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Cardiac troponin is associated with cardiac outcomes in men and women with atrial fibrillation, insights from the ARISTOTLE trial

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Abstract. Røsjø H, Hijazi Z, Omland T, Westerbergh J, Lyngbakken MN, Alexander JH, Gersh BJ, Granger CB, Hylek EM, Lopes RD, Siegbahn A, Wallentin L (Uppsala University, Uppsala, Sweden; Akershus University Hospital, Lørenskog; University of Oslo, Oslo, Norway; Uppsala University, Uppsala, Sweden; Akershus University Hospital, Lørenskog, Norway; Duke Clinical Research Institute, Duke Health, Durham, NC; Mayo Clinic College of Medicine, Rochester, MN; Boston University Medical Center, Boston, MA, USA; Uppsala University, Uppsala, Sweden). Cardiac troponin is associated with cardiac outcomes in men and women with atrial fibrillation, insights from the ARISTOTLE trial. *J Intern Med* 2020; **288**: 248–259.

Background. Cardiac troponin T (cTnT) and I (cTnI) concentrations provide strong prognostic information in anticoagulated patients with atrial fibrillation (AF). Whether the associations between cardiac troponin concentrations and mortality and morbidity differ by sex is not known.

Objectives. To assess whether men and women have different concentrations and prognostic value of cTnT and cTnI measurements in anticoagulated patients with AF.

Methods. cTnT and cTnI concentrations were measured with high-sensitivity (hs) assays in EDTA plasma samples obtained from the multicentre ARISTOTLE trial, which randomized patients with AF and at least one risk factor for stroke or systemic embolic event to warfarin or apixaban. Patients were stratified according to sex and the associations between hs-troponin concentrations, and all-cause death, cardiac death, myocardial infarction, stroke or systemic embolic event and major bleeding were assessed in multivariable regression models.

Results. We found higher cardiac troponin concentrations in men (n = 9649) compared to women (n = 5331), both for hs-cTnT (median 11.8 [Q1-3 8.1–18.0] vs. 9.6 [6.7–14.3] ng L^{-1}, $P < 0.001$) and hs-cTnI (5.8 [3.4–10.8] vs. 4.9 [3.1–8.8] ng L^{-1}, $P < 0.001$). Adjusting for baseline demographics, comorbidities and medications, men still had significantly higher hs-troponin concentrations than women. C-reactive protein and N-terminal pro-B-type natriuretic peptide concentrations were higher in female patients. Both hs-cTnT and hs-cTnI concentrations were associated with all clinical outcomes similarly in men and women (p-value for interaction >0.05 for all end-points).

Conclusion. Men have higher hs-troponin concentrations than women in AF. Regardless of sex, hs-troponin concentrations remain similarly associated with adverse clinical outcomes in anticoagulated patients with AF.

Keywords: atrial fibrillation, biomarker, troponin, gender, prognostication.

Clinical Trial Registration: URL: http://clinicaltrials.gov. Unique identifier: NCT00412984

Introduction

The prevalence of atrial fibrillation (AF) is increasing, and AF constitutes a major risk factor for mortality and cardiovascular morbidity [1]. Recent data have demonstrated that the established biomarkers cardiac troponin I and T provide important prognostic information in anticoagulated patients with AF, including for all-cause mortality, cardiac death, incident myocardial infarction, stroke or systemic embolism and major bleeding [2-4]. However, given the reportedly higher mortality risk for women over men with AF [1], there is a need to specifically examine sex-related differences for cardiac troponin measurements in anticoagulated patients with AF.

Cardiac troponin I and T are proteins that are part of the contractile apparatus in cardiac myocytes. Dynamic release of cardiac troponin molecules from the myocardium to the circulation in patients with symptoms or objective signs of myocardial ischaemia is considered diagnostic for acute myocardial infarction [5]. Men have higher cardiac troponin concentrations on average than women during myocardial infarction, but no relevant sex-related differences have been reported for the prognostic value of cardiac troponin elevations in acute coronary syndromes [6]. In contrast, recent data from general populations have suggested that cardiac troponin I measurements may have a stronger relationship to outcomes in women than in men [7,8]. Although increasing cardiac troponin I concentrations were associated with all-cause mortality, heart failure and incident myocardial infarction in the total cohort, we found stronger associations between cardiac troponin I concentrations and clinical outcomes amongst women (n = 5281) than men (n = 4431) in a large Norwegian community-based cohort [7,8]. Similar results have also been found in another community-acquired cohort with stronger associations between both cardiac troponin T and I concentrations and all-cause mortality for women over men [9]. Still, it is possible that characteristics of the cohort may impact such sex-dependent differences as no differences in the prognostic value of cardiac troponin I for men and women were found in elderly subjects from Sweden [10]. Whilst cardiac troponin I and T concentrations are known to provide strong prognostic information in anticoagulated patients with AF [2-4], no information is available whether the prognostic value of troponin measurements in AF differs according to sex. Accordingly, the aim of this study was to assess whether cardiac troponin elevations hold the same prognostic value in men and women amongst anticoagulated patients with AF.

