Diagnostic and prognostic value of sex- and age-specific cutpoints for high-sensitivity Troponin T in non-ST-elevation acute coronary syndrome

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ABSTRACT

Introduction: Sex- and age-specific high-sensitivity Troponin T (hs-cTnT) cutpoints for the diagnosis and prognosis in acute coronary syndromes are not well established. We evaluated the use of such dichotomous thresholds for calculation of the GRACE score.
Methods: We analyzed a retrospective cohort study of 1146 patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). Sex-dependent hs-cTnT cutpoints comprised 15.5 ng/L for men and 9.0 ng/L for women, while the sex-/age-specific cutpoints comprised 17 ng/L for 50–64-year-old men and ≥65-year-old women, 31 ng/L for ≥65-year-old men and 14 ng/L for the remainder of patients.
Results: For the diagnosis of NSTEMI using sex-specific hs-cTnT cutpoints, in women, the positive likelihood ratio (LR+) was 2.04 (1.68–2.47) while in men, the negative likelihood ratio (LR−) was 0.05 (0.04–0.07). Using sex-/age-specific hs-cTnT cutpoints, in ≥65-year-old women the LR− was 0.09 (0.06–0.15), in 50 to 64-year-old men the LR− was 0.08 (0.04–0.13) while in ≥65-year-old men the LR− was 0.32 (0.28–0.37).
Sex-specific hs-cTnT cutpoints achieved an NRI of −0.020 (95% CI, −0.101–0.118) for women and 0.030 (95% CI, −0.013–0.079) for men, and the sex-/age-specific hs-cTnT cutpoints achieved an NRI of 0.061 (95% CI, −0.019–0.132) for women and 0.021 (95% CI, −0.062–0.108) for men, while net benefit and clinical utility were highest for women using the sex-/age-specific hs-cTnT cutpoints.
Conclusions: Sex-dependent hs-cTNT cutpoints imply increasing diagnostic sensitivity for women at the cost of specificity. Considering age for hs-cTNT cutoffs slightly improves risk reclassification, although the overall gain in terms of the clinical management appears negligible.

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1. Introduction

Elevated Cardiac troponin (cTnT) is essential for the diagnosis of myocardial infarction (MI) [1]. Detection of cTnT above the designated upper reference limit (URL) at the 99th percentile of a healthy reference population, using highly sensitive assays for Troponin T (hs-cTnT) or Troponin I (hs-cTnI) with precision of ≤10% coefficient of variation, is current guideline standard to diagnose MI [1]. The 99th percentile values for hs-cTnT, indicative for myocardial ischemia and necrosis, have been found consistently lower in healthy women compared to men in many different reference populations. [2–10] Accordingly, the

relevance of a sex-dependent URL for the diagnosis of myocardial infarction is currently debated and has been recommended by the IFCC and the Universal MI definition Task Force [1,11]. In addition, age has been demonstrated to considerably affect the sex-dependent URL of healthy subjects [8–10,12]. Reasons for ignoring sex- and age-dependent cutoff levels are probably the limited evidence of prognostic utility and presumed small effects on net reclassification. First studies using sex-specific cutoff levels for the diagnosis of MI have indicated negligible relevance for diagnostic and prognostic reclassification [13] whereas age-specific reference values had stronger effects [14]. Patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) show heterogeneous clinical presentation and have a risk of adverse events. Precise risk stratification is required to tailor therapy according to the individual patient's needs. Current guidelines recommend a standardized approach, e.g. including calculation of the Global Registry for Acute Coronary Events (GRACE) score, to guide triage and management

decisions. [15–17] While age and elevated cardiac markers are components of the GRACE score, sex is not considered.

The present study aims to assess sex- and sex/age-specific hs-cTnT cutoff values for the diagnosis and prognosis of NSTE-ACS in a real-world setting, adjudicating the elevation of cardiac markers by these thresholds for the calculation of the GRACE score.

2. Methods

2.1. Design and patient characteristics

The study cohort has been described previously [18]. Briefly summarized, out of 2445 consecutive patients admitted for chest pain suggestive of myocardial ischemia, all 1146 patients with NSTE-ACS were retrospectively analyzed. Thus, 710 patients with STEMI, 279 with other cardiac disease, and 310 with noncardiac chest pain were excluded. Overall, enrolment was only limited by lack of consent. Serum samples were available from all patients. The protocol did not regulate treatment decisions and was approved by the local ethics committees. The study was conducted in accordance with Declaration of Helsinki Written and informed consent was obtained from all patients.

