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# Outcomes in Patients With Chest Pain Discharged After Evaluation Using a High-Sensitivity Troponin T Assay

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## ABSTRACT

**BACKGROUND** Most patients with chest pain are discharged from the emergency department (ED) with the diagnosis "unspecified chest pain." It is unknown if evaluation with a high-sensitivity troponin T (hsTnT) assay affects prognosis in this large population.

**OBJECTIVES** The aim was to investigate whether the introduction of an hsTnT assay is associated with reduced incidence of major adverse cardiac events (MACEs) and cardiovascular (CV) risk profile in patients with chest pain discharged from the ED.

**METHODS** The study included 65,696 patients with "unspecified chest pain" discharged from 16 Swedish hospital EDs between 2006 and 2013 in which an hsTnT assay was introduced as the clinical routine. Patients evaluated with a conventional and an hsTnT assay were compared regarding the occurrence of 30-day MACE and CV risk profile based on information from national registries. Patients directly discharged and those discharged after an initial admission were analyzed separately.

**RESULTS** Fewer directly discharged patients experienced a MACE when evaluated with an hsTnT compared with a conventional assay (0.6% vs. 0.9%; odds ratio [OR]: 0.7; 95% confidence interval [CI]: 0.57 to 0.83). In contrast, more patients discharged after an initial admission experienced a MACE when evaluated with an hsTnT (7.2% vs. 3.4%; OR: 2.18; 95% CI: 1.76 to 2.72). Admitted patients had a higher general CV risk profile when evaluated with hsTnT, whereas directly discharged patients had a lower general CV risk profile with the same test.

**CONCLUSIONS** Patients directly discharged from the ED with unspecified chest pain experienced fewer MACEs and had a better risk profile when evaluated with hsTnT. Our findings suggest that more true at-risk patients were identified and admitted. The implementation of hsTnT assays in Swedish hospitals has improved evaluations in the ED.
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Chest pain is one of the most common reasons to seek medical care in the emergency department (ED) (1-3). Most patients presenting with chest pain to the ED do not have an acute cardiac event (4-7) and, after evaluation, the majority are discharged with the diagnosis "chest pain of unknown cause" or "unspecified chest pain" (2). To distinguish the patients with acute cardiac events and prevent unnecessary hospital admission, a structured evaluation should be used (8). Nevertheless, approximately 1% of patients discharged with unspecified chest pain from the ED experience a major

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adverse cardiac event (MACE) within 30 days (9). By introducing cardiac troponin T (cTnT) assays with higher sensitivity, diagnostic accuracy has improved in patients with suspected acute coronary syndrome (ACS) (1,7,10–12). However, it has not been reported previously whether the clinical use of newer troponin assays has affected the MACE rate in patients discharged with the diagnosis of unspecified chest pain.

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This study therefore aimed to investigate whether the implementation of high-sensitivity TnT (hsTnT) assays in Swedish hospitals resulted in reduced incidence of MACE in patients with chest pain discharged from the ED. A secondary objective was to study the risk factor profile of discharged patients in relation to their evaluation with different cTnT assays.

## METHODS

This registry-based cohort study included all patients age 18 years and older who were discharged with the diagnosis "unspecified chest pain" (defined as code R07.1-4 per the International Classification of Diseases-10th edition [ICD-10]) from Swedish hospitals with emergency and admission service between July 2006 and November 2013 in which an hsTnT assay was introduced as clinical routine. The study was based on data from 4 national Swedish registries: the National Inpatient Register; the National Outpatient Register; the Prescribed Drug Register; and the Causes of Death Register. Personal identification numbers were used to link information among the 4 registries; each patient was included only once. The National Board of Health and Welfare (NBHW) administers the registries and provided data for statistics and research (13). ED service was defined as hospitals with emergency and admission service, coded as 046 according to the NBHW's classification of clinics. The dataset originally included 82,922 patients and contained data from 35 Swedish hospitals (**Figure 1**). Hospitals without information on the troponin assay used were excluded. All patients in the study were divided into 2 groups depending on whether they had been discharged after an initial admission at an acute short-term ward or observation unit at the emergency service or whether they were discharged directly from the ED. All patients with a reported discharge date in addition to an admission date were considered to have been admitted. Patients with only an admission date and without a record of a following hospitalization were considered to have been sent home directly from the ED.

