Association between clinical pathways leading to medical management and prognosis in patients with non-ST-segment elevation acute coronary syndrome

Short title: Subgroups in medically managed NSTE-ACS patients

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Abstract

Introduction and objectives A large proportion of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are initially managed medically and do not undergo coronary revascularization during or immediately after the index event. The aim was to explore the clinical pathways leading to medical management in NSTE-ACS patients, and their influence on prognosis.

Methods Patient characteristics, pathways leading to medical management and 2-year outcomes were recorded in a prospective cohort of 5591 NSTE-ACS patients enrolled in 555 hospitals in 20 countries across Europe and Latin America. Cox models were used to assess the impact of hospital management on post-discharge mortality.

Results Medical management was the selected strategy in 2306 (41.2%) patients, of whom 669 (29%) showed significant coronary artery disease (CAD), 451 (19.6%) non-significant disease, and 1186 (51.4%) did not undergo coronary angiography. Medically managed patients were older with higher risk features than revascularized patients. Two-year mortality was higher in medically managed than revascularized patients (11.0% vs 4.4%, $P < .001$), with higher mortality rates in patients who did not undergo angiography (14.6%), and those with significant CAD (9.3%). Compared with revascularized patients, risk-adjusted mortality was highest for patients who did not undergo angiography (hazard ratio 1.81; 95% confidence interval [CI], 1.23-2.65), or were not revascularized in the presence of significant CAD (hazard ratio 1.90; 95% CI, 1.23-2.95).

Conclusions Medically managed NSTE-ACS patients represent a heterogeneous population with distinct risk profiles and outcomes. These differences should be considered when designing future studies in this population.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01171404.

Key Words: coronary disease, angiography, prognosis

Abbreviations

EPICOR	long-tErm follow-up of antithrombotic management Patterns In acute COROnary syndrome patients
CAD	coronary artery disease
CAG	coronary angiography
CR	coronary revascularization
MM	medical management
NSTE-ACS	non-ST-segment elevation acute coronary syndromes

Introduction

An invasive management strategy is recommended for the majority of patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS).[1-3] Nevertheless, a large proportion of NSTE-ACS patients are initially managed medically; that is, they do not undergo coronary revascularization during or immediately after the index admission.[4-6] This observation has triggered studies designed to evaluate specific therapeutic approaches for these patients.[7-13] However, patients with NSTE-ACS may be selected for medical management for a number of different reasons, and we hypothesized that patient profiles and outcomes may vary accordingly.

The aims of this analysis were to study rates of use of the different management strategies for NSTE-ACS in real-world practice from an international perspective, the main clinical pathways that lead to the non-use of coronary revascularization, and the relationship between these pathways and post-discharge outcomes.

Methods

Study design

EPICOR (long-tErm follow-up of antithrombotic management Patterns In acute CORonary syndrome patients) is a prospective, international, observational, real-life practice, cohort study. The rationale, design, definitions, site selection, and baseline patient characteristics have been published previously.[14-16] Briefly, 10 568 patients hospitalized for an ACS, with or without ST-segment elevation, within 24 hours of symptom onset and who survived until hospital discharge were enrolled in 555 hospitals in 20 countries in Northern, Southern, and Eastern Europe and Latin America between September 2010 and March 2011. Patients were excluded from the study if they had 'secondary' ACS, any condition or circumstance that may limit completion of follow-up, serious comorbidities considered likely to limit life expectancy to less than 6 months, and previous enrolment in EPICOR or another clinical trial. All patients gave informed consent. Medical treatments for ACS, diagnostic and therapeutic procedures, and clinical events during the acute phase (pre- and in-hospital) were recorded using electronic case report forms. Patients were followed up by telephone calls up to 2 years after hospital discharge. Vital status, hospitalizations, cardiovascular and bleeding events, and changes in medication were recorded for each call.

