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Implications of Introducing High-Sensitivity Cardiac Troponin T Into Clinical Practice

Data From the SWEDEHEART Registry

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ABSTRACT

BACKGROUND Cardiac troponin is the preferred biomarker for diagnosing myocardial infarction (MI).

OBJECTIVES The aim of this study was to examine the implications of introducing high-sensitivity cardiac troponin T (hs-cTnT) into clinical practice and to define at what hs-cTnT level risk starts to increase.

METHODS We analyzed data from 48,594 patients admitted because of symptoms suggesting an acute coronary syndrome and who were entered into a large national registry. Patients were divided into Group 1, those with hs-cTnT <6 ng/l; Group 2, those with hs-cTnT 6 to 13 ng/l; Group 3, those with hs-cTnT 14 to 49 ng/l (i.e., a group in which most patients would have had a negative cardiac troponin T with older assays); and Group 4, those with hs-cTnT ≥50 ng/l.

RESULTS There were 5,790 (11.9%), 6,491 (13.4%), 10,476 (21.6%), and 25,837 (53.2%) patients in Groups 1, 2, 3, and 4, respectively. In Groups 1 to 4, the proportions with MI were 2.2%, 2.6%, 18.2%, and 81.2%. There was a stepwise increase in the proportion of patients with significant coronary stenoses, left ventricular systolic dysfunction, and death during follow-up. When dividing patients into 20 groups according to hs-cTnT level, the adjusted mortality started to increase at an hs-cTnT level of 14 ng/l.

CONCLUSIONS Introducing hs-cTnT into clinical practice has led to the recognition of a large proportion of patients with minor cardiac troponin increases (14 to 49 ng/l), the majority of whom do not have MI. Although a heterogeneous group, these patients remain at high risk, and the adjusted mortality rate started to increase at the level of the 99th percentile in healthy controls. (J Am Coll Cardiol 2015;65:1655–64) © 2015 by the American College of Cardiology Foundation.

Cardiac troponin (cTn) has been the recommended and preferred biomarker for the diagnosis of myocardial infarction (MI) since 2000 (1). Evidence of myocardial necrosis has been defined as the detection of an increase and/or decrease of cTn with at least 1 value above the 99th percentile of a normal reference population (2–4). Guidelines also state that the assay used should have an optimal precision (coefficient of variation ≤10%) at this level (2–4). Due to the lack of adequate precision of many cTn assays, a new generation of sensitive cTn assays has recently been

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

cTn = cardiac troponin

cTnT = cardiac troponin T

ECG = electrocardiogram

HF = heart failure

hs-cTnT = high-sensitivity cardiac troponin T

MI = myocardial infarction

developed to comply with guideline requirements (5–8). The novel fifth-generation high-sensitivity cTnT (hs-cTnT) assay, with a validated improved analytical performance, is a modification of the fourth-generation assay, lowering the decision limit for myocardial injury from 30 ng/l (with the fourth-generation assay) to 14 ng/l with the fifth-generation hs-cTnT assay (5).

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This new assay has a better clinical sensitivity for the detection of myocardial tissue injury, including acute MI (5–11) and is more useful for risk stratification compared with the fourth-generation cTnT assay (12–22). It is, however, important to note that the detection of cTn indicates myocardial injury (not just ischemic injury), regardless of the etiology (23–25). Thus, there are concerns that the new assays may lead to lower specificity and perhaps unnecessary admissions and overuse of resources. Consequently, it is important to describe the clinical effects of introducing hs-cTnT into clinical practice.

The SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry is a nationwide registry that includes almost all patients who are admitted to a coronary care unit or other specialized facility because of symptoms suggestive of an acute coronary syndrome (ACS) (26). The main objective of this new study was to describe the patients who were identified by the hs-cTnT assay with only a minor increase (14 to 49 ng/l), i.e., a group in which most patients would have had a negative result using older cTnT assays. We evaluated baseline characteristics, in-hospital course, final diagnosis, and outcome. Using a very large cohort of patients with symptoms suggestive of an ACS, we also wanted to delineate the association between the level of hs-cTnT and subsequent long-term outcome, focusing on the lower end of the analytical range.

METHODS

For patients who are admitted to the hospital because of symptoms suggestive of an ACS, the SWEDEHEART registry collects information prospectively for 106 variables, including patient demographics, admission logistics, risk factors, medical history, previous medical treatment and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses, and discharge medications (26). The SWEDEHEART registry is regularly merged with the Swedish population registry, which includes information about the vital status of all Swedish citizens. To ensure the correctness and high quality of the registry data, hospitals are monitored on a regular basis. The degree of agreement between the hospital records and the registry is 96% (26). Patients included in the registry are informed about their participation and maintain the right to decline (26).

