Journal of the American Heart Association

ORIGINAL RESEARCH

Sex Differences in Outcomes of Acute Myocardial Injury After Stroke

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BACKGROUND: Sex differences in presentation, treatment, and prognosis of cardiovascular disorders are well recognized. Although an association between acute myocardial injury and mortality after ischemic stroke has been demonstrated, it is unclear whether prevalence and outcome of poststroke acute myocardial injury differ between women and men.

METHODS AND RESULTS: We prospectively screened consecutive patients with acute ischemic stroke and serial high-sensitivity cardiac troponin T measurements admitted to our center. Acute myocardial injury was defined as at least 1 high-sensitivity cardiac troponin T value above the upper reference limit (14 ng/L) with a rise/fall of >20%. Rates of acute myocardial injury were also calculated using sex-specific high-sensitivity cardiac troponin T cutoffs (women upper reference limit, 9 ng/L; men upper reference limit, 16 ng/L). Logistic regression analyses were performed to evaluate the association between acute myocardial injury and outcomes. Of 1067 patients included, 494 were women (46%). Women were older, had a higher rate of known atrial fibrillation, were more likely to be functionally dependent before admission, had higher stroke severity, and more often had cardioembolic strokes (all *P* values <0.05). The crude prevalence of acute myocardial injury differed by sex (29% women versus 23% men, *P*=0.024). Statistically significant associations between acute myocardial injury and outcomes were observed in women (7-day in-hospital mortality: adjusted odds ratio [aOR], 3.2 [95% CI, 1.07–9.3]; in-hospital mortality: aOR, 3.3 [95% CI, 1.4–7.6]; modified Rankin Scale score at discharge: aOR, 1.6 [95% CI, 1.1–2.4]) but not in men. The implementation of sex-specific cutoffs did not increase the prognostic value of acute myocardial injury for unfavorable outcomes.

CONCLUSIONS: The prevalence of acute myocardial injury after ischemic stroke and its association with mortality and greater disability might be sex-dependent.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03892226.

Key Words: cardiac complications ■ cardiac troponin ■ ischemic stroke ■ mortality ■ sex differences ■ sex-specific cutoffs

Cardiac complications in the setting of acute ischemic stroke are a leading cause of poststroke mortality, second only to primary neurological death.[1] For the early detection of concomitant cardiac events, current American Heart Association/American Stroke Association guidelines recommend the measurement of cardiac troponin as a biomarker of myocardial injury in all patients with acute ischemic.[2,3] Elevated high-sensitivity cardiac troponin T (hs-cTnT), defined as a concentration above the assay-specific upper reference limit (URL), is detected in up to 30% to 60% of patients with acute ischemic stroke and correlates with poor functional outcome and mortality.[4–7] However, a single elevated hs-cTnT value does not

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This article was sent to Kori S. Zachrison, MD, MSc, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.032755

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our prospective observational study with serial measurement of high-sensitivity cardiac troponin shows that the crude prevalence of acute myocardial injury after ischemic stroke is higher in women than in men.
- The association between acute poststroke myocardial injury and increased early mortality and disability was stronger in women than in men.
- The application of sex-specific high-sensitivity troponin cutoffs did not increase the prognostic value of acute myocardial injury for unfavorable outcomes.

What Are the Clinical Implications?

- Clinicians should be aware that the prevalence of acute myocardial injury after ischemic stroke and its association with mortality and greater disability might be sex-dependent.
- A sex-specific approach might be relevant for cardiac risk stratification and targeting of invasive diagnostic tests and interventions for acute myocardial injury in patients with acute ischemic stroke.
- As women may experience a more pronounced brain–heart axis dysfunction after acute brain injury, translational studies are need to investigate the role of hormonal factors in sex differences in acute cardiac complications after stroke.

Nonstandard Abbreviations and Acronyms

CORONA-IS	Cardiomyocyte injury Following Acute Ischemic Stroke
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
URL	upper reference limit

sufficiently characterize the cardiac injury, and serial hs-cTnT measurements are required to differentiate an acute myocardial injury from chronic conditions.[2,8]

Sex differences in the presentation, treatment, and outcome of both stroke and cardiac disorders are well recognized.[9,10] Overall, women with acute cardiovascular disorders are more likely to be underdiagnosed or less likely to receive guideline-directed care affecting outcomes.[11–15] Specific sex differences in poststroke cardiac complications have also recently been reported: women with stroke appear to have an 8-fold lower burden of typical atherosclerotic coronary artery disease than men yet have double the risk of developing an acute myocardial event after stroke.[16,17]

The analytical accuracy of hs-cTnT assays shows that healthy women have lower circulating hs-cTnT concentrations than men, reflecting known sex differences in cardiac structure and mass.[18–21] Consequently, expert consensus panels recommend the use of sex-specific hs-cTnT cutoff values for the diagnosis of myocardial infarction, in the attempt of reducing women's risk to be underdiagnosed with cardiac events.[2,11,22] However, whether the implementation of sex-specific hs-cTnT thresholds for early detection of stroke-related cardiac injury improves risk stratification in patients with acute ischemic stroke has not been studied yet.

We investigated sex differences in the prevalence and outcome of acute myocardial injury after stroke in a prospective cohort of patients with acute ischemic stroke, applying both sex-neutral and sex-specific hs-cTnT cutoffs. Considering the high frequency of elevated hs-cTnT in patients with stroke and the presence of concomitant cardiac disorders,[4,5] it is possible that the current hs-cTnT thresholds used for the diagnosis of myocardial infarction in the general population are not optimal for the stratification of cardiac risk in the setting of ischemic stroke. Therefore, we also attempted to identify the optimal sex-specific hs-cTnT peak cutoffs for the association with early mortality in patients with stroke.

METHODS

The data that support the findings of this study are available from the corresponding author and the last author upon reasonable request.