Definitions used in EPICOR have been presented elsewhere.[14, 16] A diagnosis of non-ST-segment elevation myocardial infarction required the presence of chest pain/discomfort, lack of persistent ST-segment elevation, left bundle

branch block or intraventricular conduction disturbances, and elevation of cardiac biomarkers (CK-MB and troponins) with at least 1 value above the 99th percentile of the upper reference limit. Unstable angina was defined as the presence of angina symptoms at rest or on minimal exercise, and transient ST-T changes, and no significant increase in biomarkers of necrosis but objective evidence of ischemia by non-invasive imaging or significant coronary stenosis at angiography. Cardiovascular events included myocardial infarction, heart failure, arrhythmia, unstable angina, ischemic stroke, and transient ischemic attack. Bleeding events included all kinds of bleeds.

Management strategies

Two management strategies were defined for patients with NSTE-ACS: "Coronary Revascularization" (CR), which included patients who underwent any kind of coronary revascularization (either percutaneous or surgical) during index admission and "Medical Management" (MM), for those discharged without CR. According to the reasons for MM, 3 subgroups were pre-defined: (i) patients who did not undergo diagnostic coronary angiography (CAG-); (ii) patients who underwent CAG and had significant (at least 1 stenosis >50% in 1 coronary artery) coronary artery disease (CAD) but did not undergo coronary revascularization (CAG+, CAD+), and (iii) patients who underwent angiography and had no significant CAD (CAG+, CAD-).[17]

Statistical analysis

Baseline characteristics, hospital management, and in-hospital outcomes for patients with NSTE-ACS were compared according to initial management strategy. Comparisons were made between CR and MM or across the 3 MM subgroups using Chi-square tests. In a second step, we investigated the independent predictors of undergoing angiography or selection for MM. We used univariate logistic regression models to assess any association between angiography or MM and individual covariates. To investigate which were the strongest independent predictors, we used multivariate logistic regression. We forced the inclusion of geographical region (Northern Europe, Eastern Europe, Southern Europe and Latin America) and type of hospital (regional, non-university general, university general and private) into the model. Additionally, we fitted a random-effect at the hospital level to account for within-hospital clustering of events. We used a forward stepwise variable selection with a *P*-value cut-off of 0.05 to select a final model. Finally, the impact of MM on 2-year outcomes was studied. Comparisons of clinical outcome rates (mortality, cardiovascular events, and bleeding events) during follow-up between the management groups were done by fitting a Cox proportional hazards model for time to death or time to first event, censored at 2 years post-discharge. In our minimally adjusted Cox models, we adjusted for age, sex, geographical region, type of hospital (as described above), and a random-effect (shared frailty) term at the hospital level. In our fully adjusted models, we additionally adjusted risk factors associated with 1-year mortality identified from our previous publication.[18]

Results

Management strategies for patients with NSTE-ACS

A total of 5625 NSTE-ACS patients were enrolled at hospital discharge. Data on in-hospital management strategies were available for all except 34 (0.7%) of these. Of the remaining 5591 patients, 4405 (78.8%) underwent CAG (Figure 1). Of these, 3954 patients (70.7%) had CAD, and 3285 (58.8%) underwent CR in hospital. Therefore, a total of 2306 patients (41.2%) were medically managed. The majority of MM patients (51.4%, n = 1186) did not undergo CAG during hospitalization (21.2% of total population), 451 (19.6% of MM, 8.1% of total population) lacked significant CAD, and 669 (29.0% of MM, 12.0% of total population) had significant CAD, but CR was not attempted (Figure 1).

Patients who received MM were older and less likely to present with non-ST-segment elevation myocardial infarction, but more often had prior cardiovascular diseases, comorbidities, and cardiovascular medications (Table 1). They also had more severe cardiac disease (Table 1). When characteristics were compared across the 3 pre-defined subgroups of MM patients, significant differences were found again, with a gradient from younger age and lower comorbidity and cardiovascular burden among CAG+ CAD- patients to older and sicker patients among CAG- patients. Significant regional differences were found in the rate of MM (data not shown).

