

Supplemental Material

Table of Contents

1. eTable 1	2
2. eTable 2	4
3. eTable 3	5
4. eTable 4	6
5. eTable 5	8
6. eTable 6	11
7. eTable 7	13
8. eTable 8	14
9. eTable 9	15
10. eTable 10	16
11. eFigure 1	17
12. eFigure 2	18
13. eFigure 3	19
14. eFigure 4	20
15. References	21

eTable 1. Meta-analysis search strategy and results by database

Database	Title / Abstract	Keywords	# of Results
Embase (OvidSP)	Coronary microvascular	Prognosis	232
Pubmed (NLM)	Coronary microvascular	Prognosis	208
Web of Science	Coronary microvascular	Prognosis	791
Cochrane	Coronary microvascular	Prognosis	19
Embase (OvidSP)	Coronary Vasospasm	Prognosis	86
Pubmed (NLM)	Coronary Vasospasm	Prognosis	42
Web of Science	Coronary Vasospasm	Prognosis	189
Cochrane	Coronary Vasospasm	Prognosis	3
Embase (OvidSP)	INOCA	Prognosis	27
Pubmed (NLM)	INOCA	Prognosis	36
Web of Science	INOCA	Prognosis	37
Cochrane	INOCA	Prognosis	3
Embase (OvidSP)	Coronary Microcirculatory	Prognosis	21
Pubmed (NLM)	Coronary Microcirculatory	Prognosis	57
Web of Science	Coronary Microcirculatory	Prognosis	122
Cochrane	Coronary Microcirculatory	Prognosis	1
Embase (OvidSP)	Non-obstructive; Coronary	Prognosis	218
Pubmed (NLM)	Non-obstructive; Coronary	Prognosis	83
Web of Science	Non-obstructive; Coronary	Prognosis	245
Cochrane	Non-obstructive; Coronary	Prognosis	21
Embase (OvidSP)	Coronary microvascular	Mortality	88
Pubmed (NLM)	Coronary microvascular	Mortality	112
Web of Science	Coronary microvascular	Mortality	1578
Cochrane	Coronary microvascular	Mortality	17
Embase (OvidSP)	Coronary vasospasm	Mortality	52

Pubmed (NLM)	Coronary vasospasm	Mortality	21
Web of Science	Coronary vasospasm	Mortality	129
Cochrane	Coronary vasospasm	Mortality	8
Embase (OvidSP)	INOCA	Mortality	6
Pubmed (NLM)	INOCA	Mortality	11
Web of Science	INOCA	Mortality	24
Cochrane	INOCA	Mortality	1
Embase (OvidSP)	Coronary microvascular	Outcome	117
Pubmed (NLM)	Coronary microvascular	Outcome	247
Web of Science	Coronary microvascular	Outcome	1944
Cochrane	Coronary microvascular	Outcome	91
Embase (OvidSP)	Coronary vasospasm	Outcome	25
Pubmed (NLM)	Coronary vasospasm	Outcome	53
Web of Science	Coronary vasospasm	Outcome	235
Cochrane	Coronary vasospasm	Outcome	40

eTable 2. Simplified criteria for vasospastic angina based on COVADIS “International standardization of diagnostic criteria for vasospastic angina”^a

Criterion 1	Presence of angina ^b
Criterion 2	Transient ischemic ECG changes during an episode of angina ^c
Criterion 3	Coronary artery spasm (spontaneous or provoked by acetylcholine or ergot derivatives) ^d

^aDefinitive vasospastic angina is diagnosed if Criterion 1 and 2 (clinical diagnosis) or Criterion 1 and 3 (invasive diagnosis) are present. Suspected vasospastic angina is diagnosed if Criterion 1 is present but Criterion 2 and 3 are equivocal.

^bDefined as nitrate-responsive angina in the COVADIS document with additional elements from clinical history needed for diagnosis. These elements were not required to be explicitly stated in the manuscript in order for a study to be included in the meta-analysis because most studies predate COVADIS document and are therefore rarely reported in this form.

^cDefined in the COVADIS document as ST segment elevation ≥ 0.1 mV, ST segment depression ≥ 0.1 mV or new negative U waves. The specific ECG changes were not required to be explicitly stated in the manuscript in order for a study to be included.

