The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 7, 2024 VOL. 391 NO. 18

Invasive Treatment Strategy for Older Patients with Myocardial Infarction

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ABSTRACT

BACKGROUND

Whether a conservative strategy of medical therapy alone or a strategy of medical therapy plus invasive treatment is more beneficial in older adults with non–ST-segment elevation myocardial infarction (NSTEMI) remains unclear.

METHODS

We conducted a prospective, multicenter, randomized trial involving patients 75 years of age or older with NSTEMI at 48 sites in the United Kingdom. The patients were assigned in a 1:1 ratio to a conservative strategy of the best available medical therapy or an invasive strategy of coronary angiography and revascularization plus the best available medical therapy. Patients who were frail or had a high burden of coexisting conditions were eligible. The primary outcome was a composite of death from cardiovascular causes (cardiovascular death) or nonfatal myocardial infarction assessed in a time-to-event analysis.

RESULTS

A total of 1518 patients underwent randomization; 753 patients were assigned to the invasive-strategy group and 765 to the conservative-strategy group. The mean age of the patients was 82 years, 45% were women, and 32% were frail. A primary-outcome event occurred in 193 patients (25.6%) in the invasive-strategy group and 201 patients (26.3%) in the conservative-strategy group (hazard ratio, 0.94; 95% confidence interval [CI], 0.77 to 1.14; P=0.53) over a median follow-up of 4.1 years. Cardiovascular death occurred in 15.8% of the patients in the invasive-strategy group and 14.2% of the patients in the conservative-strategy group (hazard ratio, 1.11; 95% CI, 0.86 to 1.44). Nonfatal myocardial infarction occurred in 11.7% in the invasive-strategy group and 15.0% in the conservative-strategy group (hazard ratio, 0.75; 95% CI, 0.57 to 0.99). Procedural complications occurred in less than 1% of the patients.

CONCLUSIONS

In older adults with NSTEMI, an invasive strategy did not result in a significantly lower risk of cardiovascular death or nonfatal myocardial infarction (the composite primary outcome) than a conservative strategy over a median follow-up of 4.1 years. (Funded by the British Heart Foundation; BHF SENIOR-RITA ISRCTN Registry number, ISRCTN11343602.)

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*A full list of the British Heart Foundation SENIOR-RITA Trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 1, 2024, and updated on October 21, 2024, at NEJM.org.

N Engl J Med 2024;391:1673-84.
DOI: 10.1056/NEJMoa2407791

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Specific pharmacologic and invasive treatment guidelines for older patients with acute coronary syndromes are lacking owing to the underrepresentation of older patients in clinical trials.[1,2] Age is an established risk factor for acute coronary syndromes, and non–ST-segment elevation myocardial infarction (NSTEMI) is the main acute coronary syndrome subtype among adults older than 75 years of age.[3,4] The clinical characteristics of the older population with NSTEMI are heterogeneous, with frailty,[5-8] coexisting conditions,[9] the level of cognitive function,[10,11] and health-related quality of life[12] playing important roles in guiding clinical care.

To date, only six small, randomized, controlled trials investigating an invasive treatment strategy in older patients with NSTEMI have published results.[4,13-18] In the After Eighty trial (457 patients; mean age, 85 years; 50.8% women), the invasive strategy was associated with a significantly lower incidence of a primary-outcome event, a composite of myocardial infarction, urgent revascularization, stroke, or death, than the conservative strategy at a median follow-up of 18 months, a result driven primarily by lower rates of myocardial infarction and revascularization.[13]

A patient-level meta-analysis that included 1479 patients showed that, as compared with conservative management, routine invasive treatment in older patients with NSTEMI was not associated with a lower risk of a composite of death from any cause or myocardial infarction within 1 year after treatment. However, the invasive-treatment strategy was associated with lower risks of myocardial infarction and urgent revascularization.[19]

Previous studies involving older patients with acute coronary syndromes treated with an invasive strategy have been limited by small sample sizes or no formal assessment of frailty, the burden of coexisting conditions, or issues related to cognitive function, which has led to inconsistent findings that limited generalizability. Clinical-practice guidelines specify that in the absence of robust clinical-trial evidence, treatment of older patients should be individualized on the basis of patient characteristics.[20] We designed the British Heart Foundation SENIOR-RITA (Older Patients with Non–ST-Segment Elevation Myocardial Infarction Randomized Interventional Treatment) trial to evaluate the potential beneficial effects of a routine invasive approach with a view to coronary revascularization as compared with a conservative approach of the best available medical treatment in a broadly representative population of older patients, including frail patients, presenting with NSTEMI and coexisting conditions.

Methods

Trial Design and Oversight

The SENIOR-RITA trial was a prospective, multicenter, open-label, randomized controlled trial that included patients who were least 75 years of age with NSTEMI to test treatment involving an invasive strategy as compared with a conservative treatment strategy. The protocol and statistical analysis plan are available with the full text of this article at NEJM.org. Written informed consent was obtained for all patients. In England, a consultee declaration (signed by a family member or caregiver) was obtained for patients with cognitive impairment. The trial was overseen by an independent steering committee and a data and safety monitoring committee. An independent clinical events committee, the members of which were unaware of the trial-group assignments, adjudicated deaths and myocardial infarction events (see the Supplementary Appendix, available at NEJM.org).

