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Highly Sensitive Cardiac Troponins: The Evidence Behind Sex-Specific Cutoffs

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ABSTRACT: Emergence of various highly sensitive cardiac troponin assays into clinical practice provides a new tool for clinicians diagnosing acute coronary syndrome. These assays also create a challenge for laboratories and clinicians who have yet to familiarize themselves with sex-specific cutoffs. Healthy men and women, studied across various age groups and geographic locations, have notable differences in baseline values of highly sensitive cardiac troponin I and T, leading to establishment of sex-specific upper reference limits and cutoffs. Several differences in cardiac physiology, size, and structure may account for baseline differences in highly sensitive cardiac troponins and outcomes between the sexes. The clinical utility of implementing sex-specific cutoffs for diagnosis and management of acute coronary syndrome remains unclear. Presently, the only prospective study failed to show improved outcomes for men or women with use of sex-specific cutoffs; however, a major limitation is the frequent lack of diagnostic, therapeutic, and preventive interventions prescribed to women with low-level troponin elevations. Based on the current literature, we posit that there may nonetheless be clinical value in the use of sex-specific cutoffs for evaluating suspected acute coronary syndrome, especially in select patient populations such as younger women who tend to have lower baseline values of highly sensitive cardiac troponins. Future studies should prospectively evaluate differences in diagnostic, pharmacologic, and interventional management in men and women using myocardial infarctions classified with sex-specific cutoffs of the highly sensitive cardiac troponin assays.

Key Words: cardiac biomarkers ■ cardiac troponins ■ highly sensitive cardiac troponins ■ sex-specific cutoffs

Measurement of cardiac troponins—troponin T and troponin I—first emerged into clinical practice in the 1990s. Even with these earliest assay iterations, they were more specific for myocardial injury than prior biomarkers, including when used in patients with decreased renal function.[1] Compared with creatinine kinase and myoglobin, cardiac troponin I and T are expressed only in cardiac myocytes, and the cardiac troponins are detectable in the serum or plasma of blood within hours after myocardial injury.[1] Elevation of cardiac troponin above the 99th percentile upper reference limit (URL) is an indicator of myocardial injury.[2–4] Along with symptoms, electrocardiographic changes, and imaging evidence, acute changes in cardiac troponins are a key component in the diagnosis of acute myocardial infarction (MI).[4]

The limit of detection (LOD) of cardiac troponin T and I assays has historically been above the 99th percentile URL and typically undetectable in the healthy population. However, with newer, highly sensitive cardiac troponin T (hs-cTnT) and highly sensitive cardiac troponin I (hs-cTnI) assay development, the LOD is now lower than the 99th percentile URL.[5] In addition, the analytic precision of these highly sensitive assays at levels near the LOD has improved substantially. Now for the first time, we are able to reliably detect sex-specific differences in troponin levels within a healthy population.[5,6] This development is incorporated into the Fourth Universal Definition of Myocardial Infarction,[4] which recommends use of sex-specific URLs for the highly sensitive cardiac troponin assays for clinical use.

The first highly sensitive cardiac troponin assay (Elecsys Troponin T Gen 5 Short Turnaround Time [STAT] immunoassay by Roche Diagnostics) was approved by the US Food and Drug Administration (FDA) in early 2017. The FDA approval included sex-specific

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Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
FDA	US Food and Drug Administration
hs-cTnI	highly sensitive cardiac troponin I
hs-cTnT	highly sensitive cardiac troponin T
LOD	limit of detection
MI	myocardial infarction
MINOCA	myocardial infarction with nonobstructive coronary arteries
NPV	negative predictive value
STAT	Short Turnaround Time
UA	unstable angina
URL	upper reference limit

cutoffs of 14 ng/L for women and 22 ng/L for men, or a single cutoff of 19 ng/L, with recommended use in conjunction with other signs and symptoms for the diagnosis of MI.[7] hs-cTnI assays by Beckman Coulter and Siemens Diagnostics are also now joined by the most recent FDA approval of ARCHITECT STAT hs-cTnI assay by Abbott Laboratories, which also has 99th percentile sex-specific cutoffs.

As various hs-cTnT and hs-cTnI assays are becoming widely accepted and incorporated into clinical practice, evaluating the data behind development of clinical decision values (uniform and sex-specific) for each assay is imperative. There is a lack of uniformity in the definition of "healthy" cohorts across various assays and studies, which has led to the development of biologically nonequivalent clinical decision values that can affect the diagnostic yield of each hs-cTnT and hs-cTnI assay.[8] In light of the ubiquitous identification of sex-specific cutoffs in highly sensitive cardiac troponins, the aim of this review is to explore the sex-specific differences in the pathophysiology of coronary artery disease, evaluate the data supporting the use of sex-specific cutoffs for various assays, and assess the implications for acute coronary syndrome (ACS) diagnosis and management on each sex.

