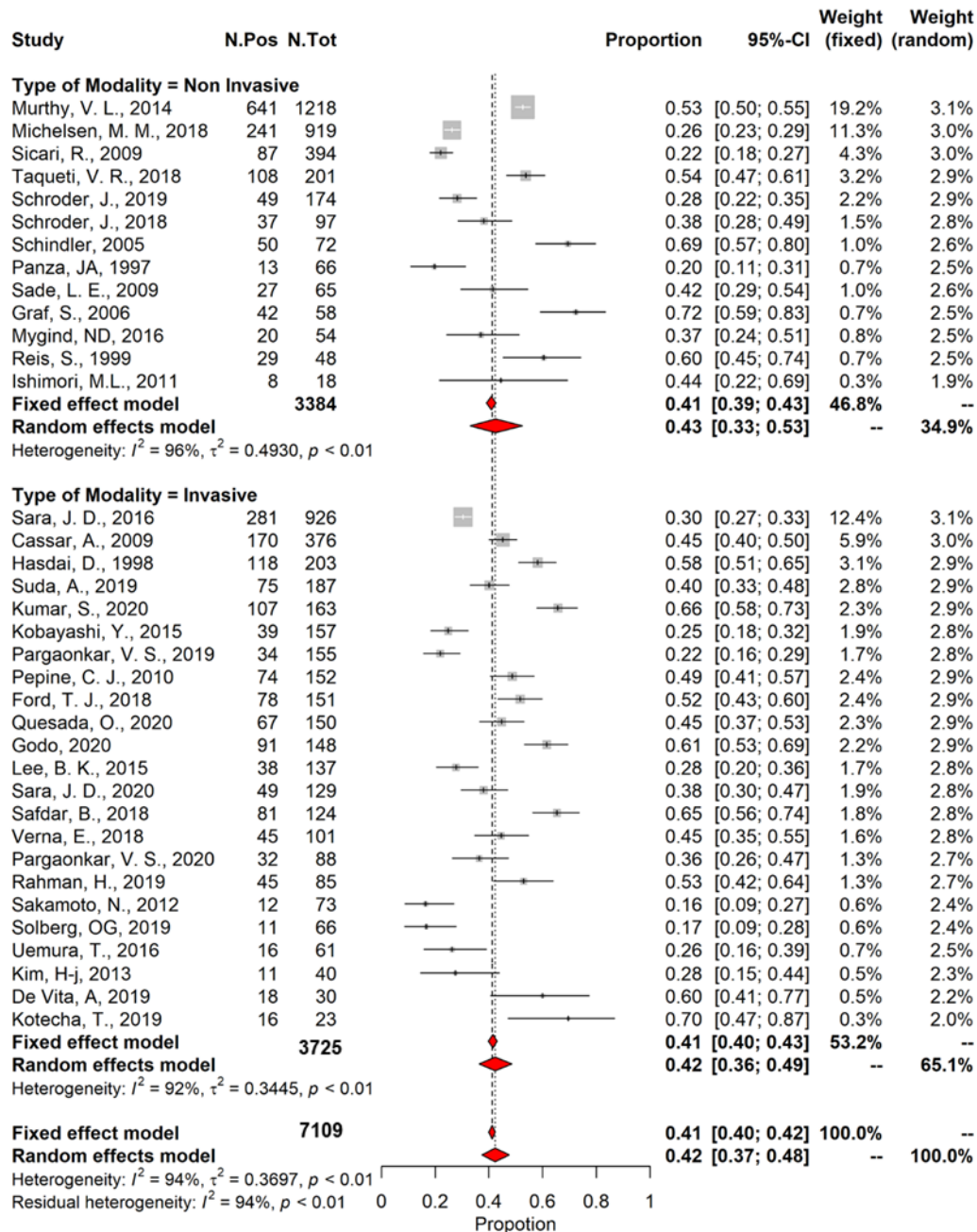
**QUADAS-2 Domain**



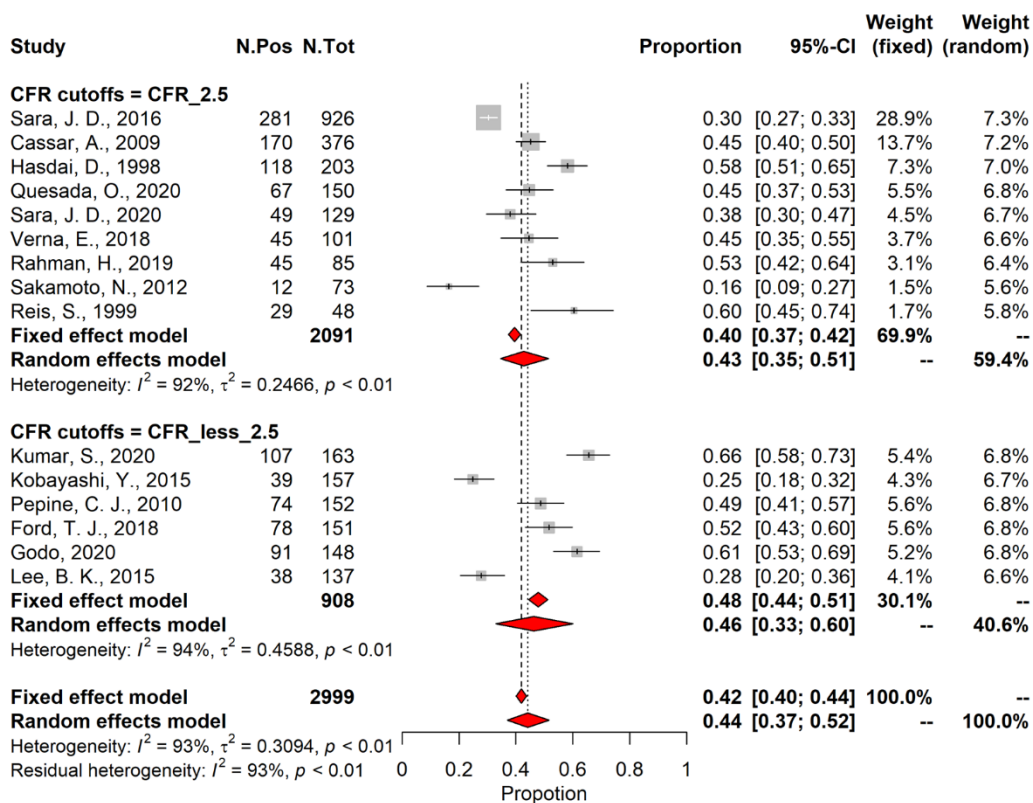
**Figure S1.** Prevalence of coronary microvascular disease after exclusion of six studies with high risk of bias due to inclusion of female patients only.



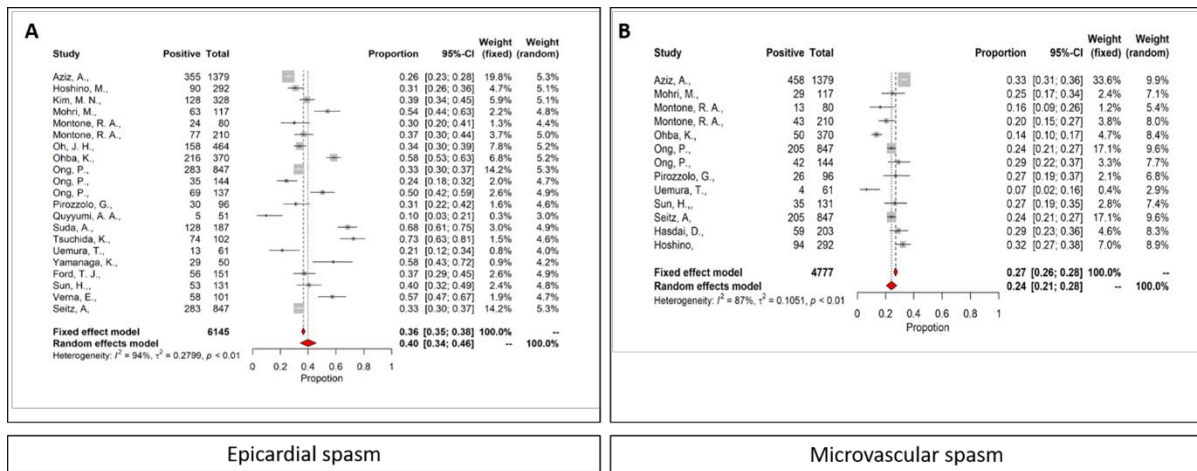
**Figure S2.** Prevalence of coronary microvascular disease in subgroups of invasive and non-invasive methods.



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



**Figure S4.** Prevalence of epicardial coronary spasm and 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,  $z = 3.47$ ,  $p=0.005$ .