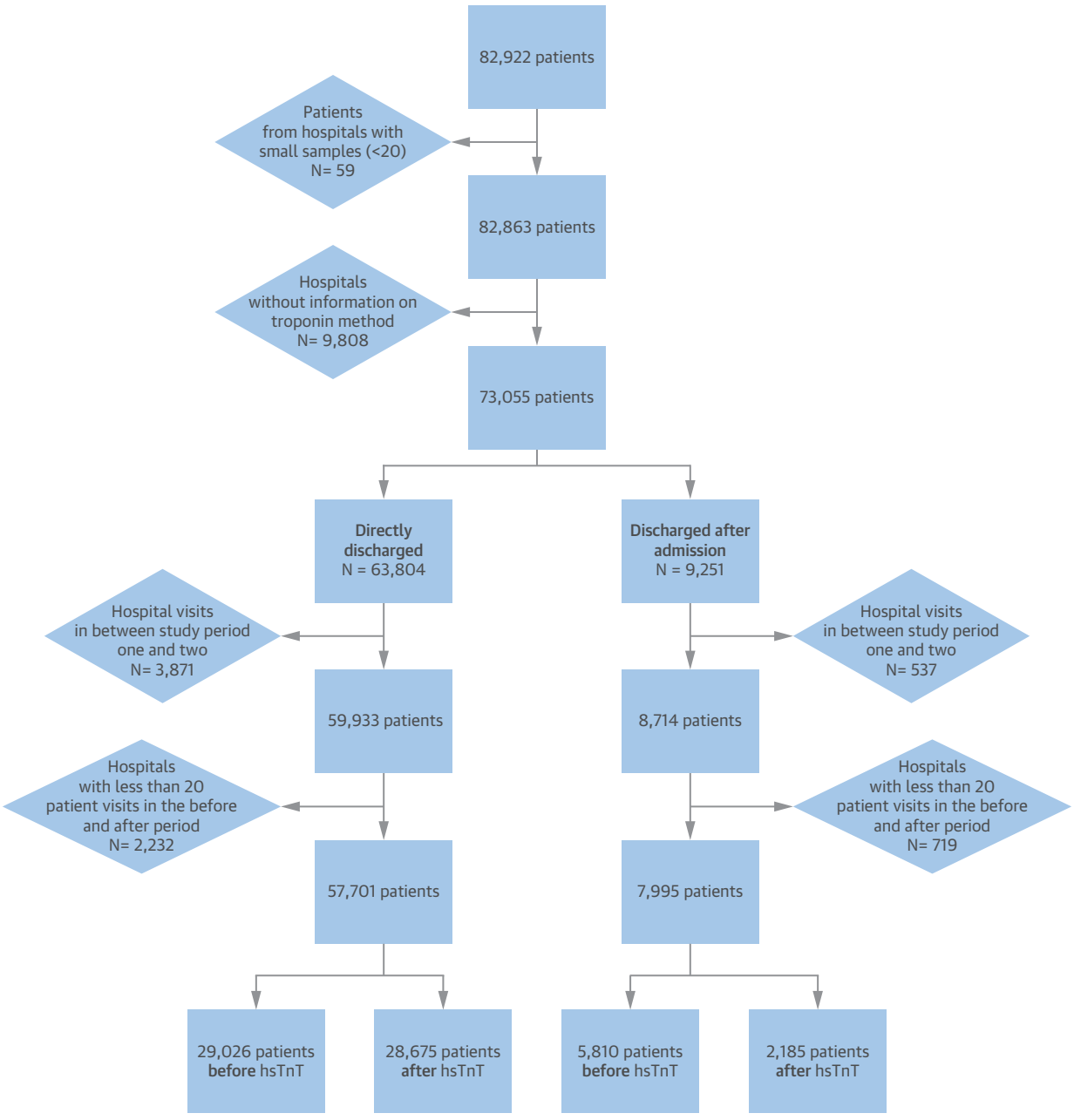
**HIGH-SENSITIVITY ASSAY USED.** During the study period, the current iteration of the cTnT assay (Roche Diagnostics, Basel, Switzerland) was the only method with higher precision in use; it was implemented in 16 hospitals. For this assay, the 99th percentile for measuring cTnT among healthy controls is 14 ng/l and the lowest concentration measurable with a 10% coefficient of variation is 13 ng/l (14). In this study, we refer to this assay with its "high sensitivity" as hsTnT. The analytical profile of conventional assays in use could be collectively termed as sensitive; these assays are referred to as "conventional." Several conventional assays were in use. The cTnT was used in 10 hospitals with a total of 16,836 visits; for this assay, the 99th percentile among healthy controls is 0.01 mg/l and the lowest concentration measurable with a 10% coefficient of variation is 0.04 mg/l. A cardiac troponin I assay (Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania) was used in 2 hospitals with a total of 3,710 visits; for this assay, the 99th percentile among healthy controls is 0.07 μg/l and the lowest concentration measurable with a 10% coefficient of variation is 0.06 μg/l. A cardiac troponin I assay (Beckman Coulter, Inc., Brea, California) assay was used in 2 hospitals with a total of 9,218 visits; for this assay, the 99th percentile among healthy controls is 0.04 μg/l and the lowest concentration measurable with a 10% coefficient of variation is 0.06 μg/l. A combination of these assays was used in 2 hospitals with a total of 4,104 visits.

