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Early Aggressive Versus Initially Conservative Treatment in Elderly Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

A Randomized Controlled Trial

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Objectives This study sought to determine the risk versus benefit ratio of an early aggressive (EA) approach in elderly patients with non–ST-segment elevation acute coronary syndromes (NSTEACS).

Background Elderly patients have been scarcely represented in trials comparing treatment strategies in NSTEACS.

Methods A total of 313 patients ≥75 years of age (mean 82 years) with NSTEACS within 48 h from qualifying symptoms were randomly allocated to an EA strategy (coronary angiography and, when indicated, revascularization within 72 h) or an initially conservative (IC) strategy (angiography and revascularization only for recurrent ischemia). The primary endpoint was the composite of death, myocardial infarction, disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding within 1 year.

Results During admission, 88% of the patients in the EA group underwent angiography (55% revascularization), compared with 29% (23% revascularization) in the IC group. The primary outcome occurred in 43 patients (27.9%) in the EA group and 55 (34.6%) in the IC group (hazard ratio [HR]: 0.80; 95% confidence interval [CI]: 0.53 to 1.19; p = 0.26). The rates of mortality (HR: 0.87; 95% CI: 0.49 to 1.56), myocardial infarction (HR: 0.67; 95% CI: 0.33 to 1.36), and repeat hospital stay (HR: 0.81; 95% CI: 0.45 to 1.46) did not differ between groups. The primary endpoint was significantly reduced in patients with elevated troponin on admission (HR: 0.43; 95% CI: 0.23 to 0.80), but not in those with normal troponin (HR: 1.67; 95% CI: 0.75 to 3.70; p for interaction = 0.03).

Conclusions The present study does not allow a definite conclusion about the benefit of an EA approach when applied systematically among elderly patients with NSTEACS. The finding of a significant interaction for the treatment effect according to troponin status at baseline should be confirmed in a larger size trial. (Italian Elderly ACS Study; NCT00510185) (J Am Coll Cardiol Intv 2012;5: 906–16) © 2012 by the American College of Cardiology Foundation

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Non–ST-segment elevation acute coronary syndromes (NSTEACS) are the most common presentation of acute ischemic heart disease in elderly individuals (1–6). However, only a minority of the patients enrolled in clinical trials of treatment strategies in NSTEACS were ≥75 years old (7). Guidelines for ACS (8,9) and percutaneous coronary intervention (PCI) (10,11) do not discriminate elderly

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individuals as a separate category but suggest that, when early angiography would be clinically indicated, the possible benefit of early revascularization—suggested by subgroup analyses of existing trials (12,13)—should be balanced with the higher risk of procedural complications typical of elderly individuals. The Italian Elderly ACS study is the first randomized trial comparing an early aggressive (EA) approach with an initially conservative (IC) approach in elderly patients with NSTEACS.

Methods

The study design has been published previously (14). The study involved 21 centers with capability of PCI and coronary artery bypass grafting (CABG) and 2 centers without such capability. The study was approved by the ethics committees of the participating hospitals. Eligible were patients with NSTEACS and an age of ≥75 years, with cardiac ischemic symptoms at rest within 48 h before randomization, together with ischemic electrocardiographic (ECG) changes and/or elevated levels of either troponin or creatine kinase-myocardial band (CK-MB). Excluded were patients with secondary causes of myocardial ischemia, ongoing myocardial ischemia or heart failure despite optimized therapy, PCI or CABG within 30 days before randomization, serum creatinine >2.5 mg/dl, a cerebrovascular accident within the previous month, recent transfusions, gastrointestinal or genitourinary bleeding within 6 weeks before randomization, platelet count <90,000 cells/μl, ongoing oral anticoagulation, severe obstructive lung disease, malignancy, or neurological deficit limiting follow-up. All patients meeting the inclusion criteria but with ≥1 of the exclusion criteria were to be included in a dedicated registry. Signature of the informed consent form was a prerequisite for enrollment either in the trial or in the registry. All patients were registered in the study by accessing a dedicated website. For patients logged in the trial file, the treatment strategy was released immediately by a computer-generated list. Patients enrolled in the trial were randomly assigned to either: 1) an EA strategy of coronary angiography within 72 h and, when indicated, coronary revascularization by either PCI or CABG according to coronary anatomy, patient preference, and local skills; or 2) IC therapy, in which case patients had to be managed with medical therapy, and coronary angiography during index hospital stay was allowed in the case of refractory ischemia, myocardial (re)infarction, heart failure of ischemic origin, or malignant ventricular arrhythmias. After discharge, coronary angiography was to be considered in the case of further admission for an ACS or recurrent ischemic symptoms. The study protocol included detailed recommendations for antithrombotic therapy (14) following the guidelines for NSTEACS and PCI published at the time of study planning (8,9), adjusted for an elderly population (7). Use of any other treatment was left according to hospital routine. Follow-up visits were planned at 30 days, 6 months, and 12 months post-randomization.