2.2. Reference diagnosis of non-ST-segment elevation MI (NSTEMI)

NSTEMI was diagnosed according to Universal Definition of MI [1]. Positive NSTEMI diagnosis required detection of a rise and/or fall of cTnT with at least one value above the 99th percentile URL. The currently recommended 14 ng/L cutoff value for the diagnosis of MI of the Roche Diagnostics hs-cTnT assay was used. Serial testing lasted at least 12 h. Unstable angina was diagnosed at cTnT levels consistently below the 99th percentile URL or persistent cTnT elevations (no rise and/or fall) during serial testing. Also, either any signs of myocardial ischemia on electrocardiogram, a history of coronary artery disease, or stenosis of ≥50% in a major coronary artery on angiography were required.

2.3. Biomarkers

Venous blood was sampled at hospital admission and serum samples were stored at −70 °C until they were thawed once for biomarker measurements. Hs-cTnT and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured by electrochemiluminescence, high-sensitivity C-reactive protein (hs-CRP) and Cystatin C by immunoturbidimetry (all Roche Diagnostics assays).

2.4. Endpoints

All patients underwent follow-up for 6 months. Nonfatal MIs (STEMI or NSTEMI) and deaths were recorded and at 6 months' patients were contacted by telephone or questionnaire. Information on cardiovascular rehospitalization was obtained from patients, spouses, and primary care physicians and the discharge letters were analyzed for documented event diagnoses. Cardiac death was defined as death during hospitalization with MI, death from progressive heart failure, death from documented cardiac arrhythmias, or sudden or unwitnessed death not related to accidents, suicide, cancer, or other ominous diagnoses. All end points were adjudicated by 2 cardiologists and at disagreement a third cardiologist provided consensus.

2.5. The GRACE score

The GRACE risk calculator is available online (www.outcomes-umassmed.org/grace/). We used the GRACE score to estimate the cumulative risks for the composite of all-cause mortality and non-fatal MIs from admission to 6 month, which was the pre-specified primary study endpoint. The GRACE score was calculated using 8 admission variables (age, heart rate, systolic blood pressure, serum creatinine concentration from routine patient care measurements, Killip class, cardiac arrest, presence of ST-segment deviation, and increased cardiac marker) [16]. We used hs-cTnT ≥14 ng/L as unisex diagnostic reference threshold to define increase of the cardiac marker for the score.

Exploratory sex- and sex/age-dependent diagnostic thresholds for hs-cTnT.

To assess the diagnostic and prognostic value of sex-dependent cutpoints for hs-cTnT in NSTE-ACS we used the 99th percentile URL of 15.5 ng/L for men and 9.0 ng/L for women, which have previously been published in the analytical validation study of the assay [19]. We also analyzed sex-/age-dependent URLs for the hscTnT Assay as recently determined in different population-based studies [12]. Accordingly, we used cutoff values for the hs-cTnT assay of 17 ng/L for men at age 50 to 64 years and for women at age ≥ 65 years, and 31 ng/L for men at age ≥ 65 years while the remainder of patients was judged by the 14 ng/L standard cutoff value.

2.6. Statistical analysis

Baseline summary statistics for continuous variables are presented as means with standard deviations or medians with interquartile ranges as appropriate, and proportions for categorical variables. Equality of the means of continuous, normally distributed variables were tested using Students' t-test. Equality of ranks of continuous, skewed distributed variables were tested using the Mann-Whitney-U test. Independent distributions of frequencies in categorical variables were tested using Pearson's chi-squared test. In addition to disease

