CLINICAL RESEARCH STUDY

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Unstable Angina in the Era of Cardiac Troponin Assays with Improved Sensitivity—A Clinical Dilemma

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ABSTRACT

BACKGROUND: There is an expectation that with the adoption of more sensitive cardiac troponin (cTn) assays, unstable angina would become a rarity. However, recent data from the SWEDEHEART registry demonstrated that 15% of patients admitted with non-ST-elevation acute coronary syndrome still were regarded as having unstable angina. We aimed to further investigate the clinical characteristics and outcome of these patients.

METHODS: This was a retrospective, registry-based analysis (SWEDEHEART) including 3204 unstable patients, 18,194 non-ST-elevation myocardial infarction (NSTEMI) patients, and 977 controls without acute cardiovascular disease. All patients had available data on peak cTnT levels (more sensitive assay) and 1-year outcome.

RESULTS: The annual proportions of patients with unstable angina (2009-2013) among those with non-ST-elevation acute coronary syndrome ranged from 9.4% to 15.3%. Only 1239 unstable angina patients (39.7%) had a peak cTnT level ≤14 ng/L. Patients with unstable angina tended to be younger than those with NSTEMI but had higher prevalence of most cardiovascular risk factors and more advanced coronary artery disease. Compared with controls, the adjusted hazard ratios (95% confidence interval) regarding major cardiovascular events were 2.97 (1.30-6.78) and 5.44 (2.54-11.65) in unstable angina patients with peak cTnT ≤14 ng/L and >14 ng/L, respectively.

CONCLUSION: The diagnosis of unstable angina is still commonly used, even in the era of more sensitive cTn assays. Minor cTnT elevation is common, which makes unstable angina difficult to distinguish from NSTEMI. Patients with unstable angina have a nonneglectable cardiovascular risk. We suggest that the clinical management of patients presenting with unstable symptoms should depend on their estimated cardiovascular risk rather than on strictly applied diagnostic criteria.

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KEYWORDS: Acute coronary syndrome; Cardiac troponin; Risk prediction; Unstable angina

INTRODUCTION

More sensitive or high-sensitivity cardiac troponin (cTn) assays are increasingly used for the assessment of patients with acute chest pain. These assays have been shown to improve the detection of small cTn elevations due to myocardial infarction that would have been missed if conventional assays had been used.[1,2] This has resulted in an expectation that with the adoption of such assays, unstable angina, formally being a cTn-negative entity mainly relying on the clinical presentation, would become a rarity.[3] In fact, studies in chest pain patients indicate that the increase in the incidence of myocardial infarction after the shift from conventional to more sensitive cTn assays is mirrored by a decrease in the incidence of unstable angina.[4,5]

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Recent real-world data from the Swedish Web-system for enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, however, demonstrated a relative increase in the incidence of unstable angina by 13% among patients admitted to Swedish coronary care units after the implementation of the more sensitive cTnT assay.[6] The aim of the present study was to explore the reasons for this unexpected finding. In particular, we wanted to investigate the characteristics of patients labeled as having unstable angina on the basis of cTnT results measured using the more sensitive assay, the clinical management of these patients, and their risk of cardiovascular events compared with patients diagnosed with myocardial infarction.

CLINICAL SIGNIFICANCE

- The diagnosis of unstable angina is still commonly used, even in the era of more precise cardiac troponin assays.
- Elevated cardiac troponin levels are common in patients considered as having unstable angina.
- Unstable angina patients have a non-neglectable risk of adverse cardiovascular events.
- The clinical management of patients with unstable symptoms should depend on an estimation of their cardiovascular risk rather than on strictly applied diagnostic criteria.

METHODS

Study Population

This study is part of the Tailoring Of Treatment in All comers with Acute Myocardial Infarction (TOTAL-AMI) project. The primary aim of TOTAL-AMI is to investigate the mechanisms and implications of different subtypes of myocardial infarction[7] and of comorbidities (eg, chronic obstructive pulmonary disease, atrial fibrillation, renal dysfunction) in myocardial infarction. TOTAL-AMI uses data from SWEDEHEART, which is a nationwide registry enrolling consecutive patients admitted to Swedish coronary care units or other specialized facilities because of suspected acute coronary syndrome. The SWEDEHEART registry prospectively collects information on >100 variables, including peak levels of biomarkers of myocardial damage. On admission, patients receive written information about the registry and have the right to deny participation.

The study population consisted of patients admitted between 2009 and 2013 to hospitals using the more sensitive cTnT assay (Roche Diagnostics, Basel, Switzerland), with 14 ng/L as cut-off to define myocardial infarction.[7,8] Only first hospital admissions were considered. Elective admissions and patients with a discharge diagnosis of ST-elevation myocardial infarction were excluded. To reduce the potential bias of systematic reporting errors, patients were also excluded if biomarker results had been obtained within 1 week before or after a hospital implemented the more sensitive cTnT assay or if different cTn assays had been used in parallel at the same hospital.

Patients with the following discharge diagnoses were considered for this analysis: unstable angina (with acute chest pain as presenting symptom according to SWEDEHEART) and non-ST-elevation myocardial infarction (presenting symptom according to SWEDEHEART: not specified). Unstable angina patients were grouped into cohorts with peak cTnT ≤14 ng/L and >14 ng/L. In addition, we defined a control group consisting of patients with cTnT ≤14 ng/L and no angiographic evidence of significant (≥50%) coronary stenoses who had been discharged without a specified diagnosis.

All data had been made anonymous before the statistical analyses. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committees.

Prognostic Evaluation

Information on outcome was obtained from the Swedish Patient Registry (hospitalization dates and discharge diagnoses based on International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes) and the Swedish Cause of Death Registry. Outcomes relevant to the present analysis included all-cause mortality, cardiovascular mortality (all primary causes of death diagnosed with ICD-10-CM codes I00-I99), and nonfatal myocardial infarction (ICD-10-CM code I21) within 1 year from admission. We also assessed the composite outcomes of cardiovascular mortality/nonfatal myocardial infarction and major cardiovascular events, the latter defined as cardiovascular mortality, nonfatal myocardial infarction, admission for heart failure (ICD-10-CM code I50), or ischemic stroke (ICD-10-CM code I63). Because of the possibility that nonfatal events in some patients might have been reported repeatedly in the registry (eg, in case of transfer from one hospital to another), only such events occurring 30 days after the index hospitalization were counted.