STUDY POPULATION. The study included a total of 48,594 consecutive patients who, over a 4-year period (2009 to 2012), were admitted and recorded in the SWEDEHEART registry in 45 Swedish hospitals that had introduced the hs-cTnT assay into their clinical practice. Only centers with more than 100 registered patients with measured hs-cTnT were included. An acute MI was defined according to current guidelines (2,3), and all hospitals used the 99th percentile in healthy controls as decision limits. However, 8 hospitals initially used higher (30 to 40 ng/l) decision limits. All data were made anonymous before statistical analyses were performed. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee.

LABORATORY ANALYSIS. The Elecsys troponin T high-sensitive assay (Roche Diagnostics Corporation, Indianapolis, Indiana) was used to determine the maximal hs-cTnT level during hospitalization. The recommended limit of blank and limit of detection of hs-cTnT are 3 ng/l and 5 ng/l, respectively (5). The 99th percentile in healthy controls is 14 ng/l (27), and the coefficient of variation (≤10%) is reached at 13 ng/l (5). The analytical range of measurement is 3 to 10,000 ng/l (5,27). Recently, 2 studies (5,27) demonstrated that cTn concentrations determined by the fourth-generation cTnT and hs-cTnT assay are not comparable at the lower end of the analytical range. Giannitsis et al. (5) showed that a cTn value of 30 ng/l according to the fourth-generation cTnT assay corresponds to ~50 ng/l according to the hs-cTnT assay. This has also been supported by others (27); therefore, we divided our study population into 4 groups according to the maximal hs-cTnT during hospitalization: Group 1 with a maximal hs-cTnT value <6 ng/l (a test result below the limit of detection [<5 ng/l] has, in the majority of cases, been registered as "5" ng/l in the registry); Group 2 with a maximal hs-cTnT value of 6 to 13 ng/l; Group 3 with a maximal hs-cTnT value of 14 to 49 ng/l (i.e., a group in which most patients would have had a negative cTnT using the old cTnT

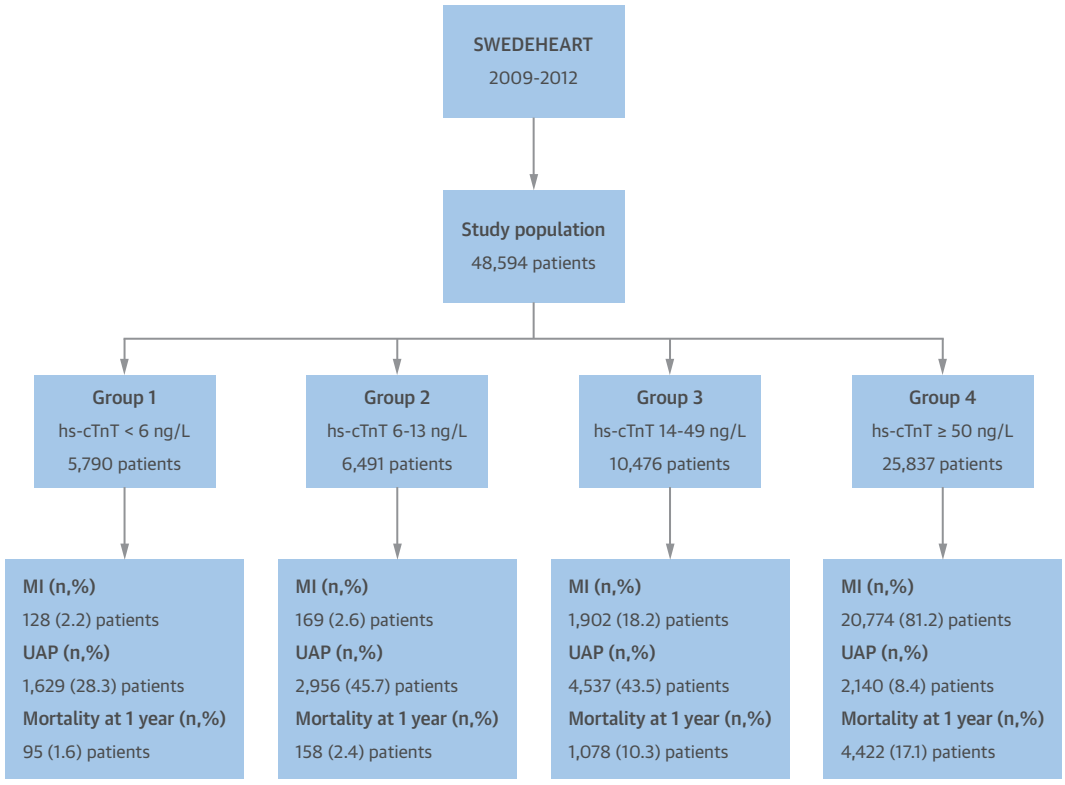
assay); and, last, Group 4 with an hs-cTnT maximal value of ≥50 ng/l (i.e., a group in which most patients would have had a positive cTnT result even if the old cTnT assay had been used).