Study Population

The CORONA-IS (Cardiomyocyte Injury Following Acute Ischemic Stroke) study (clinicaltrials.gov identifier NCT03892226) is a prospective study designed to gain mechanistic insight into stroke-associated myocardial injury. The study was approved by the local Ethics Committee of the Charité–Universitätsmedizin Berlin (EA4/123/18) and a study protocol has been published previously.[23] As described earlier, all consecutive patients with acute ischemic stroke admitted to the Stroke Unit of the Department of Neurology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin were prospectively screened for participation in the CORONA-IS study.[7] Basic demographic information and anonymized routine clinical data were entered into a screening database. As only routine clinical data were collected, informed consent was not required according to the laws and regulations of the Federal State of Berlin (§25 Landeskrankenhausgesetz). The present analysis evaluates all patients admitted between

January 2019 and December 2020. Inclusion criteria were the presence of acute ischemic stroke confirmed by neuroimaging, serial hs-cTnT measurements, and hospital admission within 48 hours of stroke symptom onset (Figure 1). This study complies with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[24]

Data Collection

Demographics (age and sex were obtained from health insurance card presented at hospital admission), cardiovascular risk factors, revascularization treatments, and stroke characteristics were collected as previously published.[7] Stroke severity and functional status were assessed with the National Institutes of Health Stroke Scale (NIHSS) at admission and the modified Rankin Scale (mRS) at discharge, respectively. Prestroke functional dependency was defined as regular nursing care at home or living in a nursing home.

Laboratory Measures

High-sensitivity Troponin T assay Roche Elecsys, Gen 5 (sex-neutral 99th percentile URL=14 ng/L according to the European package insert; 10% coefficients of variation precision=13 ng/L; lower limit of detection=5 ng/L) was obtained in all patients with acute ischemic stroke at admission and again within the first 2 days of hospitalization. Acute myocardial injury was defined as at least 1 hs-cTnT value above the URL with a rise or fall of >20% in serial measurements, based on the 2018 Fourth Universal Definition of Myocardial Infarction and as described previously.[2,7,23] If more than 2 hs-cTnT values were available, only the first and second consecutive measurements were considered. All patients with normal hs-cTnT values or elevated values but without a dynamic change >20% were classified as *no acute myocardial injury*. Rates of acute myocardial injury were first determined using the sex-neutral URL of 14 ng/L. Patients were then reclassified applying sex-specific hs-cTnT cutoffs (women URL=9 ng/L; men URL=16 ng/L), based on the original multicenter study evaluating the Roche Elecsys hs-cTnT.[25,26]

Outcomes

The main outcomes were (1) 7-day in-hospital mortality, defined as any cause of death within the first 7 days of hospitalization, (2) all-cause in-hospital mortality, and (3) functional status at discharge (based on documented mRS score at discharge). Patients who were discharged from the hospital earlier than 7 days were considered to be alive on day 7.

Statistical Analysis

Categorical variables were presented as frequencies and continuous variables as mean±SD or median with interquartile range based on their distribution. No imputation was performed for missing data. When data were missing, we reported the denominator of the population with available data. In univariable analysis, women and men were compared using an independent-sample *t* test for continuous normally distributed variables, Wilcoxon-Mann–Whitney *U* Test for

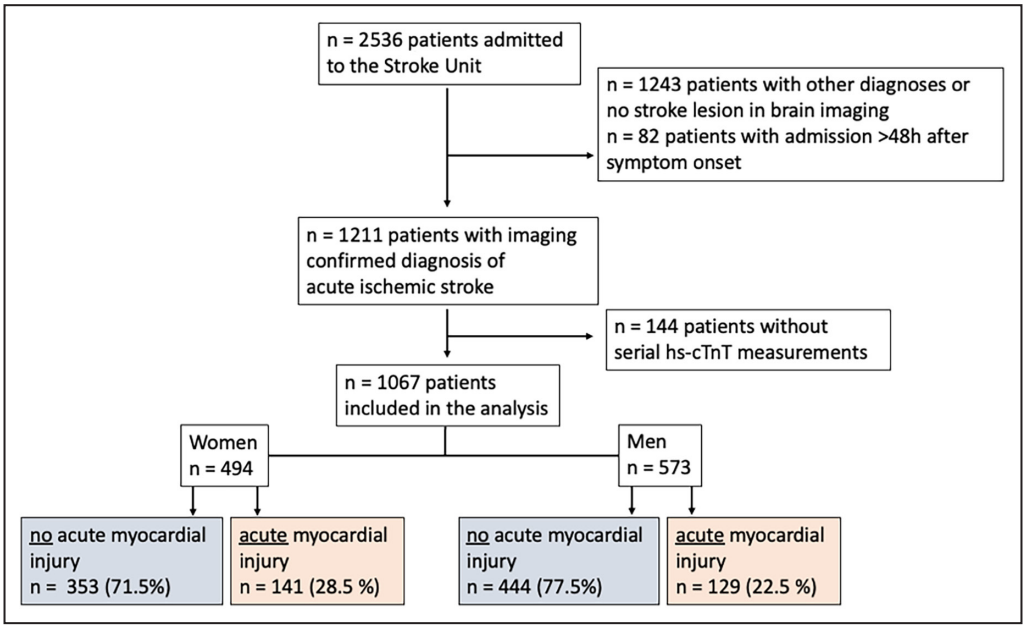

Figure 1. Flow chart of patient inclusion.
Acute myocardial injury is defined as at least 1 hs-cTnT value above the sex-neutral upper reference limit (14 ng/L) and a rise/fall >20% in serial measurement. hs-cTnT indicates high-sensitivity cardiac troponin T.

continuous non-normally distributed or ordinal variables, and chi-square or Fisher's exact test for categorical variables. Unadjusted and adjusted multivariable logistic regression analyses were performed in order to calculate odds ratios (ORs) and 95% CIs for association of sex with acute myocardial injury. Adjustments were made for age, medical history of chronic kidney disease, coronary artery disease (including history of myocardial infarction), chronic heart failure, history of known atrial fibrillation or flutter, NIHSS score at admission, and prestroke dependency. For the association between acute myocardial injury and mortality outcomes (7-day in-hospital mortality and in-hospital mortality), adjusted multivariable logistic regression analyses were performed. Ordinal logistic regression analysis was conducted to estimate the adjusted OR (aOR) for the association of acute myocardial injury and a shift toward increased disability at discharge (higher category of mRS score at discharge).