Outcome measures. An independent event adjudication committee adjudicated all serious adverse events on the basis of the review of the original source documents. All surviving patients were followed up to 1 year, even if they had reached an endpoint. The primary endpoint was the composite of all-cause mortality, nonfatal myocardial infarction (MI), disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding within 12 months. Death was classified as cardiovascular or noncardiovascular. Cardiovascular death was defined as sudden death, death due to MI, stroke, pulmonary embolism, procedure-related death, as well as unwitnessed death. Noncardiovascular death includes all other causes. All definite MIs were counted as events, whether they represented the reason for any hospital stay occurring after the index event or occurred during hospital stay. To meet the criteria as an endpoint, an

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CABG = coronary artery bypass grafting
CI = confidence interval
EA = early aggressive
ECG = electrocardiogram/electrocardiographic
HR = hazard ratio
IC = initially conservative
IQR = interquartile range
MI = myocardial infarction
NSTEACS = non–ST-segment elevation acute coronary syndrome(s)
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction

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MI had to be distinct from the qualifying event. The ECG evidence of MI required new Q waves (>0.04 s) in 2 or more contiguous leads. Cardiac marker evidence of MI required troponin or CK-MB elevations >normal limit (15). In subjects with acute MI as the index event, within the first 72 h after the index MI, enzyme criteria for recurrent MI were re-elevation of CK-MB >normal limit and increased by at least 50% over the previous value. Criteria for post-procedural MI adjudication have been previously reported (14). Stroke was defined as any new neurological deficit lasting >24 h. Computerized tomography or magnetic resonance imaging was required to confirm the stroke and to distinguish between ischemic and hemorrhagic stroke. Nonfatal strokes were to be counted in the primary endpoint of the study and further classified as disabling and nondisabling (14). Hospital stay due to cardiovascular causes included severe recurrent ischemia, coronary revascularization due to severe recurrent ischemia, or an ACS resulting in the need for an unplanned PCI or CABG, noncerebral systemic embolism, heart failure, cardiac arrhythmia, and syncope. Only severe bleedings leading to repeat hospital stay after discharge from the index event were considered among the components of the primary endpoint. Because the commonly used definitions of bleeding endpoints in ACS patients are not suitable for events occurring during long-term treatment (16), the event adjudication committee adjudicated "severe bleeding" as the main cause for repeat hospital stay on the basis of the

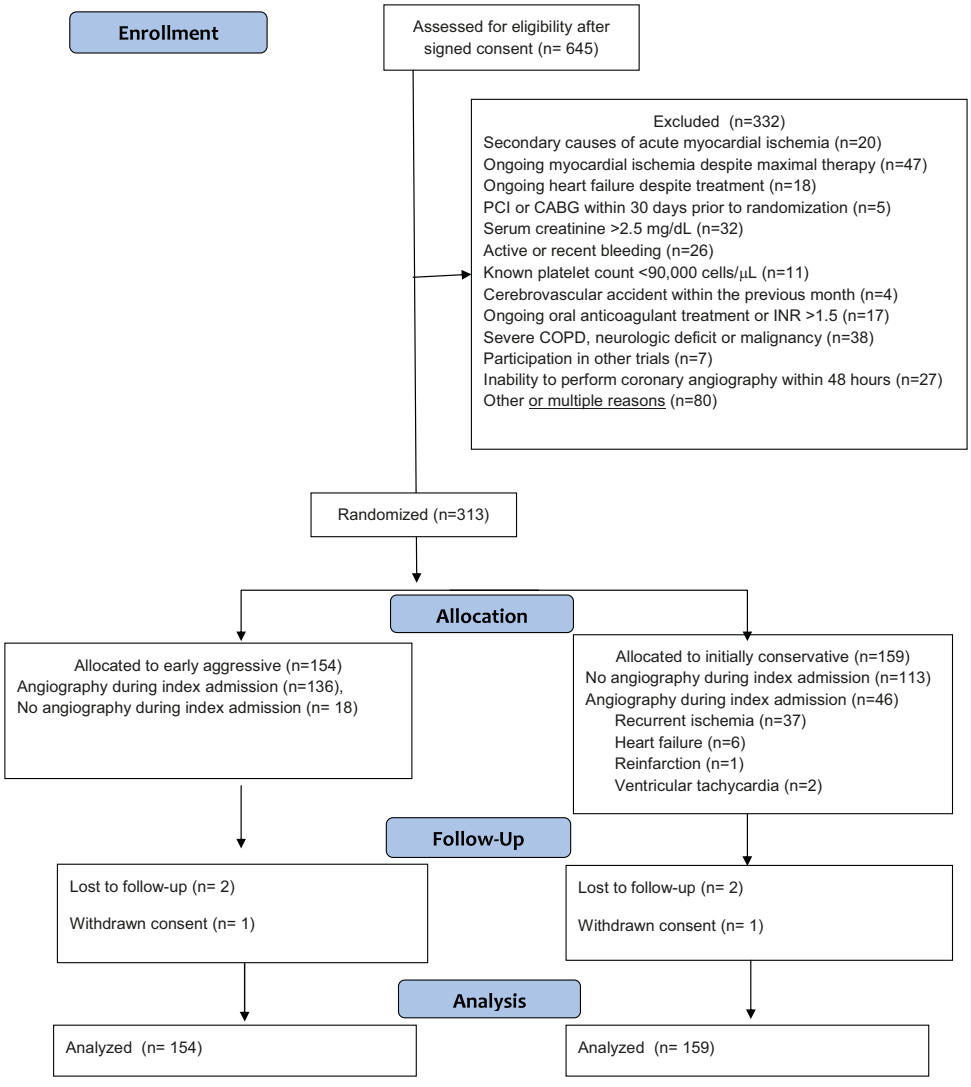

Figure 1. Study Flow Chart

Patients not enrolled in the trial for any reason were followed up for 1 year in a dedicated registry. Analysis was according to intention-to-treat. CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; INR = international normalized ratio; PCI = percutaneous coronary intervention.