Statistical Analysis

All continuous variables were skewed and are therefore reported as medians (with 25th and 75th percentiles). The Mann-Whitney *U* test was used for between-group comparisons. Categorical variables are expressed as frequencies and percentages, with differences being analyzed with the χ^2 test. Unstable angina patients with outlying cTnT values were identified using the method of Tukey.[9]

Cox regression models were used to investigate the associations of cTnT levels with outcome in the respective diagnostic groups. Covariates included admission year, age, sex, current smoking, hypertension, diabetes, previous myocardial infarction, heart failure, previous stroke, ST-segment depression, glomerular filtration rate, and in-hospital coronary revascularization. In addition, adjustment was made for hospital as a random effect in a mixed model. All continuous variables were transformed to their natural logarithm (ln) to achieve normality.

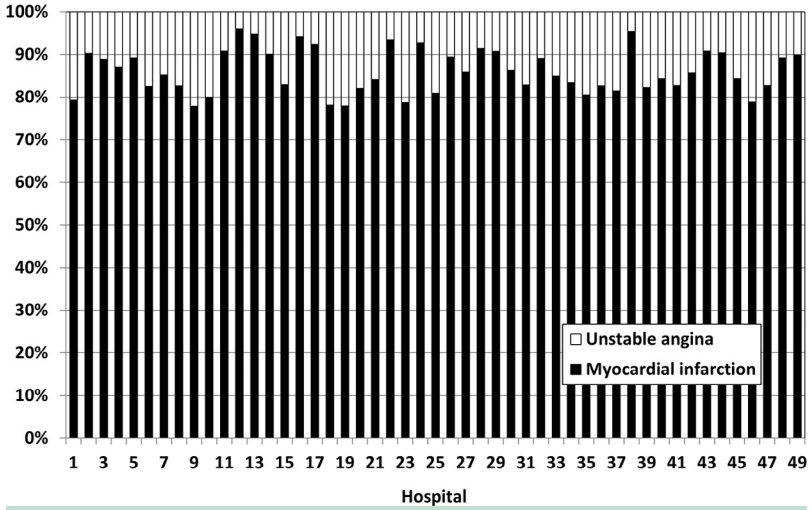

Figure 1 Proportions of patients with unstable angina among those with non-ST-elevation acute coronary syndrome per participating hospital in the Swedish Web-system for enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. Numbers of unstable angina patients admitted to the respective hospitals (listed per identification number assigned to each individual hospital in SWEDEHEART): 1: n = 41, 2: n = 39; 3: n = 12; 4: n = 28; 5: n = 71; 6: n = 48; 7: n = 105; 8: n = 103; 9: n = 51; 10: n = 179; 11: n = 33; 12: n = 16; 13: n = 13; 14: n = 29; 15: n = 82; 16: n = 8; 17: n = 35; 18: n = 205; 19: n = 23; 20: n = 111; 21: n = 41; 22: n = 30; 23: n = 244; 24: n = 14; 25: n = 172; 26: n = 15; 27: n = 28; 28: n = 35; 29: n = 60; 30: n = 57; 31: n = 165; 32: n = 95; 33: n = 84; 34: n = 41; 35: n = 98; 36: n = 87; 37: n = 103; 38: n = 15; 39: n = 43; 40: n = 60; 41: n = 155; 42: n = 81; 43: n = 17; 44: n = 11; 45: n = 28; 46: n = 75; 47: n = 52; 48: n = 36; 49: n = 72.

In all tests a 2-sided *P*-value <.05 was considered significant. The software packages SPSS 21.0 (IBM, Armonk, NY) and MedCalc 11.6 (MedCalc Software, Ostend, Belgium) were used for the statistical analyses.

RESULTS

The study population consisted of 22,375 patients following exclusions. A flowchart is presented in the Supplementary Figure (available online). In total, 3204 patients (14.3%) had received a diagnosis of unstable angina, 18,194 patients (81.3%) had non-ST-elevation myocardial infarction, and 977 patients (4.4%) served as controls. In total, 1239 unstable angina patients (39.7%) had a cTnT level ≤14 ng/L. The proportions of unstable angina patients among those with non-ST-elevation acute coronary syndrome (ie, unstable angina and non-ST-elevation myocardial infarction considered as 1 group) varied considerably between the hospitals, ranging from 4.0% to 22.2% (**Figure 1**). The proportions of unstable angina patients among those with non-ST-elevation acute coronary syndrome were 9.3% (24 of 257 patients) in 2009/2010, 14.2% (774 of 5452 patients) in 2011, 15.3% (1173 of 7652 patients) in 2012, and 15.3% (1233 of 8037 patients) in 2013. The corresponding proportions of unstable angina patients with cTnT ≤14 ng/L per admission year were 5.1% (13 of 257 patients), 6.0% (328 of 5452 patients), 5.8% (445 of 7652 patients), and 5.6% (453 of 8037 patients).

The median cTnT level (25th-75th percentiles) in patients with unstable angina was 18 (10-37) ng/L, compared with 276 (100-780) ng/L in patients with non-ST-elevation myocardial infarction. **Figure 2** demonstrates that cTnT levels in patients with unstable angina varied considerably between the hospitals. The method of Tukey identified 212 unstable angina patients with cTnT >118 ng/L as outliers.

Table 1 presents data on clinical characteristics, echocardiographic and angiographic findings, in-hospital treatments, and discharge medications. Compared with patients with non-ST-elevation myocardial infarction, those with unstable angina tended to have a higher prevalence of cardiovascular risk factors (apart from smoking) and more advanced coronary artery disease but less severe left ventricular systolic dysfunction. Unstable angina patients with cTnT >14 ng/L had a higher prevalence of cardiovascular risk features compared with those with cTnT ≤14 ng/L. Unstable angina patients overall were treated less often with subcutaneous/intravenous anticoagulants but more often underwent coronary interventions compared with patients with non-ST-elevation myocardial infarction. The rate of guideline-recommended discharge medications was high in patients with unstable angina.