Information on biomarker assays had been obtained from representatives of all hospitals participating in SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies) (15). The date of introduction of the hsTnT assay, according to SWEDEHEART, was crosschecked with information obtained from the manufacturer by personal communication. The study population was divided into 2 categories consisting of all patients with visits before the implementation of the hsTnT assay at each respective hospital (period 1) and all patients with visits thereafter (period 2). In case the date of introduction of the new assay differed between SWEDEHEART and the manufacturer, the earliest date was used for the end of period 1 and the latest date was used as the start of period 2. To avoid systematic reporting errors, patients with visits within 2 weeks after the change to the hsTnT assay were excluded.

**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndrome
**CI** = confidence interval
**cTnT** = cardiac troponin T
**ED** = emergency department
**hsTnT** = high-sensitivity troponin T
**ICD-10** = International Classification of Diseases-10th edition
**MACE** = major adverse cardiac event(s)
**MI** = myocardial infarction
**NBHW** = National Board of Health and Welfare
**OR** = odds ratio

**FIGURE 1 Exclusion Process**




After exclusions, 65,696 of the original 82,922 patients remained. "Discharged after admission" denotes patients discharged after an initial admission at the emergency service and "directly discharged" denotes patients who were discharged directly from the emergency department. hsTnT = high-sensitivity troponin T.

Each hospital was required to have a minimum of 20 observations during each of the 2 periods. After exclusions, 65,696 patients from 16 different hospitals were finally included in the data analysis.

**OUTCOME AND VARIABLES.** The outcome in this study was any MACE within 30 days of discharge. MACE was defined as a hospital stay with myocardial infarction (MI) as the main diagnosis (ICD-10: I21 or I22); unplanned revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery, defined as discharge with any operation code of FNA, FNB, FNC, FND, FNE, FNF, or FNG);

or all-cause mortality. Information about patient outcomes was collected from the Swedish National In- and Outpatients registry and the national Causes of Death registry. Patients' medical history was collected from the Swedish National In- and Outpatients registry. History of acute MI was defined as a previous hospitalization with the following main discharge diagnosis codes: ICD-9: 410 and ICD-10: I21, I22. Information about obtained prescribed medications was retrieved from the Prescribed Drug Registry. This has been described in detail previously (9).

