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Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction

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Aims We sought to investigate the impact of an invasive treatment in elderly patients presenting with non-ST elevation myocardial infarction (NSTEMI) in clinical practice.
Methods and results We analysed data of consecutive elderly patients (≥75 years) with NSTEMI who were prospectively enrolled in the German Acute Coronary Syndromes registry between July 2000 and November 2002. Overall 1936 patients were divided into two groups: 1005 (51.9%) underwent coronary angiography and/or revascularization, 931 (48.1%) received conservative treatment. In the invasive group, percutaneous coronary intervention was performed in 37.5% within 48 h and in 17.6% after 48 h, whereas 9.8% underwent coronary artery bypass grafting within the hospital stay. In-hospital death (12.5 vs. 6.0%, $P < 0.0001$) and death/myocardial infarction (17.3 vs. 9.6%, $P < 0.0001$) occurred significantly less often in patients with invasive strategy. After adjustment of the confounding factors in the propensity score analysis the invasive strategy remained superior for mortality (OR 0.55, 95% CI 0.35–0.86) and death and non-fatal myocardial infarction (OR 0.51, 95% CI 0.35–0.75) and 1 year mortality (OR 0.56, 95% CI 0.38–0.81). Major bleeding complications tended to be more frequent in the invasive group (8.8 vs. 5.8%, $P = 0.07$).
Conclusion In clinical practice, in elderly patients with NSTEMI, an invasive strategy is associated with an improved in-hospital and 1 year outcome but a trend towards more bleeding complications.

Introduction

Recent studies have demonstrated an improved clinical outcome among high-risk patients with non-ST elevation acute coronary syndromes (NSTE-ACSs) with an invasive strategy including routine use of coronary angiography and revascularization.[1–3] Traditionally elderly persons, particulary those with comorbitidies, have been underrepresented in randomized trials of ACSs relative to their disease prevalence.[4] The elderly compromise an increasing proportion of patients with NSTE-ACS. In recently published data from an Italian registry, over 35% of the patients were 75 years or older.[5] Furthermore, the elderly represent a very high-risk subgroup, but receive less optimal medical and revascularization therapies than younger patients, emphazising the growing importance of investigating treatment modalities in elderly cardiac patients.[6–10] In a randomized controlled trial that compared an early invasive management with a conservative ischaemia-guided approach, a significant reduction of death or non-fatal re-infarction was observed at 6 months among patients older than 75 years of age with NSTE-ACS. However, patients with severe comorbid conditions or other serious systemic illness were excluded.[11] So far, little is known about the efficacy of a routine cardiac catheterization and revascularization in elderly patients in clinical practice. We therefore analysed data from the German acute coronary syndromes (ACOS) registry to determine the impact of an invasive strategy on in-hospital and 1 year outcome of elderly (≥75 years) patients presenting with NSTEMI.

Methods

The acute coronary syndromes registry

The ACOS Registry is a prospective, multi-centre, observational study on current treatment of ACSs (STEMI, NSTEMI, and unstable angina pectoris). Consecutive patients were recruited within the period from June 2000 to November 2002. The participating hospitals were located throughout Germany and included university hospitals, community hospitals, and tertiary care centres all providing intensive care units and early reperfusion therapy. During the entire study period all patients with ACS were prospectively registered and

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followed during their clinical course to document patient characteristics, acute therapy, hospital course, and 12 ± 2 month outcome. However, the 1 year follow-up was not conducted by all participating hospitals and therefore the 1 year data of ~20% of the patients is not known. In the patients with prospectively planned follow-up, 1 year data were 95% complete.

This present study is an analysis of consecutive elderly patients (≥75 years) with NSTEMI who were divided into an invasive or a conservative group. Patients were included in the invasive group at the time of the coronary angiography. This is in contrast to major randomized clinical trials where invasive and conservative strategies were compared and patients initially randomized to a conservative group remained in this arm even if cardiac catheterization and/or revascularization were necessary due to ischaemia.

