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")
	Spasm: (non-obstructive OR "non obstructive" OR "non occlusive" OR epicardial) AND (ischemia OR angina OR "chest pain" OR myocardial ischemia OR coronary artery disease OR "coronary artery disease") AND (spasm OR vasospasm OR vasospastic) AND (Microci* OR Microva* OR Microvessels OR spasm OR vasospasm OR vasospastic)

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

PRIS	SM.	A 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; system atic 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
ME THOD S			
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
E ligibility 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
Dataitems	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	Sum marize 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
Condusions	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	 ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥70% 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	 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	 ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75% MVS: ischemic ECG changes and symptoms CMD - TIMI frame count as 60 counts or more in LAD and 45 or more in LCX. 	Patients with chest pain and normal coronary arteriograms (no stenosis >50%)
Schindler	2005	PET	CMD – MBF ≤40%	Patients with angina and no coronary stenosis ("smooth coronary vessels without evidence of luminal wall irregularities or diffuse caliber reduction and stenosis").
Tsuchid	2005	Ergonovine test	ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% spasm	Patients with angina and no organic stenosis (>50%)
Graf	2006	PET	CMD - CFR <2.5	Patients with angina, positive stress test and normal angiogram not older than 3 months
Cassar	2009	CFR Doppler	CMD - CFR ratio of \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 ≤ 2.0	Patients with history of chest pain, coronary angiography with stenosis <50%
Sade	2009	TTE CFR LAD	CMD - CFR<2.0	Women who underwent angiography and had no obstructive coronary artery disease
Pepine	2010	CFR Doppler	CFR <2.32	Women undergoing clinically indicated coronary

				angiography and no CAD (<50%)
Ishimori	2011	CMR	1. Any stress perfusion defect size ≥5%	Consecutive female patients presenting with typical and atypical anginal and no angiographically documented CAD (≥70% stenosis)
Ohba	2012	ACh test	 2. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 3. MVS: ischemic ECG changes and symptoms 	Patients with angina and nonobstructive CAD (<50%) undergoing ACh test.
Ong	2012	ACh test	 ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75% 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	 ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥75% 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

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

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

Ford	2018	CFR cont thermodilution IMR ACh test	3. CMD - CFR<2.0 or IMR>-25 4. ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction >=90% MVS: ischemic ECG changes and symptoms	Patients with angina and no obstructive CAD (stenosis >50% and FFR ≤0.80)
Michelsen	2018	TTE LAD - CFR	CMD = CFVR<2.0	Women with angina, left ventricular ejection fraction (LVEF) >45%, and an invasive coronary angiogram without significant stenosis (>50%).
Safdar	2018	PET	CMD - CFR<2.5	Patients with chest pain that underwent PET with no regional perfusion defect or calcification
Montone	2018	ACh test	 ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 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	 ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 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	 ES – Reproduction of typical symptoms; ECG changes and epicardial vasoconstriction ≥90% 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	$CMD = CFR \le 2.5$	Patients with chest pain and normal coronaries (stenosis < 40%)
Kumar	2020	CFR	CMD - CFR < 2.0, HMR ≥2.0	Symptomatic patients with No obstructive CAD on coronary angiography (defined as <50% luminal obstruction in one or more epicardial coronary arteries) and normal fractional flow reserve (FFR > 0.8)
Seitz	2020	ACh testing	1. ES – Reproduction of typical symptoms; ECG changes and epicardial	Patients with symptoms of myocardial ischemia but NOCA (<50% epicardial stenosis as determined by quantitative coronary angiography