SEX-SPECIFIC DIFFERENCES IN CARDIAC PHYSIOLOGY AND CLINICAL OUTCOMES

Sex-specific differences in heart anatomy and pathophysiology are well established. Structurally, among individuals without cardiovascular disease, men have greater cardiac mass compared with women on the basis of cardiac magnetic resonance imaging and echocardiography.[9,10] Echocardiography shows that this difference in cardiac mass is present in younger healthy adults (aged 20–29) as well as older healthy adults (aged 60–70), even after correction for body surface area.[10] Men also have higher end-diastolic and end-systolic volumes in the left ventricle, despite a similar left ventricular ejection fraction in both sexes.[9] These differences in cardiac mass and geometry between the sexes may be driven by sex hormones and weakly related to sex-based differences in blood viscosity.[11]

The type and distribution of coronary artery disease also differs between the sexes. In patients presenting with ACS, women are more likely to have nonobstructive coronary disease compared with men.[12–15] Non–ST-segment–elevation MI (NSTEMI) and unstable angina (UA) (as opposed to ST-segment–elevation MI [STEMI]) are more frequently diagnosed in women as compared with men with ACS (82% versus 77%, respectively).[13] Among ACS patients, women also tend to have more comorbidities but fewer high-risk angiographic features, with more focal nonculprit lesions and less plaque rupture and necrotic core.[13,14] Comorbidities that are more prevalent in women compared with men presenting with ACS include diabetes mellitus, hypertension, history of heart failure, and history of cerebrovascular disease.[13–15]

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is another clinical entity that is more commonly diagnosed in women as compared with men.[16–18] Smilowitz et al[16] specifically note that MINOCA accounts for 10.5% of all MI diagnoses in women compared with 3.4% in men.[16,17,19] MINOCA is now recognized in the Fourth Universal Definition of MI[4] and defined as MI with <50% stenosis in all epicardial vessels. Coronary microvascular dysfunction evidenced by high prevalence of abnormal vasomotion following administration of acetylcholine or adenosine is one of several likely etiologies of infarction in women with MINOCA and is associated with adverse cardiovascular events in those women.[20–22] Other likely contributors to MINOCA include coronary thromboembolism, coronary spasm, plaque disruption, and coronary dissection in addition to myocardial disorders such as myocarditis and Takotsubo cardiomyopathy.[19,23–25]

Recognition of MINOCA in recent guidelines highlights the prognostic significance of nonobstructive coronary disease in patients with ACS. Symptomatic women with nonobstructive coronary angiography have a higher rate of future cardiovascular events compared with asymptomatic women with no coronary obstruction on angiography.[26] Compared with men, women with "normal" angiography despite concerning symptoms have a higher rate of readmission and repeat catheterizations.[27] Statin and renin-angiotensin-aldosterone system blockade use has been associated with lower adverse events in MINOCA patients during a 4-year follow-up period, while there is no evidence for improved outcomes with the use of dual antiplatelet

therapy or β-blockers.[17] These findings suggest that there is a need for recognition and aggressive secondary prevention in symptomatic women without high-grade obstructive coronary obstruction.

Presentation, management, and clinical outcomes differ between men and women with ACS on several levels. Women with ACS are more likely to present with dyspnea, nausea and vomiting, and radiating chest pain compared with men.[28] After diagnosis of ACS, women are less likely to undergo percutaneous coronary intervention compared with men.[29–32] They are also less likely to receive a prescription for lipid-lowering therapy compared with men.[32] A recent retrospective study found that among all patients with MI and significant coronary artery stenosis on angiography, women had higher rates of in-hospital mortality as compared with men.[16] Survival after percutaneous coronary intervention is reportedly similar between the sexes after adjusting for comobidities[31,33,34]; however, women experience higher rates of complications in the hospital, experience more refractory angina, and are less often prescribed aspirin, glycoprotein IIb/IIIa inhibitors, and lipid lowering therapy compared with men after diagnosis of ACS.[13,31,32,34]

The role of cardiac biomarkers in the diagnosis, management, and prognosis of ACS is well established.[3,4,35,36] Guidelines for the diagnostic performance and assay validation of cardiac biomarkers have established that a decision limit for each cardiac biomarker assay for diagnosis of MI should be based on the 99th percentile URL as determined by a study of at least 120 healthy individuals.[37] The MB fraction of creatinine kinase, which was in widespread use before the introduction of cardiac troponins (and has continued use in some regions today, despite a class III recommendation for initial diagnosis of MI),[38] has a notable difference in the 99th percentile URL between the sexes. Because of this, guidelines historically have recommended that clinical laboratories establish sex-specific reference limits for the creatinine kinase MB fraction assay.[37] As data emerge on highly sensitive cardiac troponin assays, the most recent revision of the expert consensus for the diagnosis of MI also recognizes the need for sex-specific reference limits for the highly sensitive cardiac troponin assays.[4]

NINETY-NINTH PERCENTILE URL OF HS-CTNT ASSAYS

Several large cohort-specific studies across various geographic locations and age groups have evaluated hs-cTnT values in the healthy population. Table 1 includes published studies that identify sex-specific and a single 99th percentile URL in healthy populations.[5,6,39–44] Of note, there was no standard definition for a healthy population across these studies. Individuals were typically screened with a questionnaire, which excluded patients with history of coronary artery disease, symptoms of MI, diabetes mellitus, hypertension, and renal disease.[5,42,43] Some studies also defined healthy populations based on normal vital signs, spirometry, electrocardiography, echocardiography, or other cardiac biomarkers such as B-type natriuretic peptide and the MB fraction of creatinine kinase.[5,39,42] Of these, 2 studies specifically did not include self-identified marathon runners or extreme endurance athletes in the reference population.[39,43] Depending on the age and sex of the "healthy" cohort, 21% to 50% of healthy individuals were found to have a hs-cTnT value above the LOD.[5] Of note, the Elecsys Troponin T Gen 5 STAT immunoassay approval by the FDA includes an approval for use of 19 ng/L as a single cutoff, or 22 ng/L for males and 14 ng/L for females based on the 99th percentile URL in a healthy population.

