

High-Sensitivity Cardiac Troponin I Improves Cardiovascular Risk Prediction in Older Men: HIMS (The Health in Men Study)

Nick S. R. Lan, MBBS;* Damon A. Bell, MB, ChB, PhD;* Kieran A. McCaul, MPH, PhD; Samuel D. Vasikaran, MBBS, MD; Bu B. Yeap, MBBS, PhD; Paul E. Norman, BSc, MB, ChB, DS; Osvaldo P. Almeida, MD, PhD; Jonathan Golledge, BA, MB, BChir, MChir; Graeme J. Hankey, MBBS, MD; Leon Flicker, MBBS, PhD, GradDipEpid

Background—The Framingham Risk Score estimates the 10-year risk of cardiovascular events. However, it performs poorly in older adults. We evaluated the incremental benefit of adding high-sensitivity cardiac troponin I (hs-cTnI) to the Framingham Risk Score.

Methods and Results—The HIMS (Health in Men Study) is a cohort study of community-dwelling men aged 70 to 89 years in Western Australia. Participants were identified from the electoral roll, with a subset undergoing plasma analysis. Hs-cTnI (Abbott Architect i2000SR) was measured in 1151 men without prior cardiovascular disease. The Western Australia Data Linkage System was used to identify incident cardiovascular events. After 10 years of follow-up, 252 men (22%) had a cardiovascular event (CVE+) and 899 did not (CVE−). The Framingham Risk Score placed 148 (59%) CVE+ and 415 (46%) CVE− in the high-risk category. In CVE− men, adding hs-cTnI affected the risk categories of 244 (27.2%) men, with 64.8% appropriately reclassified to a lower and 35.2% to a higher category, which decreased the number of high-risk men in the CVE− to 39%. In CVE+ men, adding hs-cTnI affected the risk categories of 61 (24.2%), with 50.8% appropriately reclassified to a higher and 49.2% to a lower category and 82.5% remaining above the 15% risk treatment threshold. The net reclassification index was 0.305 ($P<0.001$). Adding hs-cTnI increased the C-statistic modestly from 0.588 (95% CI, 0.552–0.624) to 0.624 (95% CI, 0.589–0.659) and improved model fit (likelihood ratio test, $P<0.001$).

Conclusions—Adding hs-cTnI to the Framingham Risk Score provided incremental prognostic benefit in older men, especially aiding reclassification of individuals into a lower risk category. (*J Am Heart Assoc.* 2019;8:e011818. DOI: 10.1161/JAHA.118.011818.)

Key Words: aging • cardiovascular disease • cardiovascular disease prevention • cardiovascular disease risk factors • risk prediction • risk stratification • troponin

Cardiovascular disease (CVD) is a major cause of morbidity and mortality, which imposes a substantial burden on healthcare expenditure.¹ The Framingham Risk Score (FRS) is a widely used model to estimate 10-year risk of cardiovascular events and aids in deciding on the use of primary prevention therapies. However, this was validated in white

middle-aged populations.² Studies have demonstrated that the FRS performs poorly in older adults, suggesting that conventional risk factors are not as predictive of cardiovascular events in older people.^{3,4}

High-sensitivity cardiac troponin I (hs-cTnI) assays can measure 10-fold lower concentrations with more precision

From the Medical School (N.S.R.L., D.A.B., K.A.M., B.B.Y., P.E.N., O.P.A., G.J.H., L.F.), and Western Australia Centre for Health & Ageing (K.A.M., O.P.A., L.F.), University of Western Australia, Perth, Australia; Department of Clinical Biochemistry, PathWest Laboratory Medicine, Royal Perth and Fiona Stanley Hospitals, Perth, Australia (D.A.B., S.D.V.); Cardiometabolic Service, Department of Cardiology (D.A.B.), and Department of Geriatrics (L.F.), Royal Perth Hospital, Perth, Australia; Department of Endocrinology and Diabetes, Fiona Stanley Hospital, Perth, Western Australia, Australia (B.B.Y.); Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Australia (J.G.); Department of Vascular and Endovascular Surgery, The Townsville Hospital, Townsville, Australia (J.G.).

Accompanying Tables S1 through S4 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011818>

*Dr Lan and Dr Bell contributed equally to this work.

Correspondence to: Nick S. R. Lan, MBBS, Fiona Stanley Hospital, 11 Robin Warren Drive, Murdoch, 6150, Western Australia, Australia. E-mail: nick.lan@health.wa.gov.au

Received December 17, 2018; accepted February 6, 2019.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What Is New?

- Addition of high-sensitivity cardiac troponin I to the Framingham Risk Score significantly improved risk prediction in older men.
- There was a greater impact on the predicted risks for the men who did not experience a cardiovascular event during follow-up than in men who did.
- The new model was able to identify a cohort previously misclassified as high cardiovascular risk who had a lower risk of cardiovascular disease over a 10-year period.

What Are the Clinical Implications?

