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

Nicolai Tegn, Michael Abdelnoor, Lars Aaberge, Knut Endresen, Pål Smith, Svend Aakhus, Erik Gjertsen, Ola Dahl-Hofseth, Anette Hylen Ranhoff, Lars Gullestad, Bjørn Bendz, for the After Eighty study investigators

Summary

Background Non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris are frequent causes of hospital admission in the elderly. However, clinical trials targeting this population are scarce, and these patients are less likely to receive treatment according to guidelines. We aimed to investigate whether this population would benefit from an early invasive strategy versus a conservative strategy.

Methods In this open-label randomised controlled multicentre trial, patients aged 80 years or older with NSTEMI or unstable angina admitted to 16 hospitals in the South-East Health Region of Norway were randomly assigned to an invasive strategy (including early coronary angiography with immediate assessment for percutaneous coronary intervention, coronary artery bypass graft, and optimum medical treatment) or to a conservative strategy (optimum medical treatment alone). A permuted block randomisation was generated by the Centre for Biostatistics and Epidemiology with stratification on the inclusion hospitals in opaque concealed envelopes, and sealed envelopes with consecutive inclusion numbers were made. The primary outcome was a composite of myocardial infarction, need for urgent revascularisation, stroke, and death and was assessed between Dec 10, 2010, and Nov 18, 2014. An intention-to-treat analysis was used. This study is registered with ClinicalTrials.gov, number NCT01255540.

Findings During a median follow-up of 1·53 years of participants recruited between Dec 10, 2010, and Feb 21, 2014, the primary outcome occurred in 93 (40·6%) of 229 patients assigned to the invasive group and 140 (61·4%) of 228 patients assigned to the conservative group (hazard ratio [HR] 0·53 [95% CI 0·41–0·69], p=0·0001). Five patients dropped out of the invasive group and one from the conservative group. HRs for the four components of the primary composite endpoint were 0·52 (0·35–0·76; p=0·0010) for myocardial infarction, 0·19 (0·07–0·52; p=0·0010) for the need for urgent revascularisation, 0·60 (0·25–1·46; p=0·2650) for stroke, and 0·89 (0·62–1·28; p=0·5340) for death from any cause. The invasive group had four (1·7%) major and 23 (10·0%) minor bleeding complications whereas the conservative group had four (1·8%) major and 16 (7·0%) minor bleeding complications.

Interpretation In patients aged 80 years or more with NSTEMI or unstable angina, an invasive strategy is superior to a conservative strategy in the reduction of composite events. Efficacy of the invasive strategy was diluted with increasing age (after adjustment for creatinine and effect modification). The two strategies did not differ in terms of bleeding complications.

Funding Norwegian Health Association (ExtraStiftelsen) and Inger and John Fredriksen Heart Foundation.

Published Online
January 12, 2016
http://dx.doi.org/10.1016/S0140-6736(15)01166-6

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(16)00036-2

Department of Cardiology (N Tegn MD, L Aaberge MD, K Endresen MD, Prof S Aakhus MD, Prof L Gullestad MD, B Bendz MD), **Centre for Biostatistics and Epidemiology** (Prof M Abdelnoor PhD), **and Centre for Clinical Heart Research** (Prof M Abdelnoor), **Oslo University Hospital, Oslo, Norway; Faculty of Medicine, University of Oslo, Oslo, Norway** (N Tegn, Prof L Gullestad, Prof P Smith MD, B Bendz); **Department of Cardiology, Akershus University Hospital, Lørenskog, Norway** (Prof P Smith); **Department of Cardiology, Drammen Hospital, Drammen, Norway** (E Gjertsen MD); **Department of Cardiology, Lillehammer Hospital, Lillehammer, Norway** (O Dahl-Hofseth MD); **and Diakonhjemmet Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway** (Prof A H Ranhoff MD)

Correspondence to:
Dr Bjørn Bendz, Department of Cardiology, Oslo University Hospital, Rikshospitalet, 0424 Oslo, Norway
bbendz@ous-hf.no

Introduction

During the past two decades, mortality from acute coronary syndrome has reduced because of the development of modern treatment strategies—ie, revascularisation, medical treatment, and risk factor reduction in the post-discharge management. These improvements have mainly been realised in younger people (median age of 65 years) and in men.[1] According to the guidelines from the European Society of Cardiology, American Heart Association, and American College of Cardiology, patients with non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris should be stabilised medically and assessed for invasive treatment.[2–4] NSTEMI and unstable angina are frequent causes of hospital admission in patients aged 80 years or older. However, these patients are less likely to receive invasive and medical treatment according to guidelines and are at a higher risk for adverse events than younger patients.[1] In large randomised controlled trials of the effect of revascularisation versus medical treatment, patients aged 80 years or older are under-represented, making proper subanalysis of benefits and disadvantages uncertain.

The aim of the present randomised controlled trial was to investigate whether patients aged 80 years or older would benefit from an early invasive strategy versus a conservative strategy, in terms of a composite primary endpoint of myocardial infarction, need for urgent revascularisation, stroke, and death.

Research in context

Evidence before this study

We searched PubMed on April 10, 2015, for manuscripts published in English between Jan 1, 2000, and April 10, 2015, with the terms "non ST-elevation myocardial infarction in the elderly" and "acute coronary syndrome in the elderly". We had no specific inclusion or exclusion criteria for the studies searched.