In the primary model regarding the association between acute myocardial injury and each outcome of interest, we adjusted for age, sex, medical history of chronic kidney disease, coronary artery disease, chronic heart failure, history of known atrial fibrillation or flutter, NIHSS score at admission, and prestroke dependency. Analyses were performed in the whole cohort and then stratified by sex. Given the small number of outcome events for 7-day in-hospital mortality, sensitivity analyses were performed including only age and NIHSS as covariates for adjustments, to avoid overfitting. Covariates were selected a priori. Sensitivity analyses for association of acute myocardial injury and outcomes including revascularization treatments (thrombolytic and mechanical thrombectomy) were performed a posteriori. To further assess the role of sex on the predictive value of acute myocardial injury for clinical outcomes, the analyses were also performed for men and women separately. All of the analyses were repeated after acute myocardial injury was reclassified using sex-specific hs-cTnT cutoffs. Finally, receiver operating characteristic (ROC) curve analysis was used to evaluate the performance of sex-specific cutoffs of hs-cTnT peak values as markers for 7-day in-hospital mortality. The optimal cutoff with the highest Youden index and corresponding sensitivity and specificity was identified for men and women respectively.[27] The predictive performance of the sex-specific cutoff of the peak hs-cTnT value for 7-day in-hospital mortality was assessed using area under the ROC curve.

All tests were 2-tailed, and values of $P<0.05$ were considered statistically significant. No sample size estimation was performed, as this is an exploratory analysis of observational data. No corrections were made for multiple comparisons. Statistical analyses were performed using IBM SPSS (SPSS, Inc., Chicago, IL, version 29.0) and RStudio (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, version 2023.06).

RESULTS

Patient Characteristics

The final cohort consisted of 1067 patients: 494 women (46%) and 573 men (54%) (Figure 1). Detailed patient characteristics stratified by sex are summarized in Table 1.

Women were older, had higher rates of known atrial fibrillation, and were more likely to be functionally dependent before admission. Men were more likely to have experienced a previous ischemic or hemorrhagic stroke. Women had a higher median NIHSS score at admission and they had cardioembolic strokes more often. Women were found more frequently with large vessel occlusion and underwent thrombectomy more often than men.

Cardiac Troponin Values and Outcomes in Women and Men

Although no statistically significant sex differences were observed regarding the median first hs-cTnT value, a higher median second hs-cTnT value and a greater absolute difference between first and second hs-cTnT values were detected in women compared with men. Women showed a higher NIHSS score and mRS score at hospital discharge compared with men (Table 2). Median time from stroke onset to first and second hs-cTnT measurement, as well as median time between the hs-cTnT measurements, did not differ between sexes (all $P>0.05$).

Thirty patients (20 women and 10 men) died within 7 days of admission (22 from neurological causes, 5 from cardiac causes, and 3 from other conditions; Tables S1–S6). A total of 56 deaths occurred (34 women and 22 men) during hospitalization (35 from neurological causes, 8 from cardiac causes, and 13 from other conditions). Seven-day in-hospital mortality as well as overall in-hospital mortality were higher in women than men (4% versus 2%, $P=0.023$ and 7% versus 4%, $P=0.026$, respectively).

Women had a higher crude prevalence of acute myocardial injury than men (29% versus 23%, $P=0.024$). In univariable regression analysis, female sex was associated with acute myocardial injury (OR, 1.38 [95% CI, 1.04–1.81]), but this association was not statistically significant after adjustments (aOR, 1.06 [95% CI, 0.78–1.43]) (Table S2). Detailed characteristics and outcomes of women and men with acute myocardial injury are reported in Table S3.

Table 1. Demographics, Comorbidities, and Stroke Characteristics Stratified by Sex

	Total cohort (n=1067)		
	Women, n=494 (46.3%)	Men, n=573 (53.7%)	*P* value
Demographics			
Mean age, y	78.2±10.8	72.7±11.8	<0.001
Comorbidities			
Hypertension	385 (78%)	423 (74%)	0.118
Previously known atrial fibrillation	112 (22.7)	102 (17.8)	0.048
Coronary artery disease	78 (16%)	116 (20%)	0.060
Prior stroke	148 (30%)	208 (36%)	0.029
Diabetes	104 (21%)	148 (26%)	0.067
Dyslipidemia	241 (49%)	285 (50%)	0.756
Chronic kidney disease	106 (21%)	107 (19%)	0.257
Congestive heart failure	30 (6.1%)	10 (1.7%)	<0.001
Prestroke dependency*	127 (26%)	69 (12%)	<0.001
Ischemic stroke			
National Institutes of Health Stroke Scale score at admission†	4 (1–9)	3 (1–6)	<0.001
Thrombolysis	129 (26%)	158 (28%)	0.59
Thrombectomy	84 (17%)	67 (12%)	0.013
Presence of large vessel occlusion	106/427 (25%)	85/534 (16%)	<0.001
Stroke cause			
Cardioembolic	194 (39%)	172 (30%)	0.001
Small vessel disease	40 (8%)	69 (12%)	0.034

Categorical variables are presented as frequency (column percent), continuous variables are presented as mean±SD or median (interquartile range) when nonnormally distributed.

*Data available n=1065 patients (492 women and 573 men).

†Data available n=1055 patients (489 women and 566 men).

Association of Acute Myocardial Injury and Outcomes

In multivariable analysis, patients with acute myocardial injury had a higher 7-day in-hospital mortality (aOR, 2.7 [95% CI, 1.2–6.2]), in-hospital mortality (aOR, 3.0 [95% CI, 1.6–5.6]), and a shift toward greater disability on mRS score at discharge (aOR, 1.5 [95% CI, 1.1–1.9]) (Figure 2).

To further characterize the role of sex on the association between acute myocardial injury and outcomes, multivariable analyses were conducted for women and men separately. In women, a robust association was found between acute myocardial injury and all end points of interest (7-day in-hospital mortality: aOR, 3.2 [95% CI, 1.07–9.3], in-hospital mortality: aOR, 3.3 [95% CI, 1.4–7.6], and mRS score at discharge: aOR, 1.6 [95% CI, 1.1–2.4]). In men, we did not find a significant association between acute myocardial injury and outcomes (Figure 2). Sensitivity analyses for the association between acute myocardial injury and end points of interest are reported in Tables S4 and S5. In the restricted model, as well as in the sensitivity analysis including revascularization treatments as covariate, there was still a statistically significant association between acute myocardial injury and outcomes in women but not in men.

The Predictive Role of Sex-Specific hs-cTnT Cutoffs for Outcomes

With the implementation of sex-specific hs-cTnT thresholds, the crude prevalence of acute myocardial injury was 35% in women and 21% in men (*P*<0.001). A significant association between female sex and acute myocardial injury was observed after adjustments (aOR, 1.7 [95% CI, 1.28–2.33]; Table S2).