hemoglobin/hematocrit levels at the time of repeat hospital stay as well as on hospital discharge summaries and narrative summaries of the investigator. After the publication of the Bleeding Academic Research Consortium definitions (17), we have included in the primary endpoint the type 2, 3a, and 3b events. Thrombolysis In Myocardial Infarction (TIMI) major bleeding occurring during the index hospital stay, and major bleedings after bypass surgery were counted but not included in the primary endpoint.

Statistical analysis. In the lack of observational data on the 1-year outcome of elderly patients with NSTEACS, we extrapolated our estimates from the subgroup analysis of the TACTICS (Treat Angina With Aggrastat and Determine the Cost of Therapy With Invasive or Conservative Strategy) trial (13), by adapting their 6-month event rates (death, MI, or repeat hospital stay for ACS) to our more comprehensive composite endpoint. The sample size of 313 patients was based on an anticipated reduction in event rate at 12 months from 40% in the IC arm to 25% in the EA arm of the study, with an estimated power of 80% and a 2-sided alpha level of 0.05. The initial sample size of 504 patients, with the primary endpoint set at 6 months and an anticipated reduction in event rate from 30% to 20% (14), was amended on October 20, 2008, because of slower-than-expected enrollment. No interim analyses were performed. Continuous variables were compared between randomized groups with the Wilcoxon rank sum test, whereas for binary variables the Fisher exact test was used. Estimation of the cumulative primary event rate was done with the Kaplan-Meier method on an intention-to-treat basis, and events over time were compared with the log-rank test. The Cox proportional hazards model was used to estimate the treatment effect as unadjusted hazard ratio with 95% confidence intervals. A 2-sided p value <0.05 was considered significant. Subgroup analyses were limited to 4 clinically meaningful pre-randomization variables. Statistical analyses have been carried out with SAS (version 9.2, SAS, Cary, North Carolina).

Results

Between January 2008 and May 2010, 645 patients signed the consent form. Of these, 313 were enrolled in the trial, and 332 were enrolled in the registry. Patients allocated to the registry had a mean age of 82.5 ± 5 years, and the reasons for exclusion are shown in Figure 1. The baseline characteristics of the patients enrolled in the trial are shown in Table 1 and are well balanced. The median time from the qualifying symptoms to randomization was 24 h (interquartile range [IQR]: 11 to 36 h) and was similar in the 2 arms. At randomization, 73% of the patients were receiving aspirin, 6% were receiving ticlopidine, 40% were receiving clopidogrel, 8% were receiving unfractionated heparin, 28% were receiving enoxaparin, and 4% were receiving oral anticoagulants, without differences between groups.

Table 1. Baseline Characteristics at Randomization

	EA (n = 154)	IC (n = 159)	p Value
Age (yrs)	81.8 ± 4.4	81.8 ± 4.7	0.92
Male	76 (49)	81 (51)	0.78
Weight (kg)	72 ± 12	72 ± 11	0.87
Hypertension	136 (92)	123 (85)	0.03
Hypercholesterolemia	65 (44)	72 (50)	0.21
Diabetes	55 (38)	59 (41)	0.54
Previous stroke	11 (7.5)	14 (9.7)	0.26
Mean eGFR (ml/min/1.73 m^2)	51 ± 18	57 ± 45	0.16
eGFR <50 (ml/min/1.73 m^2)	69 (46)	73 (47)	0.97
Moderate mitral valve insufficiency	31 (20)	39 (25)	0.67
Prior myocardial infarction	43 (28)	54 (34)	0.51
Prior heart failure	16 (10)	14 (8.9)	0.55
Prior CABG	17 (11)	12 (7.6)	0.22
Prior PCI	16 (11)	31 (20)	0.08
Chronic angina	38 (25)	28 (18)	0.2
Serum hemoglobin (g/dl)	13.21 ± 1.79	13.13 ± 1.67	0.66
Ejection fraction (%)	49 ± 9.7	48 ± 10.6	0.63
Mean TIMI risk score	4.3 ± 1.1	4.3 ± 1.2	0.61
<4	39 ± 25	40 ± 25	0.97
≥4	115 ± 75	119 ± 75	
Atrial fibrillation	23 (15)	19 (12)	0.37
Ischemic ECG changes	92 (61)	106 (67)	0.4
Elevated troponin levels	95 (64)	95 (61)	0.6
Both ischemic ECG and high markers	56 (37)	61 (39)	0.79

Values are mean ± SD or n (%). Categorical variables are expressed as frequencies (percentages) and differences tested with the Fisher exact test. Continuous variables are expressed as mean ± SD and differences tested with the *t* test.