A meta-analysis of the FRISC II, ICTUS, and RITA-3 trials suggested that patients older than 75 years benefit from a routine invasive strategy, but data are not available for patients aged 80 years or older. Median age in these trials was less than 65 years whereas it is older in community populations. Consequently, these trials do not have adequate sample sizes to enable subgroup analysis in patients older than 80 years. The Italian Elderly Acute Coronary Syndrome study, with 196 patients older than 80 years, is the only exception, but this trial was underpowered. An early invasive strategy in selected patients aged 80 years or more with non-ST-elevation myocardial infarction (NSTEMI) or unstable angina pectoris was associated with a reduction in endpoints (a composite of myocardial infarction, stroke, death, bleeding complications, and length of hospital stay) in the 2003–10 Nationwide Inpatient Sample database and the GRACE registry. In the most cited trials, the population aged 80 years and older is under-represented or missing, making proper subanalysis of benefits and disadvantages uncertain. This difficulty explains why references targeting this population are scarce in the guidelines and also why the European Society of Cardiology, American Heart Association, and American College of Cardiology have called for trials in this age group.

Added value of this study

The After Eighty study is the first randomised controlled trial to be specifically designed for the very elderly population (aged 80 years or older) with NSTEMI and unstable angina, which are frequent causes of hospital admission in this age group. In the present randomised controlled trial, 457 patients aged 80 years or older with NSTEMI or unstable angina were randomly assigned to an invasive strategy (including early coronary angiography with immediate assessment for percutaneous coronary intervention, coronary artery bypass graft, and optimum medical treatment) or to a conservative strategy (optimum medical treatment only). The primary outcome was a composite of myocardial infarction, need for urgent revascularisation, stroke, and death. The results show that an invasive strategy is superior to a conservative one. However, a dilution of the efficacy occurred with increasing age, and for patients older than 90 years the merit of the invasive strategy was not clear. Bleeding complication rates did not differ between the two strategies.

Implications of all the available evidence

Previous randomised trials suggest an invasive strategy is beneficial after NSTEMI and unstable angina. The results from the After Eighty study support use of an invasive strategy in patients aged 80 years or older. However, a dilution of the efficacy occurred with increasing age, and for patients older than 90 years we cannot conclude if an invasive strategy is beneficial.

Methods

Study design

The After Eighty study was an open-label, randomised, controlled multicentre trial. Between Dec 10, 2010, and Feb 21, 2014, patients admitted to 16 academic and teaching hospitals without percutaneous coronary intervention facilities in the South-East Health Region of Norway were included.

The protocol was approved by the relevant institutional review boards and the regional board of research ethics and is published online on the Oslo University Hospital website. No interim analysis was done.

For the **Oslo University Hospital website** see http://www.oslo-universitetssykehus.no/om-oss/english

Participants

The trial enrolled consecutive consenting clinically stable patients aged 80 years or older, with NSTEMI or unstable angina, with or without ST-segment depression on electrocardiogram (ECG), and with normal or raised blood concentration of troponin T or I. Raised troponin was defined as a value exceeding the 99th percentile of a normal population at the local laboratory at each participating site. A local cardiologist assessed patient eligibility and clinical condition. Patients were ineligible if they were clinically unstable with continuing chest pain or other ischaemic symptoms or signs, cardiogenic shock, continuing bleeding problems, or short life expectancy (<12 months) because of serious comorbidity (such as chronic obstructive pulmonary disease, disseminated malignant disease, or other reasons). Substantial mental disorder, including severe dementia or any disorder that interfered with a patient's ability to comply with the protocol, was also an exclusion criterion. Written informed consent was obtained from each participant before inclusion in the study. All patients aged 80 years or more with a diagnosis of acute coronary syndrome were also entered into a registry irrespective of their inclusion or exclusion from the study.

Randomisation and masking

Patients were randomly assigned to one of two groups, receiving either invasive or conservative treatment strategies. The Centre for Biostatistics and Epidemiology, Oslo University Hospital, was responsible for the randomisation procedure. A permuted block randomisation was generated with stratification on the inclusion hospitals in opaque concealed envelopes, and sealed envelopes with consecutive inclusion numbers were made. The sequence was generated by the Centre

for Biostatistics and Epidemiology. After Eighty study cardiologists enrolled the patients at each participating hospital, and assigned them to the trial groups. Two of these cardiologists (NT, OD-H) were involved in data collection and interpretation.

Procedures

Patients were assessed for participation in the study within 2 days after hospital admission on a 365 days per year basis. The invasive strategy included early coronary angiography with immediate assessment for ad-hoc percutaneous coronary intervention, coronary artery bypass graft, or optimum medical treatment, whereas the conservative strategy was optimum medical treatment alone. Patients randomly assigned to an invasive strategy were transported to Oslo University Hospital 1 day after inclusion. Median transport time was 95 min (range 37–160 min). Patients undergoing percutaneous coronary intervention were returned to their local hospitals after 6–18 h, depending on the segments treated and the travel distances, whereas patients having only coronary angiography were returned after 4–6 h. The patients randomly assigned to a conservative strategy received optimum medical treatment in the community hospitals. Both groups were observed, medically treated according to existing guidelines, and finally discharged from the community hospitals.[2–4]

Aspirin and clopidogrel were used as dual antiplatelet treatment, but in both groups, a few patients received ticagrelor. The patients in the invasive strategy group had coronary angiography the day after randomisation. If the patients in the conservative group had a reinfarction, refractory angina pectoris despite optimum medical treatment, 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 two invasive cardiologists before the revascularisation strategy was decided in each patient.

