JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 82, NO. 21, 2023

Long-Term Outcomes of Invasive vs Conservative Strategies for Older Patients With Non–ST-Segment Elevation Acute Coronary Syndromes

Erlend S. Berg, MD,[a,b] Nicolai K. Tegn, MD, PhD,[a] Michael Abdelnoor, MPH, PhD,[a] Kjetil Røysland, PhD,[b] Pål Christie Ryalen, PhD,[b] Lars Aaberge, MD, PhD,[a] Christian Eek, MD, PhD,[a] Erik Øie, MD, PhD,[c] Vibeke Juliebø, MD, PhD,[d] Erik Gjertsen, MD,[e] Anette Hylen Ranhoff, MD, PhD,[f] Lars Gullestad, MD, PhD,[b] Njord Nordstrand, MD, PhD,[a] Bjørn Bendz, MD, PhD,[a,b] on behalf of the After Eighty Study Investigators

ABSTRACT

BACKGROUND Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is a frequent cause of hospital admission in older people, but clinical trials targeting this population are scarce.

OBJECTIVES The After Eighty Study assessed the effect of an invasive vs a conservative treatment strategy in a very old population with NSTE-ACS.

METHODS Between 2010 and 2014, the investigators randomized 457 patients with NSTE-ACS aged ≥80 years (mean age 85 years) to an invasive strategy involving early coronary angiography with immediate evaluation for revascularization and optimal medical therapy or to a conservative strategy (ie, optimal medical therapy). The primary endpoint was a composite of myocardial infarction, need for urgent revascularization, stroke, and death. The long-term outcomes are presented.

RESULTS After a median follow up of 5.3 years, the invasive strategy was superior to the conservative strategy in the reduction of the primary endpoint (incidence rate ratio: 0.76; 95% CI: 0.63-0.93; $P = 0.0057$). The invasive strategy demonstrated a significant gain in event-free survival of 276 days (95% CI: 151-400 days; $P = 0.0001$) at 5 years and 337 days (95% CI: 123-550 days; $P = 0.0001$) at 10 years. These results were consistent across subgroups of patients with respect to major cardiovascular prognostic factors.

CONCLUSIONS In patients aged ≥80 years with NSTE-ACS, the invasive strategy was superior to the conservative strategy in the reduction of composite events and demonstrated a significant gain in event-free survival. (The After Eighty Study: a randomized controlled trial; NCT01255540) (J Am Coll Cardiol 2023;82:2021–2030)

Cardiovascular disease plays a major role in morbidity, mortality, and quality of life of older adults. However, clinical studies targeting this population are scarce, leaving important gaps in the evidence on how to handle these patients. As the patient group over 80 years grows, eventually with a life expectancy up to 10 years or more, the absolute prevalence of cardiovascular disease is

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [b]Faculty of Medicine, University of Oslo, Oslo, Norway; [c]Department of Internal Medicine, Diakonhjemmet Hospital, Oslo, Norway; [d]Department of Cardiology, Akershus University Hospital, Nordbyhagen, Norway; [e]Department of Cardiology, Drammen Hospital, Drammen, Norway; and the [f]Department of Clinical Science, University of Bergen, Bergen, Norway.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 24, 2023; revised manuscript received September 5, 2023, accepted September 8, 2023.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2023.09.809

ABBREVIATIONS AND ACRONYMS

ΔRMST = difference in restricted mean survival time

CABG = coronary artery bypass graft

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

RMST = restricted mean survival time

expected to increase further. Guidelines recommend medical optimization followed by an invasive strategy including coronary angiography and subsequent revascularization, with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) for eligible patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS).[1,2] However, these recommendations are not age-specific. There is also considerable doubt among physicians on how to handle these patients because of uncertainty about risk vs benefit in any treatment strategy, due to the higher occurrence of comorbidities, polypharmacy, physical frailty, and cognitive decline.[3] Moreover, little information is available about the late clinical outcomes in such patients.

SEE PAGE 2031

In the randomized controlled After Eighty Study, we sought to investigate whether patients aged ≥80 years initially stabilized after NSTE-ACS would benefit from an invasive strategy vs a conservative strategy, in terms of a composite primary endpoint of myocardial infarction, need for urgent revascularization, stroke, and death.[4] Here we present the long-term outcomes.

METHODS

STUDY DESIGN AND PARTICIPANTS. Details of the trial have been previously published.[4] The After Eighty Study (NCT01255540) was a dynamic, open-label, prospective, randomized, controlled, multicenter trial. Between December 10, 2010, and February 21, 2014, we enrolled 457 patients aged ≥80 years with NSTE-ACS, who were admitted to 16 academic teaching hospitals without PCI facilities in the South-East Health Region of Norway. The patients were randomized to 1 of 2 strategies: an invasive strategy, involving early coronary angiography with immediate evaluation for PCI, CABG and optimal medical therapy (OMT), or to a conservative strategy (ie, OMT).

The study protocol was approved by all relevant Institutional Review Boards, the Norwegian Data Protection Authority, and the regional board of research ethics. The project was authorized to continuously collect, save, and analyze individual patient data until 2026.

