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Causes of ineligibility in randomized controlled trials and long-term mortality in patients with non-ST-segment elevation acute coronary syndromes ☆

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Abstract

Purpose: To determine the long-term mortality of patients with non-ST-segment elevation acute coronary syndromes (NSTEACS) that are eligible versus those not eligible in randomized controlled trials (RCT), and how each exclusion criteria is associated with outcome.
Methods: Common causes of exclusion in six published RCT on intravenous antithrombotic therapy were prospectively assessed in a cohort of 452 consecutive patients with NSTEACS that were followed for up to 3 years.
Results: Forty-one percent of patients had one or more exclusion criteria establishing the ineligible group. These patients were older, more likely to have coronary risk factors, ischemic ECG changes, heart failure at admission, higher creatinine levels and a lower ejection fraction than eligible patients. There were no differences between both groups in the antithrombotic treatment received or in the performance of revascularization procedures during hospitalization or in the prescription of antiplatelet treatment and beta-blockers at discharge. Cumulative 3-year mortality rate was 25% in ineligible patients compared to 9% in eligible patients ($p<0.001$). The hazard ratio (HR) of mortality was of 9.1 (95% CI: 4.5–18.7) for severe renal dysfunction; 6.0 (3.3–11.4) for concomitant non-vascular diseases; 3.0 (1.6–5.5) for contraindications to anticoagulation; 2.5 (1.1–5.7) for heart failure; and 2.3 (1.1–4.6) for prior cerebrovascular disease. After adjusting for baseline differences, ineligible patients had a HR of total mortality of 1.88 (1.04–3.38), and of cardiac mortality of 2 (1.01–3.98).
Conclusion: Patients with NSTEACS who are ineligible in RCT have a higher risk profile and a two-fold adjusted long-term mortality than eligible patients, especially those with comorbid conditions and those with contraindications to anticoagulation.
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Keywords: Acute coronary syndromes; Mortality; Prognosis; Clinical trials

1. Introduction

Patients enrolled in clinical trials usually have a better outcome than patients included in registries of clinical practice [1–8]. Previous studies have compared patient characteristics, medication use and procedures between patients with a ST-segment elevation acute myocardial infarction enrolled in randomized clinical trials (RCT) versus those who were not enrolled, and it has been suggested that patients included in RCT are a selected, low-risk subgroup [9–13]. However, data comparing the outcome of patients with non-ST-segment elevation acute coronary syndromes (NSTEACS) according to their eligibility in current clinical trials are scarce, retrospective, and focus on the short-term incidence of combined endpoints [14,15]. Besides, no study has prospectively analyzed the long-term mortality differences of these patients.

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The present study prospectively analyzed the outcome of an unselected cohort of patients hospitalized for NSTEACS who fulfilled the inclusion criteria of recent RCT, and compared the long-term mortality of patients found to be ineligible versus those eligible in these trials according to the presence or absence of the specified exclusion criteria. We also investigated differences in baseline characteristics and management, and how each exclusion criteria influenced long-term mortality.

2. Methods

2.1. Patients

Patients 18 years and older who presented to the emergency department with a diagnosis of a NSTEACS were included in this prospective observational study. Common criteria used in recent RCT on antithrombotic treatment in patients with NSTEACS were applied [1–6]. They included the presence of prolonged ischemic chest pain or repetitive episodes of angina at rest or during minimal exercise within 24 h prior to admission, with associated ST or T-wave changes on a 12-lead electrocardiogram ($\geq$1 mm ST segment depression or >2 mm negative T-waves in at least two contiguous leads), prior documented coronary artery disease or elevation in plasma levels of troponin I or creatine kinase myocardial band (CK-MB). Patients with suspected non ischemic chest pain, patients with chest pain with persistent ST-segment elevation and patients transferred from other hospitals were not included.

