

ORIGINAL ARTICLE

Application of High-Sensitivity Troponin in Suspected Myocardial Infarction

J.T. Neumann, R. Twerenbold, F. Ojeda, N.A. Sørensen, A.R. Chapman, A.S.V. Shah, A. Anand, J. Boeddinghaus, T. Nestelberger, P. Badertscher, A. Mokhtari, J.W. Pickering, R.W. Troughton, J. Greenslade, W. Parsonage, M. Mueller-Hennessen, T. Gori, T. Jernberg, N. Morris, C. Liebetrau, C. Hamm, H.A. Katus, T. Münzel, U. Landmesser, V. Salomaa, L. Iacoviello, M.M. Ferrario, S. Giampaoli, F. Kee, B. Thorand, A. Peters, R. Borchini, T. Jørgensen, S. Söderberg, S. Sans, H. Tunstall-Pedoe, K. Kuulasmaa, T. Renné, K.J. Lackner, A. Worster, R. Body, U. Ekelund, P.A. Kavsak, T. Keller, B. Lindahl, P. Wild, E. Giannitsis, M. Than, L.A. Cullen, N.L. Mills, C. Mueller, T. Zeller, D. Westermann, and S. Blankenberg

ABSTRACT

BACKGROUND

Data regarding high-sensitivity troponin concentrations in patients presenting to the emergency department with symptoms suggestive of myocardial infarction may be useful in determining the probability of myocardial infarction and subsequent 30-day outcomes.

METHODS

In 15 international cohorts of patients presenting to the emergency department with symptoms suggestive of myocardial infarction, we determined the concentrations of high-sensitivity troponin I or high-sensitivity troponin T at presentation and after early or late serial sampling. The diagnostic and prognostic performance of multiple high-sensitivity troponin cutoff combinations was assessed with the use of a derivation–validation design. A risk-assessment tool that was based on these data was developed to estimate the risk of index myocardial infarction and of subsequent myocardial infarction or death at 30 days.

RESULTS

Among 22,651 patients (9604 in the derivation data set and 13,047 in the validation data set), the prevalence of myocardial infarction was 15.3%. Lower high-sensitivity troponin concentrations at presentation and smaller absolute changes during serial sampling were associated with a lower likelihood of myocardial infarction and a lower short-term risk of cardiovascular events. For example, high-sensitivity troponin I concentrations of less than 6 ng per liter and an absolute change of less than 4 ng per liter after 45 to 120 minutes (early serial sampling) resulted in a negative predictive value of 99.5% for myocardial infarction, with an associated 30-day risk of subsequent myocardial infarction or death of 0.2%; a total of 56.5% of the patients would be classified as being at low risk. These findings were confirmed in an external validation data set.

CONCLUSIONS

A risk-assessment tool, which we developed to integrate the high-sensitivity troponin I or troponin T concentration at emergency department presentation, its dynamic change during serial sampling, and the time between the obtaining of samples, was used to estimate the probability of myocardial infarction on emergency department presentation and 30-day outcomes. (Funded by the German Center for Cardiovascular Research [DZHK]; ClinicalTrials.gov numbers, NCT00470587, NCT02355457, NCT01852123, NCT01994577, and NCT03227159; and Australian New Zealand Clinical Trials Registry numbers, ACTRN12611001069943, ACTRN12610000766011, ACTRN12613000745741, and ACTRN12611000206921.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Blankenberg at the University Heart Center Hamburg, Department of General and Interventional Cardiology, Martinistr. 52, 20246 Hamburg, Germany, or at s.blankenberg@uke.de.

Drs. Neumann and Twerenbold and Drs. Westermann and Blankenberg contributed equally to this article.

N Engl J Med 2019;380:2529-40.

DOI: 10.1056/NEJMoa1803377

Copyright © 2019 Massachusetts Medical Society.

CHEST PAIN SUGGESTIVE OF MYOCARDIAL infarction is a leading cause of presentation to the emergency department worldwide.¹ In addition to the electrocardiogram and clinical symptoms, the serial measurement of cardiac troponin is key in ruling out or diagnosing myocardial infarction.²⁻⁷ With the development of high-sensitivity troponin assays, rapid triage algorithms have been created to apply these tests safely in clinical practice.^{6,8-14}

However, some challenges remain. First, with high-sensitivity troponin tests it is difficult to differentiate between patients who present to the emergency department with acute myocardial infarction and those who have other causes of myocardial injury.¹⁵ Second, although it is generally accepted that the initial blood sample for troponin measurement should be obtained immediately on presentation, the appropriate timing of obtaining the second blood sample is a matter of debate, and recommendations vary between 1 hour and 6 hours.^{2,4,9,11,13,16} Third, the long-term prognosis in patients who do not have myocardial infarction but who have persistently elevated high-sensitivity troponin concentrations remains unclear. Comparing outcomes in such patients with those in the general population may increase the understanding of individual risk.¹⁷

We therefore sought to develop a tool integrating high-sensitivity troponin concentration at emergency department presentation, the dynamic change in concentration during serial sampling, and the time between the obtaining of samples in order to provide a flexible method to determine the probability of myocardial infarction and 30-day outcomes. We also sought to use the data regarding high-sensitivity troponin concentrations that had been obtained at emergency department presentation to estimate long-term risk among patients in whom myocardial infarction had been ruled out.

METHODS

STUDY DESIGN

The Calculation of Myocardial Infarction Risk Probabilities to Manage Patients with Suspicion of Myocardial Infarction (COMPASS-MI) project used individual patient-level data from 15 international cohorts of patients who had suspected

myocardial infarction in order to calculate risk probabilities for myocardial infarction with the use of high-sensitivity troponin measurements made at the time of emergency department presentation and, in conjunction with data from 11 population-based cohorts, to estimate long-term risk. The high-sensitivity troponin I and high-sensitivity troponin T assays were partly donated by Roche and Abbott, which had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and all analyses and for the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org. The Standards for Reporting of Diagnostic Accuracy (STARD) checklist for this study is provided in Table S1 in Supplementary Appendix 1, available at NEJM.org.

STUDY POPULATION WITH SUSPECTED ACUTE MYOCARDIAL INFARCTION

Patients who presented to the emergency department with acute symptoms suggestive of myocardial infarction were considered the acute study population. For this population, individual patient-level data from 15 studies prospectively enrolling 23,327 patients who presented to the emergency department with suspected myocardial infarction were combined into one data set. Most of the individual studies have been described previously^{5,9-11,14,18-21}; a detailed description of each study is provided in Supplementary Appendix 1. Patients 18 years of age or older were recruited in 13 countries in three geographic regions (Europe, North America, and Australasia). All the participating studies were approved by local ethics committees and complied with the principles of the Declaration of Helsinki.

