

REVIEW ARTICLE OPEN ACCESS

Invasive Versus Conservative Treatment Strategy in Older Patients With Non-ST Segment Elevation Acute Coronary Syndromes: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Non-ST segment elevation acute coronary syndromes (NSTEMI-ACS) are a common cause of hospital admission in older patients. Our study aims to synthesize the available evidence from randomized controlled trials (RCTs) to compare clinical outcomes with invasive versus conservative medical management in this population.

Methods: A literature search of online databases including PubMed/MEDLINE, Embase, and the Cochrane Library was conducted from inception to September 1, 2024. The search aimed to identify RCTs that reported clinical outcomes with invasive versus conservative strategies in older patients (≥ 70 years) with NSTEMI-ACS. The risk ratios (RRs) were used as summary estimates.

Results: Seven RCTs with 2998 patients were included; 1490 patients in the invasive group and 1508 patients in the conservatively managed group. The pooled analysis demonstrated no statistically significant difference between the two strategies for the risk of all-cause death (RR: 1.03, 95% CI: 0.92–1.15), cardiovascular death (RR: 1.04, 95% CI: 0.82–1.33), stroke (RR: 0.78, 95% CI: 0.53–1.15), and major bleeding (RR: 1.23, 95% CI: 0.90–1.69). However, the invasive strategy was associated with a significantly reduced risk of myocardial infarction (RR: 0.74, 95% CI: 0.57–0.96) and unplanned revascularization (RR: 0.29, 95% CI: 0.21–0.40) compared to the conservative strategy.

Conclusion: In older patients with NSTEMI-ACS, an invasive strategy reduces the risk of repeat myocardial infarction and unplanned revascularization without a significant increase in stroke or major bleeding. There was no associated reduction in all-cause or cardiovascular mortality with the invasive strategy compared to conservative management.

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Summary

- Key points
 - In older patients with NSTEMI, the invasive strategy reduces the risk of myocardial infarction and unplanned revascularization without increasing the risk of stroke or major bleeding.
 - There is no significant difference between invasive and conservative strategies regarding all-cause mortality or cardiovascular death.
- Why does this paper matter?
 - Our study provides important insights into managing older patients with non-ST segment elevation acute coronary syndromes (NSTEMI), a group often underrepresented in trials, leading to unclear treatment guidance.
 - Current practice typically favors invasive strategies like PCI or CABG, based on data from younger populations, but approaches vary regionally due to factors like resources and reimbursement.
 - By analyzing data from seven randomized controlled trials (RCTs), we found that while invasive strategies reduce myocardial infarction and unplanned revascularization risk, they do not improve all-cause or cardiovascular mortality.
 - This highlights the need for more individualized treatment strategies for older adults with NSTEMI.

1 | Introduction

Age is a well-recognized risk factor for acute coronary syndromes (ACSs), with non-ST segment elevation myocardial infarction (NSTEMI) being the predominant subtype of ACS among adults over the age of 70 [1, 2]. The prevalence of NSTEMI and unstable angina in older adults is increasing, necessitating a nuanced approach to treatment that considers both efficacy and safety. However, the management of older patients with NSTEMI and unstable angina remains a significant clinical challenge, particularly in balancing the risks and benefits of invasive versus conservative treatment strategies [3–5]. The management of NSTEMI has significantly evolved over the years, largely due to advancements in care and therapeutics, leading to improved survival rates [6, 7]. However, most of the existing evidence primarily focuses on younger patients, leaving a gap in the data for older populations who may present with different risk profiles and treatment responses.