Materials and methods

Study cohort

This study population consisted of participants from the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) trial [11,12]. In short, ARISTOTLE was a double-blind, randomized controlled clinical trial that enrolled 18,201 patients with AF and at least one risk factor for stroke or systemic embolic event, namely history of heart failure, hypertension, diabetes mellitus, stroke or age $\geq$ 75 years. All patients were randomized to warfarin and apixaban in a 1:1 fashion, and the primary end-point was stroke or systemic embolism. Patients with prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting or peripheral arterial disease were classified as having vascular disease. Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. Heart failure was defined as symptomatic congestive heart failure within 3 months or LVEF $\leq$ 40% by echocardiography, radionuclide study or contrast angiography. The results of the ARISTOTLE study have been published previously and demonstrated superiority of apixaban over warfarin for the primary end-point of stroke or systemic embolism and the secondary end-points of all-cause mortality and major bleeding [12].

The biomarker substudy of ARISTOTLE included 14 980 participants, who had a median follow-up time of 1.9 years. The main study and the biomarker substudies have all been approved by the appropriate ethics committees, and all patients signed written informed consent before study commencement.

End-points of the study

The end-points of this analysis were all-cause mortality, cardiac death, myocardial infarction (MI), stroke or systemic embolic event (SEE) and major bleeding. All end-points were adjudicated by a clinical end-point committee as previously reported [12].

Biospecimen collection and biochemical analysis

Venous blood samples were drawn at randomization and prior to drug administration. Blood samples were centrifuged, plasma-separated and frozen in aliquots at the different clinical trial sites. The aliquots were transferred frozen to the Uppsala Clinical Research Center (UCR) Laboratory, Uppsala University Hospital, Uppsala, Sweden, and thereafter stored at −70°C until biochemical analyses. We measured in EDTA plasma cardiac troponin T by the Elecsys TNT hs STAT assay (hs-cTnT; Roche Diagnostics, Penzberg, Germany) and cardiac troponin I by the ARCHITECT *STAT* High Sensitivity Troponin assay (hs-cTnI; Abbott Diagnostics, Abbott Park, IL) as previously reported [2-4]. The limit of blank for the hs-cTnT assay was reported by the manufacturer as 3 ng L^{-1}, and the coefficient of variation is below 10% at the reported 99 percentile of a healthy population (14 ng L^{-1}). Sex-specific cut-offs for hs-cTnT have been reported as 16 and 9 ng L^{-1} for men and women, respectively [13]. For the hs-cTnI assay, the limit of blank in the Uppsala Laboratory was 1.3 ng L^{-1}, the lowest concentration measurable with a coefficient of variation < 10% was 3.3 ng L^{-1}, and we used the reported 23 ng L^{-1} as the 99 percentile upper reference limit for healthy subjects [14]. We also employed sex-specific cut-offs for hs-cTnI previously reported as 36 ng L^{-1} for men and 15 ng L^{-1} for women [14]. We measured C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), growth differentiation factor-15 (GDF-15) and apolipoprotein A1 (ApoA1) as previously reported [15-18]. Estimated creatinine clearance was calculated by the Cockcroft–Gault formula [19].

Statistical analysis

Descriptive data for men and women separately are presented as median (interquartile range [IQR]) or count (percentage) and compared by Wilcoxon test and Pearson's chi-squared test, respectively. Correlation was assessed by the Spearman rank method. We performed multivariable linear regression models with hs-cTnI and hs-cTnT concentrations as the dependent variables in men and women separately to identify variables associated with increments in troponin concentration. These variables were included in the analysis: age (per 10-year increase), BMI, baseline systolic blood pressure (per 10 mmHg increase), diabetes mellitus, hypertension, calculated creatinine clearance (per 100% increase), former or current smoking, permanent vs. persistent AF, history of stroke/SEE, history of vascular disease and history of heart failure. We also included use of aspirin, warfarin, statin and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker prior to study entry in the analysis. We used an interaction test to explore whether geometric means differed between men and women for the individual variables of the multivariable linear regression models. We also performed multivariable linear regression analyses with hs-cTnI and hs-cTnT as the dependent variables and adjusting for baseline demographics and clinical history to determine whether sex was independently associated with hs-troponin concentrations at study commencement.

Associations between hs-cTnI and hs-cTnT concentrations and clinical outcomes were assessed by multivariable Cox proportional hazard regression models in men and women separately. hs-cTnI and hs-cTnT concentrations were log-transformed in the models and included as restricted cubic spline with 3 knots placed at the 10th, 50th and 90th sample percentiles. Hazard ratios (HRs) were calculated per interquartile range [18]. An interaction was applied to test whether sex influenced the associations between troponin levels and outcomes. The Cox model #1 was adjusted only for study treatment (apixaban or warfarin); model #2 adjusted for age and study treatment; model #3 adjusted for age, ApoA1, systolic blood pressure, hypertension, smoking status, diabetes mellitus and study treatment; model #4 adjusted for the variables of model #3 plus creatinine clearance, prior myocardial infarction and CRP; and model #5 adjusted for model #4 plus NT-proBNP and GDF-15. For the end-point major bleeding, we also adjusted for haemoglobin and prior bleeding in models #4 and #5. CRP, NT-proBNP and GDF-15 were log-transformed in the model and included as restricted cubic spline with 4 knots placed at the 5th, 35th, 65th and 95th sample percentiles. We calculated HRs for hs-cTnT and hs-cTnI in the total study population with sex included as a covariate in models #2-5. We also performed analysis with participants dichotomized according to the 99 percentile and with sex-specific cut-offs. *P*-values < 0.05 were considered significant for all analyses, and there were no adjustments for multiple testing. Statistical analysis was performed by using R version 3.5 [20].