Outcomes

The primary outcome was a composite of myocardial infarction, need for urgent revascularisation, stroke, and death—the first occurring event. Reinfarction was defined as new cardiac symptoms combined with a rise in troponin exceeding the 99th percentile of a normal population at the local laboratory at each participating site. Periprocedural myocardial infarction (type 4a) was defined as a rise in creatine kinase-MB or troponins to three times 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 doubling in creatine kinase-MB 6 h post-procedure.[5] Refractory angina and the need for urgent revascularisation were defined as increasing angina pectoris symptoms despite optimum medical treatment with or without ECG changes as judged by the cardiologists in the community hospitals. Stroke was defined as a new focal neurological deficit of vascular origin lasting more than 24 h.

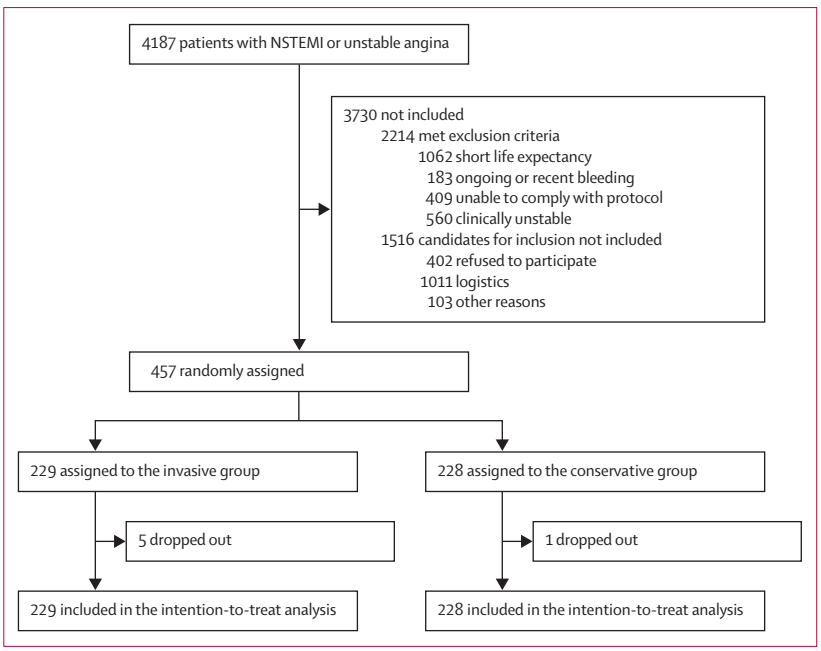

Figure 1: **Trial profile**
NSTEMI=non-ST-elevation myocardial infarction.

The secondary outcome was death from any cause. Bleeding complications during the index event and follow-up time were registered according to the Thrombolysis in Myocardial Infarction bleeding criteria.[6] All investigations were continuously assessed through feedback by phone and written reports from the local hospitals, and adverse events and unexpected patient responses in terms of cardiovascular status, biochemical status, general wellbeing, and need for readmission to hospital were recorded and made available for the Data and Safety Monitoring Board (DSMB). All serious adverse events and unexpected events were reported to the DSMB. The board had the right to advise the steering committee to first halt inclusion and subsequently to cease the study.

Statistical analysis

This randomised controlled trial was developed with an explanatory strategy.[7] The trial was analysed according to the intention-to-treat strategy in which we included the dropouts. To our knowledge, no studies targeting the elderly population existed when this study was being planned; however, in one previous study, patients aged more than 75 years with NSTEMI had an incidence of composite endpoints (death and myocardial infarction) of 21% at 6 months, whereas patients aged more than 75 years having percutaneous coronary intervention had a lower incidence of composite endpoints (10·8%).[8] This

	Invasive strategy group (n=229)	Conservative strategy group (n=228)
Mean age (range), years	84·7 (80–93)	84·9 (80–94)
Sex		
Male	125 (55%)	100 (44%)
Female	104 (45%)	128 (56%)
Weight (kg)	73·7 (13·8)	71·7 (13·2)
Medical history		
Previous myocardial infarction	107 (47%)	90 (39%)
Previous angina	124 (54%)	115 (50%)
Previous PCI	55 (24%)	46 (20%)
Previous CABG	44 (19%)	32 (14%)
Hypertension	131 (57%)	139 (61%)
Type 2 diabetes	45 (20%)	32 (14%)
Chronic obstructive pulmonary disease	24 (10%)	18 (8%)
Depression	10 (4%)	10 (4%)
Apoplexia cerebri	39 (17%)	30 (13%)
Peripheral vascular disease	19 (8%)	29 (13%)
Atrial fibrillation	49 (21%)	52 (23%)
Smoking status		
Present	18 (8%)	21 (9%)
Previous	94 (41%)	88 (39%)
Mean blood pressure		
Systolic (mm Hg)	152 (27)	153 (30)
Diastolic (mm Hg)	78 (16)	78 (16)
Heart rate (beats per min)	78 (18)	77 (19)
Killip class		
I	170 (74%)	169 (74%)
II	39 (17%)	38 (17%)
III	1 (<1%)	1 (<1%)
IV	0	1 (<1%)
EF		
EF <30%	12 (5%)	7 (3%)
EF 30–50%	64 (28%)	70 (31%)
EF >50%	104 (45%)	127 (56%)
ECG at admission		
Atrial fibrillation	49 (21%)	42 (18%)
Pathological Q wave	35 (15%)	40 (18%)
ST depression	43 (19%)	40 (18%)
Negative T wave	34 (15%)	48 (21%)
Right bundle branch block	21 (9%)	17 (7%)
Left bundle branch block	22 (10%)	24 (11%)
Troponin elevation*	216 (94%)	209 (92%)
Creatinine (mg/dL)	1·15 (0·50)	1·19 (0·94)
Glomerular filtration rate (mL/min per 1·73 m^2)	52 (12)	54 (11)
GRACE score	138 (17)	138 (19)

