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ORIGINAL RESEARCH

Temporal Changes of Stable High-Sensitivity Cardiac Troponin T Levels and Prognosis

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BACKGROUND: The prognostic implications of temporal change of previously stable high-sensitivity cardiac troponin concentrations are unknown. We investigated the prognosis associated with temporal changes of stable high-sensitivity cardiac troponin T (hs-cTnT) concentrations.

METHODS AND RESULTS: All patients presenting with cardiac symptoms and ≥2 hs-cTnT measurements at the time of their first visit to 7 different emergency departments in Sweden between December 9, 2009, and December 31, 2016, were identified (n=66 159). We included all patients with stable hs-cTnT but no acute coronary syndrome diagnosis who had ≥1 hs-cTnT measured also at a second visit >30 days from the first visit. Hazard ratios (HRs) with 95% CIs were calculated for all-cause mortality and cardiovascular events according to temporal change of hs-cTnT between the visits, using patients without myocardial injury (<15 ng/L) at the first visit and persistently stable hs-cTnT at the second visit as the reference. Altogether, 12 869 patients were included, of whom 5191 (40%) had myocardial injury (hs-cTnT ≥15 ng/L). During a median follow-up of 2.3 (interquartile range, 1.4–3.7) years, 3271 (25%) patients died. In patients with myocardial injury and a temporal increase in hs-cTnT, the adjusted all-cause and cardiovascular mortality was 4- and 5-fold elevated (HR, 4.21; 95% CI, 3.55–5.00; and HR, 5.08; 95% CI, 3.73–6.92), and the adjusted risk of heart failure hospitalization almost 3-fold (HR, 2.77; 95% CI, 2.26–3.39).

CONCLUSIONS: Temporal change of previously stable hs-cTnT is associated with the risk of death and cardiovascular outcomes, with highest risks observed in patients with myocardial injury and increasing hs-cTnT.

Key Words: cardiac biomarker ■ cardiovascular disease ■ emergency department ■ prognosis

The use of high-sensitivity cardiac troponin (hs-cTn) assays in clinical practice has improved the detection of myocardial injury in patients who present in the emergency department (ED).[1–4] Stable elevated hs-cTn concentrations, in the absence of other acute medical conditions such as acute coronary syndrome, may be indicative of ongoing chronic myocardial injury, and is associated with a high risk of death and cardiovascular events as well as long hospital stays and a high rate of readmissions.[5–8] Persistently elevated hs-cTn concentrations are related to the risk of future cardiovascular events and death in individuals with and without prior cardiovascular disease, with the highest risks observed among individuals with the most pronounced hs-cTn increases.[9–11] However, the clinical implications of temporal change of previously stable high-sensitivity cardiac troponin T (hs-cTnT) concentrations are unknown.

Using a large observational cohort of patients seeking ED care, presenting with stable hs-cTnT concentrations, we sought to investigate the risk of death and cardiovascular outcomes associated with temporal

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CLINICAL PERSPECTIVE

What Is New?

- Temporal change of previously stable high-sensitivity cardiac troponin T concentrations is associated with the risk of all-cause mortality and cardiovascular events.
- The most increased risks of cardiovascular events were observed in patients with myocardial injury and persistently stable or increasing high-sensitivity cardiac troponin T concentrations.

What Are the Clinical Implications?

- Novel management strategies for patients with stable high-sensitivity cardiac troponin concentrations are needed to improve prognosis.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular event
NPR	National Patient Register

change of previously stable hs-cTnT concentrations, and to explore predictors of persistently stable hs-cTnT concentrations without a dynamic pattern over time.

METHODS

Data Access

The authors declare that all supporting data are available within the article and its online supplemental files.

Data Sources

The study was based on data from 7 large EDs in Stockholm and Göteborg, Sweden, between December 9, 2009, and December 31, 2016. Data from each hospital's administrative databases were used to collect information on all ED visits by adult patients (≥18 years of age) during the study period. Laboratory data were obtained from local clinical chemistry databases. The Elecsys 2010 system (Roche Diagnostics, Mannheim, Germany) was used to analyze hs-cTnT levels at all sites. This assay has a detection limit of 5 ng/L, a 99th-percentile cutoff point of 14 ng/L, and a coefficient of variation of <10% at 13 ng/L.[12]

Data were thereafter sent to the Swedish National Board of Health and Welfare for linking with a range of health data registers, providing data on comorbidities, use of medication, and mortality including causes of death. Data were obtained from the National Patient Register (NPR), the Prescribed Drug Register, and the Causes of Death Register, respectively.[13,14] Detailed data on myocardial infarction (MI) diagnoses were obtained from the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) register, which is a nationwide registry that collects information on all patients admitted to a coronary care unit in Sweden.[15] Both NPR and SWEDEHEART are national registries with excellent nationwide coverage and accuracy for MI diagnoses.[13,15]

The study protocol was approved by the Regional Ethics Review Board in Stockholm, and the study complied with the principles of the Declaration of Helsinki. Informed consent was not required for this study.

Study Population and Definitions

All patients with a first visit to the ED during the study period with a primary report of cardiac symptoms (chest pain, dyspnea, or tachycardia) and who had ≥2 hs-cTnT measurements at the time of the visit were eligible for inclusion. All patients with a final diagnosis of MI or unstable angina, coded according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) in the NPR, were excluded. Among the remaining patients, we then identified all patients who presented with stable hs-cTnT concentrations, which was defined according to the change between all hs-cTnT concentrations measured at the time of the visit by the following criteria: (1) an absolute change of hs-cTnT below 3 ng/L for patients with a first hs-cTnT of <15 ng/L, or (2) a relative change of hs-cTnT below 20% for patients with a first hs-cTnT of ≥15 ng/L. The absolute change criterion was used to allow for higher corresponding relative changes at lower hs-cTnT concentrations and consequently account for exceeding conjoint biological (ie, intraindividual) and analytical variation.[16,17] All patients who then presented a second time to the ED >30 days after the first visit and who then underwent at least 1 hs-cTnT measurement were included in the final study population.

Comorbidities were classified according to all discharge diagnoses from all hospital contacts before the date of the second visit, coded according to *ICD-10* in the NPR. Ongoing medication usage was defined as ≥2 dispensed prescriptions during the year preceding the second visit. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, on the basis of the most recent creatinine measurement.[18]

Exposure

All patients were categorized according to the peak hs-cTnT concentration at the first visit as having evidence of myocardial injury (hs-cTnT ≥15 ng/L) or no

myocardial injury (hs-cTnT <15 ng/L).[19] The exposure was then defined by the temporal change of hs-cTnT concentrations between the first and second visits and classified as increasing, decreasing, or stable hs-cTnT concentrations (Figure 1). The temporal change of hs-cTnT concentrations was defined according to change between the peak hs-cTnT concentration during the first visit and the first hs-cTnT concentration analyzed at the second visit. Patients with persistently stable hs-cTnT concentrations but without myocardial injury were used as the reference group.

Outcomes

The primary outcome was long-term all-cause mortality. Cause-specific death was classified according to the underlying cause of death in the Cause of Death Register. Cardiovascular death was defined as a cause of death in the I-chapter, or R960-R961, in *ICD-10*. The secondary outcome was a first major adverse cardiovascular event (MACE), which was defined as any of the following events: acute MI (*ICD-10* codes I21 or I22 in the NPR or an MI diagnosis registered in the SWEDEHEART register), heart failure hospitalization (*ICD-10* codes I42-I43, I50, and I51), stroke (I62 or I64), or cardiovascular death. Follow-up for all outcomes started at the time of the second visit. End of follow-up for all-cause mortality was December 31, 2017, and for all other outcomes December 31, 2016, respectively.

Statistical Analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs for all outcomes, using patients with low and stable hs-cTnT concentrations as the reference group. Models were fitted both unadjusted and adjusted for the following covariates: age (expressed as a restricted cubic spline with 3 evenly placed knots), sex (as a categorical term), and eGFR at the index hospitalization (categorized as <30, 30–59, and >60 mL/min per 1.73 m^2). Models also included binary terms for prior MI, heart failure, stroke, chronic obstructive pulmonary disease, atrial fibrillation, diabetes, and hypertension, as well as binary terms for prior treatment with aspirin, $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, dipyramidol, and ticagrelor), oral anticoagulants (warfarin and direct oral anticoagulants), beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins. Adjusted all-cause cumulative mortality and corresponding cumulative mortality differences with 95% CIs was calculated comparing the different patient groups to the referent and accounting for all covariates in the adjusted model.

