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11-1-2022

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# Meta-Analysis on Invasive Versus Conservative Strategy in Patients Older Than Seventy Years With Non-ST Elevation Myocardial Infarction



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**Management of non-ST elevation myocardial infarction (NSTEMI) has evolved over the years, but most published data are from younger patients. Data on the NSTEMI management in older patients remain limited. We performed a meta-analysis of randomized controlled trials to evaluate the long-term outcomes of invasive versus conservative strategies in older patients (>70 years old) with NSTEMI. Of 1,550 reports searched, 4 randomized controlled trials (1,126 patients) were included in the analysis, with a median follow-up of 1.25 years (range: 1 to 2.5 years). The median age of included patients was 83.6 (interquartile range: 2.8 years). The invasive strategy was associated with significantly lower risk of major adverse cardiac and cerebrovascular event (odds ratio [OR] 0.60, 95% confidence interval [CI] 0.40 to 0.91,  $I^2 = 54%$ ; 3 trials) and unplanned revascularization (OR 0.31, 95% CI 0.15 to 0.64,  $I^2 = 1.7%$ ; 3 trials) than was the conservative strategy. There was no difference in all-cause mortality (OR 0.88, 95% CI 0.65 to 1.18,  $I^2 = 0%$ ; 4 trials), myocardial infarction (OR 0.70, 95% CI 0.42 to 1.19,  $I^2 = 54.7%$ ; 4 trials), or bleeding (OR 0.87, 95% CI 0.39 to 1.93,  $I^2 = 0%$ ; 3 trials) between the strategies. In conclusion, the use of initial invasive strategy in older patients presenting with NSTEMI was associated with a significantly lower risk of major adverse cardiac and cerebrovascular event and unplanned revascularization than that of the initial conservative strategy without increased bleeding. © 2022 Elsevier Inc. All rights reserved. (Am J Cardiol 2023;186:66–70)**

Management of non-ST elevation myocardial infarction (NSTEMI) has evolved over the years, with improved survival because of the advancement of care and therapeutics. Most published data, however, provide evidence for younger patients. The recent European Society of Cardiology guidelines recommend similar revascularization strategies for all patients regardless of age (class IB).<sup>1</sup> The 2014 American Heart Association/American College of Cardiology guidelines recommended goal-targeted medical treatment for older patients and invasive management when

appropriate.<sup>2</sup> However, the disease in older patients (>70 years old) remains difficult to manage, with fewer possibilities of who underwent invasive procedures after NSTEMI owing to multiple co-morbidities, higher complexity of coronary artery disease, increased risk of complications, and heterogeneous outcomes in published randomized controlled trials (RCTs).<sup>3–6</sup> Because of the lack of specific recommendations from the abovementioned guidelines and paucity of data, we performed a meta-analysis to evaluate the outcomes of invasive versus conservative strategies in older patients with NSTEMI.

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Funding: none.

See page 69 for disclosure information.

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## Methods

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>7</sup> We performed a computerized search from January 1, 1990 to December 30, 2021, using PubMed and EMBASE databases and using the following Medical Education Subject Headings terms: “invasive strategy,” “conservative strategy,” “elderly,” and “non-ST elevation myocardial infarction,” separately and in combination. To identify gray literature, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) was searched. We also searched the references of the eligible studies for any missed studies.

We included RCTs that compared long-term outcomes of invasive with conservative strategies in older patients

(defined as 70 years old or older) presenting with NSTEMI. The invasive strategy used coronary angiogram and possible intervention using percutaneous coronary intervention or coronary artery bypass graft surgery. In contrast, the conservative strategy denoted the initial management with medical therapy. Studies without a comparison arm, non-randomized trials, observational studies, and a nonolder population were excluded. Editorials, letters, and review articles were also excluded.

The studies were screened by 2 independent authors (MK and MHM). Disagreements were resolved by discussion with a third author (MM). Discrepancies were settled by consensus. The bias risk of the included studies was assessed using the Cochrane risk assessment tool for RCTs.<sup>8</sup>

The outcomes included all-cause mortality, myocardial infarction (MI), bleeding, and unplanned revascularization, and major adverse cardiac and cerebrovascular event (MACCE).

Definitions of outcomes, inclusion, and exclusion criteria, Bias risk assessment of randomized controlled trials with the Cochrane assessment tool, and Baseline Characteristics as reported by individual studies are shown in [Supplementary Table 1, 2 and 3](#) respectively.