NINETY-NINTH PERCENTILE URL OF HS-CTNI ASSAYS

In the case of hs-cTnI, multiple assays have been developed and studied across various age and geographic groups. Three hs-cTnI assays have currently been FDA approved for use in the United States—ADVIA Centaur high-sensitivity troponin I by Siemens Healthcare Diagnostics, Access high-sensitivity troponin I by Beckman Coulter, and ARCHITECT STAT high-sensitivity troponin I assay by Abbott Laboratories. The LOD is highly variable among various hs-cTnI assays, ranging from 0.009 ng/L to 2.5 ng/L; and values are not interchangeable among different hs-cTnI assays. The definition of a healthy population is also quite variable across studies establishing a reference range for the hs-cTnI assays. Although not all studies specify the selection method for healthy individuals, the common screening methods were questionnaires excluding existing health conditions[43,45–48] and abnormal labs (B-type natriuretic peptide, estimated glomerular filtration rate, and glycosylated hemoglobin or fasting blood glucose).[45–48]

Reference range studies with each of the assays consistently show a higher 99th percentile URL for men compared with women.[6,43,45–47,49] These are robust studies with close to 50% female representation in the studied population. Age remains a significant determinant of the URL across hs-cTnI assays in addition to sex.[45,47] Table 2 outlines published literature to date that specifically identify 99th percentile URL for both male and female subjects as well as a combined 99th percentile URL for both sexes in healthy population cohorts.[6,43,45–51]

CLINICAL UTILITY OF SEX-SPECIFIC CUTOFFS

Sex-specific differences in the hs-cTnT and hs-cTnI 99th percentile URL are now recognized, but

Table 1. Summary of Published Data on the Highly Sensitive Cardiac Troponin T Concentrations in a Healthy Population

Assay	Study	Population Size, n (% Female)	Location	Age Range, y* (Mean)	Single 99th Percentile URL, ng/L	Male 99th Percentile URL, ng/L	Female 99th Percentile URL, ng/L
Roche	Mingels et al (2009)[39]	479 (45)	Europe	26–71 (51)	16	18	8
Roche	Giannitsi et al (2010)[40]	616 (50)	United States and Europe	20–71 (44)	14	15	10
Roche	Koerbin et al (2010)[41]	104 (45)	Australia	25–74	13	13	11
Roche	Collinson et al (2011)[42]	545 (53)	Europe	≥45 (median, 58)	22	24	14
Roche	Apple et al (2012)[43]	524 (48)	United States	18–64	15	20	13
Roche	Gore et al (2014)[5] DHS registry	2955 (54)	United States	30–65	14	17	11
Roche	Gore et al (2014)[5] ARIC registry	7575 (61)	United States	54–74	21	26	15
Roche	Gore et al (2014)[5] CHS registry	1374 (64)	United States	≥65	28	34	24
Roche	Peacock, et al (2017)[44]	1301 (50)	United States	≥21 (median, 48)	19	22	14
Roche	Kimenia et al (2015)[6]	1540 (52)	Europe	40–75 (57)	15	16	12

ARIC indicates Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; DHS, Dallas Heart Study; and URL, upper reference limit.
*Study population age not uniformly reported; mean and median ages provided as published.

the clinical implication of using sex-specific cutoffs compared with a single cutoff remains unclear. We still do not know for certain whether routine clinical use of sex-specific cutoffs of highly sensitive cardiac troponin assays will improve the diagnosis of small MIs or MINOCA in women in a clinically meaningful way. The improved sensitivity for identifying women at risk for future adverse cardiovascular events may be offset by the increased number of women needing to undergo further evaluation for their elevated troponin levels. In addition, the increased identification of women who are at risk may come at the possible expense of identifying fewer men who are at risk for myocardial injury using sex-specific cutoffs. Only a handful of studies to date have evaluated the sensitivity and specificity of diagnosing MI in men and women using the sex-specific cutoffs as compared with a single cutoff, and there are few data on whether clinical decisions guided by sex-specific cutoffs can lead to improved outcomes.[44,52–58] Prospective studies are even more sparse. Details on the design of the studies that evaluated utility of sex-specific cutoffs are outlined in Table 3.[44,52–59]