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

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

Study		RISK (OF BIAS	APPLICABILITY CONCERNS				
	PATIENT	INDEX	REFERENC	FLOW	PATIENT	INDEX	REFEREN	
	SELECTIO	TEST	E	AND	SELECTI	TEST	CE	
	Ν		STANDARD	TIMIN	ON		STANDAR	
				G			D	
Aziz, 2017	\odot	\odot		\odot				
Cassar. 2009	8	\odot	\odot		8		\odot	
De Vita. 2019	\odot		©	\odot	\odot	©		
Ford, 2018	$\overline{\mathbf{S}}$	©	©		8	©		
Good, 2020		\odot	©		©	©		
Graf, 2006	O			©	\odot		\odot	
Hasdai, 1998	$\overline{\otimes}$	\odot	8	8	\otimes	\odot	\odot	
Hoshino, 2016		\odot		\odot	\odot	\odot	\odot	
Ishimori, 2011	$\overline{\mathbf{S}}$	\odot	$\overline{\ensuremath{\mathfrak{S}}}$	\odot	\otimes	\odot	\odot	
Kim, 2013	$\overline{\otimes}$		\odot	\odot	$\overline{\mathfrak{S}}$	\odot		
Kim, MN, 2017	©	\odot	©	\odot				
Kobayashi, 2015					\odot			
Kotecha, 2019	$\overline{\mathfrak{S}}$?	$\overline{\mathfrak{S}}$			
Kumar, 2020	$\overline{\mathfrak{S}}$	\odot			8			
Lee, 2015	8			?	8		\odot	
Michelsen, 2019	8							
Mohri, 1998	$\overline{\mathfrak{S}}$		8	?	8			
Montone, 2018	$\overline{\mathfrak{S}}$				8			
Montone, 2019	8			?	8		\odot	
Murthy, 2014	8				8			
Mygind, 2016								
Oh, 2019				?	8			
Ohba, 2012					8			
Ong, 2012	8			?	8	\odot		
Ong, 2014	$\overline{\mathfrak{S}}$				8			
Ong, 2014								
Pirozzolo, 2019	8			?	$\overline{\mathfrak{S}}$			
Pargaonkar, 2019	8				$\overline{\mathfrak{S}}$			
Pargaonkar, 2020	8			?	$\overline{\mathfrak{S}}$			
Pepine, 2010	$\overline{\boldsymbol{\otimes}}$		\odot	$\overline{\otimes}$	$\overline{\mathfrak{S}}$	\odot		
Quesada, 2020	\odot		\odot	\odot	\odot	\odot		
Quyyumi, 1992	$\overline{\mathbf{S}}$		\odot	?	\odot			
Rahman, 2019	8	\odot	\odot	8	\odot			
Reis, 1999	$\overline{\mathfrak{S}}$	\odot	\odot	?	\otimes	\odot	\odot	
Sade, 2009	$\overline{\otimes}$	\odot	\odot	8	8		\odot	
Safdar, 2018	8	\odot		\odot	8		\odot	
Sakamoto, 2012	\odot		\odot		\odot		\odot	
Sara 2016	©			Ö	\odot	\odot		
Sara 2020				0	8		<u></u>	
Schindler 2005	8	\odot	0	\odot	8	0	0	
Seitz 2003	$\overline{\bigcirc}$	$\overline{\odot}$	\odot		\odot	\odot		
Schrodor 2019	<u> </u>	<u> </u>	<u> </u>	<u> </u>	<u> </u>	0		
Schroder 2010		0	O		•	e		
Schröder, 2019	\heartsuit			\bigcirc			${\color{red}{\bullet}}$	

Sicari, 2009	8	\odot	\odot	?	$\overline{\otimes}$	\odot	\odot	
Solberg, 2019	$\overline{\otimes}$		\odot		\odot	\odot	\odot	
Suda, 2019	\odot	\odot	\odot		\odot	\odot	\odot	
Sun, 2005	$\overline{\otimes}$	\odot	\odot		$\overline{\otimes}$	\odot	\odot	
Sun, 2002	8	\odot	\odot	?	$\overline{\odot}$	\odot	\odot	
Taqueti, 2018	$\overline{\otimes}$		\odot	\odot	$\overline{\otimes}$	\odot	\odot	
Tsuchida, 2005	\odot	\odot	\odot	?	\odot	\odot	\odot	
Uemura, 2016	$\overline{\otimes}$		\odot		$\overline{\otimes}$	\odot	\odot	
Verna, 2018	$\overline{\otimes}$	\odot	\odot	\odot	$\overline{\otimes}$	\odot	\odot	
Yamanaga, 2015	\odot	\odot	\odot	\odot	\odot	\odot	\odot	
Prasada, 2014	\odot	\odot	\odot	\odot	\odot	\odot	\odot	