prevalence, summary statistics for the sex- and sex-/age-dependent diagnostic hs-cTnT cutoff values, compared to the reference unisex hs-cTnT cutoff value were calculated, such as sensitivity, specificity, positive and negative predictive values, and the likelihood ratio of a positive test (LR+) and of a negative test (LR−). Exact binomial confidence intervals are provided as appropriate. The range and distribution of estimated risk levels of hs-cTnT in men and women were compared using their predictiveness curves [20]. Furthermore, we calculated the Integrated Discrimination Improvement Index (IDI) [21] as generic measure of the GRACE risk model performance for using the sex- and sex/age-specific versus the standard diagnostic hs-cTnT cutoff values. Model calibration was assessed using the Hosmer-Lemeshow test and plots [22]. We calculated the Net Reclassification Improvement (NRI) using 2 risk categories stratified by a GRACE-Score value of 140 points. I.e. risk categories "low risk" (0–140) and "high risk" (>140). This cutoff has been shown to have outcome implications and is recommended to choose an early invasive strategy [15,23]. To assess the clinical utility of using the sex- and sex/age-specific versus the standard diagnostic hs-cTnT cutoff values in the GRACE score we performed a net benefit analysis. Decision curves were analyzed to evaluate the range of plausible risk thresholds relative to the previously designated arbitrary GRACE cutoff >140 points, i.e. 6% risk for death or myocardial infarction at 6 month [24,25]. To correct for resubstitution bias we applied 10-fold cross-validation, using random partitions of the data to obtain predicted values, and drew 1000 bootstrap samples for estimation of standard errors and confidence intervals. Statistical analyses were made using STATA (version 14.0 STATA Corp. College Station. TX. USA). Two-sided P-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Baseline characteristics are shown in Table 1. Women were older and had higher systolic blood pressure at admission than men. They also had higher baseline levels of NT-proBNP, but overall, hs-cTnT levels did not differ between women and men. However, patient management less frequently included percutaneous coronary intervention in women compared to men.

3.2. Diagnostic classification performance of sex- and sex/age-dependent hs-cTnT cutoff values

3.2.1. Standard cutoff value

Using the standard cutoff value of >14 ng/L for the differentiation between unstable angina pectoris and NSTEMI in men versus women resulted in 206 (25.4%) of the men being diagnosed with unstable angina pectoris and 604 (74.6%) with NSTEMI; in women 105 (31.3%) were diagnosed with unstable angina pectoris and 231 (68.8%) with NSTEMI.

3.2.2. Sex-dependent cutoff values

Diagnostic classification performance for the 9 ng/L vs. 14 ng/L hs-cTnT cutoff value in women and the 15 ng/L vs. 14 ng/L hs-cTnT cutoff value in men is shown in Table 2. In women, the positive likelihood ratio (LR+) for a diagnosis of NSTEMI was 2.04 (1.68–2.47). In men, a negative likelihood ratio (LR−) of 0.05 (0.04–0.07) was calculated.

3.2.3. Sex/age-dependent cutoff values

Diagnostic classification performance for the 17 ng/L vs. 14 ng/L hs-cTnT cutoff value in women older ≥65 years, and for 50 to 64-year-old men, as well as for the 31 ng/L vs. 14 ng/L diagnostic hs-cTnT cutoff value in men older ≥65 years are also shown in Table 2. In ≥65-year-old women the LR− was 0.09 (0.06–0.15), in 50 to 64-year-old men the LR− was 0.08 (0.04–0.13) and in ≥65-year-old men the LR− was 0.32 (0.28–0.37).

3.3. Prognostic performance of the GRACE score using hs-cTnT cutoff values dependent on sex alone or dependent on sex- and age

Plots of estimated disease risk vs. the distribution of risk (i.e. predictiveness curves) for the sex- and sex/age-specific versus the standard diagnostic hs-cTnT cutoff values in both sexes are shown in Fig. 1. They show that the range and distribution of estimated risk associated with the GRACE score using the sex-specific hs-cTnT cutoff is constantly

Table 1
Baseline characteristics.

	Men	Women	P-value
	N = 810	N = 336	
GRACE variables on admission			
Age, years	67 ± 11	71 ± 12	<0.001
Systolic blood pressure, mm Hg	144 ± 22	148 ± 24	0.024
Creatinine, mg/dL	2 ± 6	2 ± 7	0.74
Killip-Class			0.073
I	92.6 (750)	88.7 (298)	
II	5.9 (48)	8.3 (28)	
III/IV	1.5 (12)	3.0 (10)	
Cardiac arrest	0 (0)	0 (0)	
ST-segment deviation	13.0 (105)	11.0 (37)	0.36
Biomarkers at admission			
hs-cTnT, ng/L	30.7 (13.3–158.1)	29.6 (10.6–179.2)	0.40
NT-proBNP, ng/L	344.0 (111.1–1136.0)	593.5 (191.1–1910.5)	<0.001
Cystatin C, mg/L	0.9 (0.8–1.1)	1.0 (0.8–1.3)	0.056
hs-CRP, mg/L	2.9 (1.2–8.6)	3.0 (1.3–8.3)	0.53
No. of diseased vessels (CAD)			
0 CAD (<50% stenosis)	4 (32)	10 (27)	
1 CAD	19 (138)	24 (67)	
2 CAD	19 (139)	24 (69)	
3 CAD	57 (408)	43 (121)	<0.001
Patient management			
Coronary angiography	87.5 (709)	83.3 (280)	0.060
Percutaneous coronary intervention	59.4 (481)	52.4 (176)	0.029
Coronary artery bypass graft	2.8 (23)	3.3 (11)	0.69
Diagnosis at discharge			
Angina pectoris	47.8 (387)	49.7 (167)	0.55
NSTEMI	52.2 (423)	50.3 (169)	0.55