The crude event rates and adjusted hazard ratios are presented in **Tables 2** and **3**. There were gradients of increasing adjusted 1-year event risks across the diagnostic cohorts. For most outcomes, unstable angina patients with cTnT ≤14 ng/L

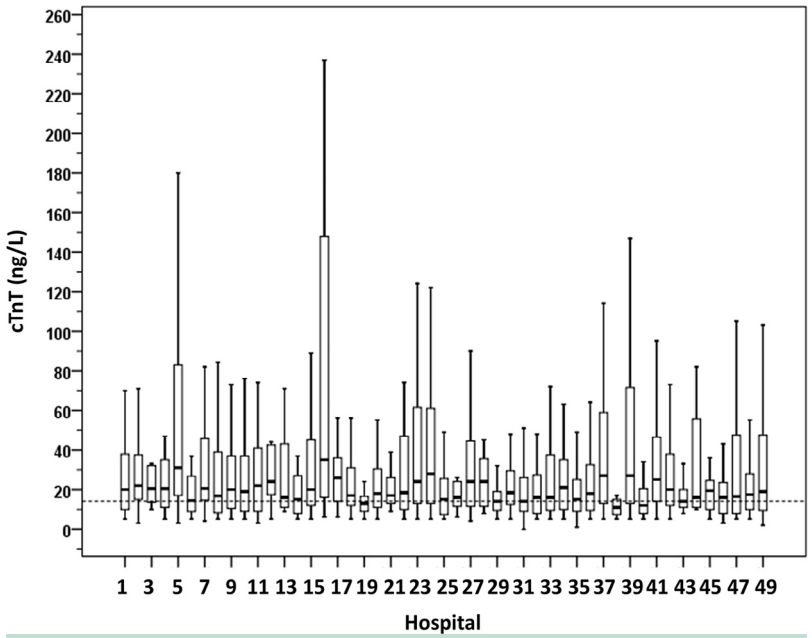

Figure 2 Cardiac troponin T levels in patients with unstable angina per participating hospital in the SWEDEHEART registry. The dotted line represents the diagnostic cTnT cut-off (14 ng/L). The number of unstable angina patients per hospital is the same as given in the footnote of Figure 1.

had significantly higher adjusted risks compared with controls, acknowledging the small number of events. Unstable angina patients with cTnT >14 ng/L had 66%-97% higher adjusted risks compared with those with cTnT ≤14 ng/L (data not shown). Patients with non-ST-elevation myocardial infarction had 70%-145% higher adjusted risks compared with unstable angina patients overall (data not shown). Among patients with non-ST-elevation acute coronary syndrome having comparable cTnT levels (ie, cTnT 15-118 ng/L), those discharged with a diagnosis of non-ST-elevation myocardial infarction had 24%-38% higher adjusted risks compared with those discharged with a diagnosis of unstable angina, a difference that did not reach formal significance regarding all-cause mortality and cardiovascular mortality (**Table 4**). There was a significant interaction of the individual hospitals (per identification number assigned to each hospital in SWEDEHEART) on the association of the discharge diagnosis (unstable angina vs non-ST-elevation myocardial infarction) with major cardiovascular events ($P = .010$).

We performed sensitivity analyses to ascertain the validity of our results. First, patients discharged with a diagnosis of stable angina were considered as having unstable angina if they had been admitted nonelectively, presented with acute chest pain, and if coronary angiography revealed significant (>50%) coronary stenoses. A total of 1383 patients with stable angina fulfilled these criteria. Supplementary Table 1 (available online) demonstrates that these patients tended to be somewhat sicker compared with unstable angina patients, with a higher prevalence of atrial fibrillation and heart failure. The median cTnT level in the 1383 stable angina patients, now considered as having unstable angina, was 17 (10-38) ng/L, similar as for the remaining unstable angina patients ($P = .179$). The event rates in both cohorts did not differ significantly (data not shown). Accordingly, the prognostic estimates for the extended unstable angina cohort remained largely unchanged (Supplementary Table 2, available online). Second, we restricted our analysis to patients with non-ST-elevation myocardial infarction in whom chest pain had been specified as the presenting symptom in SWEDEHEART (n = 14,701). Supplementary Table 3 (available online) demonstrates that these patients had lower prevalence of cardiovascular risk features compared with patients with non-ST-elevation myocardial infarction and atypical or unspecified symptoms. The crude event rates in patients with non-ST-elevation myocardial infarction admitted with chest pain were lower compared with patients with non-ST-elevation myocardial infarction having atypical or unspecified symptoms (Supplementary Table 4, available online), but their 1-year event risks were still 56%-108% higher compared with unstable angina patients in adjusted analyses (data not shown).

DISCUSSION

The adoption of cTn assays with improved analytical sensitivity has resulted in an expectation that true cTn-negative unstable angina would become a rarity, if not extinct.[3] In fact, studies in chest pain patients assessed with newer, more precise cTn assays demonstrated a relative drop in the incidence of unstable angina by 35%-61%, down to 8%-9%.[4,5] Our results from a large registry-based study of patients admitted with a clinical suspicion of acute coronary syndrome provides provocative results that contrast with these data. We noted that