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

Study	N.Pos	N.Tot		Proportion	95%-CI	Weight (fixed)	Weight (random)
100520000 0							•
Cassar, A., 2009	170	376		0.45	[0.40; 0.50]	6.9%	3.5%
De Vita, A, 2019	18	30	+	0.60	[0.41; 0.77]	0.5%	2.6%
Ford, T. J., 2018	78	151	-*	0.52	[0.43; 0.60]	2.8%	3.3%
Godo, 2020	91	148		0.61	[0.53; 0.69]	2.6%	3.3%
Graf, S., 2006	42	58	i —	- 0.72	[0.59; 0.83]	0.9%	2.9%
Hasdai, D., 1998	118	203		0.58	[0.51; 0.65]	3.7%	3.4%
Ishimori, M.L., 2011	8	18		0.44	[0.22; 0.69]	0.3%	2.2%
Kim, H-j, 2013	11	40		0.28	[0.15; 0.44]	0.6%	2.7%
Kobayashi, Y., 2015	39	157	-	0.25	[0.18; 0.32]	2.2%	3.3%
Konst R., 2021	38	103		0.37	[0.28; 0.47]	1.8%	3.2%
Kotecha, T., 2019	16	23	· · · · ·	- 0.70	[0.47; 0.87]	0.4%	2.3%
Kumar, S., 2020	107	163		0.66	[0.58; 0.73]	2.7%	3.3%
Lee, B. K., 2015	38	137	- -	0.28	[0.20; 0.36]	2.0%	3.2%
Murthy, V. L., 2014	641	1218		0.53	[0.50; 0.55]	22.5%	3.5%
Panza, JA, 1997	13	66	i	0.20	[0.11; 0.31]	0.8%	2.8%
Pargaonkar, V. S., 2019	34	155		0.22	[0.16; 0.29]	2.0%	3.2%
Pargaonkar, V. S., 2020	19	88		0.22	[0.14; 0.32]	1.1%	3.0%
Pepine, C. J., 2010	74	152	+	0.49	[0.41; 0.57]	2.8%	3.3%
Quesada, O., 2020	67	150	- `*-	0.45	[0.37; 0.53]	2.8%	3.3%
Rahman, H., 2019	45	85	÷-•	0.53	[0.42; 0.64]	1.6%	3.2%
Safdar, B., 2018	81	124		0.65	[0.56; 0.74]	2.1%	3.3%
Sakamoto, N., 2012	12	73	- -	0.16	[0.09; 0.27]	0.7%	2.8%
Sara, J. D., 2016	281	926	121	0.30	[0.27; 0.33]	14.5%	3.5%
Sara, J. D., 2020	49	129		0.38	[0.30; 0.47]	2.3%	3.3%
Schindler, 2005	50	72	i ——	0.69	[0.57; 0.80]	1.1%	3.0%
Schroder, J., 2019	49	174		0.28	[0.22; 0.35]	2.6%	3.3%
Sicari, R., 2009	87	394	-#-	0.22	[0.18; 0.27]	5.0%	3.4%
Suda, A., 2019	75	187	-*!-	0.40	[0.33; 0.48]	3.3%	3.4%
Taqueti, V. R., 2018	108	201		0.54	[0.47; 0.61]	3.7%	3.4%
Uemura, T., 2016	16	61	I	0.26	[0.16; 0.39]	0.9%	2.9%
Verna, E., 2018	45	101	<u> </u>	0.45	[0.35; 0.55]	1.9%	3.2%
Fixed effect model		5963	•	0.43	[0.42; 0.45]	100.0%	
Random effects model			•	0.43	[0.38; 0.48]		100.0%
Heterogeneity: $I^2 = 93\%$, τ	2 = 0.360	08, p < 0	0.01				
			0 0.2 0.4 0.6 0.1	8 1			
			Proportion				

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

invasive methods.