A subgroup analysis was conducted on all patients with elevated hs-cTnT concentrations at the first visit, in which the exposure was defined according to the following categories of relative change in hs-cTnT at the second visit: stable hs-cTnT (referent), >50% decrease,

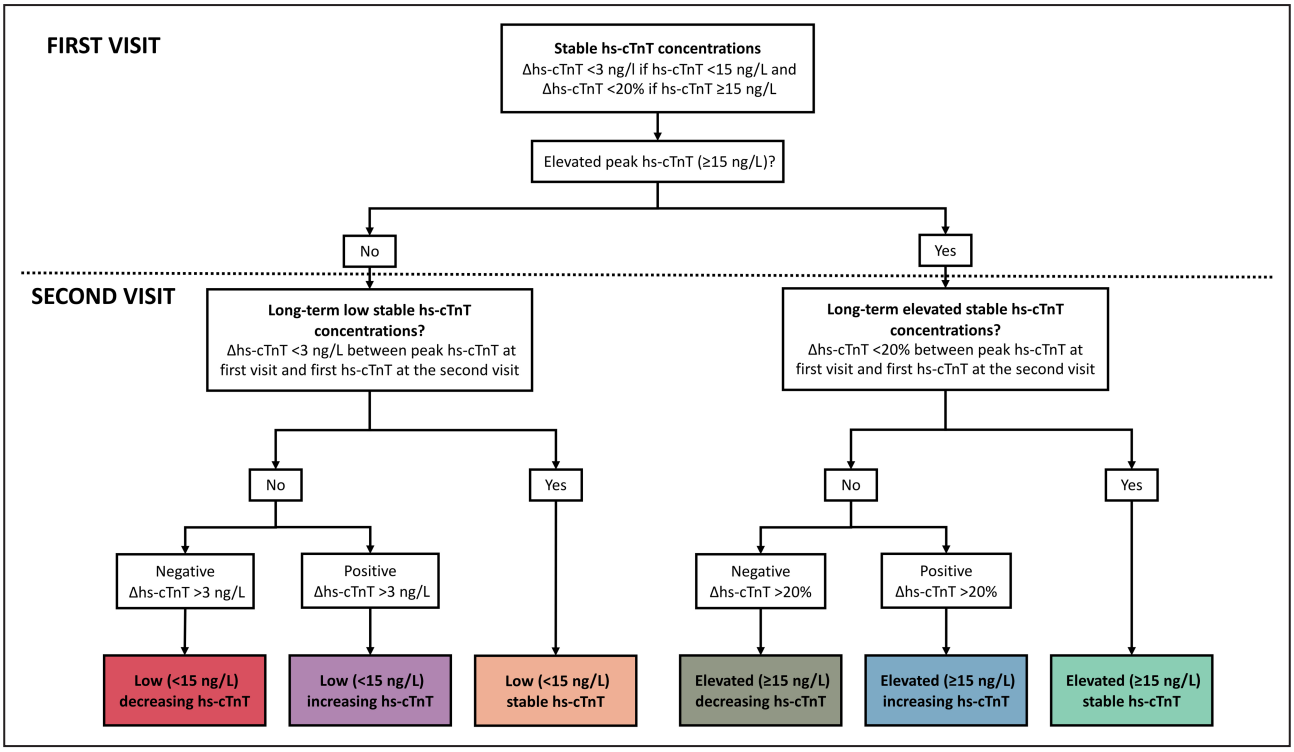

Figure 1. Selection of the study population.
Hs-cTnT indicates high-sensitivity cardiac troponin T.

Table 1. Baseline Characteristics in Patients With Stable hs-cTnT Concentrations

Hs-cTnT at the first visit	Hs-cTnT concentrations <15 ng/L			Hs-cTnT concentrations ≥15 ng/L		
Hs-cTnT at the second visit	Decrease from first visit	Stable	Increase from first visit	Decrease from first visit	Stable	Increase from first visit
Number of patients	564 (4.3)	5619 (44)	1495 (12)	1533 (12)	1993 (15)	1665 (13)
Age, y, median (IQR)	66 (54–75)	59 (48–70)	71 (62–80)	77 (67–84)	82 (74–88)	82 (74–88)
Women	252 (45)	2908 (52)	727 (49)	690 (45)	852 (43)	684 (41)
Principal symptoms at presentation						
First visit						
Chest pain	448 (79)	4921 (88)	1233 (83)	787 (51)	1192 (60)	899 (54)
Dyspnea	53 (9.4)	318 (5.7)	168 (11)	534 (35)	620 (31)	623 (37)
Palpitations	63 (11)	380 (6.8)	94 (6.3)	212 (14)	181 (9.1)	143 (8.6)
Second visit						
Chest pain	341 (60)	3523 (63)	733 (49)	624 (41)	779 (39)	475 (29)
Dyspnea	49 (8.7)	472 (8.4)	232 (16)	380 (25)	603 (30)	582 (35)
Palpitations	60 (11)	439 (7.8)	142 (9.5)	134 (8.7)	127 (6.4)	111 (6.7)
Others	114 (20)	1185 (21)	388 (26)	395 (26)	484 (24)	497 (30)
Comorbidities						
Prior MI	112 (20)	684 (12)	276 (18)	402 (26)	491 (25)	391 (23)
Prior revascularization	123 (22)	820 (15)	341 (23)	356 (23)	476 (24)	371 (22)
Prior stroke	31 (5.5)	265 (4.7)	122 (8.2)	205 (13)	268 (13)	294 (18)
Heart failure	92 (16)	564 (10)	315 (21)	765 (50)	1063 (53)	969 (58)
Diabetes	102 (18)	763 (14)	352 (24)	407 (27)	632 (32)	578 (35)
Hypertension	319 (57)	2373 (42)	984 (66)	1103 (72)	1565 (79)	1304 (78)
Atrial fibrillation	162 (29)	941 (17)	439 (29)	707 (46)	1035 (52)	847 (51)
Dialysis	1 (0.1)	4 (0.1)	1 (0.1)	44 (2.9)	50 (2.5)	47 (2.8)
COPD	60 (11)	391 (7.0)	216 (14)	290 (19)	493 (25)	409 (25)
Laboratory data at the first visit						
Hemoglobin (g/L), median (IQR)	141 (131–151)	140 (131–150)	138 (128–148)	132 (119–144)	130 (118–141)	128 (116–140)
NT-pro-BNP (ng/L), median (IQR)	437 (236–1170)	168 (60–544)	489 (134–1480)	3300 (1024–6940)	1970 (601–5013)	2900 (818–5890)
eGFR (mL/min per 1.73 m^2)						
>60	492 (87)	5196 (92)	1232 (82)	828 (54)	906 (45)	729 (44)
30–59	70 (12)	414 (7.4)	258 (17)	524 (34)	879 (44)	524 (43)
<30	2 (0.4)	9 (0.2)	5 (0.3)	181 (12)	208 (10)	219 (13)
Hs-cTnT concentrations						
First visit						
Peak hs-cTnT concentration, (ng/L), median (IQR)	11 (9–13)	5 (4.9–8)	8 (5–11)	35 (22–66)	26 (19–40)	27 (20–41)
Relative change in hs-cTnT concentrations*, median (IQR)	11% (7, 18)	0% (0, 11)	7% (0, 16)	9% (5, 13)	7% (5, 13)	7% (4, 12)
Second visit						
First hs-cTnT concentration (ng/L), median (IQR)	6 (4.9–8)	4.9 (4.9–8)	16 (11–24)	18 (12–29)	26 (19–39)	53 (34–94)
Time between hs-cTnT at the first visit and the second visit, d, median (IQR)	265 (93–487)	275 (110–614)	376 (158–765)	189 (79–429)	169 (77–373)	249 (101–559)

(*Continued*)

Table 1. (Continued)

Hs-cTnT at the first visit	Hs-cTnT concentrations <15 ng/L			Hs-cTnT concentrations ≥15 ng/L		
Hs-cTnT at the second visit	**Decrease from first visit**	**Stable**	**Increase from first visit**	**Decrease from first visit**	**Stable**	**Increase from first visit**
Relative change between hs-cTnT at the first visit and the second visit, median (IQR)	−39% (−46, −31)	0% (−6, 0)	84% (55, 183)	−41% (−63, −30)	0% (−11, 9)	61% (36, 131)
Medication						
Aspirin	200 (35)	1544 (27)	588 (39)	641 (42)	828 (42)	724 (43)
$P2Y_{12}$ inhibitors[†]	70 (12)	381 (6.8)	113 (7.6)	174 (11)	162 (8.1)	140 (8.4)
Any platelet inhibitor[‡]	222 (39)	1712 (30)	650 (43)	708 (46)	920 (46)	811 (49)
Beta-blockers	295 (52)	2149 (38)	865 (58)	1012 (66)	1356 (68)	1139 (68)
ACEi/ARB	270 (48)	1872 (33)	726 (49)	884 (58)	1226 (62)	974 (59)
CCB	146 (26)	1009 (18)	369 (25)	386 (25)	553 (28)	479 (29)
Nitrates	112 (20)	812 (14)	325 (22)	371 (24)	624 (31)	473 (28)
Statins	222 (39)	1658 (30)	604 (40)	590 (38)	821 (41)	678 (41)
Warfarin	91 (16)	465 (8.3)	229 (27)	327 (21)	538 (27)	423 (25)
DOAC	30 (5.3)	202 (3.6)	85 (5.7)	149 (9.7)	155 (7.8)	117 (7.0)
OAC[§]	117 (21)	651 (12)	305 (20)	465 (30)	680 (34)	532 (32)

Data are presented as n (%), or median with IQR. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; NT-pro-BNP, N-terminal pro B-type natriuretic peptide; OAC, oral anticoagulant; and UA, unstable angina.