The most important independent predictor of undergoing CAG during index hospitalization (Table S1 in the online-only Data Supplement) was the presence of

catheterization laboratory in the hospital (OR 46.8, 95%CI, 22.4-97.6). NSTEMI (OR, 1.72 95% CI 1.24-2.38) was associated with a higher probability of undergoing coronary angiography compared with unstable angina as well as prior myocardial infarction (OR, 1.58; 95% CI, 1.07 to 2.32), while age >75 years (OR, 0.38, 95% CI, 0.28-0.53), current smoking (OR, 0.67; 95% CI, 0.51-0.88), hemoglobin levels <13 g/dL (OR, 0.65; 95% CI, 0.48 to 0.78), prior myocardial infarction (or 0.56; 95%CI, 0.39-0.67), prior coronary artery bypass graft surgery (OR, 0.60; 95%CI, 0.38-0.94), prior heart failure (OR, 0.30; 95%CI, 0.19-0.49), and being on angiotensin-converting enzyme inhibitors at admission (OR, 0.70; 95%CI, 0.53 to 0.92) were associated with lower probabilities. Patients from Latin America (OR 0.04; 95% CI 0.02-0.11) and Eastern Europe (OR, 0.15; 95%CI, 0.06-0.35) presented a lower probability of undergoing CAG than patients from Northern Europe.

Independent predictors of not undergoing CR (Table S2 in the online-only Data Supplement) among those who underwent CAG and had significant CAD were prior cardiovascular disease (OR, 0.53; 95%CI, 0.42-0.67), prior coronary artery bypass graft (OR, 0.45; 95%CI, 0.32-0.63), age >75 years (OR, 0.73; 95%CI, 0.55-0.98) and serum creatinine >1.2 mg/dl (OR, 0.76; 95%CI, 0.58-0.99) were marginally associated with lower probabilities while male patients showed a higher probability (OR, 1.34; 95%CI 1.04-1.72) . Patients from Latin America (OR 0.29; 95% CI 0.18-0.48) and Eastern Europe (OR, 0.50; 95%CI, 0.33-0.87) presented a lower probability of undergoing revascularization after CAG than patients from Northern Europe. Admission to private hospitals was associated to

an increased probability of being revascularised during hospitalization (OR, 2.19; 95%CI 1.14 to 4.20)

In-hospital diagnostic and therapeutic procedures, and medical treatments by management strategy

In general, MM patients less frequently received diagnostic and therapeutic procedures during hospitalization compared with CR patients (Table 2). Although all antithrombotic drugs and most cardiovascular preventative treatments were prescribed in the majority of patients, MM patients were less likely to receive them in hospital. Among those who underwent CAG, multivessel disease was significantly more frequent in CR than MM patients as a whole but not in the subgroup of MM patients with significant CAD. Interestingly, the results of coronary angiography triggered small changes in antiplatelet drugs both in CR and MM patients, with the exception of clopidogrel, which was withdrawn in a substantial proportion of MM patients at discharge (Table 2).

Outcomes by management strategy

Medically managed patients had a greater incidence of in-hospital cardiovascular complications, mainly heart failure and atrial fibrillation, particularly among patients who did not undergo CAG (Table 3). The 2-year post discharge all-cause mortality rate was 7.0% in the whole cohort, with significant differences between CR and MM patients (4.4% vs 11%; $P < 0.001$) (Table 3, Figure 2A). A gradient in 2-year mortality was also found among MM patients, with patients who

196 did not receive CAG showing the highest mortality (14.6%) and those without
197 significant obstructive CAD the lowest (4.1%). Cardiovascular event rates at 2
198 years, including myocardial infarction, heart failure, arrhythmia, unstable angina,
199 ischemic stroke, and transient ischemic attack, were also significantly higher in MM
200 compared with CR patients (15.4% vs 9.6%, $P < 0.001$), and were highest in those
201 who did not receive CAG (17.4%) (Figure 2B). In contrast, bleeding events were
202 numerically but not significantly lower in MM versus CR patients (3.4% vs 4.6%, P
203 = 0.06) (Figure 2C). Among the MM subgroups, the difference in bleeding event
204 rates was not significant, but appeared lowest in those who underwent CAG and
205 had no significant CAD. Using 70% stenosis as the cut-off point for CAD+ did not
206 significantly change the results (data not shown). Compared with the results for the
207 50% cut-off point, there was a slight increase in mortality rate in both CAG+CAD+
208 and CAG+CAD- groups, as they were both composed of higher risk patients, with a
209 small change in mortality gradient between the groups. Excluding the 190 patients
210 who underwent revascularization after discharge (including 32 within the first
211 month) from the analyses, no relevant differences were found in patterns of
212 mortality or other event rates.