Table 1. *Baseline characteristics according to sex*

	n	Female *N* = 5331	Male *N* = 9649	*P*-value
Demography				
Age	14 980	72.0 (65.0–77.0)	69.0 (61.0–75.0)	<0.001[a]
Smoking status				
Never smoked	14 966	4134 (77.6%)	3745 (38.9%)	<0.001[b]
Former smoker		984 (18.5%)	4884 (50.7%)	
Current smoker		211 (4.0%)	1008 (10.5%)	
Medical history and clinical markers				
Body mass index	14 909	28.7 (24.8–33.6)	28.4 (25.5–32.1)	0.11[a]
Systolic blood pressure	14 947	130.0 (120.0–141.0)	130.0 (120.0–140.0)	<0.001[a]
Permanent atrial fibrillation	14 977	4366 (81.9%)	8345 (86.5%)	<0.001[b]
Creatinine clearance	14 928	65.4 (50.0–85.3)	78.6 (61.3–100.8)	<0.001[a]
Diabetes	14 980	1311 (24.6%)	2386 (24.7%)	0.85[b]
Prior Stroke/TIA/systemic embolic event	14 980	1090 (20.4%)	1812 (18.8%)	0.013[b]
Heart failure	14 980	1711 (32.1%)	2940 (30.5%)	0.039[b]
Prior myocardial infarction	14 979	448 (8.4%)	1478 (15.3%)	<0.001[b]
Hypertension	14 980	4803 (90.1%)	8311 (86.1%)	<0.001[b]
Medicine				
Aspirin at randomization	14 980	1562 (29.3%)	3076 (31.9%)	0.001[b]
Statin within 30 days	14 980	2113 (39.6%)	4387 (45.5%)	<0.001[b]
Warfarin within 7 days	14 951	2633 (49.5%)	5404 (56.1%)	<0.001[b]
ACE inhibitor or ARB	14 980	3737 (70.1%)	6865 (71.1%)	0.18[b]
Biomarkers				
Apolipoprotein A1 (g L^{-1})	14 884	1.2 (1.0–1.4)	1.1 (0.9–1.2)	<0.001[a]
C-reactive protein (mg L^{-1})	14 884	2.5 (1.2–5.4)	2.0 (1.0–4.4)	<0.001[a]
Growth differentiation factor-15 (ng L^{-1})	14 798	1366.0 (985.2–2004.8)	1393.0 (972.0–2072.0)	0.40[a]
NT-proBNP (ng L^{-1})	14 892	784.5 (403.0–1365.0)	672.0 (349.0–1188.8)	<0.001[a]
Troponin T (ng L^{-1})	14 897	9.6 (6.7–14.3)	11.8 (8.1–18.0)	<0.001[a]
Troponin I (ng L^{-1})	14 821	4.9 (3.1–8.8)	5.8 (3.4–10.8)	<0.001[a]

Values presented as median (Q1–Q3) or count (percentage). Percentages computed by group. Tests used:
[a]Wilcoxon test;
[b]Pearson's chi-squared test.

Results

Clinical characteristics for men and women

During median 1.9 years of follow-up, all-cause mortality was 333 (6.2%) amongst women and 742 (7.7%) amongst men ($P = 0.001$ for sex difference) with 155 (2.9%) deaths classified as cardiovascular amongst women and 392 (4.1%) cardiovascular deaths amongst men ($P < 0.001$). Moreover, 46 (0.9%) women experienced a myocardial infarction during follow-up compared to 104 (1.1%) cases for men ($P = 0.21$), 156 (2.9%) women and 241 (2.5%) men were diagnosed with incident stroke/SEE ($P = 0.12$), and the total number of major bleeding events during the study period was 230 (4.3%) for women and 444 (4.6%) for men ($P = 0.41$).