Data are n (%) or mean (SD), unless stated otherwise. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. EF=left ventricular ejection fraction. ECG=electrocardiogram. *Troponin levels exceeding the 99th percentile of a normal population.

Table 1: **Baseline characteristics**

	Invasive strategy group (n=229)	Conservative strategy group (n=228)
Medical treatment at inclusion		
Aspirin	226 (99%)	222 (97%)
Clopidogrel	195 (85%)	188 (82%)
Ticagrelor	11 (5%)	12 (5%)
Warfarin*	39 (17%)	21 (9%)
Low molecular weight heparin	173 (76%)	173 (76%)
Dabigatran	1 (<1%)	1 (<1%)
β blocker	192 (84%)	196 (86%)
Statins	206 (90%)	193 (85%)
ACE inhibitor or ARB	99 (43%)	116 (51%)
Calcium channel blocker	46 (20%)	47 (21%)
Nitrates	106 (46%)	126 (55%)
Medical treatment at discharge		
Aspirin	217 (95%)	212 (93%)
Clopidogrel	166 (72%)	166 (73%)
Ticagrelor	9 (4%)	8 (4%)
Warfarin*	50 (22%)	32 (14%)
Dabigatran	1 (<1%)	6 (3%)
Rivaroxaban	3 (1%)	3 (1%)
β blocker	196 (86%)	193 (85%)
Statins	209 (91%)	192 (84%)
ACE inhibitor or ARB	120 (52%)	123 (54%)
Calcium channel blocker	55 (24%)	53 (23%)
Nitrates	78 (34%)	109 (48%)
Coronary angiographic data†		
Three-vessel disease or left main	105 (48%)	NA
Two-vessel disease	40 (18%)	NA
One-vessel disease	35 (16%)	NA
Calcification, no significant stenosis	38 (17%)	NA
Normal	2 (1%)	NA
Revascularisation therapy		
PCI	107 (47%)	NA
CABG	6 (3%)	NA
Radial access†	198 (90%)	NA
Femoral access†	22 (10%)	NA
Angiography not done	9 (4%)	228 (100%)

Data are n (%). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. NA=not applicable. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. *No significant difference existed between the two study groups regarding medical treatment during the index episode, except for the use of warfarin, which was not an effect modifier. †The percentages are based on the 220 in the invasive strategy group who were given coronary angiography.

Table 2: **Details regarding medical treatment at inclusion, discharge, and coronary angiography**

difference represents a diminution of 10% in absolute risk and 50% in relative risk. Assuming a type I error of 5% and a power of 80%, we calculated that each intervention group would need 206 patients and therefore 412 patients would be needed for the study in total.[9] To

allow for some dropouts, because of the advanced age of the patients, we decided to enrol at least 450 patients.

The primary outcome was the composite endpoint. We used censored data with a closing date (Nov 18, 2014). Rate ratio was used to estimate the crude efficacy of the two strategies using a person time model.[10] Curves showing event-free survival were plotted with the Kaplan-Meier method. Log-rank test was used to calculate equality of event-free survival.[11] Stratification analysis using the Cochran-Mantel-Haenszel method was done to quantify confounders and the heterogeneity test to pinpoint potential effect modifiers. Adjusted efficacy as hazard ratio (HR) was estimated with the Cox regression model controlling for the confounding level of creatinine and interaction with age. The proportional hazard assumption was calculated by the Schoenfeld residuals test. A test of interaction using the log likelihood ratio was done when using the Cox model.[10] A competing risk analysis was performed using the cause-specific hazard function.[12,13] Death from other causes was the main competing risk outcome to reinfarction, revascularisation, and incidence of stroke. All p values are two-tailed.

We estimated the relation between logHR and age as a piecewise linear function. Such a model assumes that the regression between logHR and age is linear between specified points, 80–84 years, >84–90 years, and >90–94 years, and that the regression line is connected at these points. We estimated the slope of the regression lines in every interval and tested if the age effect on efficacy (logHR) is the same in intervals 80–84 years, >84–90 years, and >90–94 years.