While previous study-level meta-analyses have offered valuable insights into the management of older patients with non-ST segment elevation acute coronary syndromes (NSTEMI), they have been limited by a smaller number of included studies and relatively short follow-up periods, restricting the ability to assess long-term outcomes [8–10]. Our meta-analysis aims to address these limitations by pooling data from three additional trials, notably from the recently published SENIOR-RITA trial [11], a large-scale randomized controlled trial (RCT) with a follow-up period of 4 years. This extended follow-up enables a more thorough evaluation of long-term outcomes, offering new perspectives on the relative benefits and risks of invasive versus conservative treatment strategies in this vulnerable patient population. By pooling data from

these newly included studies, our meta-analysis aims to provide robust evidence on the comparative efficacy and safety of both approaches in this vulnerable population.

2 | Methods

This systematic review and meta-analysis adhered to the standards outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [12]. The protocol of the study was registered with PROSPERO (CRD42024585749).

2.1 | Data Sources and Search Strategy

Two independent researchers (M.A. and A.A.) conducted a comprehensive search of PubMed/MEDLINE, Embase, the Cochrane Library, and [ClinicalTrials.gov](https://www.clinicaltrials.gov), covering all records from their inception until September 1, 2024. To ensure all pertinent articles were included, the researchers also manually checked the references of studies on similar topics. The investigators searched the websites of prominent cardiology-related journals (www.nejm.org; www.onlinejacc.org; <https://www.thelancet.com/>; <https://annals.org/aim>; <https://jamanetwork.com>; <https://academic.oup.com/eurheartj>; and www.ahajournals.org/journal/circ) to identify relevant articles. The search strategy incorporated a combination of keywords and entry terms, including: (Invasive strategy OR PCI OR coronary angiography OR revascularization) AND (Conservative strategy OR medical management OR pharmacotherapy) AND (Older adults OR older OR geriatric OR aged) AND (NSTEMI OR non-ST elevation acute coronary syndrome OR unstable angina OR NSTEMI). The search strings used for major databases are provided in Table S1.

2.2 | Eligibility Criteria and Outcomes

For inclusion in this systematic review and meta-analysis, studies had to meet the following criteria: (i) published RCTs comparing invasive strategies (such as, coronary angiography, coronary revascularization by either percutaneous coronary intervention or coronary artery bypass graft) with conservative or medical management strategies; (ii) the study population must be aged 70 years or older and diagnosed with NSTEMI (unstable angina or NSTEMI); (iii) the study reported at least one outcome of interest.

Studies focusing on populations younger than 70 years, reviews, editorials, and commentaries were excluded.

The primary outcomes included all-cause and cardiovascular (CV) death. The secondary outcomes included myocardial infarction, major bleeding, stroke, and unplanned revascularization.

2.3 | Study Selection and Data Extraction

The studies identified through the literature search were imported into EndNote X9 (Clarivate Analytics) for the removal of duplicate entries. Two authors (A.A. and M.A.) independently screened the RCTs based on their titles and abstracts, followed by a full-text review of the selected articles. In cases of

disagreement, a third author (A.S.) was consulted to reach a consensus.

The extracted data from each eligible study included the author's name, publication year, country, study duration, sample size, patient demographics, age, timing of randomization and invasive strategy, follow-up duration, proportion of female participants, presence of comorbidities, smoking status, history of myocardial infarction, PCI, stroke, and eligible outcomes. Data extraction was conducted using a pre-piloted Excel spreadsheet.

2.4 | Risk of Bias Assessment of the Included Studies and Certainty of Evidence

The quality of the included RCTs was evaluated using the Cochrane Risk of Bias tool, version 2 (RoB 2.0) [13]. The risk of bias was assessed across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results. Each domain was rated as having a high, low, or uncertain (some concerns) risk of bias. Moreover, the bias assessment was performed for all outcomes analyzed in the meta-analysis.

The certainty of the evidence was assessed following the five grades of Recommendation, Assessment, Development, and Evaluation (GRADE) considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each body of evidence was rated as high, moderate, low, or very low certainty.