Data collection

Data on patient characteristics on admission were recorded, including age, gender, cardiovascular risk factors, concomitant diseases, prior myocardial infarction (MI), prior stroke, prior cardiovascular interventions, and chronic medical treatment, as well as data on symptoms and pre-hospital delay. Data on electrocardiografic findings, biochemical markers, reperfusion therapy, and adjunctive therapy were documented. At discharge, outcome and major cardiovascular and cerebrovascular adverse events were recorded.

Every participating centre was committed by written consent to include every consecutive patient with ACS. All patients gave informed consent for processing their anonymous data. Data were collected on three record forms by the treating physicians. Completed data sheets were sent to the central data processing centre Institut für Herzinfarktforschung Ludwigshafen for uniform monitoring and registration. Source data verification was performed by comparison of the registry data with hospital records in randomly selected patients in 20 randomly selected participating centres. The study was approved by the Ethics Committee of Landesärztekammer Mainz.

Definitions

NSTEMI was diagnosed in the presence of the two following criteria: persistent angina pectoris for >20 min and an elevation of troponin T or I. Raised levels were considered those exceeding the upper normal level at the local laboratory at each participating site. Re-infarction was defined as recurrent angina and re-elevation of cardiac markers or angiographic re-occlusion. Bleeding complications were classified as major when blood transfusions were required or considered clinical relevant by the treating physician. Stroke was defined as the occurrence of persistent specific neurological deficits. Serum creatinin >2 mg/dL was classified as renal insufficiency.

Statistical methods

Data are presented as absolute numbers, percentage, or medians with 25th and 75th percentiles as appropriate. Whenever possible, percentages were used to describe patient populations. The frequencies of categorial variables in two populations were compared by χ^2 test and by calculating odds-ratios (OR) and 95% confidence intervals (CI). Continuous variables were compared by Mann–Whitney–Wilcoxon test. The effect of an invasive treatment on hospital death and the composite of death and MI was evaluated by calculating the OR and the 95% CI. Control of potential confounders was attempted by constructing a propensity score using logistic regression.[12] The propensity score was the probability that a patient would receive either invasive or conservative strategy and was computed using a logistic regression model including the following variables: age, sex, prior MI, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), prior stroke/transient ischaemic attack (TIA), peripheral arterial disease, diabetes, smoking, hypercholesterolaemia, hypertension, obesity (BMI ≥30 kg/m^2), renal insufficiency, heart rate ≥100/min, systolic blood pressure ≤100 mmHg, cardiogenic shock, and significant first-order interaction (alpha=0.05). The C-statistic for propensity score models were 0.80. The patients were divided into quintiles defined by their probabilities (propensity scores). Balance of the covariables across the two groups was achieved after adjustment for the propensity score. The balance was tested statistically by linear regression for continuous variables and logistic regression for the dichotomous variables.

The propensity score quintiles (coded as a class variable with 4 degrees of freedom) were then added to the final logistic regression model. The balance was tested statistically by linear regression for continuous variables and logistic regression for dichotomous variables (*Table 3*).

The following variables were added for the propensity score analysis of the 12 ± 2 month follow-up: no evaluation of left-ventricular function, reduced left-ventricular function (ejection fraction <40%), treatment with aspirin, beta-blocker, ACE-inhibitor, and statin at discharge. Significant interactions of propensity score quintile and covariates were: age × propensity score, and heart rate >100 b.p.m. × propensity score. The C-statistic for propensity score models were 0.84.

P-values <0.05 were considered significant. All *P*-values are results of two-tailed tests. The analysis was performed with the SAS© system release 8.2 on a personal computer (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

From 2000 and 2002, a total of 16 817 consecutive patients from 155 hospitals with ACSs were enrolled into the ACOS registry. For the present analysis, 1936 patients (≥75 years) with NSTEMI were included and divided into two groups: 51.9% of the patients underwent coronary angiography and revascularization if indicated ($n = 1005$), 48.1% received conservative treatment ($n = 931$). The baseline characteristics of the patients in the two different groups are shown in *Table 1*.