Data are shown as mean ± standard deviation, median (interquartile range) and % (n).

higher in women than men up to a risk level of 0.10, at higher risk levels both sexes do not differ substantially; using the sex-/age-specific hs-cTnT cutoffs, estimated risk is constantly higher in women over men across the entire risk spectrum. Using both specific hs-cTnT cutoff criteria and judging by the specified risk threshold at 0.06, i.e. a GRACE risk score at admission for death or MI at 6 months of 140, the true positive and false positive fractions are higher in women than men.

In the current guideline for NSTE-ACS a GRACE Score above 140 is a high-risk criterion favoring an early invasive strategy [15]. The potential

clinical benefit achieved when sex-specific or sex-/age-specific hs-cTnT cutoffs were added to the GRACE score was assessed using the two-way category-based NRI with a threshold of 6% equal to 140. Sex-specific hs-cTnT cutoff achieved an NRI of −0.020 (95% CI, −0.101–0.118) for women and 0.030 (95% CI, −0.013–0.079) for men, likewise the sex-/age-specific hs-cTnT cutoff achieved an NRI of 0.061 (95% CI, −0.019–0.132) for women and 0.021 (95% CI, −0.062–0.108) for men (Table 3; please see Tables 4, 5 and 6 in the Supplementary material for details on events, reclassification, net benefit and relative utility statistics, respectively).

The distribution of the GRACE score points using the standard hs-cTnT cutoff value vs. using the sex- and sex/age-specific cutoff to calculate the risk score in men and women shows that, overall, the sex-specific hs-cTnT cutoff increases the percentage of higher GRACES scores >140 points in women, whereas using the sex- and age-specific hs-cTnT cutoffs there is an inverse shift in the GRACES score to <140 points in men (Supplementary Fig. 2 A and B, respectively, Supplementary material).

3.4. Decision curve analysis

The decision curves for the GRACE score using the sex- and sex/age-specific versus the standard diagnostic hs-cTnT cutoff value indicate that in men both hs-cTnT cutoff strategies are not substantially superior to the standard cut off. However, in women, using the sex-dependent diagnostic hs-cTnT cutoff values is inferior to using the standard cutoff across the range of risk thresholds. Using the sex-/age-specific hs-cTnT cutoffs indicates considerable superiority compared to using the standard hs-cTnT cutoff over the entire spectrum of risk thresholds in women. (Fig. 3, Supplementary material).

4. Discussion

This study shows that using a pure sex-dependent hs-cTnT cutoff for the diagnosis of NSTEMI increases the probability of a positive diagnosis for women whereas it largely decreases positive diagnoses in men. In contrast, considering a combination of age- and sex-dependent cutoffs leads to moderate decrease in NSTEMI diagnoses in ≥65-year-old men, whereas they are largely decreased in ≥65-year-old women and 50 to 64-year-old men as opposed to using the standard cutoff in the younger age groups in both sexes.

Uniquely, our results show sex differences in the effects of using hs-cTnT cutoff values dependent on sex alone and dependent on the

Table 2
Summary statistics for diagnostic hs-cTnT cutoff values depending on sex and both, sex and age.