- The ability to identify a group of older adults with a relatively low risk of cardiovascular disease using high-sensitivity cardiac troponin I would allow more judicious use of preventative medications in this age group, thus avoiding side effects and drug-interactions.

than older assays, and are able to accurately quantify cardiac troponin in 50% of a reference population with a coefficient of variation of <10% at the 99th percentile.⁵ Measurable concentrations of cardiac troponin I and T in the general population are associated with structural cardiac disease, heart failure, and an increase in both all-cause and cardiovascular morbidity and mortality.^{6–15} Furthermore, in stable outpatients with coronary artery disease, hs-cTnI can provide prognostic information regarding risk of future myocardial infarction and cardiovascular mortality.^{16,17} However, few studies have evaluated hs-cTnI as a prognostic indicator for older people.^{6,18}

The aim of this study was to evaluate the incremental benefit of adding hs-cTnI to the FRS for cardiovascular risk stratification in older men.

Methods

This study was conducted as part of the HIMS (Health in Men Study), which is a cohort study of community-dwelling men aged 70 to 89 years from Perth, Western Australia.¹⁹ The HIMS recruitment process and study population have been previously described in detail.¹⁹ In brief, HIMS was conducted in 2 waves; 12 203 men completed a questionnaire and underwent physical examination between 1996 and 1999, and 4248 of these men were reassessed and had venesection between 2001 and 2004.¹⁹ The population for this arm of the study was selected from wave 2, as these participants had undergone pathology testing and had stored plasma samples. All participants provided written consent, and the University

of Western Australia Human Research Ethics Committee approved the study.¹⁹ Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Western Australian Centre for Health & Ageing at wacha@uwa.edu.au.

Physical assessments were performed by research nurses and included height, weight, and blood pressure.¹⁹ Participants completed a medical history survey and various questionnaires to assess smoking status, activity, memory, and psychosocial factors as previously described.¹⁹

Hypertension was defined as blood pressure of $\geq 140/90$ mm Hg, hypertension listed in the medical history, or the use of antihypertensive medications.²⁰ Diabetes mellitus was defined as fasting blood glucose of ≥ 7.0 mmol/L, nonfasting blood glucose of ≥ 11.1 mmol/L, a stated history of diabetes mellitus, or the use of glucose-lowering medication.²⁰ Dyslipidemia was defined as a fasting high-density lipoprotein of < 0.9 mmol/L, low-density lipoprotein of ≥ 3.4 mmol/L, triglycerides of ≥ 1.8 mmol/L, total cholesterol of ≥ 5.5 mmol/L, or the use of lipid-lowering therapy.²⁰

Preexisting CVD was defined as a self-reported history of angina, myocardial infarction, stroke, or abdominal aortic aneurysm.²⁰ The FRS to estimate 10-year cardiovascular event risk was calculated only for men without prior CVD.

Blood samples were collected between 8:00 AM and 10:30 AM. Samples collected into lithium heparin plasma separator (gel) tubes were promptly centrifuged at 2000g for 10 minutes. Cholesterol, triglycerides, high-density lipoprotein cholesterol, and creatinine were analyzed on the day of collection in an accredited laboratory. Low-density lipoprotein cholesterol was calculated using the Friedewald equation.²¹ Samples of serum were prepared and frozen at -80°C in 3 ≈ 0.8 -mL aliquots.¹⁹ Measurement of cardiac troponin I was done on one of these serum aliquots, which was thawed and recentrifuged prior to analysis. Samples were analyzed for cardiac troponin I using an Abbott Architect i2000SR assay over several days using a single reagent lot. This assay has a coefficient of variation of 10% at 6 ng/L in this laboratory.²²

The Western Australia Data Linkage System was used to determine occurrence of cardiovascular events and death over 10 years of follow-up.^{20,23} This system collates information from hospital morbidity and mortality data, emergency departments, and the death registry at 6-month intervals.²³ The primary outcome measure, cardiovascular events over 10 years, was defined as a composite of coronary heart disease events (including coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular disease events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral artery disease events (including intermittent claudication), and heart failure.

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC) and STATA (StataCorp, College Station, TX). Categorical variables are described as absolute numbers and percentages. Continuous variables are described as mean and SD, while skewed data are also described as median and interquartile range. The 99th percentile value for hs-cTnI was calculated as the absolute single upper 99th percentile value using hs-cTnI results for men without preexisting CVD at baseline. Nonparametric data were compared using the Wilcoxon rank-sum test. A $P < 0.05$ was used to define statistical significance. Logistic regression was used to assess the association of hs-cTnI with 10-year mortality. Cox proportional hazards regression modeling was used to examine the association between covariates of the FRS and cardiovascular events over 10 years. Hs-cTnI was then added as a continuous predictor to the Cox regression model to form a new model. The traditional FRS was compared with the new model using the C-statistic, which measures discriminatory ability by indicating the correct ranking of each individual's risk, and the likelihood ratio test of improved model fit. Predicted 10-year risks were also compared using the continuous net reclassification improvement, which quantifies improvement offered by a new marker.²⁴ Density plots, receiver operating curves, and recalibration plots were used to graphically display differences between models.²⁴ Reclassification tables were constructed for people who did or did not experience a cardiovascular event during follow-up, where comparison is made between quartiles of risk calculated with the FRS and the new model.²⁴

Results

A total of 4248 men contributed data to the second wave of HIMS. The majority were born in Australia (62.0%), Northern Europe (26.7%), and the Mediterranean (5.2%).¹⁹ During a planned analysis of 4248 patient samples for another study, the last 2111 samples were accessible for analysis of hs-cTnI, which then formed the cohort of this study. There were 1137 men aged 70 to 74 years, 843 aged 75 to 79 years, and 131 aged 80 years or older. Baseline characteristics are presented in Table 1.

