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Invasive versus conservative strategies for non-ST-elevation acute coronary syndrome in the elderly: an updated systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Advances in managing non-ST-elevation acute coronary syndrome (NSTE-ACS) have yet to clarify the optimal treatment for elderly patients, whose complex health profiles and underrepresentation in trials add challenges to decision-making.

Methods We systematically searched PubMed, Embase, Web of Science, and Scopus for randomized controlled trials comparing invasive versus conservative strategies in elderly patients (≥ 70 years) with NSTE-ACS through October 2024. Co-primary outcomes were all-cause and cardiovascular mortalities, with secondary outcomes including myocardial infarction (MI), revascularization, stroke, decompensated heart failure, and bleeding events. Outcomes were analyzed using both risk ratios (RR) and hazard ratios (HR).

Results Analysis of 11 trials (4,114 patients) showed no significant differences in all-cause mortality (RR: 1.04, 95% CI: 0.98–1.11; HR: 1.10, 95% CI: 0.94–1.29) or cardiovascular mortality (RR: 0.98, 95% CI: 0.85–1.12; HR: 0.94, 95% CI: 0.73–1.20) between strategies. The invasive approach significantly reduced subsequent revascularization (RR: 0.41, 95% CI: 0.27–0.62; HR: 0.30, 95% CI: 0.19- 0.47; $p < 0.01$ in both analyses) and MI risk (RR: 0.75, 95% CI: 0.57–0.99, $p = 0.04$; HR: 0.64, 95% CI: 0.49–0.83, $p < 0.01$), though with some levels of heterogeneity in sensitivity analyses for MI. Stroke and heart failure outcomes were comparable between strategies. However, it significantly increased the risk of both composite major and minor bleeding risk (RR: 1.50, 95% CI: 1.02–2.20, $p = 0.04$) and major bleeding alone (RR: 1.92, 95% CI: 1.04–3.56, $p = 0.04$).

Conclusion In elderly patients with NSTE-ACS, an invasive strategy reduces revascularization needs and, potentially, MI risk without impacting survival, but at the cost of increased bleeding risk. This supports individualized treatment decisions based on patient-specific characteristics, particularly bleeding risk and geriatric factors.

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Keywords Elderly, Non-ST-Elevation Acute Coronary Syndrome, Invasive Strategy, Conservative Management, Meta-analysis

Introduction

The initial management of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) traditionally follows one of two pathways: a routine invasive strategy involving inpatient coronary angiography with potential revascularization, or a conservative strategy utilizing optimal medical therapy with selective angiography based on clinical indicators [1, 2]. While the routine invasive approach has demonstrated a reduction in composite ischemic events in the general population, its benefits must be weighed against increased risks of periprocedural complications and bleeding, particularly as it has not shown a clear mortality benefit in meta-analyses [3–7].

This risk–benefit balance becomes particularly crucial in older adults, who represent an increasing proportion of NSTE-ACS presentations and face unique challenges. These patients typically present with more complex coronary anatomy, greater comorbidity burden, and higher baseline risks for both adverse cardiovascular outcomes and procedural complications [8–11]. Despite these distinct characteristics, current guidelines largely extrapolate recommendations from younger populations, as elderly patients have been historically underrepresented in or excluded from major cardiovascular trials [1, 2, 12].

Earlier meta-analyses of studies focusing specifically on elderly patients predominantly suggest more favorable outcomes with an invasive strategy regarding reducing recurrent myocardial infarction (MI) and the need for urgent revascularization. However, the findings of these studies on mortality and bleeding events are inconsistent and inconclusive [13–17]. A recent individual patient data meta-analysis of 6 RCTs (1,479 patients) found lower rates of recurrent MI and urgent revascularization within the first year with an invasive strategy, though the composite of all-cause mortality and MI showed no difference between approaches [18]. The evidence base has recently expanded with new data, including a large open-label RCT enrolling 1,518 patients [19] and extended follow-up data from previously published trials [20, 21].

This expanding evidence landscape, coupled with persistent uncertainties, demands a fresh evaluation of management strategies for elderly NSTE-ACS patients. Our meta-analysis synthesizes this comprehensive dataset to provide contemporary guidance for this high-risk population, where optimal treatment selection remains a critical clinical challenge.

Methods

This systematic review and meta-analysis followed a prospectively registered protocol (PROSPERO: CRD42024609066) detailing our methodology, eligibility criteria, and outcomes of interest. We conducted and reported our analysis according to the Cochrane Handbook and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, respectively [22, 23].

Search strategy

We conducted a comprehensive literature search across four databases—PubMed, Embase, Web of Science, and Scopus—to identify RCTs or subanalysis of RCTs published up to October 1st, 2024, that evaluated initial management approaches in elderly (≥ 70 years old) patients with NSTE-ACS. Our search strategy combined MeSH terms and free-text keywords relevant to the research question, including terms related to invasive and conservative strategies, outcomes, and older populations. The detailed search syntax used for each database is provided in the Supplementary Materials.

Additionally, we manually searched the reference list of eligible articles and prior systematic reviews (i.e., backward citation tracking) and recent publications that have cited to the included studies (i.e., forward citation tracking) to ensure no eligible study has been missed.

Study selection and eligibility criteria

Two reviewers (E.K. and A.A.) independently screened the retrieved records with their titles and abstracts against the eligibility criteria. The full texts of potentially eligible records then were scrutinized by two investigators in duplicate. At each stage, any disagreements between the reviewers were firstly resolved through discussion and then by the adjudication of a third reviewer (A.H.) if consensus could not be reached. Only peer-reviewed, publicated RCTs or subanalyses of RCTs that investigated the comparative efficacy and safety of invasive versus conservative strategies in elderly patients with NSTE-ACS were included. Reviews, editorials, case reports, case series, conference papers, pre-proofs, preprints, and observational studies were excluded from the analysis.

The co-primary outcomes of interest were all-cause mortality and cardiovascular death. The secondary efficacy and safety outcomes included MI, stroke,

revascularization, decompensated heart failure, and bleeding events.

Data extraction

A standardized data extraction form was created to collect relevant details from each included study systematically. The two reviewers (A.G.J. and F.Y.) independently extracted data, including RCT name, first author name, publication year, study population characteristics (country, gender, comorbidities, and medical profile), incidence of all-cause mortality, cardiovascular/cardiac death, MI, revascularization, decompensated heart failure, and bleeding events in each study arm. Any discrepancies in extracted data were discussed to reach a consensus.

Risk of bias assessment

A.G.J. and E.H. evaluated the methodological quality of the research using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials [24]. This tool assesses bias across five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. Each domain was judged as "low risk of bias," "some concerns," or "high risk of bias," and an overall risk of bias judgment was assigned based on these domain-level assessments. Inconsistencies were addressed with the assistance of a third reviewer (A.H.). Publication bias was not assessed, as the number of included studies in each analysis did not exceed 10, rendering the results unreliable [25].