DIAGNOSTIC STUDIES EVALUATING HS-CTNT SEX-SPECIFIC CUTOFFS

Using the FDA-approved sex-specific cutoffs for hs-cTnT, Peacock et al[44] investigated the difference in the negative predictive value (NPV) between the use of sex-specific cutoffs (14 ng/L for women and 22 ng/L for men) as compared with a single cutoff of 19 ng/L. In this observational study, serial hs-cTnT measurements were obtained in patients undergoing a workup for ACS in 15 emergency departments across the United States. Clinicians were blinded to the result of the hs-cTnT assay, so diagnosis of ACS was made using local contemporary troponin assays. Patients were followed for 30 days for adverse events including death, acute MI, and urgent revascularization. As expected, using sex-specific cutoffs of hs-cTnT for diagnosing acute MI at the 0-hour (baseline) measurement yielded a lower NPV for men and a higher NPV for women compared with using the single cutoff. However, neither NPV was adequate for clinical decision making at 0 hours, and in practice, levels much lower than the 99th percentile need to be used to ensure safe triage at early time points. When a 3-hour serial measurement of hs-cTnT was used, there was no longer a difference in the NPV between use of sex-specific cutoffs or a single cutoff. These results suggest that use of hs-cTnT sex-specific cutoffs at the time of presentation to the emergency department can reduce the chance of missing MIs in women; however, the benefit is attenuated when serial measurements are obtained.[44]

A second study, by Giménez et al,[52] evaluated the use of hs-cTnT sex-specific cutoffs among 2734 individuals (32% women) with suspected ACS presenting to various emergency departments in Europe. Here, diagnosis of MI was based on local cardiac troponin assays in 64% of patients, while a single hs-cTnT cutoff of 14 ng/L (the European single-sex cutoff) was used clinically in the other 36% of patients. After the diagnosis of UA or NSTEMI, patients were reclassified by sex-specific hs-cTnT cutoffs, which were 9 ng/L for women and 17 ng/L for men. Not surprisingly, this study found that use of sex-specific cutoffs to diagnose acute MI increased the

Table 2. Summary of Published Data on Various Highly Sensitive Cardiac Troponin I Concentrations in a Healthy Population

Assay	Study	Population Size, n (% Female)	Location	Age Range, y* (Mean)	Single 99th Percentile URL, ng/L	Male 99th Percentile URL, ng/L	Female 99th Percentile URL, ng/L
ARCHITECT, Abbott	Apple et al (2012)[43]	524 (47)	Europe and United States	18–64	23	36	15
ARCHITECT, Abbott	Ji et al (2016)[45]	854 (50)	Korea	(50)	18	20	19
ARCHITECT, Abbott	Krintus et al (2015)[46]	634 (56)	Europe	(44)	11	13	9
ARCHITECT, Abbott	Kimenai et al (2016)[6]	1540 (52)	Europe	40–75 (57)	13	20	11
ARCHITECT, Abbott	Aw et al (2013)[49]	1120 (47)	Asia	35–65	26	33	18
Access, Beckman Coulter	Apple et al (2012)[43]	524 (47)	Europe and United States	18–64	32	52	23
Access, Beckman Coulter	Pretorius et al (2018)[50]	647 (35)	Australia	18–80 (34)	18	21	10
Access, Beckman Coulter	Di pietro et al (2019)[51]	500 (50)	Europe	18–68	…	14	6
Dimension Vista, Siemens	Apple et al (2012)[43]	503 (58)	Europe and United States	18–64	58	81	42
Dimension Vista, Siemens	Mckie et al (2013)[47]	565 (54)	United States	≥45 (54)	72	111	51
ADVIA Centuar, Siemens	Clerico et al (2019)[48]	653 (49)	Europe	18–86 (51)	40	43	32
Erenna, Singulex	Apple et al (2012)[43]	524 (47)	Europe and United States	18–64	31	36	30

URL indicates upper reference limit.
*Study population age not uniformly reported; mean and median ages provided as published.

sensitivity of the assay in women (from 91.3% with a single cutoff to 98.5% with a sex-specific cutoff) with a resultant lower specificity. Reclassification using sex-specific cutoffs in men resulted in lower sensitivity (from 90.7% with a single cutoff to 88.4% with a sex-specific cutoff) with a higher specificity.[52] Only 3 of the 2734 subjects were reclassified with the sex-specific cutoffs: 2 women were upgraded from UA to MI, while 1 man was downgraded from MI to UA. None of the 3 cases that were reclassified with sex-specific cutoffs had a major adverse cardiac event at 30 days. Reclassification with the sex-specific cutoffs also did not significantly improve prediction of all-cause death at 1 year.[52]

Gimenez et al[59] recently updated their results with a study of a total of 4048 subjects to assess the FDA-approved sex-specific cutoffs. The use of the higher FDA-approved sex-specific cutoffs (22 ng/L for women and 14 ng/L for men) compared with a single cutoff of 19 ng/L resulted in 4 women upgraded from UA to NSTEMI and 7 men downgraded from NSTEMI to UA. Among the 4 women who were upgraded using the FDA-approved sex-specific cutoffs, 3 had undergone percutaneous coronary intervention; and 4 of the 7 men who were downgraded also received revascularization. None of the reclassified patients had died at 1-year follow-up. Since reclassification was retrospective and could not affect clinical management, it is difficult to assess its impact on outcomes with these studies. The authors also noted that troponin levels among women presenting to the emergency department with possible ACS were similar to those in men. This may be due in part to the older age at which women tend to present with ACS (on average 5–10 years older) as well as the higher prevalence of comorbidites such as hypertension[15,30,57,60,61] and possibly renal dysfunction[62,63] in women with ACS. Both advanced age and comorbidities can raise troponin levels, thereby counterbalancing some of the troponin-lowering effects of female sex and blunting the utility of using sex-specific cutoffs for diagnosis of ACS.

