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

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5 **Short title:** Subgroups in medically managed NSTEMI-ACS patients

6

7

8 Tables: 4, Figures: 2, Supplementary tables: 3. References: 30

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10 **Abstract**

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

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

21 **Results** Medical management was the selected strategy in 2306 (41.2%) patients,
22 of whom 669 (29%) showed significant coronary artery disease (CAD), 451
23 (19.6%) non-significant disease, and 1186 (51.4%) did not undergo coronary
24 angiography. Medically managed patients were older with higher risk features than
25 revascularized patients. Two-year mortality was higher in medically managed than
26 revascularized patients (11.0% vs 4.4%, $P < .001$), with higher mortality rates in
27 patients who did not undergo angiography (14.6%), and those with significant CAD
28 (9.3%). Compared with revascularized patients, risk-adjusted mortality was highest
29 for patients who did not undergo angiography (hazard ratio 1.81; 95% confidence
30 interval [CI], 1.23-2.65), or were not revascularized in the presence of significant
31 CAD (hazard ratio 1.90; 95% CI, 1.23-2.95).

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

35 Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier:
36 NCT01171404.

37 **Key Words:** coronary disease, angiography, prognosis

38

39 **Abbreviations**

- 40 EPICOR long-term follow-up of antithrombotic management Patterns In acute
41 CORonary syndrome patients
- 42 CAD coronary artery disease
- 43 CAG coronary angiography
- 44 CR coronary revascularization
- 45 MM medical management
- 46 NSTEMI-ACS non-ST-segment elevation acute coronary syndromes

47 **Introduction**

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

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

62

63 **Methods**

64 **Study design**

65 EPICOR (long-term follow-up of antithrombotic management Patterns In
66 acute CORonary syndrome patients) is a prospective, international, observational,
67 real-life practice, cohort study. The rationale, design, definitions, site selection, and
68 baseline patient characteristics have been published previously.¹⁴⁻¹⁶ Briefly, 10 568
69 patients hospitalized for an ACS, with or without ST-segment elevation, within 24
70 hours of symptom onset and who survived until hospital discharge were enrolled in
71 555 hospitals in 20 countries in Northern, Southern, and Eastern Europe and
72 Latin America between September 2010 and March 2011. Patients were excluded
73 from the study if they had 'secondary' ACS, any condition or circumstance that may
74 limit completion of follow-up, serious comorbidities considered likely to limit life
75 expectancy to less than 6 months, and previous enrolment in EPICOR or another
76 clinical trial. All patients gave informed consent. Medical treatments for ACS,
77 diagnostic and therapeutic procedures, and clinical events during the acute phase
78 (pre- and in-hospital) were recorded using electronic case report forms. Patients
79 were followed up by telephone calls up to 2 years after hospital discharge. Vital
80 status, hospitalizations, cardiovascular and bleeding events, and changes in
81 medication were recorded for each call.

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

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

94

95 **Management strategies**

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

106 **Statistical analysis**

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

129 **Results**

130 **Management strategies for patients with NSTEMI-ACS**

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

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

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

151 catheterization laboratory in the hospital (OR 46.8, 95%CI, 22.4-97.6). NSTEMI
152 (OR, 1.72 95% CI 1.24-2.38) was associated with a higher probability of
153 undergoing coronary angiography compared with unstable angina as well as prior
154 myocardial infarction (OR, 1.58; 95% CI, 1.07 to 2.32), while age >75 years (OR,
155 0.38, 95% CI, 0.28-0.53), current smoking (OR, 0.67; 95% CI, 0.51-0.88),
156 hemoglobin levels <13 g/dL (OR, 0.65; 95% CI, 0.48 to 0.78), prior myocardial
157 infarction (OR 0.56; 95%CI, 0.39-0.67), prior coronary artery bypass graft surgery
158 (OR, 0.60; 95%CI, 0.38-0.94), prior heart failure (OR, 0.30; 95%CI, 0.19-0.49), and
159 being on angiotensin-converting enzyme inhibitors at admission (OR, 0.70; 95%CI,
160 0.53 to 0.92) were associated with lower probabilities. Patients from Latin America
161 (OR 0.04; 95% CI 0.02-0.11) and Eastern Europe (OR, 0.15; 95%CI, 0.06-0.35)
162 presented a lower probability of undergoing CAG than patients from Northern
163 Europe.