**STATISTICAL ANALYSIS.** Potential association between study period and continuous and categorical background variables was analyzed using 2 sample Student *t* test and chi-square test, respectively. Chi-square test was also used in the bivariate analysis between troponin assay and the different outcomes. To estimate odds ratios (ORs) between troponin assay and MACE, univariate and multivariate logistic regression was used.

To determine which variables to control for in the multivariate setting, we ran several univariate logistic regression models with MACE as outcome and age (using restricted cubic spline), sex, diabetes mellitus, hyperlipidemia, hypertension, obesity, previous MI, and previous heart failure as predictors. All variables but obesity were statistically significant in the univariate setting and were therefore included in the multivariate models. Because troponin assays are highly sampling-time dependent, we decided to adjust for date of ED visit in the multivariate models, regardless of statistical significance.

The statistics were calculated using SPSS Statistics, version 22 (IBM, Armonk, New York), and Stata, version 13 (StataCorp, College Station, Texas). A p value $<0.05$ was considered significant.

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Stockholm with ethical review numbers 2013/1529-31/3 and 2014/2049-32e.

## RESULTS

This study included a total of 65,696 patients discharged with unspecified chest pain between 2006 and 2013 from 16 Swedish hospitals that introduced the hsTnT assay during this period. The median (range) date of introduction of the hsTnT assay (start of study period 2) was May 3, 2010 (August 10, 2009, to May 10, 2011). The median (range) of study period 1 and 2 was 42 (35 to 59) months and 33 (30 to 37) months, respectively. The majority of the patients, 57,701 (88%), were discharged directly from the ED, whereas 7,995 (12%) were discharged after an initial short-term ward admission within the ED (**Figure 1**). Baseline characteristics of the study population, divided into directly discharged and patients discharged after admission, are presented in **Tables 1 and 2**. The patients discharged after admission were older and had more cardiovascular risk factors and previous cardiovascular diseases compared with the directly discharged patients, independent of study period. The proportion of those discharged with the diagnosis R07.4 after a short admission to those discharged directly was lower during study period 2 compared with study period 1 (1,972 of 7,455 [26.5%] vs. 4,908 of 10,460 [46.9%]; $p < 0.001$) in comparable hospitals.

Among patients with chest pain directly discharged from the ED, cardiovascular risk factors such as hypertension and obesity, as well as a history of cardiovascular disease, were more common when a conventional assay was in use (period 1) compared with period 2 (**Table 1**). A total of 270 patients (0.9%) experienced a MACE within 30 days before the introduction of the hsTnT assay compared with 185 patients (0.6%) after its introduction ($p < 0.001$) (**Table 3**). In univariate logistic regression analysis, the study period with use of the hsTnT assay was significantly associated with fewer MACE (OR: 0.70; 95% confidence interval [CI]: 0.57 to 0.83) (**Figure 2**).

**TABLE 1 Characteristics of Directly Discharged Patients**

| | Conventional Assays (n = 29,026) | hsTnT Assays (n = 28,675) | p Value |
|---|---|---|---|
| Age, yrs | 50.2 ± 18.2 | 48.9 ± 18.6 | <0.001 |
| Sex | | | 0.350 |
| Female | 14,845 (51.1) | 14,777 (51.5) | |
| Male | 14,181 (48.9) | 13,898 (48.5) | |
| Hospital type | | | <0.001 |
| University | 21,135 (72.8) | 22,307 (77.8) | |
| County | 2,767 (9.5) | 2,630 (9.2) | |
| Local | 5,124 (17.7) | 3,738 (13.0) | |
| Medical history | | | |
| Hypertension* | 7,946 (27.4) | 7,602 (26.5) | 0.019 |
| Hyperlipidemia* | 1,960 (6.8) | 2,043 (7.1) | 0.079 |
| Diabetes mellitus* | 2,045 (7.0) | 1,986 (6.9) | 0.573 |
| Obesity | 570 (2.0) | 792 (2.8) | <0.001 |
| Atrial fibrillation | 1,662 (5.7) | 1,586 (5.5) | 0.310 |
| Stroke | 910 (3.1) | 788 (2.7) | 0.006 |
| MI | 1,609 (5.5) | 1,356 (4.7) | <0.001 |
| Angina pectoris | 2,579 (8.9) | 1,826 (6.4) | <0.001 |
| Heart failure | 1,150 (4.0) | 993 (3.5) | 0.002 |
| Peripheral vascular disease | 293 (1.0) | 256 (0.9) | 0.149 |