Continuous variables were reported as mean with SD, and categorical variables were expressed as frequency/percentage. The odds ratio (OR) and mean difference, 95% confidence intervals (CIs), were calculated using a random-effects model using the Der Simonian-Laird method.<sup>9</sup> A  $p < 0.05$  was considered for statistical significance. Analyses were conducted using Stata version 17.0 software (Stata Corporation, College Station, Texas).

## Results

The study selection process is described in [Supplementary Figure 1](#). The initial search yielded 1,550 reports. After screening, 4 RCTs (1,126 patients) were included in the analysis.<sup>3–6</sup> All RCTs were performed in Europe. A total of 559 patients were randomized to the invasive strategy, and 567 patients were randomized to the conservative strategy. The enrollment period ranged from 2008 to 2014. The median age of the included patients was 83.6 years, with an interquartile range of 2.8 years. Approximately half the patients randomized to the invasive strategy underwent revascularization, mostly with percutaneous coronary intervention. The rate of coronary artery bypass graft surgery in the invasive arm ranged from 1.6% to 6% and seemed to be lower in more recent studies. The characteristics of included trials are shown in [Table 1](#).

Over a median follow-up period of 1.25 years (range from 1 to 2.5 years), MACCE events occurred in 159 patients (28%) in the invasive group and 223 patients (39%) in the conservative arm. The invasive strategy was associated with significantly lower risk of MACCE (OR 0.60, 95% CI 0.40 to 0.91,  $I^2 = 54%$ ; 3 trials). A total of 44 patients had unplanned revascularization, 10 (1.8%) in the invasive group versus 34 (6%) in the conservative group. The invasive strategy was associated with a lower risk of unplanned revascularization (OR 0.31, 95% CI 0.15 to 0.64,  $I^2 = 1.7%$ ; 3 trials) than was the conservative strategy.

Table 1  
Characteristics of included trials

Study	Enrollment period- country and number of centers	Age of population	Time of randomization and invasive strategy	# Invasive/ conservative/ Total	Follow-up time (years)	Notes	Percentage of PCI and CABG in the invasive arm CA/PCI/ CABG	Crossover rates (From conservative to invasive strategy)
Savonitto et al. 2012	January 2008 – May 2010 Multicenter- Italy	≥75	48 hours (randomization) 72 hours (invasive strategy)	154/159/313	1 year	Significant improvement of primary endpoints in patients with elevated troponin on admission	136/76/9 76 (49%) patients had PCI 9 (6%) patients had CABG	46 patients (28.9%) 35 patients had PCI 1 patient had CABG Due to Recurrent ischemia Heart failure Reinfarction VT Not stated
Sanchez et al. 2016 (MOSCA study)	January 2012 – March 2014 Multicenter-Spain	≥70	24 hours (randomization) 72 hours (invasive strategy)	52/54/106	2.5 years	Invasive strategy improve mortality on short term but not on long term	50% had intervention 47% PCI 3% CABG 220/107/6	Not stated
Tegn et al. 2016 (The After Eighty study)	December 2010 – February 2014 Multicenter - Norway	≥80	48 hours (randomization) 72 hours (invasive strategy)	229/228/457	Median follow-up 1.53 years	Effect of invasive dilute with increasing age		Not stated
Beider et al. 2021 (RINCAL)	May 2014 - September 2018 Multicenter – united kingdom	≥80	Not mentioned	124/126/250	1 year	The RINCAL trial was terminated early due to slow recruitment	124/61/2 61 (49.2%) PCI 2 (1.6%) CABG	11 patients had CA (8.7%)

CA = coronary angiography; CABG = coronary artery bypass graft; GI = gastrointestinal; MI = myocardial infarction; PCI = percutaneous coronary intervention.