Patients with ST-segment elevation myocardial infarction were excluded from this study. Data from 9604 patients from five cohorts available at the time of the first analyses (APACE [Advantageous Predictors of Acute Coronary Syndrome Evaluation], BACC [Biomarkers in Acute Cardiac Care] I, High-STEACS [High-Sensitive Troponin in the Evaluation of Acute Coronary Syndrome], ROMI I [Optimum Troponin Cutoffs for ACS in the ED], and stenoCardia

[Study for Evaluation of Newly Onset Chest Pain and Rapid Diagnosis of Myocardial Necrosis]) were used as the derivation data set, and the results were validated in the remaining 13,047 patients.

Concentrations of high-sensitivity troponin I (Architect platform, Abbott) and high-sensitivity troponin T (Elecsys platform, Roche) were measured as part of routine clinical care or in batches of samples that had been frozen at -80°C . Detailed times at which blood samples were obtained were documented, and the time frame between the first sample at emergency department presentation and serial resampling was grouped into two categories: early resampling (>45 to 120 minutes) and late resampling (>120 to 210 minutes). The diagnosis of myocardial infarction that was originally assigned to each study patient in each cohort was used as the basis for assigning the diagnosis for our study (that is, the diagnosis was not reassessed as part of our analysis). Additional information regarding the troponin assays and the diagnosis of myocardial infarction in the acute study population is provided in Supplementary Appendix 1.

EVALUATION OF DIAGNOSTIC PERFORMANCE IN THE ACUTE STUDY POPULATION

To identify the patients at either low or high risk for myocardial infarction, we selected a range of cutoff concentrations of high-sensitivity troponin at presentation (C1, measured in nanograms per liter) and a range of absolute changes (increase or decrease) in the concentrations of high-sensitivity troponin on serial sampling (C2, measured in nanograms per liter). The selected cutoff concentrations were chosen to represent a wide range of diagnostic performances.^{9,11,12,14,22}

To identify patients at low risk for myocardial infarction, the negative predictive value and the sensitivity for myocardial infarction, as well as the proportion of patients with troponin levels below the selected cutoff level, were calculated. A patient was deemed to be at low risk when both C1 and C2 were below the selected cutoff concentrations. To identify patients at high risk for myocardial infarction, the positive predictive value and the specificity for myocardial infarction, as well as the proportion of patients with troponin levels greater than or equal to the selected cutoff concentration, were calculated. A pa-

tient was deemed to be at high risk when either C1 or C2 was greater than or equal to the selected cutoff concentration. All the analyses were performed separately for patients with early or late resampling and for those with available data for high-sensitivity troponin I or high-sensitivity troponin T.

FOLLOW-UP AND CLINICAL END POINTS

In the acute study population data set, all the patients were followed for at least 1 month to assess death from any cause (except in the High-STEACS study, in which death from cardiac causes only was recorded) or myocardial infarction. In the APACE, BACC, Heidelberg, ProsPECTUS (Prospektive Kohortenstudie zur Evaluation der Diagnostik und der therapeutischen Strategien in der Chest Pain Unit), and stenoCardia studies, patients were followed for 2 years. The short-term prognostic end point was the composite of subsequent myocardial infarction (excluding the index event) or death from any cause at 30 days. The long-term prognostic end point was the composite of subsequent myocardial infarction (excluding the index event) or death from any cause assessed at 1 year and 2 years.

GENERAL POPULATION STUDIES

To provide estimates of long-term outcomes in patients in whom myocardial infarction was ruled out and to compare these outcomes with those in the general population, we used data from the population-based Biomarker for Cardiovascular Risk Assessment in Europe (BiomarCaRE) study, which has been described previously.^{17,23} A total of 11 cohorts from eight countries were included in the investigation, with a maximum follow-up of 28 years. Details of the included studies are provided in Supplementary Appendix 1. Follow-up data from these studies were used to estimate the incidence of myocardial infarction or death from any cause in the general population at 1 year and 2 years.

For the general population studies, the concentration of high-sensitivity troponin I was centrally measured in batched, stored samples by the Abbott Architect assay. Owing to the low percentage of young and healthy persons with detectable concentrations, high-sensitivity troponin T was not measured in persons in the general population.

LONG-TERM RISK ASSESSMENT IN PERSONS WITHOUT MYOCARDIAL INFARCTION

For the long-term risk assessment, we compared the association of single concentrations of high-sensitivity troponin with the incidence of myocardial infarction or death among patients in the acute study population who did not have myocardial infarction and among persons in the general population after detailed matching, in a 1:1 ratio, of the two data sets according to age, sex, presence or absence of hypertension, presence or absence of diabetes, smoking status, and presence or absence of dyslipidemia. Details of the risk prediction and the methods for matching are provided in Supplementary Appendix 1.

STATISTICAL ANALYSIS

The characteristics of the patients were described according to quartiles for continuous variables and according to absolute and relative frequencies for binary variables. For the evaluation of diagnostic performance, the negative predictive value, sensitivity, positive predictive value, and specificity were calculated for multiple combinations of initial troponin concentrations and serial changes in troponin concentrations (C1 and C2, as described above). To examine the generalizability of our findings, the diagnostic performance of these combinations was assessed in a derivation data set and confirmed in a validation data set. For prognostic evaluation, the probabilities of myocardial infarction or death during follow-up were estimated for various concentrations of high-sensitivity troponin with the use of Cox regression analyses. No adjustment for multiple testing was performed. All statistical methods were implemented in R statistical software, version 3.5.0. Details of the statistical methods are provided in Supplementary Appendix 1.

RESULTS**STUDY POPULATION WITH SUSPECTED MYOCARDIAL INFARCTION**

Overall, 22,651 patients with suspected myocardial infarction in the acute study population were enrolled for the present analysis, after the exclusion of 676 patients with ST-segment elevation myocardial infarction (Fig. S1 in Supplementary Appendix 1). Evaluation of diagnostic performance was performed in 9604 patients

and validated in 13,047 patients. The characteristics of the patients at baseline are presented in Table 1 for all patients, and in Table S2 in Supplementary Appendix 1 for each contributing study separately. The final diagnosis of myocardial infarction was adjudicated in 3455 of 22,651 patients (15.3%). Results of early serial sampling (>45 to 120 minutes) of high-sensitivity troponin I and high-sensitivity troponin T were available in 7833 and 9562 patients, respectively; and the results of late serial sampling (>120 to 210 minutes) in 9905 and 10,950 patients, respectively (Table S3 in Supplementary Appendix 1). Information about the diagnostic accuracy of the high-sensitivity troponin tests, as well as assessments of data validation, error, and calibration, are provided in Table S4 and Figures S2 through S10 in Supplementary Appendix 1.