	hs-cTnT cutoff values depending on sex		hs-cTnT cutoff values depending on sex and age		
	Women	Men	Women ≥65 years	Men 50–64 years	Men ≥65 years
NSTEMI	n = 281/336	n = 594/810	n = 173/247	n = 155/229	n = 398/505
hs-cTnT cutoff (ng/L)	9.0 vs. 14.0	15.5 vs. 14.0	17.0 vs. 14.0	17.0 vs. 14.0	31.0 vs. 14.0
Change in diagnosis	n = 53/108 (49.1%)	n = 30/216 (13.9%)	n = 16/173 (9.2%)	n = 12/155 (7.7%)	n = 129/398 (32.4%)
Correct diagnostic reclassification					
of reclassified patients	n = 5/53 9.4 (3.1–20.7%)	n = 4/30 13.3% (3.8–30.7)			
of NSTEMI patients	n = 5/281 1.8 (0.6–4.1%)	n = 4/594 0.7% (0.2–1.7)			
of all patients	n = 5/336 1.5% (0.5–3.4%)	n = 4/810 0.5% (0.1–1.3)			
Death	0	0	0	0	2
Non-lethal MI	0	0	0	0	7
Prevalence of NSTEMI (%)	67.9 (62.6–72.8)	73.3 (70.1–76.4)	70.0 (63.9–75.7)	67.7 (61.2–73.7)	78.8 (75.0–82.3)
Sensitivity (%)	100.0 (98.4–100.0)	94.9 (92.9–96.6)	90.8 (85.4–94.6)	92.3 (86.9–95.9)	67.6 (62.7–72.2)
Specificity (%)	50.9 (41.1–60.7)	100.0 (98.3–100.0)	100.0 (95.1–100.0)	100.0 (95.1–100.0)	100.0 (96.6–100.0)
ROC area	0.75 (0.71–0.80)	0.97 (0.97–0.98)	0.95 (0.93–0.98)	0.96 (0.94–0.98)	0.84 (0.81–0.86)
Likelihood ratio (+)	2.04 (1.68–2.47)				
Likelihood ratio (−)		0.05 (0.04–0.07)	0.09 (0.06–0.15)	0.08 (0.04–0.13)	0.32 (0.28–0.37)
Positive predictive value (%)	81.1 (76.1–85.5)	100.0 (99.3–100.0)	100.0 (97.7–100.0)	100.0 (97.5–100.0)	100.0 (98.6–100.0)
Negative predictive value (%)	100.0 (93.5–100.0)	87.8 (83.1–91.6)	82.2 (72.7–89.5)	86.0 (76.9–92.6)	45.3 (38.9–51.9)

A

Integrated predictiveness and classification plot
GRACE with sex-dependent hs-cTnT cutoff

risk threshold (high) = 0.06
Men 100 - risk percentile: 36.3
Women 100 - risk percentile: 55.7
Men TPF: 0.731
Women TPF: 0.846
Men FPF: 0.339
Women FPF: 0.535

B

Integrated predictiveness and classification plot
GRACE with sex-/age-dependent hs-cTnT cutoff

risk threshold (high) = 0.06
Men 100 - risk percentile: 36.7
Women 100 - risk percentile: 45.8
Men TPF: 0.731
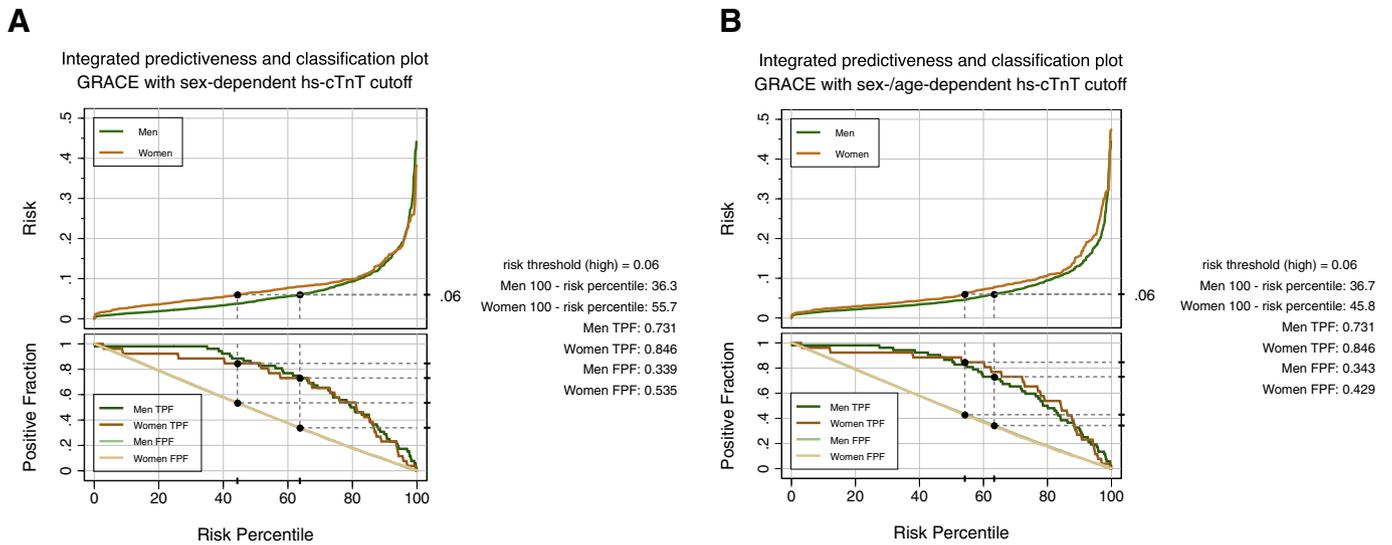Women TPF: 0.846
Men FPF: 0.343
Women FPF: 0.429