^dDefined as >90% constriction, with angina and ECG changes for definitive angina. We included all studies that document coronary spasm regardless of the specific cutoff used in the study and considered lower cutoffs to represent “equivocal” result for Criterion 3 and therefore “possible” vasospastic angina.

eTable 3. Simplified criteria for microvascular angina based on COVADIS “International standardization of diagnostic criteria for microvascular angina”^a

Criterion 1	Presence of angina
Criterion 2	Absence of obstructive coronary artery disease ^b
Criterion 3	Objective evidence of myocardial ischemia ^c
Criterion 4	Evidence of impaired coronary microvascular function ^d

^aDefinitive microvascular angina is diagnosed if all four criteria are present. Suspected microvascular angina is diagnosed if both Criterion 1 and 2 are present in addition to either Criterion 3 or Criterion 4.

^bBy computed tomographic angiography (CTA) or invasive coronary angiography.

^cIschemic electrocardiogram (ECG) changes during an episode of chest pain, positive exercise or imaging stress test.

^dDefined as impaired coronary flow reserve (CFR), abnormal coronary microvascular resistance indices (e.g. index of microcirculatory resistance (IMR)), coronary slow flow phenomenon defined as thrombolysis in myocardial infarction (TIMI) frame count >25 or coronary microvascular spasm (chest pain and ECG changes during acetylcholine testing in the absence of epicardial coronary spasm).

eTable 4. Characteristics of included studies for vasospastic angina

Author and Year	Mode of diagnosis	Medication to induce spasm	Spasm cutoff (%) [*]	COVADIS criteria	Number of patients (N)	Mean or Median Follow up (years)	Mean age	Female (%)	Hypertension (%)	Hyperlipidemia (%)	Diabetes (%)	Smoking (%)
Aboukhou dir et al ¹ , 2016	Invasive	Methylexgonovine	>70	Possible	29	1.5	56	31	28	74	31	72
Bory et al ² , 1996	Invasive or clinical	Methylexgonovine	>50	Possible	232	7.4	54	26	29	39	7	72
Bott-Silverman et al ³ , 1983	Invasive or clinical	Ergonovine	>75	Possible	59	5.9	NA	54	NA	NA	NA	NA
Egashira et al ⁴ , 1987	Invasive	Ergonovine	>50	Possible	90	4.0	58	16	NA	NA	NA	NA
Figueras et al ⁵ , 2013	Invasive or clinical	Ergonovine or acetylcholine	Multiple	Possible	273	11.7	53	18	32	56	4	74
Hung et al ⁶ , 2013	Invasive	Methylexgonovine	>70	Possible	495	8.5	59	30	44	NA	19	45
Kashima et al ⁷ , 2001	Invasive	Ergonovine	>90	Definitive	65	3.9	59	11	37	NA	NA	39
Kim et al ⁸ , 2020	Invasive	Ergonovine	>50	Possible	1838	2.1	55	38	38	16	10	27
Lee et al ⁹ , 2017	Invasive	Ergonovine	>90	Definitive	986	4.4	56	15	39	21	23	28
Lee et al ¹⁰ , 2017	Invasive	Acetylcholine	>75	Possible	647	3.9	56	44	46	19	11	29
Lee et al ¹¹ , 2014	Invasive	Ergonovine	>80	Possible	430	3.6	NA	34	35	10	10	31
Masumoto et al ¹² , 2001	Invasive	Acetylcholine	>75	Possible	169	3.3	62	41	46	63	21	48
Nishimiya et al ¹³ ,	Invasive	Acetylcholine	>90	Definitive	232	2.8	NA	53	50	45	18	30

2021												
Oh et al ¹⁴ , 2013	Invasive or clinical	Ergonovine or acetylcholine	>90	Possible	279	7.6	51	44	44	40	11	32
Sakata et al ¹⁵ , 2005	Invasive	Acetylcholine	>90	Definitive	105	4.7	NA	13	23	27	10	14
Schoenenberger et al ¹⁶ , 2016	Invasive	Acetylcholine	>50	Possible	142	11.3	57	45	45	68	8	47
Schöll et al ¹⁷ , 1988	Invasive	Methylegonovine	>75	Possible	48	3.9	49	23	NA	NA	NA	NA
Seitz et al ¹⁸ , 2020	Invasive	Ergonovine	>75	Possible	26	5.0	NA	NA	NA	NA	NA	NA
Suda et al ¹⁹ , 2019	Invasive	Acetylcholine	>90	Definitive	67	2.5	NA	NA	NA	NA	NA	NA
Takatsu et al ²⁰ , 2011	Invasive	Ergonovine	>90	Possible	1248	11.7	NA	16	47	NA	3	79
Waters et al ²¹ , 1983	Clinical	NA	NA	Definitive	63	1.3	NA	NA	NA	NA	NA	NA

