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Invasive versus Conservative Strategy for Older Patients with Myocardial Infarction.

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*A full list of the The British Heart Foundation older patients with non-ST SEgmeNt elevatIOn myocaRdial infarction Randomized Interventional TreAtment Trial investigators is provided in the Supplementary Appendix, available at NEJM

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ABSTRACT

BACKGROUND: Whether optimal medical therapy or an invasive strategy plus optimal medical therapy is beneficial in older adults with non-ST-segment elevation myocardial infarction (NSTEMI) remains unclear.

METHODS: We conducted a prospective multicenter randomized trial at 48 sites in the United Kingdom that randomly assigned in a 1:1 ratio 1518 adults age ≥75 years with NSTEMI to a conservative strategy of optimal medical therapy or an invasive strategy of coronary angiography and revascularization plus optimal medical therapy. Patients who were frail or had a high burden of co-morbidities were eligible for enrollment. The primary outcome was the time to cardiovascular death or non-fatal myocardial infarction.

RESULTS: A total of 753 patients were assigned to the invasive group and 765 to the conservative group. The median age of patients was 82 years, 45% were female, and 32% were frail. The primary outcome occurred in 193 patients (25.6%) in the invasive group and 201 patients (26.3%) in the conservative 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% and 14.2% in the invasive and conservative groups, respectively (hazard ratio, 1.11; 95% CI, 0.86 to 1.44). Non-fatal myocardial infarction occurred in 11.7% and 15.0% in the invasive and conservative groups, respectively (hazard ratio, 0.75; 95% CI, 0.57 to 0.99). Procedural complications occurred in <1% of patients.

CONCLUSION: Among older adults with NSTEMI, an invasive strategy did not reduce the composite outcome of cardiovascular death or non-fatal myocardial infarction compared with a conservative strategy over a median of 4.1 years.

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There is a lack of specific pharmacological and invasive treatment guidelines for older patients with acute coronary syndromes due to 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 older adults more than 75 years of age.[3,4] Clinical characteristics of the older population with NSTEMI are heterogeneous with frailty,[5-8] comorbidities,[9] cognitive function[10,11] and health-related quality of life[12] playing important roles in guiding clinical care. To date, only six small sized randomized controlled trials investigating an invasive strategy in older patients with NSTEMI have published results.[4,13-18] The After Eighty trial that enrolled 457 patients (mean age 85 years, 50.8% female) showed a significantly lower incidence of the primary composite outcome of myocardial infarction, urgent revascularization, stroke, and death in the invasive versus a conservative strategy at a mean follow-up of 18 months; a result driven primarily by lower rates of myocardial infarction and revascularization.[13] An individual patient level meta-analysis that included 1479 patients found that routine invasive treatment for older patients with NSTEMI did not reduce the risk of a composite of all-cause mortality or myocardial infarction within one year compared with conservative management. However, the invasive treatment strategy was associated with a lower hazard of myocardial infarction and of urgent revascularization.[19]

Previous studies of 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 comorbidities, or cognitive function leading to inconsistent findings that limited generalizability. Clinical practice guidelines specify that, in the absence of robust clinical trial evidence, management of older patients should be individualized based on patient characteristics.[20] We designed the British Heart Foundation SENIOR-RITA trial to evaluate the potential beneficial effects of a routine invasive approach with a view to coronary

revascularization versus a conservative approach of optimal medical therapy in a broadly representative population of older frail patients with comorbidities presenting with NSTEMI.

METHODS

TRIAL DESIGN AND OVERSIGHT

The SENIOR-RITA trial was a prospective, multicenter, open-label, randomized controlled trial that recruited patients at least 75 years of age with NSTEMI to test an invasive versus a conservative treatment strategy. The study protocol and analysis plan are available with the full text of this article at NEJM.org. Written informed consent was obtained for all patients. In England, consultee declaration (from family members or caregivers) was obtained for cognitively impaired patients. An independent trial steering committee and a data safety monitoring committee oversaw the trial. An independent clinical events committee, blinded to trial group assignments, adjudicated death and myocardial infarction events (see the Supplementary Appendix at NEJM.org). The Newcastle Clinical Trials Unit managed and coordinated the trial. Newcastle University Biostatistics Research Group was responsible for statistical oversight and performed statistical analyses. The trial was funded by the British Heart Foundation (CS/15/7/31679) and sponsored by Newcastle upon Tyne Hospitals NHS Foundations Trust. The protocol was approved by the UK Health Research Authority (16/NE/0238). The lead author (VK) had access to the trial data and vouches for its completeness and accuracy, and wrote the initial draft of the manuscript.