After reclassification using sex-specific cutoffs, the association of acute myocardial injury with all 3 outcomes of interest remained statistically significant (7-day in-hospital mortality: aOR, 2.4 [95% CI, 1.04–5.6], in-hospital mortality: aOR, 2.7 [95% CI, 1.4–5.1], functional outcome: aOR, 1.3 [95% CI, 1.02–1.7]; Figure 2). When regression analyses were performed separately for women and men, the implementation of sex-specific thresholds did not strengthen the association between acute myocardial injury and outcomes. In women, the association of acute myocardial injury persisted only for in-hospital mortality (aOR, 2.6 [95% CI, 1.1–6.2]; Figure 2); no association

Table 2. Cardiac Troponin Values, Acute Myocardial Injury, and Outcomes Stratified by Sex

	Total cohort (n=1067)		
	Women, n=494 (47.3%)	Men, n=573 (53.7%)	*P* value
First hs-cTnT	17 (10–31)	16 (9–26)	0.108
Second hs-cTnT	20 (11–40)	19 (11–31)	0.010
Median delta first to second hs-cTnT	3 (1–7.25)	2 (1–5.5)	0.019
Time from symptoms onset to first hs-cTnT	10 (3–19)	8 (3–19)	0.315
Time from symptoms onset to second hs-cTnT	25 (18–37)	25 (16–36)	0.981
Time interval between first and second hs-cTnT	16 (7–21)	16 (6–21)	0.217
First hs-cTnT >URL (14 ng/L)	285 (58%)	305 (53%)	0.144
Second hs-cTnT >URL (14 ng/L)	328 (66%)	357 (62%)	0.164
Acute myocardial injury	141 (29%)	129 (23%)	0.024
7-d in-hospital mortality	20 (4%)	10 (2%)	0.023
In-hospital mortality	34 (7%)	22 (4%)	0.026
National Institutes of Health Stroke Scale score at discharge	2 (0–5)	1 (0–3)	<0.001
Modified Rankin Scale score at discharge	2 (1–4)	2 (0–4)	<0.001

Acute myocardial injury is defined as at least 1 hs-cTnT above the sex-neutral upper reference limit and a rise/fall of >20% in serial measurement (following the 2018 Fourth Universal Definition of Myocardial Infarction). Categorical variables are presented as frequency (column percent), continuous variables are presented as median (interquartile range) when nonnormally distributed. hs-cTnT indicates high-sensitivity cardiac troponin T; IQR, interquartile range; and URL, upper reference limit.

between acute myocardial injury and outcomes was observed in men.

The ROC-derived optimal sex-specific cutoffs of hs-cTnT peak values with the highest Youden index for predicting early in-hospital mortality were 29.5 ng/L in women (sensitivity: 0.75, specificity: 0.67, Youden index: 0.42, area under the ROC curve=0.73, negative predictive value [NPV]: 98.46%) and 66 ng/L in men (sensitivity: 0.60, specificity: 0.91, Youden index: 0.51, area under the ROC=0.84, NPV: 99.23%). Figure 3 shows the ROC curve of hs-cTnT peak values for 7-day in-hospital mortality in women and men.

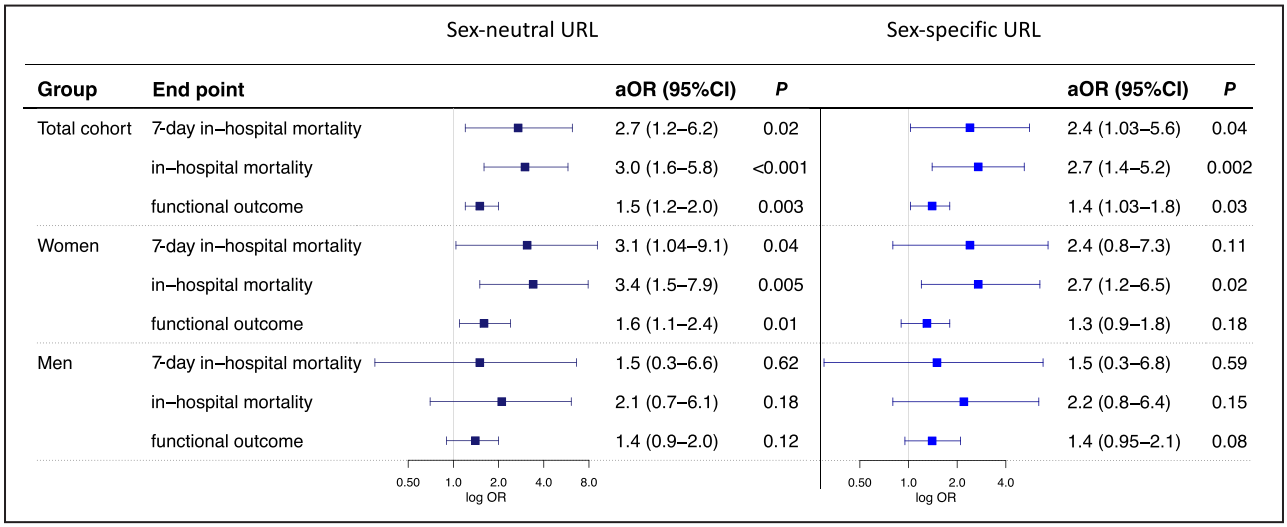

Figure 2. Adjusted logistic and ordinal regression analysis of association of acute myocardial injury (identified with sex-neutral and sex-specific thresholds) and main outcomes for the whole cohort and stratified per sex.
Adjusted odd ratios (aORs) and corresponding 95% CIs for association of acute myocardial injury and 7-day in-hospital mortality, in-hospital mortality, functional outcome based on modified Rankin Scale score (mRS) at discharge in the total cohort, in women, and in men. On the left side aOR for acute myocardial injury is based on a sex-neutral cutoff (14 ng/L), on the right side it is based on a sex-specific cutoff (9 ng/L for women and 16 ng/L for men). Adjustments were made for age, medical history of chronic kidney disease, coronary artery disease, congestive heart failure, previous atrial fibrillation or flutter, National Institutes of Health Stroke Scale at admission, and prestroke dependency. URL indicates upper reference limit.