Values are mean ± SD or n (%). *Diagnosis and/or prescriptions for drugs to treat the condition. hsTnT = high-sensitivity troponin T; MI = myocardial infarction.

**TABLE 2 Characteristics of Patients Discharged After Admission**

| | Conventional Assays (n = 5,810) | HsTnT Assays (n = 2,185) | p Value |
|---|---|---|---|
| Age, yrs | 61.8 ± 15.6 | 63.3 ± 15.8 | <0.001 |
| Sex | | | 0.460 |
| Female | 2,790 (48.0) | 1,029 (47.1) | |
| Male | 3,020 (52.0) | 1,156 (52.9) | |
| Hospital type | | | <0.001 |
| University | 4,908 (84.5) | 1,972 (90.3) | |
| County | 870 (15.0) | 153 (7.0) | |
| Local | 32 (0.6) | 60 (2.8) | |
| Medical history | | | |
| Hypertension* | 2,718 (46.8) | 1,153 (52.8) | <0.001 |
| Hyperlipidemia* | 588 (10.1) | 307 (14.1) | <0.001 |
| Diabetes mellitus* | 840 (14.5) | 366 (16.8) | 0.011 |
| Obesity | 135 (2.3) | 86 (3.9) | <0.001 |
| Atrial fibrillation | 650 (11.2) | 281 (12.9) | 0.038 |
| Stroke | 420 (7.2) | 171 (7.8) | 0.363 |
| MI | 958 (16.5) | 319 (14.6) | 0.040 |
| Angina pectoris | 1,281 (22.1) | 445 (20.4) | 0.103 |
| Heart failure | 534 (9.2) | 243 (11.1) | 0.009 |
| Peripheral vascular disease | 141 (2.4) | 88 (4.0) | <0.001 |

Values are mean ± SD or n (%). *Diagnosis and/or prescriptions for drugs to treat the condition. Abbreviations as in Table 1.

Among admitted patients, more had cardiovascular risk factors during study period 2, but there was no difference in medical history of cardiovascular diseases (Table 2). A total of 199 patients (3.4%) experienced a MACE within 30 days before compared with 157 patients (7.2%) after the introduction of the hsTnT assay ($p < 0.001$). The individual variables in the composite endpoint MACE (MI, unplanned revascularization, or death) can be seen in Table 3.

In contrast to the directly discharged patients, there was a significant increase in the number of MACE events after the introduction of hsTnT (OR: 2.18; 95% CI: 1.76 to 2.72) among admitted patients. In multivariate logistic regression, when adjusted for age, sex, type of hospital, and medical history (variables included in Tables 1 and 2), the association between the study period (before and after the implementation of the hsTnT assay) and the MACE rate was not significant, neither among directly discharged or patients discharged after admission.

## DISCUSSION

To our knowledge, this is the first study investigating whether the implementation of an hsTnT assay is associated with the incidence of MACE in chest pain patients discharged from the ED. Although the absolute risk reduction was low, patients with chest pain who were directly sent home from the ED after the implementation of the hsTnT assay suffered fewer MACEs within the next 30 days (Central Illustration) and had significantly less cardiovascular disease and fewer risk factors compared with patients analyzed with the conventional assays. Conversely, patients who were discharged after a short admission with the diagnosis of unspecified chest pain had, in general, more cardiovascular risk factors as well as a higher incidence of MACE when the hsTnT assay was in use compared with those analyzed with the conventional assays.