*Delta change between minimum and peak hs-cTnT concentrations during the first visit.

[†]Includes treatment with clopidogrel, ticagrelor, dipyradimol, or prasugel.

[‡]Includes treatment with aspirin or $P2Y_{12}$ inhibitors.

[§]Includes treatment with a DOAC or warfarin.

20% to 50% decrease, 20% to 50% increase, 50% to 100% increase, and >100% increase, respectively.

Finally, linear regression models were used to estimate predictors of stable hs-cTnT concentrations at the second visit with 95% CIs, and was conducted unadjusted and adjusted for the following covariates: age, sex, eGFR, cardiovascular comorbidities, and the time between the first and second visits. Also, we included the 5 most common discharge diagnoses during the first visit to investigate their predictive value of stable hs-cTnT concentrations.

RESULTS

Study Population

A total of 12 869 patients were included, of whom 5191 (40%) had myocardial injury at the first visit (Figure S1, Table 1). Patients with myocardial injury were older and had a higher prevalence of renal dysfunction, cardiovascular comorbidities, and usage of cardiovascular medications, respectively. Background characteristics in patients with myocardial injury were similar across categories of temporal change of hs-cTnT, while patients with low hs-cTnT concentrations and a subsequent change at the second visit (increase or decrease) had more comorbidities and lower eGFR compared with patients with low and persistently stable hs-cTnT concentrations. Baseline characteristics in patients who had persistently stable hs-cTnT concentrations, that is, that remained stable between the first and the second visits, are presented in Table S1. Patients with versus without myocardial injury had more cardiovascular comorbidities and treatment with cardiovascular medications.

The most common discharge diagnoses for all patients were symptom diagnoses (R00-R09 in *ICD-10*), and heart failure being second most common in patients with myocardial injury at both the first and second visit (Figure S2).

Predictors of Stable hs-cTnT Concentrations

A total of 7612 (59%) patients had stable hs-cTnT concentrations at the second visit. In these patients, higher age, male sex, and a lower eGFR were associated with higher hs-cTnT concentrations in both unadjusted and adjusted models (Table 2). Cardiovascular comorbidities were related to higher hs-cTnT in univariate models, but estimates were attenuated after multivariate adjustments. The strongest predictor among comorbidities

Table 2. Linear Regression Predictors of Stable hs-cTnT Concentrations

	Unadjusted model	Adjusted model
	Parameter estimate of hs-cTnT, ng/L (95% CI)	
Age, y		
<64	6.9 (6.3–7.5)	8.6 (7.7–9.4)
64–75	13.7 (12.8–14.5)	11.6 (10.6–12.7)
76–84	21.4 (20.4–22.4)	14.5 (13.2–15.8)
>84	32.2 (31.0–33.3)	22.1 (20.6–23.6)
Sex		
Women	12.0 (11.4–12.7)	17.2 (15.8–18.6)
Men	16.2 (15.5–16.8)	22.1 (20.6–23.6)
eGFR (mL/min per 1.73 m^2)		
≥60	9.3 (8.9–9.8)	22.1 (20.6–23.6)
30–60	27.0 (26.1–27.9)	30.2 (28.7–31.8)
<30	58.4 (56.2–60.6)	58.5 (56.0–60.9)
Time between the first and second visits		
<1 y	14.3 (13.8–14.8)	22.1 (20.6–24.0)
>1 y	13.4 (12.3–14.5)	22.3 (20.6–23.6)
Diagnosis at the first visit*		
Chest pain, unspecified‡	10.5 (9.9–11.2)	20.0 (18.5–21.5)
Heart failure	39.6 (37.0–42.1)	26.2 (23.6–28.9)
Atrial fibrillation	16.3 (13.9–18.8)	20.3 (17.7–22.9)
Angina pectoris	16.8 (14.5–19.2)	19.3 (16.9–21.6)
Other uspecified diagnoses†	10.9 (8.5–13.3)	19.3 (16.9–21.7)
Prior CAD		
No	12.6 (12.1–13.1)	22.1 (20.6–23.6)
Yes	19.6 (18.6–20.6)	22.5 (20.8–24.1)
Prior atrial fibrillation		
No	10.7 (10.2–11.2)	22.1 (20.6–23.6)
Yes	23.8 (22.9–24.6)	24.6 (23.0–26.2)
Prior heart failure		
No	10.1 (9.6–10.5)	22.1 (20.6–23.6)
Yes	29.5 (28.5–30.4)	28.8 (27.1–30.6)
Prior diabetes		
No	12.3 (11.8–12.8)	22.1 (20.6–23.6)
Yes	22.2 (21.1–23.2)	25.4 (23.6–27.1)
Prior COPD		
No	12.9 (12.4–13.4)	22.1 (20.6–23.6)
Yes	23.5 (22.2–24.8)	24.6 (22.8–26.4)

CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; and *ICD-10*, *International Classification of Diseases, Tenth Revision*.

*The 5 most common discharge diagnoses of all patients with stable concentrations of hs-cTnT during the first visit.

†*ICD-10* codes R00-09.

‡*ICD-10* code Z03.

was prior heart failure, and a discharge diagnosis of heart failure was associated with higher hs-cTnT concentrations compared with other discharge diagnoses (Table 2).

All-Cause Mortality and Cause-Specific Death

One fourth (3271, 25%) of all patients died during a median follow-up of 2.3 (interquartile range [IQR], 1.4–3.7) years (Table 3). All-cause mortality was higher among patients with myocardial injury, among whom 2517 (48%) died. The highest crude cumulative mortality at 1 year in both patients with and without myocardial injury was observed among patients with increases in hs-cTnT between the first and the second visits (11% and 38%, respectively).

An increase of hs-cTnT at the second visit was associated with a higher risk of all-cause mortality, with adjusted incidence differences being 6.3% (95% CI, 4.4–8.0) and 17.6% (95% CI, 15.6–19.6) at 1 year of follow-up in patients without and with myocardial injury and increasing hs-cTnT concentrations, respectively, compared with the reference group (Figure 2). Corresponding differences at 5 years were 14.9% (95% CI, 10.7–19.1) and 34.3% (95% CI, 30.2–38.4). Similarly, a stable hs-cTnT concentration in patients with myocardial injury was associated with a 9.5% (95% CI, 7.9–11.1) and a 21.3% (95% CI, 17.5–25.1) higher adjusted cumulative mortality at 1 and 5 years.

During a median follow-up of 1.4 (IQR, 0.6–2.8) years, 1165 (9.1%) cardiovascular and 1378 (11%) noncardiovascular deaths occurred in the overall cohort. Both cardiovascular and noncardiovascular mortality rates were higher among patients with myocardial injury, in whom rates of cardiovascular mortality ranged from 8.6 and 11, to 21 deaths per 100 person-years in patients with decreasing, stable, and increasing hs-cTnT concentrations, respectively (Table 3). The adjusted cardiovascular mortality risk was 3- to 5-fold higher among patients with myocardial injury compared with the reference group, with the highest risk observed among patients with increasing hs-cTnT levels (HR, 5.08; 95% CI, 3.73–6.92). The majority of cardiovascular causes of death were related to ischemic heart disease (42%) (Table S2, Table S3). Adjusted cause-specific mortality risks associated with elevated hs-cTnT concentrations were most pronounced for death related to heart failure (Table S2).