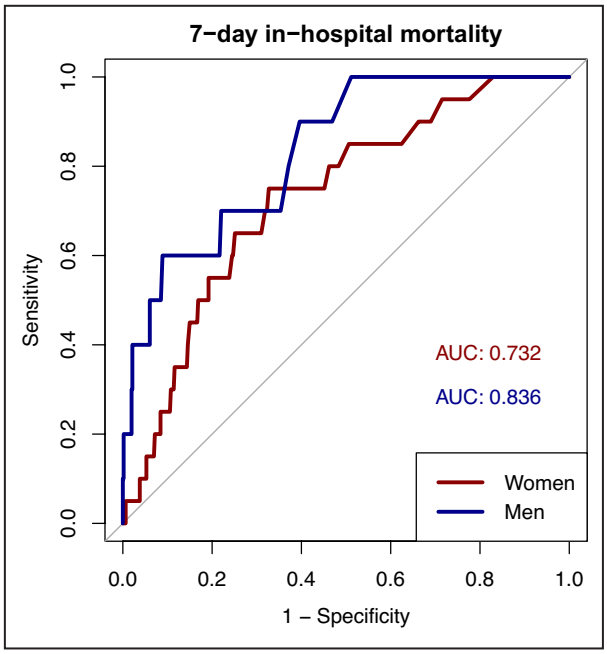

Figure 3. Receiver operating characteristic curve of sex-specific high-sensitivity cardiac troponin (hs-cTn) peaks for 7-day in-hospital mortality.
Sensitivity and specificity for 7-day in-hospital mortality of the optimal sex-specific hs-cTn peak levels (identified with the highest Youden index) in women (29.5 ng/L) and men (66 ng/L). AUC indicates area under the receiver operating characteristic curve.

DISCUSSION

The findings of our study add to the growing evidence supporting sex differences in the prevalence and outcomes of cardiac complications after stroke (Figure 4). First, in our cohort of prospective patients with acute ischemic stroke, the crude prevalence of acute myocardial injury was higher in women than men. Second, as previously reported, the presence of acute myocardial injury was associated with a higher risk of discharge disability and mortality.[7] However, when stratifying by sex, a statistically significant association between acute myocardial injury and outcomes was observed in women but not in men. Third, the application of sex-specific hs-cTnT cutoffs did not increase the prognostic value of acute myocardial injury for unfavorable outcomes. Finally, the optimal hs-cTnT values for the prediction of early in-hospital mortality in our cohort were higher than current cutoff values, were sex-specific, with women's hs-cTnT values being approximately half of those of men, and showed a high NPV.

Women in our cohort were older and more likely to be care dependent before hospital admission. They more frequently had known atrial fibrillation, more severe strokes, higher mortality rates, and less favorable functional outcomes at hospital discharge than men, which is consistent with previous studies (Table S6).[28–31] Looking at the overall cohort, rate of female participants was lower than male participants (46% women versus 54% men), whereas this was reversed for the prevalence of acute myocardial injury (52% women versus 48% men, using the sex-neutral hs-cTnT cutoff). Because age, stroke severity, and premorbid functional status play an important role in sex differences on stroke outcomes,[28–30] the higher crude prevalence of acute myocardial injury in women in our cohort should also be considered in the context of baseline demographic sex differences. However, when the association of acute myocardial injury and unfavorable outcomes was stratified by sex, women had statistically significantly increased odds of 7-day and in-hospital mortality and greater disability at discharge. On the other hand, we did not find a significant association between acute myocardial injury and prespecified outcomes in men. Because sex differences in the cause and extent of cardiac injury after acute ischemic stroke have already been suggested,[17,32] it is possible that women may have a more pronounced brain–heart axis dysfunction after acute brain injury, which in turn leads to worse outcomes.

Biologically, sex hormones play an important role in modulating sex differences of sympathovagal balance and, with aging and menopause, important changes in the regulation of the brain–heart axis occur.[33,34] Estrogen, in particular, is an important regulator of endothelial function and catecholamine-mediated vasoconstriction: age-related estrogen deprivation and sex differences in myocardial sensitivity to catecholamine have already been shown to increase the susceptibility of elderly women for Takotsubo syndrome.[35,36] Further, an elevated baseline cardiac sympathetic tone associated with a higher stress-induced neural activity might render elderly women more susceptible to neurocardiogenic injury (stroke–heart syndrome).[37,38] The role of hormonal factors in sex differences in acute cardiac complications after stroke needs to be further investigated.

As women with acute coronary syndrome are frequently underdiagnosed and experience higher morbidity and mortality compared with men,[14,18,30] the implementation of sex-specific hs-cTnT cutoffs for the diagnosis of myocardial infarction is currently recommended to reduce sex disparities.[2,11,22] However, although a sex-specific approach appears to be relevant for risk stratification and targeting of preventive treatments for cardiovascular disease in the general population, it does not seem to alter clinical management and prognosis of patients with suspected acute coronary syndrome.[39,40]

To assess the impact of applying sex-specific hs-cTnT cutoffs for cardiac risk stratification in the setting of acute ischemic stroke, we tested the predictive value

