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CLINICAL CHARACTERISTICS AND ONE-YEAR OUTCOMES OF ELDERLY PATIENTS WITH ST-ELEVATION OR NON-ST-ELEVATION ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Clinical significance points

1. There is little data comparing Non-ST Elevation Acute Coronary Syndrome vs ST Elevation Myocardial Infarction elderly patients treated by percutaneous coronary intervention.
2. Despite more favorable baseline characteristics, elderly patients with ST Elevation Myocardial Infarction treated by percutaneous coronary intervention have twice the risk of one-year mortality and stroke compared to Non-ST Elevation Acute Coronary Syndrome patients.
3. These findings may be important for tailoring follow-up strategies.

CLINICAL CHARACTERISTICS AND ONE-YEAR OUTCOMES OF ELDERLY PATIENTS WITH ST-ELEVATION OR NON-ST-ELEVATION ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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running title: Prognostic role of ECG on admission in ACS patients

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ABSTRACT

Introduction: Acute coronary syndromes have been classified according to the finding of ST-segment elevation on the presenting ECG, with different treatment strategies and practice guidelines. However, a comparative description of the clinical characteristics and outcomes of acute coronary syndrome elderly patients undergoing percutaneous coronary intervention during index admission has not been published so far.

Methods: Retrospective cohort study of patients enrolled in the Elderly-ACS 2 multicenter randomized trial. Main outcome measures were crude cumulative incidence and cause-specific hazard ratio (cHR) of cardiovascular death, non-cardiovascular death, reinfarction and stroke.

Results: Of 1443 ACS patients aged >75 years (median age 80, IQR 77-84), 41% were classified as ST Elevation Myocardial Infarction (STEMI), and 59% had Non-ST Elevation ACS (NSTEACS) (48% NSTEMI and 11% unstable angina). As compared to those with NSTEACS, STEMI patients had more favorable baseline risk factors, less prior cardiovascular events and less severe coronary disease, but lower ejection fraction (45% vs 50%, p<0.001). At a median follow up of 12 months, 51 (8.6%) STEMI patients had died, versus 39 (4.6%) NSTEACS patients. After adjusting for sex, age and previous myocardial infarction, the hazard among the STEMI group was significantly higher for cardiovascular death (cHR- 1.85; 95% CI 1.02-3.36), non-cardiovascular death (cHR 2.10; 95% CI 1.01-4.38), and stroke (cHR 4.8; 95% CI 1.7-13.7).

Conclusions: Despite more favorable baseline characteristics, elderly STEMI patients have worse survival and a higher risk of stroke compared to NSTEACS patients after percutaneous coronary intervention.

Key words: elderly; myocardial infarction; acute coronary syndrome.

The clinical spectrum of acute coronary syndrome (ACS) has been classified according to the presenting ECG into ST-Elevation Myocardial Infarction (STEMI) and Non-ST Elevation ACS (NSTEACS). As testified by the fact that separate Practice Guidelines exist for the two clinical conditions,[1-4] this subdivision has important pathophysiological and, more importantly, therapeutic implications, since immediate reperfusion therapy is recommended in STEMI [either using fibrinolytic therapy or primary percutaneous coronary intervention][1,2], whereas NSTEACS mandates early risk stratification and a more graded invasive approach[3,4]. Patients with NSTEACS have been shown to be older than STEMI patients, with worse baseline characteristics and to have worse long-term outcomes.[5] Part of this unfavorable outlook may also depend on the fact that only about two-thirds of NSTEACS patients are suitable for revascularization, as compared to the almost totality of STEMI patients. However, it is uncertain whether the differences in clinical characteristics and outcome persist in the elderly patients with ACS.

In the present study, we investigated the clinical and coronary angiographic characteristics of patients aged ≥75 years with either STEMI or NSTEACS treated by percutaneous coronary intervention in the Elderly ACS 2 randomized trial[6] and followed-up them for 12 months to compare their major cardiovascular outcomes.