Eggers et al[53] evaluated 48 250 patients in a retrospective registry of consecutive patients admitted to Swedish hospitals with suspected ACS (excluding STEMI). In this analysis, patients with a diagnosis of acute MI using criteria that included peak hs-cTnT >14 ng/L and symptoms of ischemia were retrospectively reclassified with sex-specific cutoffs of >16 ng/L for men and >9 ng/L for women. Use of sex-specific cutoffs reclassified 3.0% of men from troponin positive to troponin negative, and 8.4% of women in the reverse direction from troponin negative to troponin positive. One quarter of the men who were reclassified from troponin positive to troponin negative (ie, those who had hs-cTnT values from 15

Table 3. Description of Diagnostic Studies Comparing A Single Cutoff to Sex-Specific Cutoffs in Highly Sensitive Cardiac Troponin Assays

Studies	Assay	Patient Selection	Design	Comparison	Follow-Up
Peacock et al, 2017[44]	Elecsys Gen 5 STAT, Roche Diagnostics	1600 patients presenting to the ED with suspected ACS, age >21 years	Central adjudication of the MI diagnosis, adjudicating physicians were blinded to the hs-cTnT results Practicing clinicians were blinded to hs-cTnT results	A single cutoff of 19 ng/L versus sex-specific cutoffs (male, 22 ng/L; female, 14 ng/L) was compared with the adjudicated diagnoses in this observational study to determine sensitivity and specificity of the hs-cTnT assay	30-d follow-up for adverse cardiac events including death, repeat MI, or urgent coronary revascularization
Gimenez et al, 2016[52]	Elecsys Gen 5 STAT, Roche Diagnostics	2734 patients presenting to the ED with suspected ACS Excluded patients with STEMI or where diagnosis was unclear after adjudication	Adjudication was centrally performed with contemporary assay with readjudication 1 y later with hs-cTnT results Practicing clinicians were blinded to hs-cTnT results	Outcomes were retrospectively compared between the initially adjudicated diagnoses to the reclassified diagnoses derived from readjudication single cutoff of 14 ng/L versus sex-specific cutoffs (male, 15.5 ng/L; female, 9 ng/L)	30-d follow-up for adverse cardiac events and long-term (360-d) mortality
Gimenez et al, 2018[59]	Elecsys Gen 5 STAT, Roche Diagnostics	4048 patients presenting to the ED with suspected ACS Excluded patients with STEMI or where diagnosis was unclear after adjudication	Adjudication was centrally performed with contemporary assay with readjudication 1 y later with hs-cTnT results Practicing clinicians were blinded to the hs-cTnT results	Outcomes were retrospectively compared between the initially adjudicated diagnoses to the reclassified diagnoses derived from readjudication using a single cutoff of 19 ng/L vs sex-specific cutoffs (male, 22 ng/L; female, 14 ng/L)	1-y follow-up for mortality and cardiac interventions
Eggers et al, 2016[53]	Elecsys Gen 5 STAT, Roche Diagnostics	48 250 patients presenting to Swedish cardiac facilities with suspected ACS	No central adjudication Practicing clinicians were not aware of hs-cTnT results	Retrospective comparison of the predictive value of a single cutoff of 14 ng/L compared with sex-specific cutoffs (male, 16 ng/L; female, 9 ng/L)	Predictive assessment of 1-y all-cause mortality and cardiovascular events (cardiovascular death or nonfatal MI)
Mueller-Hennessen et al, 2016[54]	Elecsys Gen 5 STAT, Roche Diagnostics	1282 patients presenting to the ED with ACS symptoms	Adjudicating physicians had access to 30-d follow-up data but were blinded to local cardiac troponin and hs-cTnT measurements Practicing clinicians were not aware of hs-cTnT results	Retrospective comparison of diagnoses made with adjudication and with application of a single cutoff of 14 ng/L versus sex-specific cutoffs (male, 15.5 ng/L; female, 9 ng/L)	1-y follow-up for mortality
Shah et al, 2015[56]	ARCHITECT STAT, Abbott Laboratories	1126 patients presenting with suspected ACS, excluded patients not residing in the local area	Initial adjudication was performed with the contemporary assay result only Diagnoses were then readjudicated with hs-cTnI results Practicing clinicians were blinded to the hs-cTnI results	Outcomes were compared between the initially adjudicated diagnoses to the reclassified diagnoses derived from readjudication using a single cutoff of 26 ng/L compared with sex-specific cutoffs (male, 34 ng/L; female, 16 ng/L in this obeservational study)	1-y follow-up for myocardial infarction and death
Cullen et al, 2016[55]	ARCHITECT STAT, Abbott Laboratories	2841 patients aged >18 who present with ACS symptoms, excluding STEMI, ECG evidence of ischemia, or significant arrhythmias	Central adjudication was performed without knowledge of the hs-cTnI results Practicing clinicians were blinded to the hs-cTnI results	Observational assessment of diagnoses made using contemporary assays as compared with reclassification using hs-cTnI single cutoff of 26 ng/L vs sex-specific cutoffs (male, 34 ng/L; female, 16 ng/L)	1-y follow-up of rates of MI, coronary revascularization and death to assess predictive and prognostic utility of reclassification

