# Supplemental Material

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**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")<br><br>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")<br><br>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%<br>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%<br>2. MVS: ischemic ECG changes and symptoms<br>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%<br>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%<br>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%<br>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%<br>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<br>1. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90%<br>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%<br>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<br><br>IMR<br>ACh test | 3. CMD - CFR<2.0 or IMR>-25<br>4. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction >=90%<br>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%<br>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%<br>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%<br>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%<br>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,<br>CFR – bolus thermodilution | CMD – CFR <2.0<br>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 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |

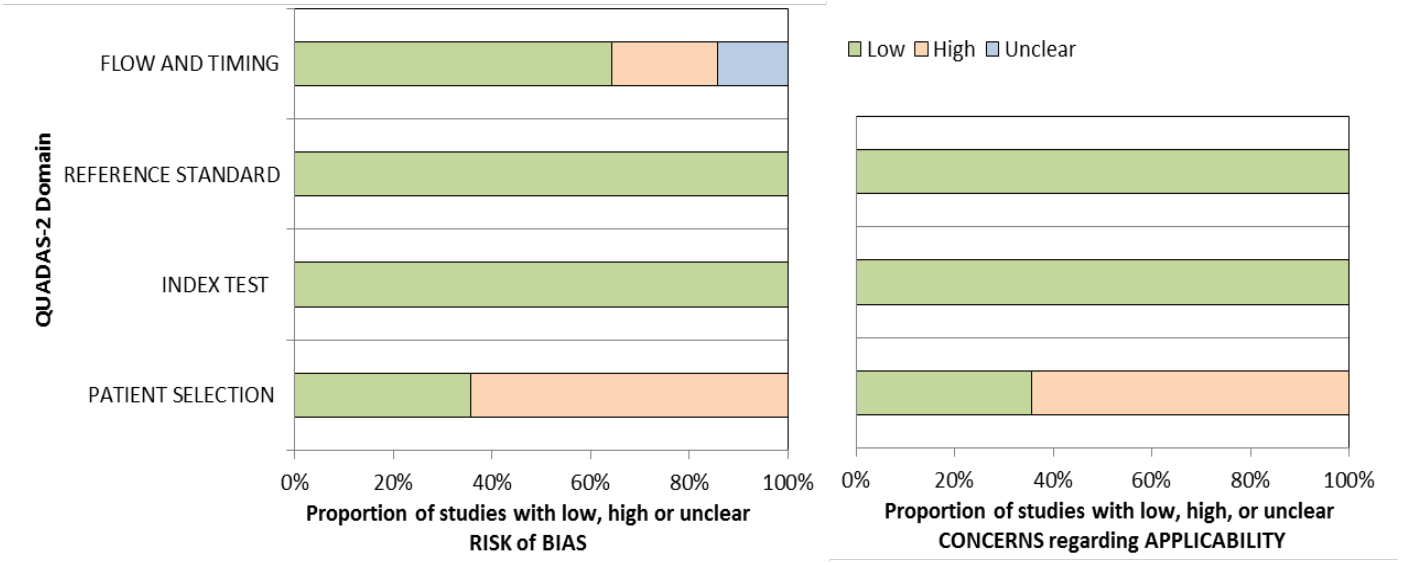


**Figure S1.** Prevalence of coronary microvascular disease after exclusion of six studies with high risk of bias due to inclusion of female patients only.