Statistical analysis

Our analysis employed two complementary statistical approaches. First, a random-effects model with the DerSimonian-Laird method was used to calculate risk ratios (RR) with corresponding 95% confidence intervals (CI) for the outcomes. For analyses including at least 5 studies, the 95% prediction intervals (PI) were also calculated to estimate the expected range of true effects in future studies. For this approach, sensitivity analyses were performed using the "leave-one-out" method to assess if omitting any of the included studies could change the results significantly. Also, a separate sensitivity analysis for bleeding outcomes was performed, including studies using TIMI bleeding definitions to address heterogeneity in bleeding outcomes. Additionally, we conducted a subgroup analysis of all outcomes for octogenarians ($\geq$80 years) and meta-regression analyses to explore the relationship between mean age and treatment effects. Second, we conducted time-to-event analyses using hazard ratios (HR) by combining data from two individual patient data meta-analyses by Kotanidis et al. and Damman et al. with a newly published large RCT (SENIOR-RITA by Kunadian et al.) [18, 26, 27]. The results of the studies were combined using the generic inverse variance method.

Effect estimates were considered statistically significant when p-value < 0.05, indicated by their respective 95% CI not encompassing the null value. Heterogeneity was quantified using I^2 statistics, with $I^2 > 50\%$ considered to represent significant heterogeneity. Tests for assessing the publication bias were not conducted since less than 10 studies were included for analysis.

All the analyses reported in this meta-analysis were undertaken in R Software version 4.3.2 using "meta" and "metafor" packages.

Results

A PRISMA flow diagram outlines the study selection process and results (Fig. 1). Our comprehensive database search identified 2941 records screened for duplicates, leaving 2224 studies for title/abstract review. We excluded 2158 papers at this stage as it was clear from the title and abstract that the topic or outcomes were irrelevant to this review or methodologically did not fit the eligibility criteria. The full texts of the remaining 66 articles were assessed for eligibility based on the predefined criteria. The details for excluded studies after reviewing full-texts are available in Table S1. Following a full-text review, 14 publications derived from 11 randomized controlled trials met the inclusion criteria for quantitative synthesis. These publications comprised: five independent trials specifically designed for elderly patients (represented by five publications) [26, 28–31], two dedicated elderly trials with both primary results and extended follow-up analyses (4 publications) [20, 21, 32, 33], one secondary analysis of elderly subgroup data from a general population trial (1 publication) [9], and one patient-level pooled analysis of elderly participants from three independent RCTs (FRISC II [34], RITA 3 [35], and ICTUS [36]) known collectively as FIR trials (1 publication) [27, 34–36].

Study characteristics

Study characteristics and patient population

Our systematic review identified 11 randomized controlled trials published between 2000 and 2024, enrolling a total of 4114 elderly patients with NSTE-ACS. The sample sizes varied considerably, from 106 patients in the MOSCA trial to 1,518 patients in the SENIOR-RITA trial [26, 30]. These trials were conducted across multiple European and North American countries. One noticeable variation among these RCTs is the age threshold defining "elderly," which ranged from $\geq$70 to $\geq$80 years. Three trials—After Eighty [33], the 80 + study [29], and RINCAL

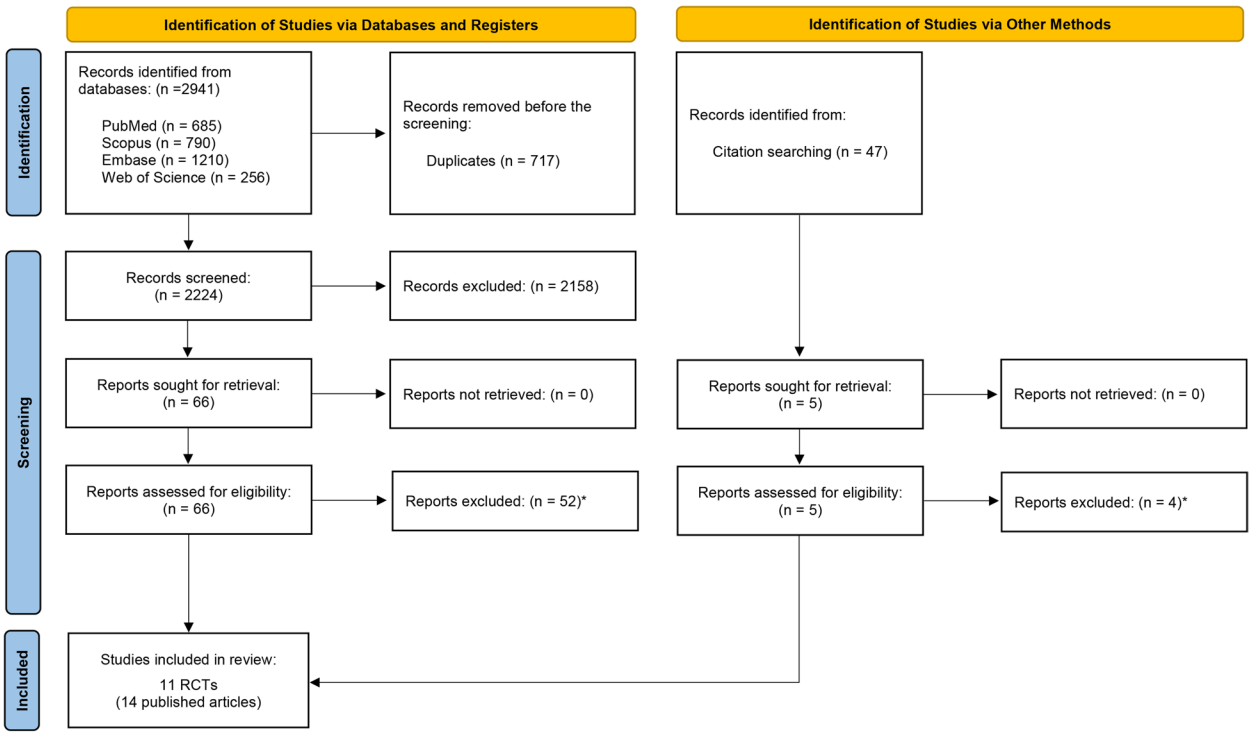

Fig. 1 Flow chart of study selection for inclusion in the systematic review and meta-analysis

[28]—specifically focused on octogenarians, while others employed lower age thresholds. Nevertheless, the approximate mean age of the total included population in this analysis is over 80 and provides a representative sample of elderly patients, enhancing the generalizability of our findings.

Cardiovascular risk profiles and comorbidities

As shown in Table 1, cardiovascular risk profiles and comorbidity patterns varied widely across studies. Hypertension prevalence ranged from 59% in the After Eighty study to 92% in the MOSCA-FRAIL trial. Diabetes mellitus prevalence showed similar variation, from 15% in FIR trials to 56% in MOSCA-FRAIL. Prior MI was common across studies (27–44%), with the highest rates in MOSCA and lowest in the RINCAL. Renal dysfunction prevalence ranged markedly, from 21% in SENIOR-RITA to 69% in the 80 + study. Atrial fibrillation prevalence showed moderate variability (13–27%), highest in MOSCA-FRAIL and lowest in the Italian Elderly ACS study. Previous revascularization rates also differed, with prior PCI ranging from 4 to 31% and CABG from 3 to 18%.

These differences in comorbidity profiles likely reflect variations in inclusion criteria and recruitment strategies across trials. While earlier trials, like TACTICS–TIMI 18 and FIR trials, employed broader inclusion criteria, more recent trials incorporated specific geriatric assessments [9, 27]. The MOSCA trial uniquely focused on patients with multiple comorbidities, requiring at least two major comorbidities for inclusion [30]. Notably, the MOSCA-FRAIL and SENIOR-RITA trials systematically assessed frailty, with SENIOR-RITA also evaluating cognitive function [26, 32].