Table 1 Baseline Characteristics

Characteristic	Controls (n = 977)	Unstable Angina with cTnT ≤14 ng/L (n = 1239)	Unstable Angina with cTnT >14 ng/L (n = 1965)	NSTEMI (n = 18,194)	*P* value*	*P* value†
Risk factors						
Male	487 (49.8)	886 (71.5)	1469 (74.8)	11.413 (62.7)	.044	<.001
Age (y)	58 (50-66)	65 (58-72)	71 (63-78)	73 (64-82)	<.001	<.001
Current smoking	171 (17.5)	198 (16.0)	264 (13.4)	3243 (17.8)	.050	<.001
Hypertension	371 (38.3)	670 (54.1)	1158 (59.0)	9975 (54.8)	.007	.020
Diabetes	117 (12.0)	293 (23.6)	528 (26.9)	4390 (24.1)	.042	.070
Hyperlipidemia	252 (25.8)	655 (52.9)	966 (49.2)	6496 (35.7)	.042	<.001
Body mass index (kg/m^2)	26.7 (24.0-30.0)	27.1 (24.6-29.8)	27.1 (24.6-30.0)	26.5 (23.9-29.4)	.852	<.001
eGFR (mL/min/1.73 m^2)	84.7 (74.0-96.8)	84.7 (73.3-98.1)	78.0 (63.1-92.2)	75.1 (57.9-90.9)	<.001	<.001
History						
Previous MI	74 (7.6)	362 (29.2)	690 (35.1)	5149 (28.3)	.001	<.001
Previous PCI/CABG	72 (7.4)	459 (37.0)	751 (38.2)	4184 (23.0)	.525	<.001
Heart failure	21 (2.1)	67 (5.4)	186 (9.5)	1854 (10.2)	<.001	<.001
Previous stroke	23 (2.4)	47 (3.8)	151 (7.7)	1860 (10.2)	<.001	<.001
Medication on admission						
Aspirin	250 (25.6)	665 (53.7)	1082 (55.1)	7888 (43.4)	.445	<.001
P2Y12 blockers	30 (3.1)	158 (12.8)	222 (11.3)	1347 (7.4)	.218	<.001
Oral anticoagulants	22 (2.3)	66 (5.3)	153 (7.8)	1176 (6.5)	.008	.439
β-Blockers	251 (25.7)	628 (50.7)	963 (49.0)	7772 (42.7)	.365	<.001
RAAS inhibitors	230 (23.6)	529 (42.7)	956 (48.9)	7503 (41.5)	.001	<.001
Statins	252 (25.9)	653 (52.7)	960 (49.1)	6474 (35.8)	.046	<.001
ECG findings						
Sinus rhythm	953 (97.7)	1177 (95.0)	1761 (89.7)	15,428 (85.0)	<.001	<.001
Atrial fibrillation/flutter	16 (1.6)	49 (4.0)	154 (7.8)	2144 (11.8)	<.001	<.001
ST-depression	112 (11.5)	167 (13.5)	396 (20.2)	5685 (31.3)	<.001	<.001
In-hospital examinations						
Echocardiography‡	598 (61.1)	804 (65.1)	1377 (70.1)	13,518 (74.3)	.004	<.001
LVEF ≥0.50	573 (95.8)	723 (90.5)	1079 (79.7)	8700 (64.7)	<.001	<.001
LVEF 0.40-0.49	22 (3.7)	62 (7.8)	168 (12.2)	2510 (18.7)		
LVEF 0.30-0.39	3 (0.5)	11 (1.4)	73 (5.3)	1468 (10.9)		
LVEF <0.30	0	3 (0.4)	38 (2.8)	770 (5.7)		
Coronary angiography§	977 (100)	1102 (88.9)	1714 (87.2)	13,015 (71.5)	.149	<.001
Normal	–	89 (8.2)	110 (6.5)	1579 (12.3)	<.001	<.001
1-2 vessel disease	–	698 (64.2)	968 (57.4)	7286 (57.0)		
LM/3 vessel disease	–	301 (27.7)	609 (36.1)	3927 (30.7)		
In-hospital treatments						
SC/IV anticoagulants	356 (36.4)	652 (52.6)	1248 (63.5)	14,106 (77.5)	<.001	<.001
PCI/CABG	56 (5.7)	970 (78.3)	1423 (72.4)	10,087 (55.4)	<.001	<.001
Medication at discharge‖						
Aspirin	342 (35.0)	1165 (94.1)	1806 (92.1)	16,062 (91.6)	.040	.018
P2Y12 blockers	43 (4.4)	912 (73.7)	1424 (72.7)	13,496 (77.0)	.540	<.001
Oral anticoagulants	20 (2.0)	80 (6.5)	192 (9.8)	1632 (9.3)	.001	.153
β-blockers	349 (35.8)	1018 (82.2)	1589 (81.1)	15,240 (87.0)	.427	<.001
RAAS inhibitors	318 (32.6)	825 (66.6)	1419 (72.4)	13,149 (75.0)	.001	<.001
Statins	393 (40.3)	1159 (93.6)	1791 (91.4)	14,972 (85.4)	.021	<.001

Data are given as number (percentage) or median (25th-75th percentile). Patients with missing data were excluded from the analyses.

CABG = coronary artery bypass grafting; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LM = left main; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; RAAS = renin–angiotensin–aldosterone system; SC/IV = subcutaneous/intravenous.

**P* values refer to comparisons between unstable angina patients with cTnT ≤14 ng/L and >14 ng/L.

†*P* values refer to comparisons between patients with unstable angina and NSTEMI.

‡Available information on LVEF: n = 16,221.

§Available information on angiographic findings: n 16,544.

‖Data from hospital survivors; n = 21,701.

Table 2 Prognostic Evaluation: Crude Event Rates

Parameter	Controls (n = 977)	Unstable Angina with cTnT ≤14 ng/L (n = 1239)	Unstable Angina with cTnT >14 ng/L (n = 1965)	NSTEMI (n = 18,194)
All-cause mortality	6 (0.6)	15 (1.2)	103 (5.2)	2622 (14.4)
CV mortality	2 (0.2)	8 (0.6)	52 (2.6)	1636 (9.0)
CV mortality/nonfatal MI	6 (0.6)	23 (1.9)	112 (5.7)	2315 (12.7)
MACE	7 (0.7)	33 (2.7)	163 (8.3)	2842 (15.6)

Data are given as number (percentage).
CV = cardiovascular; MACE = major cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction.

roughly 15% of patients admitted with non-ST-elevation myocardial acute coronary syndrome received a diagnosis of unstable angina. There was no trend toward smaller proportions of unstable angina with more time elapsed from the introduction of the more sensitive cTnT assay, which would have been expected if there had been a learning curve among clinicians.