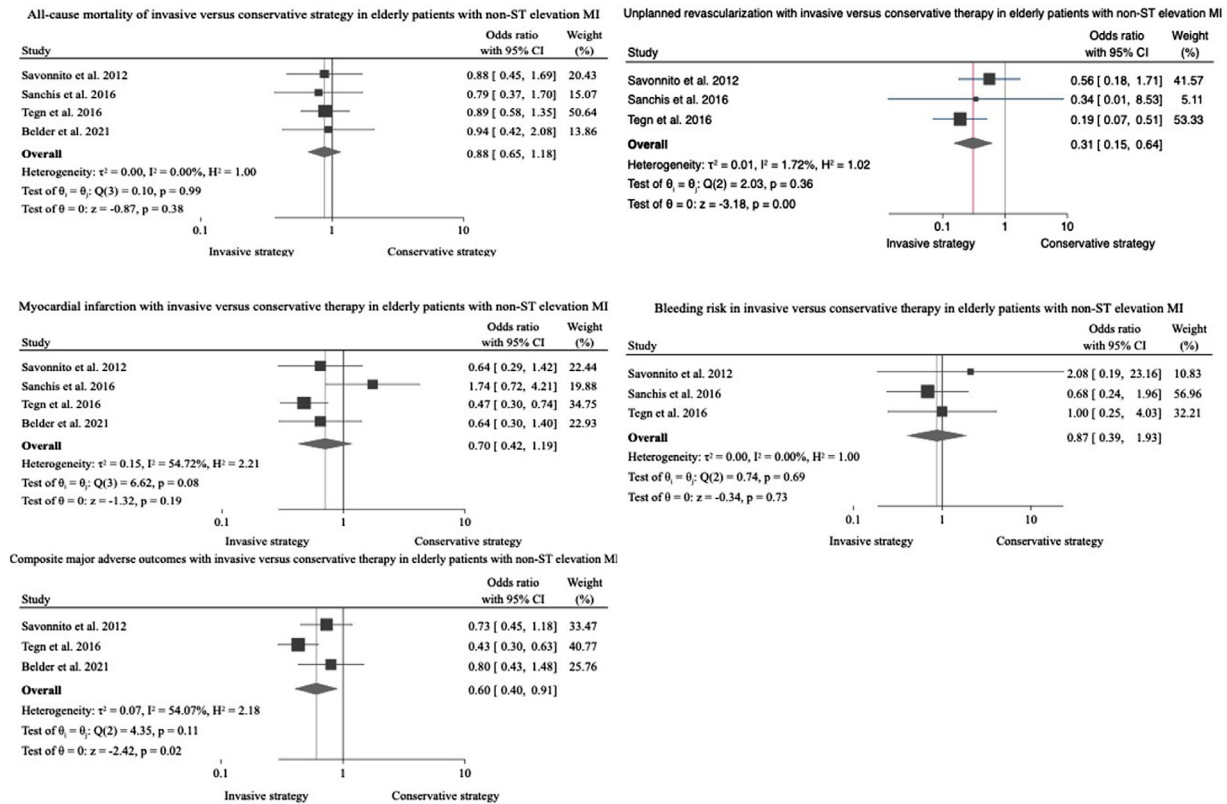


Figure 1. Forest plots of the study outcomes: all-cause mortality, unplanned revascularization, myocardial infarction, bleeding risk, and composite major outcome.

There was no difference in all-cause mortality, 20% in invasive versus 22% in conservative group (OR 0.88, 95% CI 0.65 to 1.18,  $I^2 = 0\%$ ; 4 trials), MI, 14% in invasive versus 20% in conservative group (OR 0.70, 95% CI 0.42 to 1.19,  $I^2 = 54.7\%$ ; 4 trials), or bleeding, 2.3% in invasive versus 2.6% in conservative group (OR 0.87, 95% CI 0.39 to 1.93,  $I^2 = 0\%$ ; 3 trials), between both strategies (Figure 1).

## Discussion

The main findings of our study can be summarized as follows: (1) there are only 4 RCTs that compared outcomes of the invasive and conservative strategies in NSTEMI management in the older patients. All trials were performed outside the United States, and the latest trial was terminated early owing to slow enrollment; and (2) over a median follow-up of 1.25 years, the invasive strategy was associated with a significantly lower risk of MACCE, led by a lower risk of unplanned revascularization with no difference in all-cause mortality, MI, and bleeding. In other words, a decrease in MACCE is primarily because of a reduction in unplanned revascularization in the invasive strategy.

The present study provides evidence on the safety of invasive strategy in patients >70 years old presenting with NSTEMI. Our analysis showed a significant benefit in avoiding unplanned revascularization with the invasive strategy without an increased risk of bleeding. The higher risk of unplanned revascularization in the conservative group is likely related to the unvascularized culprit vessel, which

can introduce bias in evaluating such an outcome. However, the urgent need for revascularization remains an undesirable outcome, especially when the indication is hemodynamic or electric instability. Our results confirm that invasive strategy is preferable to conservative strategy even in older patients, consistent with the published guidelines.<sup>1,2</sup>

In our analysis, there was no difference in mortality or recurrent MI over a median follow-up of 1.25 years. The absence of mortality benefit is likely because of this patient population's advanced age and co-morbidities. It can also be related to the low number of patients and the absence of power to identify differences in mortality. Moreover, only half these patients underwent revascularization, a decision heavily dependent on local expertise in interventional cardiology and surgery teams. In patients with complex coronary disease, most teams would default to medical therapy, diluting the possible beneficial effect of the invasive strategy.