This study is registered with ClinicalTrials.gov, number NCT01255540.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. NT received grants from the funder. The steering committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The median follow-up of this dynamic trial was 1·53 years. During the inclusion period, 4187 patients aged 80 years or older were admitted to the participating hospitals with the diagnosis NSTEMI or unstable angina (figure 1). 2214 (53%) of these patients met the exclusion criteria whereas 1973 (47%) patients were candidates for inclusion. 457 (23%) of the candidates for inclusion gave written consent and were randomly assigned to the invasive group (229 patients) or the conservative group (228 patients) between Dec 10, 2010, and Feb 21, 2014, (figure 1). Within 24 h after being randomly assigned, five (2%) patients dropped out of the invasive group as did one (<1%) from the conservative group. The dropouts in the invasive group were because of discussions the patients had had with their relatives, and in the conservative group, the single dropout was because of severe sepsis. As a result of the intention-to-treat strategy, all randomly assigned patients were analysed as far as the outcome and adverse events, including the dropouts. 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.

No crossovers occurred between the two strategy groups. Reinfarction, refractory angina pectoris, development of malignant ventricular arrhythmias, or increasing symptoms of heart failure were deemed to require urgent revascularisation—ie, an endpoint. Except for the use of warfarin and nitrates, baseline characteristics and medical treatment at inclusion and discharge were similar between the groups (tables 1, 2).

In the invasive group, 107 (47%) patients had percutaneous coronary intervention and six (3%) had coronary artery bypass graft. Nine (4%) patients in the invasive group did not have coronary angiography because of dropouts (five patients, 2%), stroke (one, <1%), gastrointestinal bleeding (two, 1%), and refractory delirium (one, <1%) shortly after randomisation. 198 (90%) of the coronary angiographies were done via

	Invasive strategy group (n=229)	Conservative strategy group (n=228)	Rate ratio	p value
Primary endpoint				
Composite endpoint	93 (41%)	140 (61%)	0·48 (0·37–0·63)	0·0001
Follow-up patient years	419·54	307·07		
Components of the primary endpoint				
Myocardial infarction	39 (17%)	69 (30%)	0·50 (0·33–0·75)	0·0003
Follow-up patient years	510·76	444·37		
Need for urgent revascularisation	5 (2%)	24 (11%)	0·19 (0·05–0·52)	0·0001
Follow-up patient years	588·12	536·69		
Stroke	8 (3%)	13 (6%)	0·61 (0·22–1·60)	0·26
Follow-up patient years	590·41	577·45		
Death from any cause	57 (25%)	62 (27%)	0·87 (0·59–1·27)	0·53
Follow-up patient years	496·92	481·26		
Complications (bleeding)				
Major	4 (2%)	4 (2%)	NA	NA
Gastrointestinal	2 (1%)	2 (1%)	NA	NA
Pericardial tamponade	1 (<1%)	0	NA	NA
Traumatic epidural haematoma	1 (<1%)	0	NA	NA
Traumatic subdural haematoma	0	1 (<1%)	NA	NA
Subarachnoid haemorrhage	0	1 (<1%)	NA	NA
Minor	23 (10%)	16 (7%)	NA	NA
Gastrointestinal	14 (6%)	11 (5%)	NA	NA
Other	9 (4%)	5 (2%)	NA	NA

Data are number of patients with event (%) or bleeding complications according to the Thrombolysis in Myocardial Infarction bleeding criteria.[6] NA=not applicable.

Table 3: **Clinical outcomes and complications**

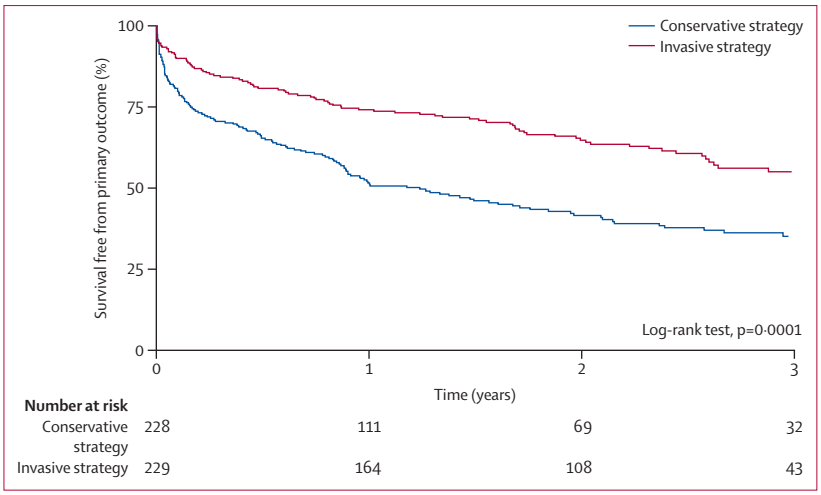

Figure 2: **Kaplan-Meier curves of survival free from composite outcome**
The primary outcome was a composite of myocardial infarction, need for urgent revascularisation, stroke, and death.