Patients with unstable angina differed from those with non-ST-elevation myocardial infarction in several aspects. They tended to be younger and had a higher prevalence of most cardiovascular risk factors and less pronounced left ventricular systolic dysfunction, but they had a greater burden of coronary artery disease. A total of 1239 unstable angina patients (39.7%) had a peak cTnT level ≤14 ng/L (ie, below the diagnostic cut-off for myocardial infarction) and could have been regarded as having true cTn-negative unstable angina. The remaining unstable angina patients (ie, the majority) had a peak cTnT level >14 ng/L. Unfortunately, we cannot present data on cTnT changes in these patients because such information is not registered in SWEDEHEART. Some of the unstable angina patients with cTnT >14 ng/L might have presented with unstable symptoms but stable cTnT elevation due to chronic conditions, such as structural heart disease or end-stage renal failure. Dynamic cTnT changes, a prerequisite for the diagnosis of myocardial infarction,[7] might also have been lacking in some late presenters with small infarctions who had reached a cTnT plateau across serial measurements,[10] and these patients might accordingly have been labeled as having unstable angina instead of non-ST-elevation myocardial infarction. We assume that these patients are more frequently detected when using a more sensitive cTn assay with improved low-end precision. The importance of these issues has been emphasized in a recent position paper from Sandoval et al.[11]

Patients regarded as having unstable angina had a considerable risk of mortality and cardiovascular events. The risk among unstable angina patients increased along with higher cTnT levels. However, even true unstable angina patients with

Table 3 Prognostic Evaluation: Adjusted Hazard Ratios

Parameter	Controls (n = 869) (HR)	Unstable Angina with cTnT ≤14 ng/L (n = 1155)		Unstable Angina with cTnT >14 ng/L (n = 1840)		NSTEMI (n = 17,335)	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause mortality	Ref.	2.06 (0.79-5.39)	<.001	4.43 (1.93-10.16)	<.001	8.14 (3.63-18.23)	<.001
CV mortality	Ref.	3.14 (0.67-14.83)	.148	5.53 (1.34-22.84)	.018	12.22 (3.04-49.15)	<.001
CV mortality/nonfatal MI	Ref.	2.67 (1.08-6.61)	.034	4.34 (1.90-9.94)	.001	7.41 (3.31-16.61)	<.001
MACE	Ref.	2.97 (1.30-6.78)	.010	5.44 (2.54-11.65)	<.001	8.15 (3.86-17.19)	<.001

Analyses adjusted for admission year, hospital, age, sex, current smoking, hypertension, diabetes, previous myocardial infarction, heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate and in-hospital revascularization.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction.

Table 4 Crude Event Rates and Adjusted Hazard Ratios in Patients with Non-ST-Elevation Acute Coronary Syndrome and cTnT 15-188 ng/L

Parameter	Unstable Angina (n = 1753)		NSTEMI (n = 5143)		
	Crude Event Rate, n (%)	HR (95% CI [n = 1645])	Event Rate, n (%)	HR (95% CI [n = 4878])	*P* value
All-cause mortality	86 (4.9)	Ref.	412 (8.0)	1.27 (1.00-1.62)	.055
CV mortality	47 (2.7)	Ref.	234 (4.5)	1.31 (0.94-1.82)	.114
CV mortality/nonfatal MI	94 (5.4)	Ref.	425 (8.3)	1.38 (1.09-1.75)	.007
MACE	137 (7.8)	Ref.	553 (10.8)	1.24 (1.04-1.51)	.036

Analyses adjusted for admission year, hospital, age, sex, current smoking, hypertension, diabetes, previous myocardial infarction, heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate, and in-hospital revascularization.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction.

cTnT ≤14 ng/L had crude event rates that were twice as high as compared with controls. Notably, for patients labeled with unstable angina having moderate cTnT elevation (ie, cTnT 15-118 ng/L), the mortality risk approached estimates seen in patients with non-ST-elevation myocardial infarction and a similar degree of cTnT elevation.

Interaction analyses indicated that the prognostic implications of a diagnosis of unstable angina (vs non-ST-elevation myocardial infarction) varied between the hospitals participating in SWEDEHEART. This suggests that variations in the local perception of unstable angina as a clinical entity exist despite rather homogeneous routines for the management of non-ST-elevation acute coronary syndrome in Sweden.[12,13] However, these potential variations were not reflected by temporal changes in the proportions of unstable angina patients among those admitted with non-ST-elevation acute coronary syndrome. It is also noteworthy that the adherence to guideline-recommended treatments was high in patients with unstable angina.

Our data emphasize that improved criteria to define unstable angina clearly are needed. In the context of more precise cTn assays, the current dichotomization of patients with non-ST-elevation acute coronary syndrome into cTn-positive and cTn-negative entities is no longer appropriate, as discussed above. Unfortunately, this not only applies to the distinction between unstable angina and non-ST-elevation myocardial infarction but also to the distinction between unstable angina and high-risk stable angina, as demonstrated by our first sensitivity analysis. Clinical criteria are, thus, unreliable estimates for diagnostic classifications. In the absence of true and reliable myocardial ischemia markers, this poses a clinical challenge that is further fueled by the 2015 European Society of Cardiology guidelines, suggesting assessment of unstable angina patients in the outpatient setting.[14] Recent data from a large cohort of Swedish chest pain patients with cTnT >14 ng/L but considered as having no myocardial infarction demonstrated a considerable degree of underinvestigation, with rates of echocardiography and stress testing of only 33% and 5%, respectively.[15] The need for better-defined management routines in these patients is obvious.

There are ways out of this dilemma. Managing patients with unstable symptoms depending on their cardiovascular risk might overcome the problems related to the strict adherence to diagnostic classifications, acknowledging their inherent uncertainties. Such an approach would also take into account the fact that acute presentations of coronary artery disease encompass a continuum ranging from stable angina to large myocardial infarction with corresponding gradients of risk, rather than entities that are strictly distinct from each other. Examples of more complex although easy-to-use risk prediction tools are the History, Electrocardiogram, Age, Risk factors and initial Troponin score[16] and the 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker pathway,[17] both incorporating cTn results and having been shown to perform well.

