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ORIGINAL ARTICLE

Percutaneous coronary intervention in the very elderly with NSTE-ACS: the randomized 80+ study

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ABSTRACT

Objective: The treatment strategy in the very elderly with NSTE-ACS is debated, as they are often under-represented in clinical trials. The aim of this multicenter randomized controlled trial was to compare invasive and conservative strategies in the very elderly with NSTE-ACS.

Methods: We randomly assigned patients $\geq$ 80 years of age with NSTE-ACS to an invasive strategy with coronary angiography and optimal medical treatment or a conservative strategy with only optimal medical treatment. The primary outcome was the combined endpoint of major adverse cardiac and cerebrovascular events (MACCE). Sample size was powered for a 50% reduction of event rate in MACCE with an invasive strategy. We used intention-to-treat analysis.

Results: Altogether, 186 patients were included between 2009 and 2017. The study was terminated prematurely due to slow enrollment. At 12-month follow-up, the primary outcome occurred in 31 (33.3%) of the invasive treatment group and 34 (36.6%) of the conservative treatment group, with a hazard ratio (HR) of 0.90 (95% CI 0.55–1.46; $p = 0.66$) for the invasive group relative to the conservative group. The corresponding HR value for urgent revascularization was 0.29 (95% CI 0.10–0.85; $p = 0.02$), 0.56 (95% CI 0.27–1.18; $p = 0.13$) for myocardial infarction, 0.70 (95% CI 0.31–1.58; $p = 0.40$) for all-cause mortality, 1.35 (95% CI 0.23–7.98; $p = 0.74$) for stroke, and 1.62 (95% CI 0.67–3.90; $p = 0.28$) for recurrent hospitalization for cardiac reasons.

Conclusion: In the very elderly with NSTE-ACS, we did not find any significant difference in MACCE between invasive and conservative treatment groups at 12-month follow-up, possibly due to small sample size.

ClinicalTrials.gov: NCT02126202

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angina; mortality; non-ST elevation acute coronary syndrome – acute coronary syndrome; percutaneous coronary intervention; unstable angina; very elderly

Introduction

The prevalence of coronary heart disease increases with increasing age [1], and the elderly constitute a high proportion of patients that present with non-ST elevation acute coronary syndrome (NSTE-ACS) [2,3]. Several randomized controlled trials (RCTs) have shown that invasive treatment with percutaneous coronary intervention (PCI) together with optimal medical treatment is superior to optimal medical treatment alone in patients with NSTE-ACS [4–7]. An invasive treatment strategy is therefore the standard of care in NSTE-ACS. However, elderly patients have been under-represented in many RCT studies [8,9] and are less likely to receive evidence-based therapies [10,11]. Current guidelines from European Society of Cardiology recommend elderly patients to be considered for invasive treatment with PCI, and guidelines of the American Heart Association/American College of Cardiology for the management of patients without ST elevation (NSTE-ACS) recommend invasive treatment and revascularization if appropriate in patients who are >75 years [12,13]. Few studies have suggested that PCI may have a beneficial effect on survival of the elderly with NSTE-ACS [10,11,14,15]. A recent RCT [16] showed that invasive treatment was superior to conservative treatment in reduction of myocardial infarction and need for urgent revascularization, but no significant difference was found in mortality. A recent meta-analysis [17] highlighted the need

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Supplemental data for this article can be accessed here.

for further RCTs to determine the effect of invasive treatment in elderly patients.

In the present study, our primary aim was to compare an invasive treatment strategy with conservative treatment in the very elderly with NSTE-ACS, in terms of major adverse cardiac and cerebrovascular events (MACCE). Secondary aims were to compare bleeding events and angina class between invasive and conservative treatment strategies at follow-up. Our hypothesis was that invasive treatment would be superior to conservative treatment in reducing the combined endpoint of MACCE within 12 months, with low risk of bleeding.

