

Early invasive *versus* conservative strategy in acute coronary syndrome in older adults: systematic review and meta-analysis

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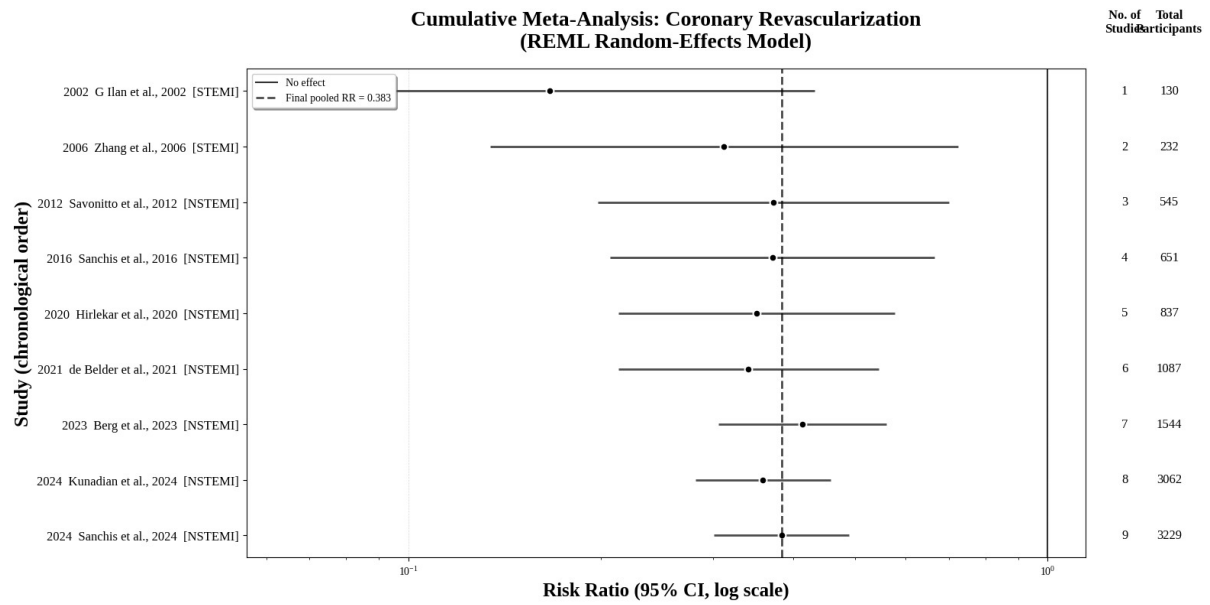
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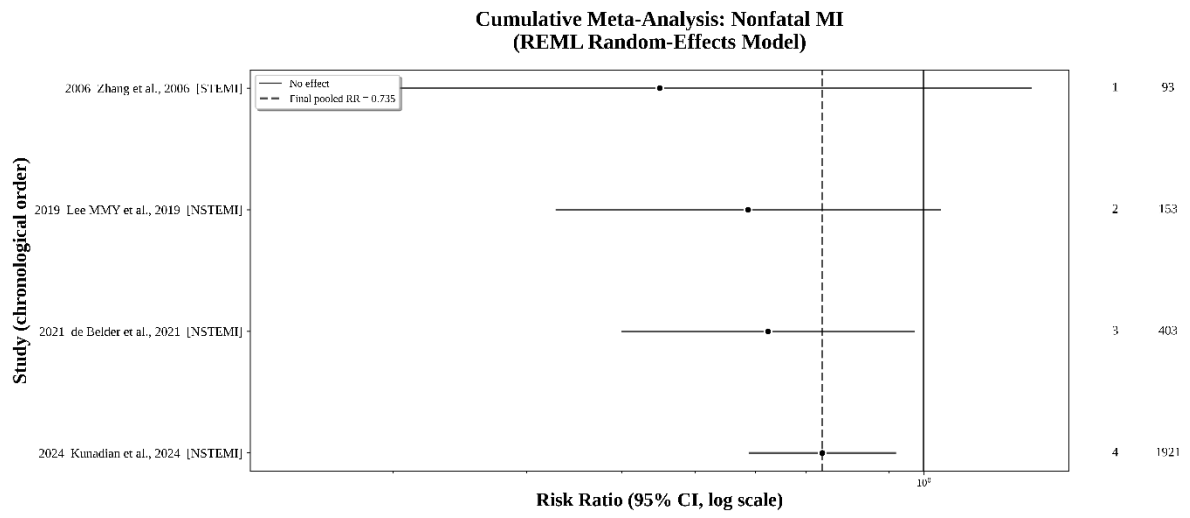
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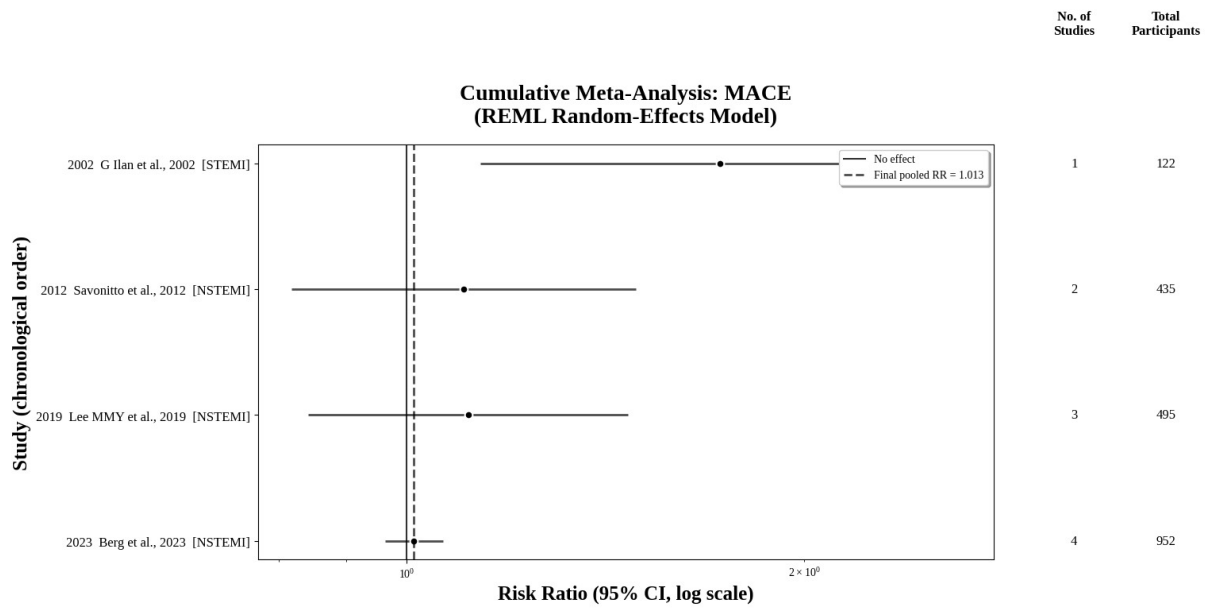
Supplementary figures and supplementary tables