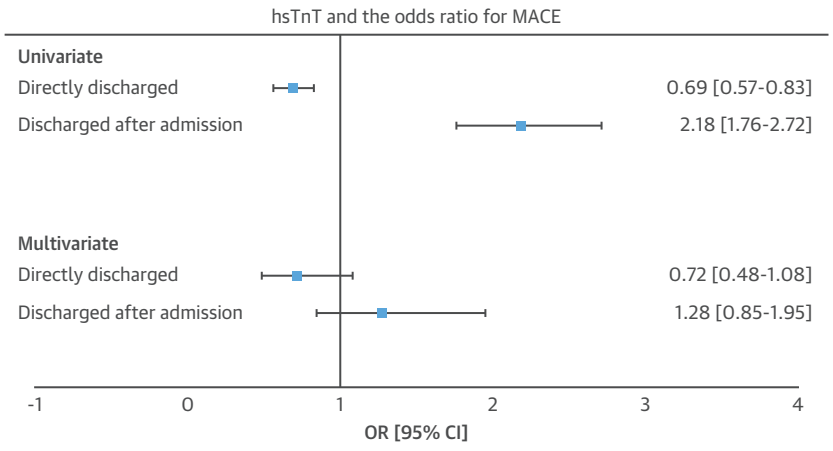
**ASSAY USE AND ADVERSE EVENTS IN DIRECTLY DISCHARGED PATIENTS WITH CHEST PAIN.** We are not aware of any previous studies that have reported if implementation of a high-sensitivity assay was associated to a change in hard outcomes in this clinical context. A previous large retrospective study conducted by Eggers et al. investigated the implementation of cardiac troponin with improved sensitivity by comparing it with a conventional assay in patients admitted to coronary care units (10). They reported that more at-risk patients were admitted, suitable for beneficial therapies, and that there was a significant increase in ACS, both MI and unstable angina; whereas, in a smaller study, there was a reported increase in MI but a decrease of unstable angina (16). Several studies have shown that hsTnT assays have a higher sensitivity for acute MI compared with a conventional assay (4,10,11) as well as a better negative predictive value (11). The results from several studies have advocated that low-risk patients presenting with chest pain at the ED can be discharged safely with a rapid rule-out after the hsTnT assay results (17) alone or in combination with a risk score or algorithm as a tool for rule out (18-20). A large prospective multicenter cohort study by Body et al. also showed that patients with suspected

**TABLE 3 Outcomes**

| | Conventional Assays | hsTnT Assays | p Value |
|---|---|---|---|
| Directly discharged, n | 29,026 | 28,675 | |
| MACE | 270 (0.90) | 185 (0.60) | <0.001 |
| MI | 181 (0.60) | 96 (0.30) | <0.001 |
| Revascularization | 124 (0.40) | 72 (0.30) | <0.001 |
| Death | 60 (0.20) | 51 (0.20) | 0.429 |
| Discharged after admission, n | 5,810 | 2,185 | |
| MACE | 199 (3.43) | 157 (7.19) | <0.001 |
| MI | 142 (2.44) | 110 (5.03) | <0.001 |
| Revascularization | 89 (1.53) | 87 (3.98) | <0.001 |
| Death | 33 (0.57) | 25 (1.14) | 0.007 |

Values are n (%) unless otherwise indicated.
MACE = major adverse cardiac event(s); other abbreviations as in Table 1.

**FIGURE 2 Probability of MACE**




The association between evaluation with an hsTnT assay and major adverse cardiac event(s) (MACE) within 30 days of discharge from the emergency department with unspecified chest pain presented as crude odds ratios (ORs) with 95% confidence intervals (CIs). Abbreviation as in Figure 1.