Procedural characteristics and management strategies

Recent trials showed notable procedural advancements, particularly with increased radial access rates (> 80% in SENIOR-RITA and After Eighty), which may have influenced bleeding complications [26, 32].

As shown in Tables 2 and 3, the variability in the timing and approach to invasive management was also observed. The allowed delay in the timing of angiography in invasive arms ranged from a maximum of 48 h in the TACTICS–TIMI 18 trial [9] up to 7 days in SENIOR-RITA and FRISC II [26, 34], with most trials mandating 72 h limit. Revascularization rates in these arms spanned 50% to 62% of randomized patients. Conservative arms showed distinct differences in cross-over criteria for angiography, and all trials allowed for refractory

Table 1 Baseline characteristics of the final included studies

RCT Name	TACTICS–TIMI 18	FIR Trials	Italian Elderly ACS	MOSCA	After Eighty	80 + study	RINCAL	MOSCA-FRAIL	SENIOR-RITA
First Author, Year	Bach, 2004 [9]	Damman, 2012 [27]	Savonitto, 2012 [31]	Sanchis, 2016 [30]	Tgen, 2016 [33] Berg, 2023 [21]	Hirlekar, 2020 [29]	de Belder, 2021 [28]	Sanchis, 2023 [32] Sanchis, 2024 [20]	Kunadian, 2024 [26]
Region/ Country	Multinational (Nine countries in North America and Europe)	**FRISC II**: Sweden **ICTUS**: Netherlands **RITA-3**: United Kingdom	Italy	Spain	Norway	Sweden	United Kingdom	Spain	United Kingdom
Study Population, N *(Invasive / Conservative)*	278 (139 / 139) NSTE-ACS	839 (437 / 402) NSTE-ACS	313 (154 / 159) NSTE-ACS	106 (52 / 54) NSTEMI	457 (229 / 228) NSTE-ACS	186 (229 / 228) NSTE-ACS	250 (229 / 228) NSTEMI	167 (84 / 83) NSTEMI	1518 (753 / 765) NSTE-ACS
Age Range	Subgroup of ≥ 75 years	Subgroup of ≥ 75 years	≥ 75 years	≥ 70 years	≥ 80 years	≥ 80 years	≥ 80 years	≥ 70 years	≥ 75 years
Female, % *(Invasive / conservative)* *	NS *(NS / NS)*	37 *(NS / NS)*	49 *(51 / 49)*	47 *(44 / 50)*	51 *(45 / 56)*	45 *(49 / 41)*	47 *(48 / 46)*	53 *(62 / 43)*	45 *(45 / 45)*
Hypertension, % *(Invasive / conservative)* *	NS *(NS / NS)*	39 *(NS / NS)*	82.7 *(88 / 77)*	89 *(94 / 85)*	59 *(57 / 61)*	61 *(59 / 63)*	68 *(70 / 66)*	92 *(92 / 92)*	65 *(65 / 65)*
Diabetes mellitus, % *(Invasive / conservative)* *	NS *(NS / NS)*	15 *(NS / NS)*	36 *(36 / 37)*	46 *(46 / 46)*	17 *(20 / 14)*	19 *(17 / 22)*	21 *(27 / 15)*	56 *(60 / 52)*	31 *(31 / 31)*
Dyslipidemia, % *(Invasive / conservative)* *	NS *(NS / NS)*	16 *(NS / NS)*	44 *(42 / 45)*	69 *(75 / 63)*	NS *(NS / NS)*	20 *(23 / 17)*	NS *(NS / NS)*	77 *(75 / 78)*	31 *(32 / 30)*
Current smoker, % *(Invasive / conservative)* *	NS *(NS / NS)*	12 *(NS / NS)*	NS *(NS / NS)*	6 *(8 / 4)*	9 *(8 / 9)*	3 *(2 / 3)*	6 *(8 / 3)*	3 *(4 / 2)*	5 *(5 / 6)*
Histoy of prior MI, % *(Invasive / conservative)* *	NS *(NS / NS)*	33 *(NS / NS)*	40 *(28 / 34)*	44 *(46 / 43)*	43 *(47 / 39)*	34 *(32 / 38)*	28 *(27 / 29)*	31 *(23 / 39)*	31 *(33 / 30)*
Previous PCI, % *(Invasive / conservative)* *	NS *(NS / NS)*	36 *(NS / NS)*	15 *(10 / 20)*	20 *(23 / 17)*	22 *(24 / 20)*	17 *(16 / 17)*	37 *(17 / 13)*	31 *(23 / 40)*	20 *(22 / 18)*
Previous CABG, % *(Invasive / conservative)* *	NS *(NS / NS)*	22 *(NS / NS)*	9 *(11 / 8)*	13 *(19 / 7)*	17 *(19 / 14)*	18 *(20 / 15)*	9 *(10 / 8)*	10 *(6 / 13)*	12 *(13 / 11)*
Previous stroke, % *(Invasive / conservative)* *	NS *(NS / NS)*	NS *(NS / NS)*	8 *(7 / 9)*	NS *(NS / NS)*	NS *(NS / NS)*	13 *(11 / 16)*	21 *(20 / 21)*	18 *(16 / 21)*	15 *(17 / 13)*

* Data is presented as: The total percentage (*The percentage within the invasive strategy arm / The percentage within the conservative management arm*)

CABG Coronary artery bypass graft, *MI* Myocardial infarction, *NS* Not specified, *PCI* Percutaneous Coronary Intervention

symptoms or clinical deterioration. However, thresholds varied, leading to coronary angiography rates from 0% in After Eighty to 49% in the TACTICS–TIMI 18 trial, with subsequent revascularization rates ranging from 0 to 32% [9, 33]. These differences likely stemmed from varying definitions of conservative and invasive strategies, criteria for medical therapy failure, and thresholds for rescue angiography. As outlined in Table 3, follow-up durations

Table 2 Included studies protocol for invasive and conservative strategies during the index hospitalization

RCT Name	Intervention Arm (Invasive strategy)	Control Arm (Conservative strategy)
FRISC II [34]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that all invasive procedures be performed within 7 days after starting OMT	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: refractory/recurrent symptoms or severe ischemia at predischarge exercise test
RITA 3 [35]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that the initial invasive coronary angiography be performed as soon as possible, ideally within 72 h after randomization	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: recurrent ischaemic pain at rest or on minimum exertion, with transient or persistent ECG evidence of ischemia or the inability to withdraw intravenous antianginal or antithrombotic treatment without recurrence of ischaemic pain
TACTICS–TIMI 18 [9]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that the initial invasive coronary angiography be performed within 4–48 h after randomization	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: prolonged angina at rest, hemodynamic instability, documented ischemia during predischarge exercise test, moderate to severe stable angina, recurrent UA, or a new MI
ICTUS [36]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that the initial invasive coronary angiography to be performed within 24–48 h after randomization	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: refractory angina, hemodynamic/rhythmic instability, or clinically significant ischemia on the predischarge exercise test
Italian Elderly ACS [31]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that the initial invasive coronary angiography be performed within 72 h of admission	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: refractory/recurrent ischemia, myocardial (re)infarction, heart failure of ischemic origin, or malignant ventricular arrhythmias
MOSCA [30]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that the initial invasive coronary angiography be performed within 72 h of admission	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: refractory/recurrent ischemia, worsening heart failure, or positive predischarge non-invasive stress test
After Eighty [21, 33]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that the initial invasive coronary angiography be performed within 72 h of admission	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: refractory angina, myocardial (re)infarction, heart failure, or malignant ventricular arrhythmias
80 + study [29]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * No clear timeframe has been proposed within the study protocol for the invasive coronary angiography	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: refractory angina, hemodynamic instability (including cardiogenic shock), heart failure, or life-threatening arrhythmias
RINCAL [28]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * No clear timeframe has been proposed within the study protocol for the invasive coronary angiography	OMT alone; patients were permitted to have diagnostic angiography if there was ongoing chest pain with or without dynamic ECG changes and/or further rise in troponin levels