Materials and methods

Study design

The study was an open-label, randomized, controlled multicenter trial involving patients ≥80 years with NSTE-ACS. The trial had two parallel treatment arms: an invasive group and a conservative group. Patients were recruited from three different hospitals in the southwestern Sweden. For details of patient allocation and recruitment time for each hospital, see Supplementary Table 1. The study protocol has been published [18].

Recruitment

The study nurse screened patients who were eligible for inclusion. The inclusion criteria were: (1) ≥80 years; (2) NSTE-ACS with ischemic symptoms (chest pain) lasting over 10 min in the previous 72 h; and (3) ischemic ST-segment depression ≥1 mm and/or elevated troponin I, troponin T, or CK-MB. The exclusion criteria were: (1) PCI within 30 days prior to randomization; (2) ongoing active internal bleeding; (3) ST-segment elevation of ≥1 mm in two contiguous leads on ECG; (4) enrolled in another study that has not completed follow-up; (5) known allergy to aspirin or P2Y12 antagonists; (5) severe dementia; (6) expected limited 1-year survival due to other diseases; and/or (7) unwillingness to participate or expected problems with compliance. All patients signed an informed consent document before randomization.

Randomization and procedures

After patients had given informed consent, they were randomized with a permuted block randomization 1:1 to one of two treatment strategies, using sealed envelopes. The invasive treatment included coronary angiography and, if appropriate, revascularization with PCI or coronary artery bypass grafting (CABG), and optimal medical treatment [12]. The conservative treatment strategy included optimal medical treatment without coronary angiography. Patients in the conservative treatment group were to undergo coronary angiography if refractory chest pain, hemodynamic instability, heart failure, or life-threatening cardiac arrhythmias and revascularized if appropriate. After inclusion, evaluation of the degree of frailty was assessed at bedside according to the Canadian Study of Health and Aging clinical frailty scale [19]. The severity of angina was graded by the study nurse by telephone. All patients were assessed for adverse events and serious adverse events by telephone and from medical records.

Outcome

The primary outcome was the first event of the combined endpoint of MACCE within 12 months. MACCE was a combination of the following: myocardial infarction, urgent revascularization, all-cause mortality, stroke, and recurrent hospitalization for cardiac reasons. The secondary outcomes included: MACCE within 1-month, all-cause mortality, myocardial infarction, death and/or myocardial infarction within 12 months, major and minor bleeding within 1-month, and angina class, assessed at 1-month and 12-month follow-up using the Canadian cardiovascular society (CCS) scale.

Definitions

Recurrent hospitalization for cardiac reasons was defined as due to new onset atrial fibrillation or heart failure. Stroke was defined as cerebral ischemic events including transitory ischemic attack. Recurrent intervention was any unplanned revascularization after the index hospitalization. Major bleeding was defined as either intracranial bleeding, a decrease in haemoglobin level of more than 50 g/L, or bleeding requiring surgery. Minor bleeding was defined as a decrease in haemoglobin of more than 30 g/L but less than 50 g/L, spontaneous gross haematuria, haematemesis, haematoma, or pseudoaneurysm requiring treatment (other than surgery) [20].

Sample size

Based on a sub-study in the TACTICS-TIMI 18 trial [15], we expected a MACCE rate of 40% within 12 months in those allocated to conservative treatment. To detect a reduction in MACCE rate of 50%, with a power of 80% and a significance level of 0.05, 82 individuals were required in each group. To ensure enough patients for evaluation, our intention was to include a total of 100 individuals in each group.

Statistical analysis

The main analysis was intention-to-treat. However, we performed also per-protocol analysis of the primary endpoint (MACCE) for details see Supplementary table 4.

The (absolute) standardized difference, was used to assess balance between the two treatment groups regarding baseline characteristics.

For MACCE during 12-month follow-up, Kaplan-Meier curves regarding survival free from MACCE for the two treatment groups were constructed and compared using the log-rank test. In the tables and results, outcome rates at 1 and 12 months are given as percentages calculated as 100 minus Kaplan-Meier estimates and Cox proportional

hazards regression was used for calculation of hazard ratios with corresponding 95% confidence intervals, except for angina class at 1 and 12 months, where crude percentages are given and the groups were compared using Mann-Whitney U-test.