PATIENTS AT LOW RISK FOR MYOCARDIAL INFARCTION

Patients at low risk for myocardial infarction were likely to have very low concentrations of high-sensitivity troponin I or high-sensitivity troponin T at presentation and small absolute changes on serial sampling, resulting in a high negative predictive value for myocardial infarction (for detailed data, see Supplementary Appendix 2, available at NEJM.org). In addition, these patients were at very low risk for myocardial infarction or death from any cause at 30 days. With increasing concentrations of high-sensitivity troponin I or high-sensitivity troponin T at presentation and increasing absolute changes, the negative predictive value steadily decreased, while the overall proportion of patients who were classified as being at low risk increased.

For data presentation, low-risk patients were grouped according to negative predictive value categories of 100 to 99.5%, 99.4 to 99.0%, 98.9 to 98.0%, and 97.9 to 97.0%. Combinations of the high-sensitivity troponin cutoff concentrations were used to assign patients to each of these four categories and to show a wide range of diagnostic performance (Fig. 1). For example, if an institution uses a high-sensitivity troponin I concentration of less than 6 ng per liter at presentation to the emergency department and an absolute change of less than 4 ng per liter after 45 to 120 minutes to identify patients at low risk for myocardial infarction, the negative predictive value for myocardial infarction would be 99.5%

Table 1. Baseline Characteristics of All Patients with Suspected Myocardial Infarction Included in the Diagnostic Evaluation.*

Characteristic	All Patients (N=22,651)	Derivation Data Set (N=9604)	Validation Data Set (N=13,047)	P Value
Median age (IQR) — yr	62.5 (51.0–74.0)	63.0 (51.0–74.0)	62.1 (51.0–74.0)	0.34
Male sex — no./total no. (%)	14,045/22,648 (62.0)	6120/9604 (63.7)	7925/13,044 (60.8)	<0.001
History of hypertension — no./total no. (%)	13,506/22,523 (60.0)	5966/9539 (62.5)	7540/12,984 (58.1)	<0.001
History of hyperlipoproteinemia — no./total no. (%)	10,019/21,167 (47.3)	4911/9508 (51.7)	5108/11,659 (43.8)	<0.001
Diabetes — no./total no. (%)	4045/22,471 (18.0)	1624/9487 (17.1)	2421/12,984 (18.6)	0.003
Smoking status — no./total no. (%)				
Current smoking	4660/22,340 (20.9)	2260/9489 (23.8)	2400/12,851 (18.7)	<0.001
Former smoking	6389/19,317 (33.1)	3287/9488 (34.6)	3102/9829 (31.6)	<0.001
History of CAD — no./total no. (%)	7508/20,911 (35.9)	3059/8625 (35.5)	4449/12,286 (36.2)	0.28
History of myocardial infarction — no./total no. (%)	5507/22,466 (24.5)	2268/9509 (23.9)	3239/12,957 (25.0)	0.05
History of stroke — no./total no. (%)	1813/20,661 (8.8)	959/9482 (10.1)	854/11,179 (7.6)	<0.001
Ischemia signs on ECG — no./total no. (%)	3982/19,001 (21.0)	2083/8471 (24.6)	1899/10,530 (18.0)	<0.001
Symptom onset <3 hr before presentation — no./total no. (%)	7120/19,295 (36.9)	2288/8966 (25.5)	4832/10,329 (46.8)	<0.001
Median body-mass index (IQR)	26.9 (24.2–30.4)	26.6 (24.0–29.7)	27.2 (24.4–30.9)	<0.001
Laboratory measurements				
Median creatinine (IQR) — mg/dl	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.22
Median high-sensitivity troponin I (IQR) — ng/liter				
At emergency department presentation	4.3 (2.0–14.5)	5.0 (2.3–17.4)	3.6 (1.9–11.1)	<0.001
At >45–120 min	4.6 (2.1–15.9)	5.0 (2.2–18.0)	4.1 (2.0–13.2)	<0.001
At >120–210 min	5.0 (2.2–16.2)	6.0 (3.0–21.3)	3.6 (1.9–11.3)	<0.001
Median high-sensitivity troponin T (IQR) — ng/liter				
At emergency department presentation	9.0 (4.6–21.1)	8.6 (4.0–20.0)	9.3 (4.8–22.0)	<0.001
At >45–120 min	8.4 (4.0–19.0)	8.5 (4.6–21.0)	8.3 (4.0–17.3)	0.006
At >120–210 min	9.9 (4.8–26.0)	9.0 (4.4–23.6)	10.0 (4.9–28.0)	<0.001
Cardiac examinations				
Angiography — no./total no. (%)	5064/18,610 (27.2)	2110/8074 (26.1)	2954/10,536 (28.0)	0.004
Revascularization — no./total no. (%)	2563/17,237 (14.9)	1217/8070 (15.1)	1346/9167 (14.7)	0.48
Echocardiography — no./total no. (%)	4979/12,354 (40.3)	1748/3251 (53.8)	3231/9103 (35.5)	<0.001
Final diagnosis of myocardial infarction — no. (%)	3455 (15.3)	1571 (16.4)	1884 (14.4)	<0.001

* Data were missing as follows: on age, for 12 patients in the validation data set; on body-mass index (the weight in kilograms divided by the square of the height in meters) for 2868 in the derivation data set and for 3330 in the validation data set; on the creatinine level, for 216 and 1699, respectively; on the high-sensitivity troponin I concentration, for 478 and 5194, respectively, at emergency department presentation, for 4966 and 9852 at early resampling (>45 to 120 minutes), and for 4232 and 8514 at late resampling (>120 to 210 minutes); and on the high-sensitivity troponin T concentration, for 1808 and 1562 at emergency department presentation, for 4697 and 8392 at early resampling, and for 5098 and 6603 at late resampling. CAD denotes coronary artery disease, ECG electrocardiogram, and IQR interquartile range.

(95% confidence interval [CI], 99.2 to 99.7), with an associated 30-day risk of myocardial infarction or death of 0.2% (95% CI, 0.1 to 0.4); a total of 56.5% (95% CI, 55.4 to 57.6) of the patients in the acute study population would be classified as being at low risk.