Major Adverse Cardiovascular Events

During a median follow-up of 0.9 (IQR, 0.2–2.2) years, a total of 3632 (28%) first MACEs occurred (Table S4). More than half (56%) of all patients with myocardial injury and increasing hs-cTnT concentrations suffered from any MACE. Incidence rates ranged from 23 events per 100 person-years among patients with low but increasing hs-cTnT concentrations, to 37, 49, and 88 events per 100 person-years among patients

Table 3. Long-Term All-Cause, Cardiovascular and Noncardiovascular Mortality According to the Temporal Change of hs-cTnT Concentrations at a Second Visit >30 Days After the Visit in the Emergency Department

Hs-cTnT at the first visit	Stable hs-cTnT concentrations <15 ng/L			Stable hs-cTnT concentrations ≥15 ng/L		
Hs-cTnT at the second visit	Decrease from first visit	Stable	Increase from first visit	Decrease from first visit	Stable	Increase from first visit
Number of patients	564 (4.3)	5619 (44)	1495 (12)	1533 (12)	1993 (15)	1665 (13)
All-cause mortality						
Number of deaths	57 (10)	375 (6.7)	322 (22)	578 (38)	922 (46)	1017 (61)
1-y crude cumulative mortality, % (95% CI)	2.8 (1.7–4.6)	1.8 (1.5–2.2)	11 (9.2–12)	20 (18–22)	23 (21–25)	38 (35–40)
Deaths per 100 person-years (95% CI)	3.3 (2.6–4.3)	2.2 (2.0–2.4)	7.9 (7.1–8.8)	16 (15–18)	21 (20–23)	37 (35–40)
Unadjusted HR (95% CI)	1.51 (1.15–2.00)	Ref.	3.54 (3.05–4.11)	7.14 (6.27–8.13)	9.39 (8.32–10.6)	15.7 (14.0–17.7)
Multivariable adjusted HR‡ (95% CI)	1.21 (0.87–1.67)	Ref.	2.00 (1.65–2.42)	2.66 (2.24–3.16)	2.58 (2.17–3.05)	4.21 (3.55–5.00)
Cardiovascular death						
Number of deaths	11 (2.0)	84 (1.5)	89 (6.0)	221 (14)	350 (18)	410 (25)
Deaths per 100 person-years (95% CI)	0.9 (0.5–1.7)	0.7 (0.6–0.9)	3.1 (2.5–3.8)	8.6 (7.6–9.8)	11 (10–12)	21 (19–23)
Unadjusted HR (95% CI)	1.28 (0.69–2.41)	Ref.	4.32 (3.21–5.82)	11.7 (9.09–15.0)	15.1 (11.9–19.1)	26.4 (20.8–33.4)
Multivariable adjusted HR‡ (95% CI)	0.94 (0.47–1.89)	Ref.	2.08 (1.44–2.99)	3.02 (2.21–4.14)	2.94 (2.15–4.01)	5.08 (3.73–6.92)
Noncardiovascular death						
Number of deaths	28 (5.0)	187 (3.3)	157 (11)	237 (15)	347 (17)	422 (25)
Deaths per 100 person-years (95% CI)	2.3 (1.6–3.4)	1.6 (1.4–1.8)	5.5 (4.7–6.4)	9.3 (8.1–11)	11 (10–12)	21 (19–23)
Unadjusted HR (95% CI)	1.47 (0.99–2.19)	Ref.	3.41 (2.76–4.22)	5.65 (4.66–6.84)	6.72 (5.63–8.04)	12.3 (10.3–14.6)
Multivariable adjusted HR‡ (95% CI)	1.15 (0.71–1.84)	Ref.	2.08 (1.58–2.73)	2.70 (2.10–3.48)	2.53 (1.97–3.25)	4.19 (3.26–3.48)

Data are presented as n (%). End of follow-up for all-cause mortality was December 31, 2017, and for cause-specific death it was December 31, 2016. HR indicates hazard ratio; and hs-cTnT, high-sensitivity cardiac troponin T.

*Multivariable adjustment was made for age, sex, estimated glomerular filtration rate, prior myocardial infarction, heart failure, prior stroke, prior chronic obstructive pulmonary disease, atrial fibrillation, diabetes, the time between the hs-cTnT concentrations measured at the first visit and the second visit (days), and treatment with aspirin, $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, dipyramidol, and ticagrelor), oral anticoagulants (warfarin and direct oral anticoagulants), beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and statins.

with myocardial injury and decreasing, stable, and increasing hs-cTnT concentrations, respectively. In these groups of patients, the adjusted risk of MACE was doubled compared with patients with low, stable hs-cTnT concentrations.

Heart Failure, MI, and Stroke

A total of 2321 (18%) heart failure hospitalizations were observed during a median follow-up of 1.1 (IQR, 0.3–2.5) years (Table S4). More than 1 in 3 (34%) patients with myocardial injury were hospitalized because of heart failure, in whom the highest incidence rate was observed in patients with increasing hs-cTnT. The adjusted risk was increased in patients without myocardial injury but increasing hs-cTnT concentrations (HR, 1.66; 95% CI, 1.32–2.08), and almost 3-fold in those with myocardial injury and increasing hs-cTnT (HR, 2.76; 95% CI, 2.36–3.23).

Altogether, 810 (6.3%) MIs occurred during a median follow-up of 1.4 (IQR, 0.5–2.7) years (Table S4). Among patients without myocardial injury, the incidence rate was higher in those with increasing hs-cTnT versus stable ha-cTnT levels, while the highest rate of 15 events per 100 person-years was observed in patients with myocardial injury and increasing hs-cTnT. The adjusted HR of MI was 4- to 5-fold increased in patients with increasing hs-cTnT (HR, 4.36; 95% CI, 3.23–5.85; and HR, 4.89; 95% CI, 3.54–6.76, in patients with and without myocardial injury, respectively).

A total of 647 (5.0%) strokes occurred (Table S4). Although incidence rates were increased in all groups of myocardial injury at the first visit, adjusted risks were not markedly increased.

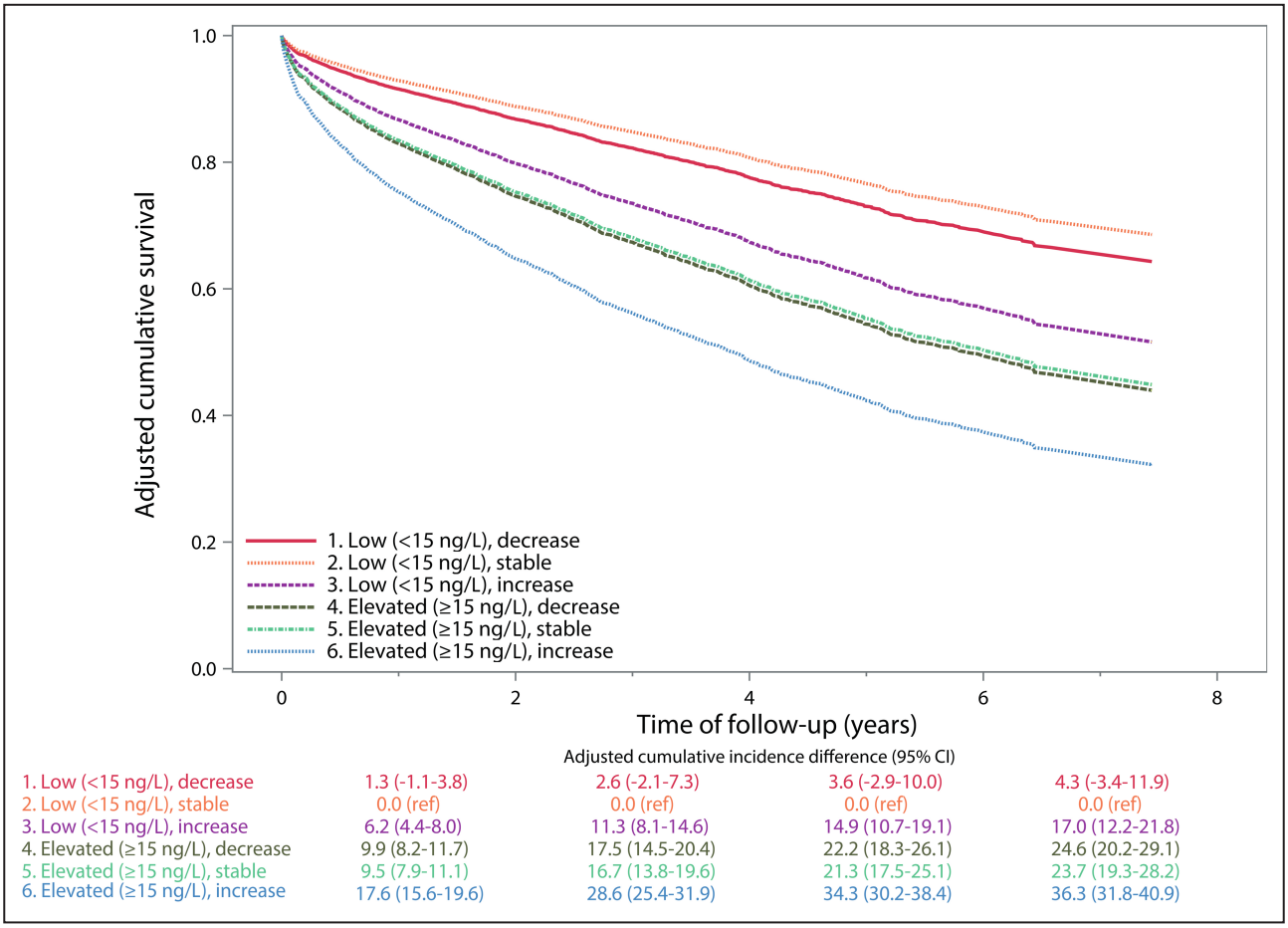

Figure 2. Adjusted cumulative mortality according to temporal change of hs-cTnT concentrations.
Hs-cTnT indicates high-sensitivity cardiac troponin T.