213 Lack of CAG was found to be an independent predictor of 2-year mortality,
214 adjusted for age, gender, and post-discharge mortality predictors as previously
215 described in the EPICOR cohort[18] (hazard ratio , 1.81; 95% confidence interval,
216 1.23-2.65, $P < 0.001$). Among patients who underwent CAG, MM patients with
217 significant CAD had an increased adjusted mortality risk (hazard ratio, 1.90; 95%
218 confidence interval, 1.23-2.95, $P < 0.001$), while those without significant CAD did

not (hazard ratio, 0.68; 95% confidence interval, 0.20-2.21, $P < 0.001$) (Table S3 in the online-only Data Supplement).

Discussion

The results of this large international cohort study can help us to understand the heterogeneity of patients with NSTE-ACS, the main clinical pathways leading to medical management, and its influence on prognosis. Our observations also allow us to estimate post-discharge event rates in relation to these pathways in a large cohort of unselected patients surviving NSTE-ACS. This information can be particularly helpful for risk stratification, clinical follow-up planning, and designing future studies in this field.

Patients surviving ACS are at high risk of subsequent cardiovascular events, even if optimally treated.[19] Despite recommendations by the main European guidelines,[1, 2] less than 60% of patients undergo CR during hospitalization for NSTE-ACS. This is clinically relevant given the abundance of data coming from randomized trials[13, 20, 21] and observational studies[22] suggesting an improvement in mid- and long-term prognosis for patients with NSTE-ACS managed invasively. In our study, the most frequent clinical situation associated with MM is lack of CAG during hospitalization, which accounts for roughly half of MM cases. Our study is consistent with previous studies using similar analytical methods insofar as older and sicker patients are more often MM while younger and lower risk patients consistently receive more aggressive treatment. This is also true among subgroups

of MM patients, as those not undergoing CAG show the highest risk profile. Similar findings were reported in an analysis from the French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction (FAST-MI), in which MM patients with non-ST-segment elevation myocardial infarction who did not undergo CAG had a higher 5-year mortality rate than those who did, even compared with CAG+ patients with multivessel disease.[23] Moreover, our findings are consistent with the risk paradox found in several national and international registries,[23-27] with a gradient in age, cardiovascular burden, and comorbidities between revascularized patients, patients undergoing CAG but not CR and, finally, those not receiving CAG. Although selection bias may partially explain the higher risk observed in MM patients, CR remains independently associated with lower 2-year mortality risk in our population after adjustment for all factors associated with post-discharge mortality in a previously developed predictive model.[18]

While CAG per se is unlikely to provide any benefit, it has been suggested that patient selection (ie, whether or not to perform angiography) plays a crucial role.[28] In the EPICOR study, NSTE-ACS patients who did not undergo CAG were more likely to be older, with unstable angina rather than non-ST-segment elevation myocardial infarction, and to have hypertension or diabetes. In the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial, the most frequent reasons for not undergoing CAG were patient refusal, lack of on-site facilities, and either unsuitable coronary anatomy or other contraindications.[10] Non-catheterized patients were also more likely to be older, female, and to have a diagnosis of

unstable angina rather than non-ST-segment elevation myocardial infarction, and less previous coronary intervention. In a retrospective analysis from the TRILOGY ACS trial, NSTE-ACS patients who did not undergo angiography also had significantly poorer outcomes compared with those who did: at 30 months, cardiovascular death rates were 8.2% and 4.7%, respectively, with all-cause death rates of 9.6% and 5.8%.[7] In EPICOR as in other studies,[29] lack of immediate access to coronary intervention facilities was one of the most important reasons for initial conservative management. This is true despite the fact that transfers between hospitals and reasons for transfer were recorded in EPICOR.[30]

The regional differences in the probability of undergoing coronary angiography and coronary revascularization as well as the increased probability of undergoing revascularization are worth mentioning. These are probably explained largely by differences in resources, insurance level and care access opportunities, procedural cost for patients and reimbursement.