All tests were two-sided and p-values less than 0.05 were considered statistically significant. No interim analysis was performed. All analyses were performed using SAS for Windows version 9.4.

Ethics

The local ethics committee in Gothenburg approved the study protocol on 28 April 2009 (registration number 157-09). The study was registered at ClinicalTrials.gov (NCT02126202).

Results

From September 2009 to September 2017, 186 patients aged ≥80 years with NSTE-ACS were randomly assigned at three centers to invasive strategy (93 patients) or conservative strategy (93 patients) (Figure 1). The trial was terminated prematurely due to slow enrollment. During follow-up, five patients withdrew informed consent.

Baseline characteristics

Baseline characteristics of study patients are presented in Table 1. Although patients were randomized, the groups were rather imbalanced in the following aspects: patients in the conservative group generally had a higher pulse, more often renal dysfunction, and more often atrial fibrillation. In the invasive group, 21% were considered frail compared to 13% in the conservative group.

During index hospitalization, 89 patients in the invasive treatment group had a coronary angiography performed, followed by 57 PCIs and 1 CABG . Of those treated with PCI, 33% were completely revascularized. Drug-eluting stents (DES) were used in 44% of all PCIs. In the conservative treatment group, four patients had coronary angiography performed, followed by 3 PCIs and 1 CABG. Of the invasive treatment patients, 91 were discharged alive opposed to 92 in the conservative group. Medications at discharge were similar in the two groups.

Primary outcome

During 12-month follow-up, MACCE occurred in 31 patients in the invasive group and in 34 in the conservative group (HR = 0.90 (95% CI 0.55–1.46; $p = 0.66$)) (Table 2 and Figure 2). Accordingly, the HR was 0.56 (95% CI 0.27–1.18; $p = 0.13$) in the invasive group relative to the conservative group regarding myocardial infarction, 0.29 (95% CI 0.10–0.85; $p = 0.02$) regarding need of urgent revascularization, 0.70 (95% CI 0.31–1.58, $p = 0.40$) regarding all-cause mortality, 1.35 (95% CI 0.23–7.98; $p = 0.74$) regarding stroke, and 1.62 (95% CI 0.67–3.90; $p = 0.28$) regarding recurrent hospitalization for cardiac reasons, for details see Table 2. Six patients died from a cardiovascular cause in the invasive group and 11 in the conservative group. Analysis of primary outcome excluding recurrent hospitalization due to cardiac reasons was HR 0.72 (95% CI 0.41–1.22; $p = 0.22$) with 24 (26.7%) events in invasive group and 31 (34.4%) in the conservative group. Primary outcome excluding recurrent hospitalization and non-cardiovascular death was HR 0.65 (95% CI 0.37–1.14; $p = 0.13$) (for details, see Supplementary Table 2).

Secondary outcome and bleeding

There was no significant difference in any secondary outcome between the two treatment groups. None of the patients had a major bleeding within 1 month, but four had a minor bleeding in the invasive group and two had a minor bleeding in the conservative group (Table 2).