CABG = coronary artery bypass grafting; EA = early aggressive; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; IC = initially conservative; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

During admission, 136 (88.3%) of the patients randomized to the EA strategy and 46 (28.9%) of those randomized to the IC strategy underwent cardiac catheterization, at a median of 24 h (IQR: 15 to 46 h) and 67 h (IQR: 24 to 113 h), respectively, from randomization. The reasons for not performing coronary angiography among the EA patients were heart failure in 6 cases, withdrawn consent in 5, bleeding in 2, sepsis in 2, and death, transient ischemic attack, and acute renal insufficiency in 1 case each. The indications for catheterization in the IC arm were recurrent ischemia in 36 cases, heart failure in 6, (re)infarction in 1, and sustained ventricular tachycardia in 2. The cardiac revascularization procedures during admission are shown in Table 2, and the technical details are shown in Table 3. In the EA group, 85 patients underwent revascularization (55% of those randomized, 62% of those who underwent angiography), including 76 PCIs and 9 CABG. In the IC group, 36 patients (23% of those randomized, 78% of those undergoing angiography) underwent PCI, and 1 underwent

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Table 2. Cardiac Procedures During Initial Hospital Stay and Within 1 Year, According to Study Group

Procedure	Initial Hospital Stay		Within 1 Year	
	EA (n = 154)	IC (n = 159)	EA (n = 154)	IC (n = 159)
Catheterization	136 (88)	46 (29)		
PCI	76 (50)	35 (23)	79 (51)	46 (29)
CABG	9 (5.8)	1 (0.6)	11 (7)	4 (2.5)
Any revascularization	85 (56)	36 (23)	90 (58)	50 (31)

Values are n (%).
Abbreviations as in Table 1.

CABG. None of the patients undergoing CABG died during index hospital stay. The antithrombotic medications during index hospital stay and at discharge are shown in Table 4. Other medications at discharge were similar in the 2 groups, with 92% of the patients taking aspirin, 60% taking beta-blockers, 80% taking angiotensin-converting enzyme inhibitors, and 80% taking statins.

Table 3. Details of Angiography and Revascularization Procedures During Index Admission

	EA (n = 154)	IC (n = 159)
Coronary angiography		
Performed	136 (88)	46 (29)
Time from randomization (h)	24 (15–46)	67 (24–113)
Treatment		
PCI immediate	65 (48)	32 (71)
PCI delayed *	13 (9.6)	4 (8.9)
Vascular access		
Radial	55 (71†)	28 (78†)
Treated vessel		
Left main coronary artery	5 (6.6)	3 (8.6)
Left anterior descending artery	43 (56)	22 (63)
Circumflex artery	27 (36)	9 (26)
Right coronary artery	29 (38)	12 (34)
Graft	5 (6.6)	1 (2.9)
Stent type	73 (96)	34 (97)
Only BMS	35 (46)	15 (43)
Only DES	35 (46)	18 (51)
BMS + DES	3 (3.9)	1 (2.9)
Procedural success‡	74 (97)	35 (100)
Angiographic indication to CABG	19 (14)	3 (6.7)
CABG performed	9 (5.8)	1 (0.6)
≥1 arterial graft	9 (100)	1 (100)
Aortic valve replacement	1	0
Surgical success§	9 (100)	1 (100)

Values are n (%) or median (interquartile range). *2 patients in the EA group and 1 in the IC group underwent 2 PCI procedures during index admission. †Percentage of PCI procedures. ‡Success after PCI as seen on angiography was defined as technical success (normal coronary artery flow and <50% stenosis in the luminal diameter after balloon angioplasty and <20% after stent implantation, as assessed by visual estimation of the angiograms before and after the procedure) without the occurrence of in-hospital myocardial infarction, emergency CABG, or death. §Surgical success was defined by the surgeon as technical success without post-procedural myocardial infarction or in-hospital death.
BMS = bare-metal stent(s); DES = drug-eluting stent(s); other abbreviations as in Table 1.

Table 4. Antithrombotic Treatments During Index Hospital Stay and at Discharge

	EA (n = 154)	IC (n = 159)	p Value
During hospital stay			
Aspirin	146 (95)	154 (99)	0.14
Ticlopidine	7 (4.6)	3 (1.9)	0.34
Clopidogrel	138 (90)	145 (92)	0.68
GP IIb/IIIa inhibitors	26 (17)	9 (6)	0.005
GP IIb/IIIa inhibitors in PCI patients	18 (24*)	6 (17*)	0.44
Unfractionated heparin	39 (25)	37 (24)	0.13
Enoxaparin	96 (64)	91 (59)	0.64
Bivalirudin	6 (3.8)	2 (1.3)	0.57
Fondaparinux	11 (8.5)	11 (8.5)	0.82
At discharge	(n = 146)	(n = 154)	
Aspirin	135 (92)	149 (97)	0.17
Ticlopidine	4 (2.7)	3 (1.9)	0.37
Clopidogrel	106 (73)	132 (86)	0.01

Values are n (%). Binary variables were compared with Fisher exact test. *Percentage value referred to number of patients undergoing PCI.
GP = glycoprotein; other abbreviations as in Table 1.