The trial enrolled consecutive consenting clinically stable patients (ie, no symptoms/signs of ischemia after medical treatment and mobilization). Patients were ineligible if they were clinically unstable with ongoing chest pain or other ischemic symptoms/signs, cardiogenic shock, ongoing bleeding problems, or short life expectancy (<12 months) because of serious comorbidity, such as chronic obstructive pulmonary disease, disseminated malignant disease, or other reasons. Significant mental disorder, including severe dementia or any condition that interfered with a patient's ability to comply with the protocol, was also an exclusion criterion.

RANDOMIZATION AND MASKING. The Centre for Biostatistics and Epidemiology, Oslo University Hospital, was responsible for the randomization procedure. A permuted block randomization was generated with stratification on the inclusion hospitals in opaque concealed envelopes, and sealed envelopes with consecutive inclusion numbers were made. All investigations were continuously evaluated, and adverse events and/or unexpected patient responses in terms of cardiovascular status, biochemical status, general well-being, and need for rehospitalization were recorded and made available for the Data and Safety Monitoring Board. All serious adverse events and/or unexpected events were reported to the Data and Safety Monitoring Board. The board had the right to advise the steering committee to first halt inclusion and subsequently terminate the study.

PROCEDURES. Patients were evaluated for participation in the study within 2 days after hospital admission on a 365 d/y basis. After giving written informed consent, patients were randomized to an invasive strategy involving early coronary angiography the following day at Oslo University Hospital with immediate evaluation for ad hoc PCI, CABG, or OMT, or to a conservative strategy (ie, OMT). The patients randomized to a conservative strategy received OMT in the community hospitals. Both groups were observed, medically treated according to existing guidelines, and finally discharged from the community hospitals.[5,6] If the patients in the conservative group had a reinfarction, refractory angina pectoris despite OMT, malignant ventricular arrhythmias, or increasing symptoms of heart failure, they were considered for urgent coronary angiography. The coronary angiograms were reviewed to the point of consensus by at least 2 invasive cardiologists before the revascularization strategy was decided in each patient. The secondary endpoint was death from any cause. Specific causes of death were collected from the Norwegian Cause of Death Registry from the Norwegian Institute of Public Health.

OUTCOMES. The primary endpoint was a composite of myocardial infarction, need for urgent

revascularization, stroke, and death (ie, the first occurring event). Endpoints and adverse events were collected through continuous feedback from the local hospitals, study site visits with review of patients records, and finally adjudicated by the Steering Committee according to the protocol. Reinfarction was defined as new typical cardiac symptoms combined with a rise in troponin T or I levels exceeding the 99th percentile of a normal population at the local laboratory at each participating site. Elevated troponin levels without an appropriate clinical observation consistent with type 1 myocardial ischemia (ie, type 2 myocardial infarction and non-ischemic myocardial damage) was not considered an endpoint. Periprocedural myocardial infarction was defined as a rise in creatine kinase-MB or troponins 3× the 99th percentile, assuming normal biomarkers before the procedure. If the cardiac biomarkers were elevated before the procedure, the periprocedural myocardial infarction was defined as a double rise in creatine kinase-MB 6 hours post procedure. Reinfarction, refractory angina pectoris, development of malignant ventricular arrhythmias, or increasing symptoms of heart failure were considered as indicating the need for urgent revascularization (ie, an endpoint). Stroke was defined as a new focal neurological deficit of vascular origin lasting >24 hours.

STATISTICAL ANALYSIS. This randomized controlled trial (RCT) was developed with an explanatory strategy.[7] Analysis of the trial was performed according to the intention-to-treat strategy in which we included the dropouts. Previous studies targeting the very old population were lacking when the study was being planned, but an a priori power analysis was done.[4] The de facto power analysis in the present study demonstrated a power of 96% to detect a type 1 error of 5%. The current analysis represents an extension of the previously published results.[4]

The primary outcome was the composite endpoint. We used censored data with a closing date (January 1, 2023). Incidence rate ratio was used to estimate the crude efficacy of the 2 strategies using a person-time model.[8] Curves showing event-free survival were plotted with the Kaplan-Meier method for the primary composite endpoint (**Central Illustration**).[9] Given the nature of this long-term follow-up, representing the remaining lifetime perspective of this very old population, it was unreasonable to assume proportional hazard, which is graphically illustrated by the convergence and crossing of the respective Kaplan-Meier curves for the primary endpoint. Restricted mean survival time (RMST) and difference in restricted mean survival time (ΔRMST) represent a model-free, novel, and robust alternative measure in survival analysis when the proportional hazards assumption is violated.[10,11] ΔRMST represents the mean absolute difference of event-free survival associated with the invasive strategy, an easily interpretable effect estimate. The RMST plots and ΔRMST plots of the primary endpoint and for myocardial infarction/death with time-to-event curves for each treatment strategy were made (**Central Illustration**, Supplemental Figure 1). ΔRMST curves were also plotted for subgroups (Supplemental Figures 2 to 6). For the point estimates for ΔRMST to numerically illustrate the difference between the different treatment strategies, we chose 5 years as a pragmatic (close to median time to death) and clinically relevant milestone time point in addition to 10 years (Supplemental Table 1). All survival analyses were done under the assumption of independent censoring. To illustrate incidence of cardiovascular vs noncardiovascular deaths and myocardial infarction with competing risk of death, cumulative incidence curves were plotted (**Figures 1 and 2**, respectively). The chi-square test was used to study the proportion of women and men with obstructive coronary artery disease and the proportion of patients with renal failure and diabetes with regard to extent of coronary disease and intervention. All *P* values are 2-tailed. The statistical analyses were performed using R (R Foundation) and STATA-17 (StataCorp LLC).

