ORIGINAL ARTICLE

Sex Differences in Cardiac Troponin I and T and the Prediction of Cardiovascular Events in the General Population

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Abstract: 250

Word count: 3,346

Tables and Figures: 5

References: 40

Key words: Sex, cardiac troponin, risk factors, cardiovascular events

List of abbreviations

Hs-cTn: High-sensitivity cardiac troponin

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

LoB: Limit of blank

LoD: Limit of detection

ICD-10: 10th revision of the International Classification of Diseases

HR: Hazard ratio

ROC: Receiver operating characteristic

AUC: Area under the curve

CI: Confidence interval

ARIC: Atherosclerosis Risk in Communities study

HUNT: Nord-Trøndelag Health Study

ActiFE: Activity and Function in the Elderly in Ulm study

PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors study

AGES-Reykjavik: Age, Gene/Environment Susceptibility-Reykjavik study

MESA: Multi-Ethnic study of Atherosclerosis study

Abstract

Background: Cardiac troponin concentrations differ in women and men, but how this influences risk prediction and whether a sex-specific approach is required is unclear. We evaluated whether sex influences the predictive ability of cardiac troponin I and T for cardiovascular events in the general population.

Methods: High-sensitivity cardiac troponin (hs-cTn) I and T were measured in the Generation Scotland Scottish Family Health Study of randomly selected volunteers drawn from the general population between 2006 and 2011. Cox-regression models evaluated associations between hs-cTnI and hs-cTnT and the primary outcome of cardiovascular death, myocardial infarction or stroke.

Results: In 19,501 (58% women, age 47 years) participants the primary outcome occurred in 2.7% (306/11,375) of women and 5.1% (411/8,126) of men during the median follow-up period of 7.9 [IQR,7.1-9.2] years. Cardiac troponin I and T levels were lower in women than men ($P<0.001$ for both), and both were more strongly associated with cardiovascular events in women than men. For example, at a hs-cTnI level of 10 ng/L, the hazard ratio relative to the limit of blank was 9.7 (95% confidence interval [CI] 7.6-12.4) and 5.6 (95% CI 4.7-6.6) for women and men, respectively. The hazard ratio for hs-cTnT at a level of 10 ng/L relative to the limit of blank was 3.7 (95% CI 3.1–4.3) and 2.2 (95% CI 2.0-2.5) for women and men, respectively.

Conclusions: Cardiac troponin concentrations differ in women and men and are stronger predictors of cardiovascular events in women. Sex-specific approaches are required to provide equivalent risk prediction.

Introduction

Cardiovascular disease remains the main cause of death worldwide with 17.6 million people dying each year (1, 2). The development of approaches to improve the prediction and targeting of effective preventative therapies to those at highest risk may help minimize the impact of cardiovascular disease on the population. It is important that these approaches are equitable for women and men (2). In both primary and secondary care, guidelines have been established in populations where men are over represented and women seem to be disadvantaged and received fewer preventative treatments (3-5).

Cardiac biomarkers may provide an unbiased aproach towards the prediction of cardiovascular events in women and men. Increasingly, high-sensitivity cardiac troponin is considered an useful marker of risk outwith the setting of acute coronary syndromes to evaluate asymptomatic individuals and guide therapeutic approaches to prevent the onset of cardiovascular disease (6-11). Recent major improvements in analytical performance have greatly enhanced assay sensitivity, such that with high-sensitivity assays we are now able to accurately measure cardiac troponin concentrations in the majority of healthy individuals (12). In a recent meta-analysis of apparently healthy individuals, 43% of participants with cardiac troponin concentrations in the top third developed cardiovascular disease over the next eight years (13).