*Severity of coronary vasospasm reported as % diameter stenosis during provocative testing

eTable 5. Characteristics of included studies for microvascular angina

Author and Year	Mode of diagnosis	Type of test	CFR or IMR cutoff	Number of patients (N)	Mean or Median Follow up (years)	Mean age	Female (%)	Hypertension (%)	Hyperlipidemia (%)	Diabetes (%)	Smoking (%)
Addison et al ²² , 2014	non-invasive	SPECT	NA	49	1.6	51	43	86	NA	38	57
Akhiyat et al ²³ , 2023	invasive	NA	CFR <2.0	18	12	56	68	37	68	5	58
AlBadri et al ²⁴ , 2019	invasive	NA	CFR <2.32	77	9.7	NA	NA	NA	NA	NA	NA
Balasz et al ²⁵ , 2010	non-invasive	Dipyridamole stress echo	CFR <2.2	21	8.5	55	100	71	29	19	NA
Bugiardini et al ²⁶ , 2004	non-invasive	SPECT	NA	22	10.3	52	100	36	NA	NA	38
Chauhan et al ²⁷ , 1993	non-invasive	ETT	NA	82	3.0	NA	56	NA	NA	NA	33
Cortigiani et al ²⁸ , 2014	non-invasive	Dipyridamole stress echo	CFR <2.0	35	2.4	65	46	77	86	100	23
Delcour et al ²⁹ , 2009	non-invasive	SPECT	NA	48	7.4	61	0	NA	74	29	40
Fragasso et al ³⁰ , 2009	non-invasive	ETT	NA	34	15.0	NA	78	38	44	4	34
Fragasso et al ³¹ , 2014	non-invasive	SPECT	NA	156	3.6	61	33	76	59	22	NA
Huang et al ³² , 2010	non-invasive	Undefined stress test	NA	108	5.0	65	25	62	22	NA	18
Kaski et al ³³ , 1995	non-invasive	ETT	NA	99	7.0	49	79	NA	29	NA	29
Lamendola et al ³⁴ , 2010	non-invasive	ETT	NA	155	11.4	59	74	56	49	NA	16
Lanza et al ³⁵ , 2017	non-invasive	ETT	NA	250	16.0	55	73	59	49	14	9
Lee E.M. et al ¹⁰ , 2017	invasive	Acetylcholine-induced microvascular spasm		1371	3.9	55	65	44	18	13	17
Lin et al ³⁶ , 2012	non-invasive	ETT	NA	611	7.9	63	31	NA	NA	NA	NA

Liu et al ³⁷ , 2021	non-invasive	SPECT	NA	77	1.3	62	63	45	10	14	18
Marks et al ³⁸ , 2004	invasive	NA	CFR <3.0	60	8.5	51	73	88	NA	33	NA
Masumoto et al ¹² , 2001	invasive	Acetylcholine-induced microvascular spasm		66	3.3	60	69	46	29	15	31
Mone et al ³⁹ , 2022	Invasive and non-invasive	NA	NA	2874	1	NA	55	39	35	31	30
Monroy-Gonzalez et al ⁴⁰ , 2019	non-invasive	N-13 PET	CFR <2.0	34	8	51	71	36	27	4	9
Nishimiya et al ¹³ , 2021	invasive	Acetylcholine-induced microvascular spasm		45	3.6	61	53	47	45	20	31
Radice et al ⁴¹ , 1995	non-invasive	SPECT	NA	30	12.3	51	73	NA	17	NA	20
Radico et al ⁴² , 2022	non-invasive	ETT +/- imaging	NA	956	6.6	63	45	65	78	19	38
Reynolds et al ⁴³ , 2021	non-invasive	Stress echo (undefined)	NA	208	1.0	63	66	64	NA	19	41
Schoenenberger et al ¹⁶ , 2016	invasive	Acetylcholine-induced microvascular spasm		283	11.3	57	61	55	70	9	41
Schroder et al ⁴⁴ , 2021	non-invasive	Dipyridamole stress echo	CFR <2.25	723	4.5	66	100	62	64	15	59
Seitz et al ¹⁸ , 2020	invasive	Ergonovine-induced microvascular spasm		32	5	NA	NA	NA	NA	NA	NA
Shimokawa et al ⁴⁵ , 2021	invasive and non-invasive	Various	CFR <2.5	678	1.1	61	64	52	52	17	16
Shintani et al ⁴⁶ , 2003	non-invasive	ETT	NA	44	6.4	55	93	23	16	7	NA
Sicari et al ⁴⁷ , 2005	non invasive	Dobutamine or dipyridamole stress echo	NA	43	7.1	NA	NA	NA	NA	NA	NA
Sicari et al ⁴⁸ , 2009	non invasive	Dipyridamole stress echo	CFR <2.0	87	4.3	65	63	71	NA	16	25
Sucato et al ⁴⁹ , 2019	non-invasive	ETT	NA	132	10	61	40	NA	NA	NA	NA
Suda et al ¹⁹ ,	invasive	NA	IMR >18	14	2.5	NA	NA	NA	NA	NA	NA