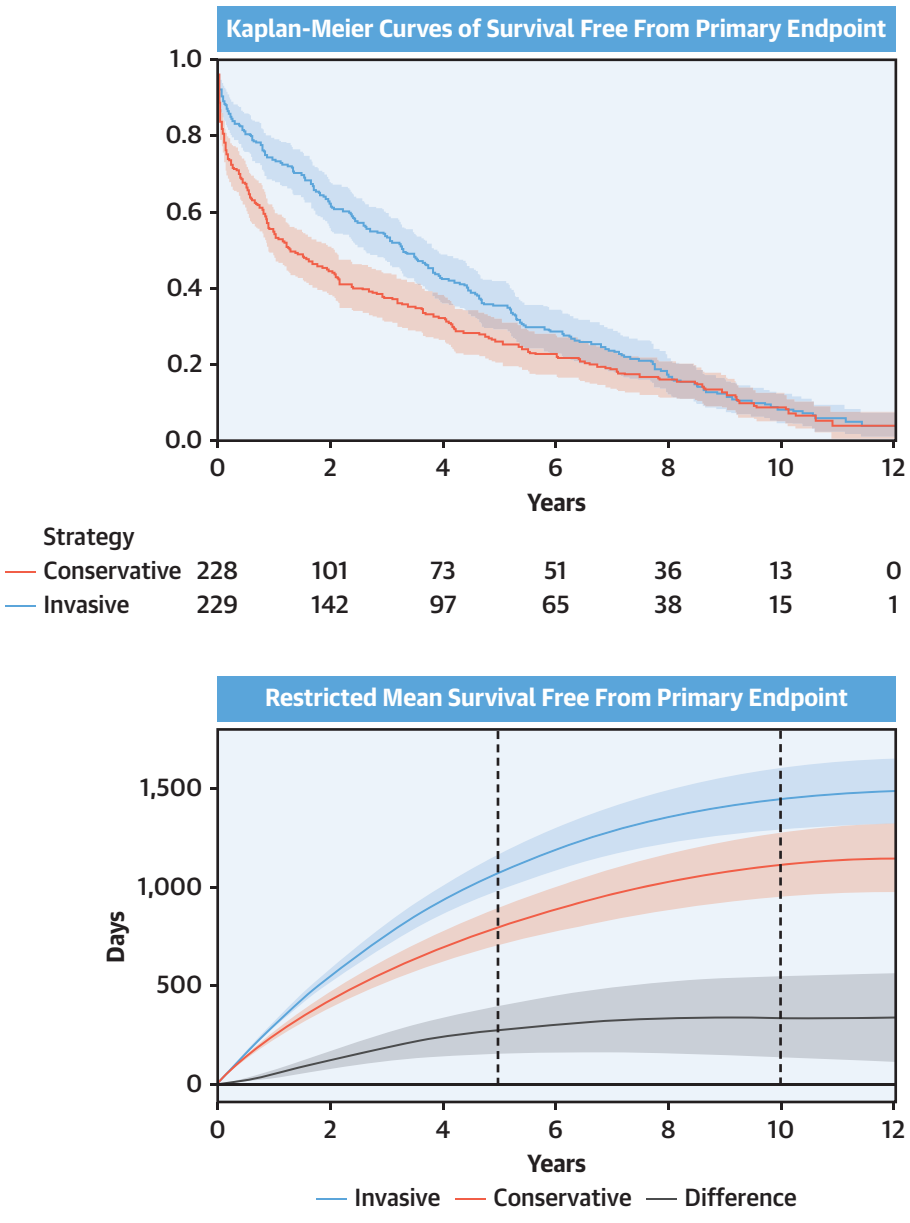
ROLE OF THE STEERING COMMITTEE. The Steering Committee had unrestricted access to the data after the database was locked and had full responsibility for the decision to submit for publication.

RESULTS

During the inclusion period, 2010 to 2014, a total of 4,187 patients aged ≥80 years were hospitalized with NSTE-ACS in the participating hospitals, and 1,973 patients (47.1%) were candidates for inclusion. Ultimately, 457 patients (23.2%) gave written consent and were randomized. As a result of the intention-to-treat strategy, these 457 patients remained in the follow-up study population, with 229 patients (mean age: 84.7 years) in the invasive group and 228 patients (mean age: 84.9 years) in the conservative group (Supplemental Figure 7). There were no crossovers between the 2 strategy groups. Reinfarction and new need of revascularization after randomization are accounted for as study endpoints. This included 10 patients in the conservative group with new