The Newcastle Clinical Trials Unit managed and coordinated the conduct of the trial. The Newcastle University Biostatistics Research Group was responsible for statistical oversight and performed statistical analyses. The trial was funded by the British Heart Foundation and sponsored by Newcastle upon Tyne Hospitals NHS Foundations Trust. The protocol was approved by the U.K. Health Research Authority. The first author, who wrote the first draft of the manuscript, had access to the trial data and vouches for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Trial Population

Patients who were at least 75 years of age and had presented with a clinical diagnosis of NSTEMI were eligible. Patients with a type 1 NSTEMI during the index hospitalization were included. Patients were excluded if they had STEMI or unstable angina or cardiogenic shock, had a life expectancy of less than 1 year, were previously included in the SENIOR-RITA trial, or were deemed to be unable to undergo invasive coronary angiography (addi-

tional details about inclusion and exclusion criteria are provided in the Supplementary Appendix).

FRAILTY, COEXISTING CONDITIONS, AND COGNITIVE IMPAIRMENT

Frailty was assessed with the use of the Fried Frailty Index (three categories of patient frailty graded on five criteria: frail, indicated by the presence of three or more criteria; intermediate or prefrailty, indicated by the presence of one or two criteria; and robust, no criteria present)[21] and the modified Rockwood Clinical Frailty Scale (ranging from 1 [very fit] to 7 [severely frail], with a score of 5 or greater indicating frailty).[22] The degree of coexisting conditions was graded according to age-adjusted scores based on the Charlson Comorbidity Index (range, 0 to 37, with higher scores indicating a greater burden of coexisting conditions).[23] Cognitive impairment was evaluated with the use of the Montreal Cognitive Assessment (MoCA; range, 0 to 30, with a score of 26 or higher indicating normal cognitive function) (see the Supplementary Appendix for details regarding the assessments).[24]

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive treatment according to an invasive-treatment strategy of coronary angiography (and if appropriate, coronary revascularization) plus the best available medical therapy (the invasive-strategy group) or to receive only the best available medical therapy (the conservative-strategy group). Randomization was conducted with the use of a variable-length block-stratified method with randomly selected block sizes of two, four, six, and eight. Stratification was according to site and scores on the Rockwood scale. Randomization was performed at each site with the use of a secure Web-based system.

Components of the best available medical therapy included, in the absence of contraindications, aspirin (at a dose of 75 mg daily), a $P2Y_{12}$ receptor antagonist, statin therapy, a beta-blocker (to reach a target heart rate of 60 to 70 beats per minute), and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. Management of hypertension, diabetes, and hypercholesterolemia was in accordance with the relevant clinical practice guidelines.

Coronary angiography was performed in accordance with local practice and the protocol. On the basis of angiographic findings, coronary revascularization was performed within 3 to 7 days, when feasible, by either percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) at the discretion of the attending cardiologist and the multidisciplinary team. In the conservative-therapy group, coronary angiography was allowed if the patient had clinical deterioration and the procedure was clinically indicated in the judgment of the treating physicians.

OUTCOMES AND FOLLOW-UP

The primary outcome, assessed in a time-to-event analysis, was a composite of cardiovascular death or nonfatal myocardial infarction, as defined by the fourth universal definition of myocardial infarction.[25] Key secondary outcomes were cardiovascular death, nonfatal myocardial infarction, a composite of death from any cause or nonfatal myocardial infarction, death from any cause, recurrent myocardial infarction, subsequent coronary angiography, subsequent coronary revascularization, hospitalization for heart failure, stroke, transient ischemic attack, and bleeding (as defined by the Bleeding Academic Research Consortium criteria).[26] Safety outcomes included procedural and in-hospital complications occurring in patients in the invasive-strategy group. Patients were followed up by means of telephone or in-person visits at 6 months, 1 year, and yearly thereafter until 5 years.

STATISTICAL ANALYSIS

We assumed a 20% risk of a primary-outcome event in the conservative-therapy group at 12 months and aimed to detect a 16% risk of a primary-outcome event in the invasive-therapy group, which corresponds to a hazard ratio of 0.78. We estimated that a sample of 1668 patients would provide at least 688 events of cardiovascular death or nonfatal myocardial infarction (with a minimum follow-up period of 1 year and maximum of 5 years), which would provide the trial with 90% power to detect a hazard ratio of 0.78 at a two-sided type I error rate of 0.05 with the use of a log-rank test. We estimated that 520 events would be required to provide the trial with 80% power.

Analyses used all available data, up to a maximum of 5 years of follow-up, and were performed on an intention-to-treat basis. Missing data for