Fig. 1. Integrated predictiveness and classification plots for the diagnostic hs-cTnT cutoff values dependent on sex- (A) or sex and age (B). Bottom Annotation: The criterion is risk 0.06 corresponding to GRACE risk score at admission for death or MI at 6 months of 140. TPF: true positive fraction; FPF: false positive fraction.

combination of sex- and age on the prognostic performance of the GRACE score: the sex-specific hs-cTnT cutoff leads to higher GRACE scores >140 points in women, whereas using the sex-/age-specific hs-cTnT cutoffs inversely shifts the GRACE scores to <140 points in men. The predictiveness curves suggest that the GRACE risk estimates change to higher values in women than men within the clinically meaningful risk range up to 0.10. This includes the risk threshold at 0.06, which represents the GRACE risk score at admission for death or MI at 6 months of 140 points, for which an earlier invasive strategy previously suggested improved outcome. Interestingly, the decision curve analysis suggests that the sex-dependent hs-cTnT cutoff strategy is inferior to the standard cutoff in women while the combined sex-/age-specific cutoffs are considerably superior over the standard hs-cTnT cutoff in women, whereas no considerable difference exists for men.

Overall, these hypotheses-generating results transfer the discussion over the clinical implications of sex differences in troponin levels, as detected by a high sensitive assay, from judgement by only diagnostic accuracy to prognostic relevance in patients with acute coronary syndrome. In NSTE-ACS current ESC Guidelines recommend a standardized approach

that uses validated scoring systems, i.e. the Global Registry for Acute Coronary Events (GRACE) score, to guide triage and management decisions [15], such as early invasive treatment.

Recently, differences in the distribution of hs-cTnT in healthy reference populations have stimulated interest in the relevance of applying sex-specific troponin cutoff levels for the diagnosis and management of NSTE-ACS [26]. Especially because their use has already been recommended by various professional societies, including the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction [1,11].

In many population-based cohorts the 99th percentile of hs-cTnT was found lower in women compared to men [3,12]. Potential explanations comprise greater cardiac mass [27], more subclinical coronary artery disease (CAD) in men [28], and less coronary atherosclerosis [29], less left ventricular (LV) hypertrophy [30], and less cardiomyocyte apoptosis in women [31]. This increased the awareness and analytical consideration of sex-specific troponin cutoff levels [11,32]. However, sex differences in troponin levels are additionally affected by sex differences in age, renal function, co-morbidities and coronary anatomy, with women frequently

Table 3
Generic measures of the GRACE risk score performance and prediction increments using diagnostic hs-cTnT cutoff values depending on only sex- or both, sex and age.

	GRACE score using hs-cTnT cutoffs			
	Sex-dependent		Sex-/age-dependent	
	Women	Men	Women	Men
Goodness of fit (reference)	0.5221	0.5142	0.5221	0.5142
Goodness of fit (reference + new)	0.3907	0.7034	0.3732	0.4104
Events (n)	26	52	26	52
Nonevents (n)	310	758	310	758
IDI	0.005	0.004	0.009	0.002
	(0.001, 0.010)	(0.002, 0.007)	(0.003, 0.020)	(−0.000, 0.015)
IDI$_{events}$	0.005	0.004	0.008	0.002
	(0.001, 0.009)	(0.002, 0.006)	(0.003, 0.018)	(−0.000, 0.014)
IDI$_{nonevents}$	0.000	0.000	0.001	0.000
	(0.000, 0.001)	(0.000, 0.000)	(0.000, 0.002)	(−0.000, 0.001)
Reclassification (%)	8.63	2.84	4.76 (2.08, 11.31)	5.68 (0.25, 16.23)
	(2.68, 21.43)	(1.23, 6.60)		
NRI (6% cut-off)	−0.020	0.030	0.061	0.021
	(−0.101, 0.118)	(−0.013, 0.079)	(−0.019, 0.132)	(−0.062, 0.108)
NRI$_{events}$ (change in true-positive rate)	0.038	0.019	0.038	0.000
	(0.000, 0.179)	(0.000, 0.080)	(0.000, 0.122)	(−0.073, 0.090)
NRI$_{nonevents}$ (change in false-positive rate)	−0.058	0.011	0.023	0.021
	(−0.146, 0.000)	(−0.018, 0.015)	(−0.025, 0.046)	(−0.014, 0.059)