The hs-cTnI distribution for the entire cohort (n=2111) was nonparametric, as shown in Figure 1. Overall, the mean hs-cTnI was 9.4 ng/L, with a median of 5.9 ng/L and an interquartile range of 4.6 ng/L. The 25th and 75th percentiles were 4.2 and 8.8 ng/L, respectively. There were 42 men with hs-cTnI concentrations ≥ 40.0 ng/L, with a range of 40.7 to 398.5 ng/L. Increased age, current smoking, presence of baseline comorbidities, and CVD were associated with increased hs-cTnI concentration, as presented in Table 2.

Table 1. Baseline Characteristics

| Characteristic* | Without CVD (n=1151) | With CVD (n=960) | Overall (n=2111) |
|--------------------------------------|----------------------|------------------|------------------|
| Age, y | | | |
| 70 to 74 | 700 (60.8) | 437 (45.5) | 1137 (53.9) |
| 75 to 79 | 437 (38.0) | 406 (42.3) | 843 (39.9) |
| >80 | 14 (1.2) | 117 (12.2) | 131 (6.2) |
| Smoking status | | | |
| Never | 424 (36.8) | 280 (29.1) | 704 (33.3) |
| Former | 656 (57.0) | 620 (64.6) | 1276 (60.4) |
| Current | 71 (6.2) | 60 (6.3) | 131 (6.2) |
| BMI, kg/m² | | | |
| <20 | 21 (1.8) | 22 (2.3) | 43 (2.0) |
| 20 to <25 | 374 (32.5) | 272 (28.4) | 646 (30.6) |
| 25 to <30 | 599 (52.0) | 493 (51.5) | 1092 (51.8) |
| ≥ 30 | 157 (13.7) | 170 (17.8) | 327 (15.5) |
| Diabetes mellitus | 137 (11.9) | 187 (19.5) | 324 (15.3) |
| Hypertension | 450 (39.1) | 579 (60.3) | 1029 (48.7) |
| Dyslipidemia | 433 (38.9) | 674 (72.2) | 1107 (54.1) |
| Malignancy | 223 (19.4) | 191 (19.9) | 414 (19.6) |
| Biochemistry | | | |
| Troponin, ng/L | 5.3 (3.5) | 7.0 (6.8) | 5.9 (4.6) |
| Creatinine, μ mol/L | 90.5 (20.0) | 101.7 (36.9) | 95.6 (29.5) |
| eGFR, mL/min per 1.73 m ² | 79.0 (16.5) | 71.9 (19.2) | 75.8 (18.2) |

BMI indicates body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

*Troponin is expressed as median (interquartile range). Creatinine and eGFR are expressed as mean (SD). All other variables are expressed as count (%).

Figure 1 also shows the distribution of hs-cTnI concentrations for men without CVD (n=1151) at baseline. The mean hs-cTnI for this group was 6.9 ng/L, with a median of 5.3 ng/L and an interquartile range of 3.5 ng/L. The 25th and 75th percentiles were 3.9 and 7.4 ng/L, respectively. The 99th percentile for all men without CVD was 30.0 ng/L (95%CI, 24.1–50.3 ng/L). There were 9 men with hs-cTnI concentrations ≥ 40.0 ng/L, with a range of 41.6 to 216.2 ng/L.

All-cause mortality after 10 years was 23.2% and CVD mortality was 7.8% in the men without prior CVD. The FRS to estimate 10-year cardiovascular event risk was calculated for men without prior CVD (n=1151).² After 10 years of follow-up, 252 (22%) had a cardiovascular event (CVE+) and the remaining 899 (78%) did not (CVE–). The score placed 148 (59%) CVE+ men and 415 (46%) CVE– men in the high-risk category (10-year risk >20%).

The addition of log(troponin) increased the C-statistic modestly from 0.588 (95% CI, 0.552–0.624) to 0.624 (95% CI,