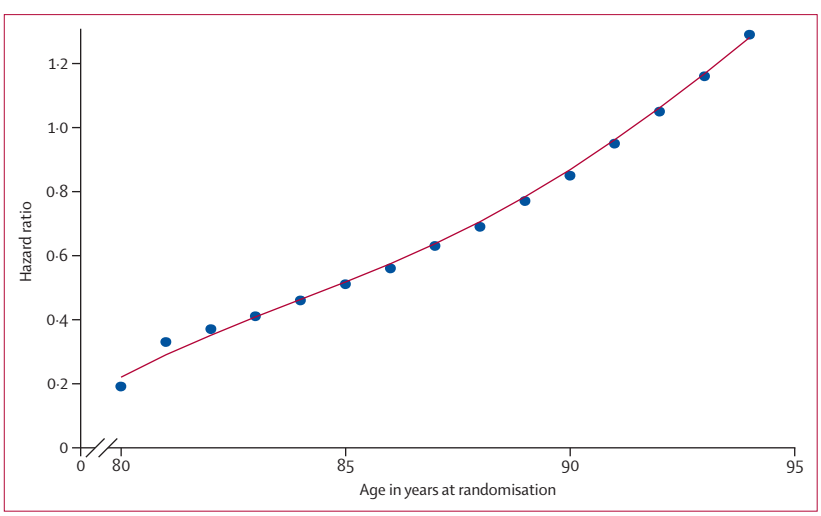

Figure 3: **Hazard ratio of efficacy versus age**
Lowess smoother of hazard ratio versus age controlling for logcreatinine.

the radial artery (table 2). Mean time to angiography was 3 days (SD 1·6) whereas mean length of overall hospital stay was 6 days (SD 3·2) in the invasive group and 5 days (SD 3·5) in the conservative group.

During follow-up, the primary endpoint occurred in 93 (41%) patients in the invasive group and in 140 (61%) patients in the conservative group (HR 0·53 [95% CI 0·41–0·69], p=0·0001). HR for the components of the primary composite endpoint were 0·52 (0·35–0·76; p=0·0010) for myocardial infarction, 0·19 (0·07–0·52; p=0·0010) for the need for urgent revascularisation, 0·60 (0·25–1·46; p=0·2650) for stroke, and 0·89 (0·62–1·28; p=0·5340) for death from any cause (table 3, figure 2, appendix). The estimated number needed to treat was 4·8 (95% CI 3·4–8·5).

See Online for appendix

The invasive group had four (2%) major and 23 (10%) minor bleeding complications whereas the conservative group had four (2%) major and 16 (7%) minor bleeding complications (table 3). Most bleeding was of gastrointestinal origin. One (<1%) major bleeding in the invasive group was related to the percutaneous coronary intervention procedure (pericardial tamponade) and was successfully treated. Two (1%) minor bleeding complications in the invasive group were related to the access site. Seven (3%) patients in the invasive group and four (2%) in the conservative group had a creatinine elevation of more than 25% during the index hospital stay. Two (1%) of these seven patients in the invasive group had a urinary tract infection. In the remaining five (2%) patients with a rise in creatinine blood concentration of more than 25%, contrast-induced nephropathy could not be ruled out. 14 (6%) patients in the invasive group and ten (4%) in the conservative group had a glomerular filtration rate of less than 30 mL/min per 1·73 m² at the time of randomisation.

The results were consistent when stratifying by sex, type 2 diabetes, creatinine blood concentration of more than 103 µmol/L, use of warfarin, and age older than 90 years. However, creatinine showed a confounding effect and age older than 90 years an effect modification (appendix). Another multivariate Cox analysis estimated efficacy of the invasive strategy controlling for log creatinine and interaction with age.

The interaction between invasive strategy and age as a continuous variable was p=0·009. A dilution of HR efficacy occurred with increasing age (figure 3). A fitted logHR on age using a piecewise linear function for age was done (appendix). The knots are placed on age intervals (80–84, >84–90, and >90–94 years). The coefficients (slopes) of the segments' regression lines for the different age groups were 0·18 (80–84 years), 0·09 (>84–90 years), and 0·108 (>90–94 years). A test of the effect of age intervals on logHR showed differences between interval 80–84 years compared with >84–90 years (p=0·0176) and with >90–94 years (p=0·0277). No difference in age effect between the age intervals was recorded for ages >84–90 years and >90–94 years (p=0·6260).

Considering the adjusted log creatinine Cox model with dichotomised older than 84 years as interaction term with treatment (interaction term p=0·017) with a satisfactory proportional hazard assumption to all the covariates and interaction in the model, we found age 84 years or younger had an HR of 0·36 (95% CI 0·24–0·54; p=0·0001) and age more than 84 years had an HR of 0·69 (0·49–0·98; p=0·0400). Thus, a change of effect occurs in magnitude but not in direction.

Considering age older than 90 years as interaction term with treatment (interaction term p=0·033) with a satisfactory proportional hazard assumption to all the covariates and interaction in the model, we found age 90 years or less had an HR of 0·47 (95% CI 0·35–0·62; p=0·0001) and age more than 90 years had an HR of 1·21

(0·53–2·7; p=0·6420). Thus, a change of effect occurs in magnitude and presumably in direction. However, because of a low number of patients older than 90 years in the study (n=34), we cannot be conclusive.

Of the 39 cases of myocardial infarction in the invasive strategy group, 11 (28%) were related to the percutaneous coronary intervention (type 4a). None of these patients became clinically unstable during or after the procedure, and no new pathological Q waves were seen on ECG.

In the conservative group, two (1%) patients had a reinfarction (NSTEMI), and eight (4%) patients had refractory angina pectoris a few days after inclusion. Percutaneous coronary intervention was done in eight (4%) of these patients, and the remaining two (1%) were ineligible for revascularisation.