METHODS

Patient Population

The Elderly ACS 2 trial[6] was a randomized, multicenter study carried out at 32 centers in Italy, comparing reduced-dose prasugrel (5 mg once daily) and standard-dose clopidogrel (75 mg once daily) in patients aged ≥75 years undergoing percutaneous coronary intervention. The trial was designed as event-driven and enrolment had to continue until at least 492 primary adjudicated

events had occurred in the combined treatment groups. The trial started in November 2012 and was interrupted on January 25, 2017 due to futility for efficacy after the results of a planned interim analysis of the first 1000 patients with completed 12-month follow-up. Overall, 1443 patients were enrolled across the ACS spectrum including STEMI and NSTEACS.

Outcomes

The original endpoint of the Elderly ACS 2 study was a composite of all-cause mortality, myocardial (re)infarction, disabling stroke and re-hospitalization for cardiovascular causes or bleeding, within one year.[6] For the present study, we considered cardiovascular mortality and in addition non-cardiovascular mortality, re-infarction and overall stroke. All the study characteristics, inclusion and exclusion criteria, as well as endpoint definitions have been reported previously[6].

Statistical Analysis

Continuous variables were tested for normality using the Shapiro-Wilk test and are reported as mean and standard deviation if normally distributed, or medians and 25th and 75th percentiles if they did not satisfy the normal assumption. Categorical variables are shown as frequencies and percentages in each ACS group.

To describe the first signal of unfavourable outcome, the numbers and percentages of first events observed during the follow-up were reported in a table separately by ACS group. The data were provided separately for the type of first event (cardiovascular mortality, non-cardiovascular mortality, re-infarction, stroke) distinguishing between the events observed up to the first 30 days and in the whole follow-up.

In each ACS group, the cumulative probability of observing the single type of first event (crude cumulative incidence function, CCI) was estimated as a function of time by the Aalen Johansen estimator for competing risks. This estimator was used to remove the bias due to the presence of right censoring from the percentages of events observed up to 30 days and in the whole follow-up.

The CCIs of a given type of first event were compared between ACS groups by the Gray's test[7]. Of note, the CCI of the single type of first event is affected by the indirect protection of the competing events, since the more the competing event occurs as first, the lower is the proportion of patients that may develop the type of first event under analysis. This motivates that to evaluate the prognostic role of the ACS group we resorted to cause specific rates in time windows and cause specific hazard of each type of first event. The rate of the single type of first event was calculated in each ACS group splitting follow-up time in the first 30 days and from the 31st day on. The rates of a given type of first event were compared between ACS groups by the exponential model.

The cause specific hazard ratio (cHRs) and corresponding 95% confidence intervals (Cis) for patients with STEMI versus NSTEACS were calculated by using univariate Cox regression models. Cox regression models were also adjusted for age (entered as the following four dummy variables: 75-79, 80-84, 85-89, ≥90 years), gender and previous MI. Visual inspection of the Shoenfeld residual plot and the test proposed by Grambsch [8] were used to assess the proportional hazards assumption. The analyses were performed using STATA version 14 (Stata Corp., College Station, TX) and R software 3.5.1, and R version 3.4.1 (2017-06-30).

RESULTS

Study population

The distribution of patients' baseline clinical characteristics, features of the index ACS event, angiographic and percutaneous coronary intervention data, and drug therapy during admission and at discharge, are summarized in **TABLES 1-3** by ACS group (STEMI vs NSTEACS). On the presenting ECG, 595 (41.0%) were classified as STEMI, whereas 848 (59.0%) had NSTEACS. Based on cardiac troponin levels, 100% of the ST Elevation patients were classified as STEMI, whereas among the NSTEACS patients 694 (82%) were Non-ST Elevation myocardial infarction

and 154 (18%) unstable angina. Women were more frequent among STEMI patients, whereas age and body mass index were almost comparable. Diabetes, hypertension, hypercholesterolemia, chronic respiratory failure as well as previous cardiovascular events (prior myocardial infarction, prior percutaneous coronary intervention, prior bypass surgery and peripheral vascular disease) were less frequent among STEMI as compared to NSTEACS patients, whereas the prevalence of current smokers was comparable. Ongoing cardiovascular medications were also less frequent in the STEMI group.