Table 2 (continued)

RCT Name	Intervention Arm (Invasive strategy)	Control Arm (Conservative strategy)
MOSCA-FRAIL [20, 32]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has mandated that the initial invasive coronary angiography be performed within 72 h of admission	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: refractory/recurrent ischemia
SENIOR-RITA [26]	Initial management: OMT + invasive coronary angiography* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * The study protocol has recommended that the initial invasive coronary angiography be performed within 3–7 days of randomization	Initial management: OMT ± invasive coronary angiography if indicated* ± coronary revascularization (PCI/CABG) based on coronary angiography's findings * Indications of invasive coronary angiography within the index hospitalization: clinical deterioration that the angiography is deemed to be needed at the discretion of the treating physician

CABG Coronary artery bypass graft surgery, *CAG* Coronary angiography, *MI* Myocardial infarction, *OMT* Optimal medical therapy, *PCI* Percutaneous coronary intervention, *UA* Unstable angina

Table 3 Details of procedural treatments in intervention and control arms during the index hospitalization

RCT Name	Intervention Arm (Invasive strategy)		Control Arm (Conservative strategy)		Follow-up Duration
	Coronary angiography	Coronary revascularization (PCI/CABG)	Coronary angiography	Coronary revascularization (PCI/CABG)	
TACTICS–TIMI 18 [9]	+ (95% of the patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined	± (61% of the patients randomized to this arm)	± (49% of the patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (32% of the patients randomized to this arm)	6 months
FIR Trials [27]	Not Specified	Not Specified	Not Specified	Not Specified	5 years
Italian Elderly ACS [31]	+ (88% of the patients randomized to this arm underwent coronary angiography with a median of 24 h interval from the time of randomization)	± (56% of the patients randomized to this arm)	± (29% of the patients randomized to this arm underwent coronary angiography with a median of 67 h interval from the time of randomization)	± (23% of the patients randomized to this arm)	1 year
MOSCA [30]	+ (100% of the patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (58% of the patients randomized to this arm)	± (20% of the patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (9% of the patients randomized to this arm)	Median follow-up of 1.9 years
After Eighty [21, 33]	+ (96% of the patients randomized to this arm underwent coronary angiography with a mean of 3 days interval from the time of randomization)	± (50% of the patients randomized to this arm)	± (None of the patients randomized to this arm underwent coronary angiography)	± (None of the patients randomized to this arm underwent revascularization)	Median follow-up of 5.3 years
80 + study [29]	+ (96% of the patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (62% of the patients randomized to this arm)	± (4% of patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (4% of the patients randomized to this arm underwent revascularization)	1 year
RINCAL [28]	+ (92% of the patients randomized to this arm underwent coronary angiography with a mean of 2 days interval from the time of randomization)	± (51% of the patients randomized to this arm)	± (9% of patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (3% of the patients randomized to this arm underwent revascularization)	Median follow-up of 1 year

Table 3 (continued)

RCT Name	Intervention Arm (Invasive strategy)		Control Arm (Conservative strategy)		Follow-up Duration
	Coronary angiography	Coronary revascularization (PCI/CABG)	Coronary angiography	Coronary revascularization (PCI/CABG)	
MOSCA-FRAIL [20, 32]	+ (98% of the patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (60% of the patients randomized to this arm)	± (11% of patients randomized to this arm underwent coronary angiography; the time interval between randomization and coronary angiography has not been determined)	± (10% of the patients randomized to this arm underwent revascularization)	Median follow-up of 3 years
SENIOR-RITA [26]	+ (90% of the patients randomized to this arm underwent coronary angiography with a median of 3 days intervals from the time of randomization)	± (50% of the patients randomized to this arm)	± (6% of patients randomized to this arm underwent coronary angiography within 7 days of randomization)	± (The proportion of patients randomized to this arm and underwent revascularization has not been determined)	Median follow-up of 4.1 years

CABG Coronary artery bypass graft surgery, *PCI* Percutaneous coronary intervention

also varied, ranging from a minimum of 6 months to a median of 5.3 years [9, 20]. Unfortunately, both the 80 + study and RINCAL were terminated prematurely due to recruitment challenges.

Clinical endpoint definitions and assessment

The definition of MI evolved over time, with earlier trials using older universal definitions of MI, while more recent trials like SENIOR-RITA employed the Fourth Universal Definition [37]. The bleeding outcome definition had some levels of heterogeneity across the studies, as the classification of bleeding outcomes was according to the Bleeding Academic Research Consortium (BARC) definition [38] in 3 trials (SENIOR-RITA, RINCAL, and Italian Elderly ACS) and according to Thrombolysis in Myocardial Infarction (TIMI) criteria [38] in 4 trials (80 +, After Eighty, MOSCA, and TACTICS–TIMI 18) while one study (MOSCA-FRAIL) used a separate definition (Table S2).

Bleeding outcomes were harmonized across trials using established criteria from the BARC and TIMI classifications (Table S3) [38]. Major bleeding was defined as BARC type 3b or higher and its TIMI equivalent, encompassing fatal bleeding, symptomatic intracranial hemorrhage, hemodynamic compromise requiring intervention, and bleeding requiring transfusion of ≥ 5 units of whole blood/red cells. Minor bleeding was defined as BARC type 2-3a or its TIMI equivalent, characterized by overt bleeding requiring medical intervention or antithrombotic therapy modification without meeting major bleeding criteria. The data for major and minor bleeding were available separately in 5 trials (SENIOR-RITA, RINCAL, 80 +, After Eighty, and TACTICS–TIMI 18) while among the three remaining trials, the bleeding outcomes had been reported as a composite of major and minor bleeding in two trials (MOSCA-FRAIL and MOSCA), and in one study (Italian Elderly ACS) the bleeding outcome had been considered as a composite of BARC type 2, 3a, and 3b bleeding. Despite different classification systems, the fundamental criteria defining major bleeding events remained consistent between BARC and TIMI scales, enabling reliable cross-trial comparisons [38].

Risk of bias assessment

As summarized in Table 4, all studies were categorized as low-risk in terms of overall bias. While some concerns were noted regarding deviations from the intended intervention due to the open-label design and crossover rates, these did not significantly impact the overall assessments.