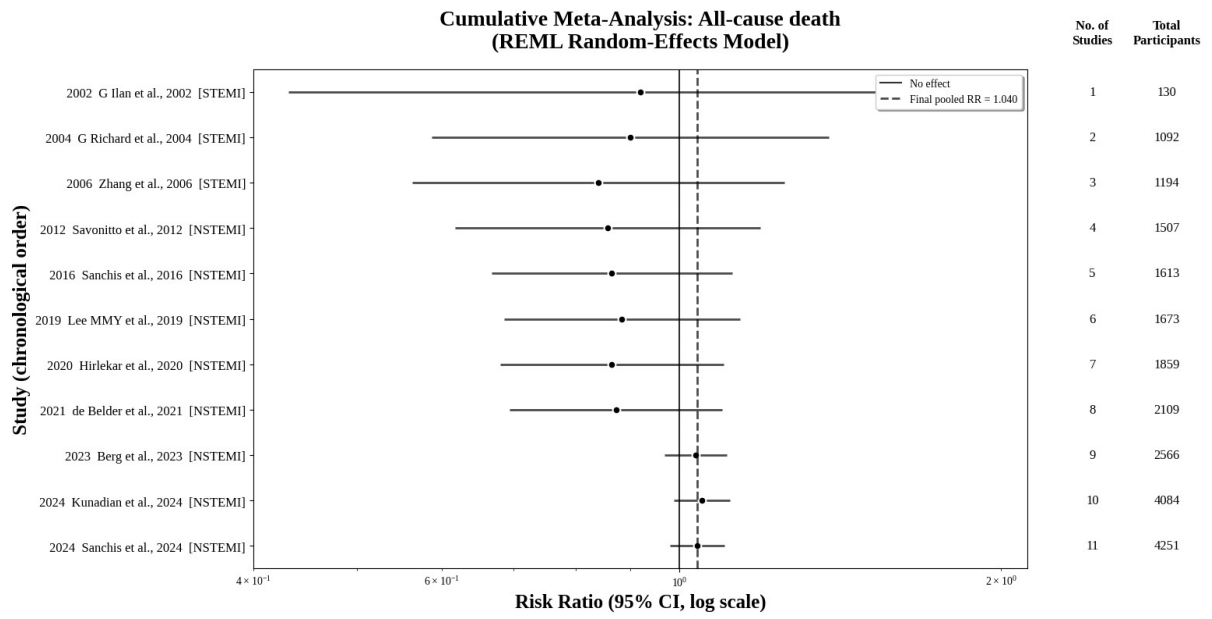
Supplementary figure 1. Cumulative Meta-Analysis of Coronary Revascularization



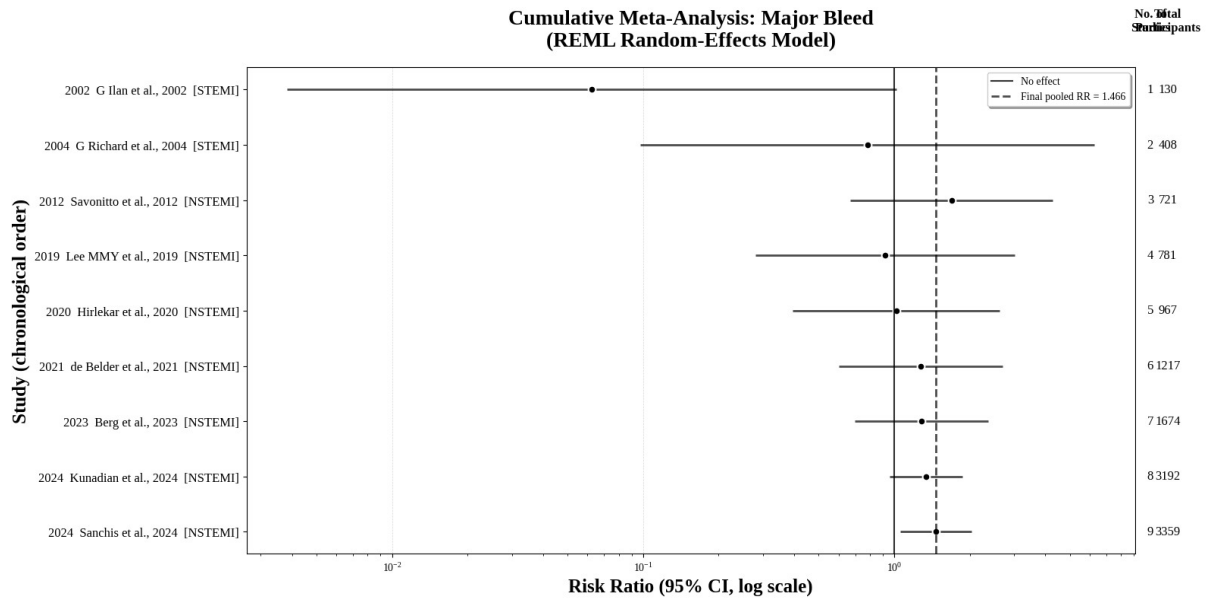
Supplementary figure 2. Cumulative Meta-Analysis of Nonfatal MI



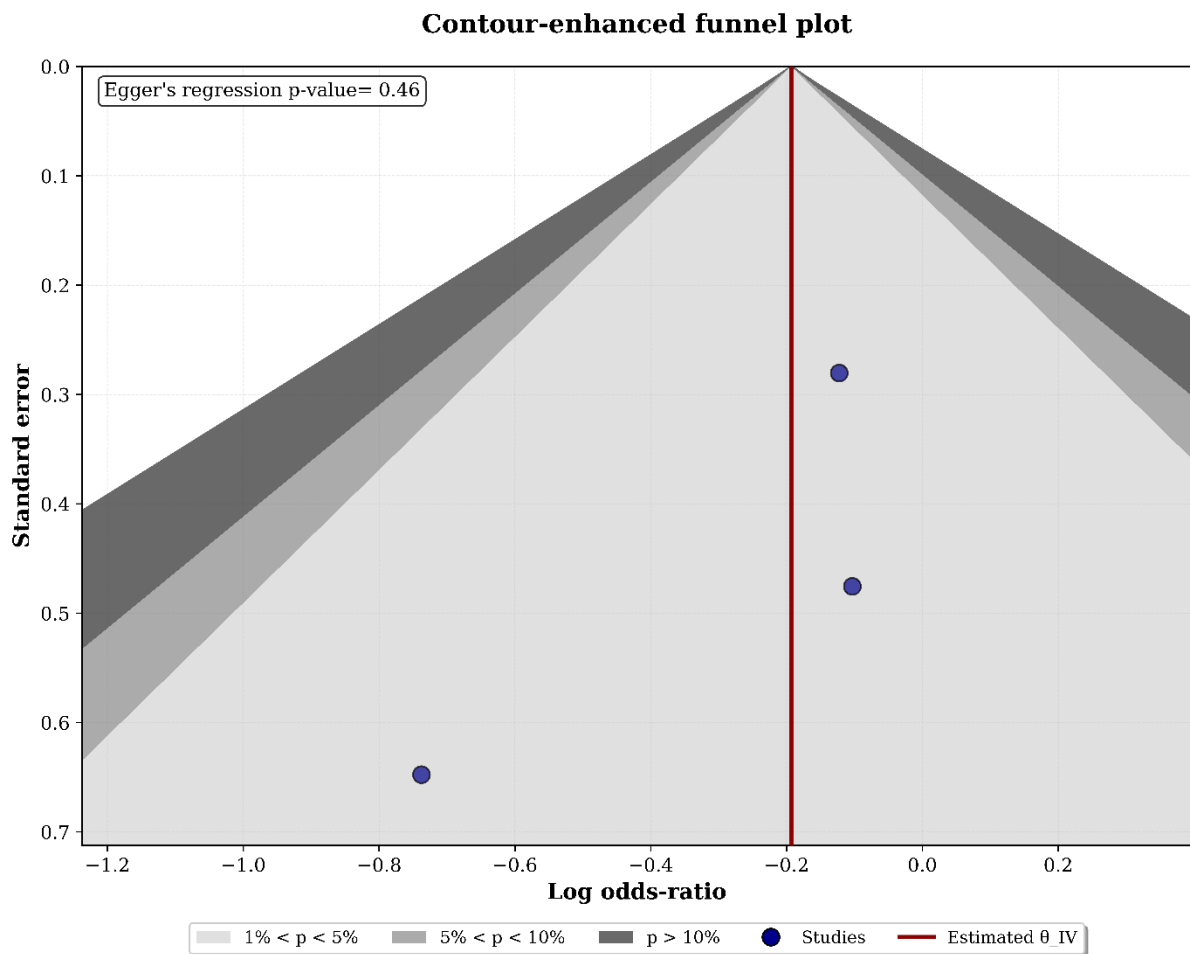
Supplementary figure 3. Cumulative Meta-Analysis of MACE