It remains unclear in practice how best to harness this prognostic information to guide the use of primary and secondary prevention, and whether sex-specific troponin thresholds should be considered. The use of high-sensitivity assays has identified important differences in troponin concentrations between men and women, with the 99th centile upper reference limits used for diagnosis of myocardial infarction up to 2-fold higher in men (14). In our recent systematic

review we demonstrated that this observation is consistent for all troponin assays across multiple cohorts from different ethnic backgrounds (15). Furthermore, we recently demonstrated in the Generation Scotland Scottish Family Health Study, where both cardiac troponin I and troponin T were measured in the same cohort, that differences in the 99th centile between men and women exist for both biomarkers across all age groups (16). Although a number of studies have investigated cardiac troponins in relation to cardiovascular outcomes in the general population (7, 11, 13, 17, 18), few have evaluated how sex influences risk prediction and it remains unclear whether a different approach is required in women and men. Our aim was to determine whether sex influences the predictive ability of cardiac troponin I and T for cardiovascular events in the general population.

Material and Methods

Study population

The Generation Scotland Scottish Family Health Study is a well-phenotyped family-based cohort that enrolled 24,090 participants aged between 18 and 98 years and has been described previously (7, 16, 19). Briefly, individuals between 35 and 65 years old were identified at random from participating general medical practices in Scotland between 2006 and 2011. Participants were asked to identify at least one first-degree relative who was at least 18 years old that would also enrol. For this study, we excluded participants with missing cardiac troponin measurements. Study participants provided written informed consent, including linkage to their medical records. The study was conducted according to principles of the Declaration of Helsinki and was approved by the National Health Service Tayside Committee on Medical Research Ethics (REC Reference Number: 05/S1401/89). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Clinical characteristics

Participants completed a health questionnaire, and had physical characteristics and clinical characteristics measured according to a standardized protocol (19). Past medical history, including a diagnosis of diabetes mellitus, previous myocardial infarction or stroke, and use of medications was self-reported. Family history of cardiovascular disease was defined as a self-report of parents or siblings having heart disease or stroke. Blood samples were taken, according to a standard operating procedure, and serum was prepared. Total cholesterol, high-density lipoprotein cholesterol, and serum creatinine, were measured at the time of collection, and additional aliquots were stored at –80°C for future analyses. The Scottish Index of Multiple Deprivation (2009) scores were derived from participants' postcodes: they denote nationally compiled composite measures of small-area deprivation (20).

Cardiac troponin measurements

Serum cardiac troponin I was measured on ARCHITECT *i*1000SR high sensitive cardiac troponin I assay (Abbott Diagnostics) and cardiac troponin T was measured on Cobas e411 high sensitive cardiac troponin T (Roche Diagnostics) assay. During the conduct of this study, we participated in the National External Quality Assurance Scheme (https://ukneqas.org.uk/) for these biomarkers. Both assays were calibrated and quality controlled using the manufacturer's reagents. Coefficient of variations for cardiac troponin I were 6.2%, 6.0% and 4.6% for the low, intermediate and high control, respectively. Coefficient of variations for cardiac troponin T were 5.0% and 3.4% for the low and high control, respectively. Cardiac troponin T has a limit of blank (LoB) of 3 ng/L and limit of detection (LoD) of 5 ng/L. Cardiac troponin I has a LoB of 1.2 ng/L and LoD of 1.9 ng/L (21).

Clinical outcome

We used the Information Services Division National Health Service record linkage for Scotland to collect clinical outcome data until the end of September 2017. Information on cause of death was obtained using the National Health Service Central Register. Clinical outcomes were classified using the 10^{th} revision of the International Classification of Diseases (ICD-10). The primary outcome was a composite endpoint of cardiovascular events including the following component endpoints: 1) cardiovascular death (I00 to I99), 2) myocardial infarction (I21, I22) and 3) stroke (I63, I64, G45). Secondary outcomes were cardiovascular death, non-cardiovascular death and all-cause death.

Statistical analysis

Continuous variables are presented as mean (SD) or median [25^{th}-75^{th} percentile], as appropriate. Categorical variables are presented as absolute numbers (%). For continous analyses, troponin values below the LoB were set to the LoB value divided by 2. The correlation between cardiac troponin I and T was assessed by Spearman correlation. Sex-specific incidence rates were calculated per 1,000 person-years for clinical outcomes.