(*Continued*)

Table 3. Continued

Studies	Assay	Patient Selection	Design	Comparison	Follow-Up
Trambas et al, 2016[57]	ARCHITECT STAT, Abbott Laboratories	23 576 patients with at least 1 cardiac troponin check at one of the enrolling centers	No adjudication Practicing clinicians were aware of hs-cTnI results and sex-specific cutoffs at each center	Retrospective comparison of frequency of MI diagnosis using a uniform contemporary assay cutoff to sex-specific cutoffs (female, 16 ng/L; male, 26 ng/L at one center; male, 34 ng/L at another center)	6-mo follow-up for the contemporary assay and 6-mo follow-up of hs-cTnI assay to determine change in rate of MI diagnosis and angiography between men and women
Lee et al, 2019	ARCHITECT STAT, Abbott Laboratories	48 282 consecutive patients presenting with suspected ACS in Scotland with paired contemporary and trial assay	Central adjudication was performed for all patients with hs-cTnI above 99th percentile Validation phase—practicing clinicians were provided result of the contemporary assay Implementation phase—only hs-cTnI result was reported to the clinicians	Prospective comparison of incidence of myocardial injury, diagnostic approach, and therapy between men and women in the validation phase as compared with the implementation phase where myocardial injury was defined by peak hs-cTnI above 16 ng/L in women and 34 ng/L in men	1-y follow-up with primary outcome being type 1 and type 4b myocardial infarction or cardiovascular death

ACS indicates acute coronary syndrome; ED, emergency department; hs-cTnI, highly sensitive cardiac troponin I; hs-cTnT, highly sensitive cardiac troponin T; MI, myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

to 16 ng/L) were considered to have ACS and treated as such. Only 14% of women who were reclassified as troponin positive (hs-cTnT between 10 and 14 ng/L) were diagnosed with ACS and thus treated as such. A substantial 68% of the reclassified women with hs-cTnT 10 to 14 ng/L who underwent coronary angiography had normal or near-normal results. The authors found that in men, 1-year risk of cardiovascular death or recurrent MI began to increase at levels well below the sex-specific cutoff of 16 ng/L; while in women, risk began to increase at levels slightly above the sex-specific cutoff of 9 ng/L but below the single cutoff of 14 ng/L. In both sexes, the range where risk of adverse cardiovascular events or death within 1 year began to increase was around 10 to 12 ng/L.[53] One of the important limitations of this study is that men and women were retrospectively reclassified, so subjects received treatment according to their original classification. There was a statistically significant different rate of coronary angiography and percutaneous coronary intervention between those who were troponin negative by both criteria, those who were reclassified, and those who were consistently troponin positive, in both men and women. Thus, outcomes and risk assessment were likely skewed by the treatment differences between the groups.[53]

In another study published in 2016, Mueller-Hennesen et al[54] retrospectively reclassified patients presenting to the emergency department with symptoms suggestive of ACS. They studied both a single hs-cTnT cutoff of 14 ng/L as well as sex-specific cutoffs (9 ng/L in women and 15.5 ng/L in men). This study found that reclassification with sex-specific cutoffs resulted in 6% more women and 2% fewer men being diagnosed with myocardial injury. There was no difference in outcomes between male and female patients classified by sex-specific cutoffs as compared with a single cutoff at 12 months. Several limitations are again noteworthy here. Patients enrolled were presenting with typical chest pain, with likely exclusion of patients with atypical symptoms of ACS. Additionally, practicing clinicians had access to only contemporary cardiac troponin assays, so as in the previously discussed studies, the impact of sex-specific cutoffs on diagnostic approach, interventions, and outcomes could not be evaluated.

DIAGNOSTIC STUDIES EVALUATING HS-CTNI SEX-SPECIFIC CUTOFFS

In the case of hs-cTnI, there are several different commercially available assays, but the current research landscape has growing data on the sex-specific cutoffs for the ARCHITECT STAT high-sensitivity assay,

which is the focus of the following studies. In 2015, Shah et al[56] published a study of 1126 consecutive patients with suspected ACS. In this study, clinical decisions were made on the basis of the local cardiac troponin I assay, while clinicians were blinded to results of hs-cTnI. Patients were later reclassified on the basis of a single cutoff of 26 ng/L as well as the sex-specific cutoffs of 16 ng/L in women and 34 ng/L in men.[56] The incidence of recurrent MI or death from any cause at 1 year was 6-fold higher in women reclassified as MI using the sex-specific cutoff (ie, women with hs-cTnI in the 17–26 ng/L range) compared with those women with hs-cTnI <16 ng/L. This suggests that the improved sensitivity of the lower cutoff in women resulted in clinically meaningful reclassification, correctly identifying women at risk for adverse outcomes.[56] Other findings of note were that women were less likely than men to be referred to a cardiologist when presenting with ACS, and women with MI that was discernible using only sex-specific hs-cTnI cutoffs were less likely to receive evidence-based treatments and had the highest rates of death and reinfarction at 1 year. In fact, women identified using only the lower sex-specific threshold had the highest risk of death or recurrent MI, with an event rate 6-fold higher than those in women with hs-cTnI <16 ng/L. Thus, the authors conclude that failure to use sex-specific hs-cTnI cutoffs is contributing to inequality in treatment and outcomes for MI in women.[56]