A total of 452 consecutive patients met the above mentioned inclusion criteria and were included in the study during a two-year period. The study was approved by the local ethic's committee on human research. All demographic, clinical, and laboratory data were prospectively collected on standard forms. Troponin levels and creatine kinase myocardial bands greater than the upper limit of normal were used as a cardiac marker of necrosis. They were determined at baseline and after 6, 12, 24, and 48 h.

The common exclusion criteria used in 6 RCT performed on the efficacy of intravenous antithrombotic therapy in patients with NSTEACS [1–6] were prospectively recorded as follows: 1) pregnant or nursing woman and woman of childbearing potential; 2) angina precipitated by provoking factors (e.g., arrhythmia, severe anemia, hyperthyroidism; 3) coronary angioplasty within 6 months or coronary artery bypass surgery within 1 month; 4) inability to interpret ST-T segment changes on ECG (left bundle branch block, atrial fibrillation or pacemaker); 5) severe hypertension at admission (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110 mm Hg); 6) history of cerebrovascular disease or active intracranial pathologic process; 7) severe congestive heart failure (acute pulmonary edema or cardiogenic shock); 8) contraindications to anticoagulation: thrombolytic therapy within 48 h prior to enrolment, recent (<1 month) bleeding disorder, known coagulopathy, platelet disorder or history of thrombocytopenia, severe trauma within 3 months prior to admission, major surgical procedure within 1 month prior to admission or any invasive procedure within 14 days of enrollment that would significantly increase the risk of bleeding; 9) severe non-cardiac disease: pulmonary, hepatic, endocrine, neurological or hematological disorders; and 10) severe renal failure (serum creatinine >2.5 mg/dL). Patients with any of these exclusion criteria defined the group of ineligible patients.

3. Diagnostic and revascularization procedures

An echocardiogram was performed within the first 72 h after admission in order to measure left ventricular ejection fraction (EF) and to rule out the presence of valvular disease or cardiomyopathies. Eighty-five percent of patients had a measured EF. Patients were managed following a selectively invasive strategy. Indications for early coronary angiography were the presence of severe or recurrent ischemia at presentation or hemodynamic instability. A positive stress test, the presence of significant ventricular dysfunction (EF<40%) and the inability to perform a stress test due to cardiac causes (recurrent angina or heart failure) were indication for elective coronary angiography. Patients with a coronary angiography who presented appropriate coronary features for revascularization underwent percutanous coronary intervention or coronary aortic bypass grafting as appropriate.

3.1. Follow-up

After discharge, all patients were followed clinically for up to 3 years by personal interview at an outpatient clinic or by telephone contact when the former was not possible. All deaths were confirmed by hospital or death records. Cardiac death was defined as any death with a clear cardiac or vascular cause, sudden death, unobserved and unexpected death. All-cause mortality was considered as the primary end-point of the study and cardiac mortality as the secondary end-point.

4. Statistical analysis

Categorical variables are expressed as numbers and percent of patients, continuous variables as means±SD; they were compared using chi-square and unpaired *t*-tests as appropriate. All tests of significance were two-tailed. Difference in time to event distributions was examined using Kaplan–Meier curves and compared using the long-rank test. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) of total and of cardiac mortality were estimated using Cox regression analysis. The initial adjustment included all baseline and clinical variables from history listed in Tables 1 and 2 that were