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Invasive Strategy (N=753)	Conservative Strategy (N=765)
Age		
Mean — yr	82.5±4.7	82.2±4.7
Distribution — no. (%)		
≥75 to <80	211 (28.0)	246 (32.2)
≥80 to <85	304 (40.4)	291 (38.0)
≥85 to <90	182 (24.2)	171 (22.4)
≥90 to <95	47 (6.2)	51 (6.7)
≥95	9 (1.2)	6 (0.8)
Female sex — no. (%)	337 (44.8)	342 (44.7)
Median no. of days from admission to randomization (IQR)	2 (1–3)	2 (1–3)
MoCA score†		
Median (IQR)	25 (21–27)	24 (21–26)
Impaired — no./total no. (%)	433/724 (59.8)	476/731 (65.1)
Rockwood Clinical Frailty Scale score‡		
Median (IQR)	3 (2 to 4)	3 (2 to 4)
Category — no./total no. (%)		
Frail	153/753 (20.3)	164/765 (21.4)
Very fit	103/752 (13.7)	97/763 (12.7)
Well, without active disease	134/752 (17.8)	155/763 (20.3)
Well, with treated coexisting conditions	198/752 (26.3)	214/763 (28.0)
Apparently vulnerable	165/752 (21.9)	134/763 (17.6)
Mildly frail	97/752 (12.9)	108/763 (14.2)
Moderately frail	47/752 (6.2)	48/763 (6.3)
Severely frail	8/752 (1.1)	7/763 (0.9)
Fried Frailty Index score§		
Median (IQR)	2 (1–3)	2 (1–3)
Category — no./total no. (%)		
Robust	150/716 (20.9)	153/730 (21.0)
Prefrail	335/716 (46.8)	339/730 (46.4)
Frail	231/716 (32.3)	238/730 (32.6)
Median age-adjusted Charlson Comorbidity Index score (IQR)¶	5 (4–6)	5 (4–6)
Smoking status — no./total no. (%)		
Current smoker	35/748 (4.7)	45/756 (6.0)
Former smoker	358/748 (47.9)	336/756 (44.4)
Never smoked	355/748 (47.5)	375/756 (49.6)

Table 1. (Continued.)

Characteristic	Invasive Strategy (N=753)	Conservative Strategy (N=765)
Hypertension — no./total no. (%)	490/753 (65.1)	500/764 (65.4)
Diabetes — no./total no. (%)	232/753 (30.8)	234/764 (30.6)
Hypercholesterolemia — no./total no. (%)	242/752 (32.2)	231/763 (30.3)
History of renal disease — no./total no. (%)	156/753 (20.7)	158/764 (20.7)
Previous MI — no./total no. (%)	247/753 (32.8)	227/764 (29.7)
Previous PCI — no./total no. (%)	163/752 (21.7)	139/764 (18.2)
Previous CABG — no./total no. (%)	101/753 (13.4)	80/764 (10.5)
History of peripheral vascular disease — no./total no. (%)	57/753 (7.6)	61/764 (8.0)
History of TIA or stroke — no./total no. (%)	128/753 (17.0)	101/764 (13.2)
History of COPD — no./total no. (%)	115/753 (15.3)	118/764 (15.4)
History of congestive heart failure — no./total no. (%)	73/753 (9.7)	70/764 (9.2)

* Percentages were calculated from the number of participants for whom data were available. Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, IQR interquartile range, MI myocardial infarction, PCI percutaneous coronary intervention, and TIA transient ischemic attack.
† Scores on the Montreal Cognitive Assessment (MoCA) range from 0 to 30, with scores of 26 or higher indicating normal cognitive function and scores of 25 or lower indicating impairment.
‡ Scores on the modified Rockwood Clinical Frailty Scale range from 1 (very fit) to 7 (severely frail), with a score of 5 or higher indicating frailty.
§ The Fried Frailty Index measures three categories of patient frailty graded on five criteria: frail, indicated by the presence of three or more criteria; intermediate or prefrailty, indicated by the presence of one or two criteria; and robust, no criteria present.
¶ Age-adjusted scores based on the Charlson Comorbidity Index range from 0 to 37, with higher scores indicating a greater burden of coexisting conditions.

clinical outcomes were minimal, and unobserved event times were assumed to be censored at random. Cumulative incidence was estimated with Kaplan–Meier methods, and the assigned treatment strategies were compared with the use of a log-rank test stratified according to the Rockwood frailty status at baseline. The effect of an invasive strategy as compared with a conservative strategy was estimated with the use of a proportional-hazards model, with adjustment for Rockwood frailty status, and the results are presented as hazard ratios and 95% confidence intervals. There was no adjustment for multiplicity, and the widths of the confidence intervals should not be used to infer treatment effect.

For outcomes that were subject to competing risks, cumulative incidence was also estimated with the use of Aalen–Johansen estimates, and treatment effects were estimated with the use of Fine and Gray regression models adjusted for Rockwood frailty status. If the proportional-hazards assumption of the Cox model was violated, the difference in the restricted mean event-free time at 5 years was estimated. All analyses were performed with the use of Stata software, version 18 (StataCorp).

RESULTS

PATIENTS

From November 2016 through March 2023, a total of 6977 eligible patients from 48 National Health Service trusts across England and Scotland underwent screening (Fig. S1 in the Supplementary Appendix). Among patients who underwent screening but not randomization (mean age, 82 years; 47% women), 55% received invasive treatment, 44% received conservative care, and 1% received palliative care (Tables S1, S2, and S3). A total of 1518 patients underwent randomization — 753 were assigned to the invasive-strategy group and 765 to the conservative-strategy