STEMI patients had less extensive coronary artery disease, including left main and 3-vessel disease. However, STEMI patients had significantly lower residual left ventricular ejection fraction. Among the patients treated with stenting [539 STEMI (96.4%) and 787 with NSTEACS (94.2%)], the proportion of patients who implanted drug eluting stents was significantly smaller in STEMI patients (66% vs 75% in NSTEACS, $p<0.001$).

Finally, STEMI patients were more commonly treated with glycoprotein IIb/IIIa antagonists and bivalirudin in the periprocedural period. Medications at discharge were comparable.

The length of hospital stay was significantly longer for STEMI patients (median 6 days, IQR 5-9 days) compared to patients with NSTEMI (median 6, IQR 4-8 days) ($p<0.01$).

One-year outcome

The median follow-up duration was 12 months (range, 3–13 months), with 23 patients (1.5%) lost to follow-up. The number of observed events (as first event) in STEMI and NSTEACS patients is shown in **TABLE 4**. Among STEMI patients, a total of 44 deaths from any cause (7.4%) were observed. Three out of 7 patients with reinfarction and 4 out of 15 patients with stroke died within the end of follow up; among the 3 patients died after reinfarction, 2 died the same day when myocardial infarction occurred, whereas in the third death occurred 6 months after myocardial infarction. Among the 4 patients dead after stroke, death occurred a few days after stroke in 3 cases,

whereas in 1 case the patient experienced a non-disabling in-hospital stroke and died after 11 months.

Among NSTEACS patients, a total of 35 deaths from any cause were observed. Four patients out of 31 with reinfarction died within the end of follow up, in 3 cases a few days after myocardial infarction and in 1 case 5 months later.

Nineteen patients experienced stent thrombosis (ST), classified as definite in 5 cases [2 (0.3%) among STEMI and in 3 (0.3%) among NSTEACS patients] and probable in 14 [9 (1.5%) among STEMI and 5 (0.5%) among NSTEACS patients]. Three patients had non-fatal myocardial infarction, 14 had sudden cardiac death, whereas 2 patients (both with STE as presenting ECG) had fatal myocardial infarction (in 1 patient death occurred after 6 months and in 1 patient occurred the same day, 6 days after study inclusion). Eleven patients (2.0%) among STEMI and 38 (4.5%) among NSTEACS patients had BARC 2-5 bleeding events (p=0.02). Only one patient with NSTEACS at admission experienced a fatal bleeding.

The CCI functions for cardiovascular mortality, non-cardiovascular mortality, re-infarction and stroke are displayed in **Figure 1.** A higher incidence of cardiovascular mortality, non-cardiovascular mortality and stroke was observed among STEMI patients, whereas the incidence of re-infarction was higher among patients with NSTEACS. The 30-day and one-year crude cumulative rates of study outcomes according to the presenting ECG are reported in **TABLE** 4.

Results on the prognostic impact of the ACS group regarding the different types of first events are reported in **TABLE** 5. As compared to NSTEACS patients, those with STEMI had a higher rate of cardiovascular mortality in the first 30-day time window, a lower rate of infarction and a higher rate of stroke in the time window from the 31st day on. In the Cox regression model, the presence of STEMI was associated to higher cardiovascular (cHR 1.70; 95% CI 0.97-3.01) and non-cardiovascular mortality (cHR 2.01; 95% CI 0.99-4.11), stroke (cHR 4.25; 1.55-11.7) and with a

lower risk of myocardial infarction (cHR 0.33; 95% CI 0.14-0.74). After adjusting for sex, age and previous MI, STEMI remained a significant and independent predictor of cardiovascular death (cHR 1.85; 95% CI 1.02-3.36), non-cardiovascular death (cHR 2.10; 95% CI 1.01-4.38) and stroke (cHR 4.80; 95% CI 1.68-13.7), whereas the association with reinfarction became nonsignificant (cHR 0.44, 95% CI 0.19-1.03).