Limitations

This study is based on registry data and, therefore, subject to the limitations of observational studies, ie, potential bias and confounding. The role of patient preferences in the decision to undergo CAG and CR was not recorded, and this may have had an additional influence on the outcomes that could not be measured. The analysis of only hospital procedures excludes cases in which scheduled CAG or CR might have been performed. However, when we used wider time frames for CR – 10 days (as in TRILOGY ACS) and 30 days – no significant

changes in our results were found, confirming the consistence of our findings. As mentioned previously, although our multivariable analysis included a rigorous adjustment using a previously developed model for mortality prediction,[18] unmeasured confounders, such as known CAD not amenable for CR, dementia, too sick for other medical reasons, or patient preferences, could have affected the apparent protective role of CAG and CR. In addition, clinical events during follow-up were not centrally adjudicated. Finally, although we attempted to show representative examples of real-life practice in each country, by careful selection of local centers, caution for generalizing the results is warranted.

Conclusions

Medically managed patients with NSTE-ACS constitute a heterogeneous group according to the clinical pathways leading to non-use of CAG or CR. Compared with CR patients, those who do not undergo CAG during hospitalization are older, and present with greater comorbidity. They also have the highest adjusted mortality risk after discharge, followed by those not revascularized despite significant CAD. Therefore, the clinical pathways leading to medical management are clinically relevant and should be taken into consideration in studies addressing this patient group, given the observed differences in baseline characteristics and clinical outcomes. Continuing efforts are needed to improve compliance with guidelines recommendations, particularly for NSTE-ACS patients admitted to hospitals without a catheterization laboratory.

Key points

What is known about the topic?

- Despite guidelines recommendations for an invasive strategy in most patients with NSTE-ACS, a large proportion of these patients are initially medically managed
- Different clinical pathways lead to the selection of medical management in NSTE-ACS patients
- NSTE-ACS patients who do not undergo coronary angiography, and hence do not undergo coronary revascularization, are at highest risk of cardiovascular morbidity and mortality in the long-term

What does the study add?

- Medical management is independently associated with higher 2-year adjusted mortality risk compared with revascularization.
- The different clinical pathways leading to the selection of medical management in NSTE-ACS patients have an important influence on patient outcomes.
- Therefore, the reasons for medical management should be taken into consideration in future studies addressing this patient population

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Table 1. Baseline characteristics of non-ST-segment elevation acute coronary syndrome patients by management strategy

	Coronary Revascularization n=3285 58.8%	Medical Management n=2306 41.2%	*P*-Value (CR versus MM)	Medical Management			
				CAG- n=1186 21.2%	CAG+ CAD+ n=669 12.0%	CAG+ CAD- n=451 8.1%	*P*-Value
Diagnosis							
NSTEMI (n=5591)	2491 (75.8%)	1482 (64.3%)	<0.0001	725 (61.1%)	454 (67.9%)	303 (67.2%)	0.0051
UA (n=5591)	794 (24.2%)	824 (35.7%)	<0.0001	461 (38.9%)	215 (32.1%)	148 (32.8%)	0.0051
Basic characteristics							
Age >75 years (n=5591)	559 (17.0%)	553 (24.0%)	<0.0001	346 (29.2%)	139 (20.8%)	68 (15.1%)	<0.0001
Male (n=5591)	2513 (76.5%)	1463 (63.4%)	<0.0001	750 (63.2%)	484 (72.3%)	229 (50.8%)	<0.0001
CV risk factors							
Hypertension (n=5525)	2084 (64.3%)	1603 (70.2%)	<0.0001	874 (74.3%)	466 (70.4%)	263 (59.1%)	<0.0001
Hypercholesterolemia (n=5373)	1716	1228	0.311	617	399	212	<0.0001