Coronary angiography

The distribution of one-, two-, and three-vessel disease in the invasive group was 26, 27, and 47%, respectively.

Revascularization

From the invasive group, 377 patients (37.5%) were treated with PCI within 48 h, another 177 patients (17.6%) during the index hospital stay. Ninety-eight patients (9.8%) underwent CABG during the index hospitalization. Overall 353 patients (35.1%) of the invasive group were not revascularized (*Table 2*).

Medical treatment

The elderly who underwent an invasive procedure were more likely to receive guideline-recommended medication. They were more often treated with aspirin, clopidogrel, GP IIb/IIIa inhibitors, beta-blockers, and statins. More conservative patients received low-molecular weight heparin, more invasive patients intravenous heparin. The percentage of patients treated with ACE-inhibitors was similar in both groups (*Table 2*).

Table 1 Baseline characteristics of the patients with non-ST elevation myocardial infarction

	Invasive strategy, $n = 1005$	Conservative strategy, $n = 931$	*P*-value
Baseline demographics			
Age (years), mean	78.7 (76.7–81.2)	82.2 (78.8–87.2)	<0.0001
Women (%)	485 (48.3)	546 (58.6)	<0.0001
BMI (%)	26.0 (23.9–28.4)	25.2 (22.8–27.7)	<0.0001
Medical history			
Prior myocardial infarction (%)	275 (27.4)	315 (33.8)	<0.01
Prior PCI or CABG (%)	218 (21.7)	111 (11.9)	<0.0001
Prior stroke/TIA (%)	99 (9.9)	168 (18.0)	<0.0001
Peripheral arterial disease (%)	99 (9.9)	126 (13.5)	<0.05
Risk factors			
Hypertension (%)	796 (79.2)	696 (74.8)	<0.05
Diabetes mellitus (%)	337 (33.5)	367 (39.4)	<0.01
Hypercholesterolaemia[a] (%)	626 (62.3)	463 (49.7)	<0.0001
Smoking (%)	84 (8.4)	59 (6.3)	0.09
Renal insufficiency[b] (%)	45 (4.5)	86 (9.2)	<0.0001
Findings on admission			
Cardiogenic shock (%)	45 (4.5)	80 (8.5)	<0.001
Heart rate >100 b.p.m (%)	151 (15.3)	304 (32.3)	<0.0001
Systolic blood pressure <100 mmHg (%)	50 (5.0)	93 (10.0)	<0.0001

BMI, body mass index.
[a]LDL cholesterol >130 mg/dL and/or history of hypercholesterolaemia and/or actual medication for hypercholesterolaemia.
[b]Creatinin >2 mg/dL.

Table 2 Treatments during the index hospitalization

	Invasive strategy, $n = 1005$	Conservative strategy, $n = 931$	*P*-value
Revascularization			
PCI (<48 h)	377 (37.5)	–	
PCI (>48 h)	177 (17.6)	–	
CABG	98 (9.8)	–	
No revascularization	353 (35.1)	931 (100)	<0.0001
Medical treatment (<48 h)			
Aspirin	901 (89.7)	796 (85.5)	<0.01
Clopidogrel	536 (53.3)	206 (22.1)	<0.0001
GP IIb/IIIa inhibitors	404 (40.2)	86 (9.2)	<0.0001
Low molecular weight heparin	278 (27.7)	352 (37.8)	<0.0001
Unfractionated heparin	753 (74.9)	606 (65.1)	<0.0001
Beta-blockers	789 (78.5)	608 (65.3)	<0.0001
ACE-inhibitors	669 (66.6)	606 (65.1)	0.49
Statins	604 (60.1)	374 (40.2)	<0.0001