Women were older than the men, and the prevalence of hypertension, stroke/SEE and heart failure was higher amongst women (Table 1). Women had a lower creatinine clearance than men but both were in the normal range. Fewer women were taking aspirin and warfarin prior to the start of the study. In contrast, more male participants had

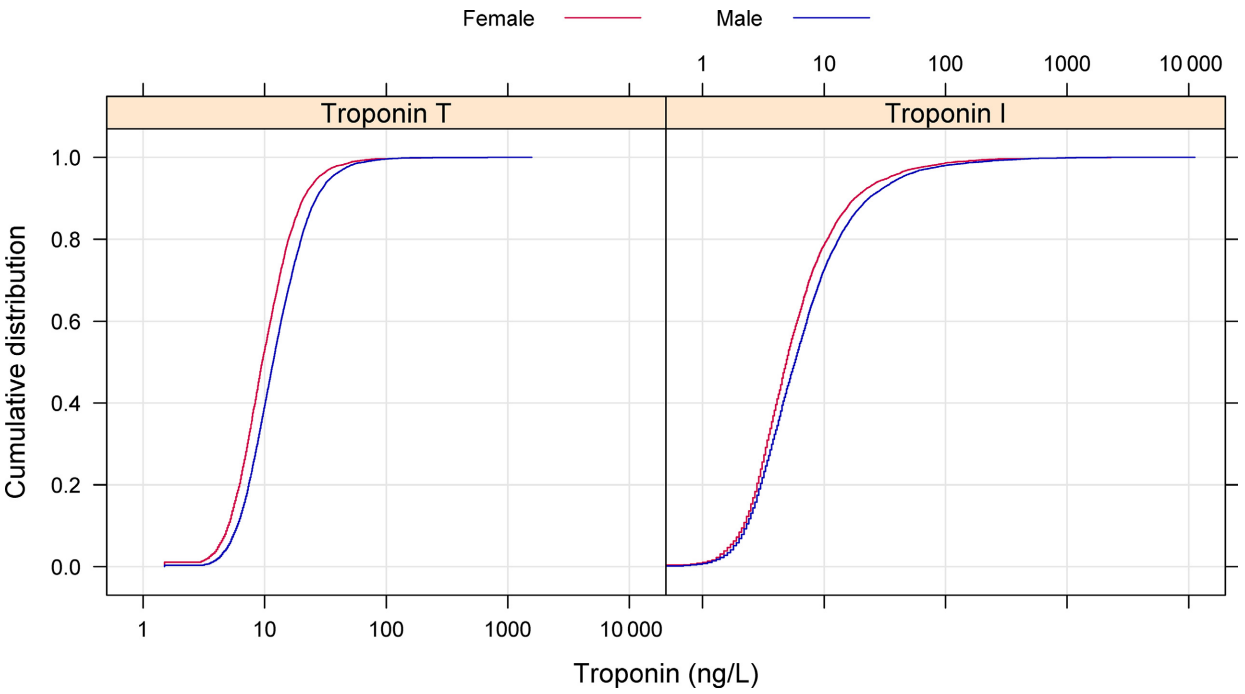

Fig. 1 *Cumulative distribution of hs-cTnT (left) and hs-cTnI concentrations (right) with patients stratified according to sex*

experienced a previous myocardial infarction and the prevalence of permanent AF and current or past smoking was higher amongst men.

Cardiac troponin I and T concentrations for men and women

We found higher cardiac troponin concentrations in men (n = 9649) compared to women (n = 5331): median 11.8 (Q1-3 8.1–18.0) vs. 9.6 (6.7–14.3) ng L^{-1}) for hs-cTnT and median 5.8 (3.4–10.8) vs. 4.9 (3.1–8.8) ng L^{-1} for hs-cTnI (both P-values < 0.001; Fig. 1). hs-cTnT and hs-cTnI concentrations correlated amongst men (ρ = 0.70, P < 0.001) and women (ρ = 0.69, P < 0.001). In contrast to the results for hs-troponin, concentrations for CRP, NT-proBNP and ApoA1 were higher in women compared to men (Table 1).

Several clinical variables on univariate analysis were associated with higher hs-cTnT and hs-cTnI concentrations in men and women (Table 2). High BMI, history of heart failure and established vascular disease were associated with elevated hs-troponin concentrations in both men and women, but for these variables we identified stronger effects on hs-troponin concentrations in male patients (Table 2). We also found a significant interaction between sex, calculated creatinine clearance, and hs-cTnI with higher increments in hs-cTnI concentrations for men compared to women with impaired renal function. Adjusting for baseline demographics, comorbidities and medication, female sex was still associated with lower hs-cTnI and hs-cTnT concentrations (Table 3). In total, 34% of the participants had hs-cTnT concentration above the established 99 percentile of a healthy population and 9% had hs-cTnI concentrations above the 99 percentile. Employing sex-specific cut-offs, 54% of women and 31% of men had elevated hs-TnT concentrations and 13% of women and 6% of men had elevated hs-cTnI concentrations.

hs-cTnI and hs-cTnT concentrations and clinical outcomes in men and women

hs-cTnT and hs-cTnI concentrations at baseline were associated with all clinical outcomes, including models that adjusted for study treatment, clinical risk factors and cardiac biomarkers (Table 4). No significant interactions were found between sex and hs-troponin concentrations for any clinical outcomes, although we observed a trend for stronger associations between hs-troponin concentrations and incident MI in women.