The study population was further divided into 4 groups according to main (primary) diagnosis at discharge: 1) ACS (acute MI and unstable angina pectoris); 2) other cardiac diseases (e.g., myocarditis, atrial fibrillation); 3) other noncardiac or unknown diseases; and 4) heart failure (HF). To examine the relationship between maximal hs-cTnT and all-cause mortality, patients were further subdivided according to maximal hs-cTnT level into 10 to 20 equally large groups (except for the group with no measurable hs-TnT [<6 ng/l], which could not be further divided). Glomerular filtration rates were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (28). Follow-up of patients to assess all-cause mortality was done at 1 year from admission.

STATISTICAL ANALYSIS. Categorical variables were summarized as numbers and percentages, and continuous data by median (interquartile range). Categorical variables were analyzed using the chi-square test and continuous variables were compared using the Kruskal-Wallis test.

A multivariable Cox proportional hazards model, using the group with maximal hs-cTnT <6 ng/l (i.e., no measurable hs-cTnT) as the reference group, was used to assess the adjusted association between maximal hs-cTnT and all-cause mortality for all patients and in 4 groups according to the main diagnosis at discharge. Factors included in the model were age, male, smoking, hypertension, diabetes mellitus, previous HF, previous MI, previous stroke, previous percutaneous coronary intervention, previous coronary artery bypass grafting, sinus rhythm on the admission electrocardiogram (ECG), atrial fibrillation/flutter on the admission ECG, ST-segment depression on the admission ECG, ST-segment elevation on the admission ECG, percutaneous coronary intervention during hospitalization, coronary artery bypass grafting during hospitalization, and glomerular filtration rate.

FIGURE 1 Summary of the Study Population



Number of patients with different levels of high-sensitivity cardiac troponin T (hs-cTnT) and subsequent 1-year mortality. MI = myocardial infarction; UAP = unstable angina.

All data analyses were performed using the SPSS version 20 software (IBM Corp., Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. There were 5,790 patients (11.9%) with a maximal hs-cTnT <6 ng/l (Group 1), 6,491 (13.4%) with a maximal hs-cTnT of 6 to 13 ng/l (Group 2), 10,476 (21.6%) with a maximal hs-cTnT of 14 to 49 ng/l (Group 3), and 25,837 (53.2 %) patients with a maximal hs-cTnT ≥50 ng/l (Group 4) (Figure 1). Baseline characteristics in relation to hs-cTnT level are shown in Table 1. When baseline characteristics were compared, Group 3 was similar to Group 4 with regard to age, sex, and the presence of risk factors. Compared with Group 4, Group 3 had more patients with previous cardiac disease (such as previous MI, revascularization, and HF) and atrial fibrillation/flutter on admission, and, consequently, these patients were more often treated with antiplatelet therapy, beta-blockers, statins, and angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. With increasing levels of maximal hs-cTnT, there was an increase in the proportion of patients presenting with ST-segment deviation.

Characteristics of the patients during hospitalization are shown in Table 2. When Groups 1, 2, 3, and 4 were compared, there was a stepwise increase in the use of coronary angiography and echocardiography. In patients who underwent coronary angiography,