Table 1
Clinical characteristics of eligible and ineligible patients

	All patients $n=452$	Eligible patients $n=266$	Ineligible patients $n=186$	p-value*
Coronary risk factors				
Age (years)	66±11	65±11	68±10	0.001
Female	131 (29%)	71 (27%)	60 (32%)	0.20
Hypertension	252 (56%)	137 (52%)	115 (62%)	0.03
Hypercholesterolemia	224 (49%)	145 (55%)	79 (43%)	0.01
Diabetes	133 (29%)	69 (26%)	64 (34%)	0.05
Smoking, actual	102 (23%)	63 (24%)	39 (21%)	0.50
Prior history				
Myocardial infarction	192 (42%)	111 (42%)	81 (44%)	0.70
Angina	241 (53%)	139 (52%)	102 (55%)	0.58
PCI	55 (12%)	24 (9%)	29 (16%)	0.03
CABG	74 (16%)	46 (17%)	28 (15%)	0.53
Physical examination				
Heart rate (beats/min)	77±17	76±15	80±20	0.01
SBP (mm Hg)	147±28	141±21	155±35	<0.001
DBP (mm Hg)	85±17	82±14	89±20	<0.001
Killip class >1	37 (8.1%)	9 (3.4%)	28 (15.1%)	<0.001
Initial ECG pattern				
ST depression ≥1 mm	225 (50%)	113 (43%)	112 (60%)	<0.001
Negative T-waves	198 (45%)	124 (47%)	74 (42%)	0.34
Positive cardiac markers	209 (46%)	120 (45%)	89 (48%)	0.58
Serum creatinine (mg/dL)	1.17±0.30	1.15±0.28	1.21±0.35	0.04
EF (%) ($n=382$)	51±13	53±13	49±14	0.007

Continuous variables are presented as mean±SD. CABG=coronary artery bypass graft surgery; EF: left ventricular ejection fraction; DBP=diastolic blood pressure; PCI=percutanous coronary intervention; SBP=systolic blood pressure. *p-values for the comparisons between eligible and ineligible patients.

statistically different between eligible and ineligible patients at a p-value of <0.10, including coronary risk factors, prior cardiac events, presentation physical examination, ECG changes, and treatment applied. The second adjustment included the same variables and EF that were measured in 85% of patients. Continuous variables were entered without categorization. The model entry criteria were $p<0.05$ (Likelihood Ratio Test) and the stay-in criteria were $p<0.10$. Data analysis was performed with the SPSS statistical package version 11.5. A p-value less than 0.05 was considered statistically significant.

5. Results

Of the 452 consecutive patients with a NSTEACS that were included, 186 patients (41%) had one or more of the ten pre-specified exclusion criteria, establishing the ineligible group. These patients had a mean of 1.44±0.7 exclusion criteria per patient, with 175 patients with one, 45 with two and 17 with three or more exclusion criteria. The main reasons for ineligibility were the presence of severe hypertension at admission, contraindications to anticoagulation, a prior cerebrovascular accident and the inability to interpret ST-T segment changes on ECG (Fig. 1).

5.1. Baseline characteristics

The patients' baseline characteristics and coronary risk factors are listed in Table 1. The mean age was 66±11 years and 29% of patients were female. Compared to eligible patients, the ineligible group were significantly older and were more likely to have a history of arterial hypertension, diabetes mellitus and of percutanous coronary revascularization. At presentation, they also were more likely to have higher heart rate, blood pressure, and creatinine serum levels, to be in heart failure and to show ST-segment depression on the admission ECG. Mean ejection fraction was also lower in non-eligible patients.

5.2. Management

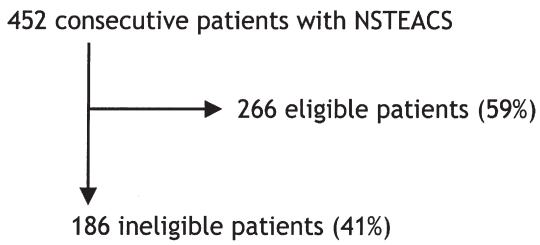
At admission, ineligible patients received less often oral beta-blockers and more often intravenous nitroglycerin and calcium channel blockers. However, there were no differences in the antiplatelet and anticoagulant treatment received or in the performance of coronary angiography or revascularization procedures between both groups (Table 2). At the time of hospital discharge, no differences were observed in the prescription of antiplatelet treatment (92% versus 94%, $p=0.87$), oral anticoagulant treatment (11.7% versus 11.3%, $p=0.91$) and beta-blockers (62% versus 70%, $p=0.07$) in ineligible versus eligible patients. However, ineligible patients were prescribed more often angiotensin-converting-enzyme inhibitors (52% versus 43%, $p=0.05$).