Table 2. Medical Therapy and Invasive Procedures.*

Therapy or Procedure	Invasive Strategy (N=753)	Conservative Strategy (N=765)
Antiplatelet therapy		
Aspirin — no./total no. (%)	682/752 (90.7)	663/762 (87.0)
$P2Y_{12}$ receptor antagonist, overall — no./total no. (%)	674/752 (89.6)	719/762 (94.4)
Clopidogrel	348/752 (46.3)	405/762 (53.1)
Ticagrelor	322/752 (42.8)	313/762 (41.1)
Prasugrel	4/752 (0.5)	1/762 (0.1)
No. of agents — no./total no. (%)		
None	20 (2.7)	8 (1.0)
Single	108/752 (14.4)	126/765 (16.5)
Dual	624/752 (83.0)	628/762 (82.4)
Anticoagulant therapy — no./total no. (%)		
Overall	170/753 (22.6)	183/762 (24.0)
Apixaban	51 (6.8)	71 (9.3)
Rivaroxaban	44/752 (5.9)	38/765 (5.0)
Warfarin	28/753 (3.7)	34/762 (4.5)
Edoxaban	16 (2.1)	15 (2.0)
Dabigatran	2 (0.3)	4 (0.5)
Other	29/753 (3.9)	21/762 (2.8)
Triple therapy — no. (%)†	100 (13.3)	91 (11.9)
Lipid-lowering therapy — no./total no. (%)		
Overall	682/752 (90.7)	688/762 (90.3)
Atorvastatin	595/752 (79.1)	608/762 (79.8)
Simvastatin	40 (5.3)	43 (5.6)
Rosuvastatin	31 (4.1)	25 (3.3)
Pravastatin	12 (1.6)	9 (1.2)
Ezetimibe	4 (0.5)	3 (0.4)
Invasive procedures		
Angiography — no. (%)	680 (90.3)	NA
Radial access — no./total no. (%)	607/680 (89.3)	NA
Median no. of days from admission to angiography (IQR)	5 (3 to 7)	NA
Median no. of days from randomization to angiography (IQR)	3 (1 to 5)	NA
Reason why angiography was not performed — no. (%)		
Clinical decision)	35 (4.6)	NA
Participant decision	21 (2.8)	NA
Participant too unwell	13 (1.7)	NA
Participant died	3 (0.4)	NA
Not known	1 (0.1)	NA

Table 2. (Continued.)

Therapy or Procedure	Invasive Strategy (N=753)	Conservative Strategy (N=765)
Revascularization — no. (%)	376 (49.9)	NA
PCI — no. (%)	351 (46.6)	NA
CABG — no. (%)	25 (3.3)	NA
Median no. of days from admission to PCI (IQR)	5 (3 to 7)	NA
Median no. of days from randomization to PCI (IQR)	2 (1 to 4)	NA
Median no. of days from admission to CABG (IQR)	18 (13 to 27)	NA

* Percentages were calculated from the number of participants for whom data were available. NA denotes not applicable.
† Triple therapy consists of a combination of an oral anticoagulant and dual antiplatelet therapy.

group — at a median time of 2 days from the time of hospitalization. Four participants were found to be ineligible after randomization (Table S4).

The characteristics of the patients at baseline and the medical therapy they had received are summarized in Tables 1 and 2 and Table S5. The mean age of the patients who underwent randomization was 82 years, 44.7% were women, and 32.4% were frail according to the Fried Frailty Index. The median score on the Charlson Comorbidity Index was 5, and the median MoCA score was 24. Medical therapy was similar in the two groups, with the majority of the patients having received guideline-recommended pharmacotherapy for the management of NSTEMI (Tables S6, S7, and S8).

INVASIVE TREATMENT

Among the patients who were assigned to the invasive-strategy group, 680 (90.3%) underwent coronary angiography, with the radial artery used as the access site in 89.3% of the patients (Table S9). Some patients did not undergo angiography, and the reasons are listed in Table 2. The median time from hospital admission to coronary angiography was 5 days, and the median time from randomization to coronary angiography was 3 days. A total of 376 patients (49.9%) in the invasive-strategy group underwent a revascularization procedure: 46.6% of the patients underwent PCI, with multivessel PCI performed in 29.9% of the patients, including 4.9% who received balloon angioplasty only, and 3.3% underwent CABG (Table 2 and Table S10).

PRIMARY OUTCOME

Follow-up data were available for at least 98.9% of the patients across all time points, and the median length of follow-up was 4.1 years (data were censored at the date of death or withdrawal from the trial). Reasons for withdrawal are listed in Table S11. Cardiovascular death or nonfatal myocardial infarction occurred in 193 of the patients (25.6%) in the invasive-strategy group and in 201 of the patients (26.3%) in the conservative-strategy group (hazard ratio, 0.94; 95% confidence interval [CI], 0.77 to 1.14; P=0.53) (Table 3 and Fig. 1). These findings appeared to be generally consistent across all prespecified subgroups (Fig. 2) and after adjustment for additional prognostic factors and competing risks (Table S12 and Fig. S2).

The proportional-hazards assumption of the Cox model was violated. At 1 year after randomization, a primary-outcome event had occurred in 12.8% (95% CI, 10.5 to 15.4) of the patients in the invasive-strategy group and 16.8% (95% CI, 14.3 to 19.7) of the patients in the conservative-strategy group, whereas by 5 years after randomization, a primary-outcome event had occurred in 35.4% and 34.8% of the patients in the invasive-strategy and conservative-strategy groups, respectively. Analysis of the restricted mean event-free time showed that over a 5-year period, invasive treatment resulted in, on average, an additional 29 days (95% CI, −40 to 98) free from cardiovascular death or nonfatal myocardial infarction, as compared with conservative treatment (Table S13). The time-dependent hazard ratio is shown in Figure S3.