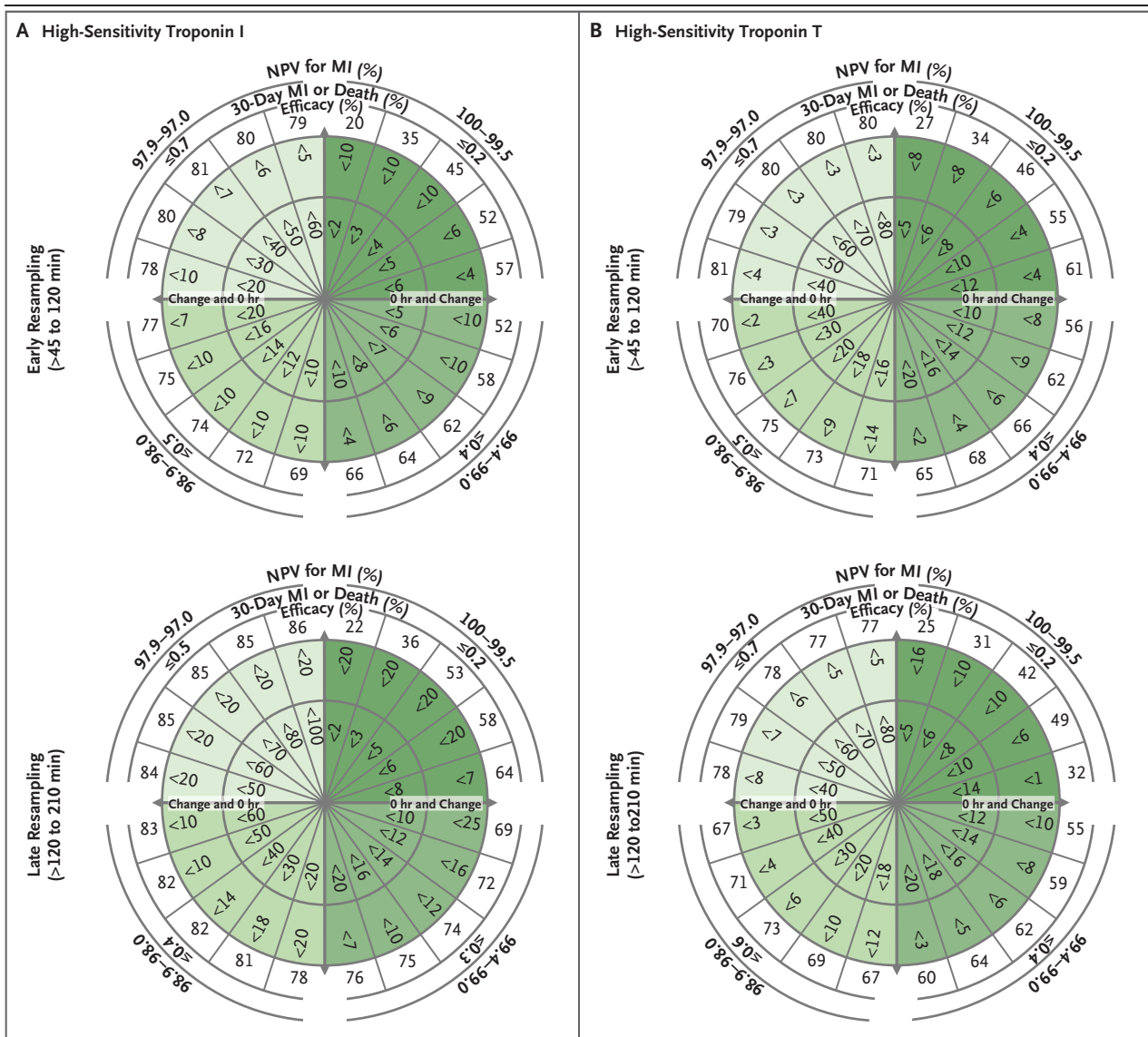


Figure 1. Risk-Assessment Tool for Defining Low Risk of Myocardial Infarction (MI) on the Basis of High-Sensitivity Troponin Cutoff Concentrations.

Panel A shows data during early resampling (top) and late resampling (bottom) of the high-sensitivity troponin I concentration, and Panel B during early resampling (top) and late resampling (bottom) of the high-sensitivity troponin T concentration. To use these diagrams, select the figure panel corresponding to the high-sensitivity troponin assay used (troponin I or troponin T) and determine whether the second blood sample for troponin measurement was obtained early after the first sample (>45 to 120 minutes) or late (>120 to 210 minutes). Then select the cutoff concentration for the initial high-sensitivity troponin measurement (time 0; values in nanograms per liter) from the innermost circle of the panel, and the cutoff concentration for the change (increase or decrease; values in nanograms per liter) in the high-sensitivity troponin concentration on resampling from the second circle. The third circle shows the efficacy of this troponin combination (the proportion of patients who will be designated to have low risk if both values are below the cutoff). The fourth circle shows the 30-day risk of MI or death (excluding the index event) with this troponin combination. The outermost circle shows the negative predictive value (NPV) of this troponin combination for MI. All calculations were based on the overall data set including patients with suspected acute MI and were not adjusted for multiple testing. For simplicity, the values shown in this figure are presented without 95% confidence intervals. Full lists of data according to each increment of high-sensitivity troponin I or high-sensitivity troponin T together with 95% confidence intervals are provided in Supplementary Appendix 2. An interactive risk calculator is provided in Supplementary Appendix 3 and at www.compass-mi.com.

PATIENTS AT HIGH RISK FOR MYOCARDIAL INFARCTION

Patients at high risk for myocardial infarction were likely to have higher concentrations of high-sensitivity troponin I or high-sensitivity troponin T at presentation to the emergency department or a larger absolute change during serial sampling than those at low risk (see Supplementary Appendix 2). In addition, these patients were at higher risk for myocardial infarction or death from any cause at 30 days than were patients in the low-risk category. With decreasing concentrations of high-sensitivity troponin I or high-sensitivity troponin T at presentation or decreasing absolute changes, the positive predictive value was reduced, while the proportion of patients classified as being at high risk increased.

For data presentation, high-risk patients were grouped according to positive predictive value categories of 80.0% or higher, 79.9 to 75.0%, 74.9 to 70.0%, and 69.9 to 65.0%. Combinations of the high-sensitivity troponin cutoff concentrations were used to assign patients to each of these four categories and to show a wide range of diagnostic performance (Fig. 2). For example, in a patient with a high-sensitivity troponin T concentration of at least 100 ng per liter at presentation or an absolute change of at least 12 ng per liter in the window of more than 120 minutes to 210 minutes, the positive predictive value for myocardial infarction would be 76.5% (95% CI, 74.4 to 78.6) with an associated 30-day risk of subsequent myocardial infarction or death of 4.8% (95% CI, 3.7 to 6.0); a total of 14.7% (95% CI, 14.1 to 15.4) of the patients in the acute study population would be classified as being at high risk.