Invasive vs. conservative management outcomes

Analysis of the primary outcomes revealed comparable mortality rates between treatment strategies. Both all-cause mortality (RR: 1.04, 95% CI: 0.98–1.11, 95% PI: 0.97–1.12, $p = 0.18$) and cardiovascular mortality (RR: 0.98, 95% CI: 0.85–1.12, 95% PI: 0.82–1.16, $p = 0.68$) showed no significant differences between approaches, with completely homogeneous findings across studies ($I2 = 0\%$, $Tau2 = 0$ for both outcomes) (Fig. 2A and B). Sensitivity analyses demonstrated remarkable stability in these findings, with all-cause mortality RRs ranging from 0.96–1.05 (all p-values > 0.05) and

Table 4 Risk of bias assessment of included studies

RCT Name	D1	D2	D3	D4	D5	Overall Risk
FRISC II [34]	Low	Some concerns	Low	Low	Low	Low
RITA 3 [35]	Low	Some concerns	Low	Low	Low	Low
TACTICS–TIMI 18 [9]	Low	Some concerns	Low	Low	Low	Low
ICTUS [36]	Low	Some concerns	Low	Low	Low	Low
Italian Elderly ACS [31]	Low	Some concerns	Low	Low	Low	Low
MOSCA [30]	Low	Some concerns	Low	Low	Low	Low
After Eighty [21, 33]	Low	Some concerns	Low	Low	Low	Low
80 + study [29]	Low	Some concerns	Low	Low	Low	Low
RINCAL [28]	Low	Some concerns	Low	Low	Low	Low
MOSCA-FRAIL [20, 32]	Low	Some concerns	Low	Low	Low	Low
SENIOR-RITA [26]	Low	Some concerns	Low	Low	Low	Low

Bias Domains:

D1: bias arising from the randomization process

D2: bias due to deviations from intended interventions

D3: bias due to missing outcome data

D4: bias in the measurement of the outcome

D5: bias in the selection of the reported result

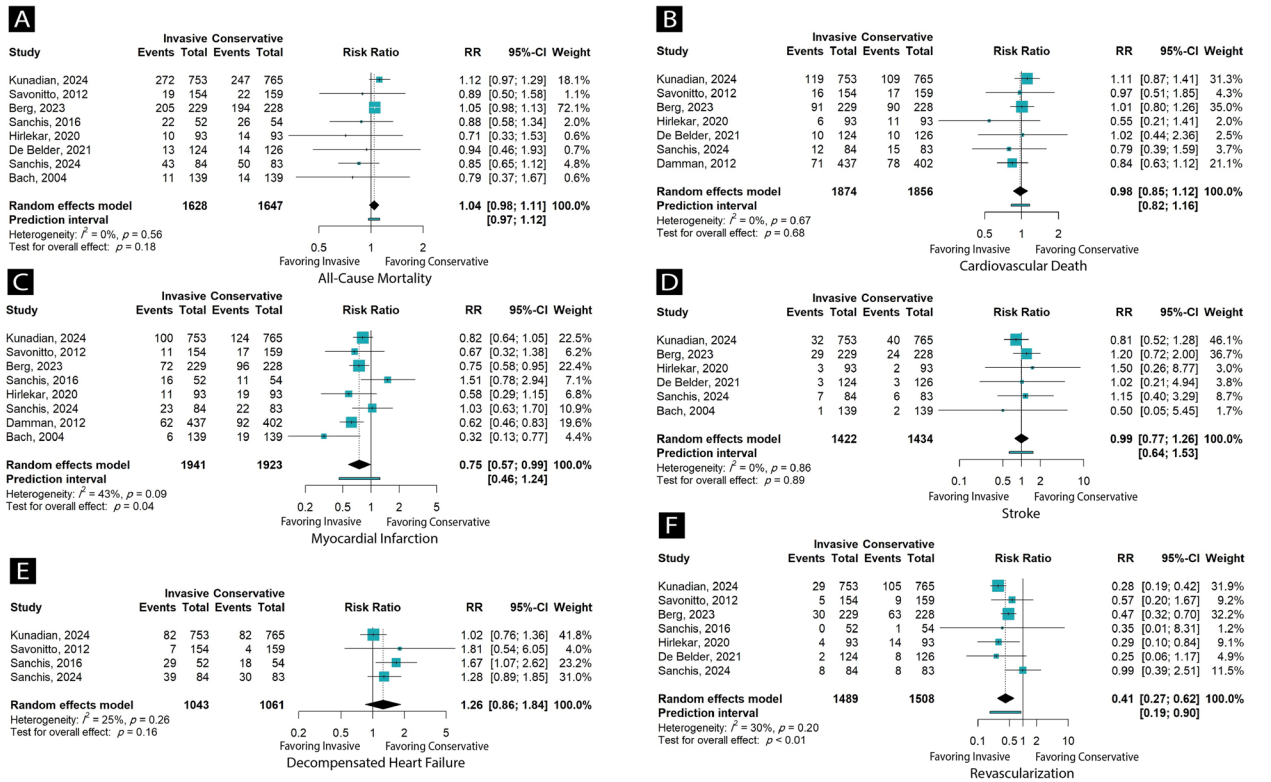

Fig. 2 Forest plots showing the risk ratios (RR) for adverse clinical outcomes comparing invasive and conservative strategies in elderly patients with NSTE-ACS. **A** All-cause mortality, **B** Cardiovascular death, **C** Myocardial infarction, **D** Stroke, **E** Decompensated heart failure, and (**F**) Revascularization

cardiovascular mortality RRs ranging from 0.92–1.02 (all p-values > 0.05) across all leave-one-out iterations (Fig. 3A and B). The narrow nonsignificant 95% PIs also suggest consistency across studies, as most future studies are also likely to show no clear survival benefit or harm from either strategy.

The invasive strategy significantly reduced the need for subsequent revascularization procedures (RR: 0.41, 95% CI: 0.27–0.62, 95% PI: 0.19–0.90, $p < 0.01$; I2 = 30%, Tau2 = 0.0621) and the risk of MI (RR: 0.75, 95% CI: 0.57–0.99, 95% PI: 0.46–1.24, $p = 0.04$; I2 = 43%, Tau2 = 0.1768) (Fig. 2F and C). Sensitivity analyses confirmed the robustness of the revascularization benefit, with consistent RRs (0.37–0.49) maintaining statistical significance across all iterations (p-values < 0.01) and moderate heterogeneity (I2: 0–42%) (Fig. 3F). The 95% PI confirms this potential benefit in future studies. The MI risk reduction showed more variability in sensitivity analyses (RRs: 0.72–0.79; I2: 24–51%), with statistical significance being lost in some analyses when certain studies were omitted (p-values: 0.01–0.13), suggesting less stable but still potentially meaningful benefit (Fig. 3C). Furthermore, the wide 95% PI crossing null value for MI suggests that the observed risk reduction might not be consistent across all future populations or trials.

Analysis of stroke outcomes showed no significant difference between strategies (RR: 0.99, 95% CI: 0.77–1.26, 95% PI: 0.64–1.53, $p = 0.89$) with excellent homogeneity (I2 = 0%, Tau2 = 0) (Fig. 2D). Sensitivity analyses maintained this finding (RRs: 0.88–1.16, all $p > 0.05$) with consistent absence of heterogeneity (Fig. 3D). The 95% PI reinforces this finding, suggesting that future studies will likely produce mixed findings. For decompensated heart failure, the invasive strategy showed a non-significant trend toward increased risk (RR: 1.26, 95% CI: 0.86–1.84, $p = 0.16$) with moderate heterogeneity (I2 = 25%, Tau2 = 0.1274) (Fig. 2E). This pattern persisted in sensitivity analyses (RRs: 1.13–1.45, all $p > 0.05$), while heterogeneity varied (I2: 0–49%) with study omissions (Fig. 3E).