Table 3. Primary and Key Secondary Outcomes.*

Outcome	Invasive Strategy (N=753)	Conservative Strategy (N=765)	Hazard Ratio for Treatment Effect (95% CI)†
	number (percent)		
Primary outcome: cardiovascular death or nonfatal MI‡§	193 (25.6)	201 (26.3)	0.94 (0.77–1.14)
Cardiovascular death§	119 (15.8)	109 (14.2)	1.11 (0.86–1.44)
Nonfatal MI	88 (11.7)	115 (15.0)	0.75 (0.57–0.99)
Secondary outcomes			
Composite of death from any cause or nonfatal MI§	319 (42.4)	321 (42.0)	0.97 (0.83–1.13)
Death from any cause§	272 (36.1)	247 (32.3)	1.13 (0.95–1.34)
Noncardiovascular death	153 (20.3)	138 (18.0)	1.14 (0.90–1.43)
Fatal or nonfatal MI	100 (13.3)	124 (16.2)	0.79 (0.61–1.02)
Coronary angiography	42 (5.6)	185 (24.2)	0.20 (0.14–0.28)
Coronary revascularization	29 (3.9)	105 (13.7)	0.26 (0.17–0.39)
Stroke	32 (4.2)	40 (5.2)	0.81 (0.51–1.28)
TIA	18 (2.4)	9 (1.2)	2.05 (0.92–4.56)
Hospitalization for heart failure	82 (10.9)	82 (10.7)	1.02 (0.75–1.39)
Bleeding: BARC type 2 or greater¶	62 (8.2)	49 (6.4)	1.28 (0.88–1.86)

* Data are shown for patients with at least one event. CI denotes confidence interval.
† Hazard ratios are shown for the invasive strategy as compared with the conservative strategy, with adjustment for frailty status (defined by the Rockwood Clinical Frailty Scale) at randomization.
‡ P=0.53 for the primary outcome. P value was calculated with the use of a log-rank test stratified according to frailty status (defined by the Rockwood Clinical Frailty Scale) at randomization.
§ Analyses did not satisfy the proportional-hazards assumption for the Cox model. Analyses of the restricted mean event-free time were also performed and produced consistent interpretation.
¶ Bleeding Academic Research Consortium (BARC) bleeding types range from 0 (no evidence of bleeding) to 5 (bleeding that is probably or definitely fatal). BARC type 2 bleeding is bleeding that requires medical intervention.

Cardiovascular death occurred in 119 patients (15.8%) in the invasive-strategy group and in 109 patients (14.2%) in the conservative-strategy group (hazard ratio, 1.11; 95% CI, 0.86 to 1.44). Nonfatal myocardial infarction occurred in 88 patients (11.7%) in the invasive-strategy group and in 115 patients (15.0%) in the conservative-strategy group (hazard ratio, 0.75; 95% CI, 0.57 to 0.99).