TRIAL POPULATION

Patients presenting to hospitals who were at least 75 years old with a clinical diagnosis of NSTEMI were eligible for participation in the trial. Patients with a Type 1 NSTEMI during the index hospitalization were included. Patients were excluded if they presented with a STEMI or

unstable angina; cardiogenic shock; life expectancy <1 year; previous inclusion in SENIOR-RITA; unable to undergo invasive coronary angiography (see the Supplementary Appendix for additional details).

FRAILTY, COMORBIDITY AND COGNITIVE IMPAIRMENT

Frailty was assessed using the Fried Frailty Index (Frail: ≥3 criteria present; Intermediate or Pre-Frail:1 or 2 criteria present; Robust: 0 criteria)[21] and the Rockwood Frailty Score (≥5 frail). [22] Comorbidity was graded using the Charlson Comorbidity Index. The overall Charlson Comorbidity Index score is a sum of the scores for specified comorbidities and age. The score ranges from 0 to 37.[23] Cognitive impairment was evaluated by the Montreal Cognitive Assessment (MOCA: scores ≥26 classified as normal, <26 as cognitive impairment) (see the Supplementary Appendix for additional details).[24]

RANDOMIZATION AND TREATMENT

Following consent, patients were randomly assigned in a 1:1 ratio to an invasive strategy of coronary angiography and, if appropriate, coronary revascularization plus optimal medical therapy or to a conservative management strategy of optimal medical therapy alone. Randomization was on 1:1 basis using a variable-length block stratified method with randomly selected block sizes of two, four, six and eight. Stratification was by site and by Rockwood Frailty Score. Randomization was performed at each site using a secure web-based system.

Optimal medical therapy included, in the absence of contraindications, aspirin 75mg daily, a $P2Y_{12}$ receptor antagonist, statin therapy, a beta-blocker to achieve a target a heart rate of 60-70 beats per minute, and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. Management of hypertension, diabetes and hypercholesterolemia were per the clinical practice guidelines.

Patients assigned to the invasive group underwent coronary angiography with coronary revascularization if appropriate and received optimal medical therapy. Coronary angiography was performed as per local practice and in accordance with trial mandated standards. Based on the angiographic findings, coronary revascularization was performed within 3-7 days where feasible by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery at the discretion of the attending cardiologist and the multi-disciplinary team. For patients assigned to the conservative arm, coronary angiography was allowed if there was clinical deterioration and it was clinically indicated at the discretion of the treating physicians.

OUTCOMES AND FOLLOW-UP

The primary composite outcome was time to cardiovascular death or non-fatal myocardial infarction defined by the 4th universal definition of myocardial infarction.[25] Secondary outcome measures were a composite of all cause death or myocardial infarction, all cause death, cardiovascular death, non-cardiovascular death, recurrent myocardial infarction, subsequent coronary angiography, subsequent coronary revascularization, hospitalization for heart failure, stroke, transient ischemic attack and bleeding (as per the bleeding academic research consortium criteria).[26] Safety outcomes included procedural and in-hospital complications occurring in patients assigned to the invasive strategy. Site level follow-up was performed at 6 months, 1 year and then yearly until 5 years either via telephone or in person visit.

STATISTICAL ANALYSIS

We assumed a primary event rate of 20% in the conservative therapy arm at 12 months and aimed to detect a reduction to 16% in the invasive therapy arm, corresponding to hazard ratio of 0.78. Based on a log-rank test with 90% power and 5% two-sided type I error, 688 events were required to detect a hazard ratio of 0.78; 520 events were required to achieve 80% power.

The target sample size was 1668 patients, which was estimated to provide at least 688 events with a minimum 1-year and maximum 5-year follow-up.