Table 3 Covariables across both groups before and after adjustment for the propensity score

	P-value before adjustment	*P*-value after adjustment
Age (years), mean	<0.001	0.16
Women (%)	<0.001	0.94
Obesity (%)	<0.05	0.73
Prior myocardial infarction (%)	<0.01	0.87
Prior PCI or CABG (%)	<0.001	0.73
Prior stroke/TIA (%)	<0.001	0.67
Peripheral arterial disease (%)	<0.05	0.90
Hypertension (%)	<0.05	0.86
Diabetes mellitus (%)	<0.01	0.75
Hypercholesterolaemia[a] (%)	<0.001	0.80
Smoking (%)	0.09	0.87
Renal insufficiency[b] (%)	<0.001	0.78
Cardiogenic shock(%)	<0.001	0.90
Heart rate>100 b.p.m (%)	<0.001	0.53
Systolic blood pressure<100 mmHg (%)	<0.001	0.73

[a]LDL cholesterol >130 mg/dL and/or history of hypercholesterolaemia and/or actual medication for hypercholesterolaemia.
[b]Creatinin >2 mg/dL.

Hospital complications

In-hospital mortality (6.0 vs. 12.5%, $P < 0.0001$) and the combined endpoint of death and non-fatal re-infarction (9.6 vs. 17.3%, $P < 0.0001$) were lower in the patients undergoing cardiac catheterization compared with the group with conservative strategy (*Figure 1*). The C-statistic for propensity score models were 0.80. The patients were divided into quintiles defined by their probabilities (propensity scores). Balance of the covariables across the two groups as shown in *Table 3* was achieved after adjustment for the propensity score. The balance was tested statistically by linear regression for continuous variables and logistic regression for the dichotomous variables. After adjustment for baseline variables in the propensity score analysis, the invasive strategy remained superior for mortality and death and non-fatal re-infarction (*Table 4*). The incidence of non-fatal stroke was lower in the patients assigned to coronary angiography (1.1 vs. 2.8%, $P < 0.01$)

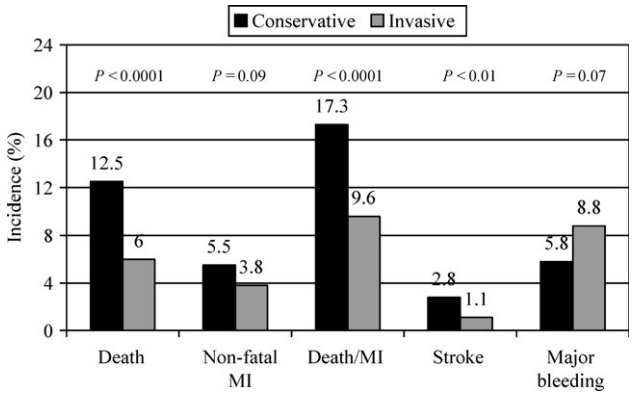

Figure 1 Hospital complications in two groups with a conservative or invasive strategy in the univariate analysis.

(*Figure 1*). There was a trend towards a higher rate of major bleeding complications in the invasive group (8.8 vs. 5.8%, $P=0.07$) (*Figure 1*). Among patients with an invasive strategy, the incidence of death was 5.5% in the PCI group, 8.2% in the CABG group, and 6.1% in the conservatively treated group, respectively. The rates of death and non-fatal re-infarction in the three subgroups were 10.0, 13.3, and 7.8% (*Figure 2*).

Follow-up

Mortality (10.7 vs. 27.9%, $P < 0.0001$) was lower in patients with an invasive strategy 12 ± 2 months after discharge. Among invasive patients, the incidence of death was 11.1% in the PCI group, 14.5% in the CABG group, and 15.2% in the conservatively treated group. After adjustment in the propensity score analysis a significant risk reduction in mortality persisted in patients with invasive strategy (*Table 4*).