Subgroup Analysis

In patients with myocardial injury, the adjusted all-cause and cardiovascular mortality was more than doubled among those with the most pronounced (>100%) increase in hs-cTnT concentrations compared with patients with stable hs-cTnT at the second visit (Figure 3). Conversely, a lowering of hs-cTnT concentrations of >50% was associated with corresponding risk reductions of 70% and 50%, respectively.

DISCUSSION

In a large cohort of patients with cardiac symptoms in the ED and stable hs-cTnT concentrations but no acute coronary syndrome, we investigated the prognostic implications of temporal change of previously stable hs-cTnT concentrations and predictors of persistently stable hs-cTnT without change at a second visit. We report 5 major findings.

First, we found that the change of hs-cTnT levels in relation to a second visit was associated with elevated risks of all-cause and cardiovascular death and with cardiovascular events. The highest risks were observed in patients with myocardial injury and persistently stable or increasing hs-cTnT levels. Prior studies have found that patients with chronic myocardial injury, as characterized by nondynamic elevated hs-cTn concentrations in the absence of an acute MI or any other ongoing acute medical condition, have a comparable adjusted risk of all-cause mortality as patients with acute myocardial injury and a high risk of cardiovascular events.[5,20–22] However, current clinical guidance on appropriate investigation and treatment strategies to reduce the associated risks is limited[19,23] and perhaps reflects the absence of an overall prognostic improvement associated with implementation of hs-cTn assays into clinical practice.[2] The higher cardiovascular risk associated with temporal increases of stable hs-cTnT, in particular among patients with concentrations indicative of myocardial injury, is consistent with prior prognostic studies on long-term temporal hs-cTnT change in nonhospitalized individuals with and without cardiovascular comorbidities.[9–11,24] This finding suggests that

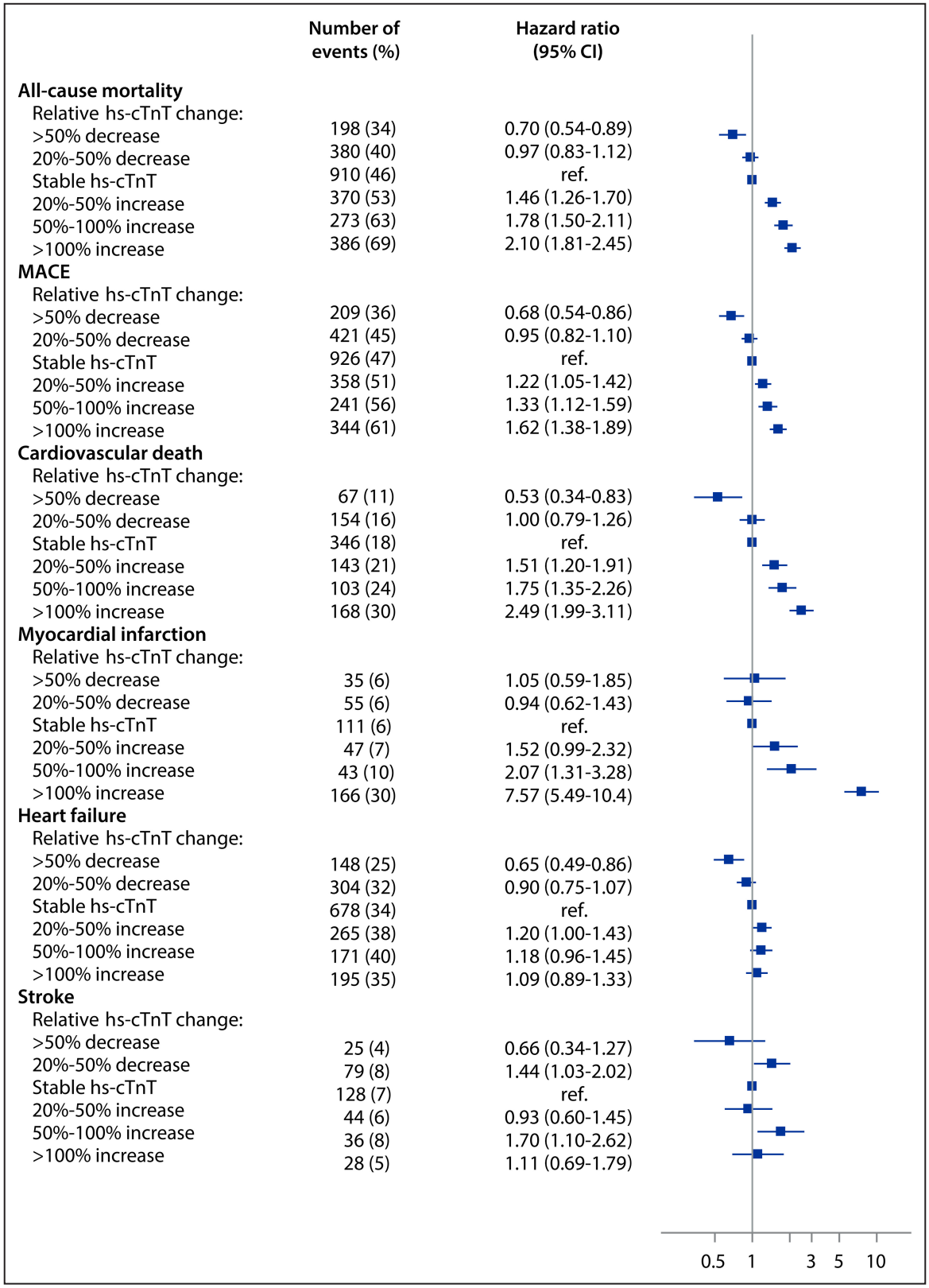

Figure 3. Adjusted risk of all-cause mortality, cardiovascular death and cardiovascular events according to the relative change in hs-cTnT concentrations among patients with elevated hs-cTnT concentrations.
HR indicates hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; and MACE, major adverse cardiovascular event.

serial determination of hs-cTnT concentrations could be useful in prognostic assessments and risk monitoring.

Second, one-third of all patients with myocardial injury at the first visit were hospitalized because of heart failure during the follow-up, and the adjusted risk was almost 3-fold among those with increasing hs-cTnT concentrations. Heart failure was the second most common discharge diagnosis among patients with elevated hs-cTnT at both visits. In patients with myocardial injury among whom hs-cTnT concentrations remained stable between the first and the second visit, the association with risk of heart failure was more pronounced than for ischemic events, both when expressed as absolute and adjusted relative risks, which is consistent with prior studies on nonischemic myocardial injury.[5,25–27] These observations are supported by the association between temporal increases in hs-cTn levels and the prevalence of structural cardiac abnormalities, for example, left ventricular mass and the prevalence of left ventricular hypertrophy.[24,25,28] Hs-cTnT levels have been related to both myocardial nonischemic fibrosis on magnetic resonance imaging consistent with early subclinical remodeling and longitudinal imaging evidence of progressive subclinical cardiac replacement fibrosis in individuals without established heart disease.[25] The potential use of long-term temporal change in stable hs-cTnT concentrations for monitoring progression and targeting prevention strategies for clinical and subclinical structural heart disease should merit further attention.