Table 2. *Variables associated with concentrations of cardiac troponin T and cardiac troponin I in AF with participants stratified according to sex and with* P*-values calculated for interaction with sex*

	Female	Male	
	Ratio geometric mean	Ratio geometric mean	*P*-value
	Cardiac troponin T		
Age, per 10 year increase	1.127 (1.103–1.150)	1.122 (1.105–1.139)	0.746
BMI, per one unit increase	1.018 (1.015–1.021)	1.028 (1.025–1.031)	<0.001
Baseline systolic BP, per 10 mmHg increase	1.013 (1.004–1.022)	1.006 (0.999–1.013)	0.219
Creatinine clearance, per 100% increase	0.647 (0.621–0.673)	0.645 (0.625–0.665)	0.902
Former smoker vs never smoker	1.017 (0.979–1.056)	1.003 (0.980–1.026)	0.531
Current smoker vs never smoker	1.092 (1.014–1.176)	1.057 (1.018–1.097)	0.441
Atrial fibrillation, permanent vs persistent	1.148 (1.106–1.192)	1.100 (1.066–1.135)	0.083
Diabetes	1.167 (1.128–1.208)	1.185 (1.156–1.216)	0.479
Prior Stroke/TIA/Systemic Embolism	1.036 (0.999–1.073)	1.055 (1.026–1.084)	0.429
Prior MI/PAD/PCI/CABG	1.104 (1.061–1.149)	1.159 (1.129–1.189)	0.047
Heart failure	1.123 (1.088–1.159)	1.239 (1.209–1.269)	<0.001
Medically treated hypertension	0.949 (0.901–1.000)	0.978 (0.946–1.011)	0.343
Aspirin at randomization	1.030 (0.996–1.065)	0.998 (0.974–1.022)	0.130
Statin within 30 days of screening	0.977 (0.947–1.007)	0.957 (0.934–0.980)	0.303
On warfarin treatment at randomization	0.982 (0.952–1.013)	0.972 (0.950–0.995)	0.612
ACE inhibitor or ARB	1.048 (1.013–1.083)	1.086 (1.060–1.114)	0.089
	Cardiac troponin I		
Age, per 10 year increase	1.043 (1.006–1.082)	1.015 (0.989–1.042)	0.227
BMI, per one unit increase	1.006 (1.001–1.011)	1.022 (1.018–1.027)	<0.001
Baseline systolic BP, per 10 mmHg increase	1.046 (1.031–1.062)	1.043 (1.031–1.056)	0.742
Creatinine clearance, per 100% increase	0.665 (0.620–0.713)	0.602 (0.569–0.636)	0.027
Former smoker vs never smoker	0.968 (0.906–1.034)	1.002 (0.962–1.043)	0.386
Current smoker vs never smoker	1.101 (0.967–1.254)	1.095 (1.025–1.169)	0.938
Atrial fibrillation, permanent vs persistent	1.264 (1.184–1.350)	1.188 (1.124–1.254)	0.150
Diabetes	1.140 (1.074–1.210)	1.105 (1.057–1.156)	0.419
Prior Stroke/TIA/Systemic Embolism	1.075 (1.010–1.144)	1.118 (1.065–1.173)	0.327
Prior MI/PAD/PCI/CABG	1.237 (1.155–1.326)	1.353 (1.294–1.415)	0.034
Heart failure within 3 months	1.262 (1.194–1.333)	1.502 (1.439–1.566)	<0.001
Medically treated hypertension	0.949 (0.867–1.038)	0.966 (0.912–1.024)	0.744
Aspirin at randomization	1.035 (0.977–1.097)	0.989 (0.948–1.031)	0.211
Statin within 30 days of screening	0.863 (0.818–0.911)	0.838 (0.804–0.873)	0.400
On warfarin treatment at randomization	0.940 (0.890–0.992)	0.947 (0.909–0.985)	0.838
ACE inhibitor or ARB	1.129 (1.064–1.197)	1.176 (1.126–1.229)	0.267

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Also, there was no statistically significant association between sex and any outcome. That is, when adjusting for differences in risk profile, hs-troponin concentrations provided similar risk assessment in men and women. Dichotomizing patients according to sex-specific cut-offs, we did not find interactions between sex and the clinical outcomes for hs-cTnI measurements (Table S1). In contrast, although

Table 3. *Impact of sex on baseline variables on concentrations of cardiac troponin after adjustment for other variables*

	Effect	SE	*t* value	*P*-value
	Cardiac troponin T			
Female sex	0.34	0.01	32.89	<0.001
	Cardiac troponin I			
Female sex	0.27	0.02	15.02	<0.001

Multivariable linear regression analyses in the total population (n = 14 980) with $_{log}$hs-cTnT and $_{log}$hs-cTnI as dependent variables, with baseline demographics, clinical history and medication included as covariates.

hs-cTnT concentrations above the established cut-offs for both men and women were associated with incident myocardial infarction, women with elevated hs-cTnT concentrations had higher hazard ratio compared to men with elevated hs-cTnT concentrations (Table S1).

Discussion

The main finding from this study was that hs-cTnT and hs-cTnI concentrations provided strong prognostic information regarding all-cause mortality, cardiovascular mortality, incident myocardial infarction, stroke/SEE and major bleeding in anticoagulated patients with AF, irrespective of sex. We also demonstrate that hs-troponin concentrations are higher in men than women with AF, despite hypertension, history of stroke, heart failure and renal impairment being more prevalent amongst the female participants in the ARISTOTLE biomarker substudy.