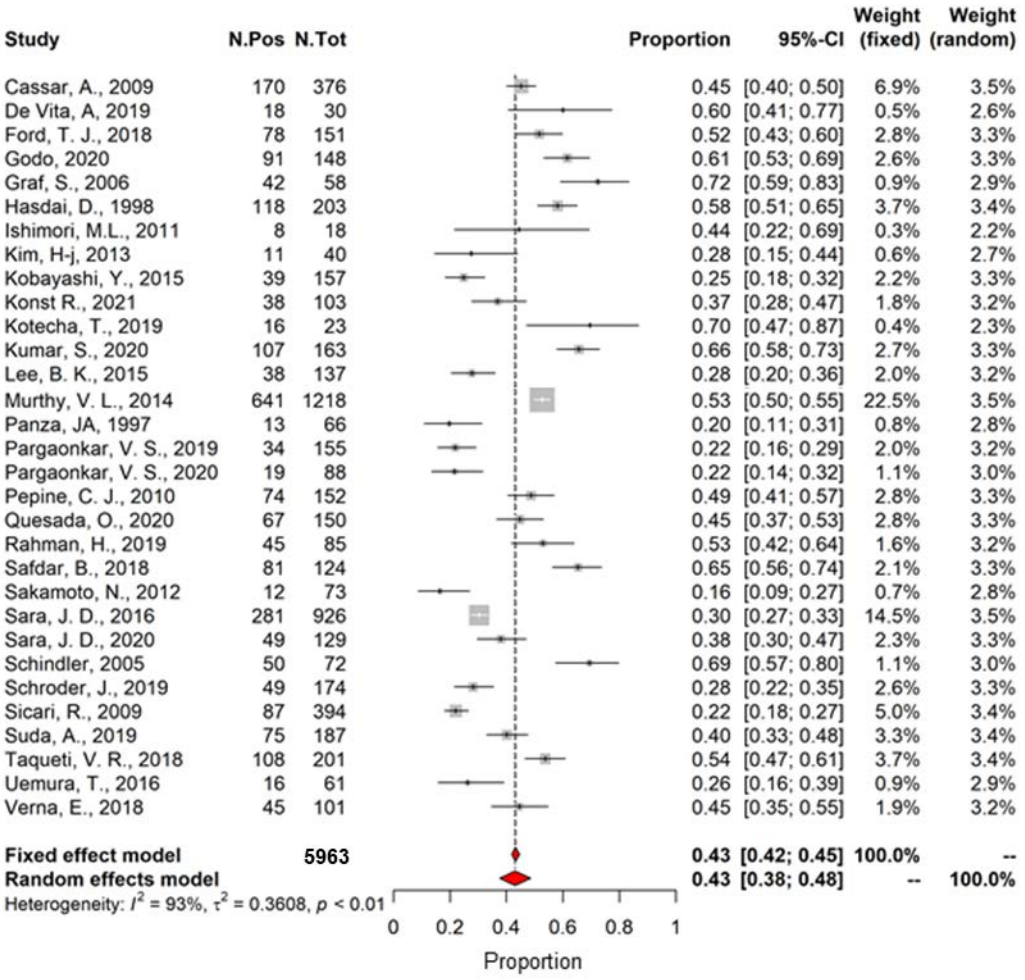


**Figure S2.** Prevalence of coronary microvascular disease in subgroups of invasive and non-invasive methods.

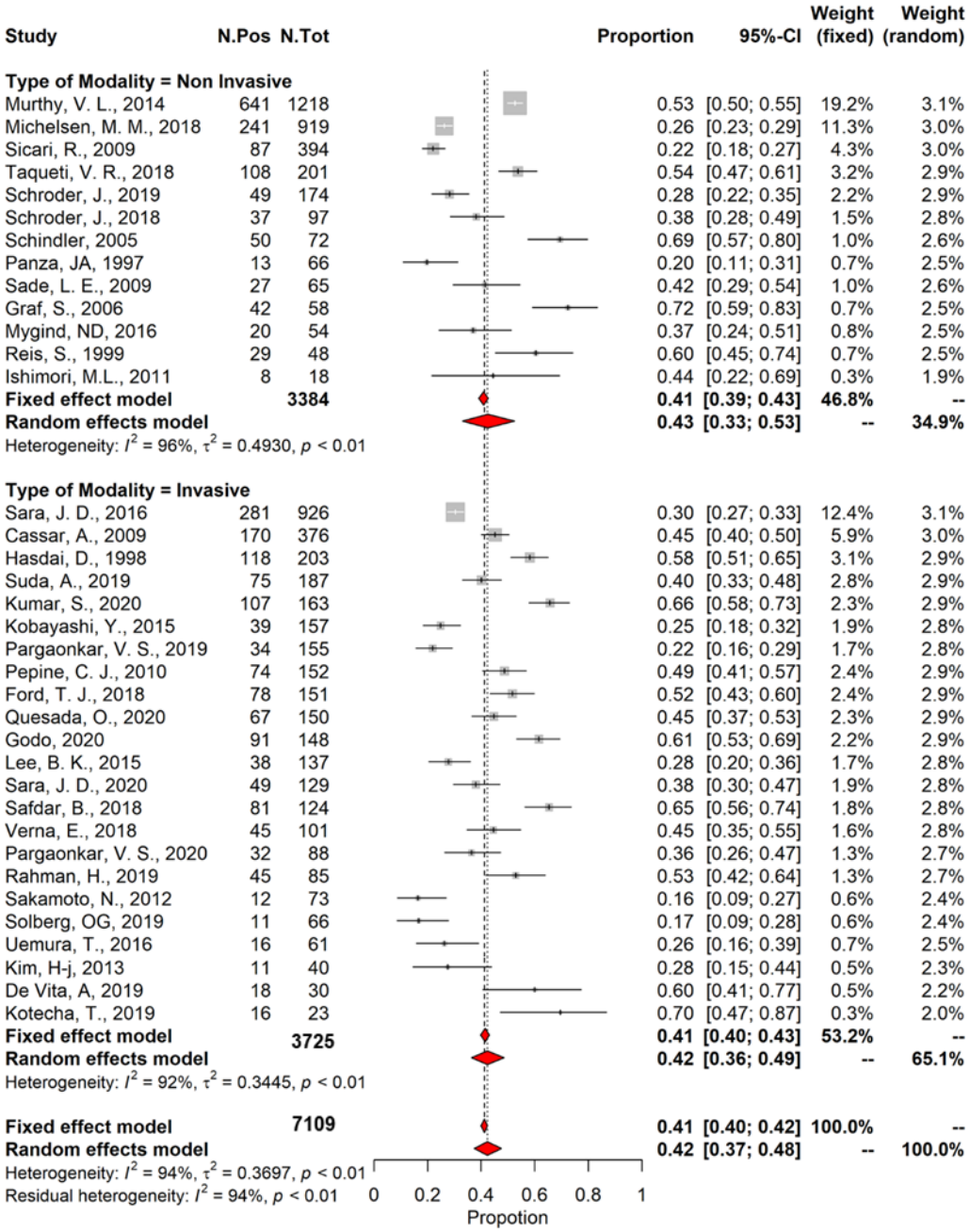


**Figure S3.** Prevalence of coronary microvascular disease in subgroups, based on definitions of CMD using different CFR thresholds (e.g., abnormal CFR considered ≤2.5 or ≤2.0).