A subgroup analysis of octogenarians ($n = 893$) from three trials (After Eighty, 80+, RINCAL) showed similar patterns and point estimates to the overall population, though with wider confidence intervals and loss of statistical significance for several outcomes. In this subgroup, the invasive strategy showed no significant difference in all-cause mortality (RR: 1.05, 95% CI: 0.94–1.17) or cardiovascular death (RR: 0.98, 95% CI: 0.65–1.47) (Figure

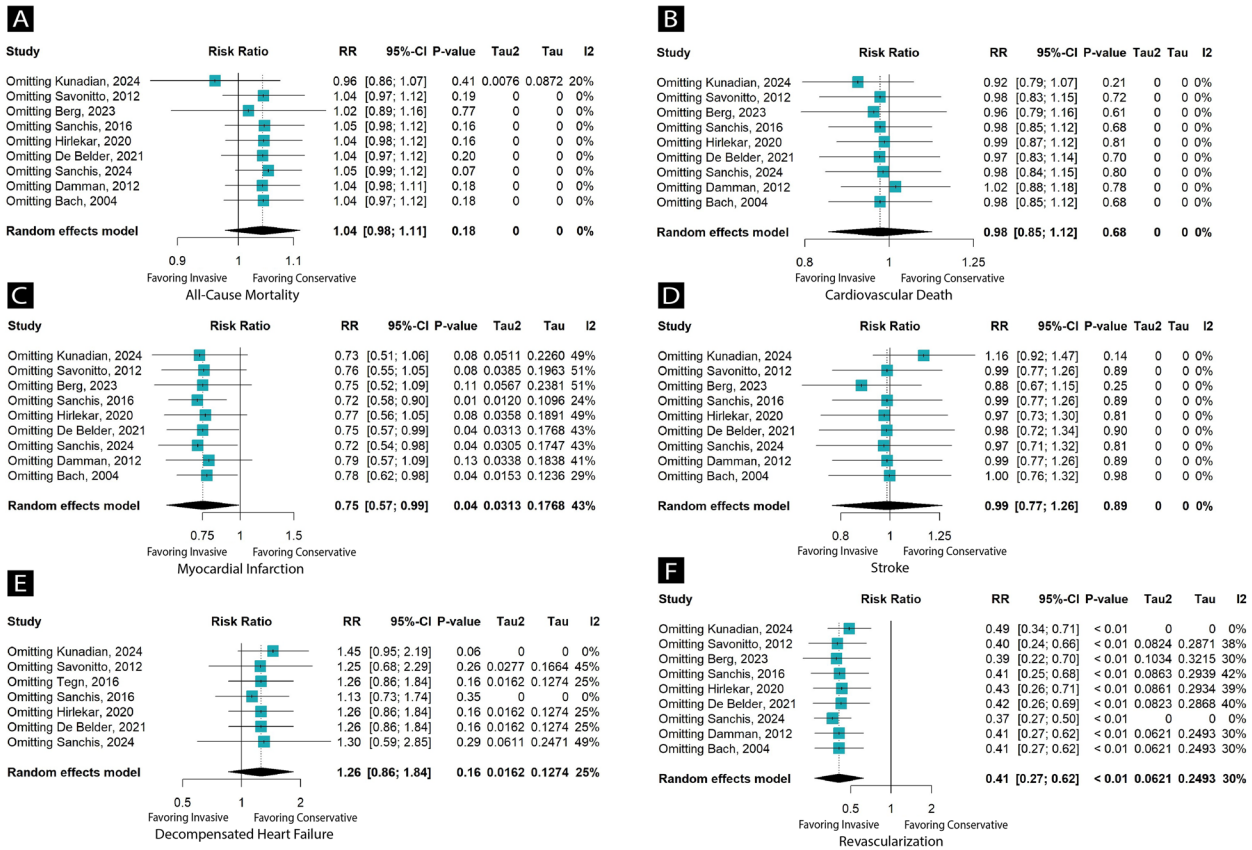

Fig. 3 Leave-one-out sensitivity analysis results. **A** All-cause mortality, **B** Cardiovascular death, **C** Myocardial infarction, **D** Stroke, **E** Decompensated heart failure, and (**F**) Revascularization

S1 A-B). Although MI risk showed a similar trend toward reduction with the invasive strategy (RR: 0.73, 95% CI: 0.26–2.02), the loss of statistical significance compared to the overall analysis suggests particular caution in interpreting this benefit in the very old adults (Figure S1C). The reduction in revascularization needs remained significant even in this older subgroup (RR: 0.43, 95% CI: 0.23–0.81, $p=0.03$) (Figure S1E). In contrast to the neutral effect in the overall population, stroke risk trended higher with the invasive strategy in octogenarians (RR: 1.20, 95% CI: 0.85–1.90), though this difference did not reach statistical significance (Figure S1D).

Meta-regression analyses exploring the relationship between mean age and treatment effects showed no statistically significant age-dependent trends for any of the clinical outcomes. Notably, stroke risk demonstrated a positive clinically relevant trend with advancing age ($\beta=0.1505$, 95% CI: -0.1068 to 0.4079, $p=0.2517$). The detailed results of meta-regression analyses are presented in Table S4 and visualized in Figure S2.

As demonstrated in Fig. 4, safety analyses revealed significant increases in bleeding risk with the invasive strategy. The composite of major and minor bleeding was increased by 50% (RR: 1.50, 95% CI: 1.02–2.20, 95% PI: 0.77–2.91, $p=0.04$) with moderate heterogeneity (I2 = 30%, Tau2 = 0.1894) (Fig. 4A), while major bleeding alone was nearly doubled (RR: 1.92, 95% CI: 1.04–3.56, $p=0.04$) with no heterogeneity (I2 = 0%) (Fig. 4C). Sensitivity analyses demonstrated consistent effect directions with all point estimates above 1.0, though statistical significance varied. For the composite endpoint of major and minor bleeding, RRs ranged from 1.36 to 1.59 across leave-one-out iterations (p-values: 0.02–0.17), with stable heterogeneity (I2: 17–33%) (Fig. 4B). The isolated major bleeding outcome showed similar stability, with RRs ranging from 1.54 to 2.13 (p-values: 0.04–0.17) and persistent absence of heterogeneity (I2 = 0% throughout) (Fig. 4D). The 95% PI for the composite of major and minor bleeding suggests potential variability, as it spans a wide range and includes the null value, indicating the increase in bleeding risk associated with an invasive strategy may not be consistent across all clinical contexts.