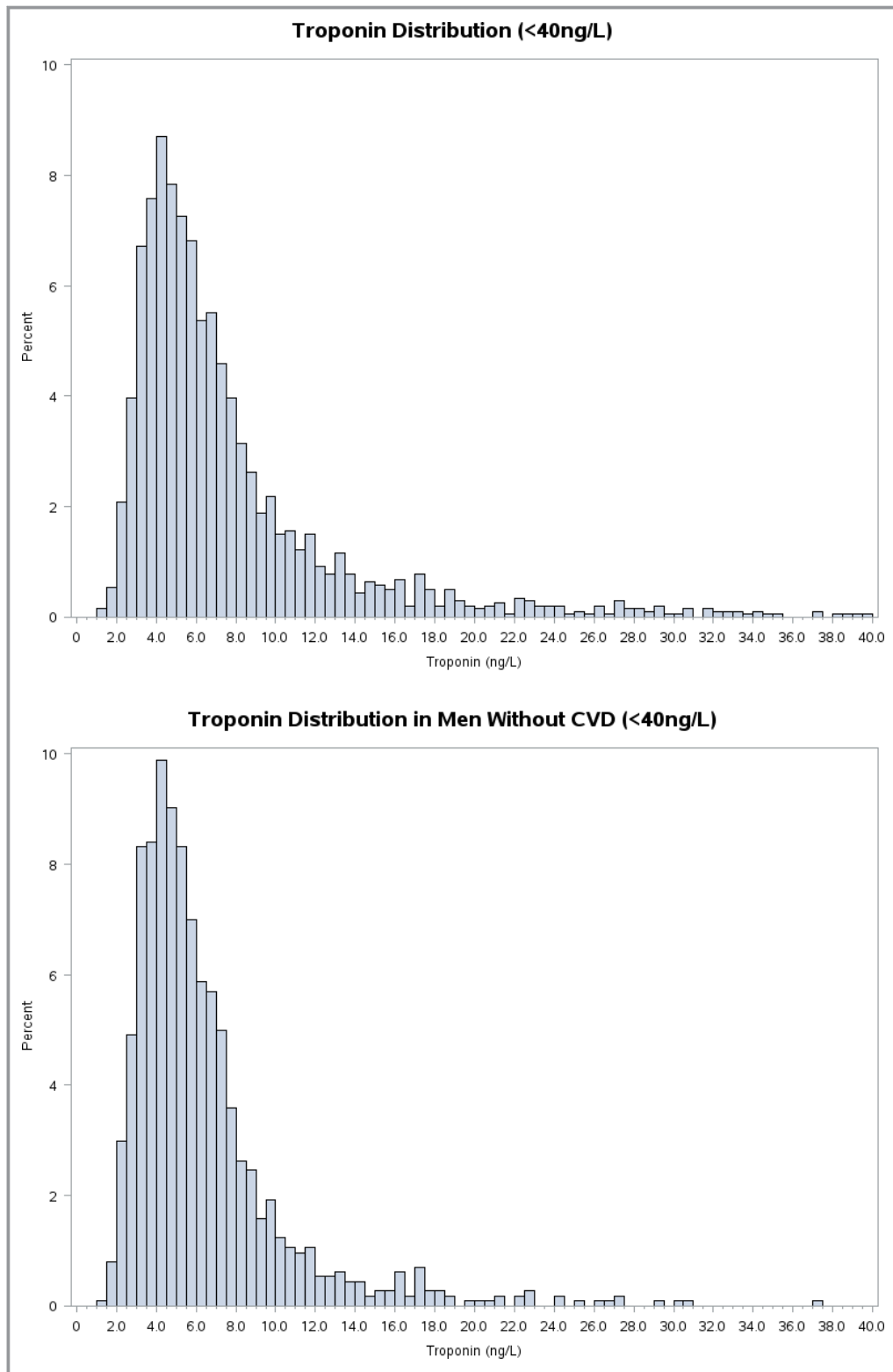


Figure 1. The distribution of high-sensitivity cardiac troponin I for the entire cohort (top) and for men without prior cardiovascular disease (CVD) (bottom).

0.589–0.659) but significantly improved model fit (likelihood ratio test of improvement in fit, $P < 0.001$). Receiver operating characteristic curves showing improvement in the model with

addition of hs-cTnI (C-statistic 0.624 versus 0.588) is shown in Figure 2. Comparison of the 2 models using regression analysis is presented in Table 3. The addition of hs-cTnI to the

Table 2. Troponin Concentration by Baseline Characteristic

| Characteristic | Mean (SD)* | 25th Percentile | Median | 75th Percentile |
|---|-------------|-----------------|--------|-----------------|
| Age (y)[†] | | | | |
| 70 to 74 | 8.9 (22.1) | 3.9 | 5.2 | 7.8 |
| 75 to 79 | 9.9 (13.3) | 4.8 | 6.6 | 9.7 |
| ≥80 | 10.6 (7.1) | 5.6 | 8.3 | 13.9 |
| Smoking status[†] | | | | |
| Never | 8.4 (12.0) | 4.1 | 5.7 | 8.3 |
| Former | 9.8 (20.1) | 4.3 | 6.0 | 9.3 |
| Current | 10.5 (26.7) | 4.9 | 6.8 | 8.6 |
| BMI (kg/m²)[†] | | | | |
| <20 | 6.1 (3.5) | 3.6 | 4.7 | 7.9 |
| 20 to <25 | 9.0 (18.8) | 4.2 | 5.8 | 8.6 |
| 25 to <30 | 9.3 (16.5) | 4.2 | 5.8 | 8.8 |
| ≥30 | 11.0 (23.5) | 4.4 | 6.5 | 10.1 |
| Diabetes mellitus[†] | | | | |
| No | 9.1 (18.2) | 4.2 | 5.8 | 8.6 |
| Yes | 11.0 (19.0) | 4.7 | 6.5 | 10.5 |
| Hypertension[†] | | | | |
| No | 8.2 (16.4) | 3.9 | 5.2 | 7.8 |
| Yes | 10.7 (20.1) | 4.7 | 6.6 | 10.4 |
| Dyslipidemia[†] | | | | |
| No | 8.0 (11.8) | 4.1 | 5.7 | 8.2 |
| Yes | 10.3 (20.3) | 4.3 | 6.3 | 9.8 |
| Malignancy | | | | |
| No | 9.4 (17.5) | 4.2 | 5.9 | 8.8 |
| Yes | 9.3 (21.2) | 4.3 | 6.0 | 8.8 |
| CVD[†] | | | | |
| No | 6.9 (9.3) | 3.9 | 5.3 | 7.4 |
| Yes | 12.3 (24.9) | 4.7 | 7.0 | 11.5 |

BMI indicates body mass index; CVD, cardiovascular disease.
 *Troponin concentrations are in ng/L.
[†]Significant difference in troponin values between groups ($P < 0.05$).