Cardiac troponin I and T, as measured with hs-assays, have been found to provide strong prognostic information concerning a number of different clinical outcomes in anticoagulated patients with AF [2-4]. Cardiac troponin measurements also add prognostic information to other strong prognostic biomarkers, including NT-proBNP [2-4]. This is analogous to results also from other cohorts, including patients with subclinical and established heart failure [21] and stable cardiovascular disease [22,23]. Of particular interest for anticoagulated patients with AF, hs-troponin measurements provide strong prognostic information for other end-points than stroke/SEE. We now add to previous information by demonstrating that hs-cTnI and hs-cTnT were associated with all of these outcomes in anticoagulated patients with AF, regardless of sex. This is important information as adequate therapy with anticoagulation can mitigate the risk for incident stroke/SEE, but has less impact on all-cause mortality in AF [1]. Accordingly, high hs-troponin concentrations in anticoagulated patients with AF, in both men and women, signal a need to target additional pathophysiologic processes than only the risk for thromboembolism. This information may enable future strategies that could reduce total mortality and morbidity in anticoagulated patients with AF.

To use hs-cTnI and hs-cTnT measurements to guide therapy in anticoagulated patients with AF, there is a need for a more detailed understanding of the pathophysiology reflected by hs-troponin concentrations in AF patients. Unfortunately, this information is currently not established. Extrapolating from community-based studies and studies of patients with established cardiovascular disease, hs-troponin concentrations seem closely associated with indices of structural heart disease and especially LV mass [24-26]. A more recent study in patients with aortic stenosis validated this model and found a close correlation between hs-cTnI concentration and LV fibrosis, as measured by T1-weighted cardiac magnetic resonance imaging [27]. Hence, hs-troponin concentrations in stable patients should be considered a surrogate marker for structural heart disease, which could explain the strong prognostic information from hs-troponin across different cohorts [21]. As a large proportion of elderly patients with AF are known to suffer from subclinical and clinical heart failure [1], the model of hs-troponin concentrations as a surrogate marker for structural heart disease should be valid also in patients with AF. It is also likely that hs-troponin concentrations will reflect severity of coronary artery disease in selected patients [28,29]. Pertinent to this point; studies in patients with established coronary artery and subjects recruited from the general population have previously found hs-troponin concentrations to be associated with incident myocardial infarction [23,30]. We validate these findings in men and women with AF that use anticoagulation, and we especially find women with hs-cTnT concentrations above the sex-specific cut-off at high risk of experiencing myocardial infarction during follow-up. Hence, anticoagulated AF patients with high hs-troponin concentrations should be evaluated for interventions that target structural heart disease and coronary artery disease to reduce morbidity and mortality.

Table 4. *Associations between troponin concentrations and clinical outcomes with patients stratified according to sex*

