

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

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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).<sup>1-3</sup>  
50 <sup>3</sup> 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.<sup>4-6</sup> This observation has triggered studies  
53 designed to evaluate specific therapeutic approaches for these patients.<sup>7-13</sup>  
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.<sup>14-16</sup> 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.<sup>14, 16</sup> 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-).<sup>17</sup>

## 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.<sup>18</sup>



## 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 cohort<sup>18</sup> (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.<sup>19</sup> Despite recommendations by the main European  
232 guidelines,<sup>1, 2</sup> 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<sup>13, 20, 21</sup> and observational studies<sup>22</sup> 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.<sup>23</sup> Moreover, our findings are consistent  
247 with the risk paradox found in several national and international registries,<sup>23-27</sup> 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.<sup>18</sup>

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.<sup>28</sup> 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.<sup>10</sup> 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%.<sup>7</sup> In EPICOR as in other studies,<sup>29</sup> 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.<sup>30</sup>

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,<sup>18</sup>  
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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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%	
<b>Diagnosis</b>							
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
<b>Basic characteristics</b>							
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
<b>CV risk factors</b>							
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
<b>Chronic kidney disease (n=5591)</b>	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
<b>Chronic CV medication</b>							
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.

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

		<b>Coronary Revascularization n=3285 58.8%</b>	<b>Medical Management n=2306 41.2%</b>	<b>P-Value (CR versus MM)</b>	<b>Medical Management</b>			<b>P-Value</b>
					<b>CAG- n=1186 21.2%</b>	<b>CAG+ CAD+ n=669 12.0%</b>	<b>CAG+ CAD- n=451 8.1%</b>	
<b>Antithrombotic Medications</b>								
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
<b>Diagnostic/therapeutic procedures</b>							
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%)						
<b>Other discharge medications</b>							
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

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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%	
<b>Hospital outcomes</b>							
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
<b>2-year outcomes</b>							
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**

<b>Adjusted for</b>	<b>Group</b>	<b>Hazard ratio for death vs revascularized</b>
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