FRS adjusted for only the effect of age, with no effect on the other covariates.

The predicted risk using the FRS and with the addition of hs-cTnI are presented as reclassification tables (Tables 4 and 5). The net reclassification index was 0.305 ($P < 0.001$). There was a greater impact on the predicted risk in the CVE– men than in CVE+ men. In the 899 CVE– men, the addition of hs-cTnI affected the risk categories of 244 (27.2%). In these men, 64.8% were appropriately reclassified to a lower category and 35.2% to a higher category. This decreased the number of men in the high-risk category from 46% with the FRS model to 39% with the FRS plus hs-cTnI model. In the

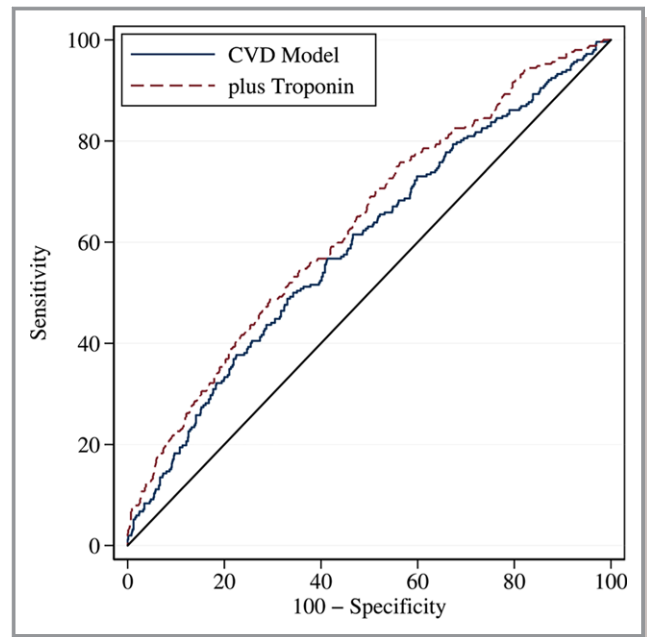


Figure 2. Receiver operating characteristic curves showing improvement of the cardiovascular disease (CVD) model with addition of high-sensitivity cardiac troponin I.

252 CVE+ men, the addition of hs-cTnI affected the risk categories of 61 (24.2%). In these men, 50.8% were appropriately reclassified to a higher risk category and 49.2% to a lower risk category, with 82.5% remaining above the treatment threshold of 15% risk.

Density plots showing improvements in predicted risk for CVE– and for CVD+ men are presented in Figure 3. Calibration plots showing improvement in the prediction of 10-year risk of cardiovascular events for those CVE– and CVD+ men are shown in Figure 4.

A modified 10-year CVD risk calculator was derived using the original FRS variables (Table S1) and with the addition of hs-cTnI (Table S2). The risk associated with individual scores is shown in Tables S3 and S4. Hs-cTnI was independently associated with risk of cardiovascular events, even at concentrations considerably lower than the 99th percentile, with increasing hs-cTnI concentrations predicting elevated cardiovascular risk. Furthermore, hs-cTnI had a greater impact on the risk score compared with other covariates due to the wider range of points allocated, which allowed for a wider range of 10-year risk estimates (Tables S1 through S4).

Discussion

This is the first study to demonstrate that the addition of hs-cTnI to the FRS significantly improves the prediction of cardiovascular events in this cohort, and identifies a cohort of elderly men previously misclassified as high cardiovascular

Table 3. Regression Analysis for Comparison of Models

| Variable | Framingham Model | | Framingham Model Plus log(troponin) | |
|-------------------------|------------------|------|-------------------------------------|------|
| | β | SE | β | SE |
| log(age) | 5.134 | 2.03 | 3.042 | 2.05 |
| log(cholesterol) | 0.951 | 0.42 | 0.793 | 0.42 |
| log(HDL) | -0.414 | 0.28 | -0.395 | 0.28 |
| log(SBP), untreated | -0.727 | 0.60 | -1.105 | 0.59 |
| log(SBP), treated | 2.130 | 0.89 | 2.184 | 0.87 |
| Hypertension treated | | | | |
| No | 0.000 | | 0.000 | |
| Yes | 0.322 | 0.15 | 0.230 | 0.15 |
| Current smoker | | | | |
| No | 0.000 | | 0.000 | |
| Yes | 0.350 | 0.25 | 0.254 | 0.25 |
| Prior diabetes mellitus | | | | |
| No | 0.000 | | 0.000 | |
| Yes | 0.182 | 0.19 | 0.081 | 0.19 |
| log(troponin) | | | 0.619 | 0.10 |
| AIC | 3483.326 | | 3453.170 | |
| BIC | 3523.713 | | 3498.605 | |
| C | 0.588 | | 0.624 | |

AIC indicates Akaike Information Criterion; BIC, Bayesian Information Criterion; C, C-statistic; HDL, high-density lipoprotein; SBP, systolic blood pressure.

risk who had a lower risk of cardiovascular events over a 10-year period. There was a greater impact on the predicted risks for the men who did not experience a cardiovascular event than in men who did.