Outcome	n[a]	Events[a]	Hazard ratio (95% CI) Model 1[b]	Model 2[b]	Model 3[b]	Model 4[b]	Model 5[b]	P-value[c] for interaction
			Cardiac troponin T					
All-cause death								
Both	14 980	1075	2.74 (2.40–3.12)	2.49 (2.17–2.85)	2.47 (2.15–2.83)	2.19 (1.90–2.51)	1.71 (1.47–1.98)	0.141
Female	5331	333	2.46 (2.10–2.87)	2.26 (1.92–2.65)	2.26 (1.92–2.66)	2.04 (1.73–2.41)	1.60 (1.35–1.90)	
Male	9649	742	2.98 (2.57–3.47)	2.70 (2.31–3.15)	2.66 (2.27–3.11)	2.32 (1.98–2.72)	1.81 (1.53–2.14)	
Cardiac death								
Both	14 980	547	3.29 (2.68–4.03)	3.22 (2.60–3.98)	3.25 (2.63–4.03)	2.88 (2.32–3.58)	2.33 (1.84–2.94)	0.484
Female	5331	155	3.02 (2.37–3.84)	3.00 (2.34–3.83)	3.06 (2.39–3.92)	2.77 (2.15–3.56)	2.22 (1.71–2.90)	
Male	9649	392	3.42 (2.72–4.28)	3.39 (2.68–4.28)	3.41 (2.69–4.31)	2.97 (2.34–3.78)	2.41 (1.87–3.12)	
Myocardial infarction								
Both	14 980	150	3.38 (2.27–5.02)	3.12 (2.07–4.71)	3.00 (1.99–4.54)	2.63 (1.74–4.00)	2.59 (1.66–4.03)	0.090
Female	5331	46	4.03 (2.50–6.52)	3.75 (2.30–6.11)	3.64 (2.23–5.94)	3.28 (2.00–5.36)	3.19 (1.91–5.31)	
Male	9649	104	3.04 (2.00–4.62)	2.78 (1.80–4.29)	2.65 (1.72–4.10)	2.27 (1.46–3.53)	2.23 (1.40–3.57)	
Stroke/SEE								
Both	14 980	397	1.63 (1.38–1.92)	1.60 (1.34–1.91)	1.65 (1.38–1.97)	1.60 (1.33–1.92)	1.34 (1.10–1.63)	0.448
Female	5331	156	1.52 (1.22–1.90)	1.46 (1.17–1.84)	1.52 (1.21–1.92)	1.48 (1.17–1.88)	1.26 (0.99–1.61)	
Male	9649	241	1.82 (1.47–2.25)	1.73 (1.39–2.16)	1.77 (1.41–2.21)	1.71 (1.36–2.15)	1.41 (1.11–1.79)	
Major bleeding								
Both	14 949	705	2.07 (1.79–2.38)	1.76 (1.51–2.04)	1.75 (1.50–2.03)	1.65 (1.41–1.93)	1.44 (1.22–1.69)	0.890
Female	5322	230	2.01 (1.66–2.43)	1.72 (1.42–2.09)	1.72 (1.42–2.09)	1.63 (1.34–1.99)	1.45 (1.18–1.78)	
Male	9627	444	2.16 (1.82–2.56)	1.79 (1.50–2.13)	1.76 (1.48–2.11)	1.66 (1.38–1.99)	1.43 (1.18–1.73)	
			Cardiac troponin I					
All-cause death								
Both	14 980	1075	3.13 (2.70–3.62)	2.81 (2.43–3.26)	2.74 (2.37–3.18)	2.45 (2.11–2.84)	2.00 (1.72–2.32)	0.146
Female	5331	333	2.81 (2.38–3.32)	2.54 (2.15–3.01)	2.49 (2.11–2.95)	2.28 (1.93–2.70)	1.88 (1.59–2.23)	
Male	9649	742	3.31 (2.83–3.87)	3.00 (2.56–3.52)	2.91 (2.49–3.41)	2.57 (2.19–3.02)	2.09 (1.77–2.46)	
Cardiac death								
Both	14 980	547	4.29 (3.38–5.43)	4.01 (3.15–5.09)	3.94 (3.10–5.00)	3.48 (2.74–4.43)	2.84 (2.22–3.63)	0.561
Female	5331	155	4.23 (3.25–5.51)	4.01 (3.07–5.23)	3.96 (3.04–5.16)	3.58 (2.74–4.67)	2.93 (2.24–3.85)	
Male	9649	392	4.21 (3.30–5.39)	4.01 (3.13–5.13)	3.93 (3.07–5.03)	3.43 (2.67–4.40)	2.78 (2.15–3.59)	
Myocardial infarction								

Table 4 (*Continued*)

Outcome	n[a]	Events[a]	Hazard ratio (95% CI) Model 1[b]	Model 2[b]	Model 3[b]	Model 4[b]	Model 5[b]	P-value[c] for interaction
Both	14 980	150	3.29 (2.21–4.88)	2.97 (1.99–4.43)	2.88 (1.93–4.29)	2.47 (1.65–3.69)	2.36 (1.56–3.56)	0.088
Female	5331	46	3.94 (2.44–6.34)	3.58 (2.21–5.79)	3.48 (2.15–5.63)	3.08 (1.90–4.98)	2.92 (1.79–4.77)	
Male	9649	104	2.98 (1.99–4.48)	2.73 (1.81–4.12)	2.64 (1.75–3.98)	2.22 (1.46–3.36)	2.11 (1.37–3.23)	
Stroke/SEE								
Both	14 980	397	1.69 (1.42–2.02)	1.63 (1.36–1.95)	1.58 (1.32–1.89)	1.52 (1.27–1.83)	1.33 (1.10–1.60)	0.679
Female	5331	156	1.74 (1.40–2.16)	1.65 (1.33–2.05)	1.60 (1.29–2.00)	1.55 (1.24–1.94)	1.36 (1.09–1.71)	
Male	9649	241	1.69 (1.39–2.06)	1.61 (1.31–1.97)	1.56 (1.28–1.91)	1.50 (1.22–1.85)	1.30 (1.06–1.61)	
Major bleeding								
Both	14 949	705	1.58 (1.39–1.81)	1.38 (1.21–1.58)	1.36 (1.19–1.56)	1.30 (1.13–1.49)	1.17 (1.02–1.34)	0.504
Female	5322	230	1.62 (1.36–1.94)	1.41 (1.17–1.69)	1.39 (1.16–1.67)	1.34 (1.12–1.61)	1.22 (1.01–1.46)	
Male	9627	444	1.56 (1.35–1.81)	1.36 (1.17–1.58)	1.35 (1.16–1.57)	1.27 (1.09–1.48)	1.14 (0.97–1.33)	

Hazard ratios for troponin are between the first and third quartile based on all troponin values regardless of sex. SEE, systemic embolic event.
[a]Based on the total number of individuals in the biomarker cohort (n = 14 980). Number of individuals and events can differ between models since some variables contain missing values.
[b]Model 1, adjusted for treatment arm. Model 2, adjusted for treatment arm, sex (analysis over both sexes only) and age. Model 3, model adjusted for treatment arm, sex (analysis over both sexes only), age, ApoA1, systolic blood pressure, hypertension, smoking status and diabetes. Model 4, adjusted for treatment arm, sex (analysis over both sexes only), age, ApoA1, systolic blood pressure, hypertension, smoking status, diabetes, creatinine clearance, prior myocardial infarction and CRP (for outcome major bleed also prior bleeding and Hb included). Model 5, adjusted for treatment arm, sex (analysis over both sexes only), age, ApoA1, systolic blood pressure, hypertension, smoking status, diabetes, creatinine clearance, prior myocardial infarction, CRP, NT-proBNP and GDF-15 (for outcome major bleeding also prior bleeding and Hb included).
[c]P-value for the interaction between sex and troponin for model 5.