One of the most concerning issues is bleeding after invasive intervention, especially in older patients, from mandatory antiplatelet therapy.<sup>10,11</sup> It becomes complicated with associated co-morbidities, dementia, polypharmacy, and so on. The results of the present analysis might alleviate the potential fear of increased bleeding tendency in older patients.

Treatment of the older population is challenging owing to the paucity of data about this population. Despite evidence of the effectiveness of the invasive strategy, Tegn et al indicated dilution of the efficacy with the advancement of age and with patients >90 years old, with the difference between interval (84 to 90 years) compared with (80 to 84 years). This makes it hard to conclude that the invasive strategy is of



benefit for this population.<sup>6</sup> In our analysis, the invasive strategy was associated with better outcomes in patients with a median age of 83.6 years, and until we have further evidence, we do not recommend the generalization of our findings to patients with increasingly older age.

One of the major reasons cardiologists are hesitant to implement the invasive strategy for older patients is the perceived feeling of an undesirable risk-to-benefit ratio. Our analysis illustrated the safety of invasive strategy in older patients, given the absence of difference in MI or bleeding between both treatment strategies. Our findings can help inform the discussion with patients and families during shared decision-making. The in-depth discussion with the patient and family should include the absence of a mortality benefit but safely reduce adverse events with the invasive strategy. Moreover, patients co-morbidities, frailty status, medication compliance, and life expectancy should be considered before deciding on the invasive approach.<sup>12,13</sup>

Our study provides guidance on the management of NSTEMI in older patients. However, larger dedicated RCTs are needed, especially to reflect the current practice of safer invasive strategies (e.g., radial access, intravascular ultrasound, and so on) and better medical management (newer P2Y12 inhibitors and so on). The ongoing SENIOR-RITA (British Heart Foundation Older Patients With Non-ST Segment elevation myocardial Infarction Randomized Interventional Treatment) trial enrolling 1,668 participants (age >75 years with NSTEMI) (NCT03052036) would provide more evidence for NSTEMI treatment in the much older population.<sup>14</sup>

Our findings have limitations, our study results should be interpreted within the light of their limitations. First, we only included 4 studies with 1,126 patients, which can still be underpowered to detect differences between both strategies. Second, there is a risk of unmeasured heterogeneity between trials, especially because the door-to-invasive strategy time was not clearly reported in all studies and could not be evaluated. Third, our meta-analysis did not include individual patient data. Fourth, we could not evaluate long-term outcomes given the limitations of the included studies. Finally, in evaluation of MACCE, there is just 1 trial that considered stroke. Furthermore, MACCE analysis included all-cause mortality, and caution should be exercised in its interpretation because after the initial follow-up, the risk of noncardiovascular death exceeds that of cardiovascular death in some of these populations.

In conclusions, the use of initial invasive strategy in older patients presenting with NSTEMI was associated with a significantly lower risk of MACCE and unplanned revascularization than was the initial conservative strategy without increased bleeding.

## Disclosures

Dr. Alaswad receives consulting/speaker honoraria from Boston Scientific, Cardiovascular Systems Inc., Abbott Vascular, and Teleflex. Dr. Basir undertakes consulting and is a speaker for Abbott Vascular, Abiomed, Cardiovascular Systems, Chiesi, and Zoll. Dr. Brilakis receives consulting/speaker honoraria from Abbott Vascular, American Heart Association (associate editor *Circulation*), Amgen, Asahi

Intecc, Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), ControlRad, CSI, Elsevier, GE Healthcare, IMDS, InfraRedx, Medtronic, Medtronic, OpSens, Siemens, and Teleflex; receives research support from Boston Scientific and GE Healthcare; is an owner of Hippocrates LLC; and is a shareholder in MHI Ventures, Cleerly Health, and Stallion Medical. Dr. Garcia is a consultant for and receives grant support from Boston Scientific. The remaining authors have no conflicts of interest to declare.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2022.10.011>.

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