The FRS is unable to identify older adults with relatively low cardiovascular risk, as it attributes points based on age. Furthermore, the association between conventional risk factors such as hypertension and hyperlipidemia with CVD in older adults is not the same as it is for younger populations.^{3,4} The original FRS performs relatively poorly in older men, with a C-statistic of 0.588, found in both the

current study and an American study, compared with a C-statistic of 0.76 in the Framingham cohort.^{2,3} The addition of hs-cTnI to the model resulted in a C-statistic of 0.624 and an improvement in model fit (likelihood ratio test, $P < 0.001$).

Recently, an Australian study on hs-cTnI in older women with a mean age of 75 years and a Swedish study on hs-cTnI in men aged 70 years found that hs-cTnI was independently associated with cardiovascular events.^{6,18} Both studies also found that the addition of cTnI to the FRS may improve risk prediction.^{6,18} Using a cohort twice the size and a wider age range, our study supports the concept that hs-cTnI can aid in prognostic discrimination and, in addition, can significantly improve reclassification.

The ability to identify a group of older adults with a relatively low risk of cardiovascular events using hs-cTnI would allow more judicious use of preventative medications in this age group, thus avoiding side effects and drug interactions. There is currently insufficient evidence for statin use in older adults for primary prevention, with some studies showing a possible increase in mortality in this setting.^{25,26}

On the other hand, reclassification into a high-risk category may prompt clinicians to consider preventative therapies.^{10,13} In a randomized controlled trial of patients without CVD and a normal cholesterol, those with higher concentrations of hs-cTnI had a greater reduction in absolute risk of cardiovascular events while on rosuvastatin therapy.¹⁴ This was however, conducted in a relatively younger cohort.

Our study also establishes the 99th percentile of hs-cTnI using the Abbott Architect assay in this community-based cohort of men aged over 70 years. Various studies have published different results for the 99th percentile of hs-cTnI, which can be due to differences in reference population selection.²⁷ The 99th percentile for older men without a history of self-reported CVD in our study was 30.0 ng/L, which is similar to that reported in other studies of people from a wide range of age groups.^{28,29} In addition, there have been studies in presumably healthy and considerably younger men that have quoted slightly higher concentrations of between 33 and 36 ng/L using the same assay.³⁰⁻³³ However, the 25th percentile, median and 75th percentile

Table 4. Predicted Risk in Men Who Did Not Experience a Cardiovascular Event

| Framingham Risk Score | Framingham Risk Score Plus Troponin I | | | | Total |
|-----------------------|---------------------------------------|------------|------------|------------|------------|
| | 6% to 10% | 11% to 15% | 16% to 20% | >20% | |
| 6% to 10% | 0 (0.00) | 3 (0.26) | 0 (0.00) | 0 (0.00) | 3 (0.33) |
| 11% to 15% | 33 (2.87) | 62 (5.39) | 19 (1.65) | 10 (0.87) | 124 (13.8) |
| 16% to 20% | 18 (1.56) | 145 (12.6) | 132 (11.5) | 62 (5.39) | 357 (39.7) |
| >20% | 1 (0.09) | 16 (1.39) | 124 (10.8) | 274 (23.8) | 415 (46.2) |
| Total | 52 (5.78) | 226 (25.1) | 275 (30.6) | 346 (38.5) | 899 (100) |

Table 5. Predicted Risk in Men Who Experienced a Cardiovascular Event

| Framingham Risk Score | Framingham Risk Score Plus Troponin I | | | | Total |
|-----------------------|---------------------------------------|------------|------------|------------|------------|
| | 6% to 10% | 11% to 15% | 16% to 20% | >20% | |
| 6% to 10% | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| 11% to 15% | 3 (0.26) | 12 (1.04) | 5 (0.43) | 4 (0.35) | 24 (9.52) |
| 16% to 20% | 2 (0.17) | 21 (1.82) | 33 (2.87) | 24 (2.09) | 80 (31.7) |
| >20% | 0 (0.00) | 6 (0.52) | 29 (2.52) | 113 (9.8) | 148 (58.7) |
| Total | 5 (1.98) | 39 (15.5) | 67 (26.6) | 141 (56.0) | 252 (100) |

of 3.9, 5.3, and 7.4 ng/L, respectively, in our study is higher than 2.0, 3.2, and 4.6 ng/L or 1.5, 2.7, and 4.6 ng/L, respectively, in other studies in younger adults.^{13,31}

Some studies have found that elevations of hs-cTnI are commonly seen in older adults, independent of comorbidities.³⁴ As such, there is debate over whether older adults should have higher diagnostic thresholds for the diagnosis of acute myocardial infarction.^{35,36} Our findings demonstrate that the 99th percentile of hs-cTnI in healthy older men is comparable to that in healthy younger men.^{30–33} Taken together, these findings suggest that increasing cardiac troponin I concentrations may reflect concurrent morbidity or progressive myocardial impairment rather than a benign process associated with aging.⁶

Additionally, we found that hs-cTnI increased with age, comorbidities, and the presence of CVD. Although hs-cTnI was greater in current smokers compared with never smokers, as one may expect, this finding is in contrast with that from another large cohort study.³⁷ The complex relationship between smoking, hs-cTnI, and cardiovascular risk therefore requires further elucidation in subsequent studies.

The strengths of our study include the large population and wide age range for an older population. This study also includes a long period of follow-up, in excess of 10 years in older adults, which has not been previously reported. Moreover, the study had very robust data linkage ensuring that mortality and morbidity data are captured. HIMS benefited from an extensive initial recruitment process, as participants were invited from the electoral role, where enrollment to vote is compulsory in Australia. Furthermore, the study involved collection of very extensive baseline data from which to draw associations. However, further validation studies are required for our modified risk prediction model.

