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REVIEW

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

Abu Huraira Bin Gulzar,[1] Mirza Ammar Arshad,[2] Bakhtawara Alam,[3] Syed Sarmad Javaid,[4] Hafsa Azam,[5] Fausto J. Pinto,[6] Evangelos Giannitsis[7]

[1]Department of Medicine, Services Institute of Medical Sciences, Lahore, Punjab, Pakistan; [2]Department of Medicine, Rahbar Medical and Dental College, Lahore, Punjab, Pakistan; [3]Department of Medicine, Rehman Medical College, Peshawar, Pakistan; [4]Department of Medicine, The University of Mississippi Medical Center, Jackson, MS, USA; [5]Department of Medicine, Jinnah Sindh Medical University, Karachi, Sindh, Pakistan; [6]Department of Cardiology, University of Lisbon, Lisbon, Portugal; [7]Department of Internal Medicine III, Cardiology, University Hospital of Heidelberg, Germany

Abstract

Acute coronary syndrome (ACS) disproportionately affects older adults, who face higher risks of mortality and complications due to frailty and comorbidities. Whether an early invasive strategy improves outcomes compared with conservative medical therapy in adults aged ≥65 years remains uncertain. Thus, we aimed to compare the efficacy and safety of early invasive therapy versus conservative medical management in older adults with ACS. We systematically searched PubMed, Embase, and Cochrane CENTRAL from inception to January 2026 for trials enrolling adults aged ≥65 years with ACS. The primary outcome was all-cause mortality, while secondary outcomes included recurrent myocardial infarction (MI), coronary revascularization, stroke, major bleeding, major adverse cardiovascular events (MACE), and major adverse cardiac and cerebrovascular events (MACCE). Risk ratios (RRs) were pooled using random-effects models, with heterogeneity assessed by the I^2 statistic. Additionally, cumulative meta-analyses were performed to examine trends over time. Eleven trials comprising 4251 patients were included. Most participants were aged >70 years, predominantly male, and primarily presented with non-ST-elevation myocardial infarction. Follow-up ranged from 6 months to 5 years. Early invasive therapy did not reduce all-cause mortality compared with conservative management (RR 1.04, 95% CI 0.98-1.10; p=0.19). However, it significantly reduced recurrent MI (RR 0.74, 95% CI 0.64-0.86; p<0.001) and coronary revascularization (RR 0.39, 95% CI 0.27-0.56; p<0.001). Major bleeding was increased with the invasive strategy (RR 1.67, 95% CI 1.08-2.59; p=0.02), while stroke rates were similar (RR 0.97, 95% CI 0.72-1.32; p=0.87). No significant differences were observed for MACE (RR 1.11, 95% CI 0.79-1.56; p=0.57) or MACCE (RR 0.92, 95% CI 0.65-1.29; p=0.62). Cumulative meta-analysis demonstrated stable effect estimates over time with no mortality benefit. In older adults with ACS, an early invasive strategy does not improve survival but reduces recurrent MI and subsequent revascularization while increasing major bleeding risk. These findings support individualized treatment decisions based on ischemic risk, bleeding risk, frailty, comorbidity burden, and patient preference rather than chronological age alone.

Key words: acute coronary syndrome; older adults; elderly; early invasive strategy.

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**Correspondence to: Abu Huraira Bin Gulzar, Services Institute of Medical Sciences, Ghaus-ul-Azam (Jail Road), Shadman 1, Lahore, Punjab 54000, Pakistan.*
E-mail: abu.huraira.bin.gulzar@gmail.com

Introduction

Acute coronary syndrome (ACS) is a major form of coronary heart disease, encompassing ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina.[1] ACS affects both younger and older adults; however, with advancing age and comorbidities, older individuals experience higher prevalence and more severe clinical consequences.[2] Nearly half of ACS cases occur in people aged ≥65 years,[3] making this population particularly vul-

nerable to adverse outcomes, including increased mortality and complications. Understanding optimal management strategies for older adults with ACS is therefore of significant clinical importance.

Current evidence regarding the management of ACS in older adults remains conflicting. Observational studies suggest that early invasive intervention may reduce the risk of death and recurrent myocardial infarction (MI).[4-6] However, recent randomized trials have challenged these findings. The After Eighty Study, with a mean follow-up of nearly five years, found that early invasive intervention did not significantly decrease the risk of death or major adverse cardiovascular events (MACE).[7] Similarly, the SENIOR-RITA trial, published in 2024, reported no significant reduction in cardiovascular death or nonfatal MI over four years of follow-up.[8]

Several recent meta-analyses have evaluated invasive *versus* conservative management in older adults with ACS or NSTE ACS, and their conclusions have generally shown a similar pattern: invasive therapy reduces recurrent MI and revascularization but does not clearly improve survival and may increase bleeding risk. However, most prior reviews mainly reported final pooled estimates. They did not clearly show how the evidence changed over time, when the mortality estimate became stable, or whether large contemporary trials changed the direction, magnitude, or precision of treatment effects. This gap is clinically important because physicians need to know whether newer trials shifted the prior evidence or only made the existing conclusion more precise. Therefore, we conducted an updated systematic review and meta-analysis of RCTs comparing early invasive *versus* conservative therapy in older adults with ACS. In addition to estimating pooled efficacy and safety outcomes, we performed cumulative meta-analysis by year of study publication to assess how the evidence evolved over time for mortality, recurrent MI, coronary revascularization, major bleeding, MACE, and MACCE.

Materials and Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] Institutional Review Board approval was not required, as the study involved previously published data from publicly accessible sources.

Search strategy and study selection

We systematically searched five databases, including ClinicalTrials.gov, Cochrane CENTRAL, PubMed, EMBASE, and Scopus, using a comprehensive strategy to identify studies from inception until January 2026. The search combined Medical Subject Headings (MeSH) terms and keywords such as adults, older adults, acute coronary syndrome, and unstable angina, connected with Boolean operators. The full search strings for each database are provided in Supplementary Table S1.

Study inclusion and selection criteria

We included studies enrolling adults aged 65 years or older who had experienced ACS. The intervention of interest was an invasive procedure, including coronary angiography, percutaneous coronary intervention (PCI), revascularization, or coronary artery bypass grafting (CABG). The comparator was conservative management consisting of guideline-directed medical therapy, including antiplatelet agents, β-blockers, ACE inhibitors, nitrates, and statins, unless contraindicated. Only studies reporting prespecified outcomes, either primary or secondary, were considered. There were no language restrictions.

Studies were excluded if the population was younger than 65 years. We also excluded studies with designs other than randomized controlled trials (RCTs), including observational studies (retrospective or prospective), cohort studies, case-control studies, case series, case reports, conference abstracts, editorials, and commentaries.

Outcomes

The primary outcome of this study was all-cause mortality. Secondary outcomes included recurrent MI, major bleeding, coronary revascularization, stroke, MACE, and major adverse cardiac and cerebrovascular events (MACCE).

Data extraction

Two reviewers independently screened titles and abstracts and assessed full-text articles for eligibility according to the predefined inclusion and exclusion criteria (AHBG and MAA). Discrepancies were resolved by consulting a third reviewer to provide an independent assessment (SSJ). From the included studies, the following data were extracted: country, inclusion criteria, participants, intervention, timing of intervention, comparator, outcomes, follow-up months, complete revascularization, crossover from conservative to invasive strategy.

Data synthesis and statistical analysis

Effect sizes for each study were estimated as risk ratios (RRs) comparing the early invasive and conservative groups. Hazard ratios were not pooled due to inconsistent reporting across studies. RRs were calculated by dividing the event risk in the invasive group by the event risk in the conservative group. Each study's effect was analyzed on the natural logarithm scale, and within-study variance was computed from the reported event counts. Between-study heterogeneity was estimated using the restricted maximum likelihood method, and summary effects were obtained via inverse-variance weighting. A random-effects model was applied to account for variation in treatment effects across studies.[10,11] Statistical heterogeneity was assessed using Cochrane's Q test, and the I^2 statistic was used to quantify the degree of heterogeneity, with I^2<25% considered low, 25-50% moderate, and >50% high. Given the low heterogeneity across

pooled outcomes, Wald statistics were used to construct 95% confidence intervals (CIs).