2.5 | Statistical Analysis

Data analysis was performed using R version 4.3.2, employing the “meta” and “metasens” packages via RStudio. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using the random effects model and were depicted in forest plots [14], and the Paule-Mandel estimator was used to calculate τ^2 [15]. Heterogeneity was evaluated according to the Cochrane Handbook of Systematic Reviews of Interventions, using arbitrary cutoff values for the Higgins I² statistic, along with results from the χ^2 test: 0%–40% indicating low heterogeneity, 30%–60% indicating moderate heterogeneity, 50%–90% indicating substantial heterogeneity, and 75%–100% indicating considerable heterogeneity [16]. The hazard ratios (HRs) reported by trials were pooled in a secondary analysis where possible (for any outcome if ≥ 2 studies reported the HRs). The HRs were not used as summary estimates in the primary analysis due to their inconsistent reporting by trials. The summary effect sizes from the meta-analysis were applied to the baseline risk in conservative treatment groups for all RCTs to determine the absolute risk differences using GRADEpro GDT. Moreover, a leave-one-out sensitivity analysis was conducted to determine whether any study had a high influence on summary estimates. A p -value of less than 0.05 was considered statistically significant.

3 | Results

The literature search identified 626 records. The duplicate articles were removed, and 375 studies were screened by two

investigators who independently reviewed their titles and abstracts. Three hundred and fifty-one studies not related to the review topic were excluded, and full texts of 24 studies were retrieved. After a review of full texts, 7 RCTs were included in the systematic review and meta-analysis (PRISMA flowchart Figure S1). The reasons for the exclusion of other full texts are reported in Table S2.

The included studies [4, 5, 11, 17–20] reported data for 2998 older patients with NSTEMI-ACS. 1490 patients received invasive management while 1508 patients were conservatively managed. The mean age of included patients ranged from 81 to 86 years. The mean duration of follow-up ranged from 1 to 4.1 years. Female patients made up 48.6% of the study sample. Most patients (68.1%) had a history of hypertension, 29.5% of patients had diabetes, and 4.9% were smokers. Among the participants, 33.2% had experienced a myocardial infarction in the past, and 19.7% had undergone PCI prior to being recruited into the trials. The detailed characteristics are provided in Tables 1 and S3. The details of invasive and conservative treatment strategies in each RCT are reported in Table S4. Some concerns were observed in two included studies [4, 18] while other included RCTs had a low risk of bias (Figure S2). On performing bias assessment for individual outcomes, a low risk of bias was observed for all-cause death, CV death, stroke, and major bleeding. However, some concerns were observed for myocardial infarction and unplanned revascularization related to performance and detection bias (Figures S3–S8).

3.1 | Outcomes

3.1.1 | All-Cause Death

The pooled analysis demonstrated a nonsignificant difference between invasive and conservative treatment strategies for the risk of all-cause death (27.5% with invasive strategy versus 26.9% with conservative therapy; RR: 1.03, 95% CI: 0.92 to 1.15, $p=0.62$, high certainty, Figure 1A and Table 2) with no evidence of heterogeneity ($I^2=0\%$). Similar results were observed in the secondary analysis by pooling HRs (HR: 1.04, 95% CI: 0.90–1.19, $p=0.61$, Figure S9).

3.1.2 | CV Death

No statistically significant difference was observed between invasive and conservative strategies for CV death (14% with invasive strategy versus 13.4% with conservative therapy; RR: 1.04, 95% CI: 0.82–1.33, $p=0.73$, high certainty, Figure 1B). Low heterogeneity was observed ($I^2=4\%$).