2019											
Sun et al ⁵⁰ , 2001	non-invasive	SPECT	NA	33	7.1	71	15	NA	NA	NA	NA
Suzuki et al ⁵¹ , 2002	non-invasive	ETT	NA	86	7.2	59	59	NA	NA	NA	NA
Yang et al ⁵² , 2019	non-invasive	Adenosine stress echo	CFR <2.0	20	5.3	58	60	65	80	60	65
Zampella et al ⁵³ , 2023	non-invasive	Rb-82 PET	CFR <2.0	82	3.1	NA	NA	NA	NA	NA	NA
Zhang et al ⁵⁴ , 2023	non-invasive	CZT SPECT	CFR <2.52	36	1.3	NA	NA	NA	NA	NA	NA

CFR, coronary flow reserve; SPECT, single photon emission computed tomography; ETT, exercise treadmill test; NA, not available; PET, positron emission tomography; IMR, index of microcirculatory resistance; CZT, Cadmium Zinc Telluride

Supplemental Table 6. Study definitions of MACE

Study	Study definition of MACE
Aboukhoudir et al., 2016	death, MI, recurrent angina, unplanned revascularization
AlBadri et al., 2019	cardiovascular death, nonfatal MI, nonfatal stroke, heart failure
Akhiyat et al., 2023	myocardial infarction, revascularization for stable angina, percutaneous coronary intervention or coronary artery bypass grafting, and stroke
Bory et al., 1996	sudden death, MI or persistent angina
Cortigiani et al., 2014	death or non-fatal MI
Fragasso et al., 2014	all cause death and hospitalization for cardiovascular causes
Huang et al., 2010	death, non-fatal MI, stroke, rehospitalization for unstable angina, revascularization
Hung et al., 2013	death, nonfatal myocardial infarction, and recurrent angina pectoris requiring repeat coronary angiography
Kashima et al., 2001	cardiac death, MI, unstable and stable angina
Kim et al., 2020	cardiac death, acute coronary syndrome, ventricular tachycardia or fibrillation, and atrioventricular block
Lanza et al., 2017	death, MI, coronary revascularization
Lee D.H. et al., 2017	cardiac death, MI, revascularization and rehospitalization due to recurrent angina
Lee E.M. et al., 2017	total death, stroke, MI, revascularization
Lee S.Y. et al., 2014	cardiac death, MI and rehospitalization
Liu et al., 2020	cardiovascular death, nonfatal MI, revascularization, stroke, heart failure, angina-related hospitalization
Monroy-Gonzalez et al., 2019	cardiac death, hospitalization for CHF, MI or revascularization
Nishimiya et al., 2021	cardiac death, non-fatal MI and urgent hospitalization for unstable angina or heart failure
Oh et al., 2013	cardiac death, aborted sudden cardiac death or fatal arrhythmia
Radico et al., 2021	all cause death and non-fatal MI
Sakata et al., 2005	acute ischemic syndrome, cardiac death
Schoenenberger et al., 2016	cardiovascular death or non-fatal MI
Shimokawa et al., 2021	cardiovascular death, MI, hospitalization for unstable angina of CHF
Sicari et al., 2009	death and non-fatal ACS
Suda et al., 2019	cardiac death, MI and hospitalization
Takatsu et al., 2011	acute MI, Unstable Angina, development of severe coronary disease
Yang et al., 2019	unstable angina, nonfatal MI, PCI
Zampella et al., 2023	cardiac death, MI or late (>3 months coronary revascularization)