Cumulative meta-analysis was conducted to examine the stability of effect estimates over time.[12] Outcomes were pooled sequentially in chronological order to evaluate consistency in the direction of effects, their magnitude, and the width of confidence intervals. Two-sided p<0.05 was considered statistically significant.

Leave-one-out sensitivity analyses were performed for outcomes exhibiting high heterogeneity to identify studies contributing disproportionately to variability in the pooled estimates.[13] The certainty of evidence for each outcome was assessed using the GRADE approach, evaluating five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[14]

All data were pooled using RevMan Web.[15] Cumulative meta-analyses, Egger's regression tests for small-study effects, and all associated plots were implemented programmatically in Python (v3.1) using the pandas, NumPy, matplotlib, and math libraries.

Risk of bias assessment

The Cochrane Risk of Bias tool was used to assess methodological rigor of the included studies.[16,17] This tool assesses bias across the following domains: randomization, deviations from interventions, missing outcome data, measurement of the outcome, and selection of reported results.

Publication bias

We evaluated publication bias using both visual and statistical methods. Funnel plots were used to display their effect sizes against their standard errors. A symmetric funnel suggests the absence of small-study effects, while asymmetry indicates possible publication bias. Furthermore, Egger's regression test was conducted, which statistically tests for funnel plot asymmetry by regressing the effect size on its standard error. A significant intercept indicates potential publication bias. In this study, non-significant intercepts supported the absence of bias (Supplementary Figures S6–13 and Supplementary Table S2).

Results

Search results and study attributes

The systematic search identified relevant studies comparing an early invasive *versus* conservative strategy in older adults with ACS. After removal of duplicates and screening of titles and abstracts, full-text articles were assessed for eligibility. A total of 11 RCTs met the inclusion criteria and were included in the final analysis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Across the included trials, most participants were aged >70 years and predominantly presented with NSTEMI. Only three studies enrolled patients with STEMI presenting within 12 hours of symptom onset. Sample sizes ranged from 60 to 1518 participants, with a higher proportion of men than women. The majority of studies included frail older adults with significant comorbidities, including prior CABG, anemia, cognitive impairment, and renal dysfunction. Follow-up duration varied from 6 months to 5 years (Table 1, Supplementary Table S3).

Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Overall methodological quality was high, with most trials judged to be at low risk of bias. Five studies were rated as having some concerns, primarily related to deviations from intended interventions or aspects of the randomization process. No study was considered at high overall risk of bias. Detailed assessments are provided in Supplementary Table S4.

Results of the meta-analysis

Risk of all-cause mortality

Eleven studies evaluated all-cause mortality in older adults with ACS. Pooled analysis showed no significant difference in the risk of all-cause mortality between early invasive and conservative strategies (RR: 1.04; 95% CI: 0.98-1.10; I^2=0%; p=0.19) (Figure 2).

Risk of recurrent myocardial infarction

Eleven studies evaluated recurrent MI in older adults with ACS. Pooled analysis demonstrated a significant reduction in the risk of recurrent MI with early invasive therapy compared with conservative management (RR: 0.74; 95% CI: 0.64-0.86; I^2=0%; p<0.0001) (Figure 3).

Risk of major bleeding

Eight studies evaluated major bleeding events in older adults with ACS receiving early invasive *versus* conservative therapy. Pooled analysis showed that early invasive therapy was associated with an increased risk of major bleeding compared to conservative therapy (RR: 1.67; 95% CI: 1.08-2.59; I^2=28%; p=0.02) (Figure 4).

Risk of coronary revascularization

Nine studies evaluated rates of coronary revascularization. Pooled analysis demonstrated that early invasive therapy significantly reduced the risk of revascularization compared with conservative management (RR: 0.39; 95% CI: 0.27-0.56; I^2=39%; p<0.01) (Figure 5).

Risk of stroke

Eight studies evaluated stroke outcomes. Pooled analysis demonstrated no significant difference between early invasive and conservative strategies (RR: 0.97; 95% CI: 0.72-1.32; I^2=0%; p=0.81) (Figure 6).

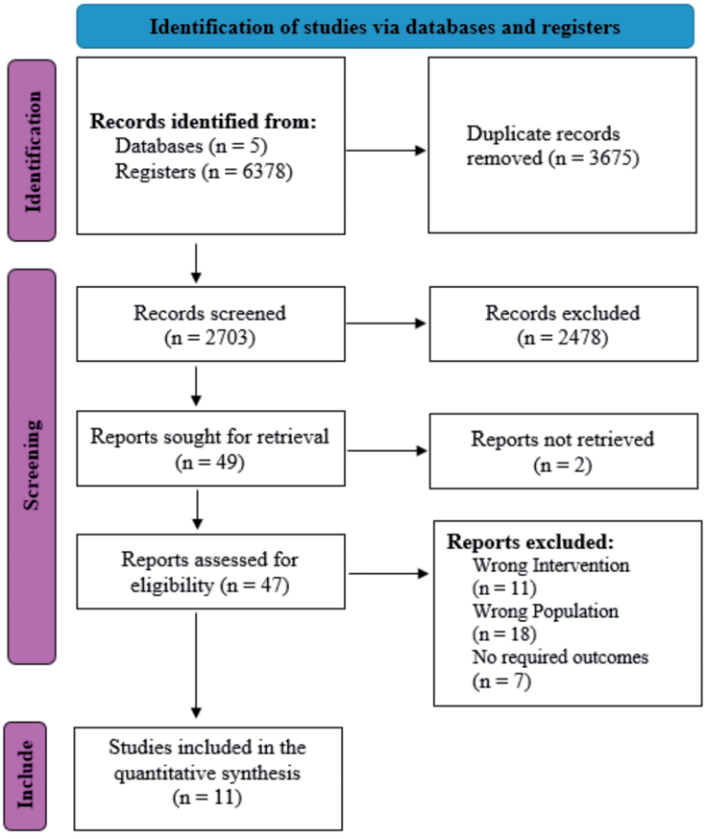
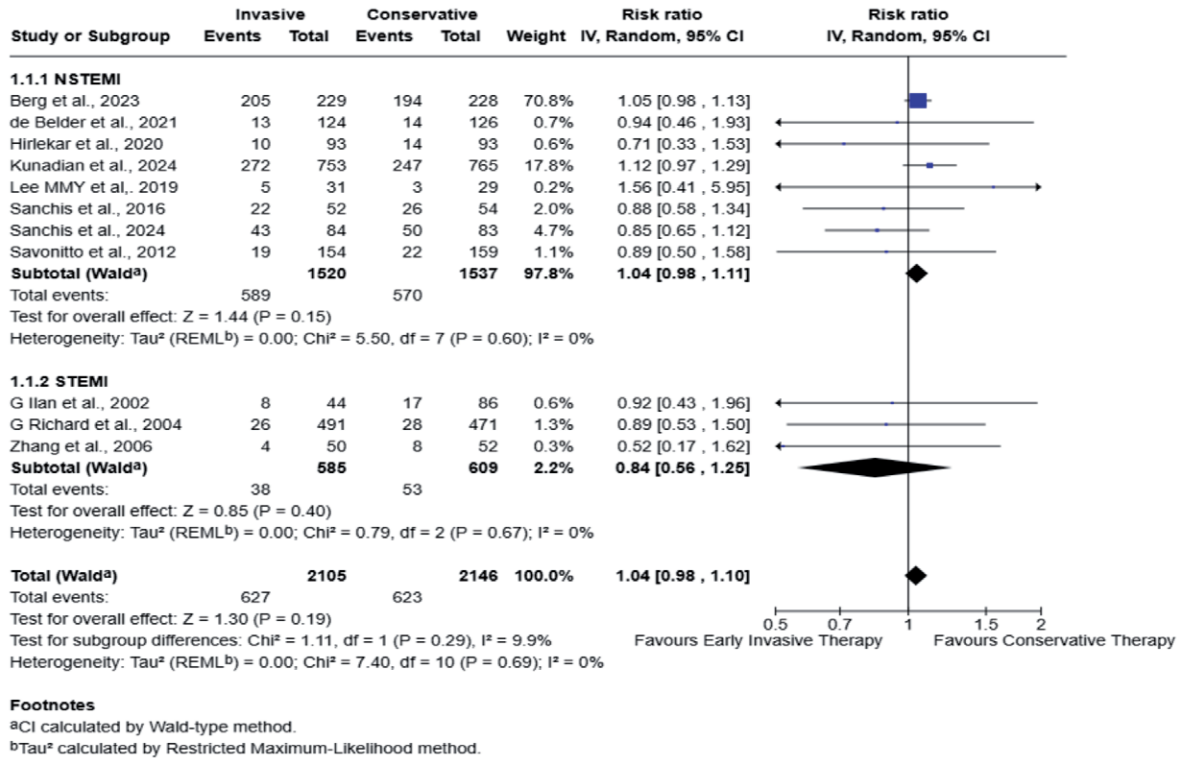