Another observational study, by Cullen et al,[55] included 2841 patients in the emergency department with possible ACS and used the same assay and cutoffs as the Shah et al[56] study. Use of a sex-specific cutoff reclassified 25 women (2%) with MI compared with the use of a single cutoff.[55] Seven of the women (28%) who were upgraded to a diagnosis of MI had a major adverse cardiac event within 1 year (defined as MI, emergent revascularization, or death). Thus, the sex-specific cutoffs improved detection of women at risk for adverse events. Simultaneously, the sex-specific cutoff use resulted in 29 (2%) fewer men receiving the diagnosis of MI, of whom 12 (41%) developed a major adverse cardiac event at 1 year. Overall, the net reclassification improvement was nonsignificant. Although the use of sex-specific cutoffs improved diagnosis of MI in women, the net effect on all patients presenting to the emergency department with chest pain was minimal (overall 9.3% had elevated troponin using the single cutoff versus 9.2% with sex-specific cutoffs).[55]

In contrast to the findings of Shah et al[56] and Cullen et al[55] described above, Trambas et al[57] did not find a significant increase in the rate of MI diagnosis in women after switching from a single cutoff with an earlier-generation troponin assay to a sex-specific cutoff with a highly sensitive assay. This was a retrospective study of patients presenting with possible ACS at 2 centers in Australia and New Zealand. The authors compared the rate of diagnosis of MI in men and women during the 6 months before and after instituting the hs-cTnI assay—thus evaluating not just a switch to sex-specific cutoffs, but also a change from a contemporary to a highly sensitive assay.[57] A significantly higher number of women were identified as having an abnormal hs-cTnI, while there was no change in men. Women were more likely to be admitted to the hospital for a "cardiovascular" indication, which included ACS as well as heart failure, pericardial disease, and arrhythmia diagnoses following the institution of sex-specific reference intervals. However, there was no significant increase in the rate of angiography or the rate of MI diagnosis in women or men.[57] A limitation of this study is that there was no central adjudication of MI diagnoses; rather, the outcomes were based on the local, "real-world" diagnosis only—thus, some women with elevated troponin and true MI may have been underdiagnosed.

More recently, a prospective study by Lee et al[58] evaluated the incidence of MI diagnosis, use of diagnostic studies, and initiation of medical therapy in a large cohort of patients with suspected ACS in whom diagnosis was made using a contemporary cardiac troponin I assay during a validation phase, and compared with diagnoses made with the hs-cTnI assay in the implementation phase. Although hs-cTnI assays were performed in both phases and provided to the adjudicating physicians, the practicing physicians had only the contemporary cardiac troponin I assay result (with a single cutoff for both sexes) during the validation phase. In contrast, the clinicians in the implementation phase were provided the hs-cTnI result with sex-specific cutoffs of 16 ng/L in women and 34 ng/L in men. This is one of the few studies to prospectively evaluate the integration of sex-specific curoffs into routine clinical care, and thus able to comment on real-world application. In the implementation phase, type I MI diagnosis was made in 25% more women using the hs-cTnI sex-specific cutoffs as compared with the validation phase. The rate of type I MI diagnosis in men also increased but at a much lower rate of 6%. The use of sex-specific cutoffs in the hs-cTnI assay also led to more type 2 MI diagnoses (39% increase in women and 9% increase in men) and diagnoses of nonischemic myocardial injury (67% increase in women and 12% increase in men).[58] There was an increase in the percentage of women with myocardial injury undergoing coronary angiography (18% versus 26%) and revascularization (10% versus 15%) in the implementation phase, but the authors found that there was no difference in primary outcomes for either sex in the validation versus implementation phase. The lack of improved

outcomes in women despite much higher frequency of MI diagnosis and revascularization is possibly attributed to the observation that rates of angiography and revascularization were still lower in women with type I MI compared with men with type I MI across both study phases. Women were also less frequently started on dual-antiplatelet therapy, statins, and β-blockers as compared with men. The use of sex-specific cutoffs did identify a higher-risk group of women; conversely, men with troponin below their sex-specific cutoff were at low risk, suggesting that the use of a higher 99th percentile cutoff for men did not result in inappropriate exclusion of those who may have benefitted from more aggressive treatment.

CONCLUSIONS AND FUTURE DIRECTIONS

Cardiac structural differences between men and women may account for the sex-specific differences in highly sensitive cardiac troponins in healthy individuals. At any given age, the prevalence and distribution of coronary artery disease is also different between the sexes. While ACS with obstructive coronary artery disease has established diagnostic approaches, other types of coronary artery disease, including MINOCA, are more recently acknowledged as clinically significant entities. With variability in the type of coronary artery disease and extent of comorbidities between the sexes, establishing therapeutic approaches and improving outcomes among both men and women remains a clinical challenge. Multiple studies have suggested that normal or nonobstructive coronary angiography does not rule out coronary artery disease nor fully predict cardiovascular morbidity and mortality. Thus, the use of sex-specific highly sensitive troponin assays to detect small MIs (including MINOCA) in women may be a way to significantly address the disparity in clinical outcomes, especially if appropriate therapeutic and preventive interventions can be instituted in cases that might have been considered "false positive" in the past.