Zhang et al., 2023	cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, heart failure, late coronary revascularization, or hospitalization for unstable angina
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eTable 7. Subgroup analysis of incidence of all –cause death and MI

Characteristics	No. of Studies	Incidence Rate per 100 patient-years (95% CI)	I ² (%)	p
Endotype				0.137
Vasospastic angina (VSA)	20	0.7 (0.4-1.0)	90.3	
Microvascular angina (MVA)	33	1.1 (0.7-1.6)	92.5	
Cutoff for VSA diagnosis				0.923
>=90%	6	0.8 (0.7-1.0)	8.4	
Others	14	0.7 (0.3-1.3)	92.4	
COVADIS criteria				0.210
Definitive VSA	5	1.1 (0.3-2.4)	82.3	
Possible VSA	15	0.6 (0.3-0.9)	91.6	
MVA by type of stress test				0.001
Abnormal CFR	7	4.7 (2.0-8.4)	93.6	
Positive exercise stress test	9	0.5 (0.1-1.1)	93.0	
Positive imaging stress test	10	1.1 (0.5-2.0)	67.5	

MVA= microvascular angina; VSA=vasospastic angina.

eTable 8. Subgroup analysis of incidence of MACE

Characteristics	No. of Studies	Incidence Rate per 100 patient-years (95% CI)	I ² (%)	p
Endotype				0.025
Vasospastic angina (VSA)	20	1.1 (0.5-1.9)	97.3	
Microvascular angina (MVA)	30	2.5 (1.6-3.6)	96.7	
Spasm cutoff for VSA Diagnosis				0.911
>=90%	6	1.1 (0.1-3.0)	98.4	
Others	14	1.1 (0.3-2.1)	96.5	
COVADIS criteria				0.141
Definitive VSA	5	2.4 (0.5-5.5)	94.8	
Possible VSA	15	0.8 (0.3-1.4)	96.1	
MVA by type of stress test				0.223
Abnormal CFR	4	5.9 (2.1-11.2)	93.8	
Positive exercise stress test	8	2.5 (1.4-3.9)	91.8	
Positive imaging stress test	10	3.5 (1.2-6.8)	93.8	

MVA= microvascular angina; VSA=vasospastic angina.