The adverse clinical events during index admission are shown in Table 5. Patients in the EA arm had slightly more cases of death and heart failure, whereas those in the IC arm had significantly more cases of severe recurrent ischemia. There was only 1 case of TIMI major bleeding during admission in the IC arm. The median length of hospital stay was 7 days (IQR: 4 to 10 days) in the EA arm and 7 days (IQR: 5 to 9 days) in the IC arm. Of the patients surviving to hospital discharge, 95% were sent home, 3.3% were sent to cardiac rehabilitation, and 1.5% were sent to a hospice, equally distributed between groups.

Table 5. Adverse Clinical Events During Index Hospital Stay

Adverse Clinical Event	EA (n = 154)	IC (n = 159)	p Value
Death	8 (5.2)	5 (3.1)	0.36
Myocardial infarction	3 (1.9)	5 (3.1)	0.50
Post-procedural	3 (1.9)	4 (2.5)	
Severe recurrent ischemia	1 (0.6)	15 (9.4)	0.0004
Heart failure	11 (7.1)	4 (2.5)	0.06
Cardiac arrhythmia	3 (1.9)	3 (1.9)	0.97
TIMI major bleeding	0	1 (0.6)	0.27
CABG-related bleeding/transfusion	4 (2.6)	0	0.11
Non-CNS systemic embolism	1 (0.6)	0	0.30
Infection/sepsis*	2 (1.3)	1 (0.6)	0.51

Values are n (%). Adjudicated events: these do not necessarily coincide with the events leading to urgent angiography in the IC arm (Fig. 1), which was left to the discretion of the treating physician. Binary variables were compared with Fisher exact test. *Nonadjudicated.
CNS = central nervous system; other abbreviations as in Table 1.

Follow-up. The primary endpoint occurred in 43 (27.9%) patients in the EA group and 55 (34.6%) patients in the IC group (hazard ratio: 0.80; 95% confidence interval: 0.53 to 1.19; log rank p = 0.26) (Table 6). No significant differences between groups were observed for each of the primary endpoint components. The Kaplan-Meier curves for the primary endpoint and its components are shown in Figure 2. There was no significant heterogeneity of treatment effect with regard to the primary outcome in subgroups stratified according to age, sex, and baseline ischemic ECG changes (Fig. 3). However, statistically significant heterogeneity in treatment effect was observed with regard to troponin levels at trial entry: although patients with normal troponin levels on admission had no benefit from an EA approach, those with elevated troponin had a significant 57% reduction in the primary endpoint rate (p for interaction = 0.0375). As shown in Figure 4, patients with elevated troponin level on admission had higher rates of death and MI at 1 year compared with those with normal troponin level but similar rates of repeat hospital stay.

Discussion

In the first randomized trial comparing treatment strategies in elderly patients with NSTEACS, we enrolled patients for whom there was no indication for emergency angiography (8,9) or the need for medical stabilization and re-evaluation (such as those with secondary causes of acute ischemia or severe renal failure). In this scenario, patients with IC treatment experienced significantly more ischemic events during index admission, although these were mostly episodes of recurrent ischemia prompting urgent angiography. Within 1 year, we observed a 20% difference in the rates of our primary endpoint between the EA and the IC cohorts. This difference was not statistically significant in the present trial, which was powered for a 40% difference in the primary endpoint rate. However, patients with elevated troponin levels on admission randomized to an EA approach had a significant 57% reduction of the primary endpoint rate: albeit with the methodological limitation of a subgroup finding in a negative trial, this observation is clinically sound and in line with prior studies in the general population of NSTEACS patients. Just recently, Damman et al. (18) have published the long-term follow-up of the FIR (FRISC II–ICTUS–RITA 3) trials comparing routine invasive or selective invasive strategy in NSTEACS, also showing the results in patients of ≥75 years of age. Although the cohort ≥75 years had a mean age of just 76 years (compared with 82 years in our study), a 29% reduction in cardiovascular death or MI at 5 years was achieved by a routine invasive approach in elderly patients.

Almost as predicted by our working hypothesis, 35% of the patients in the IC arm reached the primary endpoint within 1 year, although in this patient population, we had hypothesized higher rates of urgent repeat hospital stays. The low rate of recurrent admissions in the present study is remarkable, especially when compared with the TIME

Table 6. Cumulative Rates of Composite Primary Endpoint and Its Components Within 1 Year After Randomization

Outcome	EA (n = 154)	IC (n = 159)	HR (95% CI)	Log-Rank p Value
Primary composite endpoint	43 (27.9%)	55 (34.6%)	0.80 (0.53–1.19)	0.26
Death	19 (12.3)	22 (13.8)	0.87 (0.49–1.56)	0.65
Cardiovascular	16 (10.4)	17 (10.7)		
Noncardiovascular	3 (2.0)	4 (2.5)		
Unknown	—	1 (0.6)		
Myocardial infarction	11 (7.1)	17 (10.7)	0.67 (0.33–1.36)	0.27
Death + myocardial infarction	28 (18.2)	34 (21.4)	0.85 (0.52–1.41)	0.53
Disabling stroke	0	0		
Repeat hospital stays for				
CV causes or severe bleeding	18 (11.7)	22 (13.8)	0.81 (0.45–1.46)	0.49
Cardiovascular causes	16 (10.4)	21 (13.2)		
Severe recurrent ischemia	0	4 (2.5)		
Revascularization	5 (3.3)	9 (5.7)		
Heart failure	7 (4.6)	4 (2.5)		
Non-CNS embolism	0	1 (0.6)		
Cardiac arrhythmia	4 (2.6)	3 (1.9)		
Severe bleeding*	2 (1.3)	1 (0.6)		
Noncardiovascular causes	8 (5.2)	5 (3.3)		

Values are n (%). *Bleeding Academic Research Consortium grades 2, 3a, and 3b.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; other abbreviations as in Tables 1 and 5.