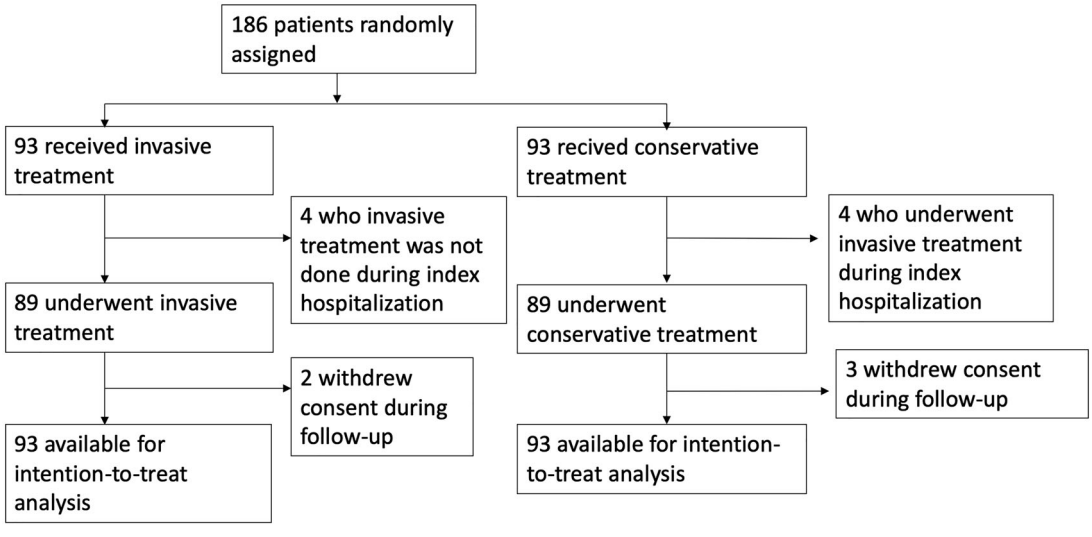

Figure 1. Trial profile.

Table 1. Baseline characteristics.

	Invasive treatment group ($n = 93$)	Conservative treatment group ($n = 93$)	Standardized difference[#]
Age	84 (81,90)	84 (81,89)	0.10
Male sex	47 [50.5%]	55 [59.1%]	0.17
Weight, kg (1/5)*	73 (59,94)	73 (56,94)	0.02
Systolic blood pressure, mmHg	142 (120,174)	142 (119,180)	0.05
Diastolic blood pressure, mmHg	79 (64,98)	80 (68,100)	0.18
Heart rate, beats/min (0/1)	69 (56,92)	80 (55,99)	0.45
Renal dysfunction (eGFR <60)	59 [63.4%]	70 [75.3%]	0.26
Elevated troponin T or I or CK-MB **	92 [98.8%]	88 [94.6%]	0.25
Previous medical history:			
Angina pectoris (1/1)	36 [39.1%]	41 [44.6%]	0.11
Myocardial infarction (2/0)	29 [31.9%]	35 [37.6%]	0.12
PCI (1/0)	15 [16.3%]	16 [17.2%]	0.02
CABG	19 [20.4%]	14 [15.1%]	0.14
Hypertension	55 [59.1%]	59 [63.4%]	0.09
Diabetes mellitus	16 [17.2%]	20 [21.5%]	0.11
Hyperlipidemia	21 [22.6%]	16 [17.2%]	0.13
Heart failure	10 [10.8%]	8 [8.6%]	0.07
Peripheral artery disease	3 [3.2%]	6 [6.5%]	0.15
Stroke	10 [10.8%]	15 [16.1%]	0.16
Atrial fibrillation (1/1)	10 [10.9%]	17 [18.5%]	0.22
Medication at inclusion:			
Beta blocker	37 [39.8%]	48 [51.6%]	0.24
ACE inhibitor (1/0)	23 [25.0%]	26 [28.0%]	0.07
ARB inhibitor (1/0)	18 [19.6%]	24 [25.8%]	0.15
Calcium channel blocker (1/0)	23 [25.0%]	20 [21.5%]	0.08
Long-acting nitrates	25 [26.9%]	20 [21.5%]	0.13
Rapidly acting nitrates	26 [28.0%]	30 [32.3%]	0.09
Aspirin	51 [54.8%]	50 [53.8%]	0.02
Clopidogrel (0/2)	8 [8.6%]	7 [7.7%]	0.03
Warfarin	7 [7.5%]	12 [12.9%]	0.18
Statins (1/0)	30 [32.6%]	37 [39.8%]	0.15
Diuretics (0/1)	33 [35.5%]	39 [42.4%]	0.14
Digitalis	5 [5.4%]	3 [3.2%]	0.11
Oral diabetic treatment	11 [11.8%]	12 [12.9%]	0.03
Insulin (1/0)	6 [6.5%]	5 [5.4%]	0.05
Frailty scale: (12/11)			0.10
1	5 [6.2%]	4 [4.9%]	
2	20 [24.7%]	21 [25.6%]	
3	26 [32.1%]	32 [39.0%]	
4	13 [16.0%]	14 [17.1%]	
5	12 [14.8%]	9 [11.0%]	
6	5 [6.2%]	2 [2.4%]	
7	0 [0.0%]	0 [0.0%]	
5–7	17 [21.0%]	11 [13.4%]	0.20
Smoking status: (4/5)			
Present	2 [2.2%]	3 [3.4%]	0.07
Previous	33 [37.1%]	39 [44.3%]	0.15
Ejection fraction (8/19)	55 (35,60)	54 (35,60)	0.02
ECG at admission:			
ST depression (4/5)	35 [39.3%]	39 [44.3%]	0.10
LBBB (6/3)	6 [6.9%]	12 [13.3%]	0.21
During index hospitalization:			
Coronary angiography	89 [95.7%]	4 [4.3%]	
PCI	57 [61.3%]	3 [3.2%]	
CABG	1 [1.1%]	1 [1.1%]	
LM	16 [18%]	2 [50%]	
3-vessel disease	20 [22%]	1 [25%]	
2-vessel disease	21 [24%]	0	
1- vessel disease	19 [21%]	1 [25%]	
No significant stenosis	13 [15%]	0	
Discharged alive	$n = 91$	$n = 92$	
Medication at discharge:			
Beta blocker (1/0)	79 [87.8%]	83 [90.2%]	0.08
ACE inhibitor (2/0)	40 [44.9%]	43 [46.7%]	0.03
ARB inhibitor (2/0)	17 [19.1%]	24 [26.1%]	0.17
Calcium channel blocker (3/0)	16 [18.2%]	21 [22.8%]	0.12
Long-acting nitrates (4/0)	32 [36.8%]	44 [47.8%]	0.22
Rapidly acting nitrates (3/1)	65 [73.9%]	72 [79.1%]	0.12
Aspirin (1/0)	82 [91.1%]	82 [89.1%]	0.07
P2Y12 inhibitor (1/0)	80 [88.9%]	81 [88.0%]	0.03
Warfarin (4/2)	9 [10.3%]	15 [16.7%]	0.19
Statins (2/1)	71 [79.8%]	74 [81.3%]	0.04
Diuretics (1/1)	34 [37.8%]	42 [46.2%]	0.17
Digitalis (2/1)	5 [5.6%]	3 [3.3%]	0.11
Oral diabetes treatment (2/0)	8 [9.0%]	13 [14.1%]	0.16
Insulin (2/0)	6 [6.7%]	5 [5.4%]	0.05