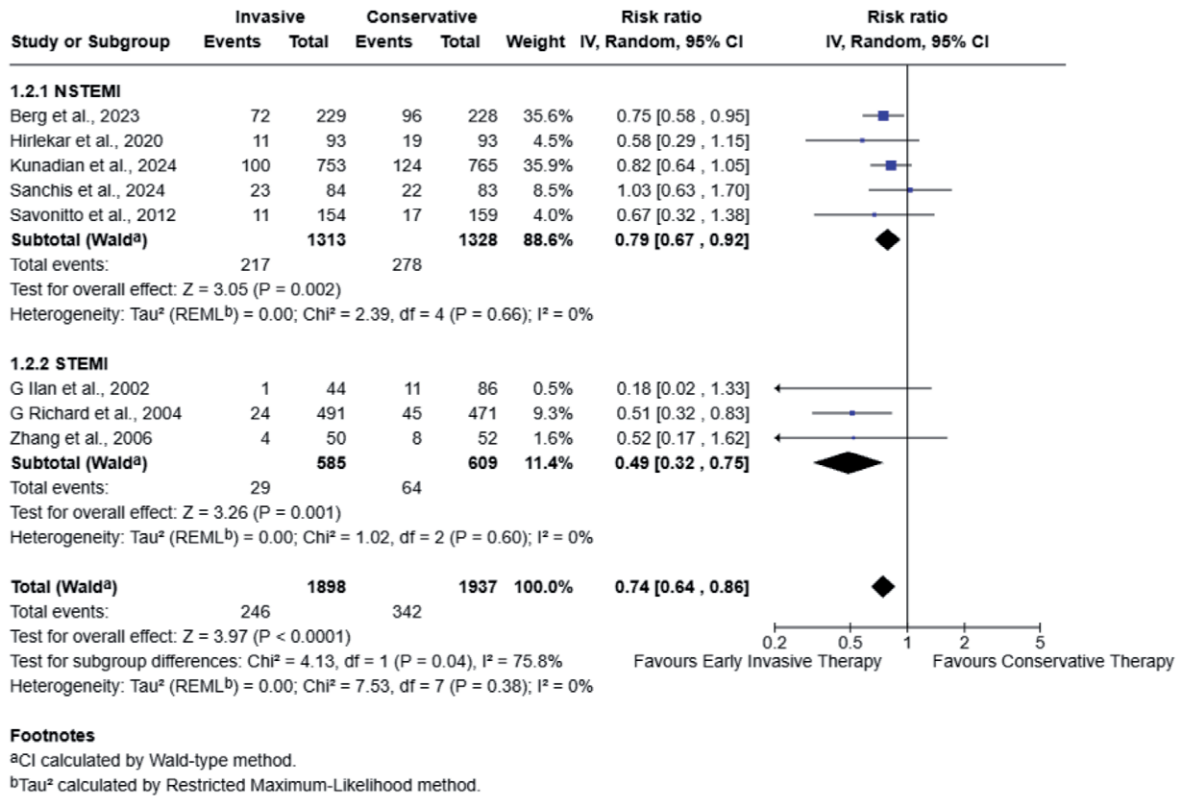
Figure 1. PRISMA flow diagram illustrating study identification and selection.



Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk ratio IV, Random, 95% CI
1.1.1 NSTEMI						
Berg et al., 2023	205	229	194	228	70.8%	1.05 [0.98 , 1.13]
de Belder et al., 2021	13	124	14	126	0.7%	0.94 [0.46 , 1.93]
Hirlekar et al., 2020	10	93	14	93	0.6%	0.71 [0.33 , 1.53]
Kunadian et al., 2024	272	753	247	765	17.8%	1.12 [0.97 , 1.29]
Lee MMY et al,. 2019	5	31	3	29	0.2%	1.56 [0.41 , 5.95]
Sanchis et al., 2016	22	52	26	54	2.0%	0.88 [0.58 , 1.34]
Sanchis et al., 2024	43	84	50	83	4.7%	0.85 [0.65 , 1.12]
Savonitto et al., 2012	19	154	22	159	1.1%	0.89 [0.50 , 1.58]
Subtotal (Wald[a])		**1520**		**1537**	**97.8%**	**1.04 [0.98 , 1.11]**
Total events:	589		570			
Test for overall effect: Z = 1.44 (P = 0.15)						
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 5.50, df = 7 (P = 0.60); I² = 0%						
1.1.2 STEMI						
G Ilan et al., 2002	8	44	17	86	0.6%	0.92 [0.43 , 1.96]
G Richard et al., 2004	26	491	28	471	1.3%	0.89 [0.53 , 1.50]
Zhang et al., 2006	4	50	8	52	0.3%	0.52 [0.17 , 1.62]
Subtotal (Wald[a])		**585**		**609**	**2.2%**	**0.84 [0.56 , 1.25]**
Total events:	38		53			
Test for overall effect: Z = 0.85 (P = 0.40)						
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.79, df = 2 (P = 0.67); I² = 0%						
Total (Wald[a])		**2105**		**2146**	**100.0%**	**1.04 [0.98 , 1.10]**
Total events:	627		623			
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Chi² = 1.11, df = 1 (P = 0.29), I² = 9.9%						
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 7.40, df = 10 (P = 0.69); I² = 0%						

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Figure 2. All-cause mortality in older adults with acute coronary syndrome, comparing early invasive vs conservative therapy.