	(54.2%)	(55.6%)		(55.0%)	(61.8%)	(48.1%)	
Diabetes mellitus (n=5526)	800 (24.7%)	705 (30.9%)	<0.0001	412 (35.2%)	213 (32.1%)	80 (17.9%)	<0.0001
Current smoking (n=5198)	996 (32.5%)	851 (39.9%)	<0.0001	451 (41.2%)	221 (35.6%)	179 (43.0%)	0.0263
Glucose >160 mg/dL (n=4856)	548 (19.4%)	475 (23.4%)	0.0007	294 (26.8%)	136 (23.4%)	45 (12.7%)	<0.0001
Hemoglobin <13 mg/dL (n = 5217)	656 (21.4%)	668 (31.1%)	<0.0001	401 (35.5%)	174 (28.3%)	93 (23.0%)	<0.0001
Previous CVD							
Prior CVD (n=5547)	1372 (42.1%)	1288 (56.3%)	<0.0001	695 (58.8%)	399 (60.4%)	194 (43.4%)	<0.0001
Prior MI (n=5510)	730 (22.5%)	728 (32.1%)	<0.0001	428 (36.5%)	213 (32.6%)	87 (19.6%)	<0.0001
Prior PCI (n=5511)	710 (21.9%)	452 (19.9%)	0.081	195 (16.7%)	165 (25.2%)	92 (20.7%)	<0.0001
Prior CABG (n=5544)	267 (8.2%)	264 (11.5%)	<0.0001	130 (11.0%)	120 (18.2%)	14 (3.1%)	<0.0001
Heart failure (n=5514)	158 (4.9%)	259 (11.4%)	<0.0001	188 (16.1%)	46 (7.0%)	2 (5.6%)	<0.0001
Arial fibrillation (n=5531)	158 (4.9%)	210 (9.2%)	<0.0001	117 (10.0%)	54 (8.2%)	39 (8.8%)	0.4139
TIA/stroke (n=5535)	197 (6.1%)	168 (7.4%)	0.0548	98 (8.3%)	48 (7.3%)	22 (4.9%)	0.0634

PVD (n=5474)	212 (6.6%)	171 (7.6%)	0.1396	92 (8.0%)	62 (9.5%)	17 (3.8%)	0.0018
Chronic kidney disease (n=5591)	151 (4.6%)	162 (7.0%)	0.0003	110 (9.3%)	42 (6.3%)	10 (2.2%)	<0.0001
Serum creatinine >1.2 mg/dL (n=5291)	680 (21.9%)	636 (29.0%)	<0.0001	361 (31.7%)	189 (29.9%)	86 (20.6%)	<0.0001
Chronic CV medication							
Antiplatelets (n=5591)	1425 (43.4%)	1179 (51.1%)	<0.0001	606 (51.1%)	387 (57.8%)	186 (41.2%)	<0.0001
Aspirin (n=5590)	1347 (41.0%)	1108 (48.1%)	<0.0001	571 (48.2%)	365 (54.6%)	172 (38.1%)	<0.0001
Clopidogrel (n=5585)	435 (13.3%)	397 (17.2%)	<0.0001	211 (17.8%)	112 (16.8%)	74 (16.4%)	0.7445
Anticoagulants (n=5591)	122 (3.7%)	145 (6.3%)	<0.0001	84 (7.1%)	34 (5.1%)	27 (6.0%)	0.2241
ACE inhibitors/ARBs (n=5577)	1358 (41.5%)	1148 (49.9%)	<0.0001	645 (54.5%)	316 (47.4%)	187 (41.6%)	<0.0001
Beta-blockers (n=5582)	1208 (36.9%)	995 (43.2%)	<0.0001	533 (45.0%)	303 (45.3%)	159 (35.3%)	0.0008
Statins (n=5573)	1272 (38.8%)	948 (41.3%)	0.0634	473 (40.2%)	301 (45.0%)	174 (38.8%)	0.0606

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAG, coronary angiography; CR, coronary revascularization; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; MM, medically managed; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack; UA, unstable angina.

460 **Table 2. Hospital procedures and hospital and discharge treatments by management strategy**