LBBB: left bundle branch block. The data in the two main columns are median (10th, 90th percentile) or n [per cent].
*Number of patients for whom information was missing in the two groups, respectively. ** Elevated biochemical marker more than three times the normal level. [#](Absolute) standardized difference.

Table 2. Primary and secondary outcome.

	Invasive treatment group ($n = 93$)	Conservative treatment group ($n = 93$)	HR (95% CI)[#]	p-value
Primary outcome (MACCE)	31 (34.4%)	34 (37.4%)	0.90 (0.55–1.46)	0.66
Components of MACCE:*				
Myocardial infarction	11 (12.9%)	19 (22.3%)	0.56 (0.27–1.18)	0.13
Urgent revascularization	4 (4.6%)	14 (16.5%)	0.29 (0.10–0.85)	0.02
All-cause mortality	10 (11.0%)	14 (15.2%)	0.70 (0.31–1.58)	0.40
Stroke	3 (3.7%)	2 (2.3%)	1.35 (0.23–7.98)	0.74
Recurrent hospitalization due to new AF or HF	13 (15.2%)	8 (9.4%)	1.62 (0.67–3.90)	0.28
Secondary outcome and bleeding				
Any MACCE within 1 month	11 (11.9%)	15 (16.2%)	0.72 (0.33–1.56)	0.40
All-cause mortality within 12 months	10 (11.0%)	14 (15.2%)	0.70 (0.31–1.58)	0.40
Myocardial infarction within 12 months	11 (12.9%)	19 (22.3%)	0.56 (0.27–1.18)	0.13
Death and/or myocardial infarction within 12 months	20 (22.2%)	26 (28.9%)	0.74 (0.41–1.33)	0.31
Major bleeding within 1 month	0 (0.0%)	0 (0.0%)		1.00
Minor bleeding within 1 month	4 (4.4%)	2 (2.2%)	1.81 (0.34–9.61)	0.49