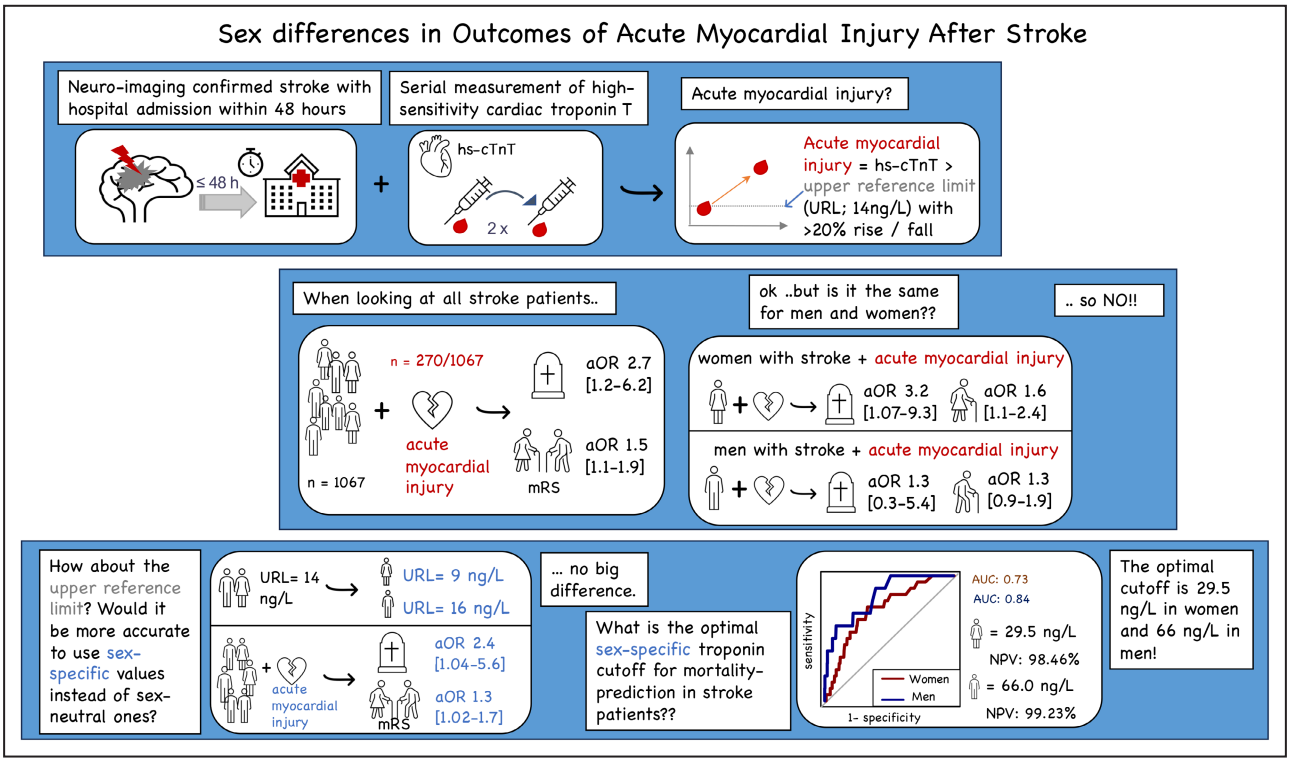

Figure 4. Summary of the main findings of the study.
aOR indicates adjusted odds ratio; hs-cTnT, high-sensitivity cardiac troponin T; NPV, negative predictive value; and URL, upper reference limit.

of sex-specific hs-cTnT cutoffs in this population. As expected, the implementation of sex-specific hs-cTnT cutoffs increased the prevalence of acute myocardial injury after stroke in women and decreased it in men.

In contrast to analyses using sex-neutral cutoffs, using sex-specific cutoffs resulted in a weaker and in part not statistically significant association between acute myocardial injury and unfavorable outcomes in women. The implementation of sex-specific cutoffs and the subsequent reclassification of women with lower hs-cTnT values as having acute myocardial injury might explain this loss of specificity. The results in men remained widely unchanged with no significant associations of acute myocardial injury and unfavorable outcomes regardless of the use of sex-neutral or sex-specific cutoffs. Our results show that the application of URL-based sex-specific cutoffs has no major prognostic benefit in the acute ischemic stroke population, but smaller effects cannot be ruled out.

Consistent with previous studies reporting that elevated hs-cTnT levels are detected in up to 30% to 60% of patients with acute ischemic stroke,[4,5] we found 58% of women and 53% of men with a first hs-cTnT value above URL (14 ng/L). The sex-specific optimal cutoffs for the prediction of 7-day in-hospital mortality in patients with ischemic stroke were double in women and almost 5 times higher in men compared with the sex-neutral standard cutoff for myocardial injury detection. This suggest that only more severe myocardial injury is associated with higher short-term mortality after acute ischemic stroke. Although sensitivity and specificity were only moderate in women, specificity was high (0.91) in men. NPVs were high for both women and men. An optimal hs-cTn threshold, double that of sex-neutral URL, was already reported for the prediction of in-hospital mortality; however, specific optimal thresholds for women and men were not obtained.[4] Our results suggest that a sex-specific approach might improve risk stratification for early mortality in patients with stroke and elevated hs-cTnT values.

The major strengths of our study are its prospective nature and the availability of serial hs-cTnT measurements. As women and patients with concomitant clinically diagnosed acute myocardial infarction are usually underrepresented in randomized clinical stroke trials,[41] the generalizability of our observational study allows us to report the real world prevalence of acute myocardial injury in acute ischemic stroke. However, our results should be interpreted in the context of several limitations. First, as this is a single-center study, the external validity of our results may be limited. Second, we cannot exclude some selection bias effects, considering that almost 12% of the admitted patients with acute ischemic stroke were excluded from the analysis due

to lack of serial hs-cTnT measurements. However, rates of missing serial hs-cTnT measurements between men and women were well balanced (12.2% versus 12.8%, respectively). Third, as we cannot identify the cause of myocardial injury in our patients from the available data, we cannot discuss the pathophysiological mechanisms of cardiac complications after stroke between sexes. Fourth, despite this being a prospective observational cohort, the reclassification with sex-specific hs-cTnT cutoffs was retrospective. Fifth, a potential lack of validity for the adjusted association between acute myocardial injury and short-term mortality cannot be excluded given the small number of patients who died within 7 days of hospitalization. In particular, our analyses could be underpowered for the association between acute myocardial injury and outcomes in men, given their small number of 7-day in-hospital mortality events (n=10 in men versus n=20 in women). A significant association in men might still be detected in a population with a larger sample size. Sixth, outcomes beyond the in-hospital phase were not available. Finally, the identified ROC-derived optimal hs-cTnT cutoffs for the prediction of early in-hospital mortality showed relative low sensitivity and specificity and were not validated in our cohort.

CONCLUSIONS

In conclusion, our observational study reveals that the crude prevalence of acute myocardial injury after stroke is higher in women than in men and that the association of acute myocardial injury with outcomes in the setting of acute ischemic stroke may be sex-specific. Women with acute poststroke myocardial injury based on hs-cTnT measurements have a higher risk of early mortality and greater disability, whereas this association was not observed in men. Finally, the implementation of current sex-specific cutoffs does not increase the prognostic value of acute myocardial injury for unfavorable outcomes in patients with stroke, as it leads to a loss of specificity in identifying women with *more severe* acute myocardial injury. Our proposed sex-dependent cutoffs for predicting short-term mortality showed a high NPV and deserve independent validation.