164 Independent predictors of not undergoing CR (Table S2 in the online-only
165 Data Supplement) among those who underwent CAG and had significant CAD
166 were prior cardiovascular disease (OR, 0.53; 95%CI, 0.42-0.67), prior coronary
167 artery bypass graft (OR, 0.45; 95%CI, 0.32-0.63), age >75 years (OR, 0.73;
168 95%CI, 0.55-0.98) and serum creatinine >1.2 mg/dl (OR, 0.76; 95%CI, 0.58-0.99)
169 were marginally associated with lower probabilities while male patients showed a
170 higher probability (OR, 1.34; 95%CI 1.04-1.72) . Patients from Latin America (OR
171 0.29; 95% CI 0.18-0.48) and Eastern Europe (OR, 0.50; 95%CI, 0.33-0.87)
172 presented a lower probability of undergoing revascularization after CAG than
173 patients from Northern Europe. Admission to private hospitals was associated to

174 an increased probability of being revascularised during hospitalization (OR, 2.19;
175 95%CI 1.14 to 4.20)

176

177 **In-hospital diagnostic and therapeutic procedures, and medical treatments** 178 **by management strategy**

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

189 **Outcomes by management strategy**

190 Medically managed patients had a greater incidence of in-hospital
191 cardiovascular complications, mainly heart failure and atrial fibrillation, particularly
192 among patients who did not undergo CAG (Table 3). The 2-year post discharge all-
193 cause mortality rate was 7.0% in the whole cohort, with significant differences
194 between CR and MM patients (4.4% vs 11%; $P < 0.001$) (Table 3, Figure 2A). A
195 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 cohort¹⁸ (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

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

221

222 **Discussion**

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

230 Patients surviving ACS are at high risk of subsequent cardiovascular events,
231 even if optimally treated.¹⁹ Despite recommendations by the main European
232 guidelines,^{1, 2} less than 60% of patients undergo CR during hospitalization for
233 NSTEMI-ACS. This is clinically relevant given the abundance of data coming from
234 randomized trials^{13, 20, 21} and observational studies²² suggesting an improvement in
235 mid- and long-term prognosis for patients with NSTEMI-ACS managed invasively. In
236 our study, the most frequent clinical situation associated with MM is lack of CAG
237 during hospitalization, which accounts for roughly half of MM cases. Our study is
238 consistent with previous studies using similar analytical methods insofar as older
239 and sicker patients are more often MM while younger and lower risk patients
240 consistently receive more aggressive treatment. This is also true among subgroups

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

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

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

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

278 **Limitations**

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

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

295 **Conclusions**

296 Medically managed patients with NSTEMI-ACS constitute a heterogeneous
297 group according to the clinical pathways leading to non-use of CAG or CR.
298 Compared with CR patients, those who do not undergo CAG during hospitalization
299 are older, and present with greater comorbidity. They also have the highest
300 adjusted mortality risk after discharge, followed by those not revascularized despite
301 significant CAD. Therefore, the clinical pathways leading to medical management
302 are clinically relevant and should be taken into consideration in studies addressing
303 this patient group, given the observed differences in baseline characteristics and
304 clinical outcomes. Continuing efforts are needed to improve compliance with
305 guidelines recommendations, particularly for NSTEMI-ACS patients admitted to
306 hospitals without a catheterization laboratory.
307

308 **Key points**

309 **What is known about the topic?**

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

318 **What does the study add?**

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

325

326

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449 acute coronary syndrome patients: Findings from the EPICOR study. *Eur*
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452

453 **Table 1. Baseline characteristics of non-ST-segment elevation acute coronary syndrome patients by management**
 454 **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%	
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
Atrial 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

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

459

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

461 ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, CAD, coronary artery disease; CAG, coronary
462 angiography; CR, coronary revascularization; GP, glycoprotein; LVEF, left ventricular ejection fraction; MM, medically managed; PCI,
463 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.

468 **Table 4. Hazard ratios for 2-year all-cause death in subgroups of medically**
 469 **managed versus revascularized NSTEMI-ACS patients by management**
 470 **strategy. Model adjusted for hospital type (regional, non-university general,**
 471 **university general, private) and geographical region, using a multi-level**
 472 **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)

473
 474 CAD, coronary artery disease; CAG, coronary angiography; NSTEMI-ACS, non ST-segment elevated
 475 acute coronary syndrome.

476 **Figure 1. Distribution of EPICOR NSTEMI-ACS patients according to initial**
477 **revascularization strategy and clinical pathways leading to medical**
478 **management**

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

482

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

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

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

491