DISCUSSION

The present study confirms that, even in older adults, STEMI and NSTEACS are two different clinical syndromes of acute coronary artery disease. It has long been established that, as compared to STEMI patients, those with NSTEACS are older and have a longer history of coronary artery disease, including prior MIs end revascularization procedures[5]. These worse characteristics persist at present time and are independent from the age difference between the two patient populations. Therefore, even in the elderly, the STEMI presentation is indicative of an abrupt closure of a major coronary segment in the lack of collateral circulation and myocardial preconditioning, these two conditions being more typical of patients with longer history of coronary artery disease and revascularization procedures, such as those with NSTEACS. Besides the different pathogenetic mechanism, and due to the lack of collateral circulation, on average the STEMI presentation is associated with larger myocardial damage and lower residual left ventricular function, as also shown in the present study.

A further mechanism is the possible protective effect of several cardiovascular medications more frequently in use among NSTEACS patients at the time of admission. Some of these medications (aspirin and clopidogrel) may have prevented complete coronary occlusion, whereas others (statins, betablockers and ACE-inhibitors) may have reduced plaque instability and myocardial oxygen requirement.

A surprising and new finding of the present study is the 50% higher risk of cardiovascular and non-cardiovascular death at 12 months observed among STEMI patients, as compared to those with NSTEACS. This finding was observed with similar post-discharge drug therapy in the two groups. To this regard, it should be considered that the whole study population was made of patients undergoing percutaneous coronary intervention during the index admission, a feature that has selected a subset of NSTEACS patients suitable for percutaneous coronary intervention procedures. A significant and quantitatively remarkable reduction in cardiovascular events, including mortality, was observed among elderly NSTEACS patients treated invasively (mostly with percutaneous coronary intervention) both in observational registries[9] and in randomized trials[10-13]. The low mortality rate observed in the whole study, and particularly among NSTEACS patients, may well reflect current mortality rates among elderly ACS patients treated by percutaneous coronary intervention, and has been observed in similar contemporary trials[14] and registries[15]. Therefore, whereas the paradigm of NSTEACS patients having worse baseline characteristics is confirmed by our study in current practice in the elderly population, mortality seems to be lower now, as compared to elderly STEMI patients treated with primary percutaneous coronary intervention.

As compared to STEMI patients, those with NSTEACS had a higher rate of re-infarction at one year, a ratio that has not changed compared to twenty years ago[5], though the absolute rates have been dramatically reduced in both groups. This finding can be explained by the more severe coronary disease in NSTEACS patients. On the other hand, stroke rate was significantly higher in the STEMI group, maybe due to embolism from the infarcted left ventricle, or a higher rate of post-myocardial infarction atrial fibrillation associated with left ventricular dysfunction. These two aspects require specific investigation. Bleeding events were significantly higher among NSTEACS patients, a further proof of the greater frailty of these patients.

The characteristic of the present study, based on a population enrolled in a randomized clinical trial, limits the applicability of our findings to patients treated by percutaneous coronary intervention

early during index admission. However, the study exclusion criteria were limited to patients with recent severe bleeding and those with an indication to anticoagulant therapy, including atrial fibrillation. These clinical conditions, more prevalent among NSTEACS patients[16], are associated with worse outcomes across the ACS spectrum. We did not carry corelab quantification of the echocardiography-measured left ventricular ejection fraction values, which were based on the individual investigator assessment as in clinical practice. Similarly, we did not collect blood samples to perform corelab measurements of cardiac troponin levels, and the many different analytical methods in use in the 32 participating Centers preclude a uniform estimate of the amount of myocardial damage. However, the lower ejection fraction and higher amount of myocardial damage in STEMI, as compared to NSTEACS, is a consolidated data even in the current era of universal invasive approach to ACS[17,18]. The larger acute myocardial damage and decreased residual left ventricular dysfunction in STEMI patients are most likely to have significantly affected patient's outcome.