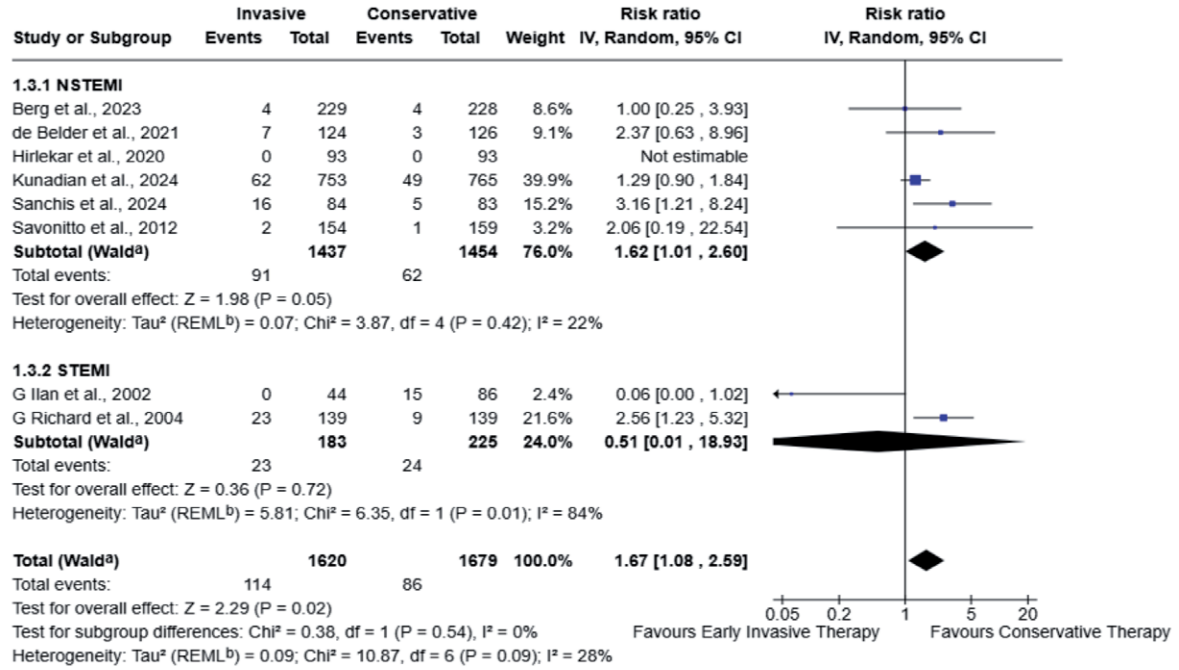


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Figure 3. Recurrent myocardial infarction in older adults with acute coronary syndrome, comparing early invasive *vs* conservative therapy.



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Figure 4. Major bleeding in older adults with acute coronary syndrome, comparing early invasive *vs* conservative therapy.

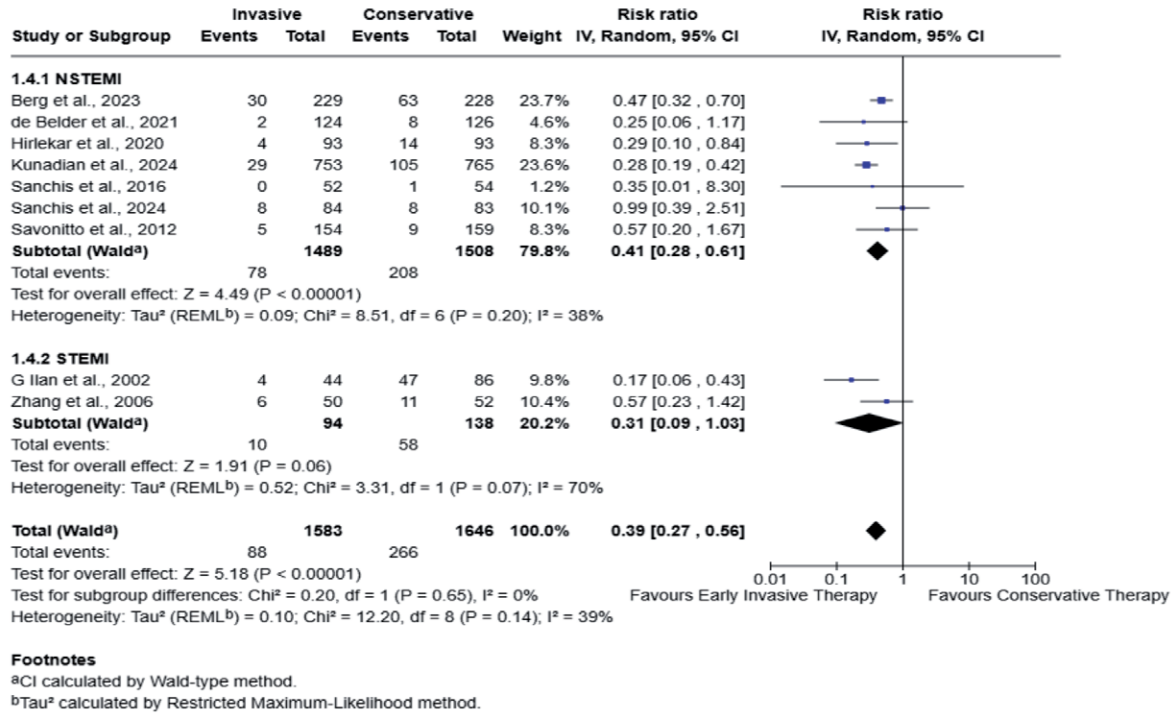


Figure 5. Coronary revascularization in older adults with acute coronary syndrome, comparing early invasive *vs* conservative therapy.

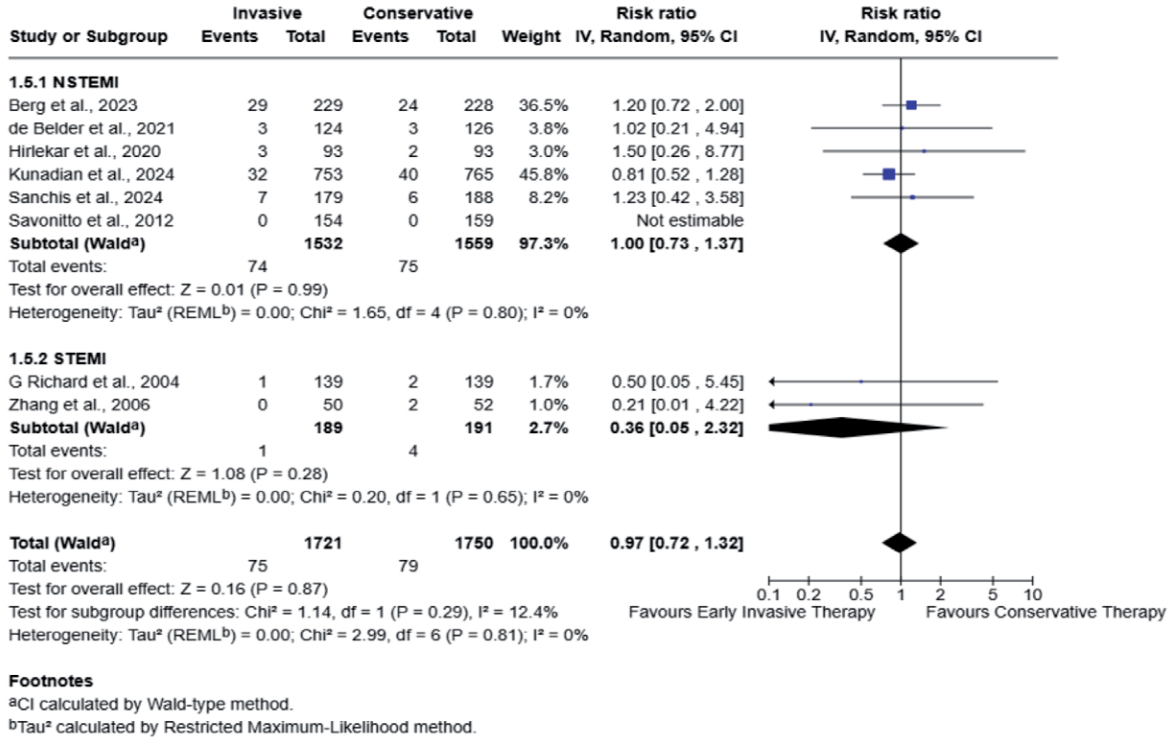


Figure 6. Risk of stroke in older adults with acute coronary syndrome, comparing early invasive and conservative therapy.

Table 1. Baseline characteristics of the included studies.