TABLE 1 Baseline Characteristics

	hs-cTnT				
	<6 ng/l (n = 5,790)	6-13 ng/l (n = 6,491)	14-49 ng/l (n = 10,476)	≥50 ng/l (n = 25,837)	p Value
Age, yrs	58 (48-66)	66 (58-74)	73 (64-81)	72 (63-81)	<0.001
Male	2,991 (51.7)	3,976 (61.3)	6,671 (63.7)	16,774 (64.9)	<0.001
Risk factors					
Smoking	1,167 (20.2)	967 (14.9)	1,331 (12.7)	4,923 (19.1)	<0.001
Diabetes mellitus	693 (12)	1,211 (18.7)	2,680 (25.7)	6,050 (23.5)	<0.001
Hypertension	2,131 (36.9)	3,322 (51.3)	5,948 (57)	13,238 (51.3)	<0.001
Previous cardiovascular disease					
Myocardial infarction	1,250 (21.7)	2,226 (34.4)	4,227 (40.5)	8,038 (31.2)	<0.001
Heart failure	272 (4.7)	658 (10.2)	1,830 (17.5)	3,437 (13.3)	<0.001
Stroke	244 (4.2)	476 (7.4)	1,094 (10.5)	2,647 (10.3)	<0.001
PCI	1,194 (20.7)	2,019 (31.2)	3,058 (29.3)	4,623 (17.9)	<0.001
CABG	308 (5.3)	740 (11.4)	1,696 (16.2)	2,924 (11.3)	<0.001
Medication on admission					
Aspirin	2,141 (37.1)	3,315 (51.2)	5,451 (52.2)	10,949 (42.5)	<0.001
$P2Y_{12}$ receptor blocker	536 (9.3)	953 (14.7)	1,526 (14.6)	2,615 (10.1)	<0.001
Beta-blocker	2,192 (38)	3,397 (52.5)	5,861 (56.2)	11,083 (43)	<0.001
Statin	2,069 (35.9)	3,163 (48.9)	5,126 (49.1)	9,235 (35.8)	<0.001
ACEI/ARB	1,747 (30.3)	2,957 (45.7)	5,350 (51.3)	10,298 (39.9)	<0.001
Cardiogenic shock at admission	7 (0.1)	18 (0.3)	39 (0.4)	284 (1.1)	<0.001
Main reason for presentation					
Chest pain	5,020 (87)	5,591 (86.8)	8,046 (77.5)	20,307 (79.1)	<0.001
Dyspnea	167 (2.9)	231 (3.6)	1,091 (10.5)	2,565 (10.0)	<0.001
Cardiac arrest	8 (0.1)	15 (0.2)	40 (0.4)	466 (1.8)	<0.001
Other*	574 (9.9)	603 (9.4)	1,200 (11.6)	2,333 (9.1)	<0.001
Electrocardiography					
Sinus rhythm	5,315 (92.1)	5,582 (86.6)	7,870 (75.7)	21,274 (82.8)	<0.001
Atrial fibrillation/flutter	350 (6.1)	670 (10.4)	1,914 (18.4)	3,322 (12.9)	<0.001
ST-segment depression	582 (10.1)	714 (11.1)	1,676 (16.2)	5,902 (23)	<0.001
ST-segment elevation	302 (5.3)	355 (5.5)	564 (5.4)	7,328 (28.5)	<0.001
Systolic blood pressure, mm Hg	145 (130-160)	149 (131-165)	149 (130-167)	145 (125-165)	<0.001
Diastolic blood pressure, mm Hg	82 (75-92)	82 (73-91)	80 (70-90)	82 (70-95)	<0.001
Heart rate, beats/min	74 (64-86)	72 (63-85)	76 (65-92)	80 (68-97)	<0.001
GFR, ml/min	91.3 (78.7-101.4)	82.7 (68.5-93.3)	70.7 (53.6-85.9)	71.2 (50.5-87.7)	<0.001

Values are median (interquartile range) or n (%), unless otherwise indicated. *Include symptoms suggestive of possible acute coronary syndrome other than chest pain and dyspnea, such as nausea, abdominal discomfort, and general malaise.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; GFR = glomerular filtration rate; hs-cTnT = high-sensitivity cardiac troponin T; PCI = percutaneous coronary intervention.

TABLE 2 In-Hospital Course

	hs-cTnT				
	<6 ng/l (n = 5,790)	6-13 ng/l (n = 6,491)	14-49 ng/l (n = 10,476)	≥50 ng/l (n = 25,837)	p Value
Coronary angiography	1,419	2,247	4,808	18,017	
Nonconclusive	2 (0.1)	8 (0.4)	19 (0.4)	59 (0.3)	0.533
Normal/atheromatosis	806 (56.8)	876 (39.0)	1,373 (28.6)	2,157 (12.0)	<0.001
1–2 VD	456 (32.1)	924 (41.1)	2,222 (46.2)	10,684 (59.3)	<0.001
LM or 3 VD	155 (10.9)	439 (19.5)	1,194 (24.8)	5,117 (28.4)	<0.001
Echocardiography (LVEF)	2,122	2,474	5,157	18,613	
Normal, ≥50%	1,913 (90.2)	2,088 (84.4)	3,626 (70.3)	10,243 (55.0)	<0.001
Mild/moderate dysfunction, 31%–49%	186 (8.8)	334 (13.5)	1,124 (21.8)	6,867 (36.9)	<0.001
Severe dysfunction, ≤30%	23 (1.1)	52 (2.1)	407 (7.9)	1503 (8.1)	<0.001
Treatment					
IV UFH, LMWH, or fondaparinux	1,123 (19.6)	1,652 (25.7)	4,295 (41.2)	15,428 (59.8)	<0.001
IV beta-blocker	145 (2.5)	232 (3.6)	613 (5.9)	2,996 (11.6)	<0.001
IV diuretic agent	102 (1.8)	251 (3.9)	1,461 (14.0)	6,159 (23.9)	<0.001
IV inotropic agent	6 (0.1)	23 (0.4)	94 (0.9)	1,066 (4.1)	<0.001
IV nitroglycerin	227 (4)	373 (5.8)	663 (6.4)	3,212 (12.5)	<0.001
CPAP	16 (0.3)	26 (0.4)	194 (1.9)	1,477 (5.7)	<0.001
Interventions					
PCI	490 (8.5)	986 (15.2)	2,421 (23.1)	12,708 (49.2)	<0.001
CABG	86 (1.5)	209 (3.2)	411 (3.9)	1,457 (5.6)	<0.001
Complications					
Cardiogenic shock	2 (0.0)	9 (0.1)	54 (0.5)	511 (2.0)	<0.001
Cardiac arrest	7 (0.1)	16 (0.2)	65 (0.6)	626 (2.4)	<0.001
Atrial fibrillation	83 (1.4)	130 (2)	346 (3.3)	1,284 (5.0)	<0.001
Medication at discharge (survivors)					
Aspirin	2,683 (47.9)	3,980 (63.5)	7,170 (71.0)	21,310 (88.0)	<0.001
$P2Y_{12}$ receptor blocker	917 (16.4)	1,751 (27.9)	3,946 (39.1)	17,414 (71.9)	<0.001
Warfarin	397 (7.1)	810 (12.9)	1,956 (19.4)	2,457 (10.1)	<0.001
Beta-blocker	2,743 (49)	4,131 (65.9)	7,798 (77.2)	20,950 (86.5)	<0.001
Statin	2,653 (47.4)	3,998 (63.8)	7,008 (69.4)	20,054 (82.8)	<0.001
ACEI/ARB	2,071 (37)	3,459 (55.2)	6,703 (66.4)	18,159 (75)	<0.001
Diagnosis at discharge					
ACS	1,757 (30.5)	3,125 (48.3)	6,439 (61.7)	22,914 (89.6)	<0.001
Myocardial infarction	128 (2.2)	169 (2.6)	1,902 (18.2)	20,774 (81.2)	<0.001
Unstable angina pectoris	1,629 (28.3)	2,956 (45.7)	4,537 (43.5)	2,140 (8.4)	<0.001
Heart failure	71 (1.2)	141 (2.2)	688 (6.6)	699 (2.7)	<0.001
Other cardiac disease	581 (10.1)	715 (11.1)	1,270 (12.2)	1,129 (4.4)	<0.001
Unknown or other noncardiac disease	3,357 (58.2)	2,488 (38.5)	2,035 (19.5)	851 (3.3)	<0.001