Third, in a subgroup analysis on patients with myocardial injury, a decrease of hs-cTnT >50% was related to a lower adjusted risk of both long-term all-cause and cardiovascular mortality and MACE compared with the reference group of patients with persistently stable hs-cTnT. These data would further suggest that hs-TnT changes may be used in strategies for monitoring of cardiovascular risk. Prior studies indicate that statin therapy may be paralleled by a lowering of hs-cTn levels and the associated risk for cardiovascular events in mainly healthy individuals,[24] and in a prior clinical trial an early and sustained reduction of hs-cTn levels was observed in patients with chronic HF randomized to treatment with an angiotensin-neprilysin inhibitor.[29]

Fourth, cardiovascular comorbidities were related to higher concentrations of persistently stable hs-cTnT in univariate models, but estimated differences between patients with and without cardiovascular disease diminished after multivariate adjustments with traditional factors associated with hs-cTnT concentrations including age, sex and eGFR.[30–32] These observations indicate that the predictive value of prior cardiovascular disease on concentrations of stable hs-cTnT elevations may be limited. For example, similar estimated hs-cTnT concentrations were observed in patients with and without prior CAD in the fully adjusted model. However, elevated stable hs-cTnT concentrations is associated with cardiovascular outcomes and death independent of traditional factors, for example, in patients with a reduced eGFR, and should therefore not be considered harmless in these patient groups.[5]

Fifth, the most common discharge diagnoses registered were symptom diagnoses, meaning that no specific medical conditions was diagnosed. This was observed even in patients with myocardial injury and increasing hs-cTnT at the second visit. We believe that this finding might reflect the uncertainty in how to properly manage patients who present with stable hs-cTnT concentrations but without any obvious acute medical condition, and is consistent with a recent report on health care resource use in patients with chronic myocardial injury.[8]

Strengths

To our knowledge, this is the first study investigating the implications of temporal change in hs-cTn concentrations among patients with stable hs-cTnT. We retrieved data on background characteristics and outcomes from validated health care registers with complete nationwide coverage.[13,14] The large sample size and the long study period allowed us to investigate outcomes in several groups of patients according to long-term temporal change in hs-cTnT concentrations. The study was conducted at several hospital sites across different regions in Sweden, and we therefore believe that the study findings could be generalized to other national and international health care settings where hs-cTn assays are routinely used.

Limitations

We were not able to adjudicate the discharge diagnoses. Consequently, it was not possible to distinguish patients with stable hs-cTnT concentrations and chronic myocardial injury from those with acute nonischemic myocardial injury without dynamic hs-cTnT measurements. In addition, some patients with MI at the first visit who presented late after symptom onset may have had plateaued hs-cTnT concentrations[33] and could therefore have been missed and thereby contributed to differential misclassification. However, we believe this bias would have had minor impact on our findings. Finally, only patients with cardiac symptoms were used in this study, and thus results could only be generalized to other populations with similar principal complaints in the ED.

CONCLUSIONS

In a large cohort of patients presenting with cardiac symptoms in the ED but without acute coronary

syndrome as a final diagnosis, we found that temporal increases of previously stable hs-cTnT concentrations are associated with increases in the risk of death and cardiovascular events. The highest risks were observed in patients with myocardial injury and persistently stable or increasing hs-cTnT in whom there was an especially pronounced risk of heart failure hospitalization. Novel management strategies for patients with stable hs-cTn concentrations are needed to improve prognosis.

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Disclosures

Dr Holzmann received consultancy honoraria from Idorsia and Pfizer. The remaining authors declare no conflicts of interest.

Supplemental Material

Tables S1–S4
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics in patients with stable high-sensitivity cardiac troponin T concentrations at both visits, stratified by concentrations at the first visit

	Hs-cTnT concentrations (ng/l)		
	<15	**15-49**	**≥50**
Number of patients	5619 (74)	1666 (22)	327 (4.3)
Age (years), mean (SD)	59 (48-70)	81 (73-87)	83 (75-88)
Women	2908 (52)	756 (45)	96 (29)
Principal symptoms at presentation			
First visit			
Chest pain	4921 (88)	1057 (63)	135 (41)
Dyspnea	318 (5.7)	450 (27)	170 (52)
Palpitations	380 (6.8)	159 (9.5)	22 (6.7)
Second visit			
Chest pain	3523 (63)	693 (42)	86 (26)
Dyspnea	472 (8.4)	447 (27)	156 (48)
Palpitations	439 (7.8)	115 (6.9)	12 (3.7)
Others	1185 (21)	411 (25)	73 (22)
Comorbidities			
Prior MI	684 (12)	388 (23)	103 (32)
Prior revascularization	820 (15)	395 (24)	94 (25)

Prior stroke	265 (4.7)	212 (13)	56 (17)
Heart failure	564 (10)	815 (49)	248 (76)
Diabetes	763 (14)	499 (30)	133 (41)
Hypertension	2373 (42)	1297 (78)	268 (82)
Atrial fibrillation	941 (17)	832 (50)	203 (62)
Dialysis	4 (0.1)	14 (0.8)	36 (11)
COPD	391 (7.0)	408 (25)	85 (26)
Laboratory data at the first visit			
Hemoglobin (g/l), median (IQR)	140 (131-150)	131 (120-142)	124 (110-136)
Nt-pro-BNP (ng/l), median (IQR)	168 (60-544)	1511 (512-3920)	4260 (1720-9050)
eGFR (ml/min/1.73 m2)			
>60	5196 (92)	832 (50)	74 (23)
30-59	414 (7.4)	727 (44)	152 (46)
<30	9 (0.2)	107 (6.4)	101 (31)
Hs-cTnT concentrations			
First visit			
Peak hs-cTnT concentration, (ng/l), median (IQR)	5 (4.9-8)	24 (18-32)	69 (56-95)
Relative change in hs-cTnT concentrations*, median (IQR)	0% (0, 11)	7% (4, 13)	7% (4, 11)
Second visit			

First hs-cTnT concentration (ng/l), median (IQR)	4.9 (4.9-7.7)	24 (18-31)	69 (56-89)
Time between hs-cTnT at the first visit and the second visit, days, median (IQR)	275 (110-614)	175 (79-391)	146 (73-315)
Relative change between hs-cTnT at the first visit and the second visit, median (IQR)	0% (-6, 0)	0% (-10, 9)	-3% (-12, 8)
Medication			
Aspirin	1544 (27)	689 (41)	139 (43)
P2Y12 inhibitors†	381 (6.8)	136 (8.2)	26 (8.0)
Any platelet inhibitor‡	1712 (30)	765 (46)	155 (47)
Beta-blockers	2149 (38)	1122 (67)	234 (72)
ACEi/ARB	1872 (33)	1008 (61)	218 (67)
CCB	1009 (18)	465 (28)	88 (27)
Nitrates	812 (14)	513 (31)	111 (34)
Statins	1658 (30)	689 (41)	132 (40)
Warfarin	465 (8.3)	443 (27)	95 (29)
DOAC	202 (3.6)	135 (8.1)	20 (6.1)
OAC‖	651 (12)	569 (34)	111 (34)

Data are presented as n (%), or median with IQR. *Delta change between minimum and peak hs-cTnT concentrations during the first visit. †Includes treatment with Clopidogrel, Tikagrelor, Dipyradimol or Prasugel. ‡Includes treatment with Aspirin or P2Y12 inhibitors. ‖Includes treatment with DOAC or Warfarin. Abbreviations: ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB: calcium channel blocker; COPD: chronic obstructive pulmonary disease; hs-cTnT:

high-sensitivity cardiac troponin T; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; DOAC: direct oral anticoagulants; NSTEMI: non-ST-segment-elevation myocardial infarction; Nt-pro-BNP: N-terminal pro b-type natriuretic peptide; OAC: oral anticoagulants, UA: unstable angina.

Table S2. Cause-specific mortality according to the temporal change of high-sensitivity cardiac troponin T concentrations at a second visit >30 days after the visit in the emergency department

	Hs-cTnT concentrations at the first visit					
	Stable hs-cTnT concentrations <15 ng/l			**Stable hs-cTnT concentrations ≥15 ng/l**		
Relative change in hs-cTnT >30 days after the first visit	Relative decrease	Stable	Relative increase	Relative decrease	Stable	Relative increase
Number of patients	564 (4.3)	5619 (44)	1495 (12)	1533 (12)	1993 (15)	1665 (13)
<u>Cardiovascular death</u>						
I. Ischemic heart disease						
Number of deaths	3 (0.5)	35 (0.6)	45 (3.0)	90 (5.9)	148 (7.4)	169 (10)
Unadjusted HR (95% CI)	0.84 (0.26-2.73)	Ref.	5.24 (3.37-8.15)	11.5 (7.78-17.0)	15.4 (10.7-22.3)	26.5 (18.4-38.2)
Multivariable adjusted HR* (95% CI)	0.48 (0.11-2.02)	Ref.	2.36 (1.39-4.00)	2.85 (1.77-4.60)	3.17 (1.99-5.05)	4.96 (3.10-7.94)
II. Heart failure/CMP						
Number of deaths	4 (0.7)	7 (0.1)	6 (0.4)	41 (2.7)	59 (3.0)	82 (4.9)
Unadjusted HR (95% CI)	5.60 (1.64-19.1)	Ref.	3.52 (1.18-10.5)	25.5 (11.4-56.9)	29.9 (13.6-65.5)	60.9 (28.1-132)
Multivariable adjusted HR* (95% CI)	5.17 (1.15-23.2)	Ref.	2.12 (0.52-8.64)	8.14 (2.75-24.1)	6.46 (2.16-19.3)	13.6 (4.60-40.2)