Analyses used all available data, up to a maximum of 5 years follow-up, and were performed on an intention-to-treat basis. Missing data for clinical outcomes were minimal and unobserved event times were assumed to be censored at random. Cumulative incidence was estimated using Kaplan-Meier methods with treatment comparison using a log-rank test stratified by baseline Rockwood frailty status. The effect of an invasive strategy compared to a conservative strategy was estimated using a proportional hazards model adjusted by Rockwood frailty status with hazard ratios and 95% confidence intervals (CI). There was no adjustment for multiplicity and the widths of the CI should not be used to infer treatment effect. For outcomes subject to competing risks cumulative incidence was also estimated using Aalen-Johansen estimates and treatment effects estimated using Fine and Gray regression models adjusted for Rockwood frailty status. If proportional hazards assumption of the Cox model was violated the estimated difference in the restricted mean event-free time at 5 years was estimated. All analyses were performed using Stata version 18.

RESULTS

PATIENTS

From November 2016 to March 2023, a total of 6977 eligible patients were screened from 48 National Health Service trusts across England and Scotland (Fig. S1). Among patients that were screened but not randomized (median age 82 years, 47% female), 55% received invasive treatment, 44% conservative care and 1% palliative care (Tables S1-S3). A total of 1518 patients underwent randomization: 753 to the invasive strategy and 765 to the conservative strategy at a median of 2 days from the time of hospitalization. Four participants were found to be ineligible after randomization (Table S4).

Patient baseline characteristics and medical therapy are summarized in Tables 1 and 2, respectively (See also Table S5). The median age of randomized patients was 82 years; 44.7% women; 32.4% frail using the Fried frailty index; the median Charlson comorbidity index was 5; and the median MOCA score was 24. Medical therapy appeared balanced between the two groups with the majority of patients receiving guideline recommended pharmacotherapy for the management of NSTEMI (Tables S6-S8).

PROCEDURAL DETAILS

Among patients assigned to invasive management, 680 (90%) underwent coronary angiography with the radial artery used as the access site in 89.3% of patients (Table S9). Reasons for not performing angiography are provided in Table 2. The median time from hospital admission to coronary angiography was 5 days and from randomization to coronary angiography was 3 days. A total of 376 patients (49.9%) in the invasive arm had a revascularization procedure: 46.6% had PCI with multivessel PCI performed in 30%, including 4.9% receiving balloon angioplasty only, and 3.3% received CABG (Table 2; Tables S9-S10).

PRIMARY OUTCOME AND COMPONENTS OF PRIMARY OUTCOME

Follow-up data were available for at least 98.9% of patients across all time points (Fig. S1) and the median length of follow-up (censored at date of death or withdrawal) was 4.1 years. Reasons for withdrawal are provided in Table S11. The primary outcome occurred in 193 patients (25.6%) in the invasive group and 201 patients (26.3%) in the conservative group (hazard ratio, 0.94; 95% CI, 0.77 to 1.14; P=0.53; Table 3 and Fig. 1). These findings appeared consistent across all pre-specified sub-groups (Fig. 2) and after adjusting for additional prognostic factors and competing risks (Table S12, Fig. S2). The proportional hazards assumption of the Cox model was violated; at one-year after randomization, the cumulative

event rate was 12.8% (95% CI, 10.5 to 15.4) in the invasive group and 16.8% (95% CI, 14.3 to 19.7) in the conservative group, whereas by five years the cumulative event rate was 35.4% and 34.8% in the invasive and conservative groups, respectively. Analysis of the restricted mean event-free time showed treatment with an invasive strategy resulted in an additional 29 days (95% CI, -40 to +98 days) free from cardiovascular death or non-fatal myocardial infarction on average compared to treatment with a conservative strategy over a five-year period (Table S13). The time-dependent hazard ratio is provided in Fig. S3.

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

SECONDARY OUTCOMES

Secondary outcomes are shown in Table 3 and Figs. S4-S14. The composite of all-cause death or non-fatal myocardial infarction occurred in 319 patients (42.4%) in the invasive group and in 321 patients (42.0%) in the conservative group (hazard ratio, 0.97; 95% CI 0.83 to 1.13). Non-fatal and fatal myocardial infarction occurred in 13.3% and 16.2% in the invasive and conservative arms respectively (hazard ratio, 0.79; 95% CI, 0.61 to 1.02) (Table S14).