Source	Country	Inclusion criteria	Participants	Intervention	Timing of intervention	Comparator	Outcomes	Follow-up, months	Complete revascularization	Crossover from conservative to invasive strategy
Zhang *et al.*, 2006	China	Patients >75 years of age with STEMI presented within 12 hours of symptoms. STEMI was defined as ischemic chest discomfort with new or presumed new ST-segment elevation at the J point in two or more contiguous leads with the cut-off points ≥0.2 mV in leads V1, V2, or V3 and ≥ 0.1 mV in other leads, with or without elevation of cardiac enzymes.	102 Invasive = 50, Conservative = 52 Men = 57 Women = 45	Primary PCI group underwent immediate catheterization with IV heparin, balloon angioplasty and/or stent implantation for infarct-related artery (TIMI ≤2). Clopidogrel continued ≥3 months (BMS) or 9–12 months (DES); while aspirin was prescribed indefinitely.	Patients presenting within 12 hours of symptoms were transferred directly from the emergency room to the catheterization laboratory for primary PCI	Standard medical treatment with antiplatelet agents, ACE inhibitors, β-blockers, nitrates, and statins (if no contraindications)	Non-fatal MI, Stroke, Death, in-hospital stay, TVR, LVEF	12	After the index primary PCI, 60% of the patients undergo elective PCI for non-culprit artery	During the index hospital stay, about 78.8% of patients in the Conservative Group underwent elective revascularization
Savonitto *et al.*, 2012	Italy	Patients of 75 years with NSTE-ACS (presenting with cardiac ischemic symptoms at rest within 48 h before randomization, together with ischemic ECG changes and/or elevated levels of either troponin or CK-MB.	313 Invasive = 154 Conservative = 159 Men = 157 Women = 156	Early aggressive strategy: coronary angiography within 72 h, with PCI or CABG if indicated.	The early aggressive strategy mandated coronary angiography and, when indicated, revascularization within 72 hours (the actual median time observed was 24 hours from randomization)	Conservative therapy: medical management, with angiography allowed for refractory ischemia, reinfarction, ischemic heart failure, or malignant arrhythmias	Death, MI, Stroke, Major bleed, Repeat hospital stays because of; Severe recurrent ischemia, Heart Failure, Arrhythmias, Non-CNS embolism.	12	None	37 out of 159 underwent revascularization (23.3%), 46 out of 159 underwent coronary angiography (28.9%)
Sanchis *et al.*, 2024	Spain	Patients aged ≥70 years, NSTEMI with troponin elevation, and frailty (CFS ≥4)	167 Invasive= 84, Conservative= 83 Men = 79 Women = 88	Routine invasive strategy, consisting of coronary angiography within 72 hours of admission, with coronary revascularization if deemed appropriate.	Coronary angiography was performed within 72 hours of admission	Conservative strategy: medical therapy only, with catheterization allowed for recurrent ischemia; treatment per guidelines.	Death (cardiac, non-cardiac, and unknown causes), Readmission (cardiac and non-cardiac causes)	Median of 36.5 (IQR,14.5 to 47.2)	4 out of 83 in the conservative group (4.8%) 27 out of 84 in the invasive group (32.1%)	9 out of 83 in the conservative group crossed over to invasive treatment

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Table 1. Continued from previous page.

Source	Country	Inclusion criteria	Participants	Intervention	Timing of intervention	Comparator	Outcomes	Follow-up, months	Complete revascularization	Crossover from conservative to invasive strategy
Sanchis *et al*., 2016	Spain	NSTEMI (acute chest pain, non-STE ECG, troponin elevation); age ≥70 years; and ≥2 significant comorbidities: renal failure (GFR <45 ml/min/m²), neurological disease with residual deficit (Rankin >1), peripheral artery disease (ABI <0.9), dementia (≥3 errors in Pfeiffer's test), chronic pulmonary disease (FEV1 <50% or oxygen therapy), or anemia (Hb <11 g/dl).	106 Invasive = 52, Conservative = 54 Men = 56 Women = 50	The invasive management group received routine cardiac catheterization within 72 h of admission.	Routine cardiac catheterization was performed within 72 hours of admission	The conservative patients underwent only medical treatment, although cardiac catheterization was allowed in the case of poor in-hospital outcome due to recurrent ischemia or heart failure after admission, or in the case of a positive predischarge non-invasive stress test.	All-cause mortality, Reinfarction, Post-discharge revascularization, Readmission for AHF, Bleeding ≥ TIMI 2	Median of 30	None	5 out of 54 underwent revascularization (9.3%), whereas 11 out of 54 underwent coronary angiography (20.3%)
Lee 2019	United Kingdom	Unstable angina or NSTEMI; stabilized ≥12 h without recurrent chest pain/IV therapy; prior CABG.	60 Invasive= 31 Conservative= 29 Men = 43 Women = 17	Invasive group: early (≤72 h) native coronary + graft angiography; revascularization with PCI or CABG as appropriate.	Invasive management was performed early, defined as ≤72 hours wherever possible after hospital admission	Medical therapy: both groups received guideline-directed OMT (dual antiplatelet, antithrombotic, antianginal), with up-titration per investigator guidance and local/international protocols.	Primary outcome: post-randomization major adverse events (coprimary composites for efficacy and safety), comparing invasive vs conservative management. Primary efficacy: composite of all-cause death, rehospitalization for refractory ischemia/angina, MI, or HF (18-mo follow-up). Primary safety: bleeding (BARC 2–4), stroke, procedure-related MI (Type 4a), renal worsening/hemodialysis. Secondary: QoL (EQ-5D-5L, EQ-VAS at baseline + 6-mo intervals), CCS angina class, rehospitalization for refractory ischemia,	Median of 24	None	Only 1 participant crossed over to invasive management without percutaneous coronary intervention

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Table 1. Continued from previous page.

Source	Country	Inclusion criteria	Participants	Intervention	Timing of intervention	Comparator	Outcomes	Follow-up, months	Complete revascularization	Crossover from conservative to invasive strategy
							invasive management, coronary/CABG intervention during follow-up.			
Kunadian *et al.*, 2024	United Kingdom	Patients at least 75 years of age with NSTEMI. Frailty (Fried ≥3 or Rockwood ≥5), comorbidity (Charlson Index), and cognition (MoCA <26 impaired) were evaluated.	1518 Invasive= 753, Conservative= 765 Men = 839 Women = 679	Invasive group: coronary angiography ± PCI/CABG within 3–7 days plus optimal medical therapy; conservative group: medical therapy, angiography only if clinical deterioration.	The median time to coronary angiography was 3 days from randomization, and subsequent coronary revascularization was performed within 3-7 days where feasible	Optimal medical therapy: aspirin 75 mg daily, P2Y12 antagonist, statin, β-blocker (HR 60–70 bpm), ACE inhibitor/ARB; hypertension, diabetes, and hypercholesterolemia managed per guidelines.	The primary outcome was time to cardiovascular death or non-fatal myocardial infarction, while secondary outcomes included all-cause death or myocardial infarction, all-cause death, cardiovascular death, non-cardiovascular death, recurrent myocardial infarction, subsequent coronary angiography or revascularization, hospitalization for heart failure, stroke, transient ischemic attack, and bleeding as defined by BARC criteria.	Median of 49.2	105 out of 351 (29.9%)	Coronary Angiography was performed for 185 patients (24.2%) in the Conservative Group with revascularization in about 105 patients (13.7%) in the same group
Hirlekar *et al.*, 2020	Sweden	Age ≥80; NSTE-ACS with chest pain >10 min in the past 72 h; ST-depression ≥1 mm or elevated troponin/CK-MB.	186 Invasive= 93, Conservative= 93 Men = 102 Women = 84	Invasive strategy: coronary angiography ± PCI/CABG plus optimal medical therapy.	Invasive treatment (coronary angiography and PCI/CABG) was performed during the index hospitalization	Conservative strategy: optimal medical therapy without routine angiography; angiography only if refractory symptoms/instability.	Primary outcome: first MACCE event within 12 months (MI, urgent revascularization, all-cause mortality, stroke, cardiac hospitalization); secondary outcomes: MACCE at 1 month, mortality, MI, death/MI at	12	31 out of 93 (33%)	4 out of 93 (4.3%) underwent coronary angiography and revascularization

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Table 1. Continued from previous page.