AF: atrial fibrillation; HF: heart failure. The data in the two main columns are numbers (Kaplan-Meier estimate in per cent).
[#]Hazard ratio for invasive treatment group in relation to conservative treatment group, with corresponding 95% confidence interval. *Patients could experience more than one of the components (although only the first to occur was included in MACCE).

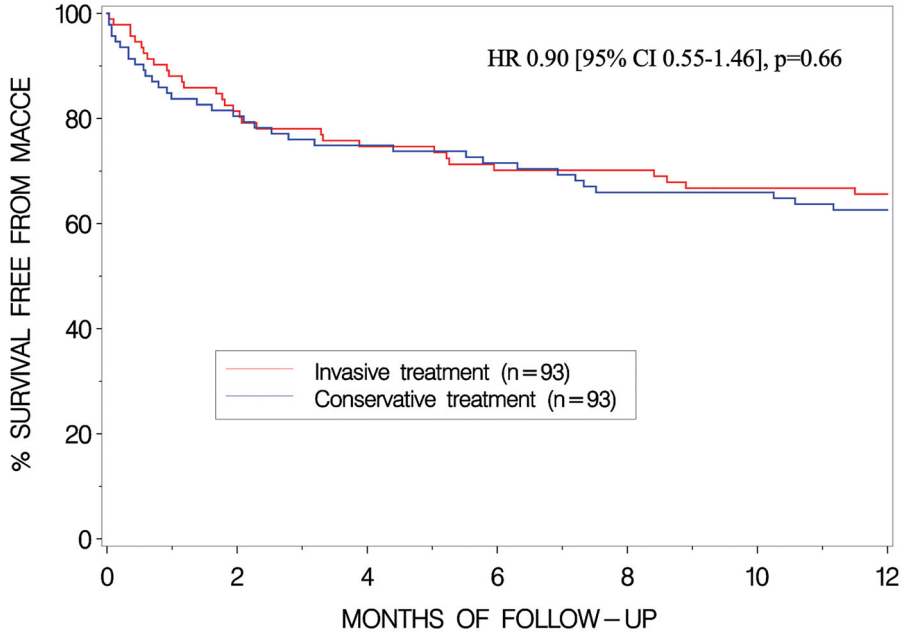

Figure 2. Kaplan-Meier curves of survival free from the primary combined outcome of MACCE at 12-month follow-up. The primary combined outcome was a composite of myocardial infarction, urgent revascularization, all-cause mortality, stroke, and recurrent hospitalization due to cardiac reason.

Angina during follow-up

There was no difference in angina severity between the two treatment groups, neither at 1-month nor at 12-months (for details, see Supplementary Table 3).

Per-protocol analysis

The per protocol analysis gave results similar to the intention-to-treat analysis, namely an HR of 0.97 (95% CI 0.58–1.62; $p = 0.92$) (for details, see Supplementary Table 4).

Discussion

The main finding was that there was no statistically significant difference in MACCE between invasive treatment and conservative treatment in the very elderly with NSTE-ACS over 12 months. In addition, we found no significant difference regarding all-cause mortality or severity of angina during follow-up. Although our results support current evidence that an invasive treatment strategy reduces the need for revascularization, there was no benefit regarding mortality.