Our new data demonstrating lower hs-cTnI and hs-cTnT concentrations in women than men amongst anticoagulated patients with AF should be interpreted in the context of hs-troponin as markers of structural heart disease and coronary artery disease. It is well known that women have lower cardiac mass compared to men from puberty [31], and therefore, lower LV mass in women could account for the differences in hs-troponin concentrations between men and women in our study. Supporting this model, lower hs-troponin concentrations have consistently been reported for women compared to men in studies from the general population [7-10,13,14]. We now provide new information by demonstrating that hs-troponin concentrations are lower in women over men, also in situations where women have higher prevalence of several cardiovascular comorbidities known to increase cardiac troponin concentration. Nonetheless as the male participants had higher prevalence of coronary artery disease, an unfavourable risk profile amongst the men may have contributed to the differences in hs-troponin concentration in our study. This is also reflected in higher mortality rates during follow-up for male compared to female participants in the ARISTOTLE biomarker substudy. Of note, the density of cardiac troponin molecules in the myocardium seems to be equal between men and women [32]. Still, although hs-troponin concentrations were higher in male than female participants in ARISTOTLE, sex did not impact on the prognostic value of hs-troponin in anticoagulated patients with AF. Accordingly; sex-related differences for hs-troponin concentrations may have been attenuated by the prevalence of cardiovascular morbidity in this population, which will be different in subjects from the general population with balanced age recruitment and less comorbidity [7-10].

Our study has some strengths and limitations. We have studied participants included in a large, multicentre, double-blind, double-dummy, randomized trial, and this ensures good quality regarding collected data and study execution, including adjudication of all clinical end-points. However, due to the inclusion criteria of ARISTOTLE, the results should also be validated in less-selected cohorts of AF patients from the community where oral anticoagulation is not indicated. Follow-up was of moderate length, but the high number of clinical events in the ARISTOTLE study should ensure that the results are valid.

Conclusion

Women with AF have lower hs-troponin concentrations than men, although several CV comorbidities were more prevalent in women. Regardless of concentrations, increments in hs-cTnI or hs-cTnT levels in anticoagulated patients with AF provided similar independent prognostic information concerning the risk of all-cause death, cardiac death, incident myocardial infarction, stroke or SEE and major bleeding in both sexes. Our results support that for anticoagulated patients with AF, the choice of measuring cTnI or cTnT can be left to the convenience and availability of the local clinical chemistry laboratory.

Conflict of interest

HR: Consultancy fees/lecture fees from SpinChip Diagnostics, Cardinor AS, Thermo Fisher BRAHMS, and Novartis. ZH: Consultancy fees/lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Meda, Roche Diagnostics. Research grants from the Swedish Society for Medical Research [S17-0133] and the Swedish Heart-Lung Foundation [20170718]. TO: Research grants from Abbott Diagnostics, Novartis, Roche Diagnostics, Singulex; consultancy/speaker honoraria from Abbott Diagnostics, Bayer, Roche Diagnostics, Siemens, SomaLogic. JW: Institutional research grant from Bristol-Myers Squibb/Pfizer. MNL: Nothing to disclose. JHA: Institutional research grants and consultancy fees/honoraria from Bristol-Myers Squibb and CSL Behring; institutional research grants from AstraZeneca, CryoLife, US Food & Drug Administration, National Institutes of Health, Sanofi, VoluMetrix, and Boehringer Ingelheim; and consultancy fees/honoraria from Pfizer, AbbVie Pharmaceuticals, NovoNordisk, Portola Pharmaceuticals, Quantum Genetics, Teikoku Pharmaceuticals, VA Cooperative Studies Program, and Zafgen. BJG: Data safety monitoring board from Boston Scientific, Cardiovascular Research Foundation, Duke Clinical Research Institute, Icahn School of Medicine at Mount Sinai, Janssen Scientific Affairs, Kowa Research Institute, Medtronic and Mount Sinai St Lukes; steering committee fees from Janssen Scientific Affairs and Thrombosis Research Institute. CBG: Research grants and consultancy/speaker fees from Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Pharmaceuticals, Pfizer, AstraZeneca and Novartis; research grants from Daichii-Sankyo, AKROS, Apple, GlaxoSmithKline

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Associations between cardiac troponin concentrations and clinical outcomes with patients stratified according to sex (cardiac troponin concentrations dichotomized according to 99th percentile cut-off values).