III. All other cardiovascular causes						
Number of events	4 (0.7)	42 (0.8)	38 (2.5)	90 (5.9)	143 (7.2)	159 (9.6)
Unadjusted HR (95% CI)	0.94 (0.34-2.61)	Ref.	3.68 (2.37-5.71)	9.52 (6.59-13.7)	12.3 (8.70-17.4)	20.4 (14.5-28.8)
Multivariable adjusted HR* (95% CI)	0.79 (0.28-2.26)	Ref.	1.79 (1.05-3.06)	2.47 (1.56-3.91)	2.26 (1.43-3.56)	3.97 (2.53-6.24)
<u>Non-cardiovascular death</u>						
I. Cancer-related death						
Number of events	14 (2.5)	71 (1.3)	70 (4.7)	63 (4.1)	89 (4.5)	78 (4.7)
Unadjusted HR (95% CI)	1.93 (1.09-3.41)	Ref.	3.97 (2.85-5.52)	3.85 (2.74-5.41)	4.38 (3.20-5.99)	5.68 (4.10-7.85)
Multivariable adjusted HR* (95% CI)	1.42 (0.74-2.75)	Ref.	1.89 (1.24-2.89)	1.74 (1.13-2.67)	1.47 (0.96-2.27)	1.63 (1.03-2.60)
II. Non-cardiovascular non-cancer-related death						
Number of events	14 (2.2)	116 (1.7)	87 (4.7)	174 (9.4)	258 (11)	244 (17)
Unadjusted HR (95% CI)	1.19 (0.68-2.07)	Ref.	3.07 (2.32-4.05)	6.76 (5.34-8.55)	8.12 (6.57-10.2)	16.6 (13.4-20.5)
Multivariable adjusted HR* (95% CI)	0.90 (0.45-1.81)	Ref.	2.15 (1.51-3.07)	3.40 (2.48-4.65)	3.31 (2.42-4.53)	6.15 (4.51-8.39)

Data are presented as n (%). Follow-up for cause-specific death was 31 December 2016. *Multivariable adjustment was made for age, sex, eGFR, prior myocardial infarction, heart failure, prior stroke, prior chronic obstructive pulmonary disease, atrial fibrillation, diabetes, the time between the hs-cTnT concentrations measured at the first visit and the second visit (days), and treatment with aspirin, P2Y12-inhibitors (clopidogrel, prasugrel, dipyramidol, and ticagrelor), oral anticoagulants (Warfarin and direct oral anticoagulants), beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and statins. Abbreviations: CI: confidence interval; CMP: cardiomyopathy; HR: hazard ratio; hs-cTnT: high-sensitivity cardiac troponin T.

Table S3. Subgroups of cause-specific deaths according to the temporal change of high-sensitivity cardiac troponin T concentrations at a second visit >30 days after the visit in the emergency department

Hs-cTnT at the first visit	**Stable hs-cTnT concentrations <15 ng/l**			**Stable hs-cTnT concentrations ≥15 ng/l**		
Hs-cTnT at the second visit	Decrease from first visit	Stable	Increase from first visit	Decrease from first visit	Stable	Increase from first visit
Number of patients	564 (4.3)	5619 (44)	1495 (12)	1533 (12)	1993 (15)	1665 (13)
Subgroups of cardiovascular death						
I. Ischemic heart disease						
Myocardial infarction	2 (0.4)	10 (0.2)	22 (1.5)	35 (2.3)	47 (2.4)	67 (4.0)
Other ischemic heart disease	1 (0.2)	25 (0.4)	23 (1.5)	55 (3.6)	101 (5.1)	102 (6.1)
II. Heart failure/CMP	4 (0.7)	7 (0.1)	6 (0.4)	41 (2.7)	59 (3.0)	82 (4.9)
III. All other cardiovascular causes						
Valvular heart disease	. (.)	3 (0.1)	. (.)	4 (0.3)	10 (0.5)	6 (0.4)
Ischemic stroke	1 (0.2)	13 (0.2)	7 (0.5)	11 (0.7)	18 (0.9)	22 (1.3)
Hemorrhagic stroke	1 (0.2)	4 (0.1)	1 (0.1)	2 (0.1)	9 (0.5)	2 (0.1)
Other cardiovascular causes	2 (0.4)	22 (0.4)	30 (2.0)	73 (4.8)	106 (5.3)	129 (7.8)
Subgroups of non-cardiovascular death						
I. Cancer-related death	14 (2.5)	71 (1.3)	70 (4.7)	63 (4.1)	89 (4.5)	78 (4.7)

II. Non-cardiovascular non-cancer-related death						
Infectious diseases	. (.)	8 (0.1)	7 (0.5)	7 (0.5)	19 (1.0)	33 (2.0)
Lung disease	4 (0.7)	31 (0.6)	20 (1.3)	70 (4.6)	93 (4.7)	119 (7.2)
Urogenital diseases	2 (0.4)	2 (0.04)	. (.)	10 (0.7)	18 (0.9)	20 (1.2)
Hematological diseases	. (.)	3 (0.1)	1 (0.1)	3 (0.2)	1 (0.1)	2 (0.1)
Endocrine diseases	. (.)	8 (0.1)	3 (0.2)	14 (0.9)	32 (1.6)	51 (3.1)
Neurologic diseases	. (.)	10 (0.2)	11 (0.7)	10 (0.7)	19 (1.0)	15 (0.9)
Kidney disease	. (.)	2 (0.04)	. (.)	10 (0.7)	18 (0.9)	20 (1.2)
Digestive system diseases	2 (0.4)	12 (0.2)	11 (0.7)	14 (0.9)	18 (0.9)	20 (1.2)
Psychiatric disease	2 (0.4)	11 (0.2)	7 (0.5)	12 (0.8)	18 (0.9)	25 (1.5)
All other non-cancer-related non-cardiovascular causes	4 (0.7)	31 (0.6)	27 (1.8)	34 (2.2)	40 (2.0)	59 (3.5)

Data are presented as n (%). Follow-up for cause-specific death was 31 December 2016. Abbreviations: CMP: cardiomyopathy; hs-cTnT: high-sensitivity cardiac troponin T.

Table S4. Cardiovascular events according to the temporal change of high-sensitivity cardiac troponin T concentrations at a second visit >30 days after the visit in the emergency department

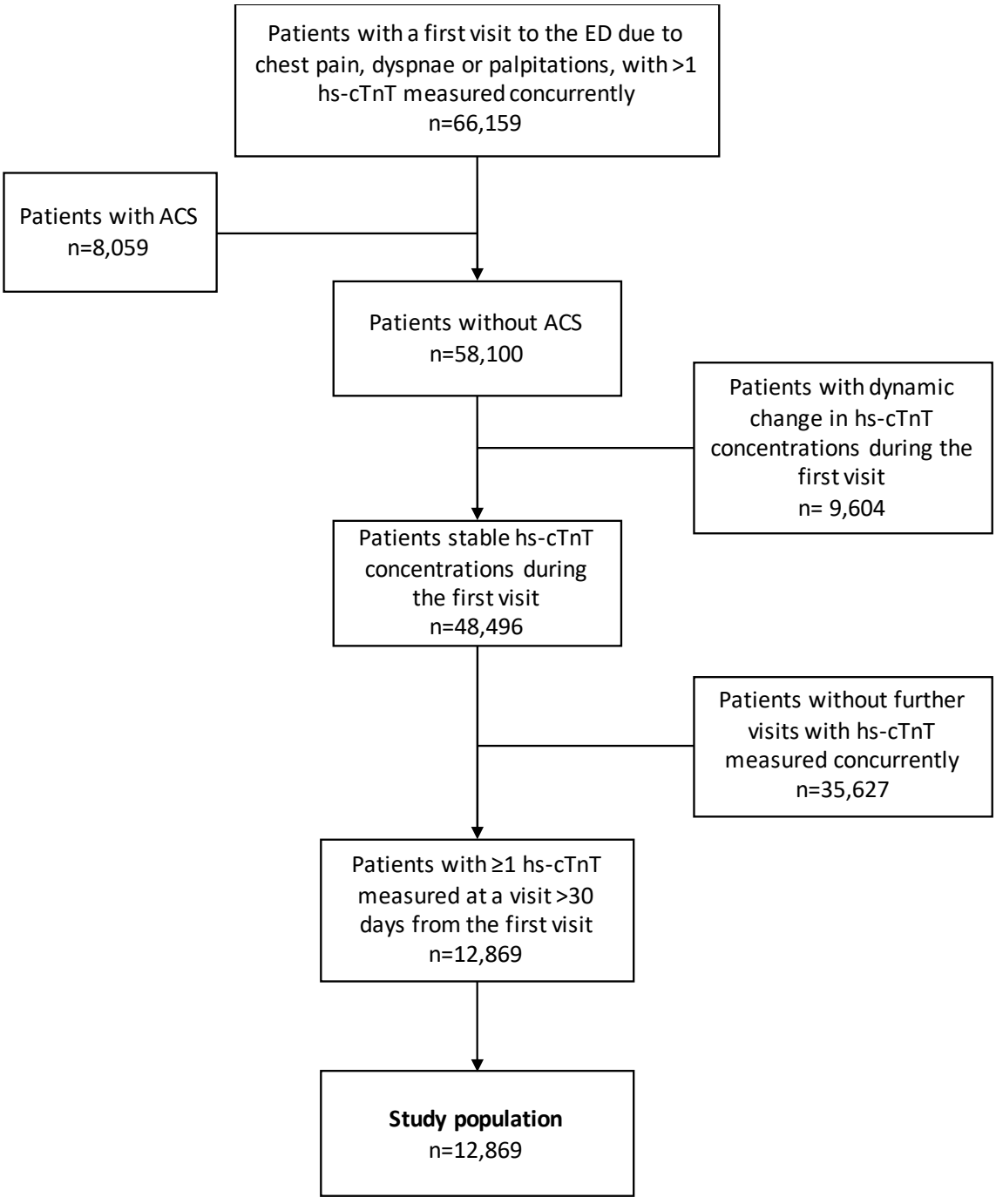
Hs-cTnT at the first visit	**Stable hs-cTnT concentrations <15 ng/l**			**Stable hs-cTnT concentrations ≥15 ng/l**		
Hs-cTnT at the second visit	Decrease from first visit	Stable	Increase from first visit	Decrease from first visit	Stable	Increase from first visit
Number of patients	564 (4.3)	5619 (44)	1495 (12)	1533 (12)	1993 (15)	1665 (13)
MACE†						
Number of events	86 (15)	574 (10)	473 (32)	630 (41)	935 (47)	934 (56)
Events per 100 person-years (95% CI)	8.3 (6.7-10)	5.5 (5.0-5.9)	23 (21-25)	37 (34-40)	49 (46-52)	88 (82-93)
Unadjusted HR (95% CI)	1.50 (1.19-1.88)	Ref.	3.63 (3.21-4.10)	5.17 (4.62-5.79)	6.23 (5.61-6.91)	8.75 (7.88-9.72)
Multivariable adjusted HR* (95% CI)	1.12 (0.85-1.48)	Ref.	2.27 (1.93-2.66)	1.98 (1.70-2.31)	2.10 (1.81-2.45)	2.76 (2.36 - 3.23)
Heart failure						
Number of events	55 (9.8)	304 (5.4)	212 (14)	452 (29)	683 (34)	626 (38)
Events per 100 person-years (95% CI)	4.9 (3.8-6.4)	2.7 (2.4-3.1)	8.3 (7.3-9.5)	23 (21-26)	31 (29-34)	47 (43-50)