Values are n (%).

ACS = acute coronary syndrome(s); CPAP = continuous positive airway pressure; IV = intravenous; LM = left main; LMWH = low-molecular weight heparin; LVEF = left ventricular ejection fraction; UFH = unfractionated heparin; VD = vessel disease; other abbreviations as in Table 1.

significant stenoses were present in 43.0%, 60.6%, 71.0%, and 87.7%, and in patients who underwent echocardiography, any left ventricular systolic dysfunction was present in 9.9%, 15.6%, 29.7%, and 45.0% in Groups 1, 2, 3, and 4, respectively. There was also a stepwise increase in the use of different intravenous treatments, use of continuous positive airway pressure, coronary interventions, complications, and use of different post-ACS medications at discharge.

In Groups 1 and 2, the most common diagnoses (58.2% and 38.5%) were unknown or other noncardiac causes, whereas ACS was considered present in 30.5% and 48.3%, respectively. In Group 3, 61.7% were considered to have an ACS, of whom 18.2% had a diagnosis of MI. In Group 4, a majority (89.6%) had a diagnosis of an ACS, including 81.2% with MI.

MORTALITY IN RELATION TO TROPONIN CONCENTRATION. Follow-up of patients for all-cause mortality was done at 1 year from admission. There were 95 (1.6%), 158 (2.4%), 1,078 (10.3%), and 4,422 (17.1%) deaths in Groups 1, 2, 3, and 4, respectively (Figure 1). Compared with Group 1, the adjusted hazard ratios were 1.07 (95% confidence interval [CI]: 0.81 to 1.41; $p = 0.66$), 2.53 (95% CI: 2.00 to 3.21; $p < 0.001$), and

4.65 (95% CI: 3.68 to 5.88; $p < 0.001$) in Groups 2, 3, and 4, respectively. When the study population was divided into 20 groups according to maximal hs-cTnT levels, crude mortality started to increase at an hs-cTnT level of 12 to 13 ng/l (Figure 2A), whereas adjusted mortality started to increase at an hs-cTnT level of 14 to 18 ng/l (hazard ratio: 1.94; 95% CI: 1.47 to 2.56; $p < 0.001$) (Figure 2B). At levels higher than 14 ng/l, the adjusted mortality increased continuously with increasing hs-cTnT.