Supplementary figure 4. Cumulative Meta-Analysis of All-Cause Death

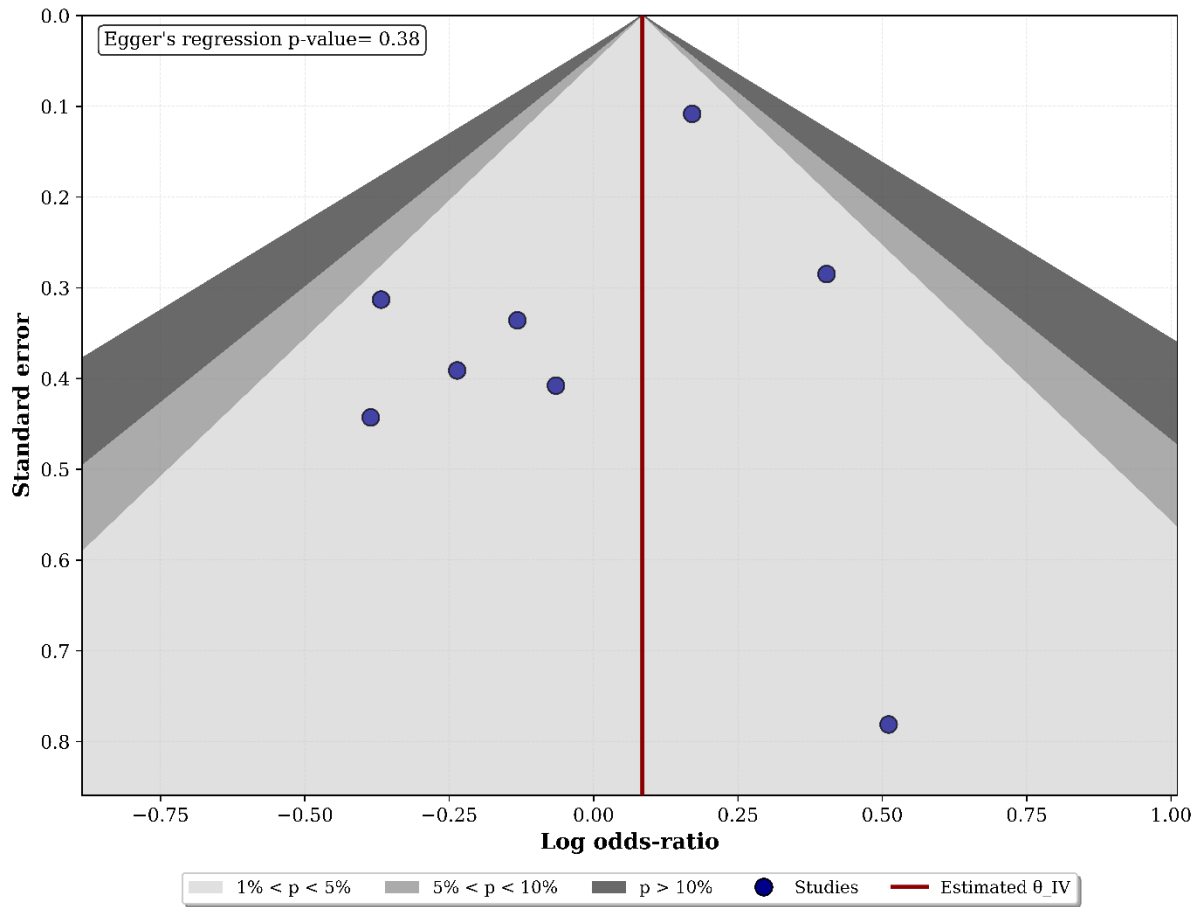


Supplementary figure 5. Cumulative Meta-Analysis of Major Bleeding



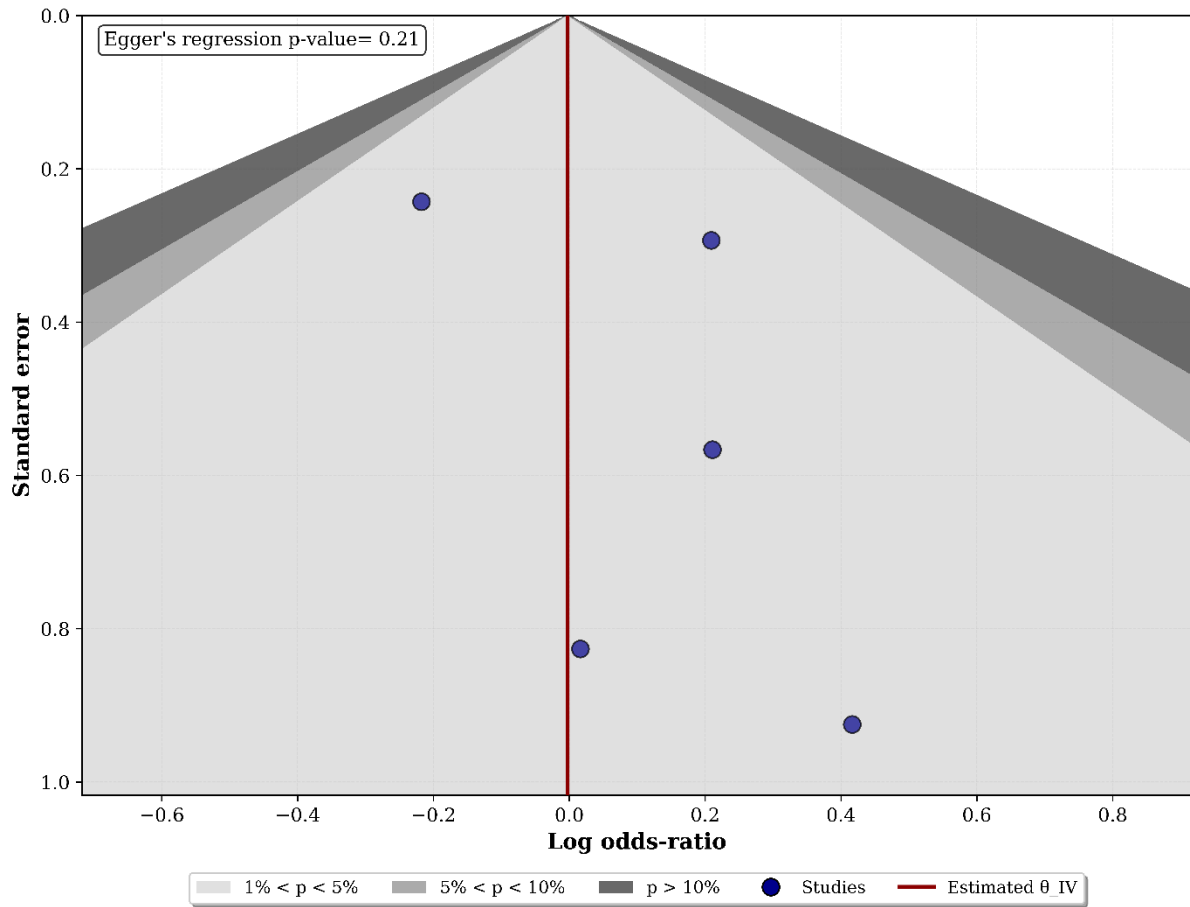
Supplementary figure 6. Funnel Plot All-cause Death (STEMI)