3.1.3 | Myocardial Infarction

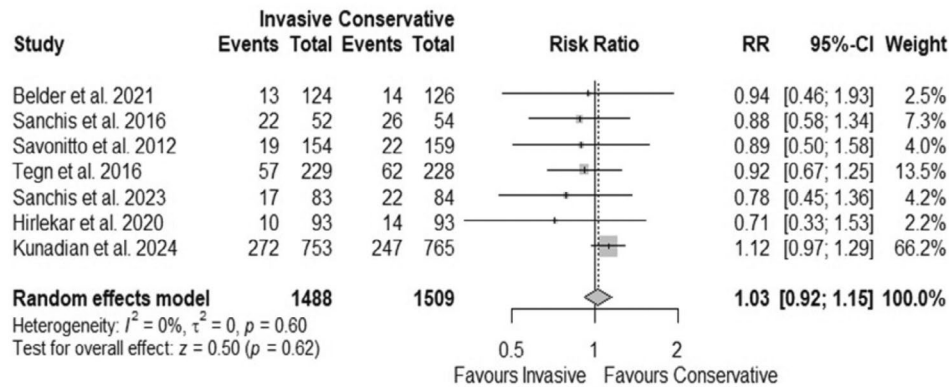
The pooled analysis demonstrated a significantly reduced risk of myocardial infarction with an invasive strategy (13% with invasive strategy versus 18.1% with conservative therapy; RR: 0.74, 95% CI: 0.57–0.96, $p=0.02$, moderate certainty, Figure 2A) as compared to the conservative approach. Moderate heterogeneity was observed ($I^2=38\%$). The results were consistent in

TABLE 1 | Baseline characteristics of the included studies.

Trial	Year	Country	Timing of the study	Sample size I/C/total	Age group of randomized patients	Time of randomization and invasive strategy	Patient population	Follow-up
Belder et al. (RINCAL) [19]	2021	United Kingdom	May 2014–September 2018	125/126/251	≥ 80	NR	NSTE-ACS	1 year
Sanchis et al. (MOSCA) [4]	2016	Spain	January 2012–March 2014	52/54/106	≥ 70	24 h (randomization) 72 h (invasive strategy)	NSTEMI	2.5 years
Savonitto et al. (Italian Elderly ACS) [5]	2012	Italy	January 2008–May 2010	154/159/313	≥ 75	48 h (randomization) 72 h (invasive strategy)	NSTE-ACS	1 year
Tegn et al. (After 80) [18]	2016	Norway	December 2010–February 2014	229/228/457	≥ 80	48 h (randomization) 72 h (invasive strategy)	NSTE-ACS	1.5 years
Sanchis et al. (MOSCA-FRAIL) [20]	2023	Spain	July 7, 2017–January 9, 2021	84/83/167	≥ 70	48 h (randomization) 72 h (invasive strategy)	NSTEMI	1 year
Hirlekar et al. (80+ study) [17]	2020	Sweden	2009–2017	93/93/186	≥ 80	NR	NSTE-ACS	1 year
Kunadian et al. (SENIOR-RITA) [11]	2024	United Kingdom	November 2016–March 2023	753/765/1518	≥ 75	48 h (randomization) 3–7 days (invasive strategy)	NSTEMI	4.1 years

Abbreviations: C, conservative group; I, invasive group; NSTE-ACS, non-ST-elevation acute coronary syndrome (NSTEMI, non-ST-elevation MI); NSTEMI, non-ST-elevation myocardial infarction; PCI, per cutaneous coronary intervention.

A)



B)

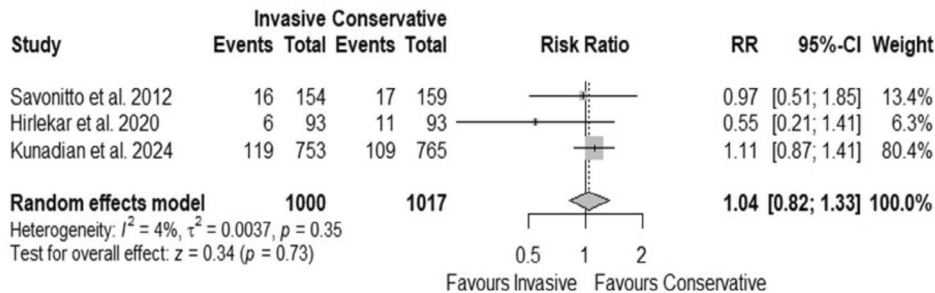


FIGURE 1 | Forest plots for (A) all-cause death and (B) cardiovascular death.

the secondary analysis (HR: 0.58, 95% CI: 0.38–0.89, $p = 0.01$, Figure S10).