To address the heterogeneity in bleeding definitions, we performed a sensitivity analysis focusing specifically on studies using TIMI bleeding criteria (Figure S3). For the composite of major and minor bleeding, the pooled

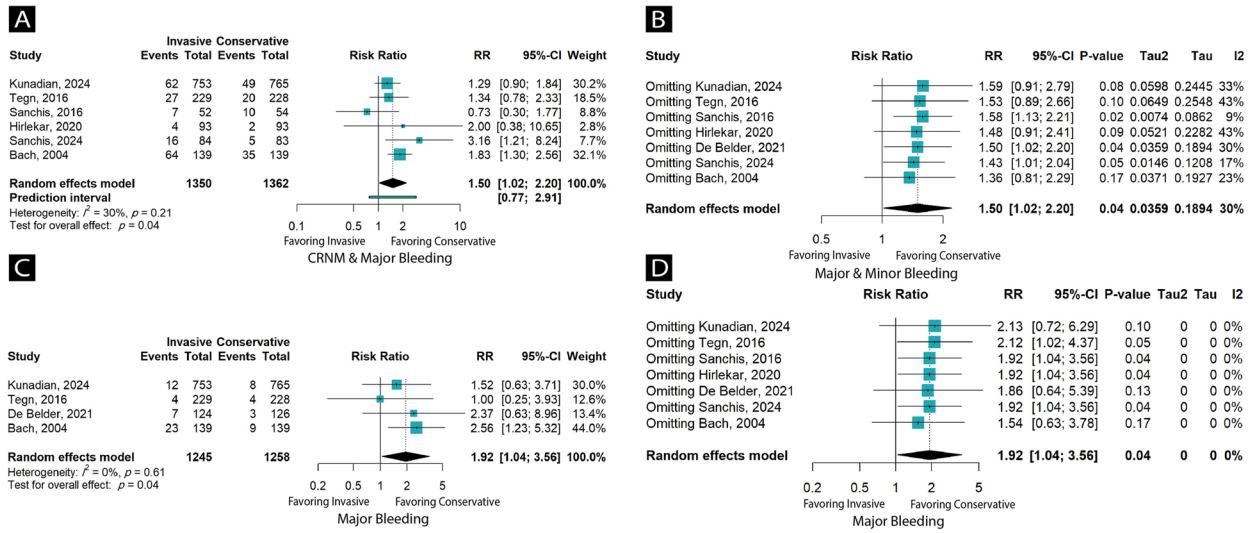

Fig. 4 Forest plots comparing the risk ratios for bleeding outcomes between invasive and conservative strategies in elderly patients with NSTE-ACS. **A** Composite of major and minor bleeding, **B** Sensitivity analysis for composite bleeding, **C** Major bleeding alone, and (**D**) Sensitivity analysis for major bleeding

analysis of four studies using TIMI criteria showed a numerically increased but non-significant risk with the invasive strategy (RR: 1.47, 95% CI: 0.81–2.64) compared to the significant increase seen in the main analysis. Similarly, the analysis of major bleeding in this subgroup showed a nonsignificant trend toward increased risk (RR: 1.92, 95% CI: 0.01–470.93), though with substantial uncertainty in the estimate.

Time-to-event analysis of pooled HRs demonstrated no significant differences in the composite endpoint of all-cause mortality and MI (HR: 0.95, 95% CI: 0.83–1.09, $p=0.48$; I2 = 0%), all-cause mortality (HR: 1.10, 95% CI: 0.94–1.29, $p=0.22$; I2 = 0%), cardiovascular mortality (HR: 0.94, 95% CI: 0.73–1.20, $p=0.60$; I2 = 36%), or stroke (HR: 1.02, 95% CI: 0.58–1.79, $p=0.94$; I2 = 48%) (Fig. 5F, A, B, and D). However, the invasive strategy significantly

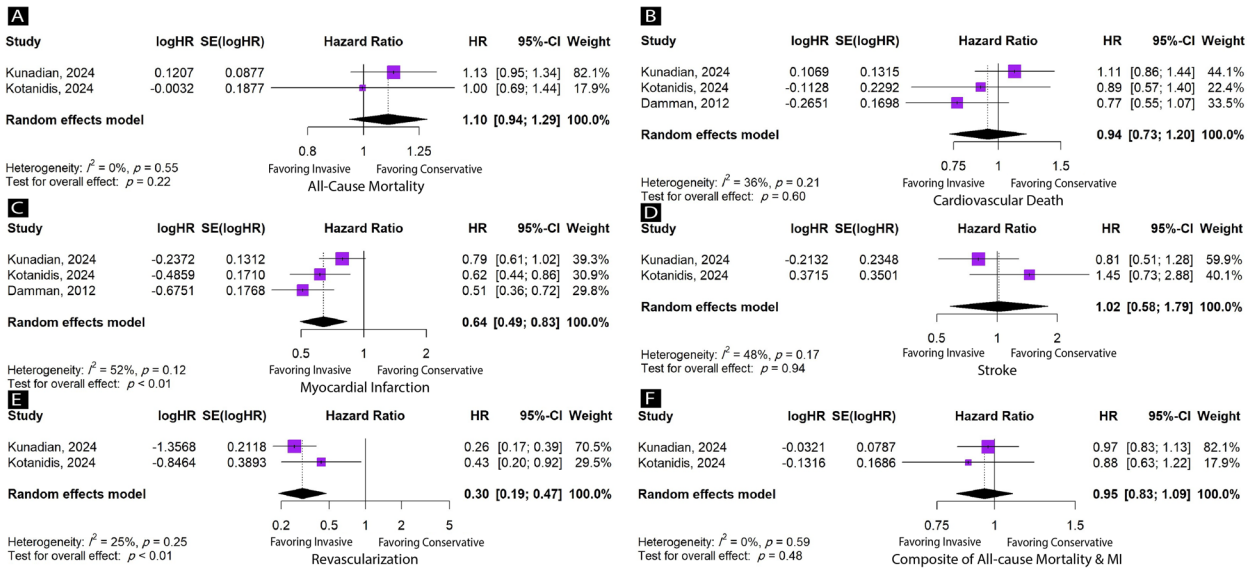

Fig. 5 Forest plots showing hazard ratios (HR) for adverse clinical outcomes comparing invasive and conservative strategies in elderly patients with NSTE-ACS. **A** All-cause mortality, **B** Cardiovascular death, **C** Myocardial infarction, **D** Stroke, **E** Revascularization, and (**F**) Composite of all-cause mortality and myocardial infarction

reduced the hazard of MI (HR: 0.64, 95% CI: 0.49–0.83, $p < 0.01$; I2 = 52%) and subsequent revascularization (HR: 0.30, 95% CI: 0.19–0.47, $p < 0.01$; I2 = 25%) (Figs. 5C and E). All studies showed consistent directions of effect for these significant outcomes, with SENIOR-RITA trial contributing the majority of the statistical weight (39.3% for MI and 70.5% for revascularization).

Discussion

This meta-analysis, including 4114 patients from 11 RCTs, represents the most comprehensive and up-to-date evaluation of the initial management strategies in elderly NSTE-ACS patients. Our findings address critical knowledge gaps in the care of this high-risk population, revealing that while invasive strategies reduce revascularization needs and may lower the risk of MI, they do not confer survival benefits and are associated with increased bleeding risk. These results have important implications for individualized patient care.

The consistency between RR and HR analyses across all outcomes strengthens the robustness of our findings. For revascularization, where results were most consistent, the HR demonstrated a 70% reduction compared to a 59% reduction in the RR analysis. For MI, the HR showed a 36% reduction compared to a 25% reduction in the RR analysis. However, our findings regarding MI warrant cautious interpretation due to moderate to high heterogeneity and sensitivity analyses showing a loss of statistical significance when certain studies were omitted. The variation in effect size between the two methods may be attributed to both the inherent methodological differences between HRs and RRs and the inclusion of different trial versions in the analyses (MOSCA-FRAIL 2023 vs. 2024 [20, 32], and After Eighty 2016 vs. 2023 [21, 33] in Kotanidis's [18] versus our current analysis, respectively).