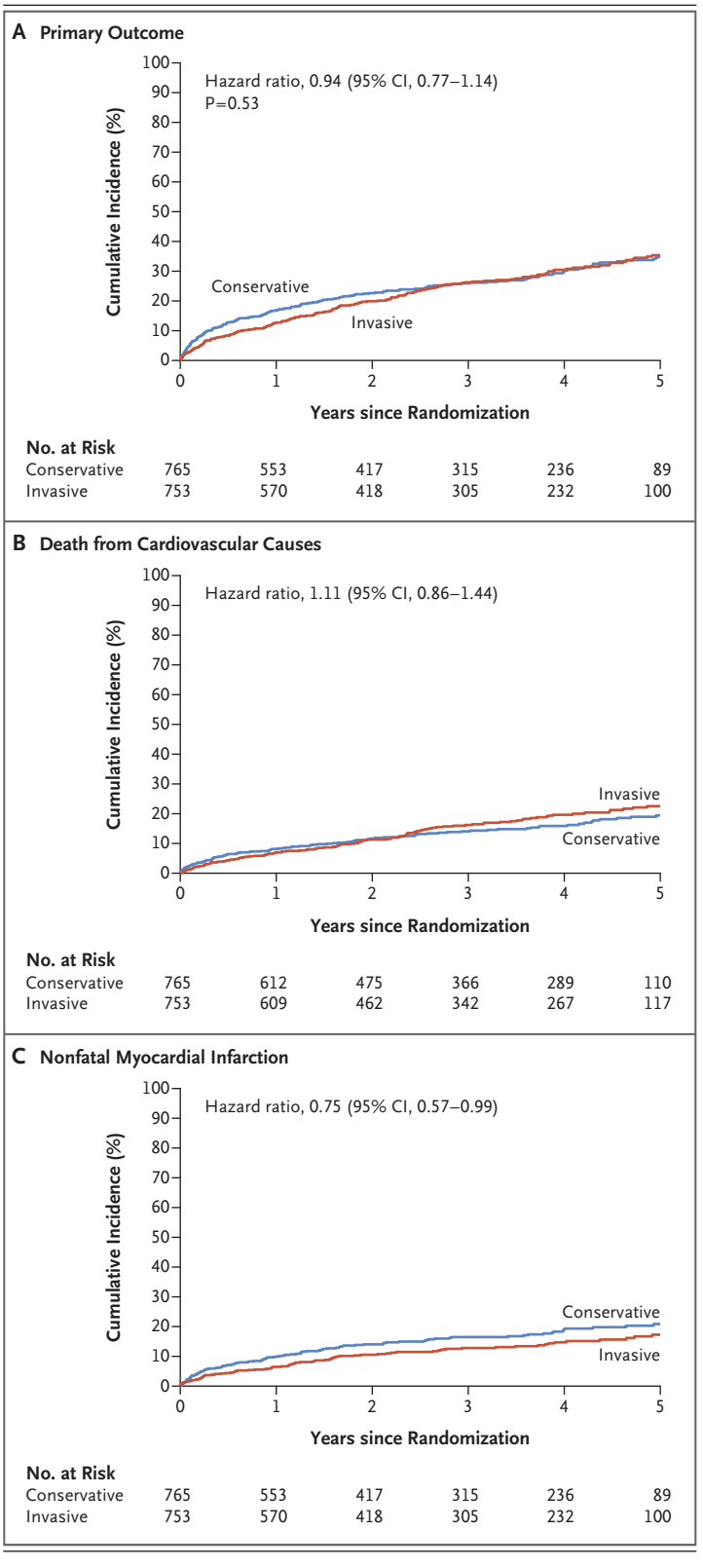
SECONDARY OUTCOMES

Secondary outcomes are shown in Table 3 and Figures S4 through S14. Death from any cause or a nonfatal myocardial infarction (a composite secondary outcome) occurred in 319 patients (42.4%) in the invasive-strategy group and in 321 patients (42.0%) in the conservative-strategy group (hazard ratio, 0.97; 95% CI 0.83 to 1.13). Nonfatal or fatal myocardial infarction occurred in 13.3% of the patients in the invasive-strategy group and in 16.2% of the patients in the conservative-strategy group (hazard ratio, 0.79; 95% CI, 0.61 to 1.02) (Table S14).

Subsequent coronary angiography, performed at the discretion of the clinician on the basis of ongoing symptoms during follow-up, was carried out in 42 patients (5.6%) in the invasive-strategy group and in 185 patients (24.2%) in the conservative-strategy group (hazard ratio, 0.20; 95% CI, 0.14 to 0.28). Subsequent revascularization-

Figure 1. Cumulative Incidence of the Composite Primary-Outcome Events.

Shown are the incidence of cardiovascular death or nonfatal myocardial infarction (the primary outcome) (Panel A) and its components: cardiovascular death (Panel B) and nonfatal myocardial infarction (Panel C). Cumulative incidence was estimated with the Kaplan–Meier method. Hazard ratios were estimated with Cox proportional-hazards models with adjustment for frailty status at randomization. P values were calculated with the use of a log-rank test with stratification for frailty status at randomization.



tion was performed in 29 patients (3.9%) in the invasive-strategy group and in 105 patients (13.7%) in the conservative-strategy group (hazard ratio, 0.26; 95% CI, 0.17 to 0.39) (Table S15).

Transient ischemic attacks occurred in 2.4% of the patients in the invasive-strategy group and in 1.2% of the patients in the conservative-strategy group (hazard ratio, 2.05; 95% CI, 0.92 to 4.56), and bleeding events occurred in 8.2% of the patients in the invasive-strategy group and in 6.4% of the patients in the conservative-strategy group (hazard ratio, 1.28; 95% CI, 0.88 to 1.86). Findings for the other secondary outcomes appeared to be similar in the two groups. Procedural complications occurred in less than 1% of the patients (Tables S16 and S17).

DISCUSSION

In the SENIOR-RITA trial, we evaluated the efficacy of a routine invasive approach to treatment, with a view toward coronary revascularization plus the best available medical therapy, as compared with that of a conservative approach of continued medical therapy alone, in an all-comer population of older patients presenting with NSTEMI. Our trial showed that among older adults with NSTEMI, the invasive strategy did not result in a significantly lower risk of a primary-outcome event, a composite of cardiovascular death or nonfatal myocardial infarction, than conservative strategy over a median follow-up period of 4.1 years.

Our trial included a subgroup of patients who were frail (32.4%) and cognitively impaired (62.5%) and had a high burden of coexisting conditions, features that emphasize the general-