Source	Country	Inclusion criteria	Participants	Intervention	Timing of intervention	Comparator	Outcomes	Follow-up, months	Complete revascularization	Crossover from conservative to invasive strategy
Richard *et al.*, 2004	United States, Canada, Belgium, Germany, Italy, the Netherlands, Poland, Spain, and the United Kingdom	Patients aged ≥18 years, angina within 24 h (accelerating/prolonged ≥20 min or recurrent at rest/minimal effort), candidates for coronary revascularization, with ≥1 of: ST-depression ≥0.05 mV, transient ST-elevation ≥0.1 mV, T-wave inversion ≥0.3 mV in ≥2 leads, elevated cardiac markers, or documented coronary disease.	962 Invasive= 491, Conservative= 471 Men = 572 Women = 390	Patients in the early invasive group underwent coronary angiography within 4–48 h post-randomization, with revascularization performed when appropriate.	Patients were scheduled to undergo coronary angiography 4 to 48 hours after randomization	Conservative group: treated medically; if stable, underwent exercise tolerance test prior to discharge.	Primary endpoint: composite of death, non-fatal MI, and ACS rehospitalization at 6 months; analysis focused on death + non-fatal MI.	6	None	None
Ilan *et al.*, 2002	Israel	Patients ≥70 years from Greater Tel-Aviv with STEMI; symptom onset ≤12 h, ≥20 min chest pain, ST elevation ≥0.1 mV (limb leads) or ≥0.2 mV (precordial leads).	130 Invasive= 44, Conservative= 86 Men = 53 Women = 77	Primary angioplasty group: infarction-related artery targeted; stents routinely used unless TIMI III flow with minimal residual stenosis; adjunct heparin and optional abciximab; post-procedure aspirin, plus ticlopidine for 4 weeks if stented.	Patients underwent immediate primary angioplasty, with a median time to treatment (balloon inflation) of 240 minutes from symptom onset	Thrombolysis group: accelerated rt-PA (max 100 mg); rescue angioplasty if failed or angina; otherwise, stress-test guided catheterization during hospitalization or event-driven post-discharge.	Primary endpoint: composite of death, recurrent MI, or revascularization for recurrent ischemia at 6 months.	6	47 out of 61 in the conservative group (77.04%), 4 out of 9 in the invasive group (44.4%)	None
de Belder *et al.*, 2021	United Kingdom	Patients ≥80 years with NSTEMI (chest pain + ischemic ECG changes + troponin rise); cardiologist confirmed suitability for either intervention-guided or conservative strategy.	250 Invasive = 124, Conservative = 126 Men = 132 Women = 118	Invasive group: coronary angiography with FFR/iFR as needed; significant lesions treated by ad hoc PCI (2nd-gen DES) or CABG (arterial conduits); non-amenable anatomy managed with OMT; troponin measured at	The mean time from randomization to coronary angiography was 2 days (± 2 days)	OMT group: diagnostic angiography allowed only if ongoing chest pain, dynamic ECG changes, or further troponin rise.	Primary endpoint: all-cause mortality + non-fatal reinfarction at 1 year (reinfarction = chest pain + troponin >99th percentile; periprocedural MI = >20% troponin rise if baseline above ULN but stable/falling). Secondary endpoints: time to death/reinfarction,	12	None	11 out of 126 (8.7%) underwent coronary angiography, and 4 out of 126 (3.2%) underwent revascularization

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Table 1. Continued from previous page.

Source	Country	Inclusion criteria	Participants	Intervention	Timing of intervention	Comparator	Outcomes	Follow-up, months	Complete revascularization	Crossover from conservative to invasive strategy
				admission, pre-test, and 16–22 h post-procedure.			unplanned revascularization, stroke (>24 h deficit), major bleeding (BARC ≥3B), renal deterioration, angina burden (3 months & 1 yr), stent thrombosis (1 yr).			
Berg *et al.*, 2023	Norway	Patients ≥80 years with NSTE-ACS.	457 Invasive = 229, Conservative = 228 Men = 225 Women = 232	Early invasive strategy: next-day coronary angiography at Oslo University Hospital with ad hoc PCI/CABG/OMT; vs conservative strategy (OMT).	Patients underwent early coronary angiography the following day after their initial evaluation for study participation	Conservative group: received OMT in community hospitals; discharged unless reinfarction, refractory angina, malignant arrhythmias, or worsening heart failure prompted urgent angiography.	Primary endpoint: composite of MI, urgent revascularization, stroke, or death; adjudicated centrally with strict definitions (reinfarction = new symptoms + troponin rise >99th percentile; periprocedural MI = biomarker rise criteria; stroke = focal deficit >24 h).	Median of 63.6	None	None

STEMI; ST-elevation myocardial infarction, NSTEMI; non-ST-elevation myocardial infarction, MI; myocardial infarction, PCI; percutaneous coronary intervention, IV; intravenous, TIMI; Thrombolysis In Myocardial Infarction, BMS; bare-metal stent, DES; drug-eluting stent, TVR; target vessel revascularization, LVEF; left ventricular ejection fraction, ACE; angiotensin-converting enzyme, NSTE-ACS; non-ST-elevation acute coronary syndrome, ECG; electrocardiogram, CK-MB; creatine kinase-myocardial band, CABG; coronary artery bypass grafting, CNS; central nervous system, CFS; Clinical Frailty Scale, IQR; interquartile range, AHF; acute heart failure, GFR; glomerular filtration rate, ABI; ankle-brachial index, FEV1; forced expiratory volume in 1 second, Hb; hemoglobin, OMT; optimal medical therapy, QoL; quality of life, EQ-5D-5L; EuroQol 5-Dimension 5-Level, EQ-VAS; EuroQol Visual Analogue Scale, CCS; Canadian Cardiovascular Society, MoCA; Montreal Cognitive Assessment, BARC; Bleeding Academic Research Consortium, HR; heart rate, bpm; beats per minute, ARB; angiotensin receptor blocker, MACCE; major adverse cardiac and cerebrovascular events, ACS; acute coronary syndrome, rt-PA; recombinant tissue plasminogen activator, FFR; fractional flow reserve, iFR; instantaneous wave-free ratio, ULN; upper limit of normal.

Risk of major adverse cardiovascular events

Four studies evaluated MACE outcomes. Pooled analysis demonstrated no significant difference in the risk of MACE between early invasive and conservative strategies (RR: 1.11; 95% CI: 0.79-1.56; I^2=75%; p=0.57) (Figure 7).

Risk of major adverse cardiac and cerebrovascular events

Two studies evaluated MACCE outcomes. Pooled analysis showed no significant difference in the risk of MACCE between early invasive and conservative strategies (RR: 0.92; 95% CI: 0.65-1.29; I^2=0%; p=0.62) (Figure 8).