3.1.4 | Stroke

The pooled analysis demonstrated a nonsignificant difference between invasive and conservative treatment strategies for the risk of stroke (3.8% with invasive strategy vs. 4.7% with conservative therapy; RR: 0.78, 95% CI: 0.53–1.15, $p = 0.21$, high certainty, Figure 2B). No heterogeneity was observed ($I^2 = 0\%$). The secondary analysis showed similar results (HR: 0.78, 95% CI: 0.53–1.16, $p = 0.23$, Figure S11).

3.1.5 | Major Bleeding

The risk of major bleeding was comparable across both groups (6.2% with invasive strategy versus 5% with conservative therapy; RR: 1.23, 95% CI: 0.90–1.69, $p = 0.19$, high certainty, Figure 3A). No heterogeneity was observed ($I^2 = 0\%$). The criteria used for describing major bleeding are listed in Table S5.

3.1.6 | Unplanned Revascularization

The invasive strategy was associated with a significantly reduced risk of unplanned revascularization (3.2% with invasive strategy vs. 11.3% with conservative therapy; RR: 0.29, 95% CI: 0.21–0.40,

$p < 0.01$, moderate certainty, Figure 3B) compared to the conservative strategy. No heterogeneity was observed ($I^2 = 0\%$). The results were consistent in the secondary analysis by pooling HRs (HR: 0.25, 95% CI: 0.18–0.36, $p < 0.01$, Figure S11).

No outlier study was identified in the leave-one-out analysis (Figures S13–S18). The PRISMA checklist is reported in Table S6.

4 | Discussion

This meta-analysis provides an evaluation of invasive versus conservative treatment strategies in older patients with NSTEMI-ACS. Our findings, including data from seven clinical trials, offer new insights into the effectiveness and safety of these treatment approaches in this older age group. The pooled analysis revealed that the invasive strategy was associated with a significantly reduced risk of myocardial infarction and unplanned revascularization compared to the conservative strategy, with a moderate certainty of evidence. However, no statistically significant difference was seen between the two strategies for the risk of all-cause death, CV death, stroke, and major bleeding, with a high certainty of evidence.

Our results differ from a previous meta-analysis [9] as our study found a significantly reduced risk of myocardial infarction with the invasive strategy, a finding not observed in the earlier meta-analysis. This may relate to the inclusion of more recent trials

TABLE 2 | Summary of findings with certainty of evidence.

Outcome	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Certainty
			Conservative treatment	Invasive treatment	
All-cause death	2997, (7 RCTs)	RR = 1.03 (0.92–1.15)	270 per 1000	278 per 1000 (248–310)	⊕⊕⊕⊕ High
Cardiovascular death	2017, (3 RCTs)	RR = 1.04 (0.82–1.33)	135 per 1000	140 per 1000 (110–179)	⊕⊕⊕⊕ High
Myocardial infarction	2830, (6 RCTs)	RR = 0.74 (0.57–0.96)	181 per 1000	134 per 1000 (103–174)	⊕⊕⊕⊕ ^a Moderate
Stroke	2411, (4 RCTs)	RR = 0.80 (0.55–1.17)	48 per 1000	38 per 1000 (26–56)	⊕⊕⊕⊕ High
Major bleeding	2644, (5 RCTs)	RR = 1.23 (0.90–1.69)	50 per 1000	62 per 1000 (45–85)	⊕⊕⊕⊕ High
Unplanned revascularization	2830, (6 RCTs)	RR = 0.29 (0.21–0.40)	113 per 1000	33 per 1000 (24–45)	⊕⊕⊕⊕ ^a Moderate

Abbreviations: CIs, confidence intervals; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; RR, risk ratio.