During follow-up, two (1%) of the myocardial infarctions in the conservative group were STEMIs whereas one (<1%) was seen in the invasive group. The remaining myocardial infarctions were NSTEMIs.

Discussion

The results of this open-label, randomised, controlled, multicentre study show that an invasive strategy including early coronary angiography and subsequent treatment with percutaneous coronary intervention, coronary artery bypass graft, or optimum medical treatment is superior to a conservative strategy of optimum medical treatment alone in the reduction of composite events in clinically stable patients aged 80 years or more after presenting with NSTEMI or unstable angina. The primary outcome was a composite of myocardial infarction, need for urgent revascularisation, stroke, or death. Of the four components, myocardial infarction and the need for urgent revascularisation reached statistical significance whereas stroke and death from any cause were not significant. A dilution of the efficacy of an invasive strategy occurred with increasing age, and for patients older than 90 years we cannot conclude if the invasive strategy is beneficial.

Treatment of elderly patients (aged 80 years or older) is challenging because they are more likely than younger patients to have atypical symptoms, such as an absence of chest pain, in acute coronary syndrome.[14] The elderly population with acute coronary syndrome is a heterogeneous group with variable frailty and differences in physiological ageing, comorbidity, functional status, and social aspects. Thus, they are rarely included in clinical trials, and guidelines are often based on extrapolation of data from a substantially younger population. Consequently, management of NSTEMI and unstable angina in the subgroup of elderly patients, especially in those aged 80 years or older, is not yet evidence based.

Existing guidelines emphasise intensive and early medical and interventional treatment, particularly for those at high risk for short-term events.[2–4] Elderly individuals represent a subgroup known to be at high risk, but practice patterns continue to show less use of cardiac drugs and invasive care, even in elderly individuals who are likely to benefit.[15] Uncertainty about risks and benefits in elderly patients could explain this practice.

In the present study, the two treatment groups were equally distributed regarding baseline characteristics and medical treatment at inclusion and discharge. Patients were not included if they were clinically unstable with continuing chest pain or other ischaemic symptoms or signs, cardiogenic shock, continuing bleeding problems, or short life expectancy. Thus, clinically unstable patients were assessed on a routine basis for an urgent invasive approach according to guidelines.[2–4] A large proportion of patients who were not included in the present study refused to participate (n=402) or were not included because of local logistics (n=1011) in the community hospitals. Thus, about half (n=1973) of the members of the screening population were candidates for an invasive strategy, and 457 (23%) of them were included in the After Eighty study.

Elderly patients in trial populations have lower rates of traditional cardiovascular risk factors, less comorbidity, and better haemodynamics and renal function than do community populations in general. Comorbidity in the present study population was more prevalent than in other trials and was similar to those of community populations.[1] Compared with the FRISC II, ICTUS, and RITA-3 trials, rates of hypertension, diabetes, prior stroke, and previous myocardial infarction were higher.[16–18]

This context not withstanding, comparing the results of the present study with those of previous trials is not straightforward.[8,16–20] Median age in previous trials was younger than 65 years but was older in the present trial and is also older in community populations.[1] Previous trials did not have adequate sample sizes to enable subgroup analysis in patients older than 80 years. The Italian Elderly Acute Coronary Syndrome study,[19] with 196 patients older than 80 years, was also underpowered and had a different design from the present study. A meta-analysis[21] of the FRISC II, ICTUS, and RITA-3 trials suggested that patients older than 75 years benefit from a routine invasive strategy, but data are not available for patients aged 80 years or more.[22] An early invasive strategy in patients aged 80 years or older with NSTEMI or unstable angina was associated with a reduction in endpoints in the 2003–10 Nationwide Inpatient Sample database and the GRACE registry.[23,24]

A comparison with previous trials is also complicated because of the different study designs (eg, invasive *vs* conservative, invasive *vs* selective invasive, early invasive *vs* delayed invasive, and further allocation into different medical treatment subgroups). Moreover, composite endpoints are most commonly used, but their components and combinations differ (eg, some

combination of myocardial infarction; need for urgent revascularisation; or readmissions because of angina or bleedings, stroke, and death). One commonality between FRISC II, ICTUS, RITA-3, and the After Eighty study is that an interventional strategy had an effect on reduction of angina pectoris, need of revascularisation, or myocardial infarction. FRISC II also had an effect on reduction of mortality. However, the incidence of myocardial infarction and death from any cause after 12 months was substantially higher in the After Eighty study than in these previous trials. In the present study, the cumulative hazard incidence of myocardial infarction was identified in 11·8% of patients in the invasive group and in 27·7% in the conservative group after 12 months. In FRISC II, ICTUS, and RITA-3 myocardial infarction rates ranged from 3·8% to 15·0% in the invasive groups, and from 4·8% to 11·6% in the conservative groups. 12-month mortality in the invasive group in the After Eighty study was 12·7% versus 2·2–4·6% in the previous trials, and 14·1% versus 2·5–3·9% in the conservative groups in the other studies. The advanced age and comorbidity of the After Eighty study population probably explain these differences.

One limitation of this study is the open-label nature of the trial, which has the risk of both performance and detection bias—eg, investigators or patients might add concomitant treatments to address insufficient efficacy, or manage risk or symptoms on the basis of their knowledge and beliefs about treatment allocation.