Statistical learning using Cox proportional hazard regression models

Unadjusted and adjusted multiple fractional polynomial Cox proportional hazard regression analysis were conducted to quantify the relationship between cardiac troponin as a continuous variable with the primary outcome, stratified by sex. The multivariable model is adjusted for age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, cigarettes smoked per day, rheumatoid arthritis, diabetes mellitus, Scottish Index of Multiple Deprivation score, family history of cardiovascular disease, use of blood pressure medications, and use of cholesterol-lowering medications. Each contininous variable was chosen through backwards-

stepwise selection of the best fractional polynomial transformation. We created hazard ratio (HR) plots for the primary outcome at 5 years of the unadjusted and adjusted cardiac troponin I and T models for women and men, and evaluated the Hazard Ratio (HR) relative to the LoB. Due to the low proportion of missing covariates (<6%) and the large number of available samples we did not use imputation techniques, focusing on complete case analysis instead. We constructed receiver operating characteristic (ROC) curves and determined the area under the curve (AUC) to assess discrimination of cardiac troponin for predicting the primary outcome at 5 years in women and men. Individuals with no events by the 5-year mark were censored. Comparisons between unpaired AUCs are tested according to the DeLong method. In secondary analyses, we evaluated the HR relative to the LoD, and we evaluated the additional outcomes of cardiovascular death, non-cardiovascular death and all-cause death. All statistical analysis was performed using R version 3.6.2.

Results

Clinical characteristics of study population

Our study population included 19,501 individuals (58% women; ***Table 1***) with a measured cardiac troponin I and T concentration available. On enrolment women and men were at similar age (47±15 years), but men were more likely to have risk factors, such as hypertension or diabetes mellitus, or to have a history of prior cardiovascular disease. Cardiac troponin concentrations were lower in women than men (cardiac troponin I, women 1.5 [1.2 to 2.5] ng/L *versus* men 2.5 [1.6 to 4.0] ng/L; cardiac troponin T, women ≤3.0 [3.0 to 4.8] ng/L *versus* men 4.6 [3.0 to 7.5] ng/L; P<0.001 for both; ***Figure 1***). The proportion of women and men with high-sensitivity cardiac troponin I concentrations above the LoD was 66.1% (7,523/11,375) and 86.8% (7,056/8,126), and for cardiac troponin T it was 42.4% (4,826/11,375) and 68.5%

(5,569/8,126). The correlation between cardiac troponin I and T concentrations was lower in women than men (r = 0.351, 95% confidence interval [CI] 0.334 to 0.370 *versus* r = 0.446, 95% CI 0.428 to 0.463; P<0.001).

Cardiac troponins and cardiovascular events in women and men

The median follow-up period was 7.9 [7.1 to 9.2] years, and a total number of 717 (3.7%) individuals experience a primary outcome event. In those participants with an incident cardiovascular event (***Table 1***), women were on average three years older than men (65 *versus* 62 years), but otherwise prior cardiovascular disease and risk factors were similar. Women had fewer events than men, with the primary outcome occuring in 306 (2.7%) women and 411 (5.1%) men during the follow-up period (***Table 2***).

Based on our unadjusted and adjusted regression models we illustrate the hazard ratio of a cardiovascular event at 5 years according to cardiac troponin I and troponin T concentrations in men and women (***Figure 2***). For estimation of HRs, covariates were standardised for both women and men to illustrate the relationship between cardiac troponin and events in women and men with similar characteristics. Both cardiac troponin I and T concentrations were more strongly associated with the primary outcome in women than men (***Figure 2A and 2C***). For example, at a cardiac troponin I threshold of 10 ng/L, the unadjusted HR relative to the LoB was 9.7 (95% CI 7.6 to 12.4) for women compared to 5.6 (95% CI 4.7 to 6.6) for men. The unadjusted HR for a cardiac troponin T threshold of 10 ng/L relative to LoB was 3.7 (95% CI 3.1 to 4.3) for women and 2.2 (95% CI 2.0 to 2.5) for men. Cardiac troponin I and T thresholds of 2.1 ng/L and 6.0 ng/L, respectively, were associated with a doubling of cardiovascular risk in women. For men, a doubling of cardiovascular risk required higher thresholds of 2.5 ng/L and 9.0 ng/L for cardiac troponin I and T, respectively. Both cardiac troponin I and T remained

strongly associated with cardiovascular events in women and men after adjustment of other risk factors, but the divergence between women and men was attenuated (***Figure 2B and 2D)***.