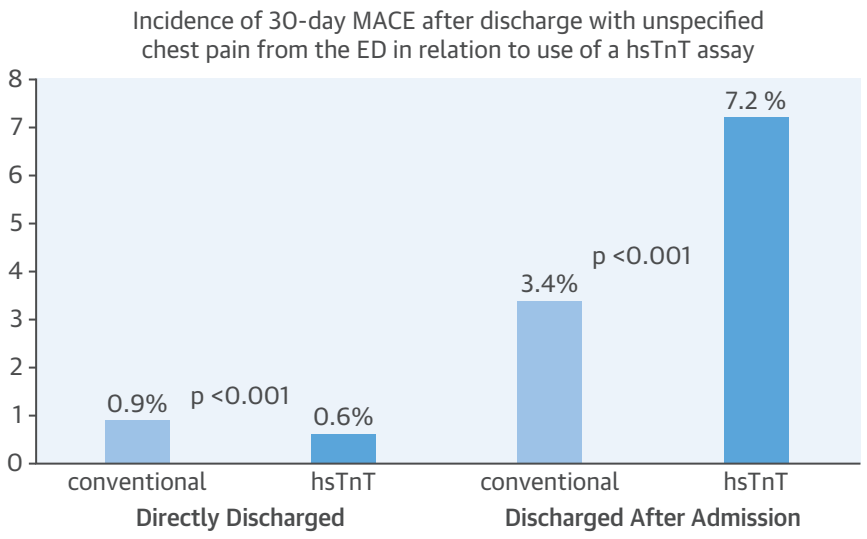
cardiac chest pain who have a negative hsTnT and no ischemia on electrocardiography could have a rapid rule-out, even without serial sampling. The incidence of 30-day MACE in these patients was 1.3%, which could be lowered to 1.1% by setting the cutoff at the limit of blank of the assay (3 ng/l) (17). Kelly et al. (21) conducted a small substudy of a prospective observational study and investigated the risk of MACE and revascularization within 30 days in patients without previously known coronary artery disease using troponin I. These patients were divided into different risk groups, and the "non-high-risk patients" were discharged directly from the ED. This subgroup had a very low risk of MACE: 0.4%, including revascularization (21).

Our results are within the range of estimations of both these studies. However, we report on discharged unselected patients, both previously healthy and with previous MI; moreover, the current study compared 2 different time periods with different assays in use. The patients included were those with unspecified chest pain, thus ruled out from ACS suspicion, and it was the largest study conducted on this patient group. Because it was registry-based, all patients with this diagnosis have been included; whereas, in previous studies, different selection criteria have been applied. We believe therefore that the current study credibly reflects clinical reality.

Evaluation of patients presenting with chest pain can pose a challenge for the physician in the ED. The current study showed that the risk of MACE within 30 days was very low in patients sent home from the ED with unspecified chest pain when using the hsTnT assay. Eggers et al. (10) and Body et al. (17) showed that the number of patients with real ACS who are admitted has increased and more healthy patients can be discharged when the hsTnT assay is used. It is important however that the results be viewed in a clinical context. The demonstrated improvements may also be due to more structured clinical evaluations in the ED. Biomarkers cannot be a substitute for a thorough clinical history, examination, and electrocardiogram, especially not in the setting of unstable angina.

**ASSAY USE AND OUTCOME AFTER ADMISSION FOR CHEST PAIN.** In the current study, we observed that patients discharged after a short admission analyzed with hsTnT had more cardiovascular risk factors and a higher incidence of MACE within 30 days compared with patients analyzed with a conventional assay. Our findings are in line with and extend those of Eggers et al. (10). Their study also showed that patients admitted after the introduction of cTnT with improved sensitivity had higher prevalence of cardiovascular risk factors, comorbidities, and previous manifestations of coronary artery disease compared with the conventional assay. They showed that hsTnT assay use led to an increase in the number of admitted ACS patients (10). A meta-analysis of 17 studies of patients with chest pain carried out by Lipinski et al. (11) also found that hsTnT better identified patients at