Limitations include that this cohort is predominantly white in origin, includes only men, and is located in a major metropolitan area. Our findings would need to be confirmed in other populations. Not all participants in the second wave of the HIMS had hs-cTnI measured, and all results are based on blood samples collected at a single point in time. It has previously been shown that dynamic changes in cardiac troponin are associated with dynamic changes in risk of CVD mortality, and serial measurements may play a future role in

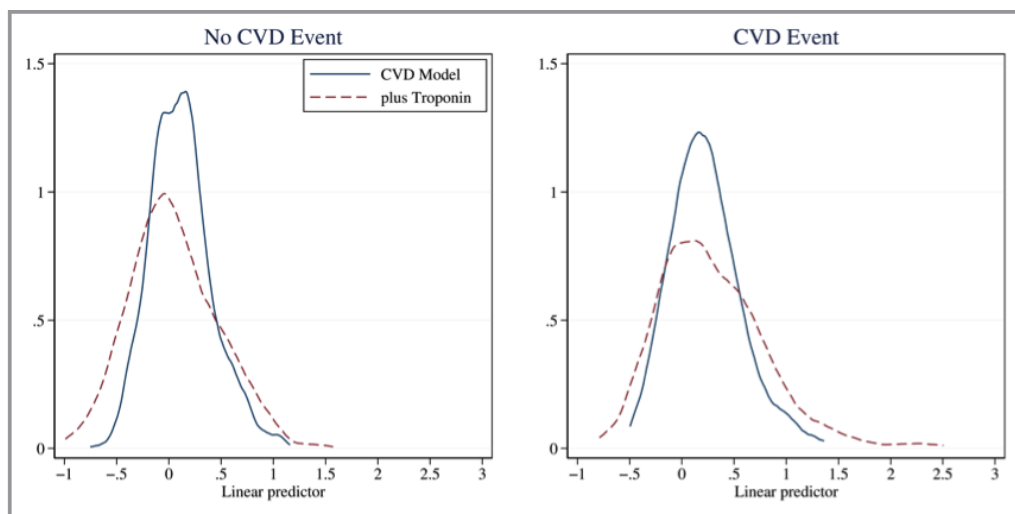


Figure 3. Density plots showing improvement in predicted risk after addition of high-sensitivity cardiac troponin I for men who did not experience a cardiovascular disease (CVD) event and for men who experienced a cardiovascular disease event during follow-up.

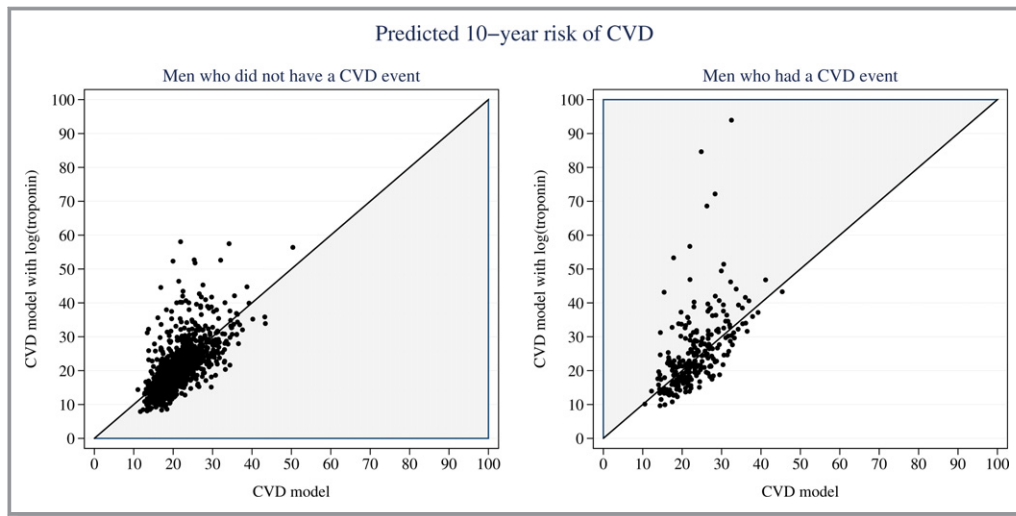


Figure 4. Calibration plots showing improvement in predicted risk after addition of high-sensitivity cardiac troponin I for men who did not experience a cardiovascular disease (CVD) event and for men who experienced a cardiovascular disease event during follow-up.

risk stratification.^{6,8,38} In addition, variations in hs-cTnI, such as that from analytical imprecision, may limit the utility of single hs-cTnI measurements for risk prediction and the performance of risk prediction tools that use hs-cTnI. In our laboratory, the coefficient of variation (analytical imprecision) for the hs-cTnI assay used is 10% at 6 ng/L.²²

We did not study the incremental benefit of adding high-sensitivity cardiac troponin T to the FRS in our cohort of patients. However, increased high-sensitivity cardiac troponin T levels, like hs-cTnI, have been associated with incident heart failure and cardiovascular mortality in older adults and could potentially add to current risk prediction scores in this cohort.⁸ In addition, the incremental benefit of other biomarkers such as N-terminal pro-brain-type natriuretic peptide and C-reactive protein was not studied.^{7,12,14} Furthermore, residual confounding due to unmeasured clinical and laboratory prognostic factors or random error are additional limitations of this study.