Overall, cardiac troponin I and T levels had a good discriminative ability to predict 5-year cardiovascular risk (***Figure 3***). For cardiac troponin I (AUC 0.73 in women *versus* AUC 0.68 in men, P=0.080), and for cardiac troponin T (AUC 0.72 in women *versus* AUC 0.66 in men, P=0.040) there was a trend towards better discrimination in women than in men.

Secondary outcomes

When using the LoD as reference value, we observed that the differences in the association with cardiac troponin I and T on the primary outcome between women and men were similar but attenuated (***Supplemental Figure 1***). Consistent with our observations for the primary composite outcome, the incidence of cardiovascular death was lower in women than men (***Table 2***). In contrast no difference was observed in the incidence of non-cardiovascular death between sexes. Both cardiac troponin I and T were strongly associated with cardiovascular death (***Supplemental Figures 2 and 3***, P<0.001 for both) and all-cause death (***Supplemental Figures 4 and 5***, P<0.001 for both) in women and men in fully adjusted models. Cardiac troponin I was not associated with non-cardiovascular death in either women (P=0.597) or men (P=0.364), whereas cardiac troponin T was for both sexes (P=<0.001 in women, P=0.004 in men; ***Supplemental Figures 6 and 7***).

Discussion

We have evaluated whether sex influences the prediction of cardiac troponin I and T for cardiovascular events in the general population. Our study has three main findings. First, cardiac troponin I and T are independent predictors of cardiovascular events in both women and men in the general population. Second, cardiac troponin concentrations differ between women and men and are stronger predictors of cardiovascular events in women. Use of the same thresholds to guide risk of future cardiovascular events in women and men would not provide equivalent prediction. Third, differences in prediction between women and men are largely explained by the prevalence of cardiovascular risk factors and prior disease, as the divergence between women and men was attenuated after adjustment of other risk factors. These findings highlight the importance of a sex-specific approach when using high-sensitivity cardiac troponin testing in isolation for risk stratification and targeting treatments to prevent cardiovascular disease. Ideally cardiac troponin would be used as a continuous measure in a cardiovascular risk prediction tool that incorporates sex and other clinical features.

Our study has several strengths. First, the Generation Scotland Scottish Family Health Study enrolled approximately 20,000 individuals and a high proportion were women. Second, we were able to evaluate both cardiac troponin I and T in almost the entire cohort, permitting direct comparisons between markers and ensuring our findings are both representative and generalisable. Third, complete follow-up for almost eight years ensured we had a sufficient number of cardiovascular events to evaluate prediction in men and women seperately.

We found that cardiac troponins are strong independent predictors of cardiovascular events and that in their unadjusted, ‘raw’ status, they are more strongly associated in women than men.

This observation is in line with the Atherosclerosis Risk in Communities (ARIC) study, the Nord-Trøndelag Health Study (HUNT) study and the Activity and Function in the Elderly in Ulm (ActiFE) study, showing an interaction between troponin and sex in relation to future cardiovascular events across different ethnicities and age groups (18, 22, 23). Apart from differences in left ventricular mass that could explain the lower troponin levels in women than men (24-26), sex-hormones may play a role in the divergent cardiovascular risk prediction of cardiac troponin levels for women and men (27). Estrogens seems to have a cardioprotective effect in premenopausal women, either directly or indirectly (28-31). Differences in body fat distribution between women and men may lead to a different cardiometabolic risk profile (32), which could influence cardiac troponin concentrations. Also, differences in the prevalence of microvascular disease may play a role (33, 34). However, in line with the ARIC study (22), ActiFE study (23), the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (35), the Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) study (36), and the Multi-Ethnic study of Atherosclerosis (MESA) (37), we showed that after adjustment of other risk factors the associations between cardiac troponins and outcome in women and men became similar. This points out that the divergent risk between sexes are at least partly explained by differences in cardiovascular risk profile. We determined previously that age, diabetes, prior cardiovascular disease and lipid-lowering- and antihypertensive medication use are important determinants for elevated cardiac troponin levels (16), and adjusting for these factors resulted in similar risk prediction for cardiac troponins in women and men.