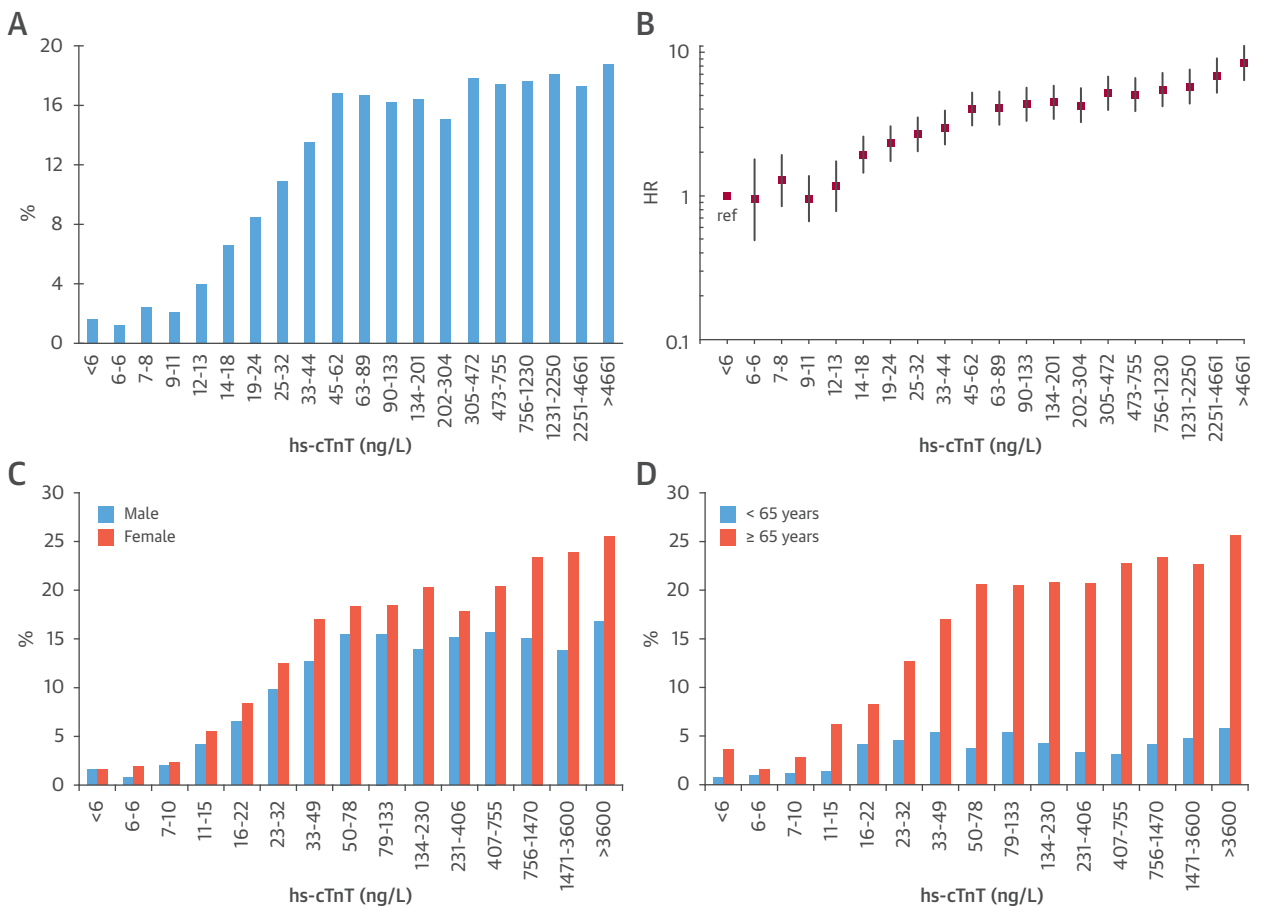
The pattern was similar in men and women and in those younger or older than 65 years of age, but with a somewhat higher crude mortality rate in women and much higher mortality rate in the elderly (Figures 2C and 2D).

When the study population was divided according to the main diagnosis at discharge, there was an association between the level of hs-cTnT and mortality in all 4 groups, on both unadjusted and adjusted analyses (Central Illustration). In patients with increased hs-cTnT (≥14 ng/l), the crude mortality rate was highest in those with a diagnosis of HF and lowest in those with a diagnosis of an ACS ($p < 0.001$). When patients with a maximal hs-cTnT <6 ng/l were used as reference, the adjusted relative effect of increased hs-cTnT was most pronounced in the group with other noncardiac causes of their symptoms.