^aThe certainty of evidence was downgraded by one level due to the risk of bias observed for these outcomes.

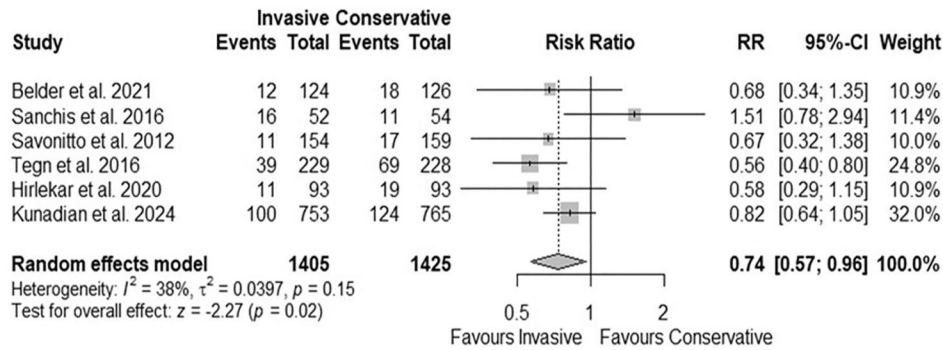
in our analysis, which might better reflect current clinical practices and patient populations.

Additionally, a significantly reduced risk of unplanned revascularization was observed with an invasive approach. The previous meta-analysis also concluded that the invasive strategy was associated with a significantly lower risk of unplanned revascularization than the conservative strategy. This aligns with the understanding that an invasive approach, which often includes coronary angiography followed by revascularization, if necessary, directly addresses the underlying coronary pathology, thereby reducing the incidence of recurrent ischemic events [21]. The invasive strategy's ability to stabilize or eliminate vulnerable coronary lesions likely contributes to the reduction in MI and the need for unplanned revascularization. However, the observed more than threefold increased risk of unplanned revascularization in patients randomized to the conservative strategy may also reflect heightened clinical vigilance. Clinicians may adopt a lower threshold for recommending repeat angiography and revascularization in these patients, concerned that untreated high-grade coronary lesions could lead to poor outcomes. This could introduce a systematic bias, as the threshold for unplanned revascularization likely differs between the invasive and conservative groups. Given these dynamics, it is important to interpret the reduced risk of unplanned revascularization with caution, taking into account the potential influence of clinician perception, trial designs, and the limited details regarding thresholds used for requesting repeat revascularization.

Our analysis found no statistically significant difference between the invasive and conservative strategies regarding all-cause mortality, CV death, stroke, and major bleeding. The invasive strategy demonstrated a reduction in myocardial infarction and unplanned revascularization; however, this benefit did not extend to improved overall survival or reduced major complications in the older population. The lack of significant differences in major complications suggests that the invasive approach could be considered a safe option for older patients, offering certain advantages without increasing the risk of adverse outcomes. Older patients often present with multiple comorbidities that can complicate both the invasive procedures and the post-procedural recovery [22, 23]. These comorbidities likely contribute to the lack of significant difference in mortality, as the risks associated with invasive strategies may counterbalance the potential benefits. Procedural risks in this population may include peri-procedural myocardial injury, arrhythmias, acute kidney injury due to contrast use, and complications related to anesthesia or vascular access [24, 25]. The similar stroke rates between the two strategies highlight the need for careful patient selection, as the invasive approach may not be suitable for all older patients, particularly, those with a high baseline risk of cerebrovascular events [26, 27]. Moreover, in older patients, the competing risk of non-CV death due to comorbidities is significant.