Strengths

A major strength of this study is the comparable recruitment and setting of STEMI and NSTEACS patients, all derived from the same clinical trial and hence undergoing standardized procedures and follow-up by the same group of physicians. In addition, we used a competing risk analysis to evaluate, beyond overall mortality, specific outcomes, including reinfarction, stroke and cardiovascular death. These results could provide new insights on the prognostic role of the different pathogenetic mechanisms involved in the two types of ACS and, perhaps, on a different therapeutic aggressiveness in STEMI vs NSTEACS patients.

Conclusions

In a contemporary cohort of elderly and very elderly patients admitted to hospital for an ACS and treated with early revascularization, ST elevation as presenting ECG is associated with worse

outcome, as compared to non-ST elevation, for at least one year of follow-up. Most of this difference accrues during the first 30 days, whereas little difference is observed thereafter. As shown by the Duke University Medical Center (Durham, NC) cohort of myocardial infarction patients undergoing coronary angiography and found to have at least one diseased coronary artery[19] (but with only two thirds of the NSTEMI patients undergoing revascularization) longer follow-up may be needed to observe worse clinical outcome in NSTEACS, consistent with the overall worse clinical characteristics and longer cardiac disease history of this population.

References

1. Ibanez B, James S, Agewall S, Antunes MJ, at al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39:119-177.

2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 127:529-555.

3. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2354-2394.

4. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation:

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37:267-315.

5. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999; 281:707-713.

6. Savonitto S, Ferri LA, Piatti L, et al, for the Elderly ACS 2 Investigators. A comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization: the Elderly ACS-2 randomised trial. Circulation 2018; 137:2435-45.

7. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988; 16:1141–1154.

8. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–526.

9. De Luca L, Olivari Z, Bolognese L, et al. A Decade of Changes in Clinical Characteristics and Management of Elderly Patients with Non-ST-Elevation Myocardial Infarction Admitted in Italian Cardiac Care Units. Open Heart 2014; 1:e000148.

10. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. Ann Intern Med. 2004; 141:186–195.

11. Damman P, Clayton T, Wallentin L, et al. Effects of age on long-term outcomes after a routine invasive or selective invasive strategy in patients presenting with non-ST segment elevation acute coronary syndromes: a collaborative analysis of individual data from the FRISC II - ICTUS - RITA-3 (FIR) trials. Heart 2012; 98:207–213.

12. Savonitto S, Cavallini C, Petronio AS, et al. Early Aggressive Versus Initially Conservative Treatment in Elderly Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. JACC Cardiovasc Interv 2012; 5:906–916.

13. Tegn N, Abdelnoor M, Aaberge L, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016; 387:1057-1065.

14. Cayla G, Cuisset T, Silvain J, et al; ANTARCTIC investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016; 388:2015-2022.

15. Casella G, Di Pasquale G, Oltrona Visconti L, et al. Management of patients with acute coronary syndromes in real-world practice in Italy: an outcome research study focused on the use of ANTithRombotic Agents: the MANTRA registry. Eur Heart J Acute Cardiovasc Care 2013; 2:27-34.

16. De Luca L, Casella G, Rubboli A, et al. Recent Trends in Management and Outcome of Patients with Acute Coronary Syndromes and Atrial Fibrillation. Int J Cardiol 2017; 248:369-375.

17. Savonitto S, Granger CB, Ardissino D, et al. The Prognostic Value of Creatine Kinase Elevations Extends across the whole Spectrum of the Acute Coronary Syndromes. J Am Coll Cardiol 2002; 39:22-29.

18. Savonitto S, Morici N, Nozza A, et al. Predictors of mortality in hospital survivors with type-two diabetes mellitus and acute coronary syndromes. Diab Cardiovasc Dis Res 2018; 15:14-23

19. Chan MY, Sun JL, Newby LK, et al. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. Circulation 2009; 119:3110-117.