Kidney dysfunction can increase the risk of bleeding in elderly populations.[25] Younger patients with renal failure are not usually refused invasive treatment. Thus, we believe that to not exclude patients with renal failure from the study was reasonable. Adequate hydration and the dose and type of contrast media used could be critical in patients at risk of contrast-induced nephropathy. Routinely, patients are well hydrated and not in a fasting condition when the angiography or percutaneous coronary intervention is done, and a computerised contrast delivery system (Acist CVi Contrast Delivery System, Bracco, Milan, Italy) for controlled infusion is used to minimise patient contrast dose. For further renal protection, the low viscosity and non-ionic iodixanol is used as the contrast medium. In the invasive group of the present study, 113 (51·4%) of the 220 patients given coronary angiography had angiography only. These factors might have reduced the risk of contrast-induced nephropathy in the invasive group despite the age of the population.

Age itself is a powerful predictor of adverse events after acute coronary syndrome.[26,27] In the present study, the rates of bleeding complications did not differ between the two groups. This result might partly be attributable to the equal use of antithrombotic treatment (table 2) in the two groups and the importance of radial access (90%) in the catheterisation laboratory.[28]

Ischaemic heart disease is the leading cause of death globally.[29] Because of the growth of the elderly population, WHO predicts that coronary heart disease deaths will increase by 120–137% during the next two decades, and a person aged 80 years can expect about 9 remaining years of life.[30] For this reason, a strategy on how to treat very elderly patients is essential. The results from the present study support an invasive strategy in octogenarians with NSTEMI and unstable angina. However, the efficacy of an invasive strategy in nonagenarians remains uncertain.

In conclusion, we have shown that an invasive strategy including optimum medical treatment together with percutaneous coronary intervention or coronary artery bypass graft is superior to a conservative strategy using optimum medical treatment alone in clinically stable patients older than 80 years with NSTEMI or unstable angina. However, the efficacy was less with increasing age, and for patients older than 90 years we cannot conclude if an invasive strategy is beneficial. No differences in complication rates were seen between the two strategies. The present results support an invasive strategy in clinically stable, very elderly patients with NSTEMI and unstable angina.

Contributors

MA, LA, KE, PS, SA, EG, AHR, LG, and BB were members of the After Eighty study Steering Committee; BB was the chairman. MA, LA, KE, PS, SA, LG, and BB wrote the study protocol. NT, MA, KE, PS, SA, EG, OD-H, AHR, and BB participated in the data collection. NT, MA, LA, KE, PS, EG, AHR, LG, and BB contributed to the data analysis and data interpretation. NT and OD-H had a major contribution to the inclusion of patients and collection of patient data. All authors were After Eighty study investigators and have contributed to finalising the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank the patients who participated in our trial, our co-investigators and colleagues, staff at the participating centres, and our dedicated research nurses. Theis Tønnessen (Department of Thoracic Surgery, Oslo University Hospital, Oslo, Norway) and Rune Wiseth (Department of Cardiology, St Olavs Hospital, Trondheim, Norway) formed the safety and data monitoring committee.

References

1 Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation* 2007; **115:** 2549–69.

2 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:** 2999–3054.

3 Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35:** 2541–619.

4 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:** e344–426.

5 Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007; **50:** 2173–95.

6 Rao SV, O'Grady K, Pieper KS, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol* 2006; **47:** 809–16.

7 Zwarenstein M, Treweek S. What kind of randomized trials do we need? *J Clin Epidemiol* 2009; **62:** 461–63.

8 Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001; **344:** 1879–87.

9 Pocock SJ, Hughes MD. Estimation issues in clinical trials and overviews. *Stat Med* 1990; **9:** 657–71.

10 Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. New York: John Wiley & Sons, 1982.

11 Kleinbaum DG, Klein M. Survival analysis: a self-learning text. New York: Springer, 2005.

12 Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? *Statist Med* 2012; **31:** 1089–97.

13 Andersen PK, Geskus RB, de Witte T, Putter H. Competing risk in epidemiology possibilties and pitfalls. *Int J Epidemiol* 2012; **41:** 861–70

14 Brieger D, Eagle KA, Goodman SG, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004; **126:** 461–69.

15 Avezum A, Makdisse M, Spencer F, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2005; **149:** 67–73.

16 Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast revascularisation during Instability in coronary artery disease. *Lancet* 2000; **356:** 9–16.

17 de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005; **353:** 1095–104.

18 Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005; **366:** 914–20.

19 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 Cardiovas Interv* 2012; **5:** 906–16.

20 Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998; **338:** 1785–92.

21 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:** 207–13.

22 Fox KA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a metaanalysis of individual patient data. *J Am Coll Cardiol* 2010; **55:** 2435–45.

23 Kolte D, Khera S, Palaniswamy C, et al. Early invasive versus initial conservative treatment strategies in octogenarians with UA/NSTEMI. *Am J Med* 2013; **126:** 1076–83.

24 Devlin G, Gore JM, Elliott J, et al. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Eur Heart J* 2008; **29:** 1275–82.

25 Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003; **24:** 1815–23.

26 Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003; **163:** 2345–53.

27 Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; **291:** 2727–33.

28 Valgimigli M, Gagnor A, Calabro P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015; **385:** 2465–76.

29 Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; **349:** 1269–76.

30 McKay J, Mensah GA. The atlas of heart disease and stroke. Geneva: World Health Organization, 2005.