The conservative approach was non-inferior to the invasive strategy concerning all-cause death, CV death, stroke, and major bleeding. These outcomes are particularly important in older patients, where the risks associated with invasive procedures may outweigh the potential benefits. Older patients are at higher risk

A)



B)

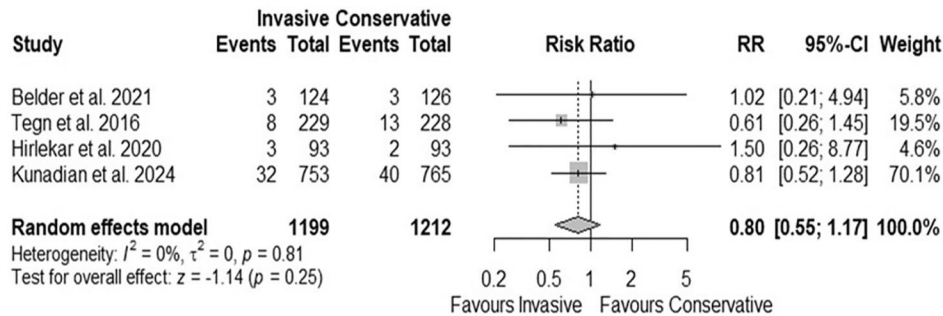
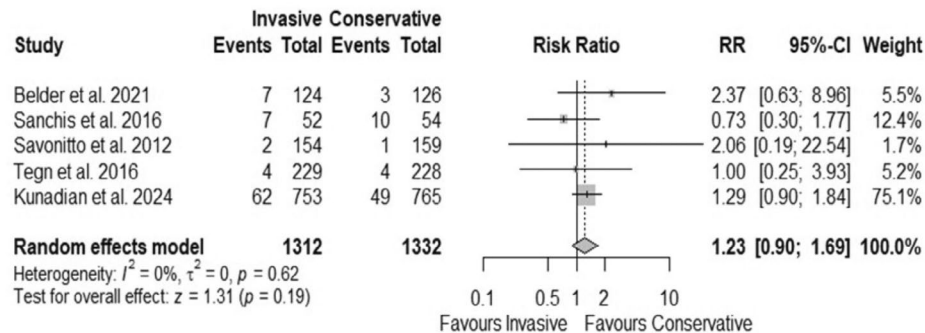


FIGURE 2 | Forest plots for (A) myocardial infarction and (B) stroke.

A)



B)

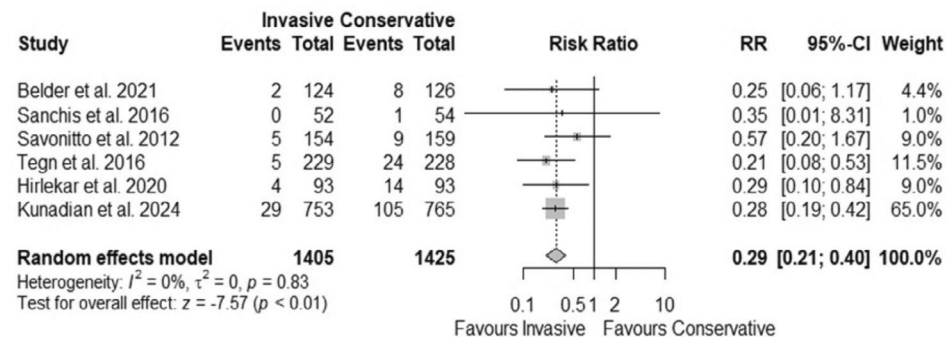


FIGURE 3 | Forest plots for (A) major bleeding and (B) unplanned revascularization.

for procedural complications, including bleeding [28], infection [29], and stroke, due to their frailty, comorbidities, and reduced physiological reserves [22]. The conservative approach, which avoids the immediate risks of invasive procedures, is, therefore, a safer alternative for many older patients, particularly, those with significant comorbid conditions. For many older patients, maintaining a good quality of life is a primary concern [30]. The conservative approach, which avoids the risks and recovery time associated with invasive procedures, may help preserve functional status and quality of life.