Previous randomized clinical trials focusing on the elderly have compared invasive and conservative treatment strategies in patients with NSTE-ACS and shown conflicting results. The Italian ACS Elderly trial [21] involving patients ≥75 years did not show any outcome benefit in elderly NSTE-ACS patients treated invasively, but a subgroup analysis did show reduced mortality in those with high troponin levels treated with PCI. In the subgroup analysis in the TACTIC-TIMI 18 trial [15] with patients aged >75 years, an early invasive treatment strategy reduced the composite endpoint of death and MI at 6 months. The After Eighty trial [16] showed a reduction in the combined endpoint of myocardial infarction, need for urgent revascularization, stroke,

and death, with an invasive treatment strategy being compared to a conservative one. In the present study, we had a different combined endpoint and a shorter follow-up compared to the After Eighty trial. Additionally, our analysis of primary outcome excluding recurrent hospitalization and non-cardiovascular death did not show any significant difference between groups.

Neither all-cause mortality nor cardiovascular death in the present study differed significantly between the two treatment strategies. This is in agreement with previous RCTs. In our study, 12-month mortality was similar to that in the Italian ACS Elderly trial and the After Eighty trial. The patients in our study had a similar comorbidity to that in these two studies. Furthermore, our cohort had low frailty, which has previously been found to be independently associated with 1-year mortality [22].

Our finding of no difference in angina class between the treatment strategies, conflicts with other studies [23], which have found greater reduction in angina with invasive treatment. One possible explanation is that the patients in our conservative treatment group received more intensive anti-angina treatment medication than those in the invasive treatment group.

Previous studies have shown that elderly patients are more liable to major bleeding after invasive treatment than with medical treatment, but this difference was not observed in a recent meta-analysis [17]. Thus, the present trial is more in line with recent publications. In Sweden, there is a high proportion of radial access in coronary angiography and a low use of Gp IIb/IIIa receptor inhibitors, which could possibly explain the low rate of bleeding events [24].

In summary, there was no statistically significant difference in MACCE between invasive treatment and conservative treatment in the very elderly with NSTE-ACS over 12 months. As our cohort was quite healthy it is uncertain that the results can be extrapolated to the more frail patients with several comorbidities that we encounter in clinical practice [25].

Strengths and limitations

The strength of this study was the use of randomization for treatment allocation, thus limiting residual confounding and confounding by indication. However, there were several limitations. Firstly, in spite of the random allocation to the two treatment strategies, there were imbalances between the groups regarding certain baseline characteristics. At 12 months the relative risk reduction in the primary endpoint was 10% between the invasive group and conservative group. The study was powered to detect a 50% reduction in the primary endpoint rate in the invasive group which was optimistic, i.e. the study was underpowered to show any benefit when the difference in event rate was so low.

There were a few crossover patients between the two treatment groups during index hospitalization. Moreover, data on eligibility for inclusion were missing from two study sites, so we were unable to include accurate information about all screened patients but we assume that the proportion of enrolled patients out of possible candidates was extremely low.

Furthermore, the slow patient enrollment rate caused a long recruitment period causing the study to terminate prematurely which is a major limitation. However, the number of randomized patients was not far from the number of required patients according to the sample size calculation. The problem with a slow enrollment has been observed in other studies [21,26] and reflects a problem with the recruitment of very elderly patients in RCTs, especially when the investigated intervention is established in younger patients. These problems must become well known to scientists who plan to start similar types of studies. We need to learn more about the difficulties and ethical problems associated with the inclusion of the very elderly in randomized clinical trials and about their preferences in the acute phase of a cardiovascular disease.

The long recruitment period became a confounder particularly due to the development of treatment in both the medical and invasive strategy group such as secondary prevention, more usage of DES and complete revascularization that may have influenced the outcome. Thereby the application of the results to current practice are limited. Finally, different study sites including patients at different rates may have influenced patient selection and thereby the generalizability of the results.

Conclusion

In the very elderly with NSTE-ACS, we did not find any significant difference in MACCE between the invasive and conservative treatment groups at 12-month follow-up, possibly due to small sample size.

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Disclosure statement

All the authors have contributed to the article and have approved the final version. None of the authors has any conflicts of interests.

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