DISCUSSION

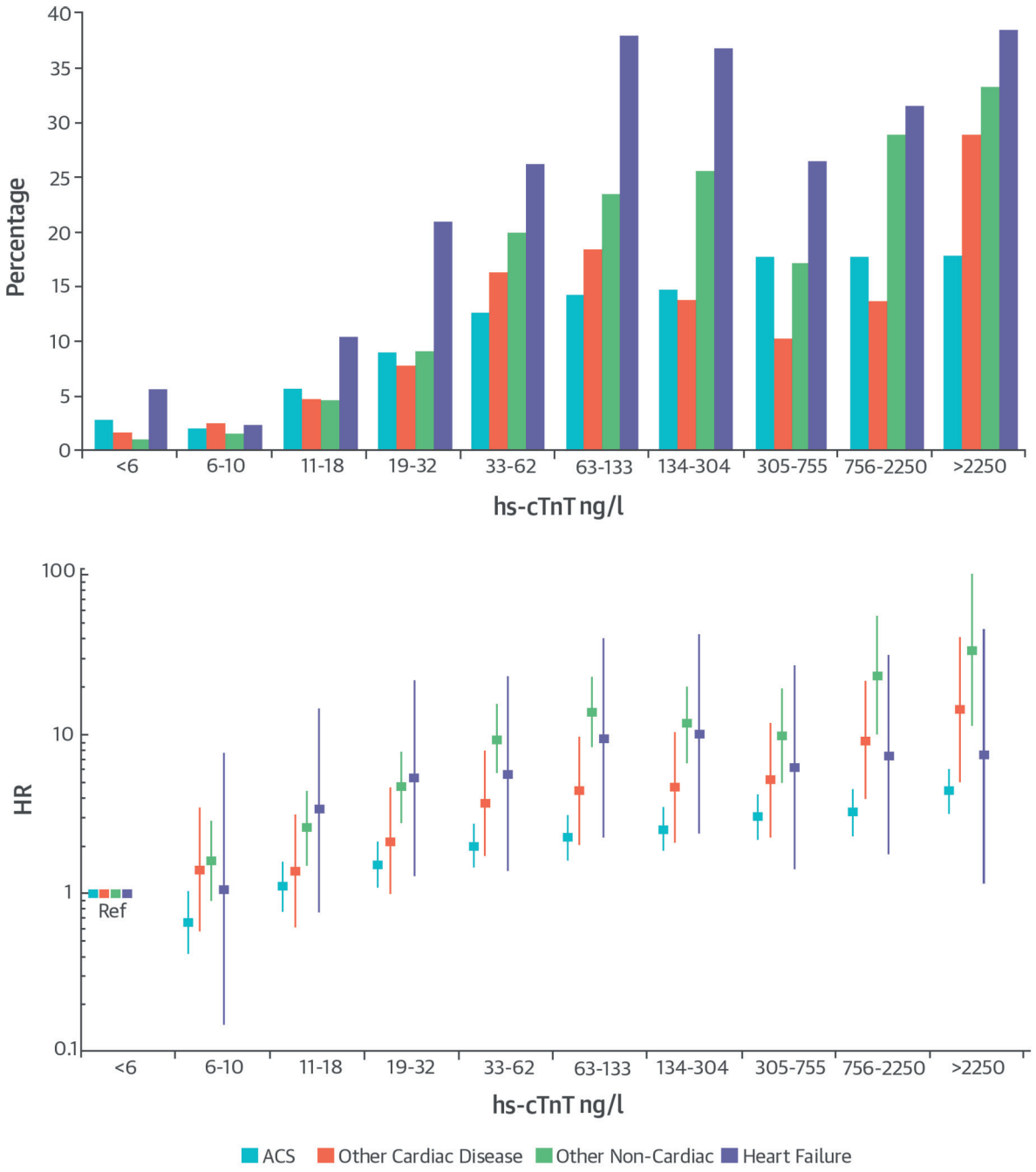
This is, so far, the largest study examining the implications of introducing hs-cTnT into clinical practice. In this nonselected but high-risk population, we found

FIGURE 2 Mortality in Relation to Troponin Concentration



Patients were subdivided into groups on the basis of high-sensitivity cardiac troponin T (hs-cTnT) levels. **(A)** Crude all-cause mortality, divided according to the level of maximal hs-cTnT, began increasing at 12 to 13 ng/l, whereas adjusted all-cause mortality per adjusted hazard ratio (HR) and 95% confidence interval **(B)** started increasing at 14 to 18 ng/l. Differences in crude all-cause mortality also were seen in relation to sex **(C)** and age **(D)**.

CENTRAL ILLUSTRATION **Mortality in Relation to Discharge Diagnosis**



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This study examined the implications of introducing high-sensitivity cardiac troponin T (hs-cTnT) as a biomarker into clinical practice and to define at what hs-cTnT level risk starts to increase. When study patients were divided according to the primary discharge diagnosis, there was an association seen between crude **(top)** and adjusted **(bottom)** all-cause mortality and level of hs-cTnT. HR = hazard ratio.

that 1 in 5 (21.6%) had a minor increase in troponin (hs-cTnT 14 to 49 ng/l), a group who may not have been identified by the previous fourth-generation cTnT assay. Our results indicate that the new hs-cTnT assay identifies a large and important subgroup of previously cTn-negative patients.

With regard to demographics and the presence of risk factors, patients with maximal hs-cTnT 14 to 49 ng/l were similar to those with maximal hs-cTnT ≥50 ng/l. The prevalence of previous cardiovascular diseases was even higher in patients with minor increase in hs-cTnT than in patients with a major increase in hs-cTnT. This is probably explained by a greater proportion of patients with chronically increased troponin levels in the former group. Compared with patients with hs-cTnT <14 ng/l, patients with hs-cTnT 14 to 49 ng/l more often had significant stenoses at coronary angiography and depressed left ventricular systolic dysfunction. Accordingly, the latter group was treated more aggressively with antithrombotic treatment and coronary interventions. It is, however, important to note that only 18.2% of those with minor increases in hs-cTnT (14 to 49 ng/l) were diagnosed with MI. The majority were considered to have unstable angina pectoris (43.5%) or no ACS at all (38.3%), which may indicate a large proportion of patients with a lack of an increase and/or decrease in troponin levels or other reasons for increased troponin.