Our study has limitations that need to be considered. Only peak cTnT values are registered in SWEDEHEART. For this reason we are unable to present data distinguishing unstable angina from non-ST-elevation myocardial infarction on the basis of dynamic cTnT changes, which moreover might have been handled in different ways at the individual hospitals participating in SWEDEHEART. However, a relative cTn change by 50% is suggested as a diagnostic criterion for myocardial infarction in SWEDEHEART.[18] We lack information on the timing of cTnT measurements. As such, some of the peak values in unstable angina patients may have occurred after coronary interventions and represent type 4a myocardial infarction,[7] an entity that had not been systematically documented in SWEDEHEART during the observation period. Although all hospitals participating in SWEDEHEART are regularly monitored, the data cannot be of the same quality as in a prospective observational study. However, a monitor annually evaluates the correctness of the data entered in the registry, and the agreement with the medical records is approximately 96%.[12] Despite multiple quality checks, we cannot exclude erroneous registrations of cTnT results or misdiagnosis in some cases, in particular because the diagnoses were set by the treating physicians without central adjudication. SWEDEHEART registers admissions to coronary care units or other specialized facilities. Selection bias might to some degree have contributed to the greater proportion of unstable angina patients compared with other studies.[4,5] For the same reason, our results cannot be extrapolated to patients seen at the emergency department, and we cannot comment on the efficacy of strategies for ruling in or ruling out of non-ST-elevation myocardial infarction[14] because of the lack of serial cTnT results.

CONCLUSIONS

Our results from a large cohort of real-world patients demonstrate that the diagnosis of unstable angina still is commonly used, even in the era of cTn assays with improved sensitivity. The proportion of true cTn-negative unstable angina among patients admitted with non-ST-elevation acute coronary syndrome is 5%-6%. However, even patients with elevated cTn levels are quite often regarded as having unstable angina and are difficult to distinguish from those with non-ST-elevation myocardial infarction. For this reason, we suggest that the clinical management of patients presenting with unstable symptoms should depend on an estimation of their cardiovascular risk rather than on strictly applied diagnostic criteria.

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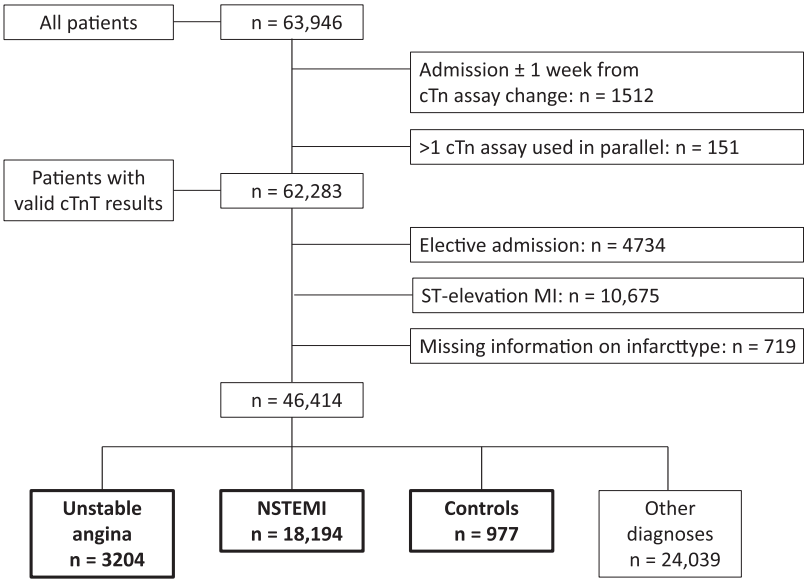
SUPPLEMENTARY DATA

Supplementary Material accompanying this article can be found in the online version at doi:10.1016/j.amjmed.2017.05.037.

APPENDIX



Supplementary Figure Flowchart—selection of patients. MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction.

Supplementary Table 1 Sensitivity Analysis—Baseline Characteristics in Patients with Unstable Angina, Including High-Risk Stable Angina Patients, Compared with Patients with Non-ST-Elevation Myocardial Infarction

	Discharge Diagnosis			New Diagnostic Classification		
Characteristic	Stable Angina (n = 1383)	Unstable Angina (n = 3204)	*P* value	Unstable Angina (n = 4587)	NSTEMI (n = 18,194)	*P* value
Risk factors						
Male	1029 (74.4)	2355 (73.5)	.534	3384 (73.8)	11.413 (62.7)	<.001
Age (y)	69 (62-76)	69 (61-76)	.128	69 (61-76)	73 (64-82)	<.001
Current smoking	179 (12.9)	462 (14.4)	.194	641 (14.0)	3243 (17.8)	<.001
Hypertension	818 (51.9)	1828 (57.1)	.268	2642 (57.6)	9975 (54.8)	.001
Diabetes	377 (27.3)	821 (25.6)	.256	1198 (26.1)	4390 (24.1)	.006
Hyperlipidemia	839 (60.7)	1621 (50.6)	<.001	2460 (53.6)	6496 (35.7)	<.001
BMI (kg/m^2)	27.1 (24.6-30.1)	27.1 (24.6-29.9)	.814	27.1 (24.6-30.0)	26.5 (23.9-29.4)	<.001
eGFR (mL/min/1.73 m^2)	79.0 (65.5-91.3)	81.2 (66.7-94.9)	<.001	80.1 (66.7-93.6)	75.1 (57.9-90.9)	<.001
History						
Previous MI	616 (44.5)	1052 (32.8)	<.001	1668 (36.4)	5149 (28.3)	<.001
Previous PCI/CABG	721 (52.1)	1210 (37.8)	<.001	1931 (42.1)	4184 (23.0)	<.001
Heart failure	159 (11.5)	253 (7.9)	<.001	412 (9.0)	1854 (10.2)	.016
Previous stroke	106 (7.7)	198 (6.2)	.070	304 (6.6)	1860 (10.2)	<.001
Medication on admission						
Aspirin	875 (63.3)	1747 (54.5)	<.001	2622 (57.2)	7888 (43.4)	<.001
P2Y12 blockers	206 (14.9)	380 (11.9)	.005	586 (12.8)	1347 (7.4)	<.001
Oral anticoagulants	135 (9.8)	219 (6.8)	.001	354 (7.7)	1176 (6.5)	.003
β-Blockers	797 (57.6)	1591 (49.7)	<.001	2388 (52.1)	7772 (42.7)	<.001
RAAS inhibitors	734 (53.3)	1485 (46.5)	<.001	2219 (48.5)	7503 (41.5)	<.001
Statins	836 (60.7)	1613 (50.5)	<.001	2449 (53.6)	6474 (35.8)	<.001
ECG findings						
Sinus rhythm	1203 (87.0)	2938 (91.7)	<.001	4141 (90.3)	15,428 (85.0)	<.001
Atrial fibrillation/flutter	129 (9.3)	203 (6.3)	<.001	332 (7.2)	2144 (11.8)	<.001
ST-depression	233 (16.8)	536 (17.6)	.581	796 (17.4)	5685 (31.3)	<.001
cTnT (ng/L)	17 (10-38)	18 (10-37)	.179	18 (10-37)	276 (100-780)	<.001
In-hospital examinations						
Echocardiography*	863 (62.4)	2184 (68.2)	<.001	3047 (66.4)	13,518 (74.3)	<.001
LVEF ≥0.50	663 (77.1)	1820 (83.7)	<.001	2483 (81.8)	8700 (64.7)	<.001
LVEF 0.40-0.49	103 (12.0)	230 (10.6)		333 (11.0)	2510 (18.7)	
LVEF 0.30-0.39	57 (6.6)	84 (3.9)		141 (4.6)	1468 (10.9)	
LVEF <0.30	37 (4.3)	41 (1.9)		78 (2.6)	770 (5.7)	
Coronary angiography†	1383 (100)	2816 (89.7)	-	4065 (88.6)	13,015 (71.5)	<.001
Normal	0	199 (7.2)	-	199 (4.8)	1579 (12.3)	<.001
1-2 vessel disease	854 (61.7)	1666 (60.0)		2520 (60.6)	7286 (57.0)	
LM/3 vessel disease	529 (38.3)	910 (32.8)		1439 (34.6)	3927 (30.7)	
In-hospital treatments						
SC/IV anticoagulants	647 (46.8)	1900 (59.3)	<.001	2547 (55.5)	14,106 (77.5)	<.001
PCI/CABG	731 (52.9)	2393 (74.7)	<.001	3124 (68.1)	10,087 (55.4)	<.001
Medication at discharge‡						
Aspirin	1242 (90.1)	2971 (92.9)	.002	4213 (92.1)	16,062 (91.6)	.366
P2Y12 blockers	761 (55.2)	2336 (73.0)	<.001	3097 (67.7)	13,496 (77.0)	<.001
Oral anticoagulants	182 (13.2)	272 (8.5)	<.001	454 (9.9)	1632 (9.3)	.211
β-Blockers	1193 (82.7)	2607 (81.5)	.380	3746 (81.9)	15,240 (87.0)	<.001
RAAS inhibitors	950 (68.9)	2244 (70.2)	.420	3194 (69.8)	13,149 (75.0)	<.001
Statins	1259 (91.4)	2950 (92.2)	.314	4209 (92.0)	14,972 (85.4)	<.001