JACC VOL. 82, NO. 21, 2023
NOVEMBER 21, 2023:2021-2030

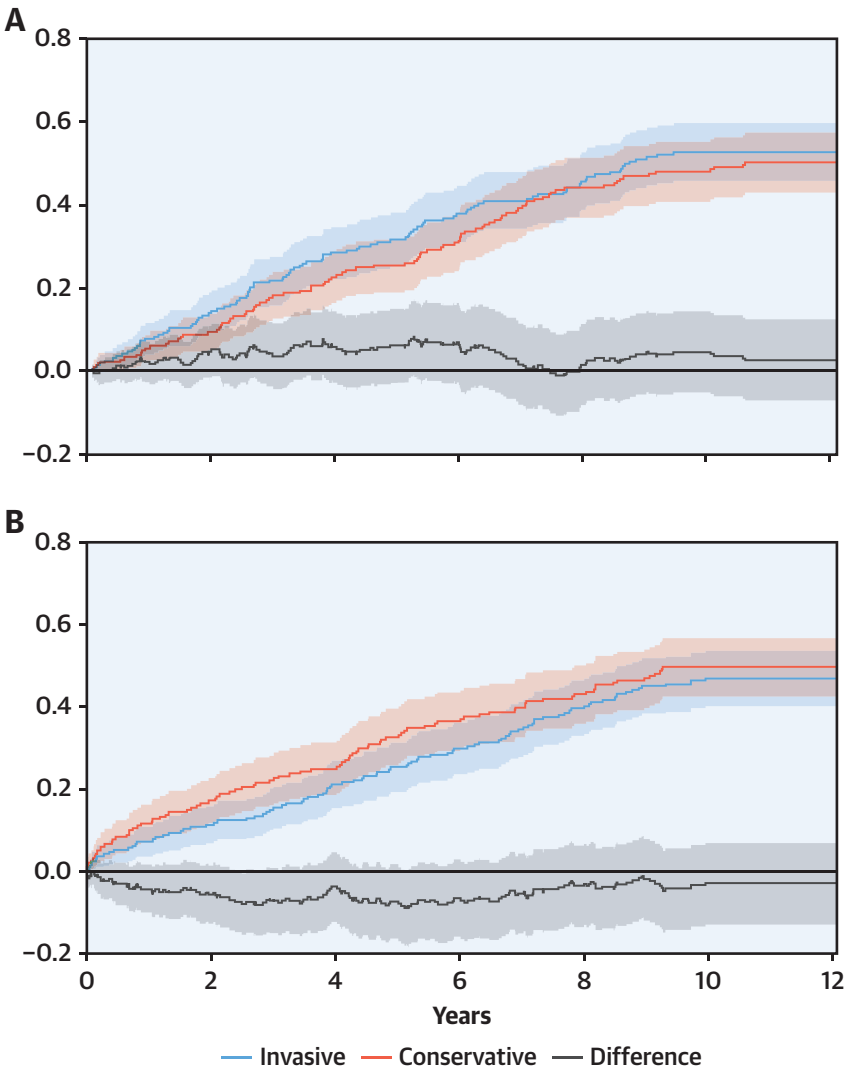
CENTRAL ILLUSTRATION **Kaplan-Meier Curves and Restricted Mean Survival Free From the Primary Endpoint**



Berg ES, et al. J Am Coll Cardiol. 2023;82(21):2021-2030.

The primary endpoint was a composite of myocardial infarction, need for urgent revascularization, stroke, and death. The Kaplan-Meier curves for the invasive (red line) and conservative (blue line) strategy, included 95% CIs, demonstrate an early and lasting benefit with the invasive strategy with a reduction in the occurrence of the primary endpoint. Representing a remaining lifetime perspective on this very old population, the curves eventually converge at the end of follow-up. The restricted mean survival time curves for each strategy and the difference in restricted mean survival time, demonstrates the superiority of the invasive strategy in terms of event-free days gained over time. Absolute event-free survival difference favoring the invasive strategy was 276 days (95% CI: 151-400 days; $P = 0.0001$) at 5 years and 337 days (95% CI: 123-550 days; $P = 0.0001$) at 10 years.

FIGURE 1 Cumulative Incidence of NCV and CV Death

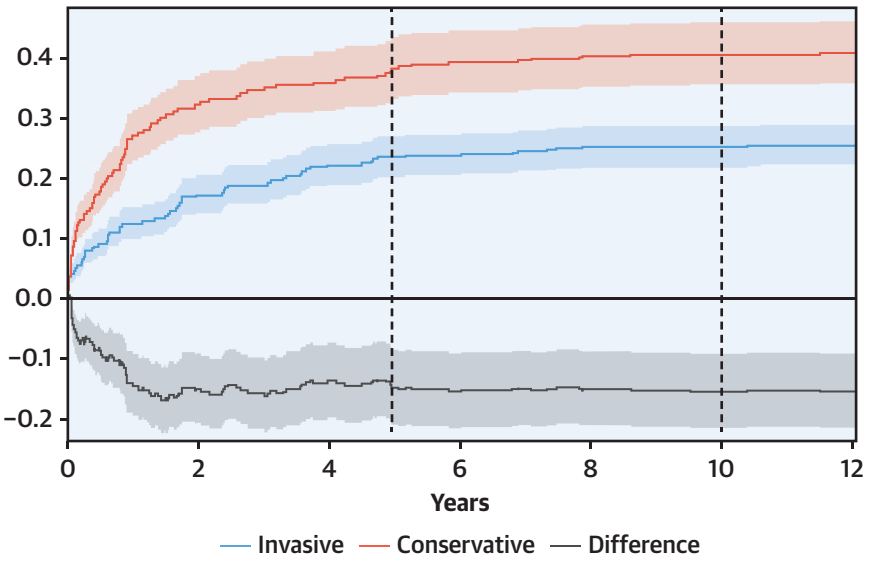


Cumulative incidence of noncardiovascular (NCV) death (A) and cardiovascular (CV) death (B). Separate curves for the invasive strategy group, the conservative strategy group and the absolute incidence difference between groups included 95% CIs show a near significant reduction in the incidence of CV death in favor of the invasive strategy. This reflects a postponement rather than a true reduction with respect to the lack of difference at the end of follow-up.