The Hosmer-Lemeshow goodness of fit was used to test calibration of the model. The 95% confidence intervals are shown in parentheses. IDI, integrated discrimination improvement; NRI, net reclassification improvement (NRI$_{events}$ + NRI$_{nonevents}$). X, reference hs-TnT cutoff of 14 ng/L; XY, new hs-TnT cutoff.

being older, having impaired renal function, diabetes and non-obstructive CAD with coronary microvascular dysfunction [33].

4.1. Sex-dependent cutoff values

Our results of higher probability of NSTEMI by using only sex-dependent hs-cTnT cutoffs raise the question to what extent hs-cTnT levels between the standard unisex cutoff and sex-specific 99th percentiles are clinically relevant. Rubini Giménez et al. [13] assessed the diagnostic reclassification by using sex-specific (women 9 ng/L; men 15.5 ng/L) vs the uniform hs-cTnT cutoff level (14 ng/L) in the diagnosis of acute myocardial infarction (AMI) in 876 women (32%) and 1858 men (68%). They reported that only 0.11% of all patients and 0.6% of AMI-patients were reclassified [13]. In our cohort 9 patients were reclassified with a diagnosis of NSTEMI using these sex specific cutoffs. This refers to 5 (9.4%) of 53 women with hs-cTnT between 9 and 14 ng/L (1.5% of all women), in whom the correct timely diagnosis is missed using the unisex hs-cTnT cutoff. Importantly, 4 (13.3%) of 30 men with hs-cTnT between 14 and 15.5 ng/L (0.5% of all men) were reclassified using the sex-specific threshold, which means that this threshold would lead to missed correct diagnoses of NSTEMI in these men. It also needs to be considered that even levels of hs-cTnT between the limit of blank (LOB; 3 ng/L) and the limit of detection (LOD; 5 ng/L) are associated with increased cardiovascular mortality [34]. In stable CVD patients at high risk for future outcomes such as myocardial infarction, stroke, or cardiovascular death, the results from the HOPE study suggest an hs-cTnT cutoff of 8 ng/L [35]. However, in subjects with hs-cTnT either below (8–14 ng/L) or slightly above the standard 99th percentile (14–21 ng/L) the HOPE study indicated similar probability for adverse cardio-vascular outcome. However, liberation of the NSTEMI threshold by using sole sex-dependent hs-cTnT cutoffs with a lower diagnostic limit in women than men, increases the false positive rate. Our data confirm that the specificity and the positive predictive value decrease considerably while the false-positive rate increases in women but not men using the sex-dependent hs-cTnT cutoff whereas the true-positive rates do not differ between men and women with either troponin-strategy. Notably, this refers to patients with no adverse outcome such as death or non-lethal myocardial infarction within 6 months' follow-up. Using the unisex standard cutoff for the diagnosis of NSTEMI, our data show that significantly fewer women than men underwent PCI. This is in accordance with previous data [36,37] and explainable through less extensive and typical manifestation of coronary artery disease [38–40] with higher rates of type II myocardial infarction [41] in women.

4.2. Sex- and age-dependent cutoff values

Mueller-Hennessen et al. [14] have previously assessed the impact of age- and sex-specific hs-cTnT cut-offs on diagnostic and prognostic reclassification in 1282 unselected patients from the TRAPID-AMI study. While they used the same sex-specific hs-cTnT cut-offs with modest effects on diagnostic and prognostic reclassification, they used a single age-specific cut-off at 28 ng/L for patients ≥65 years [14]. As a main result, they refer to a decrease in the diagnosis of AMI and better risk reclassification for 1- and 3-month mortality using the age-specific cut-off [14].