Our findings, therefore, add to the growing evidence supporting sex differences in cardiovascular disorders.[42] Whether a sex-specific approach might be relevant for cardiac risk stratification and targeting of invasive diagnostic tests and interventions for acute myocardial injury in patients with acute ischemic stroke requires further investigation.

ARTICLE INFORMATION

Received November 1, 2023; accepted January 11, 2024.

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Acknowledgments

Helena Stengl is a participant in the Berlin Institute of Health-Charité Junior Clinician Scientist Program, Simon Hellwig is a participant in the Clinician Scientist Program, and Jan F. Scheitz is a participant in the Berlin Institute of Health-Charité Advanced Clinician Scientist Program, funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health. Christian H. Nolte is a Clinical Fellow of the Berlin Institute of Health.

Sources of Funding

This work was supported by the CORONA foundation (Essen, Germany). Michela Rosso and Scott E. Kasner were supported by National Institutes of Health U24-NS-107224. Matthias Endres received funding from the German Research Association under Germany's Excellence Strategy – EXC-2049 – 390688087, Collaborative Research Center ReTune TRR 295-424778381, Bundesministerium für Bildung und Forschung, DZNE, DZHK, European Union, Corona Stiftung, and Fondation Leducq.

Disclosures

Heinrich J. Audebert received research grants from German Ministry of Research and Education, German Research Association, Innovations funds of the Federal Joint Committee, and speaker or consultation fees from AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, NovoNordisk, Pfizer Pharma, and Roche. ME reports grants from Bayer and fees paid to the Charité from Abbot, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Sanofi, Novartis, and Pfizer. Christian H. Nolte received research grants from German Ministry of Research and Education, German Center for Neurodegenerative Diseases, German Center for cardiovascular Research, and speaker or consultation fees from Abbott, Alexion, AstraZeneca, Bayer Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Novartis, Pfizer Pharma, Portola, and Takeda. Scott E. Kasner has received grant funding from Bayer, Bristol-Myers Squibb, Genentech, Medtronic, and Diamedica (all paid to institution); consulting fees from AstraZeneca, NovoNordisk, and Medtronic; and royalties from UpToDate. Jan F. Scheitz has received speaker fees from AstraZeneca and Bristol-Myers Squibb. All reported grants and fees are outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S6

REFERENCES

1. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S; VISTA Investigators. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke*. 2007;38:2295–2302. doi: 10.1161/STROKEAHA.106.471813
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158