5.3. Long-term mortality

During a 3-year follow-up 58 patients died, 41 of them because of cardiac reasons. Cumulative all-cause mortality was of 25% in the ineligible group compared with 9% in the eligible group ($p=0.0004$, Fig. 2), with an unadjusted hazard ratio (HR) of mortality of 2.5 (95% CI, 1.5–4.4).

Table 2
In-hospital medical therapy and use of invasive and non-invasive diagnostic and therapeutic techniques

	Eligible patients	Ineligible patients	p-value
Pharmacological treatment			
Antiplatelet treatment	260 (99%)	186 (100%)	0.78
Heparin	246 (94%)	167 (91%)	0.21
Beta-blockers	203 (76%)	121 (65%)	0.01
Calcium channel blockers	136 (52%)	112 (61%)	0.06
Intravenous nitroglycerin	125 (48%)	115 (63%)	0.002
Nitrates p.o./topical	216 (83%)	155 (84%)	0.65
Coronary angiography ($n=257$)	146 (56%)	112 (62%)	0.23
No. of diseased vessels			0.40
0	22 (15%)	12 (11%)	
1	32 (22%)	33 (30%)	
2	39 (27%)	31 (28%)	
3	53 (36%)	35 (32%)	
Coronary revascularization	87 (33%)	56 (30%)	0.62



Exclusion criteria	n (%)
Childbearing potential	4 (0.9)
Secondary angina	31 (6.9)
Recent PCI/CABG	19 (4.2)
LBBB/Pacemaker/AF	34 (7.5)
Severe hipertension	47 (10.4)
Prior cerebrovascular accident	35 (7.7)
Severe heart failure	22 (4.8)
Contraindications to anticoagulation	41 (9.0)
Non-Cardiovascular disease	24 (5.3)
Severe renal failure	13 (2.9)

Fig. 1. Flow-chart of the studied patients, including broad definitions of each major exclusion criteria and the number of patients in each category. AF = atrial fibrillation; CABG = coronary artery bypass grafting; CV = cardiovascular; LBBB = left bundle branch block; PCI = percutanous coronary intervention.

Corresponding figures for cardiac mortality were 19% versus 6% ($p = 0.003$; HR: 2.5 (1.3–4.7)).

Hazard ratios differed according to each exclusion criteria (Fig. 3). No significant differences in mortality were observed in women of childbearing potential, patients with secondary angina, those with a recent revascularization procedure, severe arterial hypertension or in those with inability to interpret ST-T segment changes on the ECG. On the other hand, significant differences were observed among patients with other common exclusion criteria in RCT. Thus, the unadjusted HR (95% CI) for 3-year mortality was of 9.1 (4.5–18.7) in patients with severe renal failure, 6.0 (3.3–11.4) in those with concomitant non-vascular diseases, 3 (1.6–5.5) in patients with contraindications to anticoagulant treatment, 2.5 (1.2–5.7) in those with severe heart failure, and 2.3 (1.1–4.6) in patients with prior cerebrovascular disease.

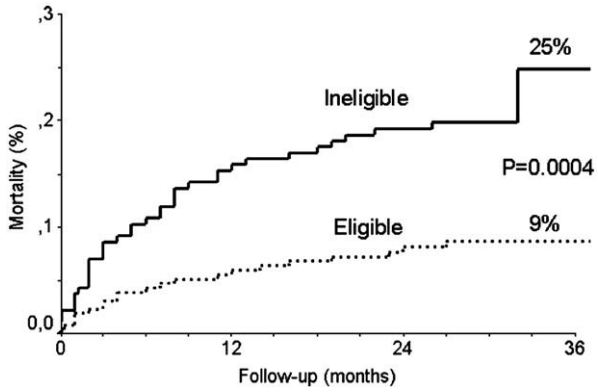


Fig. 2. Kaplan–Meier survival curves for eligible and ineligible patients.

