

Impact of the United States FDA approved Sex-specific Cut-off 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, four clinical variables seem to impact on high-sensitivity cardiac Troponin (hs-cTn) concentrations: age, renal dysfunction, time from chest pain onset and sex.¹ Among the four, sex has received most attention resulting in uncertainty regarding the need to abandon the one overall cut-off in favour of sex-specific cut-offs 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 Food and Drug Administration (FDA) until now, this does not seem necessary when applying 99th-percentiles of healthy individuals, as applied outside the United States. With these cut-offs only a very small percentage (<1%) of women were reclassified to have 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 (ED). As the consequence, the FDA-approved one overall (19ng/L) and sex-specific (women 14ng/L, men 22ng/L) 99th-percentiles are higher as compared to 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 versus the FDA-approved one overall cut-offs for hs-cTnT in a large diagnostic multicentre study enrolling patients presenting with suspected MI to the ED (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 cTn were measured using the local cTn 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 based on all available clinical information including serial measurements of hs-cTnT twice: once using the one overall cut-off value of 19ng/L and once using sex-specific cut-off values (women, 14ng/L; men, 22ng/L). The clinical impact of using sex-specific cut-offs was quantified by assessing diagnostic

reclassifications when using sex-specific values. Duration of follow-up was 365 days. The study was approved by the local ethic 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%)) using the one overall cut-off value. Among these, concentrations of hs-cTnT were already greater or equal than the one overall cut-off value at ED presentation in 551 patients (sensitivity, 86.9% [95%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%]).

After readjudication using sex-specific cut-offs, 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 (UA) to MI, and in 7 men the diagnosis was downgraded from MI to UA, overall resulting in 631 patients with a final adjudicated diagnosis of MI (versus 634 using the one overall cut-off (Figure)). None of the reclassified patients died during 365-days follow-up. Among the 7 downgraded men 3 underwent PCI and 1 bypass grafting during the index admission. Among the 4 upgraded women, 3 underwent PCI.

Using 14ng/l as the one overall cut-off 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 cut-offs corresponding to the one overall cut-off of 14 ng/L (9ng/l for women and 15.5 ng/l for men), resulted in very few reclassifications (2 women upgraded from UA to MI and 1 men downgraded from MI to UA).

These findings extend and corroborate recent observations in 2734 patients using the 99th-percentiles of healthy individuals, where readjudication using sex-specific 99th-percentile

values resulted in diagnostic reclassification regarding 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 at least in part are explained by the fact that women presenting with suspected MI are on average 5-8 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 the effect of female sex, that per se is associated with lower hs-cTn concentrations, obviating the need to adjust cut-offs.

Following the guidelines in place during enrolment, overall cut-off values were used for the diagnosis of MI and selection of investigations in the clinical care of patients. This should not have introduced a bias, as hs-cTnT concentrations were comparable in women (median 7.6ng/L (IQR 4.0-16.3) and men (median 8.7ng/L (IQR 5.0-20.0; 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 cut-offs may differ in other emerging indications.⁴

In conclusion, using the FDA-approved hs-cTnT cut-off values, the one overall 99th-percentile provides very high and near-identical sensitivity and specificity in women and men already at ED presentation. Sex-specific cut-off concentrations reclassify a small percentage of patients.

Conflict of interest and 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. Rubini 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 web sites or e-print servers.

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Figure: Diagnostic reclassifications applying sex-specific cut-offs

Flow diagram showing reclassifications among the five diagnostic categories when using sex-specific cut-offs for high-sensitivity cardiac troponin T (women 14 ng/L, men 22 ng/L), compared to the one overall cut-off (19 ng/L). NSTEMI = Non-ST-Segment Elevation Myocardial Infarction; UA = unstable Angina NCCP= non-cardiac Chest Pain