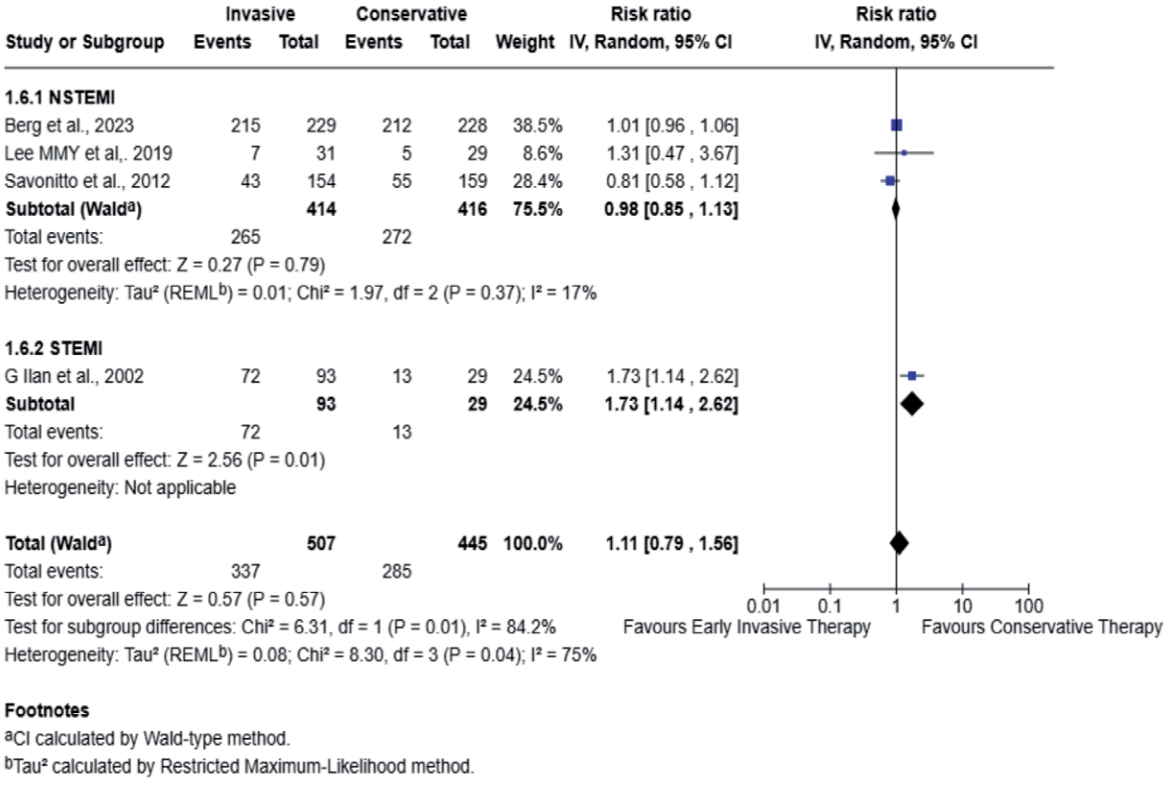

Figure 7. Risk of major adverse cardiovascular events in older adults with acute coronary syndrome, comparing early invasive and conservative therapy.

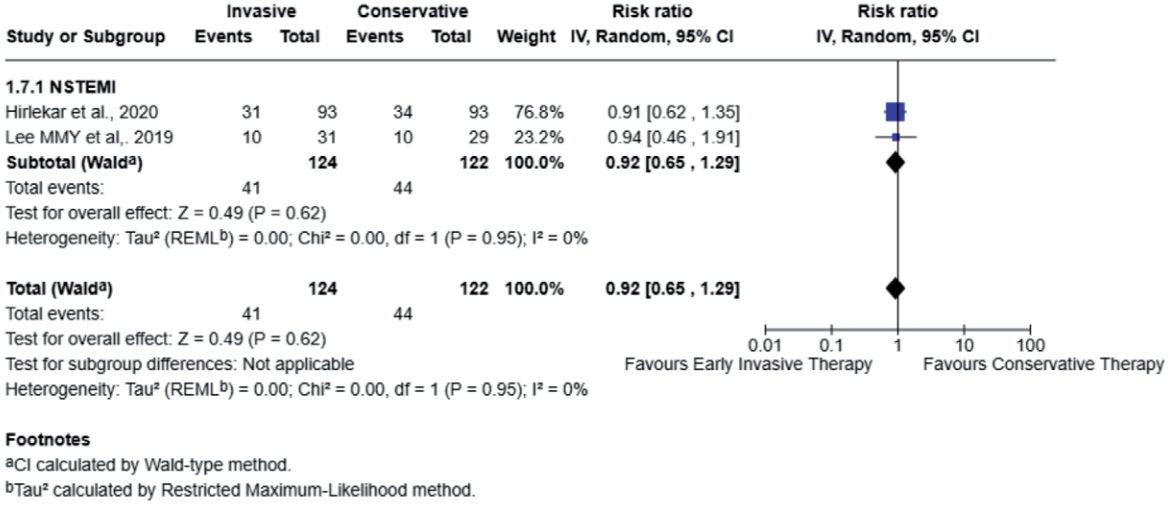

Figure 8. Risk of major adverse cardiac and cerebrovascular events in older adults with acute coronary syndrome, comparing early invasive and conservative therapy.

Results of cumulative meta-analysis

We performed a cumulative meta-analysis to assess early invasive *versus* conservative therapy across coronary revascularization, nonfatal MI, MACE, all-cause mortality, and major bleeding in patients with ACS. For coronary revascularization, cumulative estimates increasingly favored early invasive therapy as additional studies were incorporated, although statistical significance was not consistently maintained across sequential analyses. A similar directional trend was observed for nonfatal MI, with early invasive therapy remaining favorable throughout cumulative inclusion of studies. In contrast, the direction of effect for MACE shifted toward conservative therapy with increasing sample size, but without achieving statistical significance at any stage. For all-cause mortality, early cumulative analyses favored early invasive therapy; however, the effect estimate gradually moved toward conservative management once the cumulative population exceeded approximately 2500 participants, remaining non-significant throughout. Lastly, cumulative analysis of major bleeding demonstrated a consistent directional trend favoring conservative therapy, with no statistically significant overall effect observed (Supplementary Figures S1-5).

GRADE assessment

GRADE approach was used to assess the certainty of evidence for all the outcomes. Five domains were evaluated for each outcome, *i.e.*, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Risk of bias was not serious across the included trials because appropriate randomization, allocation concealment, and outcome assessment were done. Moreover, large contemporary trials contributed the most weight. Similarly, inconsistency was judged as not serious when heterogeneity was low and when effect estimates showed a consistent direction across the included studies. We judged indirectness as not serious because the populations, interventions, comparators, and outcomes closely matched the clinical question of early invasive *versus* conservative therapy in older adults with acute coronary syndromes. We downgraded the certainty for imprecision when CIs were wide or when the number of events was small. This issue mainly affected outcomes, including MACE and MACCE. We did not downgrade for publication bias because we observed no clear small-study effects. For outcomes with uncertainty around the true effect, we rated the certainty as moderate or low (Supplementary Table S5).

Discussion

In this meta-analysis of 11 RCTs involving 4251 older adults with ACS, an early invasive strategy was not associated with a reduction in all-cause mortality compared with a conservative approach. However, early invasive therapy significantly reduced the risk of recurrent MI and the need for subsequent coronary revascularization. These ischemic benefits were accompanied by a higher risk of major bleeding, while the incidence of stroke was similar between the two treatment arms. Overall, these findings highlight that in older adults, early invasive management primarily improves ischemic outcomes but does not improve survival, emphasizing the need for individualized decision-making that carefully balances the potential benefit in reducing recurrent events against the increased bleeding risk. This updated RCT-only synthesis extends prior evidence by incorporating contemporary long-term trial data and by using cumulative meta-analysis to evaluate whether treatment effects changed as evidence accrued. Its main incremental value is showing that the ischemic benefit of early invasive therapy remains consistent over time, while a durable survival benefit does not emerge.

Our results are largely consistent with previous studies. A recent study by Reddy *et al.*, including 3009 older adults found that early invasive therapy did not significantly reduce all-cause mortality (RR: 1.04; 95% CI: 0.98-1.11) but was associated with lower rates of MI (RR: 0.78), nonfatal MI (RR: 0.75), and revascularization (RR: 0.43).[18] Similarly, Rout *et al*. evaluated 2,429 patients aged ≥75 years and reported no significant improvement in all-cause mortality (OR: 0.84; p=0.30), cardiovascular death (OR: 0.85; p=0.30), stroke (OR: 0.74; p=0.39), or major bleeding (OR: 1.24; p=0.70).[19] Compared with prior reviews, our cumulative analysis adds temporal clarity by showing that the direction of effect remained stable as evidence accumulated: recurrent MI and revascularization continued to favor early invasive therapy, whereas mortality did not shift toward a durable survival advantage. This analysis was necessary because prior randomized trials and recent meta-analyses mainly reported the final pooled treatment effect. They did not clearly show how the evidence changed over time, when the mortality estimate became stable, or whether large contemporary trials changed the direction of benefit. This is important because clinicians need to know whether newer trials created a new signal or simply made the existing conclusion more precise. Our cumulative approach therefore adds context by showing the development of evidence rather than only the final summary estimate. In the cumulative analysis, the all cause mortality estimate remained close to null as evidence increased from 313 to 3057 participants, moving from RR 0.89 in 2012 to RR 1.04 after the 2024 data, with no heterogeneity. This pattern shows that newer trials increased precision but did not create a survival advantage for early invasive therapy. In contrast, nonfatal myocardial infarction showed a stable benefit after the Hirlekar *et al.* trial, with the estimate remaining significant through the final cumulative analysis. Coronary revascularization also showed an early and consistent benefit, becoming significant after the third accumulated study and remaining favorable after the addition of large contemporary trials. Major bleeding moved in the opposite direction, with the final cumulative estimate showing significantly higher risk with early invasive therapy. These results suggest that the evidence has matured toward a consistent