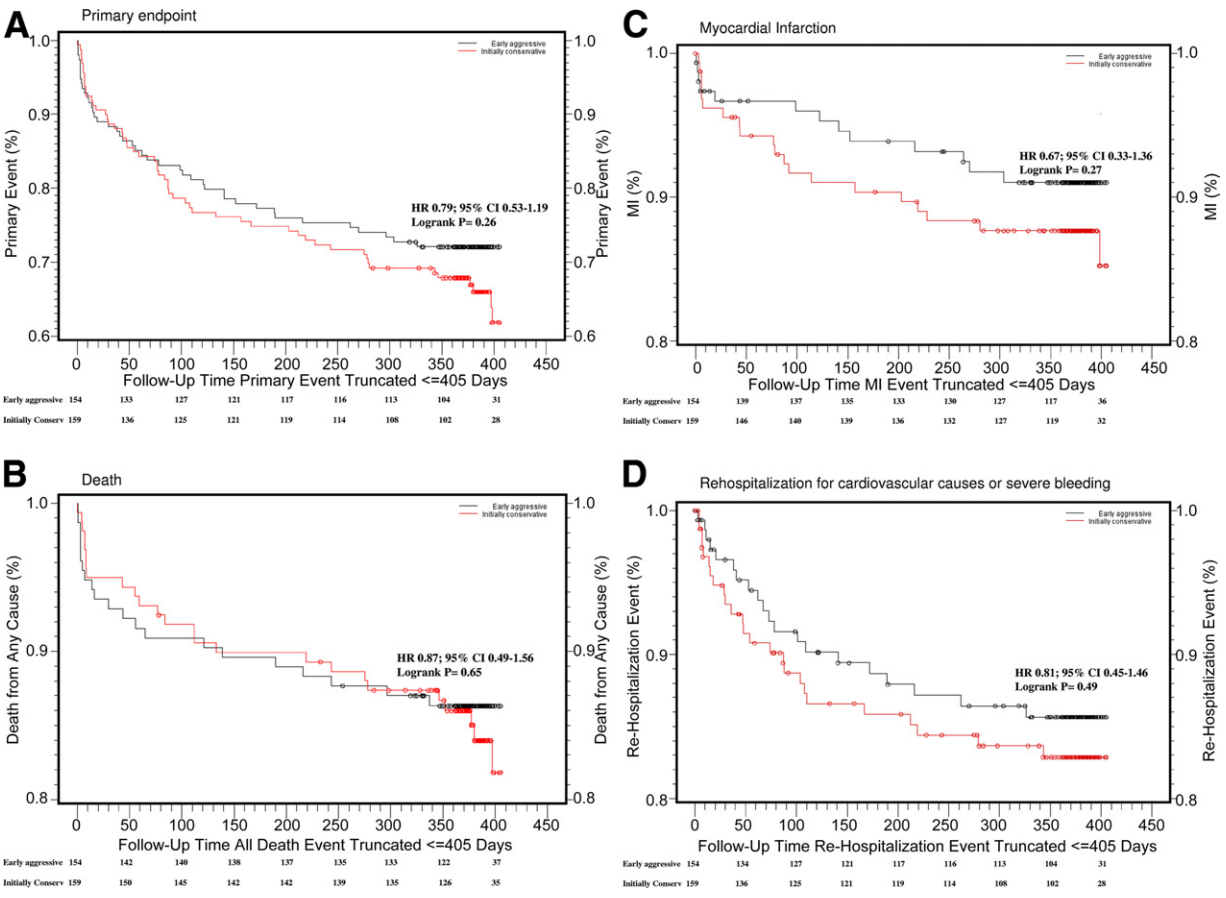

Figure 2. Kaplan-Meier Survival Curves

Kaplan-Meier survival curves **(A)** for the primary outcome (death, myocardial infarction [MI], disabling stroke, and repeat hospital stay for cardiovascular causes or bleeding), **(B)** for all-cause mortality, **(C)** for MI, and **(D)** for repeat hospital stay. CI = confidence interval; HR = hazard ratio.

(Trial of Invasive Versus Medical Therapy in Elderly Patients) trial of elderly patients with stable angina, which reported a 72% rate of hospital readmission for ACS at 12 months in the conservative group (19). Our repeat hospital stay rates were even lower than those reported in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial, which had an average age of 62 years (20). These differences are likely attributable to the strict adjudication criteria used in our study to define hospital stays due to severe recurrent ischemia or a new ACS episode (14).