eTable 9. Meta-regression of incidence of all-cause death and MI

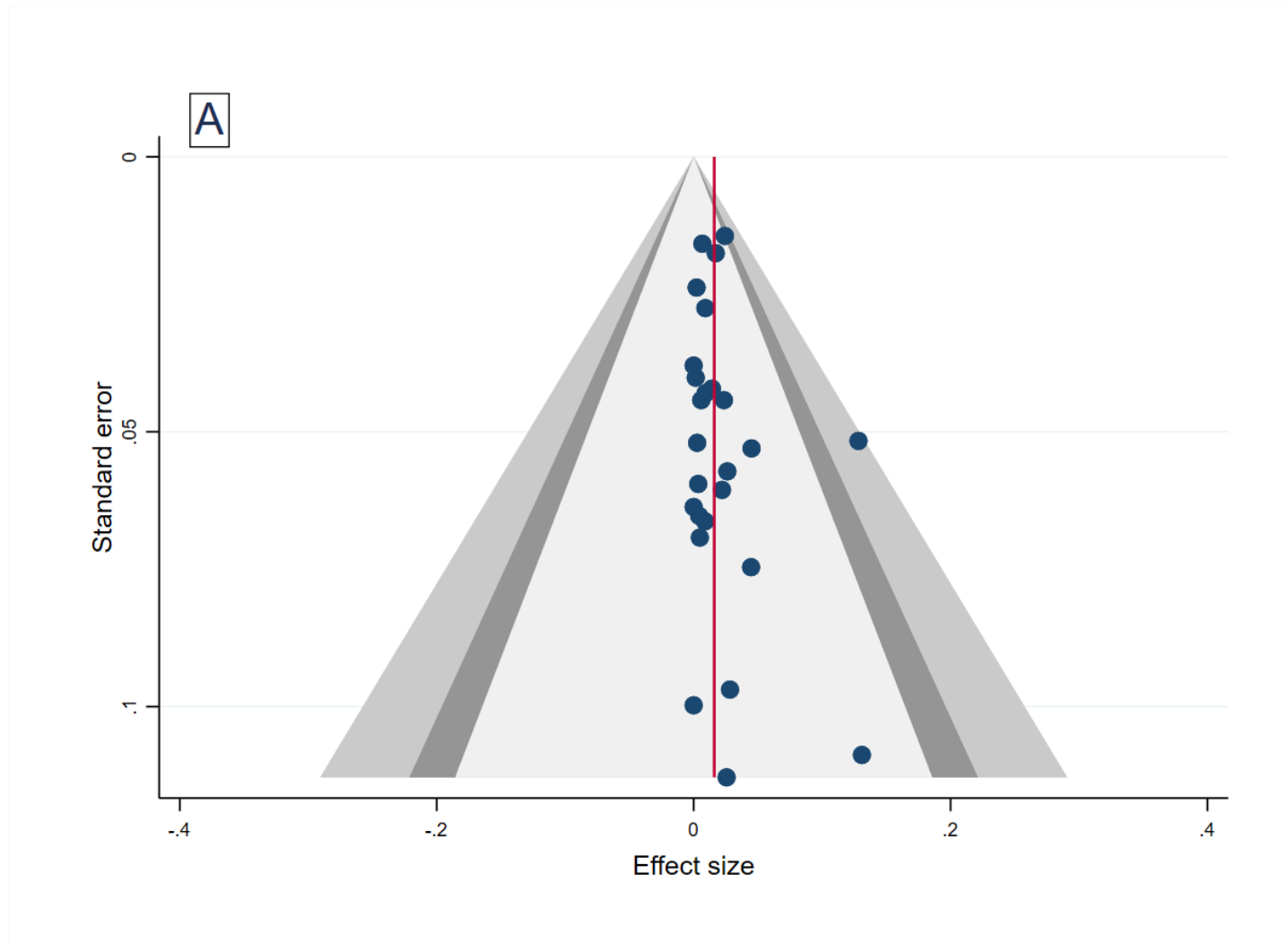
Characteristics	β (95% CI)	<i>p</i>	I^2 (%)	Adjusted R^2 (%)
Endotype				
MVA vs. VSA	0.024 (-0.050 – 0.098)	0.522	95.5	
Spasm cutoff for VSA Diagnosis				
>=90% vs. Other	-0.014 (-0.121 – 0.094)	0.803	94.7	
Mode of MVA Diagnosis				
Invasive vs. Non-invasive	-0.091 (-0.208 – 0.026)	0.128	94.5	4.2
MVA by type of test				
Stress test (any) vs. microvascular function test	-0.075 (-0.181 – 0.032)	0.169	94.8	2.9
MVA by type of stress test		0.167	94.1	5.4
Exercise treadmill test vs. microvascular function test	-0.119 (-0.258 – -0.020)	0.095		
Imaging stress test vs. microvascular function test	-0.030 (-0.174 – 0.113)	0.680		
Exercise treadmill test vs. Imaging stress test	-0.086 (-0.174 – 0.001)	0.054		
Female (%)	-0.0001 (-0.002 – 0.001)	0.862	96.1	
Hypertension (%)	0.004 (0.002– 0.007)	0.002	96.1	20.2
Hyperlipidemia (%)	0.002 (-0.0006 – 0.004)	0.010	92.8	16.1
Diabetes (%)	0.005 (-0.002 – 0.008)	<0.001	96.3	28.2

MVA= microvascular angina; VSA=vasospastic angina.