Our study shows an increase in all-cause mortality with increasing maximal hs-cTnT levels regardless of the cause of troponin increase (**Central Illustration**). A large number of studies involving similar populations have shown an increased mortality with increasing levels of cTn irrespective of the etiology of the cTn increase. Jolly et al. (29) used the GRACE registry (Global Registry of Acute Coronary Events) for risk evaluation of patients with non-ST-segment elevation ACS in relation to cTn values (29). Peak values of cTn were used in their analysis as in our study. In the study from Jolly et al. (29), which included 16,318 patients and used old cTn assays (cTn T or I), the extent of cTn increase was independently associated with all-cause mortality (29). Irfan et al. (20) showed that patients who presented at an emergency department with a noncardiac cause of chest pain but with hs-cTnT values >14 ng/l had a higher all-cause mortality compared with patients with hs-cTnT ≤14 ng/l. In a study by de Lemos et al. (30), which evaluated a general apparently healthy population, hs-cTnT (cutoff 14 ng/l) was detectable in 25% of the population and associated with all-cause mortality.

By using a new generation of sensitive troponin assays, troponin increases can be detected in more patients, leading to better risk assessment. Celik et al. (31), Aldous et al. (12), Hochholzer et al. (13), and Haaf et al. (32) showed that hs-cTnT outperformed contemporary cTn assays in predicting mortality (13,31,32) or major adverse cardiac event rate (composite of cardiovascular death, nonfatal MI, and revascularization) (12). Mueller et al. (14) also showed that hs-cTnT outperformed cardiac troponin I (using the Centaur TnI-Ultra immunoassay system, Siemens Corporation, Munich, Germany) in predicting all-cause mortality in patients with a suspected ACS. Pascual-Figal et al. (16) demonstrated that hs-cTnT performed better than fourth-generation cTnT assays in predicting death in patients with decompensated HF. The aforementioned studies used 99th percentile of healthy controls as the cutoff value. By using a very large sample, we were able to divide patients into 20 different groups according to maximal hs-cTnT level. In the adjusted analyses, there was no increase in mortality in patients with hs-cTnT <14 ng/l. There was no obvious difference between men and women in terms of the level of cTn at which risk started to increase.

STUDY LIMITATIONS. The SWEDEHEART includes mainly patients admitted to a coronary care unit because of an intermediate or high level of suspicion of an ACS. This explains the fairly high prevalence of risk factors and previous cardiovascular disease in patients with hs-cTnT <14 ng/l. Data used in this analysis were collected in a registry. Although all participating hospitals are monitored regularly, and the agreement between the hospital records and the registry has repeatedly been found to be 96% (26), the data cannot be of the same quality as in a clinical prospective, observational study. This is particularly the case when it comes to a recently introduced biomarker, such as hs-cTnT, measured as nanograms per liter instead of the previously used micrograms per liter. In this study, 2.4% of all patients with a maximal hs-cTnT <14 ng/l eventually received a diagnosis of MI. These "troponin-negative" MIs are most likely due to erroneous registrations of hs-cTnT values. However, the potential effects of this bias on the overall results are small. In the registry, only the maximal hs-cTnT value has been registered, and we have therefore been unable to differentiate between patients with dynamic changes of hs-cTnT and those without. The maximal value also may be influenced by blood sampling strategies that may vary between hospitals. The diagnoses were set by the discerning physicians and not further adjudicated. Finally, we did not include cause of death. However, most

deaths after an episode of ACS are cardiovascular in nature, and the validity of death certificates is limited.

CONCLUSIONS

In a nonselected high-risk population, the introduction of hs-cTnT has led to the identification of a large proportion of patients with minor cTn increases (14 to 49 ng/l), a group in which most patients would have had a negative cTnT if the old cTnT assay had been used. The majority of patients with a minor cTn increase did not receive diagnosis of experiencing an MI but were still at high risk. After adjusting for differences in baseline characteristics, long-term mortality starts to increase at the level of the 99th percentile in healthy controls (14 ng/l); there then is seen a stepwise increase in mortality with increasing levels of hs-cTnT, regardless of the underlying cause of cTn increase.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In an unselected high-risk population, a hs-cTnT assay identified a large proportion of patients with minor troponin increases (14 to 49 ng/l) not detected using the previous, less sensitive assay. Patients with minor cTnT increases face an increased risk of future ischemic events.

TRANSLATIONAL OUTLOOK: More studies are needed to characterize the heterogeneity of patients with minor cTnT increases, to expose underlying pathophysiological mechanisms responsible for low-level troponin release, and to enhance treatment strategies to improve long-term clinical outcomes.

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