**CENTRAL ILLUSTRATION** **MACE in Discharged Patients With Chest Pain**




**Nejatian, A. et al. J Am Coll Cardiol. 2017;69(21):2622–30.**

Risk profile and major adverse cardiac events (MACEs) were studied in patients discharged from the emergency department (ED) with unspecified chest pain at 16 different hospitals before and after the introduction of a high-sensitivity troponin T (hsTnT) assay. Directly discharged and patients discharged after admission were analyzed separately. Directly discharged patients had a lower risk profile and experienced fewer MACE when an hsTnT assay was in use, whereas the opposite was observed in patients discharged after admission. The implementation of hsTnT assays in Swedish hospitals has improved evaluations at the ED.

risk for adverse outcomes during follow-up compared with conventional assays. In patients with baseline hsTnT elevation and a negative conventional assay, there was an incremental increase in nonfatal MI or death (11). Patients presenting with stable or unstable angina had a significantly reduced survival if hsTnT was elevated when conventional assays were undetectable (22). It is of importance to note that this patient group has a higher risk of MACE (11) as even a minor increase in troponin was associated with a higher mortality rate (4). This might suggest why the hsTnT-admitted group in our study had more cardiovascular risk factors and more MACE. The newer assay has detected true at-risk patients because of the higher sensitivity of the method compared with conventional assays. Patients with elevated hsTnT only and an undetectable conventional assay have worse prognosis (11,22); such patients are more likely to have been admitted after the implementation of the hsTnT assay. Furthermore, elevated hsTnT is caused not only by acute MI but also by other factors, such as heart failure, diabetes, renal disease, and age (23-25). Studies have shown that these patients with a multidisease profile have worse prognosis when presenting with ACS (26).

**STUDY LIMITATIONS.** It was a registry-based cohort study based on data collected from 4 national Swedish registries. As such, some cases might have been misdiagnosed or results registered erroneously. Furthermore, there might have been changes in clinical routines at the different hospitals during this time. Also, the diagnosis of unspecified chest pain is based on individual evaluation. Considering the large study population and nationwide coverage, however, this probably should not affect the results. The positive predictive values of most diagnoses in the Inpatient Register are high, 85% to 95% (27), and the Swedish Prescribed Drug Register has had full coverage since 2005 (13). Because fewer hospitals use the NBHW's classification code 046 for admission service compared with emergency service, the majority of the study population consists of directly discharged patients with chest pain and the proportion of those discharged after an admission may not reflect the true proportion. Therefore, a comparison of this proportion between the 2 study periods was only performed in a subgroup with comparable hospitals. These results are only representative of patients discharged with unspecified chest pain and should not be generalized to include all patients with the chief complaint of chest

pain. In the multivariate analysis, when adjusted for age and cardiovascular risk factors, the associations between the implementation of the hsTnT assay and outcome were not significant. The proportion of patients with cardiovascular risk factors differed significantly between the 2 study periods, with more true at-risk patients identified with the hsTnT assay. Because these factors are associated with, or may be on the causal pathway to, the outcome, it was expected that the association between study period and outcome was weakened in the adjusted analysis.

## CONCLUSIONS

This large registry-based study showed that the introduction of the hsTnT assay resulted in 0.3% (3 in 1,000) fewer adverse events in patients directly discharged from the ED with unspecified chest pain. On the contrary, the opposite was observed among these patients if they had been admitted. Our findings supported the idea that more true at-risk patients were identified and admitted. Considering the change in risk factor profiles for discharged and admitted patients with chest pain, together with the very small amount of missed cases in the current study, evaluation with the hsTnT assay appears to be of great help in the ED when deciding whether a patient can be sent home or not.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE:** Discharged patients with chest pain whose evaluation included a higher-sensitivity troponin-T assay faced a lower incidence of adverse events within 30 days compared with those evaluated with conventional assays.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to identify patients in whom hsTnT assays have higher or lower accuracy for detection of acute myocardial ischemic events to optimize the utility of testing.

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**KEY WORDS** cardiovascular risk, discharge, emergency department, major adverse cardiac event