Figure legends

Figure 1. One-year crude cumulative incidence (CCI) of study outcomes according to presenting ECG. CV: cardiovascular; NSTEACS: Non ST Elevation Acute Coronary Syndrome; STEMI: ST Elevation Myocardial infarction; MI: Myocardial Infarction

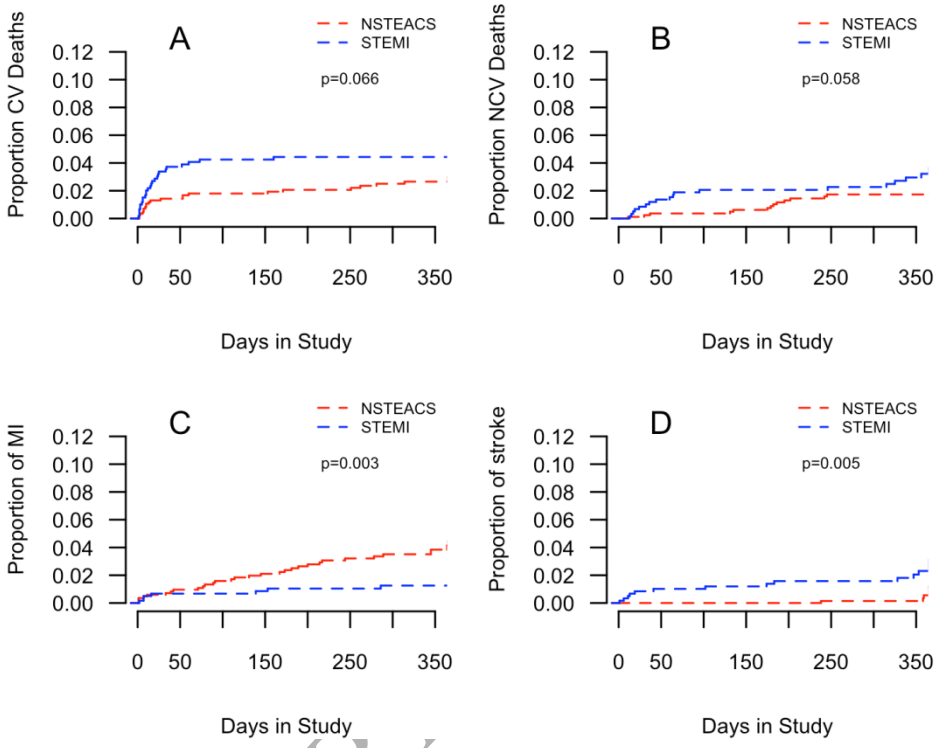

Table 1: Baseline clinical characteristics

	STEMI (n=595)	**NSTEACS** (n=848)	**p value**
Age (median, IQR)	80 (77-84)	80 (77-83)	0.232
Sex			
Female	264 (44.4)	312 (36.8)	0.004

Male	331 (55.6)	536 (63.2)	
Body-mass index (kg/m^2)	25.4 (23.5-27.8)	25.8 (23.5-28.3)	0.125
Medical history			
Family history of cardiovascular disease	88 (14.8)	127 (15.0)	0.995
Diabetes	151 (25.4)	269 (31.7)	0.009
Hypertension	426 (71.6)	694 (81.8)	<0.001
Hypercholesterolemia	228 (38.3)	416 (49.1)	<0.001
Current smoker	63 (10.6)	68 (8.0)	0.094
Chronic respiratory failure	23 (3.9)	64 (7.5)	0.004
Liver disease	10 (1.7)	14 (1.6)	0.965
eGFR[a] at admission (ml/min)	55 (43-67)	55 (42-68)	0.781
Hemoglobin at admission (g/dL)			
males	14.0 (1.4)	13.6 (1.5)	< 0.001
females	12.8 (1.4)	12.6 (1.4)	0.091
Neurological disorders	18 (3.0)	28 (3.3)	0.768
Malignancies	23 (3.9)	22 (2.6)	0.171
Previous cardiovascular events			
Myocardial infarction	52 (8.7)	222 (26.2)	<0.001
Percutaneous coronary interventions	62 (10.4)	202 (23.8)	<0.001
Coronary artery bypass grafting	22 (3.7)	106 (12.5)	<0.001
Peripheral vascular disease	36 (6.1)	89 (10.5)	0.003
Atrial fibrillation	16 (2.7)	40 (4.7)	0.050
Ongoing cardiovascular medications[b]			
Aspirin	208 (47.1)	508 (67.8)	<0.001
Clopidogrel	39 (8.8)	175 (23.4)	<0.001