tradeoff: early invasive therapy reduces ischemic events and repeat revascularization, but this benefit does not translate into lower mortality and comes with higher bleeding risk. Evidence from large RCTs, including the SENIOR-RITA trial, further supports this pattern, with similar rates of cardiovascular death between treatment groups and significantly lower rates of nonfatal MI and revascularization in the early invasive group.[8] Similarly, the After Eighty Study demonstrated a reduction in MI and revascularization but no long-term mortality benefit.[7] Taken together, these data indicate that early invasive therapy in older adults consistently provides an ischemic benefit without translating into a survival advantage. The timing and definition of the early invasive strategy also varied across trials. STEMI trials generally evaluated immediate primary PCI within 12 hours of symptom onset, whereas most NSTEMI trials used coronary angiography within 72 hours, within 3-7 days, or during the index admission depending on the trial protocol. Therefore, *early invasive* should be interpreted as a broad invasive-management strategy rather than a single fixed procedural time window.

These findings differ from observational studies,[20,21] which have reported lower mortality in older patients with ACS initially managed with invasive strategies. This discrepancy may reflect differences in patient selection. Frail patients or those with multiple comorbidities are often less likely to receive invasive management in real-world practice. RCTs, in contrast, enroll patients according to prespecified criteria, reducing selection bias, although crossovers can occur when clinically necessary. Older adults frequently have chronic conditions such as diabetes, hypertension, atherosclerosis, or cancer, which can independently impact survival.[22-24] Consequently, while observational studies may suggest a mortality benefit of early invasive therapy, RCT evidence indicates that this apparent advantage diminishes over time, likely due to a combination of rigorous trial inclusion criteria and the high burden of comorbid disease in this population. This dissociation between fewer ischemic events and unchanged mortality may be explained by the fact that invasive therapy can treat flow-limiting coronary disease and reduce recurrent MI or urgent revascularization, but survival in older adults is also strongly influenced by frailty, renal dysfunction, bleeding, infection, heart failure, cancer, and other non-cardiovascular causes. As a result, reducing coronary ischemic events alone may not be sufficient to improve all-cause mortality in this population.

Additionally, guidelines recommend an individual approach. A clinician must base their decision upon the condition of the patient and is advised to follow a risk-stratification approach. Being aged does not exclude the person from an invasive strategy; however, factors like risk of ischemia, instability of the condition, comorbidities, and bleeding must be taken into consideration before coming to a conclusion.[25,26] In our analysis, older adults gained ischemic benefit from an invasive approach, but the final treatment decision should also account for frailty, bleeding risk, comorbidities, functional status, and patient preference.[27,28] We observed an increased risk of major bleeding with the invasive strategy, underscoring the American Heart Association's recommendation to assess bleeding risk in patients with ACS prior to treatment selection.[25,26] These findings do not contradict guideline-based care but rather support a more selective application of invasive therapy in older adults.[29] Current guidelines emphasize risk stratification, ischemic risk, clinical instability, comorbidity burden, frailty, and bleeding risk when choosing an invasive or conservative approach. Therefore, the present evidence supports individualized decision-making rather than routine invasive management for all older adults with ACS.

Future trials should move beyond all-cause mortality alone and evaluate frailty-guided invasive strategies that incorporate functional status, quality of life, independence, rehospitalization, bleeding, and patient-reported outcomes.[30,31] Stratification by frailty, cognitive impairment, renal function, and bleeding risk may help identify which older adults are most likely to benefit from invasive management. Focusing on frailty and quality of life can help define how outcomes like fewer ischemic events, reduction in MI burden, and lower frailty are transforming into the daily lives of the patients, *i.e.*, suggesting meaningful long-term benefits.[32]

Despite providing updated insights, this meta-analysis has several limitations that should be considered. First, there was clinical heterogeneity among the included populations, as frail participants differed in demographics, ACS subtypes, and comorbidities, which may have influenced outcomes.[33] In addition, the timing of invasive management varied across trials, ranging from immediate PCI in STEMI to angiography within 72 hours or several days in NSTEMI, which may limit the precision of interpreting *early invasive* therapy as a uniform intervention. Second, our analysis relied on aggregate data rather than individual participant data, potentially diluting smaller effects at the patient level.[34] Third, two large trials contributed disproportionately to the pooled estimates, which may have affected overall effect measures. Fourth, crossovers within some trials could introduce bias and attenuate long-term effects.[35] Finally, the REML method may underestimate between-study variance when pooling a small number of studies.

Conclusions

Early invasive therapy in older adults with ACS does not reduce all-cause mortality compared with conservative management. It provides short-term ischemic benefits by lowering the risk of recurrent MI and the need for coronary revascularization, but these benefits are accompanied by an increased risk of major bleeding. Cumulative evidence indicates that the reduction in ischemic events does not translate into long-term survival gains, particularly in frail patients with multiple comorbidities. Clinical management should therefore be guided by individualized assessment of ischemic and bleeding risk, frailty, and overall patient comorbidity rather than chronological age alone. These findings underscore the need for careful risk-benefit evaluation when considering early invasive strategies in older adults with ACS.

Ethical approval

Not applicable.

Availability of data and material

The data supporting the findings of this study are available from the corresponding author upon reasonable request

Conflict of interest

The authors declare no potential conflict of interest.

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Authors' contributions

AHBG, MAA, BA, SSJ, and HA contributed to the study conception, literature search, data collection, and initial drafting of the manuscript. AHBG contributed to data analysis, interpretation of results, and critical revision of the manuscript. AHBG, FJP, and EG contributed to study supervision, methodological guidance, and critical revision of the manuscript for important intellectual content. All authors contributed to manuscript writing, approved the final version, and agree to be accountable for all aspects of the work.

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Online supplementary material:

Supplementary Figure S1. Cumulative Meta-Analysis of Coronary Revascularization.

Supplementary Figure S2. Cumulative Meta-Analysis of Nonfatal MI.

Supplementary Figure S3. Cumulative Meta-Analysis of MACE.

Supplementary Figure S4. Cumulative Meta-Analysis of All-Cause Death.

Supplementary Figure S5. Cumulative Meta-Analysis of Major Bleeding.

Supplementary Figure S6. Funnel Plot All-cause Death (STEMI).

Supplementary Figure S7. Funnel Plot All-cause Death (NSTEMI).

Supplementary Figure S8. Funnel plot stroke (NSTEMI).

Supplementary Figure S9. Funnel plot major bleeding (NSTEMI).

Supplementary Figure S10. Funnel plot coronary artery revascularization (NSTEMI).

Supplementary Figure S11. Funnel plot nonfatal MI (NSTEMI).

Supplementary Figure S12. Funnel plot recurrent MI (NSTEMI).

Supplementary Figure S13. Funnel plot recurrent MI (STEMI).

Supplementary Table S1. Search Strategy used in PubMed and Embase.

Supplementary Table S2. Risk of Bias Assessment Table.

Supplementary Table S3. Baseline characteristics of the patients.

Supplementary Table S4. GRADE assessment of the included outcomes.

Supplementary Table S5. Egger's Test for detecting Publication Bias in the study outcomes.