What are the implications of these observed sex differences? Women tend to be undertreated for cardiovascular risk (38), and cardiac troponin might be a tool to bridge this imbalance. We believe that differences in prediction between women and men are largely explained by the

prevalence of cardiovascular risk factors and prior disease, and therefore ideally cardiac troponin would be used as a continuous measure in a risk prediction tool that incorporates sex and other clinical features. However, if cardiac troponin is used in isolation to stratify patients into low or high-risk groups for screening purposes it is essential that a sex-specific approach is adopted. We believe that future research should focus on using cardiac troponin as continuous variable in a multivariable cardiovascular risk tool that stratifies individuals based on their likelihood of cardiovascular disease. This would be in line with the development of the use of troponins in the acute cardiac setting (8), as the awareness has been raised that cardiac troponin in a continuous fashion improves risk assessment. Another major advantage of such an approach is that cardiac troponin could be corrected for other relevant risk factors and that would eliminate the problem of under- or overestimation for other important subgroups apart from sex.

In contrast to the acute care setting, the general population contains a high proportion of individuals with cardiac troponin values below the LoD. As our study was not designed to develop a risk prediction tool, but rather to evaluate sex differences between troponins in this setting, we have used cardiac troponin over their entire concentration range. We therefore cannot exclude that the imprecision profile of these assays in individuals with very low cardiac troponin levels may have affected the accuracy of our results. When using the LoD rather than the LoB as the reference, differences between women and men were less pronounced. Women have lower troponin concentrations than men and therefore a greater proportion of women have undetectable cardiac troponin. Our analyses suggest that discrimination in the modelling of future cardiovascular events is partly dependent on being able to identify those individuals who are very low risk with the lowest cardiac troponin values. The clinical implications of this are important. For example, in the United States cardiac troponin values below the LoD are not

reported because of concerns about assay imprecision. Whilst precision is greater in those with higher values and therefore the user can be more confident in actioning the results of those identified as higher risk, it is less clear that based on current analytical precision (and reporting requirements) we are fully harnessing the potential of these tests to identify those who are lower risk. Those developing clinical tools to guide primary prevention approaches that incorporate cardiac troponin should be aware that including troponin values below the LoD may affect the accuracy of prediction and limit the future application of these tools in practice.

Another important observation in our study is that cardiac troponin T, but not cardiac troponin I predicts non-cardiovascular death in both women and men. This extends our previous finding that cardiac troponin I has a greater specificity for future cardiovascular risk (7, 16). Although the underlying mechanism of this divergence is not well understood and remains speculative, cardiac troponin T elevations appear more strongly related to chronic kidney and neuromuscular diseases (39, 40). Furthermore, the curvilinear relationship between cardiovascular risk and cardiac troponin I and T concentrations differ. For cardiac troponin I, the risk increases in the low troponin range, while for cardiac troponin T the risk accelerates more at higher cardiac troponin values. This divergence may reflect differences in assay precision at very low concentrations and could be an important consideration for the development and implementation of risk prediction tools incorporating troponin, as model performance is likely to be very sensitive to assay choice.

Several limitations merit attention. First, no cardiac imaging data was available and studying the possible structural microvascular cardiac differences between women and men in relation to troponin and outcome was not possible, though this is of secondary value as we have incident cardiovascular outcomes. Second, the majority of the Generation Scotland Family Health Study

subjects are Caucasian and generalizing our finding to other ethnic groups should be done with caution. Third, although high-sensitivity testing was used, still a high proportion of individuals had undetectable cardiac troponin concentrations, particularly for cardiac troponin T and particularly in women. Imprecision in those with very low cardiac troponin concentrations might have influenced the accuracy of our model estimates. Finally, cardiac troponin I was only measured using one manufacturer's assay, which precludes the direct extrapolation of our findings to other cardiac troponin I assays.