		Coronary Revascularization n=3285 58.8%	Medical Management n=2306 41.2%	*P*-Value (CR versus MM)	Medical Management			*P*-Value
					CAG- n=1186 21.2%	CAG+ CAD+ n=669 12.0%	CAG+ CAD- n=451 8.1%	
Antithrombotic Medications								
Aspirin	Initial (n=5591)	3122 (95.0%)	2067 (89.6%)	<0.0001	1033 (87.1%)	629 (94.0%)	405 (89.8%)	<0.0001
	Discharge (n=5586)	3230 (98.4%)	2101 (91.2%)	<0.0001	1061 (89.6%)	635 (95.1%)	405 (89.8%)	0.0001
Clopidogrel	Initial (n=5591)	2983 (90.8%)	1876 (81.4%)	<0.0001	959 (80.9%)	545 (81.5%)	372 (82.5%)	0.7499
	Discharge (n=5578)	2852 (87.0%)	1678 (73.0%)	<0.0001	946 (80.1%)	457 (68.4%)	275 (61.1%)	<0.0001
Prasugrel	Initial (n=5591)	220 (6.7%)	36 (1.6%)	<0.0001	12 (1.0%)	15 (2.2%)	9 (2.0%)	0.0862
	Discharge (n=5587)	207 (6.3%)	29 (1.3%)	<0.0001	12 (1.0%)	9 (1.3%)	8 (1.8%)	0.4532
GP IIb/IIIa inhibitor (n=5591)		455 (13.9%)	62 (2.7%)	<0.0001	18 (1.5%)	28 (4.2%)	16 (3.5%)	0.0013

Anticoagulants-parenteral (n=5591)	2627 (80.0%)	1651 (71.6%)	<0.0001	842 (71.0%)	495 (74.0%)	314 (69.6%)	0.2275
Anticoagulants-oral (n=5591)	111 (3.4%)	166 (7.2%)	<0.0001	98 (8.3%)	41 (6.1%)	27 (6.0%)	0.1255
Diagnostic/therapeutic procedures							
Echocardiography (n=5528)	2497 (76.8%)	1711 (75.1%)	0.1395	885 (75.8%)	509 (76.5%)	317 (71.1%)	0.0846
LVEF <40% (n=5074)	231 (7.8%)	222 (10.5%)	0.0007	135 (12.5%)	66 (10.4%)	21 (5.2%)	0.0002
Stress test (n=5567)	28 (0.9%)	39 (1.7%)	0.0046	19 (1.6%)	14 (2.1%)	6 (1.3%)	0.602
Coronary angiography (n=5591)	3285 (100.0%)	1120 (48.6%)	<0.0001	0	669 (100.0%)	451 (100.0%)	<0.0001
Multivessel disease (n=4239)	1746 (55.9%)	441 (39.6%)	<0.0001	0	441 (66.6%)	0	<0.0001
PCI (n=5591)	3084 (93.9%)						
CABG (n=5591)	209 (6.4%)						
Other discharge medications							
Beta-blockers (n=5567)	2848	1896	<0.0001	992	569	335	<0.0001

	(87.0%)	(82.7%)		(84.1%)	(85.1%)	(75.3%)	
ACE inhibitors/ARBs (n=5567)	2427 (74.1%)	1719 (75.0%)	0.4804	901 (76.4%)	517 (77.5%)	301 (67.5%)	0.0002
Statins (n=5561)	3083 (94.3%)	2012 (87.8%)	<0.0001	1029 (87.4%)	617 (92.4%)	366 (82.2%)	<0.0001
Diuretics (n=5559)	651 (19.9%)	630 (27.5%)	<0.0001	381 (32.3%)	173 (25.9%)	76 (17.0%)	<0.0001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, CAD, coronary artery disease; CAG, coronary angiography; CR, coronary revascularization; GP, glycoprotein; LVEF, left ventricular ejection fraction; MM, medically managed; PCI, percutaneous coronary intervention.

464 **Table 3. In-hospital and 2-year outcomes in non-ST-segment elevation acute coronary syndrome patients by**