For our study we used the combined sex-/age-dependent hs-cTnT cut-off values as proposed by Gore et al. [12] This approach of using the combination of different age- with sex-dependent cutoffs is supported by the HOPE study results, which indicated the highest probability and greatest risk for future myocardial infarction, heart failure, and cardiovascular death for patients with hs-cTnT concentrations >31 ng/L independent of sex [35]. Our study transfers the population-based reference limits [12] to the ACS setting. We observed a moderate decrease in NSTEMI diagnoses in ≥65-year-old men and large decrease in ≥65-year-old women and 50 to 64-year-old men.

4.3. Incremental prognostic value of sex- or sex/age-dependent cut-offs

Patients with NSTE-ACS are heterogeneous regarding their clinical presentation, mid-term risk of death and recurrent myocardial infarction. Therefore, risk stratification is important to adapt the intensity of therapy to the individual patient's needs. Obviously, sex provides no independent prognostic information after ACS according to the GRACE [16] score. However, apart from the diagnostic implications of using sex- or sex-/age-dependent hs-cTnT cutoffs it has not previously been analyzed if using such cutoffs increases prognostic accuracy when being used for the biomarker positivity factor of the GRACE [16] risk score.

The sole sex-dependent hs-cTnT cutoff strategy leads to a higher proportion of reclassification in women over men, which is offset by additionally considering the age effect through using the sex-/age-dependent hs-cTnT cutoffs. It introduces many more errors than corrections at the 6% risk threshold in women, meaning that the net proportion of women assigned to a more appropriate risk category is very low at −0.02. Considering also the age of the women equalizes the sex difference in the proportion of reclassification and shifts the net proportion of nonevents assigned the lower risk category from −0.058 to 0.023 in women while only showing a moderate increase from 0.011 to 0.021 in men. Additionally, using the sex-/age-dependent hs-cTnT cutoffs leads to higher IDI in women. Overall, besides numerical improvement, the amount of reclassification and discrimination improvement has only negligible clinical meaning. However, using the sex-/age-dependent hs-cTNT cutoffs leads to higher increase of net benefit and relative utility in women. This is also supported by the results of the decision curve analysis indicating superiority of using the sex-/age-dependent hs-cTNT cutoffs in women but not men across the risk spectrum.

Overall, also drawbacks of such sex- and sex-/age-dependent hs-cTnT strategies must be considered. Only few patients are reclassified into a different diagnosis. Sex-dependent hs-cTnT cutoffs will improve sensitivity at the cost of poorer specificity in women and vice versa in men. Using such cutoffs may confuse clinicians with multiple decision limits. In addition, there are analytical problems with the commonly used 99th percentile of 9 ng/L in women being below the lowest measurable concentration with a coefficient of variation <10% (11–13.5 ng/L). Moreover, whether using sex-specific cutoffs will improve outcomes by use of revascularization therapies is questionable, because women frequently have non-occlusive underlying coronary pathology with troponin elevation (i.e. type 2 myocardial infarction).

4.4. Limitations

Unfortunately, detailed information on the drug regimens at admission is not available.

There are no angiographic details, such as coronary dissection, coronary artery spasm, coronary microvascular dysfunction, Takotsubo cardiomyopathy, or coronary thromboembolism, documented in this study, which limits the analysis of Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA).

The dataset provides a complete follow-up of only 6 months and consequently, we are not able to provide information on the GRACE-2 score in our cohort.

The 99th percentile values of healthy women are significantly lower than those of men and strongly dependent on the assay (i.e. hsTnI vs. hsTnT).

Overall, the typical limitations of retrospective cohort studies apply to our analyses.

5. Conclusion

Using only sex-dependent hs-cTnT cutoff levels implies increasing diagnostic sensitivity for women at the cost of specificity. Additional consideration of age improves risk reclassification, although the overall

gain in terms of a change of the clinical management appears to be limited. Rather than restricting the utility of such cutoffs to diagnostic purposes in ACS, the prognostic utility of sex- and age-specific hs-cTnT cutoff levels needs to be addressed because they could change treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.027.

Conflict of interest

Christian Widera: *none*; Evangelos Giannitsis: *Honoraria from Roche Diagnostics*; Matthias Mueller-Hennessen: *none*; Ines Reimann: *none*; Anja Guba-Quint: *none*; Ivonne Marquardt: *none*; Kerstin Bethmann: *none*; Sven Meyer: *none*.

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