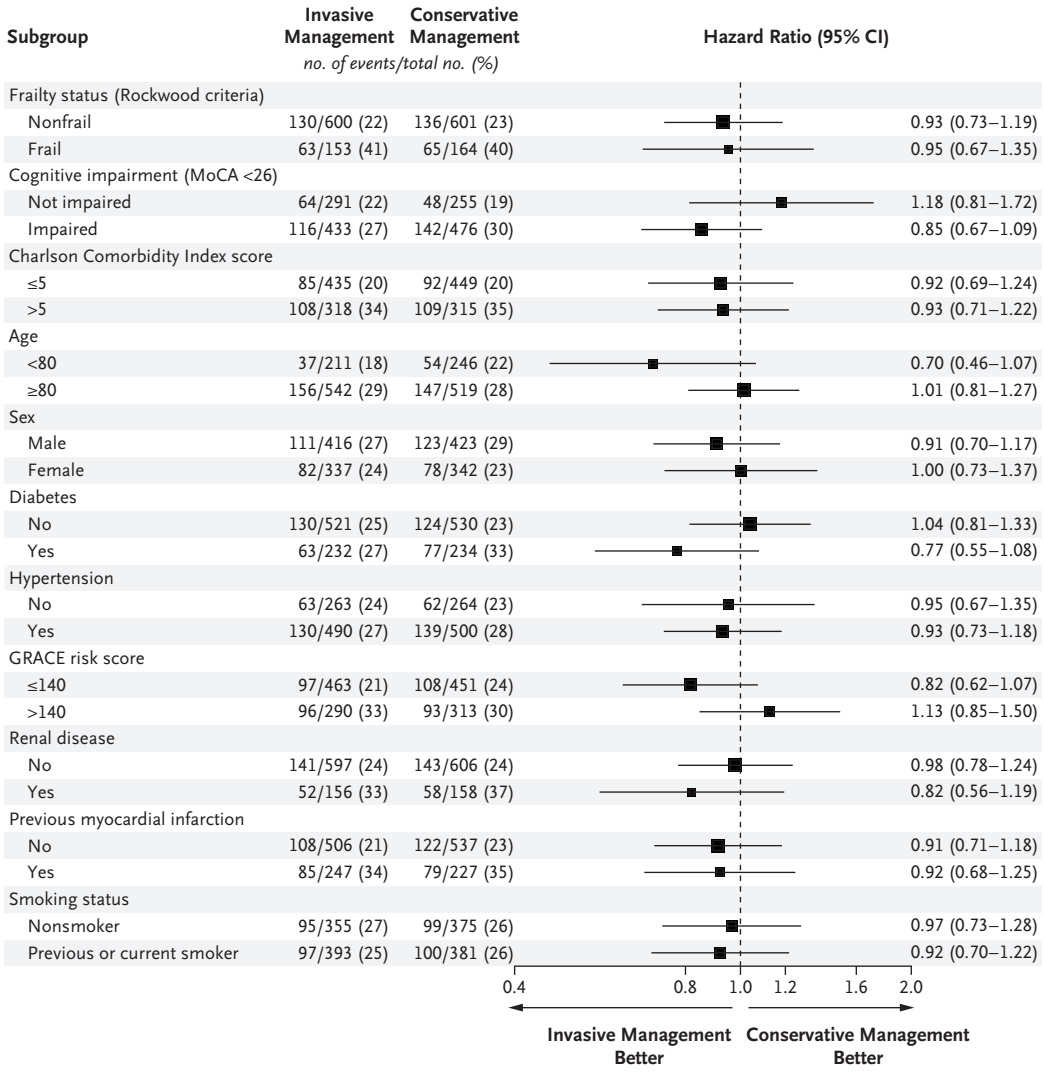


Figure 2. Subgroup Analyses of the Primary Outcome.

Shown are the results of subgroup analyses for the primary outcome, a composite of death from cardiovascular causes (cardiovascular death) or nonfatal myocardial infarction assessed in a time-to-event analysis. The size of the squares is proportional to the number of patients in each subgroup. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to reject or not reject treatment effects. Scores on the modified Rockwood Clinical Frailty Scale range from 1 (very fit) to 7 (severely frail), with a score of 5 or higher indicating frailty. Scores on the Montreal Cognitive Assessment (MoCA) range from 0 to 30, with a score of 26 or higher indicating normal cognitive function. Scores on the Charlson Comorbidity Index (range 0 to 37, with higher scores indicating a greater burden of coexisting conditions) were adjusted for age. Global Registry of Acute Coronary Events (GRACE) risk scores range from 1 to 372, with higher scores indicating greater risk. CI denotes confidence interval.

izability of our findings to the population of older adults with NSTEMI. We had previously shown that there is a high prevalence of undiagnosed cognitive impairment at baseline among older patients with NSTEMI.[10] In the current trial, all the patients received guideline-recommended pharmacotherapy for the management of NSTEMI. A total of 49.9% of the patients in the invasive-strategy group underwent revascularization, which is similar to the percentage of patients who un-

derwent revascularization in the After Eighty trial.[13]

Despite the challenges posed by the coronavirus disease 2019 (Covid-19) pandemic and the frailty of the patient population, 99% of the patients were followed across all time points, and 97.7% of the primary-outcome events were adjudicated by the clinical events committee; these results show the rigor of the methods used to conduct the trial. The median follow-up of 4.1 years allowed for evaluation of treatment strategies over a longer term than the 1-year follow-up in previous trials.

Our trial did not show a difference in the result for the primary outcome between the invasive strategy and the conservative strategy, although there were numerically fewer myocardial infarctions among the patients in the invasive-strategy group than in the conservative-strategy group, a finding that is consistent with the results of our recent meta-analysis.[19] In the case of patients in the conservative-strategy group who had serious clinical deterioration due to ongoing symptoms, the protocol allowed for further care, including angiography at the discretion of the treating clinical team.

There were fewer patients who underwent subsequent coronary angiography (5.6% vs. 24.2%) and revascularization procedures (3.9% vs. 13.7%) in the invasive-strategy group than in the conservative-strategy group. The risk of death from any cause or cardiovascular or noncardiovascular deaths did not appear to be different in the two groups. Our findings also appeared to be generally consistent across all the prespecified subgroups.

Clinicians are often reluctant to offer an invasive strategy to frail, older adults owing to a fear of bleeding and procedure-related complications. In the present study, we found that using contemporary angiography and interventional strategies, with the radial artery used as the access site in 89.3% of the patients, bleeding and procedure-related complications were minimal.