Subsequent coronary angiography based on the clinician's decision due to ongoing symptoms during follow-up was performed in 42 patients (5.6%) in the invasive group compared to 185 patients (24.2%) in the conservative group (hazard ratio, 0.20; 95% CI, 0.14 to 0.28). Subsequent revascularization occurred in 29 patients (3.9%) in the invasive group and in 105 patients (13.7%) in the conservative group (hazard ratio, 0.26; 95% CI, 0.17 to 0.39) (Table S15).

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

DISCUSSION

In the SENIOR-RITA trial we evaluated the efficacy of a routine invasive approach with a view toward coronary revascularization plus optimal medical therapy versus a conservative approach of continued optimal medical therapy alone in an all-comer older patient population presenting with NSTEMI. Our trial showed that among older adults with NSTEMI, the invasive strategy did not result in a significantly lower risk of the composite of cardiovascular death or non-fatal myocardial infarction over a median follow-up of 4.1 years compared to a conservative strategy.

The SENIOR-RITA trial included a subset of patients who were frail (32%), cognitively impaired (60%) and with a high burden of comorbidities, thereby emphasizing the generalizability of our study findings to the population of older adults with NSTEMI. We have previously shown that there is a high prevalence of undiagnosed cognitive impairment at baseline in older NSTEMI patients.[10] In our trial, all patients received guideline-recommended pharmacotherapy for the management of NSTEMI. A total of 50% of patients received revascularization in the invasive group, which is comparable to the revascularization rate in the After Eighty trial.[13] Despite the challenges posed by the COVID-19 pandemic and the frailty of the patient population, we had 99% follow-up across all time points with 97.7% of primary outcome events adjudicated by the clinical events committee, underpinning the robustness of

the study conduct. The median follow-up of 4.1 years allowed for evaluation of treatment strategies over a longer term rather than one year compared to previous studies.

In our study we did not demonstrate a difference in the primary end point in the invasive strategy compared to the conservative strategy, although there were numerically fewer myocardial infarctions among patients in the invasive compared to the conservative group as also shown in our recent meta-analysis[19]. For patients in the conservative arm, if there was significant clinical deterioration due to ongoing symptoms then the protocol allowed for further care, including angiography at the discretion of the treating clinical team. There were numerically fewer patients that underwent subsequent coronary angiography (5.6% versus 24.2%) and revascularization procedures (3.9% versus 13.7%) in the invasive arm compared to the conservative arm. The risks of all-cause, cardiovascular or non-cardiovascular deaths did not appear to be different between the treatment groups. Our study findings also appeared consistent across all prespecified sub-groups.

Clinicians are often reluctant to offer an invasive strategy to frail older adults due 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 patients, bleeding and procedure-related complications were minimal.

There are some limitations to our study. Our final sample size was 1518 patients, as opposed to the planned 1668 with lower than anticipated incidence rate of primary end point. We previously described the challenges associated with recruiting older adults to clinical research.[2] The COVID-19 pandemic affected recruitment especially of frail, older patients with a high burden of comorbidities[27] and the decision was made to end recruitment without further extension beyond the funded recruitment period. Nevertheless, our study provides valuable insights into the optimal care of such patients over a long term and strengthens the evidence base. One in every 5 patients screened were recruited into the trial, emphasizing the challenges

with recruiting all-comer older adults in research and the associated chronic clinical conditions such as cognitive impairment that prevent participation in clinical research. Importantly, patients who were not randomized had similar clinical characteristics and demographics (mean age 82 years, 47% female) to patients randomized in the study, with 55% undergoing an invasive strategy and 44% a conservative strategy, thereby strengthening the representatives of our study population and the generalizability of our study findings (Table S18).

In conclusion, among older adults with NSTEMI, an invasive strategy did not significantly reduce the composite risk of cardiovascular death or non-fatal myocardial infarction compared with a conservative strategy.