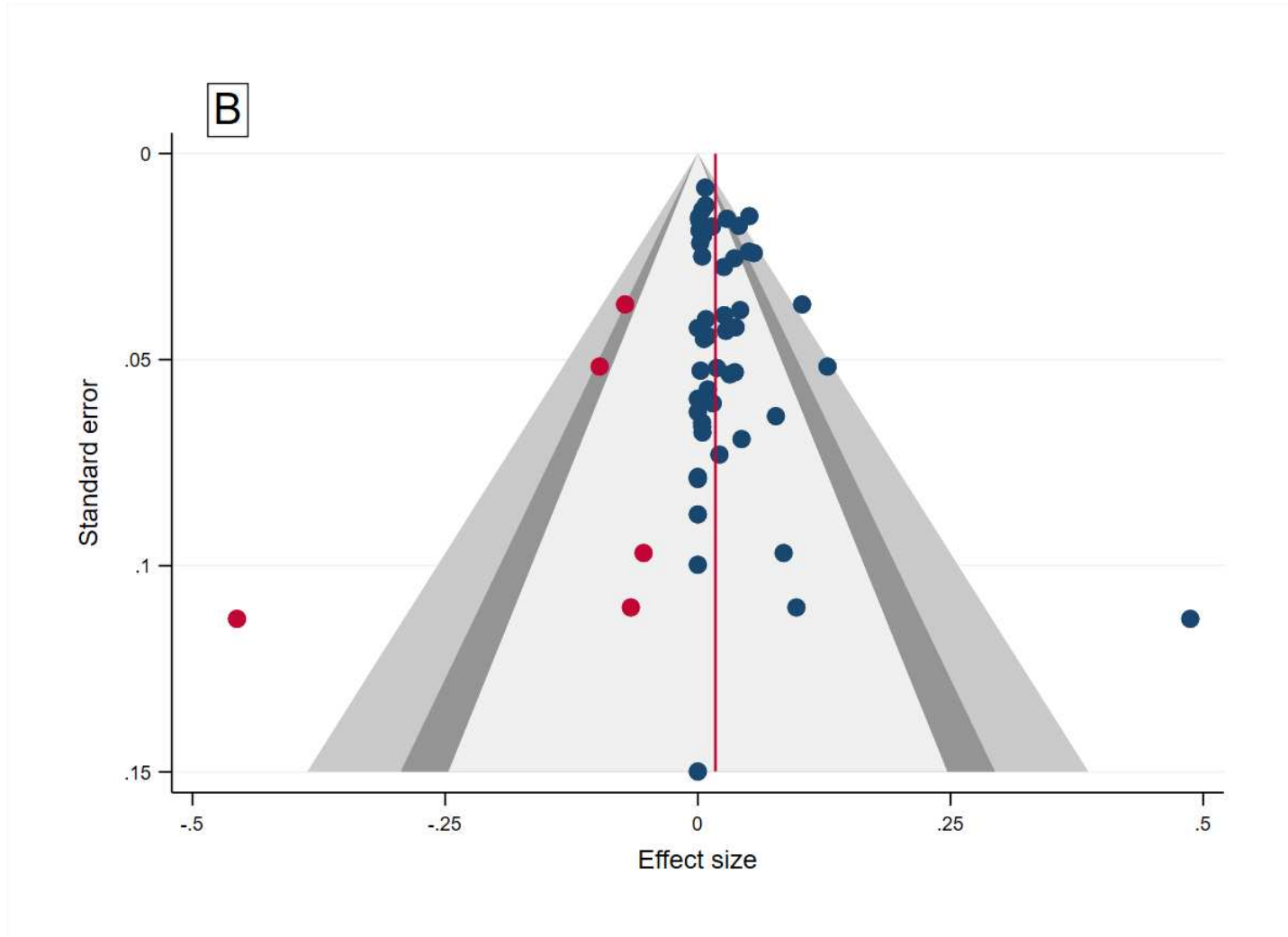
eTable 10. Meta-regression of incidence of MACE

Characteristics	β (95% CI)	<i>p</i>	<i>I</i> ² (%)	Adjusted <i>R</i> ² (%)
Endotype				
MVA vs. VSA	0.104 (-0.026 – 0.235)	.117	98.6	3.2
Spasm cutoff for VSA Diagnosis				
>=90% vs. Other	-0.009 (-0.164 – 0.146)	.904	97.6	
Mode of MVA Diagnosis				
Invasive vs. Non-invasive	-0.167 (-0.410 – 0.076)	.178	98.5	2.7
MVA by type of test				
Stress test (any) vs. microvascular function test	0.064 (-0.155 – 0.283)	.568	98.6	
MVA by type of stress test		.801	98.4	
Exercise treadmill test vs. microvascular function test	0.036 (-0.158 – 0.230)	.717		
Imaging stress test vs. microvascular function test	0.109 (-0.188 – 0.405)	.473		
Exercise treadmill test vs. Imaging stress test	-0.073 (-0.360 – 0.213)	.616		
Female (%)	0.001 (-0.002 – 0.004)	.601	98.9	
Hypertension (%)	0.011 (0.006 – 0.016)	<.001	98.8	38.6
Hyperlipidemia (%)	0.002 (-0.001 – 0.005)	.238	97.5	0.6
Diabetes (%)	0.011 (0.003 – 0.019)	.008	99.2	18.4