Betablockers	152 (34.4)	342 (45.7)	<0.001
Calcium antagonists	147 (33.1)	202 (27.0)	0.026
ACE-inhibitors/ARBs	290 (65.7)	500 (66.7)	0.075
Diuretics	125 (28.3)	297 (39.6)	<0.001
Nitrates	34 (7.7)	177 (23.6)	<0.001
Statins	135 (30.5)	394 (52.6)	<0.001

Data are n (%) for categorical variables and median (IQR) for continuous variables.
STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor antagonist.
[a]estimated Glomerular Filtration Rate by the Cockroft-Gault formula.
[b]Data available on 1191 patients (442 STEMI and 749 NSTEACS), where percentages were calculated on available data.

Table 2: Characteristics of index ACS event

	STEMI	**NSTEACS**	**p Value**
	(n=595)	(n=848)	
Left ventricular ejection fraction	45 (40-55)	50 (45-55)	<0.001
Coronary angiography			
Radial access	457 (76.8)	652 (76.9)	0.702
Number of vessels with critical stenosis[a]			<0.001
One-vessel disease	263 (44.4)	314 (37.1)	
Two-vessel disease	183 (30.9)	240 (28.4)	
Three-vessel disease or greater	141 (23.8)	291 (34.4)	
Left main	16 (2.7)	83 (9.8)	<0.001
PCI performed	587 (98.7)	846 (99.8)	0.012
Procedural treatment[b]			0.032

Stenting[b]	539 (96.4)	787 (94.2)	0.085
Drug eluting stents implanted	354 (65.7)	590 (75.0)	
Bare metal stents implanted	131 (24.3)	124 (15.8)	
Other (unknown type)	54 (10.0)	73 (9.2)	
Drug Eluting Balloons	4 (0.70)	22 (2.7)	
Plain balloon angioplasty	16 (2.9)	26 (3.1)	
Procedural success	569 (95.6)	818 (96.5)	0.891
Length of hospital stay (days)	6 (5-9)	6 (4-8)	<0.01

Data are n (%) for categorical variables and median (IQR) for continuous variables.
STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome.
[a]Data available on 1438 patients (592 STEMI and 846 NSTEACS), where percentages were calculated on available data.
[b]Data available on 1384 patients (556 STEMI and 828 NSTEACS), where percentages were calculated on available data.

Table 3: Drug therapy during admission and at discharge

	STEMI (n=595)	**NSTEACS** (n=848)	**p Value**
Peri-procedural medications[a]			
Aspirin	550 (93.2)	813 (97.1)	0.001
Glycoprotein IIb/IIIa antagonists	154 (26.1)	81 (9.7)	<0.001
Unfractionated heparin	520 (88.1)	626 (74.8)	<0.001
Low molecular weight heparin	35 (5.9)	241 (28.8)	<0.001
Bivalirudin	88 (14.9)	36 (4.3)	<0.001
Medications at discharge[b]			
Aspirin	569 (98.8)	830 (99.3)	0.329
Proton Pump Inhibitors	551 (95.7)	756 (90.4)	<0.001