In conclusion, cardiac troponin I and T are independent predictors of cardiovascular events in both women and men in the general population. Cardiac troponin concentrations differ in women and men and are stronger predictors of cardiovascular events in women. Sex-specific approaches are required to provide equivalent risk prediction when using high-sensitivity cardiac troponin testing in isolation for risk prediction and the prevention of cardiovascular disease. Ideally cardiac troponin would be used as a continuous measure in a cardiovascular risk prediction tool that incorporates sex and other clinical features.

Conflict of Interests Disclosures

ASVS has received honoraria from Abbott Diagnostics. SJRM has received research funding and lecture fees from Abbott Diagnostics and Roche Diagnostics. NS has received fees for consulting, speaking, and honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi, and research grant from Boehringer Ingelheim. NLM has acted as a consultant for Abbott Diagnostics, Roche, Beckman-Coulter, and Singulex. PW has received grant support from Roche and Boehringer Ingelheim. The other authors report no conflicts.

Research funding

Troponin measurements and analysis were supported by a Stratified Medicine Grant from the Chief Scientist Office of the Scottish Government Health Directorates (ASM/14/1). Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates (CZD/16/6) and the Scottish Funding Council (HR03006). The study was supported by Health Data Research UK which receives its funding from HDR UK Ltd (HDR-5012) funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and the Wellcome Trust. DMK is supported by a Kootstra Talent Fellowship (19.1314). CH is supported by an MRC University Unit Programme Grant MC_UU_00007/10 (QTL in Health and Disease). NLM is supported by the British Heart Foundation through a Senior Clinical Research Fellowship (FS/16/14/32023), Programme Grant (RG/20/10/34966) and a Research Excellence Award (RE/18/5/34216). The funders had no role in the study and the decision to submit this work to be considered for publication.

Acknowledgements

We thank J. Cooney and P. Stewart (University of Glasgow, UK) for excellent technical support. We are grateful to all the families who took part, the general practitioners, and the Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants, and nurses.

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Table 1. Baseline characteristics of entire study population and stratified by composite cardiovascular events

	Study population		No incident cardiovascular event		Incident cardiovacular event	
	Women (n=11,375)	**Men (n=8,126)**	**Women (n=11,069)**	**Men (n=7,715)**	**Women (n=306)**	**Men (n=411)**
Age (years)	47 (15)	47 (15)	47 (15)	46 (15)	65 (14)	62 (11)
Body mass index (kg/m^2)	26.5 (5.6)	26.9 (4.5)	26.5 (5.6)	26.8 (4.4)	27.8 (5.6)	28.3 (4.8)
Systolic blood pressure (mmHg)	128 (18)	136 (16)	128 (18)	136 (16)	141 (22)	142 (19)
Total cholesterol (mmol/L)	5.2 (1.1)	5.0 (1.1)	5.2 (1.1)	5.0 (1.06)	5.3 (1.3)	4.9 (1.2)
HDL cholesterol (mmol/L)	1.6 (0.4)	1.3 (0.3)	1.6 (0.4)	1.3 (0.3)	1.5 (0.4)	1.2 (0.4)
SIMD (score/10)	1.2 [0.7- 2.4]	1.1 [0.7-2.1]	1.2 [0.7-2.4]	1.1 [0.7-2.1]	1.5 [0.8-2.9]	1.4 [0.8-2.6]
eGFR (mL/min/1.73m^2)	94 (17)	96 (17)	95 (17)	97 (17)	76 (20)	88 (25)
Cigarettes (per day)	2.3 (6.4)	2.7 (7.6)	2.2 (6.3)	2.6 (7.5)	4.3 (9.3)	4.9 (11.9)
Family history of CVD (yes)	4516 (40.4%)	2888 (36.5%)	4401 (40.5%)	2732 (36.4%)	115 (38.1%)	156 (38.5%)
Rheumatoid arthritis (yes)	213 (1.9%)	101 (1.2%)	195 (1.8%)	88 (1.1%)	18 (5.9%)	13 (3.2%)
Baseline CVD (yes)	369 (3.2%)	508 (6.3%)	302 (2.7%)	401 (5.2%)	67 (21.9%)	107 (26.0%)
Diabetes mellitus (yes)	256 (2.3%)	306 (3.8%)	228 (2.1%)	252 (3.3%)	28 (9.2%)	54 (13.1%)
Lipid-modifying medication (yes)	604 (5.3%)	678 (8.3%)	548 (5.0%)	587 (7.6%)	56 (18.3%)	91 (22.1%)
Antihypertensive medication (yes)	832 (7.3%)	742 (9.1%)	761 (6.9%)	646 (8.4%)	71 (23.2%)	96 (23.4%)
Cardiac troponin I (ng/L)	1.5 [1.2-2.5]	2.5 [1.6-4.0]	1.5 [1.2-2.4]	2.4 [1.6-3.9]	2.9 [1.8-5.9]	3.9 [2.3-7.3]
Cardiac troponin T (ng/L)	≤3.0 [3.0-4.8]	4.6 [3.0-7.5]	≤3.0 [3.0-4.7]	4.5 [3.0-7.3]	5.7 [3.0-10.5]	7.0 [3.8-12.2]
Detectable cardiac troponin I (≥ 1.2 ng/L)	7523 (66.1%)	7056 (86.8%)	7252 (65.5%)	6663 (86.4%)	271 (88.6%)	393 (95.6%)
Detectable cardiac troponin T (≥ 3.0 ng/L)	4826 (42.4%)	5569 (68.5%)	4610 (41.6%)	5238 (67.9%)	216 (70.6%)	331 (80.5%)