By contrast, the observed mortality rate of 14% in our conservative arm was almost twice as high as that reported at 6 months in patients >75 years in the TACTICS trial (13), but the difference in favor of the EA arm was marginal. Meta-analyses of earlier trials comparing treatment strategies in the general population of NSTEACS (21,22) show an excess in mortality in the invasive arm during index admission followed by a higher mortality in the conservative arm at follow-up. However, none of the 3 larger trials showed any difference in mortality within 1 year (23–25), and in the TIME trial, mortality at 12 months was numerically higher in the revascularization arm (19).

The rates of recurrent MI observed in our study are similar to those observed in the ICTUS trial (20) at 1 year and in TACTICS at 6 months (13). There were numerically more MIs during the index hospital stay in the IC arm, and this difference was maintained at 1 year without any significant additional risk compared with the EA arm.

Both during the initial hospital course and during follow-up, the rates of major bleeding were surprisingly low, with only 2 cases occurring in the EA arm, and 2 occurring in the IC arm. The in-hospital TIMI major bleeding rate was dramatically lower, compared with that observed in patients >75 years in the TACTICS study, which reported 16.5% in the EA arm versus 6.5% in the IC arm (13). This might be explained by the much lower use of glycoprotein IIb/IIIa antagonists in our study and because >70% of the PCI procedures were by the radial approach. At follow-up,

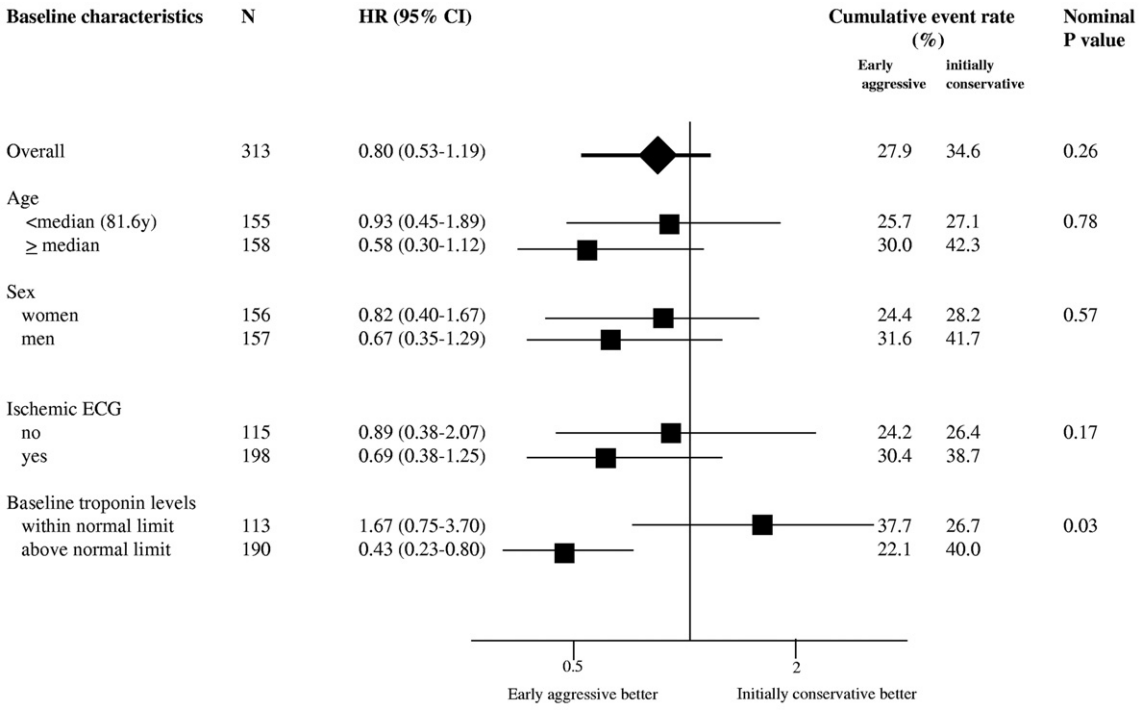

Figure 3. Cumulative Primary Event Rate in Subgroups

Chart shows the hazard ratios (HRs) and 95% confidence intervals (CIs). Nominal p values for interaction are given. The relative benefit of an early aggressive (EA) approach was higher in the higher-risk groups, and a statistically significant interaction for treatment effect was observed according to troponin status at trial entry. ECG = electrocardiogram.

hospital admissions due to severe bleeding were also extremely rare compared with published trials and registries (26,27).

Compared with other contemporary trials (13,20), the present study had a lower "crossover" rate from conservative treatment to revascularization. The moderate difference in revascularization rates between groups might be considered among the reasons for the nonsignificant difference in outcome between the EA and the IC strategy in the present study. However, although in other trials this finding was due to the high rate of revascularization in the conservative arm (20), in our study, only 30% of the patients underwent revascularization in the conservative arm, as compared with 60% in the aggressive arm, possibly because of the extensive coronary disease of the elderly population and the reluctance to perform CABG in the cases nonsuitable for PCI.