Contour-enhanced funnel plot



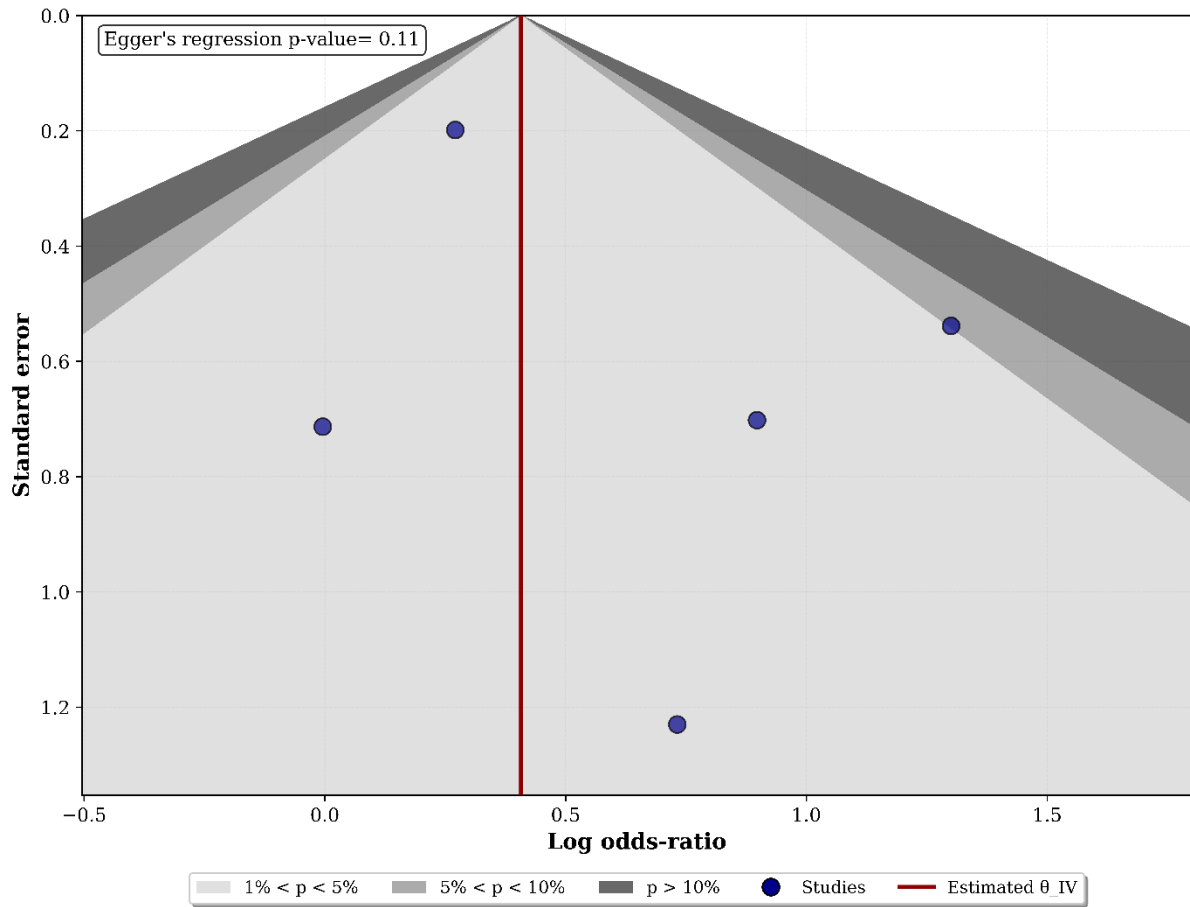
Supplementary figure 7. Funnel Plot All-cause Death (NSTEMI)

Contour-enhanced funnel plot



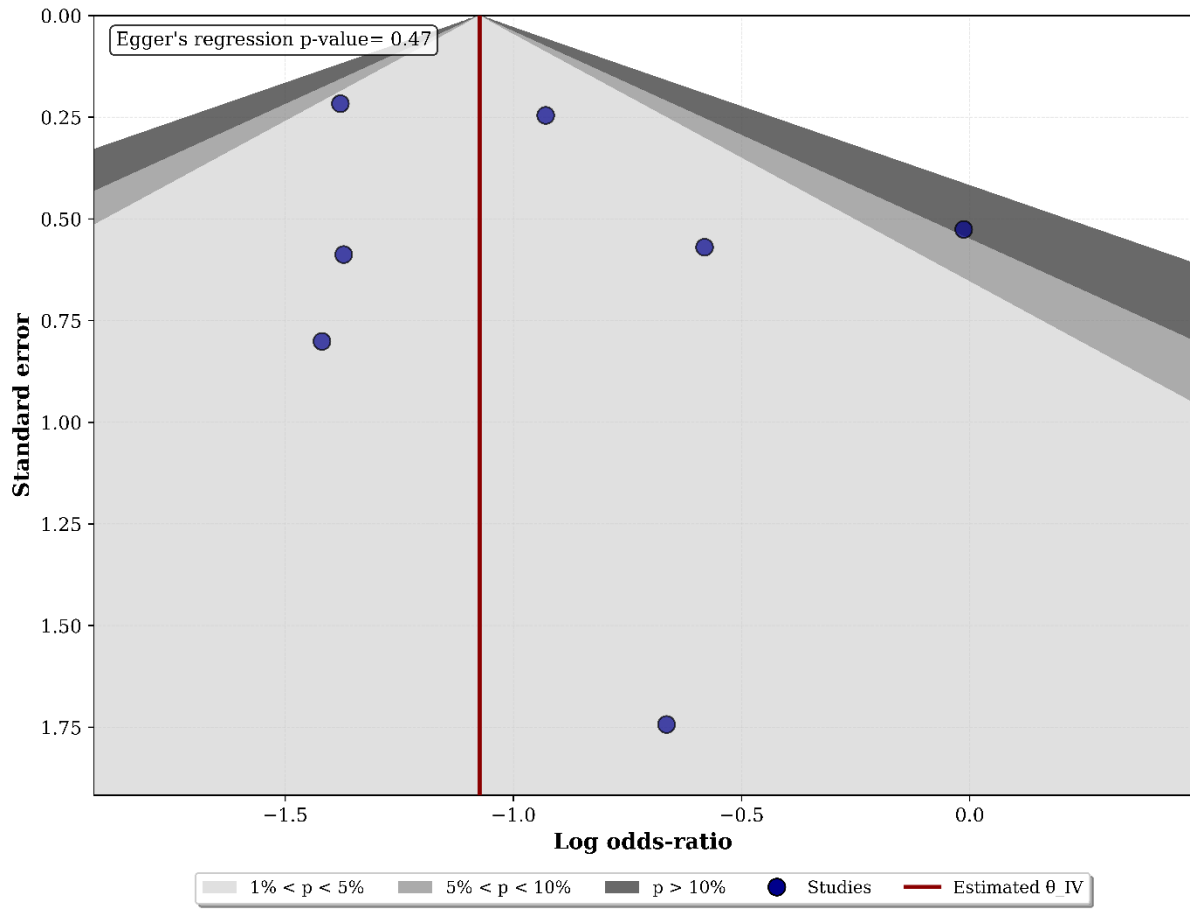
Supplementary figure 8. Funnel plot stroke (NSTEMI)