NSTE-ACS or refractory angina a few days after inclusion. Except for the use of anticoagulation and nitrates, baseline characteristics and medical treatment at inclusion and discharge were similar between the groups (Supplemental Tables 2 and 3).

In this long-term follow-up, with a median follow-up of 5.3 years (until death or end of follow-up, January 1, 2023), the invasive strategy was superior to the conservative strategy in the reduction of the primary endpoint (incidence rate ratio: 0.76; 95% CI: 0.63-0.93; $P = 0.0057$). The incidence rate ratios for the 4 components of the primary composite endpoint are presented in **Table 1**. The restricted mean survival time, including restricted mean survival difference between the 2 strategies, demonstrated an early and persisting gain in event-free survival of 276 days at 5 years (95% CI: 151-400 days; $P = 0.0001$) and 337 days at 10 years (95% CI: 123-550 days; $P = 0.0001$) (**Central Illustration**). The restricted mean survival of myocardial infarction and death at 5 years

FIGURE 2 Cumulative Incidence of Myocardial Infarction



There was an immediate reduction in the incidence of new myocardial infarctions persisting throughout follow-up. The reduction, as illustrated by the cumulative difference curve, was 14.7% at 5 years (point estimate: −0.1469; 95% CI: −0.0842 to −0.2096; $P = 0.0001$) and of 15.4% at 10 years (point estimate: −0.1540; 95% CI: −0.0902 to −0.2178; $P = 0.0001$).

demonstrated a beneficial effect of the invasive strategy (Supplemental Figure 1). Total mortality or cause of death did not differ between the 2 strategies. However, the cumulative incidence of cardiovascular death, taking into account the continuous competing risk of death from other causes, demonstrated a reduction of cardiovascular deaths during the first 6 years, but did not reach statistical significance (**Figure 1**). The cumulative incidence of myocardial infarction, taking into account the competing risk of death (ie, the probability of myocardial infarction before death), demonstrated a significant reduction in absolute incidence of 14.7% at 5 years (point estimate: −0.1469; 95% CI: −0.2096 to −0.0842; $P = 0.0001$) and of 15.4% at 10 years (point estimate: −0.1540; 95% CI: −0.2178 to −0.0902; $P = 0.0001$) (**Figure 2**). This includes 11 myocardial infarctions related to the PCI procedure (type 4a myocardial ischemia) in the invasive strategy group.

Due to the sample size (n = 457), subgroup analysis should be interpreted with caution. However, the invasive strategy demonstrated a beneficial effect of the invasive strategy across a wide range of variables (eg, established complex coronary heart disease [ie, previous CABG], diabetes mellitus, renal failure, sex, and age >85 years). Of clinical interest, the high-risk subset of patients with diabetes and renal failure demonstrated an even greater gain in event-free survival of 490 days (95% CI: 278-752 days; $P = 0.0001$) and 447 days (95% CI: 257-638 days; $P = 0.0001$) at 5 years and 673 days (95% CI: 234-1,102 days; $P = 0.0001$) and 628 days (95% CI: 322-935 days; $P = 0.0001$) at 10 years, respectively. In addition, subgroup analyses for sex and renal failure vs age (80-85, 85-89, >90 years) indicates a dilution of efficacy of the invasive strategy with increasing age (Supplemental Table 1, Supplemental Figures 2 to 6).

DISCUSSION

In this long-term follow-up of the After Eighty Study, the invasive strategy was superior to the conservative strategy in patients aged ≥80 years (mean age: 85 years) with NSTE-ACS in the reduction of composite events. With this long-term follow-up, we present the remaining lifetime perspective of this very old population.

When reviewing the results of this trial, several factors need elaboration. On average, patients in the invasive strategy group gained 276/337 days of event-free survival at 5/10 years. The reduction of the primary composite endpoint was achieved through a reduction in the occurrence of myocardial infarctions and need of revascularization. This benefit was