Categorical data are presented as n (%). Continuous variables are presented as mean (SD) or median [25th-75th percentile], as appropriate. Abbreviatons: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate, HDL, high density lipoprotein; SIMD, Scottish index of multiple deprivation.

Table 2. Incidence rates of clinical outcomes in women and men

	Women (n=11,375)		Men (n=8,126)	
	Total events (%)	**Incidence rate**	**Total events (%)**	**Incidence rate**
Composite cardiovascular event	306 (2.7%)	3.3/1000 person-years	411 (5.1%)	6.3/1000 person-years
Myocardial infarction	81 (0.7%)	0.9/1000 person-years	178 (2.2%)	2.7/1000 person-years
Ischemic stroke	93 (0.8%)	1.6/1000 person-years	112 (1.4%)	2.3/1000 person-years
Cardiovascular death	128 (1.1%)	1.4/1000 person-years	138 (1.7%)	2.1/1000 person-years
Non-cardiovascular death	206 (1.8%)	2.2/1000 person-years	168 (2.1%)	2.5/1000 person-years
All-cause death	334 (2.9%)	3.6/1000 person-years	306 (3.8%)	4.6/1000 person-years

Composite cardiovascular event = myocardial infarction, ischemic stroke or cardiovascular death

Figure legends

Figure 1. Distribution of cardiac troponins in women and men. Violin plots of cardiac troponin I (A) and T (B) distribution, stratified by sex (cardiac troponin I, women, 1.5 [1.2-2.5] ng/L *versus* men 2.5 [1.6-4.0] ng/L; cardiac troponin T, women ≤3.0 [3.0-4.8] ng/L *versus* men 4.6 [3.0-7.5] ng/L, P<0.001 for both; n=11,375 for women, and n=8,126 for men).

Figure 2. Hazard ratio plots for 5-year risk composite cardiovascular events. Troponin I (A: unadjusted model; B: adjusted model) and T (C: unadjusted model; D: adjusted model) levels in relation to composite cardiovascular events, stratified by sex (referent = LoB value). The horizontal dashed line represents the doubling in risk of having a cardiovascular event within 5 years and the vertical dashed lines (red: women; grey: men) respresents the sex-specific thresholds of the two-fold higher likelihood experiencing a cardiovascular event, accordingly.

Figure 3. Comparison of the discrimination of cardiac troponins for the prediction of the composite cardiovascular event in women and men. Receiver-operating-curve for cardiac troponin I (A) and cardiac troponin T (B) to predict composite cardiovascular event at 5 year in women and men.