Reflecting the differences in cardiac structure and mass, sex-specific 99th percentile URLs have now been identified in healthy men and women. This has led to approval of sex-specific clinical decision cutoffs for various hs-cTnT and hs-cTnI assays. Whether detecting and utilizing this baseline difference in circulating cardiac troponins between the sexes leads to improvement in clinical performance of the highly sensitive cardiac troponin assays has yet to be established. Current literature indicates that sex-specific cutoffs may lead to the identification of more women with positive biomarkers suggestive of myocardial injury, but studies do not yet demonstrate an improvement in outcomes when patients with suspected ACS are followed for up to 1 year.

The discordance in potential diagnostic benefits and lack of data suggesting improved outcomes with implementation of sex-specific cutoffs as compared with a single cutoff exists for several different reasons. First, most of the studies to date are retrospective or observational studies, which reclassify patients diagnosed with ACS using sex-specific cutoffs. Retrospective reclassification cannot translate into changes in clinical practice and cannot impact further investigations (angiography rates) or therapeutic approaches (revascularization or medical therapy) in such studies. Thus, outcomes measured at follow-up are not reflective of clinical decisions guided by highly sensitive cardiac troponin assays and do not reflect any potential shifts in management that could occur in patients reclassified as having ACS using sex-specific cutoffs.

Two of the studies[57,58] by design included a cohort of patients who were diagnosed and treated on the basis of the sex-specific hs-cTnI assay cutoffs. Although use of sex-specific cutoffs identified more men and women with myocardial injury, women in these studies were still less likely than men with a similar diagnosis to undergo coronary angiography, revascularization, and prescribed guideline-directed medical therapy despite having a similar diagnosis. This finding highlights the possibility that clinicians may consider modest cardiac troponin elevations identified by the lower sex-specific cutoff in women inconsequential to influence clinical decisions. A diagnostic test alone cannot lead to improved outcomes if it is not accompanied by a change in provider behavior.

Additionally, the majority of these studies enrolled patients presenting with typical ACS symptoms. Women with typical ACS symptoms tend to be older and have more comorbidities as compared with their male counterparts. Although this cohort represents the most common type of patients who will use and benefit from cardiac troponin measurement for diagnosis of MI, there may be special populations (such as younger women) and diseases other than type I MI that are underrepresented in the existing literature. Finally, serial monitoring of cardiac biomarkers evaluating dynamic changes may attenuate the effect of a lower sex-specific cutoff.

It is worth noting that the potential diagnostic and prognostic value in incorporating sex-specific cutoffs into clinical practice may be partially counterbalanced by simplicity in using a single cutoff. Clinical practice has historically used a single cardiac biomarker cutoff for both sexes, so clinicians at all levels of training and specialization may be more comfortable with implementing and interpreting a single clinical decision

cutoff of highly sensitive cardiac troponins for both sexes. However, multiple other assays and tests currently in practice use sex-specific cutoffs, so any learning curve should be relatively swift. Regardless, detecting differences in hs-cTnT and hs-cTnI in healthy men and women is a new tool and opportunity to assess less common and less defined cardiovascular diseases that may affect men and women disproportionately. There is a growing body of evidence in the diagnostic yield of sex-specific cutoffs of certain hs-cTnT and hs-cTnI assays as previously mentioned; however, clinicians should be cautious to extrapolate these conclusions to other hs-cTnI assays, as they may not be equivalent. The use of sex-specific cutoffs has also been suggested as a prognostic tool in disease states other than ACS, as well as in primary prevention and risk stratification, which remain areas of active research.[64,65] It is likely that sex-specific cutoffs will remain highly relevant in these nonacute settings.

In summary, it is clear that using a single troponin cutoff for both sexes results in women being systematically underdiagnosed with MI. Without prospective studies, it is impossible to know how much this underdiagnosis contributes to inequalities in the management and treatment of MI. Improved diagnosis alone cannot meaningfully impact outcomes if clinicians fail to respond with therapeutic or preventive action. However, improved diagnosis is a necessary first step. We suggest that prospective studies with long-term follow-up are needed to further assess the clinical utility of sex-specific cutoffs, which may not be uniform between assays. We also posit that sex-specific cutoffs may have a role in evaluating diseases that disproportionately affect women including MINOCA. Sex-specific cutoffs may be particularly applicable in younger women as well. Whether classifying MIs with highly sensitive assays will lead to improved pharmacologic and interventional management of small MIs including MINOCA remains an area highly worthy of ongoing investigation.

The 99th percentile cutoff, whether single or sex specific, is likely to become less relevant in the emergency department setting as accelerated diagnostic protocols using much lower values and dynamic thresholds take hold. However, as long as we are using a 99th percentile URL, we need more prospective data on the use of sex-specific thresholds so that we can make informed, evidence-based choices of how to best use highly sensitive troponin assays.

ARTICLE INFORMATION

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