TABLE 1 Clinical Outcomes

	Invasive (n = 229)	Conservative (n = 228)	Incidence Rate Ratio (95% CI)	*P* Value
Primary endpoint				
Composite endpoint	215 (93.9)	212 (93.0)		
Median time to endpoint, y	3.04	1.02		
Incidence rate (95% CI)/time, y	0.23 (0.20-0.27)/921	0.31 (0.27-0.35)/695	0.76 (0.63-0.93)	0.0057
Components of the primary endpoint				
Myocardial infarction	72 (31.4)	96 (42.1)		
Median time to endpoint, y	1.40	0.60		
Incidence rate (95% CI)/time, y	0.039 (0.031-0.049)/1,833	0.061 (0.050-0.075)/1,566	0.64 (0.47-0.88)	0.0041
Need for urgent revascularization	30 (13.1)	63 (27.6)		
Median time to endpoint, y	1.95	0.24		
Incidence rate (95% CI)/time, y	0.014 (0.010-0.020)/2,201	0.035 (0.027-0.044)/1,816	0.39 (0.25-0.62)	0.0001
Stroke	29 (12.7)	24 (10.5)		
Median time to endpoint, y	3.05	2.15		
Incidence rate (95% CI)/time, y	0.0080 (0.0051-0.0130)/2,237	0.0085 (0.0054-0.0132)/2,242	1.21 (0.68-2.17)	0.4914
Death from any cause	205 (89.5)	194 (85.1)		
Median time to endpoint, y	4.44	4.30		
Incidence rate (95% CI)/time, y	0.167 (0.146-0.192)/1,224	0.157 (0.136-1.181)/1,237	1.07 (0.87-1.31)	0.5152
Causes of death				
Cardiovascular mortality	91 (44.4)	90 (46.4)		
Noncardiovascular mortality	101 (49.3)	91 (46.9)		
Cancer-related mortality	15	19		
Infection-related mortality	55	44		
Dementia	6	8		
Other causes of mortality	25	20		
Misclassified	1 (0.5)	4 (2.1)		
Unknown[a]	12 (5.8)	9 (4.6)		

Values are n (%) or n, unless otherwise indicated. [a]Data from 2022 not available from the Norwegian Cause of Death Registry.

observed soon after randomization and persisted throughout the long-term follow-up. Both these components of the primary endpoint reflect significant clinical events requiring hospital admission with a concomitant increased risk of adverse events and hospitalization-associated disability.[12] There was no difference in the incidence of stroke or total mortality. Total mortality was 87%, and cardiovascular death was the most prevalent cause of death but with no difference between groups at the end of the study. However, in the invasive strategy group, we observed a nonsignificant reduction in the incidence of cardiovascular death during the first 6 years. The high mortality rates reflect the burden of several comorbidities and the continuous competing risk of death from other causes with increasing age (ie, cancer, infections, dementia). The long-term detrimental effect of NSTE-ACS on survival, irrespective of treatment strategy, was demonstrated by a median survival of 4.4 years in our population as compared with 7.3 years for the Norwegian population ≥80 years of age during the same time period (ie, 2010-2014). This is comparable with the observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) registry.[13]

Comparing the results of the present study with those of previous trials is not straightforward. This is due to the magnitude of study designs, strategies, and combinations of different components of endpoints. Most important, randomized clinical trials including very old patients are still scarce. A handful of RCTs have compared an early or routine invasive strategy with a conservative strategy in patients with median age <65 years.[14-18] A few studies have reported superiority of an invasive strategy in the very old with NSTE-ACS.[13,15,19,20] These studies included patients >75 years of age, but the number of octogenarians was negligible. The Italian Elderly ACS study was the first RCT specifically designed to examine a potential benefit of an invasive strategy in very old patients with NSTE-ACS. Due to slow enrollment and emendation of the original sample size the trial ended up underpowered, but nonetheless indicating a

reduction of the primary composite endpoint (death, myocardial infarction, stroke, and hospitalization for cardiovascular causes) for patients with elevated troponin values at admission after 1-year follow-up.[21] The recent 80+ (Coronary Angioplasty in Octogenarians With Emergent Coronary Syndromes) study and the RINCAL (Revascularization or Medical Therapy In Elderly Patients With Acute Anginal Syndromes) study also explored the effect of an invasive strategy vs a conservative in the very old and failed to demonstrate any difference between the 2 strategies.[22,23] Both trials were terminated prematurely due to slow enrollment and hence rendered underpowered. FRISC II (Fast Revascularization During Instability in Coronary Artery Disease), the only RCT reporting very long-term outcome comparable to our study, demonstrated a reduction in the composite endpoint of death and myocardial infarction or death and hospitalization, respectively, and a long-lasting postponement of the occurrence of the composite endpoint. However, the median age at inclusion was 66 years and there was no significant long-term benefit in survival.[24] In contrast, the SENIOR NSTEMI (Invasive vs Noninvasive Management of Older Patients With Non-ST-Elevation Myocardial Infarction) study, a propensity score-matched cohort study of patients aged ≥80 years, demonstrated a reduction in mortality of an invasive management compared with a noninvasive management.[25] Guidelines for the treatment of very old patients with NSTE-ACS are based on some of the aforementioned trials and extrapolation of data from a considerably younger patient population.[1,2] For this reason, we await the results from the ongoing randomized trial, The British Heart Foundation SENIOR RITA (Older Patients With Non-ST-Segment Elevation Myocardial Infarction Randomized Interventional Treatment Trial; NCT03052036).

In our study, the prevalence of renal failure and diabetes was 37% and 17%, respectively. Interestingly, the most beneficial effect of an invasive strategy was observed in patients with renal failure and/or diabetes. There is little evidence favoring an invasive strategy in patients with renal failure and stable coronary artery disease.[26] However, observational studies support an invasive treatment strategy in patients with renal failure and NSTE-ACS.[27] In our study, patients with renal failure presented with more complex coronary disease (ie, significantly higher SYNTAX score) and a significantly greater proportion of the patients received revascularization, possibly contributing to this finding. The beneficial effect observed within the very old diabetic population of our study could not be explained from such a finding. Nevertheless, an invasive strategy has also been shown to be potentially more beneficial in reducing mortality, myocardial infarction, and need of hospitalization in a diabetic population.[28] Despite this, several studies report a continuous underuse of an invasive treatment strategy in a diabetic population. To the best of our knowledge, there are no data reporting outcome of treatment strategies in very old patients with renal failure and/or diabetes in the setting of NSTE-ACS, but our study hypothesizes that the beneficial effect reported for younger patients may also extend to this group of very old high-risk patients.