Data are given as numbers (percentages) or median (25th-75th percentiles). Patients with missing data were excluded from the analyses.

BMI = body mass index; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LM = left main; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; RAAS = renin–angiotensin–aldosterone system; SC/IV = subcutaneous/intravenous.

*Available information on LVEF: n = 16,483.

†Available information on angiographic findings: n = 16,950.

‡Data from hospital survivors; n = 22,103.

Supplementary Table 2 Sensitivity Analysis—Crude Event Rates and Adjusted Hazard Ratios in Patients with Unstable Angina, Including High-Risk Stable Angina Patients, Compared with Patients with Non-ST Elevation Myocardial Infarction

	Controls (n = 977)		Unstable Angina (n = 4587)			NSTEMI (n = 18,194)		
Variable	Crude Event Rate, n (%)	HR (95% CI [n = 869])	Crude Event Rate, n (%)	HR (95% CI [n = 4302])	*P* value	Crude Event Rate, n (%)	HR (95% CI [n = 17,335])	*P* value
All-cause mortality	6 (0.6)	Ref.	171 (3.7)	3.55 (1.57-8.06)	.002	2622 (14.4)	7.99 (3.57-17.90)	<.001
CV mortality	2 (0.2)	Ref.	94 (2.0)	4.96 (1.22-20.21)	.026	1636 (9.0)	12.00 (2.98-48.28)	<.001
CV mortality/MI	6 (0.6)	Ref.	192 (4.2)	3.48 (1.53-7.88)	.003	2315 (12.7)	7.28 (3.25-16.31)	<.001
MACE	7 (0.7)	Ref.	291 (6.3)	4.51 (2.12-9.59)	<.001	2842 (15.6)	7.98 (3.78-16.84)	<.001

Analyses adjusted for admission year, hospital, age, sex, current smoking, hypertension, diabetes, previous myocardial infarction, heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate, and in-hospital revascularization.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major cardiovascular events.; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction.

Supplementary Table 3 Sensitivity Analysis—Baseline Characteristics in Patients with Unstable Angina Compared with Patients with Non-ST-Elevation Myocardial Infarction with Chest Pain or Atypical/Unspecified Symptoms