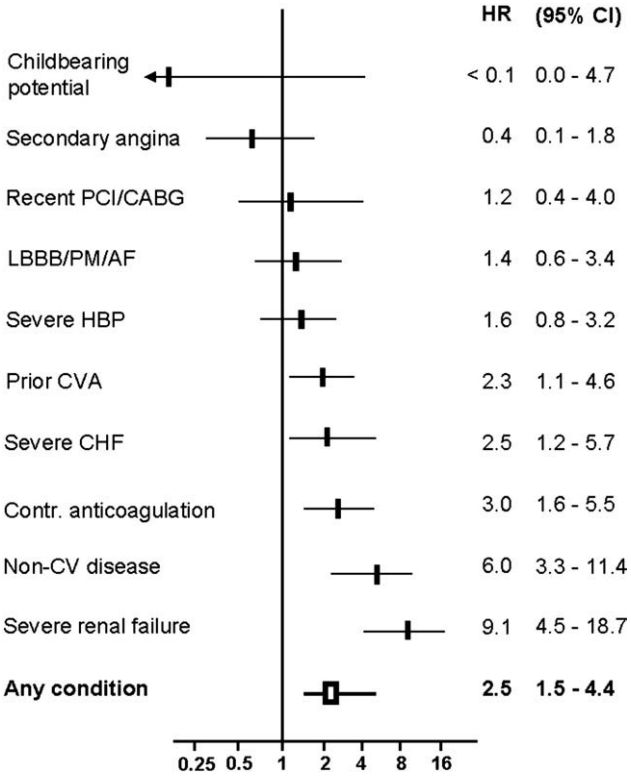


Fig. 3. Unadjusted hazard ratios and 95% confidence intervals for 3-year mortality for each major exclusion criteria versus their absence in the total population. AF = atrial fibrillation; CABG = coronary artery bypass grafting; CV = cardiovascular; LBBB = left bundle branch block; PCI = percutanous coronary intervention.

After adjusting for age, coronary risk factors, blood pressure and heart rate at admission, presence of heart failure, ECG changes, creatinine levels and treatment with i.v. nitroglycerin and oral beta-blockers, the ineligible group had a HR (95% CI) of total mortality of 2.23 (1.16–4.26), and of cardiac mortality of 2.59 (1.17–5.74). When the results were further adjusted for left ventricular ejection fraction, the HR were of 1.88 (1.04–3.38) and 2.00 (1.01–3.98) respectively. Further adjustment for admission anemia, a low platelet count, and also for discharge treatment did not change the results.

6. Discussion

Our study shows that patients with NSTEACS who are currently not eligible in randomized clinical trials have a worse risk profile and a two-fold higher mortality than potentially eligible patients. This excess of mortality depends especially on differences on comorbid conditions. These results may have clinical implications for clinical care and future research.

Previous studies have compared the clinical characteristics and outcomes of patients with acute coronary syndromes enrolled and those not enrolled in RCT. Among patients with ST-elevation myocardial infarction, those not included in thrombolytic trials have shown to have worse

outcomes and a higher risk profile than the included patients, and these differences have been accounted for differences in baselines characteristics and management [9–13].

In patients with NSTEACS the available data is scarce. In the Collet et al. study [14], patients who would not have been eligible for the ESSENCE or TIMI-11B trials had a higher risk profile, were less likely to undergo invasive diagnostic or revascularization procedures, and a higher rate of death or myocardial infarction at 30 days, compared with the eligible patients. However, the differences in outcome disappeared after adjusting for baseline differences. In the Kandzari study [15], patients not enrolled in a RCT had also a higher risk profile than the enrolled patients, and a higher unadjusted in-hospital mortality. However, after adjusting for clinical risk, not enrolled patients had a similar risk of mortality but a lower risk of reinfarction and of death or reinfarction. The retrospective quality of the analysis, the heterogeneity of the included centers and patients, and the short-term in-hospital follow-up could explain these conflicting results.