Women are commonly under-represented in clinical trials, typically constituting ~25% to 30% of a trial population. In our study, the proportion of female and male patients was balanced. In general, women presenting with NSTE-ACS are older and have more comorbidities than men do.[29] Women and men with NSTE-ACS have a comparable benefit from an invasive strategy, but women more frequently present with less significant obstructive coronary artery disease, which in part may contribute to explain the subsequent lower intervention rates.[29] Analysis of the angiographic and procedural results from the After Eighty Study also revealed a trend toward lower intervention rates among women.[30] However, this may be explained by the higher proportion of women with no significant obstructive coronary disease as compared with men, 32% vs 14%, respectively ($P = 0.001$).

Concerns have been raised as to the generalizability of the present study, specifically regarding comorbidity of the trial population. Old age is a strong predictor for adverse events and associated with multimorbidity, polypharmacy, cognitive impairment, functional decline, and frailty. Compared with the FRISC II, ICTUS (Invasive vs Conservative Treatment in Unstable Coronary Syndromes), and RITA-3 (Randomized Intervention Trial of Unstable Angina) trials, rates of hypertension, diabetes, stroke, and established coronary heart disease were higher in our study.[16-18] The total burden of comorbidity was more in resemblance to that of community populations with NSTE-ACS and comparable to that of the Italian ACS study.[13,21] Moreover, the complexity of the coronary pathology was high, with 48% of the patients in the invasive strategy group having left main or 3-vessel disease.[30] Revascularization is both an intervention and an endpoint in our study. Some might argue that this might introduce a treatment

bias during the follow-up: in other words, patients included in the conservative strategy group may be more likely to be referred to coronary angiography during follow-up. The superiority of the invasive strategy was in addition illustrated by calculating the restricted mean survival time using only myocardial infarction and all-cause death as components of the endpoint, and we still observed a significant gain in event-free survival time in favor of the invasive strategy (Supplemental Figure 1).

Questions has also been raised as to whether the Norwegian model with community hospitals and centralized third-line hospitals (hub-and-spoke referral system) automatically introduce a treatment bias regardless of angiographic results and intervention. In our study, there was no significant difference between groups in medical treatment at discharge, except for nitrates and anticoagulation as previously stated.[4] Patients having a PCI were returned to the community hospital after 4 to 12 hours, whereas patients only undergoing angiography were returned after 2 to 4 hours. Importantly, final discharge was done from the community hospitals in both groups.

Frailty was not specifically addressed in our study, but health-related quality of life was assessed at inclusion and at 1-year follow-up without evidence of a clinical meaningful difference between groups.[31] However, one may question whether the Short-Form 36 was an appropriate tool to measure health-related quality of life in this heterogenous group. The MOSCA-FRAIL (Invasive and Conservative Strategies in Elderly Frail Patients With Non-STEMI) study, comparing an invasive vs a conservative treatment strategy in frail patients aged ≥70 years with NSTE-ACS, failed to demonstrate a benefit in terms of days alive out of hospital or reduction of myocardial infarction during 1-year follow-up.[32]

STUDY LIMITATIONS. Considering the results of the After Eighty Study, we can conclude that our sample size calculation was adequate for the composite endpoint. A limitation of this study is the open-label nature of the trial that carries the risk of both performance and detection bias; in other words, investigators or patients may add concomitant treatments to address lack of efficacy or manage risk or symptoms based on their knowledge and beliefs of treatment allocation.

CONCLUSIONS

Our study demonstrates that the invasive strategy in very old patients with NSTE-ACS is superior to the conservative strategy both in a short-term and a long-term perspective. The effect was mediated through a reduction in myocardial infarctions and the need for urgent revascularization with a gain in event-free survival (ie, a postponement in the occurrence of the primary endpoint). The invasive strategy was beneficial across all subgroups and even more beneficial in the high-risk population of very old patients with renal failure and/or diabetes mellitus. Clinical decision making should be driven by randomized trials, but one may question whether we ever will have sufficient data from clinical trials to guide clinical practice in very old patients. Despite the results of the After Eighty Study, we believe that any therapy in the very old population in addition needs to be individually tailored because of serious comorbidity (eg, frailty, dementia, and life expectancy), and quality of life should also be addressed.

ACKNOWLEDGMENTS The authors thank the patients who participated in this trial, the co-investigators and colleagues, staff at the participating centers, and dedicated research nurses.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The After Eighty Study is an investigator-initiated study that received funding from the Norwegian Health Association (ExtraStiftelsen) and Inger and John Fredriksen Heart Foundation. Dr Tegn has received grants from the funders. The funders had no role in data collection, analysis, interpretation, writing of the manuscript or the decision to submit the report. All other authors have reported that they have no relationships relevant to the contents of this paper to declare.