Contour-enhanced funnel plot



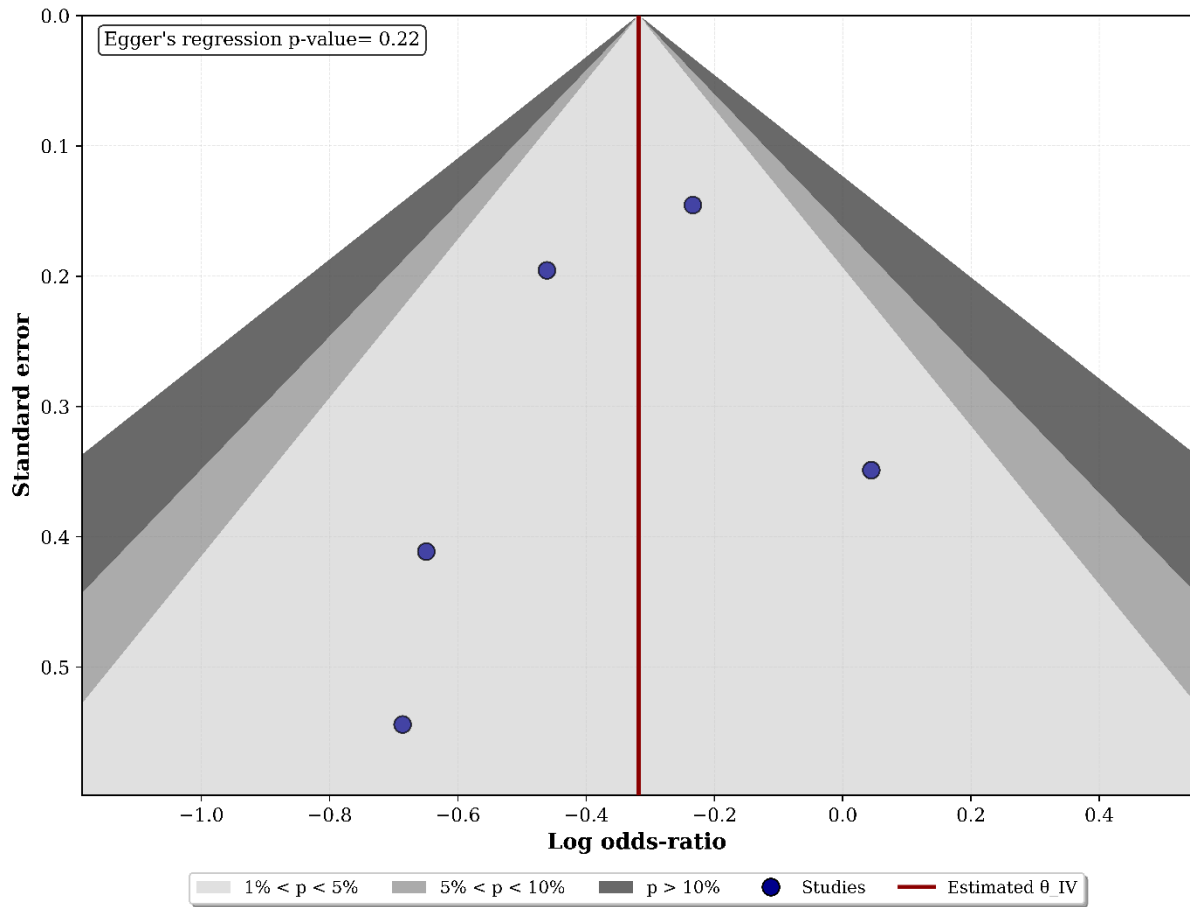
Supplementary figure 9. Funnel plot major bleeding (NSTEMI)

Contour-enhanced funnel plot



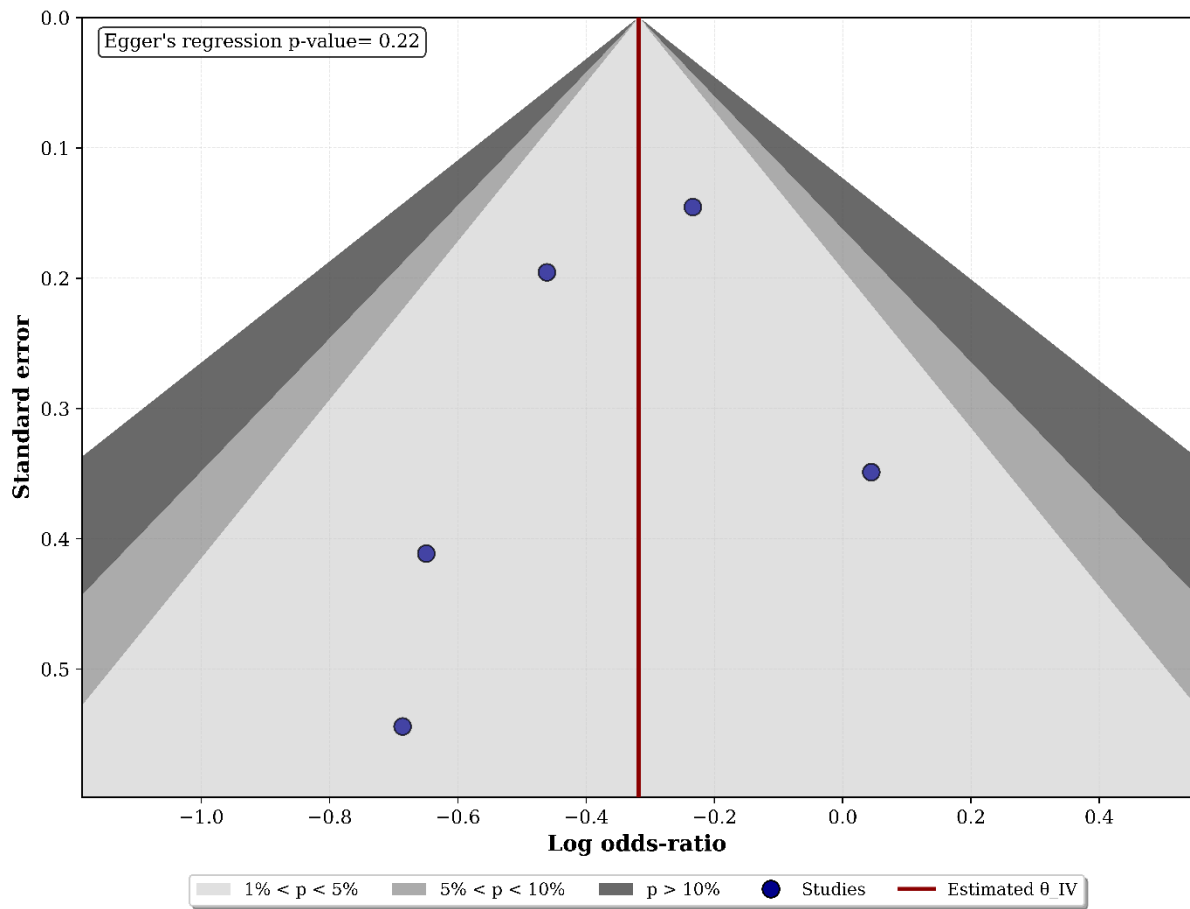
Supplementary figure 10. Funnel plot coronary artery revascularization (NSTEMI)