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

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TABLE 1: BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Characteristics	Invasive strategy (N = 753)	Conservative strategy (N = 765)
Age - yr	82.5 ± 4.7	82.2 ± 4.7
≥75 to <80 - no. (%)	211 (28.0)	246 (32.2)
≥80 to < 85 - no. (%)	304 (40.4)	291 (38.0)
≥85 to < 90 - no. (%)	182 (24.2)	171 (22.4)
≥90 to < 95 - no. (%)	47 (6.2)	51 (6.7)
≥95 - no. (%)	9 (1.2)	6 (0.8)
Female sex - no. (%)	337 (44.8)	342 (44.7)
Median days from admission to randomization — IQR	2 (1, 3)	2 (1, 3)
Median MoCA (IQR); N	25 (21, 27); 724	24 (21, 26); 731
Impaired (MoCA < 26) – no./total no. (%)	433/724 (59.8)	476/731 (65.1)
Median Rockwood Frailty score (IQR); N	3 (2, 4); 752	3 (2, 4); 763
Frail (Rockwood score ≥ 5) - no. (%)	153 (20.3)	164 (21.4)
Very fit (1)	103 (13.7)	97 (12.7)
Well, without active disease (2)	134 (17.8)	155 (20.3)
Well, with treated co-morbidities (3)	198 (26.3)	214 (28.0)
Apparently vulnerable (4)	165 (21.9)	134 (17.6)
Mildly frail (5)	97 (12.9)	108 (14.2)
Moderately frail (6)	47 (6.3)	48 (6.3)
Severely frail (7)	8 (1.1)	7 (0.9)
Median Fried Frailty score (IQR); N	2 (1, 3); 716	2 (1, 3); 730
Fried Frailty score Robust (0)	150 (20.9)	153 (21.0)
Pre-frail (1 or 2)	335 (46.8)	339 (46.4)
Frail (≥3)	231 (32.3)	238 (32.6)
Median Charlson age-adjusted co-morbidity index (IQR); N	5 (4, 6); 753	5 (4, 6); 764
Smoking status- no./total no. (%)		
Current Smoker	35/748 (4.7)	45/756 (6.0)
Ex-Smoker	358/748 (47.9)	336/756 (44.4)
Never Smoked	355/748 (47.5)	375/756 (49.6)
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 myocardial infarction - 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. (%)	57/753 (7.6)	61/764 (8.0)
History of TIA/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)

Plus-minus values are mean ±SD.

IQR denotes interquartile range, MoCA denotes Montreal Cognitive Assessment, PCI denotes percutaneous coronary intervention, CABG denotes coronary artery bypass graft, TIA denotes transient ischemic attack and COPD denotes chronic obstructive pulmonary disease

TABLE 2: MEDICAL THERAPY AND PROCEDURAL CHARACTERISTICS

DISCHARGE MEDICAL THERAPY	Invasive Strategy (N=752)	Conservative Strategy (N=762)
Antiplatelet therapies		
Aspirin - no. (%)	682 (90.7)	663 (87.0)
$P2Y_{12}$ Receptor Antagonist (Total) - no. (%)	674 (89.6)	719 (94.4)
Clopidogrel - no. (%)	348 (46.3)	405 (53.1)
Ticagrelor - no. (%)	322 (42.8)	313 (41.1)
Prasugrel - no. (%)	4 (0.5)	1 (0.1)
Antiplatelet therapy		
None - no. (%)	20 (2.7)	8 (1.0)
Single - no. (%)	108 (14.4)	126 (16.5)
Dual - no. (%)	624 (83.0)	628 (82.4)
Anticoagulant* (Total) - no. (%)	170 (22.6)	183 (24.0)
Apixaban – no. (%)	51 (6.8)	71 (9.3)
Rivaroxaban - no. (%)	44 (5.9)	38 (5.0)
Warfarin - no. (%)	28 (3.7)	34 (4.5)
Edoxaban - no. (%)	16 (2.1)	15 (2.0)
Dabigatran - no. (%)	2 (0.3)	4 (0.5)
Other – no. (%)	29 (3.9)	21 (2.8)
Triple therapy (Total) - no. (%)	100 (13.3)	91 (11.9)
Lipid lowering therapy (Total)	682 (90.7)	688 (90.3)
Atorvastatin - no. (%)	595 (79.1)	608 (79.8)
Simvastatin - no. (%)	40 (5.3)	43 (5.6)
Rosuvastatin - no. (%)	31 (4.1)	25 (3.3)
Pravastatin – no. (%)	12 (1.6)	9 (1.2)
Ezetimibe - no. (%)	4 (0.5)	3 (0.4)
PROCEDURAL CHARACTERISTICS		
Angiography performed – no. (%)	680 (90.3)	-
Radial access – no. (%)	607 (89.3)	-
Median days from admission to angiography (IQR)	5 (3, 7)	-
Median days from randomization to angiography (IQR)	3 (1, 5)	-
Reason not performed		
Clinical decision – no. (%)	35 (4.6)	-
Participant decision – no. (%)	21 (2.8)	-
Participant too unwell – no. (%)	13 (1.7)	-
Participant died – no. (%)	3 (0.4)	-
Not known – no. (%)	1 (0.1)	-
Revascularization performed – no. (%)	376 (49.9)	-
PCI – no. (%)	351 (46.6)	-
CABG – no. (%)	25 (3.3)	-
Median days from admission to PCI (IQR)	5 (3, 7)	-
Median days from randomization to PCI (IQR)	2 (1, 4)	-
Median days from admission to CABG (IQR)	18 (13, 27)	-