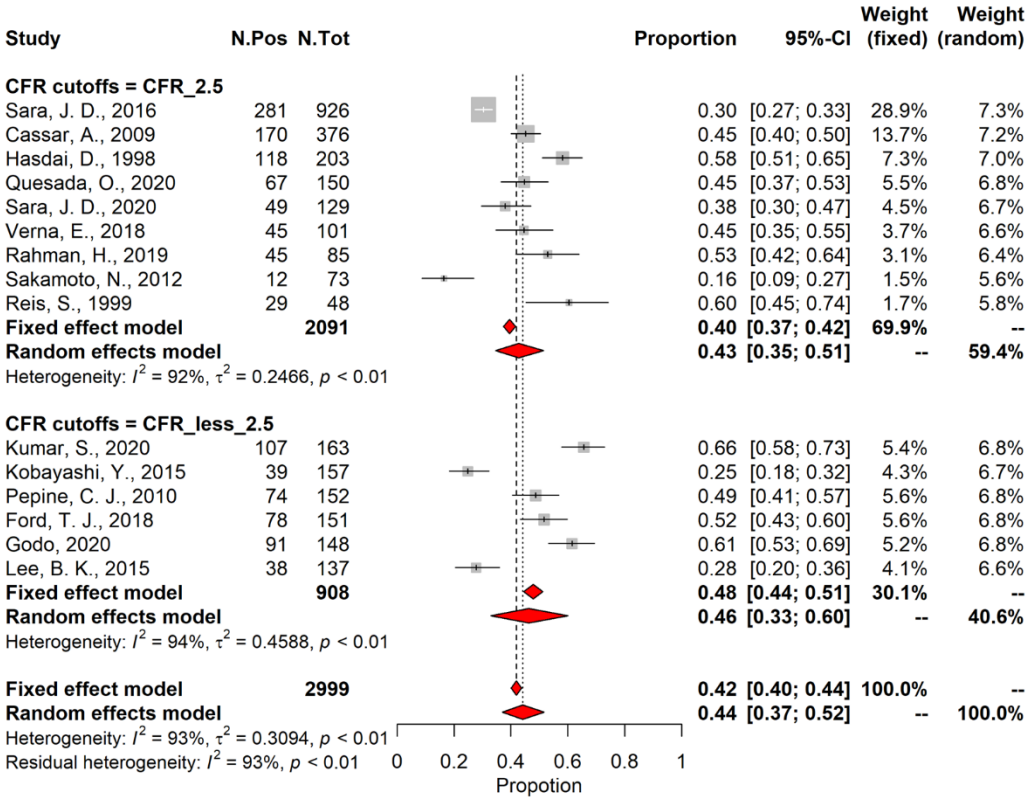
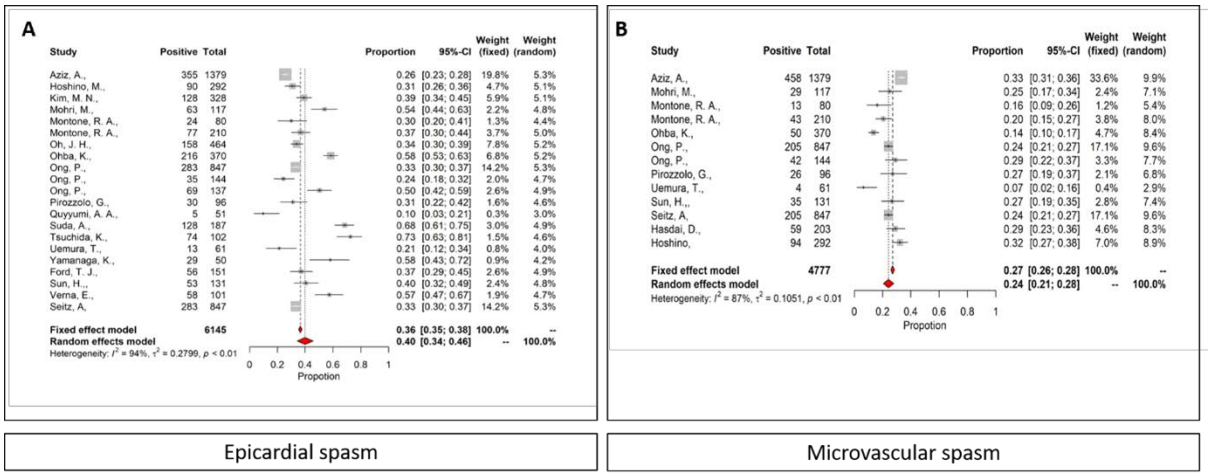


**Figure S4.** Prevalence of epicardial coronary spasm and microvascular spasm




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.