Contour-enhanced funnel plot



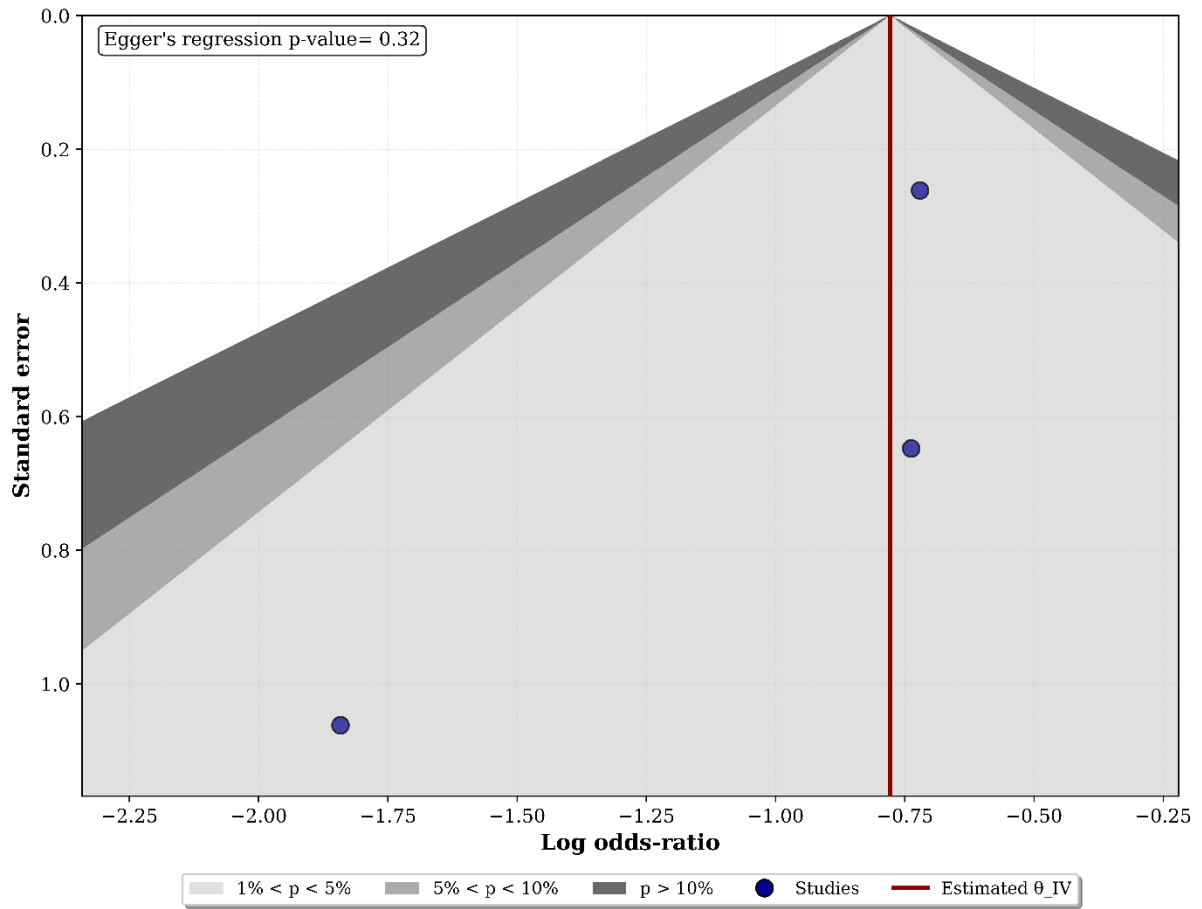
Supplementary figure 11. Funnel plot nonfatal MI (NSTEMI)

Contour-enhanced funnel plot



Supplementary figure 12. Funnel plot recurrent MI (NSTEMI)

Contour-enhanced funnel plot



Supplementary figure 13. Funnel plot recurrent MI (STEMI)

Supplementary Table 1. Search Strategy used in PubMed and Embase

Database	Search Components	Search Strategy
PubMed	Population (ACS)	("Acute Coronary Syndrome"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Unstable Angina"[Mesh] OR "Non-ST Elevated Myocardial Infarction"[Mesh] OR "Acute Coronary Syndrome" OR ACS OR "Myocardial Infarction" OR MI OR NSTEMI OR STEMI OR "ST-Elevation Myocardial Infarction" OR "Unstable Angina" OR "NSTE-ACS")
	Conservative strategy	AND ("Conservative Treatment"[Mesh] OR "Drug Therapy"[Mesh] OR "Conservative management" OR "Conservative strategy" OR "Conservative treatment" OR "Conservative therapy" OR "Medical management" OR "Medical therapy" OR "Optimal medical therapy" OR OMT OR "Ischemia-guided")
	Invasive strategy	AND ("Percutaneous Coronary Intervention"[Mesh] OR "Coronary Angiography"[Mesh] OR "Cardiac Catheterization"[Mesh] OR "Myocardial Revascularization"[Mesh] OR "Angioplasty, Transluminal, Percutaneous Coronary"[Mesh] OR "Invasive strategy" OR "Invasive management" OR "Early invasive" OR "Routine invasive" OR "Invasive approach" OR "Percutaneous coronary intervention" OR PCI OR "Angiography" OR "Revascularization" OR "Coronary artery bypass grafting" OR CABG)
EMBASE	Population (ACS)	('acute coronary syndrome'/exp OR 'myocardial infarction'/exp OR 'unstable angina'/exp OR (ACS OR "acute coronary syndrome" OR NSTEMI OR STEMI OR "unstable angina"):ti,ab,kw)
	Invasive strategy	AND (("early invasive" OR "routine invasive" OR "invasive strategy" OR "invasive management" OR "invasive approach"):ti,ab,kw OR 'percutaneous coronary intervention'/exp OR 'coronary angiography'/exp OR 'cardiac catheterization'/exp OR 'myocardial revascularization'/exp OR (PCI OR CABG OR angiograph* OR revasculari*):ti,ab,kw)
	Conservative strategy	AND (("conservative management" OR "conservative strategy" OR "selective invasive" OR "ischemia-guided" OR "ischaemia-guided" OR "medical management" OR "optimal medical therapy" OR OMT OR "standard of care" OR "non-invasive"):ti,ab,kw)
	Study design filter	AND ('randomized controlled trial'/exp OR random*:ti,ab,kw)