ACE denotes angiotensin converting enzyme, ARB Angiotensin receptor blocker, IQR interquartile range, PCI percutaneous coronary intervention, and CABG coronary artery bypass surgery.

TABLE 3: PRIMARY AND SECONDARY OUTCOMES

Outcome variables	Invasive Strategy ‡ (N=753)	Conservative Strategy ‡ (N=765)	Treatment effect Hazard Ratio* 95% CI	P value†
Primary outcome and its components: Cardiovascular death and non-fatal MI⸸ - no. (%)	193 (25.6)	201 (26.3)	0.94 (0.77-1.14)	0.53
Cardiovascular death⸸ - no. (%)	119 (15.8)	109 (14.2)	1.11 (0.86-1.44)	
Non-fatal MI – no. (%)	88 (11.7)	115 (15.0)	0.75 (0.57-0.99)	
Secondary outcomes				
All cause death and non-fatal MI⸸ - no. (%)	319 (42.4)	321 (42.0)	0.97 (0.83-1.13)	
All cause death⸸ - no. (%)	272 (36.1)	247 (32.3)	1.13 (0.95-1.34)	
Non-cardiovascular death - no. (%)	153 (20.3)	138 (18.0)	1.14 (0.90-1.43)	
Fatal and non-fatal MI - no. (%)	100 (13.3)	124 (16.2)	0.79 (0.61-1.02)	
Coronary angiography - no. (%)	42 (5.6)	185 (24.2)	0.20 (0.14-0.28)	
Coronary revascularization - no. (%)	29 (3.9)	105 (13.7)	0.26 (0.17-0.39)	
Stroke - no. (%)	32 (4.2)	40 (5.2)	0.81 (0.51-1.28)	
Transient ischemic attack - no. (%)	18 (2.4)	9 (1.2)	2.05 (0.92-4.56)	
Hospitalisation for heart failure - no. (%)	82 (10.9)	82 (10.7)	1.02 (0.75-1.39)	
Bleeding (BARC Type 2+) – no. (%)	62 (8.2)	49 (6.4)	1.28 (0.88-1.86)	

BARC denotes Bleeding Academic Research Consortium, MI Myocardial infarction, CI Confidence Interval.

‡ Data shown are the number of patients with at least one event (percent)

* The hazard ratio for invasive strategy compared to conservative strategy, with adjustment for frailty status (defined using the Rockwood frailty score) at randomization.

† P values were calculated using a log-rank test stratified for frailty status (defined using the Rockwood frailty score) at randomization.

⸸ Analyses did not satisfy the proportional hazards assumption of the Cox model. Analyses of the restricted mean event-free time were also performed and gave consistent interpretation.

FIGURE LEGENDS

FIGURE 1: Cumulative incidence of primary outcome and components of primary outcome

Shown is the composite primary outcome of cardiovascular death and non-fatal myocardial infarction (**Panel A**), cardiovascular death (**Panel B**) and non-fatal myocardial infarction (**Panel C**). Cumulative incidence was estimated using the Kaplan-Meier method. Hazard ratios were estimated from Cox proportional hazards models adjusted for frailty status at randomization. P values were calculated using a log-rank test stratified for frailty status at randomization.

FIGURE 2: Subgroup analysis of the primary outcome

Shown are the results of subgroup analyses for the primary outcome, a composite of cardiovascular death and non-fatal myocardial infarction. 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.

MoCA denotes Montreal Cognitive Assessment and CI denotes confidence interval.