4. Scheitz JF, Mochmann HC, Erdur H, Tutuncu S, Haeusler KG, Grittner U, Laufs U, Endres M, Nolte CH. Prognostic relevance of cardiac troponin T levels and their dynamic changes measured with a high-sensitivity assay in acute ischaemic stroke: analyses from the TRELAS cohort. *Int J Cardiol*. 2014;177:886–893. doi: 10.1016/j.ijcard.2014.10.036
5. Faiz KW, Thommessen B, Einvik G, Omland T, Ronning OM. Prognostic value of high-sensitivity cardiac troponin T in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2014;23:241–248. doi: 10.1016/j.jstrokecerebrovasdis.2013.01.005
6. Scheitz JF, Nolte CH, Laufs U, Endres M. Application and interpretation of high-sensitivity cardiac troponin assays in patients with acute ischemic stroke. *Stroke*. 2015;46:1132–1140. doi: 10.1161/STROKEAHA.114.007858
7. Stengl H, Ganeshan R, Hellwig S, Klammer MG, von Rennenberg R, Bohme S, Audebert HJ, Nolte CH, Endres M, Scheitz JF. Frequency, associated variables, and outcomes of acute myocardial injury according to the fourth Universal Definition of Myocardial Infarction in patients with acute ischemic stroke. *Eur Stroke J*. 2022;7:413–420. doi: 10.1177/23969873221120159
8. Sposato LA, Hilz MJ, Aspberg S, Murthy SB, Bahit MC, Hsieh CY, Sheppard MN, Scheitz JF; World Stroke Organisation Brain & Heart Task Force. Post-stroke cardiovascular complications and neurogenic cardiac injury: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76:2768–2785. doi: 10.1016/j.jacc.2020.10.009
9. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Pina IL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1545–1588. doi: 10.1161/01.str.0000442009.06663.48
10. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133:916–947. doi: 10.1161/CIR.0000000000000351
11. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144:e368–e454. doi: 10.1161/CIR.0000000000001030
12. Alabas OA, Gale CP, Hall M, Rutherford MJ, Szummer K, Lawesson SS, Alfredsson J, Lindahl B, Jernberg T. Sex differences in treatments, relative survival, and excess mortality following acute myocardial infarction: national cohort study using the SWEDEHEART registry. *J Am Heart Assoc*. 2017;6:e007123. doi: 10.1161/JAHA.117.007123
13. Brush JE Jr. Sex disparities in chest pain patients: observations and opportunities. *J Am Coll Cardiol*. 2023;81:946–948. doi: 10.1016/j.jacc.2023.01.006
14. Dawson LP, Nehme E, Nehme Z, Davis E, Bloom J, Cox S, Nelson AJ, Okyere D, Anderson D, Stephenson M, et al. Sex differences in epidemiology, care, and outcomes in patients with acute chest pain. *J Am Coll Cardiol*. 2023;81:933–945. doi: 10.1016/j.jacc.2022.12.025
15. Bruce SS, Merkler AE, Bassi M, Chen ML, Salehi Omran S, Navi BB, Kamel H. Differences in diagnostic evaluation in women and men after acute ischemic stroke. *J Am Heart Assoc*. 2020;9:e015625. doi: 10.1161/JAHA.119.015625
16. Calvet D, Touze E, Varenne O, Sablayrolles JL, Weber S, Mas JL. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. *Circulation*. 2010;121:1623–1629. doi: 10.1161/CIRCULATIONAHA.109.906958
17. Rosso M, Ramaswamy S, Kvantaliani N, Mulatu Y, Little JN, Marczak I, Brahmaroutu A, Deo R, Lewey J, Messe SR, et al. Stroke-heart syndrome: does sex matter? *J Am Heart Assoc*. 2023;12:e029799. doi: 10.1161/JAHA.123.029799
18. Vigen R, de Lemos JA. Can high-sensitivity troponins help to level the playing field in cardiovascular disease prevention between women and men? *Clin Chem*. 2021;67:1301–1303. doi: 10.1093/clinchem/hvab144
19. Omland T, de Lemos JA, Holmen OL, Dalen H, Benth JS, Nygard S, Hveem K, Rosjo H. Impact of sex on the prognostic value of high-sensitivity cardiac troponin I in the general population: the HUNT study. *Clin Chem*. 2015;61:646–656. doi: 10.1373/clinchem.2014.234369
20. Gore MO, Seliger SL, Defilippi CR, Nambi V, Christenson RH, Hashim IA, Hoogeveen RC, Ayers CR, Sun W, McGuire DK, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. *J Am Coll Cardiol*. 2014;63:1441–1448. doi: 10.1016/j.jacc.2013.12.032
21. Koerbin G, Tate J, Potter JM, Cavanaugh J, Glasgow N, Hickman PE. Characterisation of a highly sensitive troponin I assay and its application to a cardio-healthy population. *Clin Chem Lab Med*. 2012;50:871–878. doi: 10.1515/cclm-2011-0540
22. Bhatia PM, Daniels LB. Highly sensitive cardiac troponins: the evidence behind sex-specific cutoffs. *J Am Heart Assoc*. 2020;9:e015272. doi: 10.1161/JAHA.119.015272
23. Stengl H, Ganeshan R, Hellwig S, Blaszczyk E, Fiebach JB, Nolte CH, Bauer A, Schulz-Menger J, Endres M, Scheitz JF. Cardiomyocyte injury following acute ischemic stroke: protocol for a prospective observational cohort study. *JMIR Res Protoc*. 2021;10:e24186. doi: 10.2196/24186
24. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335:806–808. doi: 10.1136/bmj.39335.541782.AD
25. Mueller T, Egger M, Peer E, Jani E, Dieplinger B. Evaluation of sex-specific cut-off values of high-sensitivity cardiac troponin I and T assays in an emergency department setting–results from the Linz Troponin (LITROP) study. *Clin Chim Acta*. 2018;487:66–74. doi: 10.1016/j.cca.2018.09.026
26. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, Giannitsis E, Gustafson S, Handy B, Katus H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta*. 2011;412:748–754. doi: 10.1016/j.cca.2010.12.034
27. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3:32–35. doi: 10.1002/1097-0142(1950)3:1<32::aid-cncr2820030106>3.0.co;2-3
28. Carcel C, Wang X, Sandset EC, Delcourt C, Arima H, Lindley R, Hackett ML, Lavados P, Robinson TG, Munoz Venturelli P, et al. Sex differences in treatment and outcome after stroke: pooled analysis including 19,000 participants. *Neurology*. 2019;93:e2170–e2180. doi: 10.1212/WNL.0000000000008615
29. Di Carlo A, Lamassa M, Consoli D, Inzitari D, Gall SL, Donnan G, Dewey H, Thrift A. Sex differences in presentation, severity, and management of stroke in a population-based study. *Neurology*. 2010;75:670–671; author reply 671. doi: 10.1212/WNL.0b013e3181ec68b5
30. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7:915–926. doi: 10.1016/S1474-4422(08)70193-5
31. Reeves MJ, Fonarow GC, Zhao X, Smith EE, Schwamm LH; Get With The Guidelines-Stroke Steering Committee & Investigators. Quality of care in women with ischemic stroke in the GWTG program. *Stroke*. 2009;40:1127–1133. doi: 10.1161/STROKEAHA.108.543157
32. Sposato LA, Lam M, Allen B, Shariff SZ, Saposnik G; PARADISE Study Group. First-ever ischemic stroke and incident major adverse cardiovascular events in 93 627 older women and men. *Stroke*. 2020;51:387–394. doi: 10.1161/STROKEAHA.119.028066
33. Rossi A, Mikail N, Bengs S, Haider A, Treyer V, Buechel RR, Wegener S, Rauen K, Tawakol A, Bairey Merz CN, et al. Heart-brain interactions in cardiac and brain diseases: why sex matters. *Eur Heart J*. 2022;43:3971–3980. doi: 10.1093/eurheartj/ehac061
34. Dart AM, Du XJ, Kingwell BA. Gender, sex hormones and autonomic nervous control of the cardiovascular system. *Cardiovasc Res*. 2002;53:678–687. doi: 10.1016/s0008-6363(01)00508-9
35. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo syndrome. *Circulation*. 2017;135:2426–2441. doi: 10.1161/CIRCULATIONAHA.116.027121
36. Sader MA, Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. *Cardiovasc Res*. 2002;53:597–604. doi: 10.1016/s0008-6363(01)00473-4
37. Scheitz JF, Sposato LA, Schulz-Menger J, Nolte CH, Backs J, Endres M. Stroke-heart syndrome: recent advances and challenges. *J Am Heart Assoc*. 2022;11:e026528. doi: 10.1161/JAHA.122.026528
38. Haider A, Bengs S, Diggelmann F, Epprecht G, Etter D, Beeler AL, Wijnen WJ, Treyer V, Portmann A, Warnock GI, et al. Age- and sex-dependent changes of resting amygdalar activity in individuals free of clinical cardiovascular disease. *J Nucl Cardiol*. 2021;28:427–432. doi: 10.1007/s12350-020-02504-7
39. Lee KK, Ferry AV, Anand A, Strachan FE, Chapman AR, Kimenai DM, Meex SJR, Berry C, Findlay I, Reid A, et al. Sex-specific thresholds

of high-sensitivity troponin in patients with suspected acute coronary syndrome. *J Am Coll Cardiol*. 2019;74:2032–2043. doi: 10.1016/j.jacc.2019.07.082

40. de Bakker M, Anand A, Shipley M, Fujisawa T, Shah ASV, Kardys I, Boersma E, Brunner EJ, Mills NL, Kimenai DM. Sex differences in cardiac troponin trajectories over the life course. *Circulation*. 2023;147:1798–1808. doi: 10.1161/CIRCULATIONAHA.123.064386
41. Tsivgoulis G, Katsanos AH, Caso V. Under-representation of women in stroke randomized controlled trials: inadvertent selection bias leading to suboptimal conclusions. *Ther Adv Neurol Disord*. 2017;10:241–244. doi: 10.1177/1756285617699588
42. Carcel C, Woodward M, Wang X, Bushnell C, Sandset EC. Sex matters in stroke: a review of recent evidence on the differences between women and men. *Front Neuroendocrinol*. 2020;59:100870. doi: 10.1016/j.yfrne.2020.100870