Our trial has several limitations. Our final sample size was 1518, as opposed to the planned 1668, with a lower incidence of primary-outcome events than was anticipated. We have previously described the challenges associated with recruiting older adults to clinical research.[2] The Covid-19 pandemic affected recruitment, especially the recruitment of frail, older patients with a high burden of coexisting conditions,[27] and the decision was made to end recruitment without further extension beyond the funded recruitment period.

Nevertheless, our trial provides insights into the appropriate care of such patients over a long term and strengthens the evidence base. One in every five patients who had undergone screening was recruited into the trial, which emphasizes the challenges associated with recruiting all-comer older adults into research and the associated chronic clinical conditions, such as cognitive impairment, that prevent these patients from participating in clinical research. One strength of the trial is that the patients who did not undergo randomization had similar clinical and demographic characteristics (mean age, 82 years; 47% women) to patients who had undergone randomization, with 55% assigned to the invasive strategy and 44% to the conservative strategy, thereby strengthening the representativeness of our trial population and the generalizability of our findings (Table S18).

Among older adults with NSTEMI, an invasive strategy did not result in a lower risk of a composite of death or nonfatal infarction than a conservative strategy.

Supported by a grant (CS15/7/31679) from the British Heart Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

1. Tahhan AS, Vaduganathan M, Greene SJ, et al. Enrollment of older patients, women, and racial/ethnic minority groups in contemporary acute coronary syndrome clinical trials: a systematic review. JAMA Cardiol 2020;5:714-22.
2. Sinclair H, Batty JA, Qiu W, Kunadian V. Engaging older patients in cardiovascular research: observational analysis of the ICON-1 study. Open Heart 2016;3(2):e000436.
3. Veerasamy M, Edwards R, Ford G, et al. Acute coronary syndrome among older patients: a review. Cardiol Rev 2015;23:26-32.
4. Mills GB, Ratcovich H, Adams-Hall J, et al. Is the contemporary care of the older persons with acute coronary syndrome evidence-based? Eur Heart J Open 2022;2(1):oeab044.
5. Batty J, Qiu W, Gu S, et al. One-year clinical outcomes in older patients with non-ST elevation acute coronary syndrome undergoing coronary angiography: an analysis of the ICON1 study. Int J Cardiol 2019;274:45-51.
6. Ratcovich H, Beska B, Mills G, et al. Five-year clinical outcomes in patients with frailty aged ≥75 years with non-ST elevation acute coronary syndrome undergoing invasive management. Eur Heart J Open 2022;2(3):oeac035.
7. Gu SZ, Qiu W, Batty JA, et al. Coronary artery lesion phenotype in frail older patients with non-ST-elevation acute coronary syndrome undergoing invasive care. EuroIntervention 2019;15(3):e261-e268.
8. Beska B, Ratcovich H, Bagnall A, et al. Angiographic and procedural characteristics in frail older patients with non-ST elevation acute coronary syndrome. Interv Cardiol 2023;18:e04.
9. Beska B, Mills GB, Ratcovich H, Wilkinson C, Damluji AA, Kunadian V. Impact of multimorbidity on long-term outcomes in older adults with non-ST elevation acute coronary syndrome in the North East of England: a multi-centre cohort study of patients undergoing invasive care. BMJ Open 2022;12(7):e061830.
10. Gu SZ, Beska B, Chan D, et al. Cognitive decline in older patients with non-ST elevation acute coronary syndrome. J Am Heart Assoc 2019;8:e011218.
11. Dirjayanto VJ, Alkhalil M, Dodson J, et al. Cognitive impairment and outcomes in older adults with non-ST-elevation acute coronary syndrome. Heart 2024;110:416-24.
12. Beska B, Coakley D, MacGowan G, Adams-Hall J, Wilkinson C, Kunadian V. Frailty and quality of life after invasive management for non-ST elevation acute coronary syndrome. Heart 2022;108:203-11.
13. Tegn N, Abdelnoor M, Aaberge L, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016;387:1057-65.
14. Savonitto S, Cavallini C, Petronio AS, et al. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. JACC Cardiovasc Interv 2012;5:906-16.
15. Sanchis J, Núñez E, Barrabés JA, et al. Randomized comparison between the invasive and conservative strategies in comorbid elderly patients with non-ST elevation myocardial infarction. Eur J Intern Med 2016;35:89-94.
16. de Belder A, Myat A, Blaxill J, et al. Revascularisation or medical therapy in elderly patients with acute anginal syndromes: the RINCAL randomised trial. EuroIntervention 2021;17:67-74.
17. Hirlekar G, Libungan B, Karlsson T, Bäck M, Herlitz J, Albertsson P. Percutaneous coronary intervention in the very elderly with NSTE-ACS: the randomized 80+ study. Scand Cardiovasc J 2020;54:315-21.
18. Sanchis J, Bueno H, Miñana G, et al. Effect of routine invasive vs conservative strategy in older adults with frailty and non-ST-segment elevation acute myocardial infarction: a randomized clinical trial. JAMA Intern Med 2023;183:407-15.
19. Kotanidis CP, Mills GB, Bendz B, et al. Invasive vs. conservative management of older patients with non-ST-elevation acute coronary syndrome: individual patient data meta-analysis. Eur Heart J 2024;45:2052-62.
20. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720-826.
21. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-M156.
22. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
24. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-9.
25. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237-69.
26. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
27. Rowland B, Kunadian V. Challenges in the management of older patients with acute coronary syndromes in the COVID-19 pandemic. Heart 2020;106:1296-301.