INTERACTIVE RISK-ASSESSMENT TOOL

An interactive risk calculator for the application of individual combinations of the high-sensitivity troponin cutoff concentrations is provided in Supplementary Appendix 3 (available at NEJM.org) and at www.compass-mi.com. This calculator allows for the classification of patients into low-risk and high-risk categories.

PROGNOSIS IN PERSONS WITHOUT MYOCARDIAL INFARCTION

To explore high-sensitivity troponin concentrations as a risk-prediction marker in patients in whom myocardial infarction had been ruled out,

we matched 8345 patients in the acute study population data set with 71,150 persons in the general population data set. (The baseline characteristics of the persons from the general population studies are shown in Table S5 in Supplementary Appendix 1.) We identified 7682 matched pairs (Table 2, and Table S6 in Supplementary Appendix 1). In the matched acute study population, the median follow-up time was 730 days. During follow-up, 271 patients (Kaplan–Meier estimate, 3.9%) had the composite prognostic end point of death or myocardial infarction after 1 year and 398 (6.3%) after 2 years. Among the 7682 matched persons in the general population, the median follow-up time was 8.0 years. During follow-up, 80 persons (1.0%) had the composite prognostic end point of death or myocardial infarction after 1 year and 198 (2.6%) after 2 years. Data on the high-sensitivity troponin I or T concentrations were available for 6434 and 6468 matched patients, respectively.

In both the acute study population and the population-based cohort, high-sensitivity troponin concentrations were strongly associated with myocardial infarction or death after 1 year and 2 years (Fig. 3, and Table S7 in Supplementary Appendix 1). For example, patients presenting with acute chest pain to the emergency department who were found not to have myocardial infarction and who had a high-sensitivity troponin I concentration of more than 10 to 14 ng per liter had a risk of death or myocardial infarction of 4.8% at 1 year and 8.1% at 2 years, as compared with 1.4% and 3.4%, respectively, among persons in the general population.

DISCUSSION

Using data from more than 22,000 patients with suspected acute myocardial infarction from 13 countries, we derived and validated a risk-assessment tool to assign patients to categories of low or high risk for the diagnosis of myocardial infarction and for subsequent myocardial infarction or death at 30 days. Risk assignment was based on high-sensitivity troponin concentrations, their dynamics, and the timing of serial resampling. Furthermore, we provided an estimate of long-term risk that was based on high-sensitivity troponin concentrations in patients presenting with acute symptoms who did not receive a

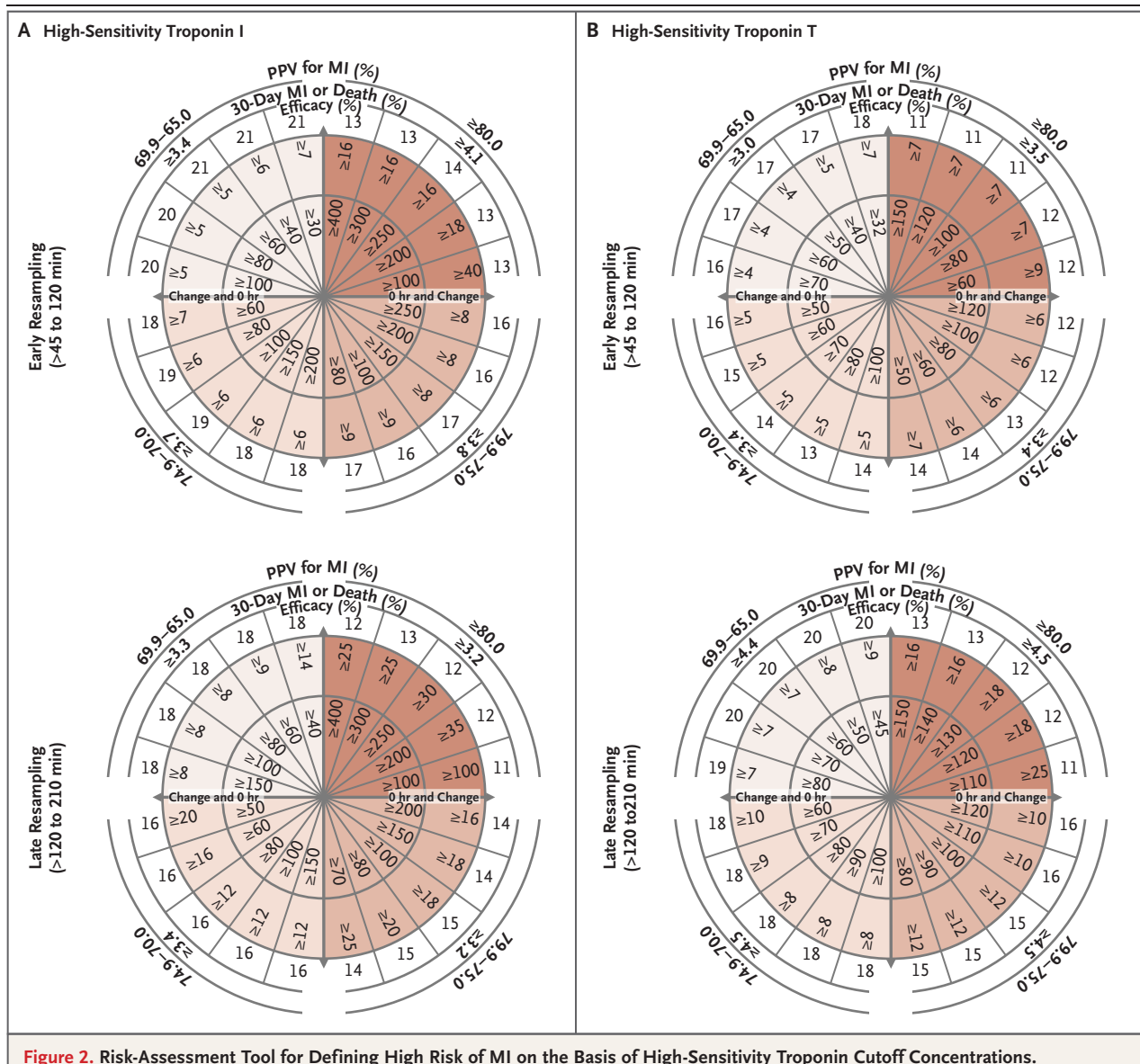


Figure 2. Risk-Assessment Tool for Defining High Risk of MI on the Basis of High-Sensitivity Troponin Cutoff Concentrations.

Panel A shows the data during early resampling (top) and late resampling (bottom) of the high-sensitivity troponin I concentration, and Panel B during early resampling (top) and late resampling (bottom) of the high-sensitivity troponin T concentration. To use these diagrams, select the figure panel corresponding to the high-sensitivity troponin assay used (troponin I or troponin T) and determine whether the second blood sample for troponin measurement was obtained early after the first sample (>45 to 120 minutes) or late (>120 to 210 minutes). Then select the cutoff concentration for the initial high-sensitivity troponin measurement (time 0; values in nanograms per liter) from the innermost circle of the figure panel, and the cutoff concentration for the change (increase or decrease; values in nanograms per liter) in high-sensitivity troponin on resampling from the second circle. The third circle shows the efficacy of this troponin combination (the proportion of patients who will be designated to have high risk if either value is greater than or equal to the cutoff). The fourth circle shows the 30-day risk of MI or death (excluding the index event) with this troponin combination. The outermost circle shows the positive predictive value (PPV) of this troponin combination for myocardial infarction. All calculations were based on the overall data set including patients with suspected MI and were not adjusted for multiple testing. For simplicity, the values shown in this figure are presented without 95% confidence intervals. Full lists of data according to each increment of high-sensitivity troponin I or high-sensitivity troponin T together with 95% confidence intervals are provided in Supplementary Appendix 2. An interactive risk calculator is provided in Supplementary Appendix 3 and at www.compass-mi.com.

Table 2. Baseline Characteristics of All Persons from the General Population and the Matched Patients without Acute Myocardial Infarction (MI) Included in the Prognostic Evaluation.*

Characteristic	Overall General Population (N=71,150)	Matched Patients without Acute MI (N=7682)	Matched Persons from General Population (N=7682)	Standardized Mean Difference
Median age (IQR) — yr	50.9 (41.6–59.7)	61.0 (50.0–72.0)	61.0 (50.0–71.2)	0.0
Male sex — no. (%)	35,048 (49.3)	4989 (64.9)	4989 (64.9)	0.0
Hypertension — no. (%)	29,378 (41.3)	5001 (65.1)	5001 (65.1)	0.0
Dyslipidemia — no. (%)	49,059 (69.0)	3643 (47.4)	3643 (47.4)	0.0
Median body-mass index (IQR)	26.1 (23.5–29.1)	26.6 (24.1–30.0)	27.1 (24.4–30.1)	0.0
Diabetes — no. (%)	3,028 (4.3)	1113 (14.5)	1113 (14.5)	0.0
Daily smoking — no. (%)	19,506 (27.4)	1765 (23.0)	1765 (23.0)	0.0
History of MI or stroke — no./total no. (%)	2,357 (3.3)	1630/7647 (21.3)	368/7682 (4.8)	0.5
Median high-sensitivity troponin I (IQR) — ng/liter†	2.5 (1.5–4.2)	4.0 (2.1–9.0)	3.2 (2.0–5.3)	0.1
Median high-sensitivity troponin T (IQR) — ng/liter‡	NA	7.0 (4.0–14.4)	NA	—

* Details about the definition of the baseline characteristics from the general population are provided in Supplementary Appendix 1. NA denotes not available.

† Data on the high-sensitivity troponin I concentrations were available for 6434 matched patients.

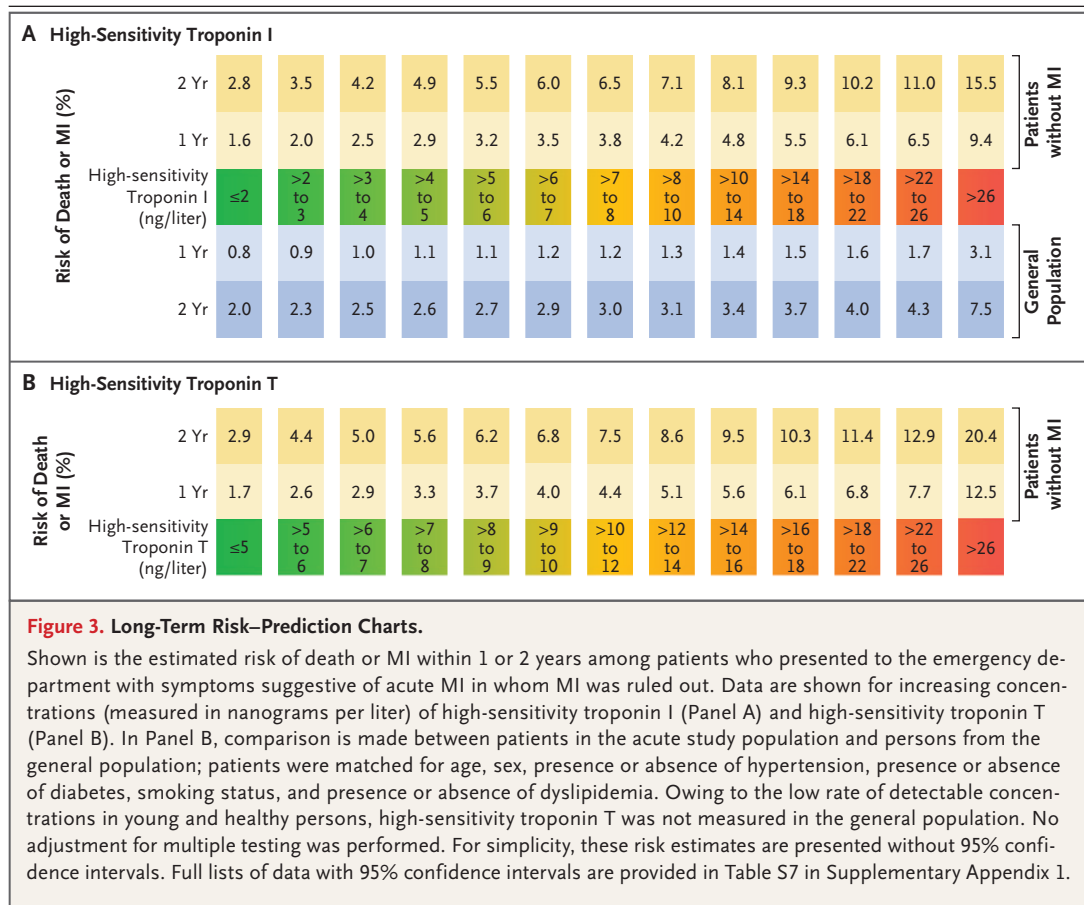
‡ Data on the high-sensitivity troponin T concentrations were available for 6468 matched patients. Owing to the low rate of detectable concentrations in young and healthy persons, high-sensitivity troponin T was not measured in the general population.

diagnosis of myocardial infarction, and we compared these results with those in the general population.

The development of high-sensitivity troponin assays allows for the identification of small-scale myocardial injuries, thus improving the detection of even small myocardial infarctions.^{5,6} However, owing to the higher analytic sensitivity of these assays, clinical management decisions have become more challenging. Consequently, algorithms have been developed to triage patients with suspected myocardial infarction efficiently. These algorithms have inflexible rules for the timing of troponin resampling and cut-off levels for the diagnosis of myocardial infarction. In contrast, the COMPASS-MI approach provides risk probabilities for myocardial infarction using a wide range of cutoff combinations of high-sensitivity troponin I or T concentrations, as well as thresholds that are based on either early or late serial sampling. The assignment of patients to the low-risk category may allow for the discharge of patients after other life-threatening causes of chest pain have been ruled out.

Patients assigned to the high-risk category have a high prevalence of myocardial infarction and a high risk of death. Therefore, the majority of these patients are candidates for early invasive strategies. It would be important for all the remaining patients (those fulfilling neither the low-risk nor high-risk criteria) to undergo detailed clinical evaluation, monitoring, further diagnostic testing, and invasive strategies as appropriate.

Previous studies have shown a strong association of high-sensitivity troponin concentrations and cardiovascular risk among patients with acute coronary syndrome and in the general population.^{17,24} However, considerable uncertainty exists with respect to patients presenting to the emergency department with persistently high but nondynamic concentrations of high-sensitivity troponin who do not receive a diagnosis of myocardial infarction. To estimate risk among such persons, we compared the incidence of myocardial infarction or death in the acute study population of patients in whom myocardial infarction had been ruled out with the incidence in the



matched general population. In both populations, high-sensitivity troponin concentrations were strongly associated with risk of subsequent myocardial infarction or death. These data suggest that the concentration of high-sensitivity troponin may be useful as a risk-prediction biomarker as well as a diagnostic test.

Some limitations of the study merit consideration. The diagnosis of myocardial infarction, which was based on adjudication within each cohort, did not involve a harmonized standard operating procedure. In addition, our analyses included study populations that had different pretest probabilities of myocardial infarction. This might lead to overestimation or underestimation of diagnostic probabilities in different scenarios. A large percentage of the final diagnosis adjudications within the individual studies was performed with the use of the high-sensitivity troponin T data. Consequently, the risk-probability calculation that was based on the high-

sensitivity troponin T data might be slightly skewed in favor of the test. High-sensitivity troponin I concentrations that were determined in the general population were measured in samples that had been stored for up to two decades, which might have affected long-term stability. However, earlier studies showed high stability even after long-term storage.^{25,26}

In conclusion, in the COMPASS-MI project, we developed a tool that integrated the high-sensitivity troponin I or troponin T concentration at presentation, its dynamic change during serial sampling, and the time between the obtaining of samples to allow for the estimation of both the probability of myocardial infarction on emergency department presentation and 30-day outcomes. We also provided estimates of long-term risk on the basis of the initial concentration of high-sensitivity troponin at presentation among patients in whom myocardial infarction was ruled out.

Supported by the German Center for Cardiovascular Research (DZHK).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Johannes T. Neumann, M.D., Raphael Twerenbold, M.D., Francisco Ojeda, Ph.D., Nils A. Sørensen, M.D., Andrew R. Chapman, M.D., Anoop S.V. Shah, M.D., Atul Anand, M.D., Jasper Boeddinghaus, M.D., Thomas Nestelberger, M.D., Patrick Badertscher, M.D., Arash Mokhtari, M.D., Ph.D., John W. Pickering, Ph.D., Richard W. Troughton, M.D., Jaimi Greenslade, Ph.D., William Parsonage, M.D., Matthias Mueller-Hennessen, M.D., Tommaso Gori, M.D., Tomas Jernberg, M.D., Niall Morris, M.D., Christoph Liebetrau, M.D., Christian Hamm, M.D., Hugo A. Katus, M.D., Thomas Münzel, M.D., Ulf Landmesser, M.D., Veikko Salomaa, M.D., Licia Iacoviello, M.D., Ph.D., Marco M. Ferrario, M.D., Simona Giampaoli, M.D., Frank Kee, M.D., Barbara Thorand, M.D., Annette Peters, Ph.D., Rossana Borchini, M.D., Torben Jørgensen, M.D., Stefan Söderberg, M.D., Susana Sans, M.D., Hugh Tunstall-Pedoe, M.D., Kari Kuulasmaa, Ph.D., Thomas Renné, M.D., Ph.D., Karl J. Lackner, M.D., Andrew Worster, M.D., Richard Body, M.B., Ch.B., Ph.D., Ulf Ekelund, M.D., Ph.D., Peter A. Kavsak, Ph.D., Till Keller, M.D., Bertil Lindahl, M.D., Philipp Wild, M.D., Evangelos Giannitsis, M.D., Martin Than, M.D., Louise A. Cullen, M.D., Nicholas L. Mills, M.D., Christian Mueller, M.D., Tanja Zeller, Ph.D., Dirk Westermann, M.D., and Stefan Blankenberg, M.D.

The authors' affiliations are as follows: the University Heart Center Hamburg (J.T.N., R.T., F.O., N.A.S., T.Z., D.W., S.B.), German Center for Cardiovascular Research (DZHK) Partner Site Hamburg-Kiel-Lübeck (J.T.N., N.A.S., T.Z., D.W., S.B.), and the Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Hamburg-Eppendorf (T.R.), Hamburg, the Department of Cardiology, Heidelberg University Hospital (M.M.-H., H.A.K., E.G.), and DZHK Partner Site Heidelberg-Mannheim (M.M.-H., H.A.K., E.G.), Heidelberg, Cardiology I (T.G., T.M.) and Preventive Cardiology and Preventive Medicine (P.W.), Center for Cardiology, and the Center for Thrombosis and Hemostasis (P.W.), University Medical Center of Johannes Gutenberg University Mainz, and the Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Mainz (K.J.L.), Mainz, DZHK Partner Site Rhine-Main and the Department of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim (C.L., C.H., T.K.), the Department of Cardiology, Justus Liebig University of Giessen and Marburg, Giessen (C.L., C.H.), the Department of Cardiology, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin Institute of Health, and DZHK Partner Site Berlin, Berlin (U.L.), and the Institute of Epidemiology, Helmholtz Zentrum, German Research Center for Environmental Health (B.T., A.P.), and DZHK Partner Site Munich Heart Alliance (A.P.), Munich — all in Germany; the Cardiovascular Research Institute Basel and the Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland (R.T., J.B., T.N., P.B., C.M.); the British Heart Foundation Centre for Cardiovascular Science (A.R.C., A.S.V.S., A.A., N.L.M.) and the Usher Institute of Population Health Sciences and Informatics (A.S.V.S., N.L.M.), University of Edinburgh, Edinburgh, the University of Manchester and Manchester University Foundation Trust, Manchester (N.M., R. Body), U.K. Clinical Research Collaboration for Public Health, Queens University of Belfast, Belfast (F.K.), and the Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, Dundee (H.T.-P.) — all in the United Kingdom; the Department of Internal and Emergency Medicine, Lund University, Skåne University Hospital, Lund (A.M., U.E.), the Department of Clinical Sciences, Danderyd University Hospital, Karolinska Institutet, Stockholm (T. Jernberg), the Department of Public Health and Clinical Medicine, and Heart Center, Cardiology, Umeå University, Umeå (S. Söderberg), and the Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, Uppsala (B.L.) — all in Sweden; the Department of Medicine, University of Otago Christchurch, and Emergency Department, Christchurch Hospital, Christchurch, New Zealand (J.W.P., R.W.T., M.T.); the Departments of Emergency Medicine (J.G., L.A.C.) and Cardiology (W.P.), Royal Brisbane and Women's Hospital, Herston, QLD, and the Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove (J.G., W.P., L.A.C.) — all in Australia; the National Institute for Health and Welfare, Helsinki, Finland (V.S., K.K.); the Department of Epidemiology and Prevention, Istituto di Ricovero e Cura a Carattere Scientifico Neuromed, Pozzilli (L.I.), the Department of Medicine and Surgery, Research Center in Epidemiology and Preventive Medicine, University of Insubria, Varese (L.I., M.M.F., R. Borchini), and the Department of Cardiovascular, Dysmetabolic, and Aging-Associated Diseases, National Institutes of Health, Rome (S.G.) — all in Italy; the Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen (T. Jørgensen), the Research Center for Prevention and Health, Capital Region of Denmark, Glostrup (T. Jørgensen), and the Medical Faculty, Aalborg University, Aalborg (T. Jørgensen) — all in Denmark; the Catalan Department of Health, Barcelona (S. Sans); and the Division of Emergency Medicine (A.W.) and the Department of Pathology and Molecular Medicine (P.A.K.), McMaster University, Hamilton, ON, Canada.

REFERENCES

1. Niska R, Bhuiya F, Xu J. National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. *Natl Health Stat Report* 2010;1-31.
2. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.
3. Westermann D, Neumann JT, Sørensen NA, Blankenberg S. High-sensitivity assays for troponin in patients with cardiac disease. *Nat Rev Cardiol* 2017;14:472-83.
4. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol* 2017;70:996-1012.
5. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;361:868-77.
6. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361:858-67.
7. Chapman AR, Lee KK, McAllister DA, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. *JAMA* 2017;318:1913-24.
8. Pickering JW, Than MP, Cullen L, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. *Ann Intern Med* 2017;166:715-24.
9. Neumann JT, Sørensen NA, Schwemer T, et al. Diagnosis of myocardial infarction using a high-sensitivity troponin I 1-hour algorithm. *JAMA Cardiol* 2016;1:397-404.

10. Mueller C, Giannitsis E, Christ M, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med* 2016;68(1):76-87.e4.
11. Rubini Gimenez M, Twerenbold R, Jaeger C, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. *Am J Med* 2015;128(8):861-870.e4.
12. Chapman AR, Anand A, Boeddinghaus J, et al. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. *Circulation* 2017;135:1586-96.
13. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA* 2011;306:2684-93.
14. Mokhtari A, Bornha C, Gilje P, et al. A 1-h combination algorithm allows fast rule-out and rule-in of major adverse cardiac events. *J Am Coll Cardiol* 2016;67:1531-40.
15. Kavsak PA, Jaffe AS, Greene DN, Christenson RH, Apple FS, Wu AHB. Total analytic error for low cardiac troponin concentrations (≤ 10 ng/L) by use of a high-sensitivity cardiac troponin assay. *Clin Chem* 2017;63:1043-5.
16. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol* 2013;62:1242-9.
17. Blankenberg S, Salomaa V, Makarova N, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur Heart J* 2016;37:2428-37.
18. Shortt C, Ma J, Clayton N, et al. Rule-in and rule-out of myocardial infarction using cardiac troponin and glycemic biomarkers in patients with symptoms suggestive of acute coronary syndrome. *Clin Chem* 2017;63:403-14.
19. Shah AS, Anand A, Sandoval Y, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet* 2015;386:2481-8.
20. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol* 2012;59:2091-8.
21. Body R, Carlton E, Sperrin M, et al. Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts. *Emerg Med J* 2017;34:349-56.
22. Rubini Giménez M, Hoeller R, Reichlin T, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. *Int J Cardiol* 2013;168:3896-901.
23. Zeller T, Hughes M, Tuovinen T, et al. BiomarCaRE: rationale and design of the European BiomarCaRE project including 300,000 participants from 13 European countries. *Eur J Epidemiol* 2014;29:777-90.
24. Goldstein SA, Newby LK, Cyr DD, et al. Relationship between peak troponin values and long-term ischemic events among medically managed patients with acute coronary syndromes. *J Am Heart Assoc* 2017;6(4):e005334.
25. Kavsak PA, Worster A, Hill SA, MacRae AR, Jaffe AS. Analytical comparison of three different versions of a high-sensitivity cardiac troponin I assay over 10 years. *Clin Chim Acta* 2017;475:51-5.
26. Zeller T, Tunstall-Pedoe H, Saarela O, et al. High population prevalence of cardiac troponin I measured by a high-sensitivity assay and cardiovascular risk estimation: the MORGAM Biomarker Project Scottish Cohort. *Eur Heart J* 2014;35:271-81.

Copyright © 2019 Massachusetts Medical Society.

POSTING PRESENTATIONS FROM MEDICAL MEETINGS ONLINE

Online posting of an audio or video recording of an oral presentation at a medical meeting, with selected slides from the presentation, is not considered prior publication. Authors should feel free to call or send email to the *Journal's* Editorial Offices if there are any questions about this policy.