Supplementary Table 2. Egger's Test for detecting Publication Bias in the study outcomes

Outcome	ACS subgroup	No. of studies	p-value	Interpretation
Stroke	NSTEMI	5	0.2123	No significant publication bias
Stroke	STEMI	2	-	Not interpretable
Myocardial Infarction	NSTEMI	5	0.2417	No significant publication bias
Myocardial Infarction	STEMI	3	0.32	No significant publication bias
Major Bleeding	NSTEMI	5	0.1088	No significant publication bias
Major Bleeding	STEMI	2	-	Not interpretable
Coronary Artery Revascularization	NSTEMI	7	0.467	No significant publication bias
Coronary Artery Revascularization	STEMI	2	-	Not interpretable
All-cause Death	NSTEMI	8	0.3844	No significant publication bias
All-cause Death	STEMI	3	0.4633	No significant publication bias

Supplementary Table 3. Baseline characteristics of the patients

Characteristic	G Richard et al., 2004**		de Belder et al., 2021		Lee MMY et al., 2019		Kunadian et al., 2024		Berg et al., 2023		G Ilan et al., 2002		Zhang et al., 2006		Sanchis et al., 2024		Savonitto et al., 2012		Sanchis et al., 2016		Hirlekar et al., 2020	
	Bach 2004 <65y (n=1258)	Bach 2004 ≥65y (n=962)	Earl y Invasive (n=124)	Conservative (n=126)	Earl y Invasive (n=31)	Conservative (n=29)	Earl y Invasive (n=753)	Conservative (n=765)	Earl y Invasive (n=229)	Conservative (n=228)	Conservative (n=86)	Earl y Invasive (n=44)	Early Invasive (n=50)	Conservative (n=52)	Earl y Invasive (n=84)	Conservative (n=83)	Early Invasive (n=154)	Conservative (n=159)	Earl y Invasive (n=52)	Conservative (n=54)	Earl y Invasive (n=93)	Conservative (n=93)
DEMOGRAPHICS																						
Mean age ± SD (years)	53.4 ± 7.2	72.9 ± 5.6	84.8 (80-95)	85.2 (80-95)	69±10	73±8	82.5 ± 4.7	82.2 ± 4.7	84.7 ± 4.0	84.9 ± 4.3	76 ± 5	77 ± 5	80.7±1.3	77.9±2.9	86±5	86±5	81.8±4.4	81.8±4.7	81 ± 5	83 ± 6	84 (81-90)*	84 (81-89)*
Female (%)	29.2	40.5	48.4	46	23	34	44.8	44.7	49.3	50.4	59	59	46	42.3	56	61.9	51	49	44	50	49.5	40.9
White ethnicity (%)	73	83.6	-	-	-	-	-	-	-	-	-	-	-	-	100	100	-	-	-	-	-	-
Body mass index (kg/m²)	-	-	-	-	-	-	-	-	25.7 ± 4.3	25.3 ± 4.2	-	-	24.1±3.3	25.3±2.1	-	-	-	-	-	-	-	-
Obesity (BMI >30 kg/m²) (%)	-	-	-	-	39	34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight (kg)	-	-	-	-	-	-	-	-	-	-	73 (59-94)	73 (56-94)	-	-	-	-	72±12	72±11	-	-	73 (59-94)*	73 (56-94)*
VITAL SIGNS																						
Systolic BP (mm Hg)	-	-	-	-	-	-	-	-	146 ± 28	148 ± 27	142 (120-174)	142 (119-180)	123±48	134±31	-	-	-	-	148 ± 35	141 ± 28	142 (120-174)*	142 (119-180)*
Diastolic BP (mm Hg)	-	-	-	-	-	-	-	-	76 ± 14	77 ± 14	79 (64-98)	80 (68-100)	69±33	75±21	-	-	-	-	73 ± 16	70 ± 14	79 (64-98)*	80 (68-100)*
Heart rate (beats/min)	-	-	-	-	-	-	-	-	77 ± 18	76 ± 17	69 (56-92)	80 (55-99)	91±22	79±38	-	-	-	-	89 ± 27	82 ± 20	69 (56-92)*	80 (55-99)*
CARDIOVASCULAR HISTORY																						
Previous MI (%)	39.6	38.3	26.8	28.5	74	62	32.8	29.7	31.4	30.3	17	25	-	-	27.4	22.6	28	34	46	43	31.9	37.6
Previous PCI (%)	-	-	17.2	12.9	-	-	21.7	18.2	20.5	19.3	16.3	17.2	2	3.8	27.4	22.6	11	20	23	17	16.3	17.2
Previous CABG (%)	-	-	9.7	8.1	-	-	13.4	10.5	11.4	10.5	20.4	15.1	-	-	-	-	11	7.6	19	7	20.4	15.1
Previous aspirin use (%)	65	68.5	-	-	94	79	-	-	55.5	52.6	-	-	-	-	-	-	-	-	-	-	54.8	53.8
History of angina (%)	12.1	14	-	-	-	-	-	-	-	-	39.1	44.6	-	-	-	-	25	18	-	-	39.1	44.6
History of CHF (%)	4.7	10.6	-	-	29	17	9.7	9.2	10.5	8.3	10.8	8.6	-	-	-	-	10	8.9	17	19	10.8	8.6
Cardiac arrhythmia/AF (%)	26.4	33.8	19.5	20	39	24	-	-	27.1	24.6	10.9	18.5	-	-	-	-	15	12	27	22	10.9	18.5
Previous stroke/CVA (%)	-	-	20.2	21	23	21	17	13.2	10.9	9.6	10.8	16.1	-	-	-	-	7.5	9.7	25	24	10.8	16.1
Peripheral vascular disease (%)	-	-	4.1	2.4	35	17	7.6	8	7.9	9.6	3.2	6.5	-	-	-	-	-	-	44	41	3.2	6.5
Aortic aneurysm (%)	-	-	0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RISK FACTORS																						
Hypertension (%)	62.1	71.3	70.2	66.1	74	66	65.1	65.4	69	71.1	51	57	70	71.2	-	-	92	85	94	85	59.1	63.4
Diabetes mellitus (%)	25.9	29.8	26.6	15.2	32	38	30.8	30.6	17.9	16.7	23	25	20	23.1	-	-	38	41	46	46	17.2	21.5
Hyperlipidemia/cholesterolemia (%)	62.2	58.6	-	-	-	-	32.2	30.3	30.1	32	42	32	34/18	28.8/19.2	-	-	44	50	75	63	22.6	17.2
Current smoker (%)	39.8	11.6	8.1	3.3	23	17	4.7	6	8.7	7.5	26	27	38	25	-	-	-	-	8	4	2.2	3.4
Ex-smoker (>3 mo) (%)	-	-	-	-	65	45	47.9	44.4	-	-	-	-	-	-	-	-	-	-	-	-	37.1	44.3
Never smoked (%)	-	-	-	-	13	38	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Family history (%)	-	-	-	-	-	-	-	-	-	-	10	7	-	-	-	-	-	-	-	-	-	-
COMORBIDITIES																						
COPD (%)	-	-	15.3	9.8	-	-	15.3	15.4	13.5	11.4	-	-	-	-	-	-	-	-	37	26	-	-