In the present study, in which each exclusion criteria was prospectively collected, patients with any of the usual exclusion criteria in recent RCT on antithrombotic treatment in NSTEACS had an unadjusted near three-fold mortality rate than the potentially eligible patients in those studies. Clinically, the excluded patients were older, had significantly more coronary risk factors, ischemic ECG changes, baseline creatinine levels and heart failure on admission. All of these characteristics define a high-risk group. Interestingly and contrary to other studies performed in patients with acute coronary syndromes, the ineligible patients were managed similarly to eligible patients during hospitalization and at the time of hospital discharge. In spite of this, ineligible patients had a two-fold higher mortality than eligible patients even after adjusting for baseline characteristics and management. Besides, cardiac mortality was also independently related to ineligibility into clinical trials. The exclusion criteria, *per se*, were the determinants of the adjusted two-fold mortality observed.

Often, the exclusion criteria specified in RCT are very strict to avoid drug-related adverse events as may occur in patients with comorbid conditions. In our study, the ten major different causes of exclusion differed in their effect with half of them having a neutral effect on mortality. The exclusion criteria that selected a group of patients with a higher mortality were, in a decreasing order of importance, the presence of severe renal failure, concomitant non-cardiovascular diseases, contraindications to anticoagulation, severe heart failure and previous cerebrovascular disease. Renal function is a major indicator of vascular risk, bleeding complications and mortality [16,17]. Sachdev and others [18,19] have previously reported the association between comorbid disease and long-term survival in patients with coronary artery disease. In these studies, renal disease, diabetes with end-organ damage, chronic obstructive pulmonary disease, and peripheral vascular disease, were the most important co-existing illnesses associated with worse outcomes. In our study, contraindications to anticoagulation were one of the exclusion criteria more strongly related to mortality. This is particularly important since most RCT on NSTEACS are performed to verify the efficacy and safety of antithrombotic treatment.

Our results also underline the discordance between RCT, clinical guidelines and current practice. Lack of consideration of external validity is the most frequent criticism by clinicians to RCT, and is a possible explanation for the widespread underuse in routine practice of treatments that have shown to be of benefit in trials and that are recommended in guidelines. Patient selection in RCT is one of the most important issues that affect the generalisability of the results [20]. Accordingly, patients included in clinical registries often differ from those in clinical trials, and have a considerable heterogeneity in patient management practices [7,8,15,21,22].

Patients with comorbid conditions usually have a high frequency of adverse events. Safety concerns about adverse outcomes and the absence of evidence-based data for this population may limit the use of guidelines-recommended therapies. Although it is usually assumed that patients at higher baseline risk of adverse outcomes will have greater net benefit with an efficacious treatment, this assumption is not always true. A recent study has reported that most clinical guidelines did not modify or discuss the applicability of their recommendations for older patients with multiple comorbidities, suggesting that strict adhesion to current clinical guidelines in caring for an older patient with several comorbidities may have undesirable effects [23]. In patients with heart failure it has been estimated that one third of patients older than 65 years receiving spironolactone in the United States do not meet the enrollment criteria of the primary RCT [24], and that this inappropriate prescription is associated with an increase of hyperkalemia-induced mortality [25]. In patients with acute coronary syndromes, the results from the CRUSADE registry show that one fourth of the patients receive excess dosing of antithrombotic agents, especially patients with comorbidities, and that these patients had an increased risk of bleeding and a higher mortality [26].

The results of our study underlines the importance of associated comorbidities in the prognosis of patients with ACS, and suggest the need for performing RCT with less restrictive exclusion criteria and even RCT focused in some groups of special risk [27] as in old patients and in patients with renal failure. Future research is also needed for large registries to complement the data obtained in clinical trials whose results could ultimately have regulatory implications for drug approval and labeling.

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