Kotanidis et al. similarly reported reduced MI risk and revascularization needs without mortality benefit [18]. Damman et al.'s age-stratified patient-level analysis of FIR trials (FRISC II [34], RITA 3 [35], and ICTUS [36]) demonstrated that while invasive strategy significantly reduced MI risk in patients over 65, it conferred no survival benefit across age groups (< 65, 65–75, and ≥ 75) [27]. In contrast, Improta et al.'s meta-analysis, which included both RCTs and adjusted observational studies, suggested a short-term survival advantage with invasive management [17]. This discrepancy is likely attributable to the inclusion of non-RCT data, which may have introduced confounding factors not present in strictly controlled trial environments. The results of the current study reinforce this observation that while invasive strategies can effectively prevent recurrent ischemic events, they do not necessarily translate into improved survival.

Recent trials have highlighted the complex relationship between geriatric conditions, including frailty, comorbidity burden, and cognitive impairment, and treatment outcomes in elderly NSTE-ACS patients [20, 26]. The MOSCA-FRAIL revealed distinct temporal patterns in frail patients (as defined by Clinical Frailty Scale score > 4) undergoing invasive strategy experiencing early adverse outcomes during the first year followed by potential later benefits, ultimately leading to neutral long-term results [20]. The SENIOR-RITA trial similarly found no significant differences in outcomes between invasive and conservative strategies in both frail and non-frail subgroups (HRs: 0.92 and 0.97, respectively) [26]. The burden of comorbidities, assessed through the Charlson Comorbidity Index with a median score of 5 in both SENIOR-RITA and MOSCA-FRAIL trials, did not significantly impact treatment effectiveness regardless of comorbidity burden. Furthermore, regarding cognitive impairment (based on Montreal Cognitive Assessment scores < 26), which affected 62.5% of the SENIOR-RITA population, there was a trend toward lower rates of composite endpoint of cardiovascular death or nonfatal MI with invasive strategy in non-impaired patients (HR 1.18, 95% CI 0.81–1.72) and with conservative strategy in cognitively impaired patients (HR 0.85, 95% CI 0.67–1.09), though these differences were not statistically significant [26]. This finding is in line with contemporary evidence demonstrating that cognitive impairment is associated with higher short- and long-term mortality in ACS patients undergoing coronary revascularization [39, 40]. The relationship between cognitive status and all-cause mortality in NSTE-ACS elderlies persists even after adjusting for frailty and other geriatric factors, as demonstrated in a recent long-term follow-up study [40]. Age-stratified subgroup analysis of SENIOR-RITA trial showed that while younger elderly patients (< 80 years) demonstrated a trend toward benefit from invasive strategy (HR 0.70, 95% CI 0.46–1.07) for the composite endpoint of cardiovascular death or nonfatal MI, patients ≥ 80 years derived no apparent benefit (HR 1.01, 95% CI 0.81–1.27). While these subgroup analyses suggest important trends, dedicated prospective studies focusing on octogenarians and incorporating cognitive function and other geriatric measures as primary endpoints are needed to guide individualized treatment decisions better.

Our subgroup analyses further highlight age-specific considerations, with octogenarians showing loss of MI benefit and a concerning trend toward higher stroke risk with the invasive strategy, though statistical significance was not reached. This vulnerability to stroke complications in the most elderly patients was further supported by our meta-regression analysis, which demonstrated a positive trend corresponding to a 15% increase in stroke

relative risk for each year of advancing age. While these parallel findings strengthen the likelihood of a true age-dependent relationship, the absence of statistical significance in both analyses warrants cautious interpretation.

Our findings strongly align with current ESC guideline recommendations for a selective approach to invasive management in elderly NSTE-ACS patients, carefully considering individual geriatric factors and balancing temporal patterns of benefits against risks [2]. The sustained reduction in revascularization needs and potential decrease in recurrent MI risk support considering invasive strategies in selected elderly patients, though this benefit must be carefully weighed against the impact of frailty, cognitive status, and other comorbidities, which can increase procedural risks and complicate recovery [2]. Thus, patient selection should incorporate several key factors. First, assessment of ischemic risk is crucial, as patients at higher risk of recurrent events may derive greater early and sustained benefit from invasive management. Second, given that mortality benefits were not observed over time, the decision should focus on quality of life and symptom improvement rather than survival advantage. We suggest future studies focus on comparing quality of life outcomes and functional status in elderly NSTE-ACS patients undergoing different management strategies. Third, the observed increase in bleeding complications emphasizes the need for thorough pre-procedural bleeding risk assessment and implementation of modern bleeding avoidance strategies, including preferred radial access [41]. Future studies are warranted to examine the impact of newer access site techniques, closure devices, and modified anticoagulation protocols on bleeding outcomes. The role of abbreviated dual antiplatelet therapy durations following invasive management in the elderly, particularly those with high bleeding risk, also deserves focused investigation. Finally, studies evaluating the relationship between bleeding events and subsequent functional decline, quality of life, and long-term outcomes could provide valuable insights for patient risk–benefit discussions.

Strengths and limitations

Our meta-analysis offers several key strengths. First, with the inclusion of the SENIOR-RITA trial (1,518 patients) [26], our sample size nearly doubles that of the recent individual patient data meta-analysis by Kotanidis et al. [18]. Second, incorporating extended follow-up data from the After Eighty and MOSCA-FRAIL trials provides more robust longitudinal evidence [20, 21]. Third, we conducted sensitivity analyses using the "leave-one-out" method, examining the robustness of our findings. Finally, our dual analytical approach using RRs and time-to-event analyses enhances the reliability of our findings.

However, several limitations merit consideration. While our exclusive focus on RCTs ensures high internal validity, it may limit generalizability to real-world elderly populations who typically present with more complex comorbidity profiles. The heterogeneity in invasive protocols and medical practices across studies could influence outcomes, although we mitigated this through random-effects modeling and comprehensive sensitivity analyses. The inclusion of data from underpowered RCT subgroup analyses might introduce reporting bias. Additionally, formal assessment of publication bias was precluded by the limited number of included studies, leaving this potential source of bias unquantified. This limitation highlights the need for further high-quality RCTs designed explicitly for elderly patients with NSTE-ACS to expand the evidence base.

Conclusion

This meta-analysis indicates that in elderly patients with NSTE-ACS, invasive strategies significantly reduce revascularization needs and may lower MI risk, though the latter finding showed moderate heterogeneity across studies. While no survival benefit was observed in either short- or long-term follow-up, invasive management increased bleeding risk. The temporal patterns of benefit and risk, along with the heterogeneous findings for some outcomes, emphasize the need for individualized treatment decisions based on patient-specific characteristics and risk factors, particularly considering bleeding risk and geriatric factors.

Abbreviations

ACS	Acute Coronary Syndrome
BARC	Bleeding Academic Research Consortium
CI	Confidence Interval
ESC	European Society of Cardiology
HR	Hazard Ratio
MI	Myocardial Infarction
NSTE-ACS	Non-ST-Elevation Acute Coronary Syndrome
PCI	Percutaneous Coronary Intervention
PI	Prediction Interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RR	Risk Ratio
TIMI	Thrombolysis in Myocardial Infarction

Supplementary Information

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Supplementary Material 1.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Claude 3.5 Sonnet and QuillBot in order to ensure English language fluency and native quality writing. These services were consulted regarding grammar, word choice, sentence structure, and overall clarity of expression. Having used these services, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Authors' contributions

EK: Writing – original draft; Methodology; Investigation SJ: Writing – original draft; Methodology; Investigation AH: Methodology; Data curation; Formal analysis AA: Writing – review and editing FY: Methodology; Investigation EH: Methodology; Investigation AGJ: Methodology; Investigation AA: Conceptualization; Writing – review and editing; Supervision.

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Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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