Discussion

Our analysis is one of the first evaluations of a large registry with NSTEMI patients, which investigates the impact of an invasive strategy in elderly on in-hospital outcome. In our study, elderly patients with a lower risk profile were more likely to undergo diagnostic coronary angiography and revascularization. First of all, the invasive patients were significantly younger. Secondly, they had a lower incidence of cardiogenic shock on admission, diabetes, renal insufficiency, and prior atherothrombotic events, suggesting that the biological age also had a major impact on the clinicians' decision to conduct a coronary angiography. Furthermore, they received more often a guideline-recommended adjunctive therapy. These findings are in concordance with prior observations of physician management of ACSs. Investigators have universally observed that the use of cardiac catheterization and antithrombotic therapy declines as the patients get older and sicker, even when no contraindications exist.[6,8–10] In this context, the uncertainty in the medical care of older patients plays a major role. In randomized controlled clinical trials conducted in patients with ACSs, the elderly have been underrepresented.[4] Moreover, due to the higher rate of comorbidity, the elderly patients face a higher risk for complications in invasive procedures relative to younger patients. However, with regard to the less favourable baseline profile, the increased frequency of complications after cardiac catheterization and revascularization is reasonable.[13–14]

In our evaluation, 56% of the patients with invasive strategy were treated with PCI and 9.8% underwent CABG during hospitalization, whereas 35.1% were not revascularized. This revascularization rate is comparable with that reported in randomized trials conducted in the elderly.[11]

The incidence of death and the composite of death and non-fatal re-infarction during the index hospitalization were significantly lower in the invasive group. However, the reduction in the rate of non-fatal re-infarction just missed the level of significancy. One possible explanation is that re-infarction might have been fatal in a high proportion of patients and events were reported in a hierachical order, therefore masking a reduction in the overall rate of fatal and non-fatal reinfarction. Among patients with invasive strategy, due to the peri-operative risk and selection bias, the incidence of hospital death and non-fatal reinfarction was highest in the CABG-patients, whereas mortality was lowest in the PCI group and re-infarction rate in the conservatively treated patients. However, at 1 year follow-up the mortality rate among the invasive group was lower in patients with PCI or CABG compared with medically managed patients.

As this evaluation is not a randomized, controlled study and the baseline characteristics between the two groups are very different a propensity score analysis was used to control potential confounders. Several factors that have a major impact on the prognosis were taken into account. After adjustment of the confounding variables as baseline characteristics, medical history, risk factors and findings at admission in the propensity score analysis, the invasive strategy remained superior in terms of hospital mortality and death/MI.

The early benefit of an invasive strategy persisted up to 1 year. A significant risk reduction for 1 year mortality could also be observed. Our results are in line with the findings of a subgroup analysis of the TACTICS-TIMI (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction) 18 trial, where patients hospitalized with unstable angina and NSTEMI were randomly assigned to an early interventional or conservative ischaemia-guided procedure. Among elderly (75 years an older), the invasive management strategy conferred to a significant reduction of non-fatal re-infarction and MACE (Major Adverse Cardiac Events) at 6 months. In patients younger than 75 years, a significant reduction of cardiovascular events could not be observed. The occurrence of death tended to be lower in elderly, but the difference was not significant.[11] As ACOS is a clinical registry for ACS and not a randomized clinical trial, high-risk patients with renal insufficiency, cardiogenic shock or resuscitation were also enrolled. The absolute reduction of hospital mortality adds up to over 6% and the relative reduction to over 46%. Due to a higher risk profile, the 'real-world' patient seems to gain even more benefit from an invasive management, compared with patients in randomized trials with partly low-risk patients.