465 **management strategy**

	Coronary Revascularization n=3285 58.8%	Medical Management n=2306 41.2%	*P*-Value (CR versus MM)	Medical Management			*P*-Value
				CAG- n=1186 21.2%	CAG+ CAD+ n=669 12.0%	CAG+ CAD- n=451 8.1%	
Hospital outcomes							
Myocardial infarction	75 (2.3%)	41 (1.8%)	0.1943	24 (2.0%)	11 (1.7%)	6 (1.3%)	0.61
Recurrent ischemia	127 (3.9%)	114 (5.0%)	0.0494	70 (6.0%)	29 (4.4%)	15 (3.3%)	0.0674
Heart failure	100 (3.0%)	188 (8.2%)	<0.0001	139 (11.8%)	41 (6.1%)	8 (1.8%)	<0.0001
Ventricular arrhythmia	63 (1.9%)	28 (1.2%)	0.0406	13 (1.1%)	7 (1.0%)	8 (1.8%)	0.4788
Atrial fibrillation/flutter	156 (4.8%)	156 (6.8%)	0.0011	102 (8.6%)	33 (4.9%)	21 (4.7%)	0.0014
Stroke	11 (0.3%)	4 (0.2%)	0.2509	2 (0.2%)	2 (0.3%)	0 (0.0%)	0.497
Bleeding	117 (3.6%)	37 (1.6%)	<0.0001	13 (1.1%)	18 (2.7%)	6 (1.3%)	0.0281
Clinically significant bleeding	86 (2..6%)	27 (1.2%)	0.9491	8 (0.7%)	14 (2.1%)	5 (1.1%)	0.4968
2-year outcomes							
Mortality	135 (4.4%)	233 (11.0%)	<0.0001	158 (14.6%)	58 (9.3%)	17 (4.1%)	<0.0001
CV mortality	59 (1.9%)	119 (5.7%)	<0.0001	83 (7.9%)	31 (5.0%)	5 (1.2%)	<0.0001

Myocardial infarction	72 (2.4%)	80 (4.1%)	0.0009	47 (4.8%)	26 (4.4%)	7 (1.8%)	0.0421
Heart failure	29 (1.0%)	37 (1.9%)	0.0073	22 (2.2%)	12 (2.1%)	3 (0.8%)	0.202
Ventricular arrhythmia	7 (0.2%)	10 (0.5%)	0.1293	2 (0.2%)	7 (1.1%)	1 (0.2%)	0.043
Atrial fibrillation/flutter	10 (0.3%)	15 (0.7%)	0.0464	6 (0.6%)	4 (0.7%)	5 (1.2%)	0.4444
Stroke	20 (0.7%)	17 (0.9%)	0.4385	10 (1.0%)	4 (0.7%)	3 (0.8%)	0.7663
Bleeding	141 (4.6%)	68 (3.4%)	0.025	35 (3.5%)	24 (3.9%)	9 (2.2%)	0.2926
Clinically relevant bleed	63 (2.0%)	37 (1.8%)	0.5399	21 (2.1%)	14 (2.3%)	2 (0.5%)	0.1113

466 CAD indicates coronary artery disease; CAG, coronary angiography; CR, coronary revascularization; CV, cardiovascular; LVEF, left ventricular
467 ejection fraction; MM, medically managed.

Table 4. Hazard ratios for 2-year all-cause death in subgroups of medically managed versus revascularized NSTE-ACS patients by management strategy. Model adjusted for hospital type (regional, non-university general, university general, private) and geographical region, using a multi-level model to adjust for clustering

Adjusted for	Group	Hazard ratio for death vs revascularized
No adjustment	CAG-	3.30 (2.54 to 4.27)
	CAG+ CAD+	2.12 (1.54 to 2.92)
	CAG+ CAD-	0.86 (0.50 to 1.47)
Age and sex	CAG-	2.52 (1.94 to 3.27)
	CAG+ CAD+	1.88 (1.36 to 2.58)
	CAG+ CAD-	0.96 (0.56 to 1.64)
EPICOR risk score covariates	CAG-	1.81 (1.23 to 2.65)
	CAG+ CAD+	1.90 (1.23 to 2.95)
	CAG+ CAD-	0.68 (0.21 to 2.21)

CAD, coronary artery disease; CAG, coronary angiography; NSTE-ACS, non ST-segment elevated acute coronary syndrome.

Figure 1. Distribution of EPICOR NSTE-ACS patients according to initial revascularization strategy and clinical pathways leading to medical management

Abbreviations. CABG, coronary artery bypass graft; CAD, coronary artery disease; CAG, coronary angiography; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention

Figure 2. Post-discharge event rates at 2 years according to management strategy: A) All-cause mortality; B) cardiovascular events; C) bleeding events

Cardiovascular events included myocardial infarction, heart failure, arrhythmia, unstable angina, ischemic stroke, and transient ischemic attack. Bleeding events included all kinds of bleeds

Abbreviations. CAD, coronary artery disease; CAG, coronary angiography; CR, coronary revascularization; MI, myocardial infarction; MM, medical management; TIA, transient ischemic attack; UA, unstable angina