Study	N.Pos	N.Tot		Proportion	95%-CI	Weight (fixed)	Weight (random)	
			r:			. ,	. ,	
Type of Modality = Nor	Invasiv	e		0.50		10.00/	0.404	
Murthy, V. L., 2014	641	1218		0.53	[0.50; 0.55]	19.2%	3.1%	
Michelsen, M. M., 2018	241	919	E	0.26	[0.23; 0.29]	11.3%	3.0%	
Sicari, R., 2009	87	394		0.22	[0.18; 0.27]	4.3%	3.0%	
Taqueti, V. R., 2018	108	201		0.54	[0.47; 0.61]	3.2%	2.9%	
Schröder, J., 2019	49	174		0.28	[0.22; 0.35]	2.2%	2.9%	
Schroder, J., 2018	37	97		0.38	[0.28; 0.49]	1.5%	2.8%	
Schindler, 2005	50	72		- 0.69	[0.57; 0.80]	1.0%	2.6%	
Panza, JA, 1997	13	66		0.20	[0.11; 0.31]	0.7%	2.5%	
Sade, L. E., 2009	27	60	Ĉ.	0.42	[0.29, 0.34]	0.7%	2.0%	
Musind ND 2016	42	50		0.72	[0.39, 0.83]	0.7%	2.5%	
Roja S 1000	20	19	6	0.37	[0.24, 0.51]	0.0%	2.5%	
Ishimori MI 2011	29	19		0.00	[0.43, 0.74]	0.7%	1.0%	
Fixed effect model	0	3384	<u> </u>	0.44	[0.22, 0.09]	46.8%	1.570	
Pandom effects model		3304		0.41	[0.33, 0.43]	40.0%	34 9%	
Heterogeneity: $I^2 = 96\%$	² = 0.493	0 n < 0.01	i.	0.45	[0.55, 0.55]		54.576	
rieterogeneity. 7 – 30%, t	- 0.495	0, <i>p</i> < 0.01	1					
Type of Modality = Inva	sive							
Sara, J. D., 2016	281	926	<u><u><u></u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u></u>	0.30	[0.27; 0.33]	12.4%	3.1%	
Cassar, A., 2009	170	376		0.45	[0.40; 0.50]	5.9%	3.0%	
Hasdai, D., 1998	118	203	<u> </u>	0.58	[0.51; 0.65]	3.1%	2.9%	
Suda, A., 2019	75	187	- <u></u>	0.40	[0.33; 0.48]	2.8%	2.9%	
Kumar, S., 2020	107	163	· · · ·	0.66	[0.58; 0.73]	2.3%	2.9%	
Kobayashi, Y., 2015	39	157		0.25	[0.18; 0.32]	1.9%	2.8%	
Pargaonkar, V. S., 2019	34	155		0.22	[0.16; 0.29]	1.7%	2.8%	
Pepine, C. J., 2010	74	152		0.49	[0.41; 0.57]	2.4%	2.9%	
Ford, T. J., 2018	78	151		0.52	[0.43; 0.60]	2.4%	2.9%	
Quesada, O., 2020	67	150	- <u>e</u>	0.45	[0.37; 0.53]	2.3%	2.9%	
Godo, 2020	91	148	<u> </u>	0.61	[0.53; 0.69]	2.2%	2.9%	
Lee, B. K., 2015	38	137		0.28	[0.20; 0.36]	1.7%	2.8%	
Sara, J. D., 2020	49	129		0.38	[0.30; 0.47]	1.9%	2.8%	
Safdar, B., 2018	81	124	с <u> </u>	0.65	[0.56; 0.74]	1.8%	2.8%	
Verna, E., 2018	45	101	10 ¹⁰	0.45	[0.35; 0.55]	1.6%	2.8%	
Pargaonkar, V. S., 2020	32	88		0.36	[0.26; 0.47]	1.3%	2.7%	
Ranman, H., 2019	45	85		0.53	[0.42; 0.64]	1.3%	2.7%	
Sakamoto, N., 2012	12	73		0.16	[0.09; 0.27]	0.6%	2.4%	
Solberg, UG, 2019	11	60		0.17	[0.09; 0.28]	0.6%	2.4%	
	10	40		0.26	[0.16, 0.39]	0.7%	2.5%	
Kim, H-J, 2013	11	40		0.28	[0.15; 0.44]	0.5%	2.3%	
De Vila, A, 2019	10	30		0.60	[0.41, 0.77]	0.5%	2.2%	
Fixed effect model	10	23		- 0.70	[0.47; 0.87]	0.3% 52.2%	2.0%	
Pixed effect model		3725	<u> </u>	0.41	[0.40; 0.43]	53.2%	CE 19/	
Heterogeneity: $I^2 = 92\%$. τ	Heterogeneity: $l^2 = 92\%$, $\tau^2 = 0.3445$, $p < 0.01$							
		7400	10 10 10					
Fixed effect model		/109	1	0.41	[0.40; 0.42]	100.0%		
Random effects model	2			0.42	[0.37; 0.48]		100.0%	
Heterogeneity: $I^2 = 94\%$, τ	~ = 0.369	7, p < 0.01						
Residual heterogeneity: /2	= 94%, p	< 0.01 0	0.2 0.4 0.6 0 Propotion	ι.ο 1				