Unadjusted HR (95% CI)	1.81 (1.36-2.41)	Ref.	2.87 (2.41-3.42)	6.98 (6.03-8.08)	8.64 (7.54-9.89)	10.8 (9.44-12.5)
Multivariable adjusted HR* (95% CI)	1.28 (0.90-1.82)	Ref.	1.66 (1.32-2.08)	2.21 (1.81-2.69)	2.41 (1.98-2.93)	2.77 (2.26 - 3.39)
Myocardial infarction						
Number of events	21 (3.7)	133 (2.4)	199 (13)	90 (5.9)	115 (5.8)	252 (15)
Events per 100 person-years (95% CI)	1.8 (1.2-2.8)	1.2 (1.0-1.4)	7.9 (6.9-9.1)	3.8 (3.1-4.6)	3.9 (3.2-4.7)	15 (13-17)
Unadjusted HR (95% CI)	1.56 (0.98-2.47)	Ref.	6.12 (4.91-7.62)	2.73 (2.09-3.56)	2.72 (2.12-3.49)	8.16 (6.61-10.1)
Multivariable adjusted HR* (95% CI)	1.21 (0.67-2.17)	Ref.	4.36 (3.23-5.85)	1.77 (1.25-2.51)	1.58 (1.11-2.25)	4.89 (3.54-6.76)
Stroke						
Number of events	19 (3.4)	198 (3.0)	90 (6.0)	104 (6.8)	130 (6.5)	106 (6.4)
Events per 100 person-years (95% CI)	1.6 (1.0-2.5)	1.5 (1.3-1.7)	3.3 (2.7-4.0)	4.3 (3.5-5.2)	4.4 (3.7-5.2)	5.5 (4.6-6.7)
Unadjusted HR (95% CI)	1.10 (0.68-1.76)	Ref.	2.15 (1.67-2.78)	2.64 (2.07-3.38)	2.64 (2.10-3.33)	3.01 (2.35-3.84)

Multivariable adjusted HR* (95% CI)	0.86 (0.47-1.57)	Ref.	1.47 (1.05-2.05)	1.41 (1.01-1.95)	1.19 (0.85-1.66)	1.26 (0.88-1.66)

Data are presented as n (%). *Multivariable adjustment was made for age, sex, eGFR, prior myocardial infarction, heart failure, prior stroke, prior chronic obstructive pulmonary disease, atrial fibrillation, diabetes, the time between the hs-cTnT concentrations measured at the first visit and the second visit (days), and treatment with aspirin, P2Y12-inhibitors (clopidogrel, prasugrel, dipyramidol, and ticagrelor), oral anticoagulants (Warfarin and direct oral anticoagulants), beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and statins. Note: data on covariates at the time of visit 2 were used. †Includes myocardial infarction, heart failure hospitalization, stroke or cardiovascular death. Abbreviations: CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular event.

Figure S1. Selection of the study population



Abbreviations: ACS: Acute coronary syndrome; ED: emergency department; hs-cTnT: high-sensitivity cardiac troponin T; MI: myocardial infarction.

Figure S2. The most common discharge diagnoses at the first and second visit.

Most common discharge diagnoses at the first visit	
Hs-cTnT <15 ng/l	**Hs-cTnT ≥15 ng/l**
1. Symptoms diagnoses, 3947 (56) (R00-09)	1. Symptoms diagnoses, 1464 (30) (R00-09)
2. AF, 441 (6.3) (I48)	2. HF, 690 (14) (I50)
3. Observation for unspecified suspected condition, 339 (4.8) (Z03)	3. AF, 516 (11) (I48)
4. AP, 310 (4.4) (I20.9)	4. COPD, 228 (4.7) (J44)
5. Unspecified pain, 210 (3.0) (M79)	5. AP, 227 (4.7) (I20.9)
Missing data: 673 (8.8)	*Missing data: 323 (6.2)*

Most common discharge diagnoses at the second visit					
Decrease in hs-cTnT from first visit	**Stable hs-cTnT**	**Increase in hs-cTnT from first visit**	**Decrease in hs-cTnT from first visit**	**Stable hs-cTnT**	**Increase in hs-cTnT from first visit**
1. Symptoms diagnoses, 213 (41) (R00-09)	1. Symptoms diagnoses, 2475 (48) (R00-09)	1. Symptoms diagnoses, 427 (30) (R00-09)	1. Symptoms diagnoses, 422 (29) (R00-09)	1. Symptoms diagnoses, 510 (27) (R00-09)	1. Symptoms diagnoses, 292 (19) (R00-09)
2. AF, 51 (10) (I48)	2. AF, 270 (5.3) (I48)	2. AF, 139 (10) (I48)	2. HF, 137 (9.6) (I50)	2. HF, 241 (13) (I50)	2. HF, 209 (13) (I50)
3. General symptoms and signs of illness, 39 (7.6) (R50)	3. General symptoms and signs of illness, 256 (5.0) (R50)	3. MI, 88 (6.3) (I21, I22)	3. AF, 110 (7.7) (I48)	3. AF, 128 (6.9) (I48)	3. MI, 111 (7.1) (I21, I22)
4. Abdominal pain, 19 (3.7) (R10)	4. Abdominal pain, 203 (4.0) (R10)	4. General symptoms and signs of illness, 64 (4.6) (R50)	4. General symptoms and signs of illness, 72 (5.0) (R50)	4. COPD, 92 (4.9) (J44)	4. AF, 93 (5.9) (I48)
5. AP, 16 (3.1) (I20.9)	5. Unspecified pain, 194 (3.8) (M79)	5. AP, 40 (2.9) (I20.9)	5. COPD, 58 (4.1) (J44)	5. General symptoms and signs of illness, 73 (3.9) (R50)	5. COPD, 93 (5.9)
Missing data: 49 (8.7)	*Missing data: 480 (8.5)*	*Missing data: 93 (6.2)*	*Missing data: 102 (6.7)*	*Missing data: 130 (6.5)*	*Missing data: 91 (18)*

Abbreviations: AF: atrial fibrillation; AP: stable angina pectoris; COPD: chronic obstructive pulmonary disease; HF: heart failure; hs-cTnT: high-sensitivity cardiac troponin T; MI: myocardial infarction.