In addition, in another analysis of a registry with over 500 elderly with NSTE-ACS, De Servi *et al.*[5] identified a conservative strategy as an independent predictor of ischaemic events at 30 days. The APPROACH (Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease)

Table 4 Risk reduction for hospital mortality, the combined endpoint of death and myocardial reinfarction, and 1 year death in the invasive group before and after adjustment in the propensity score analysis

	Odds ratio before adjustment	95% CI before adjustment	Odds ratio after adjustment	95% CI after adjustment
Death	0.45	0.32–0.62	0.55	0.35–0.86
Death and non-fatal re-infarction	0.51	0.39–0.66	0.51	0.35–0.75
1 year death	0.31	0.24–0.41	0.56	0.38–0.81

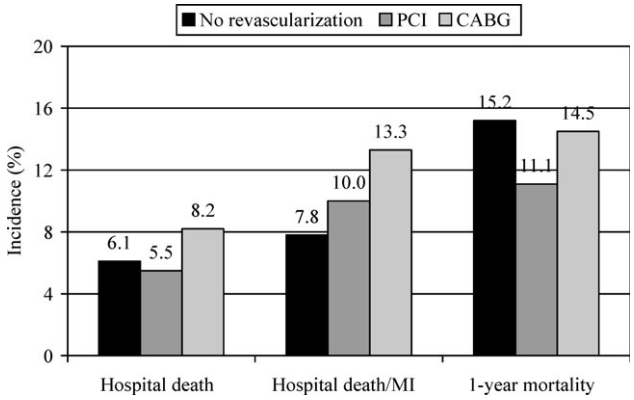

Figure 2 Hospital and 1 year event rates in patients with invasive strategy according to the revascularization therapy.

study captured all patients undergoing cardiac catheterization and revascularization in the province of Alberta (Canada) in the late 90's. Interestingly, elderly patients had greater absolute risk reductions associated with surgical or percutaneous revascularization than younger patients.[15] In the TIME (Trial of Invasive vs. Medical therapy in Elderly patients) trial, the risk–benefit ratio of invasive vs. optimized medical treatment in patients aged 75 years or older with stable angina was evaluated. After 1 year, no significant differences in the rate of death or non-fatal MI could be shown. However, among patients assigned to an invasive procedure, a later hospitalization for revascularization was less likely.[16]

Clinicians' reluctance to use an invasive strategy in elderly with NSTEMI has been potentially justified by the high-risk of complications. In a large observational study of patients with NSTE-ACS, a higher risk for stroke associated with an invasive management was observed.[17] In our analysis, we found no such increase among elderly. On the contrary, the incidence of stroke was lower in the patients assigned to coronary angiography. In the subgroup analysis of the TACTICS-TIMI trial, an increased risk of bleeding complications after routine invasive management was seen. Bach *et al.*[11] observed a higher frequency of major bleeding and blood transfusions during the index hospitalization in invasive patients. In our registry, the rate of major bleedings among patients assigned to an invasive strategy tended to be higher. The more aggressive antithrombotic treatment seems to play a decisive role. In this finding, those selected for coronary angiography were more likely to receive aspirin, clopidogrel, and GP IIb/IIIa inhibitors. In an analysis of the impact of age on outcome among patients enrolled in PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrillin Therapy), a significant increase of moderate and severe bleeding was associated with use of eptifibatide in elderly compared with younger patients with NSTE-ACS, despite a lower rate of invasive procedures.[18]

Limitations

The present analysis is not a randomized, controlled study evaluating the impact of an invasive strategy in elderly presenting with NSTEMI. In the ACOS registry, the treatment strategy was left to the discretion of the physician. This could result in selection bias, which cannot be fully eliminated by using a propensity score.

Summary

In conclusion, our data shows that elderly with a lower risk profile are more likely to undergo a coronary angiography and revascularization. In clinical practice, an invasive strategy resulted in a significant reduction of hospital mortality and death/MI, but was associated with a trend towards more bleeding complications. These results indicate that an invasive strategy is feasible in a substantial proportion of elderly with NSTEMI and is linked with a better in-hospital outcome.

Conflict of interest: none declared.

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