The invasive strategy was associated with a significantly reduced risk of myocardial infarction and unplanned revascularization; however, these benefits should be carefully weighed against potential risks and individual patient preferences to guide optimal management decisions. In older patients, where the risks of recurrent myocardial infarction must be balanced against the potential harms of invasive procedures, a tailored approach is essential. The invasive strategy could be considered when the risk/benefit ratio is favorable, taking into account coronary anatomy, patient comorbidities, and personal preferences. Clinicians may engage in shared decision-making with patients, considering the individual's risk profile, comorbidities, and preferences. The results underscore the importance of tailoring treatment strategies to the individual patient's requirements.

While our meta-analysis provides valuable insights, it is important to acknowledge certain limitations. A significant limitation of our analysis is the selection bias present in the included RCTs. The trials excluded the oldest, frailest, most multimorbid, and cognitively impaired older adults, as well as nursing home residents. Consequently, despite the advanced age of the patients included in this meta-analysis, the generalizability of our findings to the broader population of older adults, particularly those with more complex health profiles, is uncertain. Being a study-level meta-analysis, it inherently lacks access to individual patient data, limiting our ability to perform detailed subgroup analyses. Specifically, we were unable to assess outcomes stratified by age groups, sex, or frailty status. Such subgroup analyses could provide more nuanced insights into the differential effects of interventions across various patient subgroups but were not feasible in this study due to the aggregated nature of the data reported in the included trials. Moreover, the differences in baseline characteristics of patients could have influenced our findings. The trials inconsistently reported the frailty of patients, the timing of revascularization, and angiographic complexity; hence, we were unable to conduct additional subgroup analyses based on these parameters. Due to the invasive nature of the intervention, blinding was not possible in trials, and currently, we have only one trial with a long follow-up period, highlighting the need for more trials with extended follow-up periods to thoroughly evaluate long-term outcomes. It is important to mention that we were unable to account for competing risks directly in this meta-analysis due to the nature of the reported HRs in the pooled RCTs, which could affect the interpretation of statistically significant differences in MI and unplanned revascularization. Future RCTs may consider reporting both standard cox proportional HRs and competing risk-adjusted analyses to allow for better comprehensive interpretations in subsequent meta-analyses.

5 | Conclusion

This meta-analysis demonstrates that while the invasive strategy is associated with a reduced risk of myocardial infarction and unplanned revascularization in older patients with NSTEMI-ACS, it does not offer a significant advantage over the conservative approach regarding all-cause or CV mortality. Although the invasive approach may be preferred for its efficacy in preventing myocardial infarction, treatment decisions should be tailored to the individual, considering not only age but also a comprehensive assessment of geriatric and CV health. Age alone should not preclude the use of revascularization strategies, and future trials should prioritize the inclusion of older adults with a higher burden of geriatric conditions to enhance the generalizability of the findings. Long-term follow-up studies are essential to further evaluate the sustained outcomes of both treatment strategies.

Author Contributions

Mushood Ahmed: conceptualization, project administration, formal analysis of data, formal analysis, methodology, and software, writing the original draft, writing, reviewing, and editing, visualization and validation. **Areeba Ahsan:** formal analysis of data, formal analysis, methodology, and software, writing the original draft. **Aimen Shafiq:** formal analysis, methodology, and software, writing the original draft. **Tallal Mushtaq Hashmi:** writing, reviewing, and editing. **Raheel Ahmed:** writing, reviewing, and editing. **Mahboob Alam:** conceptualization, writing the original draft, writing, reviewing, and editing. **Farhan Shahid:** visualization and validation. **Jamal S. Rana:** conceptualization, data curation, and project administration, writing, reviewing, and editing. **Mamas A. Mamas:** supervision, writing, reviewing, and editing. **Gregg C. Fonarow:** supervision, writing, reviewing, and editing.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

Dr. Fonarow reported receiving personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eli Lilly, Johnson & Johnson, Medtronic, Merck, Novartis, and Pfizer outside the submitted work. The other authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.