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).

Study	N.Pos I	N.Tot		Proportion	95%-CI	Weight (fixed)	Weight (random)
CFR cutoffs = CFR 2.5	5						
Sara, J. D., 2016	281	926		0.30	[0.27; 0.33]	28.9%	7.3%
Cassar, A., 2009	170	376		0.45	[0.40; 0.50]	13.7%	7.2%
Hasdai, D., 1998	118	203		0.58	[0.51; 0.65]	7.3%	7.0%
Quesada, O., 2020	67	150	<u> </u>	0.45	[0.37; 0.53]	5.5%	6.8%
Sara, J. D., 2020	49	129	<u> </u>	0.38	[0.30; 0.47]	4.5%	6.7%
Verna, E., 2018	45	101	- <u> i</u>	0.45	[0.35; 0.55]	3.7%	6.6%
Rahman, H., 2019	45	85	<u>i</u>	0.53	[0.42; 0.64]	3.1%	6.4%
Sakamoto, N., 2012	12	73		0.16	[0.09; 0.27]	1.5%	5.6%
Reis, S., 1999	29	48		0.60	[0.45; 0.74]	1.7%	5.8%
Fixed effect model		2091	•	0.40	[0.37; 0.42]	69.9%	
Random effects mode	I			0.43	[0.35; 0.51]		59.4%
Heterogeneity: $I^2 = 92\%$,	$\tau^2 = 0.2466$	6, <i>p <</i> 0.01					
CFR cutoffs = CFR les	ss 2.5						
– Kumar, S., 2020	⁻ 107	163		0.66	[0.58; 0.73]	5.4%	6.8%
Kobayashi, Y., 2015	39	157	- m	0.25	[0.18; 0.32]	4.3%	6.7%
Pepine, C. J., 2010	74	152	÷	0.49	[0.41; 0.57]	5.6%	6.8%
Ford, T. J., 2018	78	151		0.52	[0.43; 0.60]	5.6%	6.8%
Godo, 2020	91	148		0.61	[0.53; 0.69]	5.2%	6.8%
Lee, B. K., 2015	38	137	I	0.28	[0.20; 0.36]	4.1%	6.6%
Fixed effect model		908	•	0.48	[0.44; 0.51]	30.1%	
Random effects mode	I			0.46	[0.33; 0.60]		40.6%
Heterogeneity: $I^2 = 94\%$,	$\tau^2 = 0.4588$	3, <i>p</i> < 0.01					
Fixed effect model		2999	•	0.42	[0.40: 0.44]	100.0%	
Random effects mode	I			0.44	[0.37: 0.52]		100.0%
Heterogeneity: $l^2 = 93\%$	$\tau^2 = 0.3094$	1. p < 0.01		,	,		
Residual heterogeneity: 12	² = 93% p	< 0.01 (0.2 0.4 0.6 0).8 1			
	2 3 / 0 , p		Propotion				

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.