As in previous trials (22), the effect of an EA approach was larger in patients at higher risk, such as men, those with age above median, those with ischemic ECG changes, and especially in those with elevated troponin levels on admission. We observed a trend toward harm only in patients with normal troponin levels on admission. Most likely, after exclusion of patients with severe renal dysfunction, the elevation in cardiac troponin levels is highly specific for the diagnosis of an ACS and thus indicates which patients might derive benefit from an approach specifically directed toward improving coronary circulation or acute thrombosis. Similar to our results, in the ISAR–REACT (Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment) 2 trial, elevated troponin levels at admission were the discriminator factor between benefit and no effect of abciximab among NSTEACS patients undergoing PCI (28). However, the results of the ICTUS trial—showing no benefit from an intended early invasive strategy but only from actual revascularization, among NSTEACS troponin-positive patients (29)—leave some uncertainty about the value of elevated troponin as the single determinant of treatment strategy.

The main limitation of our study is its relative lack of power, because our original sample size was amended due to slow enrollment, and we might have been too optimistic in anticipating a possible 37.5% reduction in our primary endpoint in the EA arm of the study. As a matter of fact, such a large benefit was observed only in the higher-risk patients (such as the oldest male patients and those with clearly ischemic ECG changes) and achieved statistical significance in patients with elevated troponin levels at study

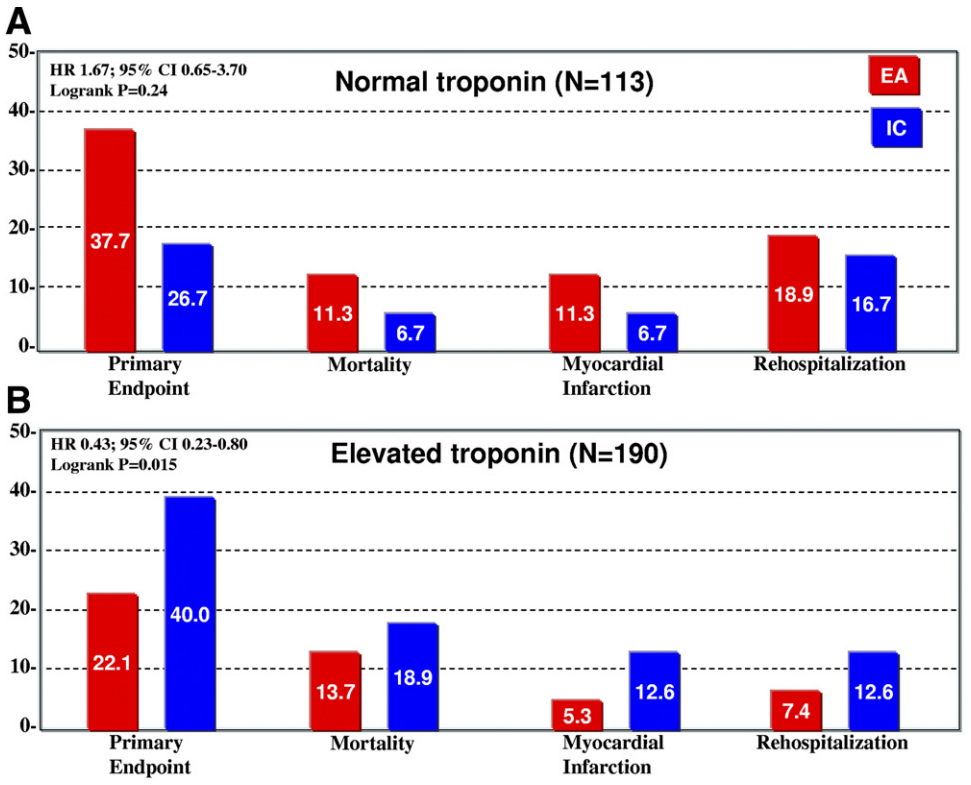

Figure 4. 1-Year Rates of Primary Endpoint and Its Components According to Treatment Strategy

1-year rates of the primary endpoint and its components according to treatment strategy, in patients with normal **(A)** or elevated troponin levels **(B)** at trial entry. In patients with elevated troponin levels, all the components of the primary endpoint were lower in the EA group, whereas the opposite was observed in troponin-negative patients. IC = initially conservative; other abbreviations as in Figure 3.

entry. A larger study would be needed to prospectively confirm these data. However, consistent trends toward the reduction in all the components of our primary endpoints were observed, and the overall relative reduction in the primary endpoint rate is consistent with those of earlier meta-analyses comparing treatment strategies in NSTEACS (21,22).

Slow enrollment and lower-than-projected sample size is a common feature of a number of trials comparing treatment strategies in high-risk patients (30–33), particularly in the elderly population (34). This problem derives from multiple causes, including the difficulty of obtaining informed consent in elderly patients, the presence of numerous comorbidities, and in the specific case, that most cardiologists prefer an EA approach irrespective of patient age. Finally, not all the patients randomized to the EA approach actually underwent angiography, and only 56% underwent revascularization, during index admission. However, these figures are not far from those of the FIR collaboration (18), which reported a 65% revascularization rate during index admission in their elderly cohort—which, however, was 6 years younger than ours.

Conclusions

Due to its limited power, the present study does not allow a definite conclusion about the benefit of an EA approach when applied systematically among elderly patients with NSTEACS. The finding of a significant interaction for the treatment effect according to troponin status at baseline, with benefit confined in troponin-positive patients, should be confirmed in a larger size trial.

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Key Words: acute coronary syndrome ■ angioplasty ■ elderly ■ revascularization ■ treatment.

APPENDIX

For a list of the contributors and investigators, please see the online version of this paper.