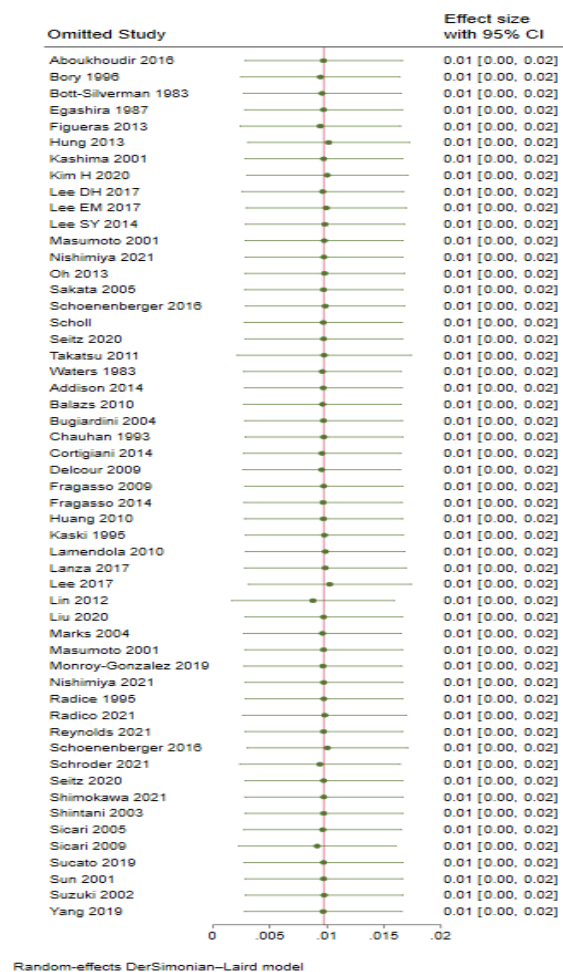
MVA= microvascular angina; VSA=vasospastic angina.

eFigure 1. Funnel plot for all-cause death and MI

eFigure 2. Funnel plot for MACE

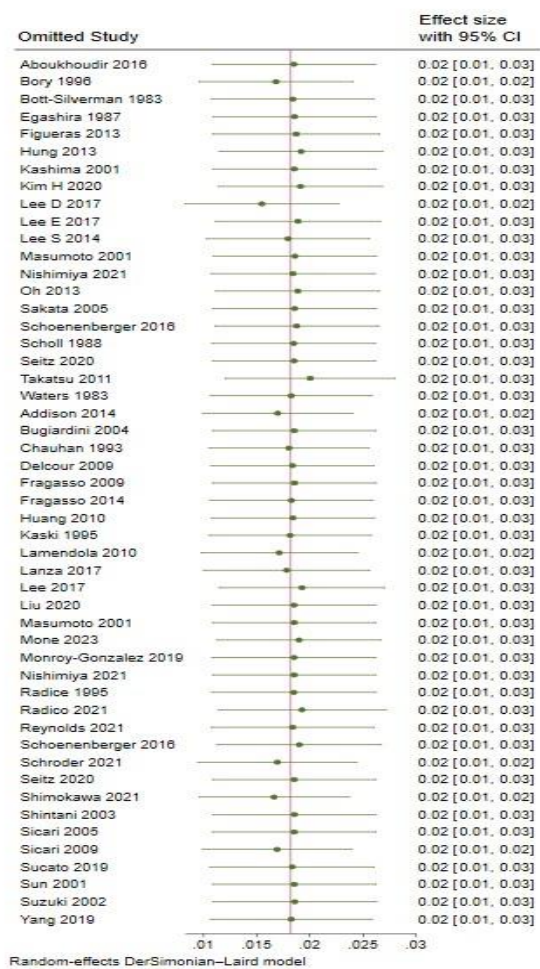


eFigure 3. Leave-one-out sensitivity analysis for all-cause death and MI



The displayed effect size corresponds to the computed overall effect size excluding that study.

eFigure 4. Leave-one-out sensitivity analysis for MACE



The displayed effect size corresponds to the computed overall effect size excluding that study.

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