ADDRESS FOR CORRESPONDENCE: Prof Bjørn Bendz, Department of Cardiology, Oslo University Hospital, Rikshospitalet, PB 4950 Nydalen, 0424 Oslo, Norway. E-mail: bbendz@ous-hf.no. #CardioTwitter, #JACC, #ACCIC, #ACCGeriatric, #cvACS, #NSTEMI.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients >80 years of age with NSTE-ACS, an invasive management strategy coupled with OMT is superior to medical therapy alone for prevention of additional myocardial infarction, further revascularization, stroke, and death.

TRANSLATIONAL OUTLOOK: Future studies should explore the effect of various treatment strategies on quality of life and long-term frailty.

REFERENCES

1. Collet J-P, Thiele H, Barbato E, et al, ESC Scientific Document Group. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020;42(14):1289–1367.

2. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21–e129.

3. Bendz B, Aaberge L. Acute coronary syndromes in older patients: does older age matter? *Lancet*. 2020;396(10251):585–587.

4. Tegn N, Abdelnoor M, Aaberge L, et al, After Eighty Study Investigators. 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(10023):1057–1065.

5. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(23):2999–3054.

6. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130(25):e344–e426.

7. Sedgwick P. Explanatory trials versus pragmatic trials. *BMJ*. 2014;349:g6694.

8. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research: Principles and Quantitative Methods*. John Wiley and Sons; 1982.

9. Kleinbaum DG, Klein M. *Survival Analysis: A Self-Learning Text*. Springer; 2005.

10. Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med*. 2011;30(19):2409–2421.

11. Perego C, Sbolli M, Specchia C, et al. Utility of restricted mean survival time analysis for heart failure clinical trial evaluation and interpretation. *J Am Coll Cardiol HF*. 2020;8(12):973–983.

12. Chodos AH, Kushel MB, Greysen SR, et al. Hospitalization-associated disability in adults admitted to a safety-net hospital. *J Gen Intern Med*. 2015;30(12):1765–1772.

13. Kochar A, Chen AY, Sharma PP, et al. Long-term mortality of older patients with acute myocardial infarction treated in US clinical practice. *J Am Heart Assoc*. 2018;7(13):e007230.

14. Boden WE, O'Rourke RA, Crawford MH, et al, Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med*. 1998;338(25):1785–1792.

15. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med*. 2004;141(3):186–195.

16. Wallentin L, Lagerqvist B, Husted S, et al, FRISC II Investigators. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. *Lancet*. 2000;356(9223):9–16.

17. de Winter RJ, Windhausen F, Cornel JH, et al, ICTUS Investigators. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med*. 2005;353(11):1095–1104.

18. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of Unstable Angina. *Lancet*. 2002;360(9335):743–751.

19. Damman P, Clayton T, Wallentin L, et al. Effects of age on long-term outcomes after a routine invasive or selective invasive strategy in patients presenting with non-ST segment elevation acute coronary syndromes: a collaborative analysis of individual data from the FRISC II - ICTUS - RITA-3 (FIR) trials. *Heart*. 2012;98(3):207–213.

20. Gnanenthiran SR, Kritharides L, D'Souza M, Lowe HC, Brieger DB. Revascularisation compared with initial medical therapy for non-ST-elevation acute coronary syndromes in the elderly: a meta-analysis. *Heart*. 2017;103(24):1962–1969.

21. 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. *J Am Coll Cardiol Intv*. 2012;5(9):906–916.

22. Hirlekar G, Libungan B, Karlsson T, Back M, Herlitz J, Albertsson P. Percutaneous coronary intervention in the very elderly with NSTE-ACS: the randomized 80+ study. *Scand Cardiovasc J*. 2020;54(5):315–321.

23. 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(1):67–74.

24. Wallentin L, Lindhagen L, Ärnström E, et al. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. *Lancet*. 2016;388(10054):1903–1911.

25. Kaura A, Sterne JAC, Trickey A, et al. Invasive versus non-invasive management of older patients with non-ST elevation myocardial infarction (SENIOR-NSTEMI): a cohort study based on routine clinical data. *Lancet*. 2020;396(10251):623–634.

26. Bangalore S, Maron DJ, O'Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med*. 2020;382(17):1608–1618.

27. Shaw C, Nitsch D, Lee J, Fogarty D, Sharpe CC. Impact of an early invasive strategy versus conservative strategy for unstable angina and non-ST elevation acute coronary syndrome in patients with chronic kidney disease: a systematic review. *PLoS One*. 2016;11(5):e0153478.

28. O'Donoghue ML, Vaidya A, Afsal R, et al. An invasive or conservative strategy in patients with diabetes mellitus and non-ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials. *J Am Coll Cardiol*. 2012;60(2):106–111.

29. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. 2008;300(1):71–80.

30. Tegn N, Eek C, Abdelnoor M, et al. Patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris randomised to an invasive versus conservative strategy: angiographic and procedural results from the After Eighty Study. *Open Heart*. 2020;7(2):e001256.

31. Tegn N, Abdelnoor M, Aaberge L, et al. Health-related quality of life in older patients with acute coronary syndrome randomised to an invasive or conservative strategy. The After Eighty randomised controlled trial. *Age Ageing*. 2018;47(1):42–47.

32. 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(5):407–415.

KEY WORDS clinical outcomes, geriatric cardiology, invasive treatment strategy, long-term follow-up, non–ST-segment elevation myocardial infarction

APPENDIX For supplemental figures, tables, and references, please see the online version of this paper.