	Discharge Diagnosis			New Diagnostic Classification		
Variable	NSTEMI with Chest Pain (n = 14,701)	NSTEMI without Chest Pain (n = 3423)	*P* value	Unstable Angina (n = 3204)	NSTEMI with Chest Pain (n = 14,701)	*P* value
Symptoms at presentation						
Chest pain	14,701 (100)	0	–	–	–	–
Dyspnea		1688 (49.3)	–	–	–	–
Cardiac arrest		158 (4.6)	–	–	–	–
Other		1563 (45.7)	–	–	–	–
Unknown		14 (0.4)	–	–	–	–
Risk factors						
Male	9538 (64.9)	1830 (53.5)	<.001	2355 (73.5)	9538 (64.9)	<.001
Age (y)	72 (62-81)	78 (69-85)	<.001	69 (61-76)	72 (62-81)	<.001
Current smoking	2699 (18.4)	531 (15.5)	<.001	462 (14.4)	2699 (18.4)	<.001
Hypertension	8044 (54.7)	1901 (55.5)	.391	1828 (57.1)	8044 (54.7)	.016
Diabetes	3381 (23.0)	994 (29.0)	<.001	821 (25.6)	3381 (23.0)	.002
Hyperlipidemia	5281 (35.9)	1193 (34.9)	.243	1621 (50.6)	5281 (35.9)	<.001
BMI (kg/m^2)	26.6 (24.1-29.7)	25.6 (22.8-29.0)	<.001	27.1 (24.6-29.9)	26.6 (24.1-29.7)	<.001
eGFR (mL/min/1.73 m^2)	77.0 (60.5-91.3)	65.9 (46.8-84.6)	<.001	81.2 (66.7-94.9)	77.0 (60.5-91.3)	<.001
History						
Previous MI	4222 (28.7)	905 (26.4)	.008	1052 (32.8)	4222 (28.7)	<.001
Previous PCI/CABG	3563 (24.2)	601 (17.6)	<.001	1210 (37.8)	3563 (24.2)	<.001
Heart failure	1330 (9.0)	523 (15.3)	<.001	253 (7.9)	1330 (9.0)	.025
Previous stroke	106 (7.7)	198 (6.2)	<.001	198 (6.2)	106 (7.7)	<.001
Medication on admission						
Aspirin	6300 (42.9)	1566 (45.7)	.002	1747 (54.5)	6300 (42.9)	<.001
P2Y12 blockers	1075 (7.3)	264 (7.7)	.426	380 (11.9)	1075 (7.3)	<.001
Oral anticoagulants	905 (6.2)	269 (7.9)	<.001	219 (6.8)	905 (6.2)	.158
β-Blockers	6231 (42.4)	1512 (44.2)	.057	1591 (49.7)	6231 (42.4)	<.001
RAAS inhibitors	5976 (40.8)	1505 (44.5)	<.001	1485 (46.5)	5976 (40.8)	<.001
Statins	5263 (35.9)	1189 (35.1)	.360	1613 (50.5)	5263 (35.9)	<.001
ECG findings						
Sinus rhythm	12,804 (87.7)	2608 (76.2)	<.001	2938 (91.7)	12,804 (87.7)	<.001
Atrial fibrillation/flutter	1526 (10.4)	617 (18.0)	<.001	203 (6.3)	1526 (10.4)	<.001
ST-depression	4601 (31.3)	1076 (31.4)	.887	536 (17.6)	4601 (31.3)	<.001
cTnT (ng/L)	258 (93-748)	349 (141-942)	<.001	18 (10-37)	258 (93-748)	<.001
In-hospital examinations						
Echocardiography*	11,058 (75.2)	2409 (70.4)	<.001	2184 (68.2)	11,058 (75.2)	<.001
LVEF ≥0.50	7609 (69.1)	1050 (44.0)	<.001	1820 (83.7)	7609 (69.1)	<.001
LVEF 0.40-0.49	1969 (17.9)	537 (22.5)		230 (10.6)	1969 (17.9)	
LVEF 0.30-0.39	988 (9.0)	477 (20.0)		84 (3.9)	988 (9.0)	
LVEF <0.30	442 (4.0)	325 (13.6)		41 (1.9)	442 (4.0)	
Coronary angiography†	11,319 (77.0)	1627 (47.5)	<.001	2816 (87.9)	11,319 (77.0)	<.001
Normal	1296 (11.7)	277 (17.2)	<.001	199 (7.2)	1296 (11.7)	<.001
1-2 vessel disease	6491 (58.4)	754 (46.8)		1666 (60.0)	6491 (58.4)	
LM/3 vessel disease	3328 (29.9)	581 (36.0)		910 (32.8)	3328 (29.9)	
In-hospital treatments						
SC/IV anticoagulants	11,669 (79.4)	2384 (69.6)	<.001	1900 (59.3)	11,669 (79.4)	<.001
PCI/CABG	8943 (60.8)	1081 (31.6)	<.001	2393 (74.7)	8943 (60.8)	<.001
Medication at discharge‡						
Aspirin	13,337 (93.0)	2662 (85.5)	<.001	2971 (92.9)	13,337 (93.0)	.911
P2Y12 blockers	11,513 (80.3)	1922 (61.7)	<.001	2336 (73.0)	11,513 (80.3)	<.001
Oral anticoagulants	1252 (8.7)	375 (12.0)	<.001	272 (8.5)	1252 (8.7)	.701
β-Blockers	12,615 (87.9)	2563 (82.3)	<.001	2607 (81.5)	12,615 (87.9)	<.001
RAAS inhibitors	10,896 (76.0)	2205 (70.8)	<.001	2244 (70.2)	10,896 (76.0)	<.001
Statins	12,642 (88.1)	2267 (72.8)	<.001	2950 (92.2)	12,642 (88.1)	<.001

Data are given as number (percentages) or median (25th-75th percentiles). Patients with missing data were excluded from the analyses.

BMI = body mass index; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LM = left main; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; RAAS = renin–angiotensin–aldosterone system; SC/IV = subcutaneous/intravenous.

*Available information on LVEF: n = 15,572.

†Available information on angiographic findings: n = 15,502.

‡Data from hospital survivors; n = 20,658.

Supplementary Table 4 Sensitivity Analysis—Crude Event Rates and Adjusted Hazard Ratios in Patients with Unstable Angina Compared with Patients with Non-ST-Elevation Myocardial Infarction with Chest Pain as Presenting Symptom or Atypical/Unspecified Symptoms

	Controls (n = 977)		Unstable Angina (n = 3204)			NSTEMI (n = 14,701)		
Variable	Crude Event Rate, n (%)	HR (95% CI [n = 869])	Crude Event Rate, n (%)	HR (95% CI [n = 2995])	*P* value	Crude Event Rate, n (%)	HR (95% CI [n = 14,092])	*P* value
All-cause mortality	6 (0.6)	Ref.	118 (3.7)	3.46 (1.51-7.92)	.001	1637 (11.1)	6.18 (2.75-13.88)	<.001
CV mortality	2 (0.2)	Ref.	60 (1.9)	4.43 (1.07-18.27)	.026	1024 (7.0)	9.30 (2.31-37.54)	.002
CV mortality/MI	6 (0.6)	Ref.	135 (4.2)	3.64 (1.59-8.31)	.002	1586 (10.8)	6.47 (2.88-14.54)	<.001
MACE	7 (0.7)	Ref.	196 (6.1)	4.44 (2.08-9.50)	<.001	1950 (13.3)	6.94 (3.28-14.67)	<.001

Analyses adjusted for admission year, hospital, age, sex, current smoking, hypertension, diabetes, previous myocardial infarction, heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate, and in-hospital revascularization.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction.