Circulation

RESEARCH LETTER

Impact of the US Food and Drug Administration–Approved Sex-Specific Cutoff Values for High-Sensitivity Cardiac Troponin T to Diagnose Myocardial Infarction

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In patients presenting with suspected myocardial infarction (MI), beyond the presence or absence of MI, 4 clinical variables seem to affect high-sensitivity cardiac troponin (hs-cTn) concentrations: age, renal dysfunction, time from chest pain onset, and sex.[1] Among the 4 variables, sex has received the most attention, resulting in uncertainty about the need to abandon the 1 overall cutoff in favor of sex-specific cutoffs for hs-cTn in the diagnosis of MI.[2,3] For high-sensitivity cardiac troponin T (hs-cTnT), the only hs-cTn assay approved by the US Food and Drug Administration (FDA) until now, this does not seem necessary when applying 99th percentiles of healthy individuals, as done outside the United States. With these cutoffs, only a very small percentage (<1%) of women were reclassified as having MI.[2] The FDA-approved use of hs-cTnT differs in using the 99th percentile upper reference limit determined in a reference population matched to the age of patients presenting with suspected MI to the emergency department. As a consequence, the FDA-approved 1 overall (19 ng/L) and sex-specific (women, 14 ng/L; men, 22 ng/L) 99th percentiles are higher compared with the 99th percentiles used outside the United States.

The aim of this analysis was to explore the diagnostic reclassifications when using the FDA-approved sex-specific cutoffs versus the FDA-approved 1 overall cutoff for hs-cTnT in a large diagnostic multicenter study enrolling patients presenting with suspected MI to the emergency department (NCT00470587). Routine clinical care included medical history, physical examination, 12-lead ECG, continuous rhythm monitoring, pulse oximetry, standard blood test, and chest radiography. Levels of cardiac troponin were measured with the local cardiac troponin assay (hs-cTnT in 49.9% of patients) at presentation and serially thereafter as long as clinically indicated. Patients presenting with ST-segment–elevation MI were excluded. The final diagnosis was centrally adjudicated by 2 independent cardiologists using all available clinical information, including serial measurements of hs-cTnT twice: once with the 1 overall cutoff value of 19 ng/L and once with the sex-specific cutoff values (women, 14 ng/L; men, 22 ng/L). The clinical impact of using sex-specific cutoffs was quantified by assessing diagnostic reclassifications when using sex-specific values. The duration of follow-up was 365 days. The study was approved by the local ethics committees, and patients gave informed consent.

Among 4048 patients (1316 women and 2732 men), MI was diagnosed in 634 patients (15.7%; 168 women [12.8%] and 466 men [17.1%]) with the 1 overall cutoff value. Among these, concentrations of hs-cTnT were already greater than or equal to the 1 overall cutoff value at emergency department presentation in 551 patients (sensitivity, 86.9% [95% confidence interval {CI}, 84.0–89.4]; specificity, 86.7% [95% CI, 85.5–87.8]) with near-identical performance in women (sensitivity, 87.5% [95% CI, 81.5–91.7]; specificity, 87.7% [95% CI, 85.7–89.6]) and men (sensitivity, 86.7% [95% CI, 83.3–89.7]; specificity, 86.1% [95% CI, 84.7–87.5]).

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Key Words: myocardial infarction ■ troponin

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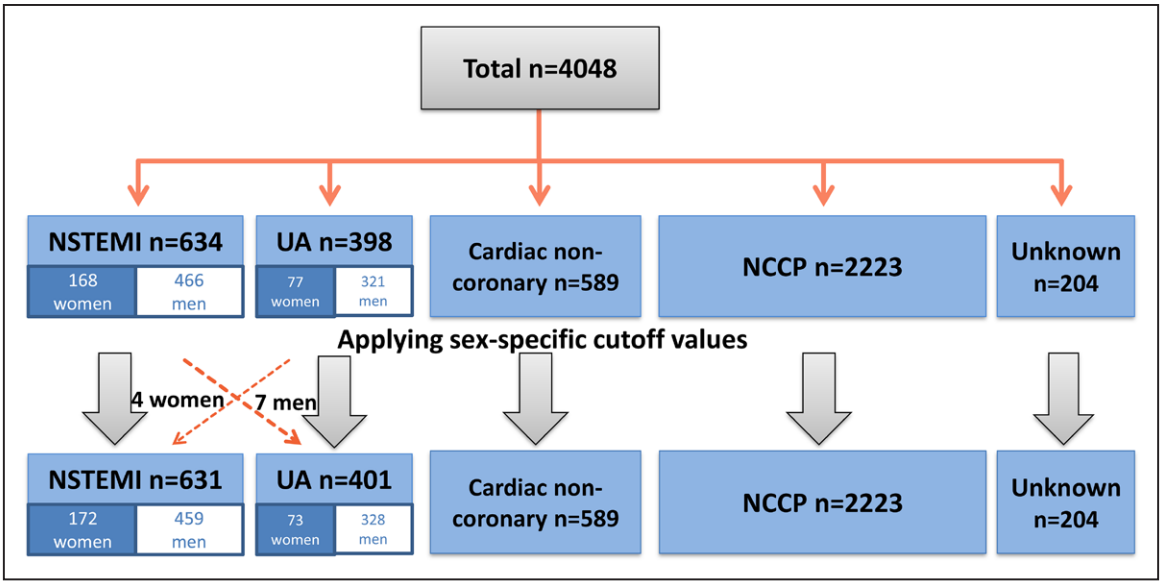

Figure. Diagnostic reclassifications applying sex-specific cutoffs.
Flow diagram showing reclassifications among the 5 diagnostic categories when sex-specific cutoffs for high-sensitivity cardiac troponin T (women, 14 ng/L; men, 22 ng/L) are used compared with the 1 overall cutoff (19 ng/L). NCCP indicates noncardiac chest pain; NSTEMI, non–ST-segment–elevation myocardial infarction; and UA, unstable angina.

After readjudication with sex-specific cutoffs, diagnostic reclassification occurred in 11 patients: 0.3% (95% CI, 0.1–0.5) of all patients and 1.7% (95% CI, 0.9–3.0) of patients with MI. In 4 women, the diagnosis was upgraded from unstable angina to MI, and in 7 men, the diagnosis was downgraded from MI to unstable angina, overall resulting in 631 patients with a final adjudicated diagnosis of MI (versus 634 with the 1 overall cutoff; Figure). None of the reclassified patients died during 365 days of follow-up. Among the 7 downgraded men, 3 underwent percutaneous coronary intervention and 1 underwent bypass grafting during the index admission. Among the 4 upgraded women, 3 underwent percutaneous coronary intervention.

With 14 ng/L used as the 1 overall cutoff value, as done outside the United States,[2] 645 patients (15.9%; 172 women [13.1%] and 473 men [17.3%]) were diagnosed with MI. Again, using the sex-specific cutoffs corresponding to the 1 overall cutoff of 14 ng/L (9 ng/L for women and 15.5 ng/L for men) resulted in very few reclassifications (2 women were upgraded from unstable angina to MI, and 1 man was downgraded from MI to unstable angina).

These findings extend and corroborate recent observations in 2734 patients using the 99th percentiles of healthy individuals in which readjudication with sex-specific 99th percentile values resulted in diagnostic reclassification for MI in 0.11% (95% CI, 0.02–0.32) of all patients and 0.6% (95% CI, 0.13–1.85) of patients with MI.[2]

These findings are explained at least in part by the fact that women presenting with suspected MI are on average 5 to 8 years older than men presenting with suspected MI.[1–3] The older age of female patients, which is associated with higher hs-cTn concentrations, seemed to compensate for the effect of female sex, which per se is associated with lower hs-cTn concentrations, obviating the need to adjust cutoffs.

Following the guidelines in place during enrollment, overall cutoff values were used for the diagnosis of MI and the selection of investigations in the clinical care of patients. This should not have introduced a bias because hs-cTnT concentrations were comparable in women (median, 7.6 [interquartile range, 4.0–16.3] ng/L) and men (median, 8.7 [interquartile range, 5.0–20.0] ng/L; *P*=0.75).

It is important to highlight that the possible clinical use of hs-cTn is currently explored in several additional indications beyond the diagnosis of MI and that pros and cons of using sex-specific cutoffs may differ in other emerging indications.[4]

In conclusion, when the FDA-approved hs-cTnT cutoff values are used, the 1 overall 99th percentile provides very high and near-identical sensitivity and specificity in women and men already at the emergency department. Sex-specific cutoff concentrations reclassify a small percentage of patients.

ARTICLE INFORMATION

Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00470587.

Data sharing: The data and analytical methods will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The study materials will be available for purchase.

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Sources of Funding

The study was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, and Singulex.

Disclosures

The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the letter, and decided to publish. Drs Gimenez, Badertscher, Twerenbold, Boeddinghaus, Nestelberger, and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the letter. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the letter. The letter and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible websites or e-print servers. Dr Gimenez has received research grants from the Swiss Heart Foundation and University of Basel and speaker honoraria from Abbott. Dr Twerenbold has received research support from the Swiss National Science Foundation (P300PB_167803) and speaker honoraria/consulting honoraria from Roche, Abbott, Siemens, Singulex, and Brahms. Dr Boeddinghaus has received research grants from the University of Basel and the Department of Internal Medicine and speaker honoraria from Siemens. Dr Reichlin has received research grants from the Goldschmidt-Jacobson-Foundation, the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the Professor Max Cloëtta Foundation, the Uniscientia Foundation Vaduz, the University of Basel, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria from Brahms and Roche. Dr Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Alere, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, BMS, Brahms, Cardiorentis, Novartis, Roche, Siemens, and Singulex. The other authors report no conflicts.

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