Betablockers	444 (77.1)	661 (79.1)	0.375
Calcium antagonists	70 (12.1)	225 (26.9)	<0.001
ACE-inhibitors or ARBs	484 (83.3)	689 (81.4)	0.365
Diuretics	224 (38.9)	335 (40.1)	0.655
Nitrates	57 (9.9)	126 (15.1)	0.004
Statins	554 (96.2)	790 (94.5)	0.147
Oral anticoagulant	20 (3.5)	17 (2.0)	0.096

Data are n (%). ACE=angiotensin-converting enzyme.
STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome. ARB=angiotensin-receptor antagonist.
[a]Data available on 1427 patients (590 STEMI and 837 NSTEACS), where percentages were calculated on available data. [b]Data available on 1412 patients (576 STEMI and 836 NSTEACS), where percentages were calculated on available data.

Table 4. Thirty-day and one-year crude cumulative incidence (CCI) and 95% confidence intervals (CIs) of study outcomes according to presenting ECG

Study outcome	Group	30-day events (n, %)	CCI at 30 days (% of patients) (95% CI)	1-year events (n, %)	CCI at 1 year (% of patients) (95% CI)
Cardiovascular death	STEMI	20 (3.4)	3.38 (3.24-3.53)	26 (4.4)	4.43 (4.26-4.60)
	NSTEACS	12 (1.4)	1.43 (1.35-1.51)	22(2.6)	2.98 (2.85-3.11)
Non-Cardiovascular death	STEMI	5 (0.8)	0.85 (0.78-0.93)	18 (3.0)	3.63 (3.45-3.80)
	NSTEACS	2 (0.2)	0.24 (0.21-0.27)	13 (1.5)	1.73 (1.64-1.83)
Myocardial infarction	STEMI	4 (0.7)	0.68 (0.61-0.74)	7 (1.2)	1.25 (1.16-1.35)
	NSTEACS	5 (=.6)	0.59 (0.54-0.64)	31 (3.7)	4.46 (4.30-4.62)
Stroke	STEMI	5 (0.8)	0.85 (0.77-0.92)	15 (2.5)	3.34 (3.16-3.51)
	NSTEACS	0	0	5 (0.6)	1.19 (1.09-1.30)

STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome. CCI: Crude Cumulative Incidence

Table 5. Estimated rates (per person-year) with lower/upper bounds of 95% confidence intervals (CIs) and cause-specific hazard ratios (HRs) with corresponding 95% CIs.

First event	*Estimated rates (95% CI)* *0-30 days*	*p value*	*Estimated rates (95% CI)* *31-365 days*	*p value*	HR[ac] (95%CI)	HR[bc] (95%CI)
Cardiovascular death STEMI NSTEACS	0.428 (0.276-0.664) 0.177 (0.100-0.312)	*0.016*	0.012 (0.005-0.027) 0.014 (0.007-0.261)	*0.805*	*1.70 (0.97-3.01)*	*1.85 (1.02-3.36)*
Non-Cardiovascular death STEMI NSTEACS	0.107 (0.044-0.257) 0.029 (0.007-0.118)	*0.124*	0.026 (0.015-0.046) 0.015 (0.008-0.028)	*0.179*	*2.01 (0.99-4.11)*	*2.10 (1.01-4.38)*
Myocardial Infarction STEMI NSTEACS	0.085 (0.032-0.228) 0.074 (0.030-0.177)	*0.826*	0.006 (0.002-0.020) 0.036 (0.025-0.053)	*0.004*	*0.33 (0.14-0.74)*	*0.44 (0.19-1.03)*
Stroke STEMI NSTEACS	0.107 (0.044-0.257) not estimable	*na*	0.020 (0.011-0.038) 0.007 (0.003-0.017)	*0.049*	4.25 (1.55-11.7)	4.80 (1.68-13.7)

STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome.

[a] *estimated from cause specific regression analysis for patients with STEMI compared to NSTEACS.*

[b] further adjusted for age classes, gender, previous myocardial infarction.

[C] estimated over 365-day follow up