Peak CPK (IU)	-	-	-	-	-	-	-	-	-	-	926 (155-7667)	955 (146-4770)	-	-	-	-	-	-	-	-	-	-	
Both ischemic ECG and elevated markers (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	37	39	-	-	-	-	
CARDIAC FUNCTION																							
LVEF at discharge (%)	-	-	-	-	-	-	-	-	-	-	55 (35-60)	54 (35-60)	0.51±0.13	0.48±0.13	-	-	-	-	53 ± 12	54 ± 12	-	-	
Ejection fraction (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	49±9.7	48±10.6	-	-	55 (35-60)	54 (35-60)	
MEDICATIONS AT ADMISSION/BASELINE																							
Aspirin (%)	65	68.5	-	-	94	79	-	-	55.5	52.6	100	100	-	-	-	-	73	73	100	95	54.8	53.8	
β-Blockers (%)	22.7	25.1	-	-	68	72	-	-	62.4	61	66	68	-	-	-	-	-	-	69	78	39.8	51.6	
Calcium channel blocker (%)	-	-	-	-	100	100	-	-	23.6	25.4	-	-	-	-	-	-	-	-	-	-	25	21.5	
Nitrates (%)	23.7	27	-	-	39	28	-	-	17	15.4	-	-	-	-	-	-	-	-	-	-	-	-	
Nicorandil (%)	-	-	-	-	48	24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
ACE inhibitors/ARB (%)	9.1	8.8	-	-	87	79	-	-	57.2	55.7	58.7	75	-	-	-	-	-	-	98	93	44.6	53.8	
Statin (%)	-	-	-	-	94	90	-	-	46.7	44.3	32.6	39.8	-	-	-	-	-	-	96	98	32.6	39.8	
P2Y12 inhibitor (%)	-	-	-	-	-	-	-	-	9.6	7.9	-	-	-	-	-	-	-	-	-	-	-	-	
Clopidogrel (%)	-	-	-	-	-	-	-	-	-	-	8.6	7.7	-	-	-	-	-	40	40	98	98	8.6	7.7
Ticagrelor (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	0	-	-	
Oral anticoagulant (%)	-	-	-	-	-	-	-	-	28.8	27.2	-	-	-	-	-	-	4	4	94	85	7.5	12.9	
Diuretic (%)	-	-	-	-	26	34	-	-	43.7	42.1	-	-	-	-	-	-	-	-	-	-	35.5	42.4	
Insulin (%)	-	-	-	-	19	14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6.5	5.4	
Oral antidiabetic therapy (%)	-	-	-	-	16	17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	11.8	12.9	
Antidepressant therapy (%)	-	-	-	-	26	17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
MEDICATIONS AT DISCHARGE																							
Aspirin at discharge (%)	-	-	-	-	-	-	90.7	87	-	-	91.1	89.1	-	-	-	-	-	-	74	72	91.1	89.1	
P2Y12 inhibitor total at discharge (%)	-	-	-	-	-	-	89.6	94.4	-	-	88.9	88	-	-	-	-	-	-	-	-	88.9	88	
Clopidogrel at discharge (%)	-	-	-	-	-	-	46.3	53.1	-	-	-	-	-	-	-	-	-	-	65	77	-	-	
Ticagrelor at discharge (%)	-	-	-	-	-	-	42.8	41.1	-	-	-	-	-	-	-	-	-	-	10	0	-	-	
Prasugrel at discharge (%)	-	-	-	-	-	-	0.5	0.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Anticoagulant at discharge (%)	-	-	-	-	-	-	22.6	24	-	-	10.3	16.7	-	-	-	-	-	-	-	-	10.3	16.7	
Lipid lowering therapy at discharge (%)	-	-	-	-	-	-	90.7	90.3	-	-	79.8	81.3	-	-	-	-	-	-	82	93	79.8	81.3	

** The study G Richard et al., 2004 did not report the baseline for the invasive and conservative groups separately

Supplementary Table 4. Risk of Bias Assessment Table:

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of the reported result	the Overall risk of bias
de Belder et al., 2021	Low	Low	Low	Low	Low	Low
Sanchis et al., 2016	Low	Some concerns	Low	Low	Low	Some concerns
Savonitto et al., 2012	Low	Low	Low	Low	Low	Low
Berg et al., 2023	Low	Some concerns	Low	Low	Low	Some concerns
Sanchis et al., 2024	Low	Low	Low	Low	Low	Low
Hirlekar et al., 2020	Low	Low	Low	Low	Low	Low
Kunadian et al., 2024	Low	Low	Low	Low	Low	Low
G Ilan et al., 2002	Some concerns	Low	Some concerns	Low	Low	Some concern
G Richard et al., 2004	Low	Some concerns	Low	Low	Low	Low
Zhang et al., 2006	Low	Some concerns	Low Some concerns	Some concerns	Low	Some concerns Some concerns
Lee et al., 2019	Low	Some concerns	Some concerns	Low	Low	Some concerns

Supplementary Table 5. GRADE assessment of the included outcomes

Outcomes	No of patients, No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Effect Measure	Absolute Risk Difference per 1000 patients	Certainty
All-cause Death	4251, 10 RCTs	Not Serious	Not Serious	Not Serious	Not Serious	Undetected	RR: 1.04 (95% CI: 0.98 to 1.10)	12 per 1000 patients (95% CI: 6 fewer to 29 more deaths)	⊕⊕⊕⊕ ⊕ High
MI	2641, 8 RCTs	Not Serious	Not Serious	Not Serious	Not Serious	Undetected	RR: 0.79 (95% CI: 0.67 to 0.92)	44 fewer per 1000 patients (95% CI: 17 to 69 fewer MI)	⊕⊕⊕⊕ ⊕ High
Major Bleeding	3299, 7 RCTs	Not Serious	Not Serious	Not Serious	Not Serious	Undetected	RR: 1.67 (95% CI: 1.08 to 2.59)	34 more per 1000 patients (95% CI: 4 to 81 more bleeds)	⊕⊕⊕⊕ ⊕ High
Coronary Artery Revascularization	3229, 9 RCTs	Not Serious	Not Serious	Not Serious	Not Serious	Undetected	RR: 0.39 (95% CI: 0.27 to 0.56)	99 fewer per 1000 patients (95% CI: 71 to 118 fewer revascularizations)	⊕⊕⊕⊕ ⊕ High
Stroke	3471, 7 RCTs	Not Serious	Not Serious	Not Serious	Not Serious	Undetected	RR: 0.97 (95% CI: 0.72 to 1.32)	1 fewer per 1000 patients (95% CI: 13 fewer to 14 more strokes)	⊕⊕⊕⊕ ⊕ High
MACE	952, 4 RCTs	Not Serious	Serious	Not Serious	Serious	Undetected	RR: 1.11 (95% CI: 0.79 to 1.56)	70 more per 1000 patients (95% CI: 134 fewer to 358 more events)	⊕⊕⊕⊕ ○ Moderate
MACCE	246, 2 RCTs	Not Serious	Not Serious	Not Serious	Serious	Undetected	OR: 0.88	29 fewer per 1000 patients	⊕⊕⊕○ ○ Low

us

(95%
CI: (95% CI: 134
0.52 fewer to 94
to more events)
1.48)