We conclude from this study of community-dwelling older men in Australia that the 99th percentile of hs-cTnI was comparable to that of younger healthy men seen in previous studies. Hs-cTnI was associated with 10-year cardiovascular events and provided incremental prognostic value when added to the FRS. The combined model especially aided in reclassification of individuals into a lower risk category and identifies a group of older adults at a relatively lower risk of cardiovascular events.

Acknowledgments

We acknowledge all the men who participated and the investigators of the original study. We also acknowledge the State Electoral

Commission; the Australian Bureau of Statistics; the Registrar General of Births, Deaths and Marriages; and The Data Linkage Unit of the Health Department of Western Australia. Furthermore, we acknowledge Abbott Diagnostics, who provided the high-sensitivity cardiac troponin I kits for the study but did not have any role in the analysis or presentation of the data.

Sources of Funding

The HIMS was supported by the National Health and Medical Research Council of Australia Project Grants 964145, 139093, 403963, and 455811, with additional funding from the National Heart Foundation and the West Australian Health Promotion Foundation (Healthway). The funding sources had no involvement in the planning, analysis, and writing of the paper.

Disclosures

None.

References

1. Australian Institute of Health and Welfare. Cardiovascular disease snapshot. 2018 Jul 24; Australian Institute of Health and Welfare: Cat. no. CVD 83. Available at: <https://www.aihw.gov.au/reports/heart-stroke-vascular-disease/cardiovascular-health-compendium/contents/how-many-australians-have-cardiovascular-disease>. Accessed January 20, 2019.
2. D'Agostino RS, Vasan R, Pencina M, Wolf P, Cobain M, Massaro J, Kannel W. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
3. Rodondi N, Locatelli I, Aujesky D, Butler J, Vittinghoff E, Simonsick E, Satterfield S, Newman AB, Wilson PW, Pletcher MJ, Bauer DC. Framingham risk score and alternatives for prediction of coronary heart disease in older adults. *PLoS One*. 2012;7:e34287.
4. de Ruijter W, Westendorp RGJ, Assendelft WJJ, Den Elzen WPJ, de Craen AJM, Le Cessie S, Gussekloo J. Use of Framingham Risk Score and new biomarkers

- to predict cardiovascular mortality in older people: population based observational cohort study. *BMJ*. 2009;338:a3083.
5. Apple FS, Sandoval Y, Jaffe AS, Ordóñez-Llanos J. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. *Clin Chem*. 2017;63:73–81.
 6. Eggers K, Venge P, Lindahl B, Lind L. Cardiac troponin I levels measured with a high-sensitive assay increase over time and are strong predictors of mortality in an elderly population. *J Am Coll Cardiol*. 2013;61:1906–1913.
 7. de Lemos J, Drazner M, Omland T, Ayers C, Khera A, Rohatgi A, Hashim I, Berry J, Das S, Morrow D, McGuire D. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304:2503–2512.
 8. deFilippi C, de Lemos J, Christenson R, Gottdiener J, Kop W, Zhan M, Seliger S. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA*. 2010;304:2494–2502.
 9. Neumann J, Havulinna A, Zeller T, Appelbaum S, Kunas T, Nikkari S, Jousilahti P, Blankenberg S, Sydow K, Salomaa V. Comparison of three troponins as predictors of future cardiovascular events—prospective results from the FINRISK and BiomaCaRE studies. *PLoS One*. 2014;9:e90063.
 10. Saunders J, Nambi V, de Lemos J, Chambless L, Virani S, Boerwinkle E, Hoogeveen R, Liu X, Astor B, Mosley T, Folsom A, Heiss G, Coresh J, Ballantyne C. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation*. 2011;123:1367–1376.
 11. Zhu K, Knuiman M, Divitini M, Murray K, Lim E, St John A, Walsh J, Hung J. High-sensitivity cardiac troponin I and risk of cardiovascular disease in an Australian population-based cohort. *Heart*. 2018;104:895–903.
 12. Willeit P, Welsh P, Evans J, Tschiederer L, Boachie C, Jukema J, Ford I, Trompet S, Stott D, Kearney P, Mooijaart S, Kiechl S, Di Angelantonio E, Sattar N. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. *J Am Coll Cardiol*. 2017;70:558–568.
 13. Blankenberg S, Salomaa V, Makarova N, Ojeda F, Wild P, Lackner K, Jørgensen T, Thorand B, Peters A, Nauck M, Petersmann A, Vartiainen E, Veronesi G, Brambilla P, Costanzo S, Iacoviello L, Lindem G, Yarnell J, Patterson C, Everett B, Ridker P, Kontto J, Schnabel R, Koenig W, Kee F, Zeller T, Kuulasmaa K; BiomaCaRE Investigators. Troponin I and cardiovascular risk prediction in the general population: the BiomaCaRE consortium. *Eur Heart J*. 2016;37:2428–2437.
 14. Everett B, Zeller T, Glynn R, Ridker P, Blankenberg S. High-sensitivity cardiac troponin I and B-type natriuretic Peptide as predictors of vascular events in primary prevention: impact of statin therapy. *Circulation*. 2015;131:1851–1860.
 15. Sinning C, Keller T, Zeller T, Ojeda F, Schluter M, Schnabel R, Lubos E, Bickel C, Lackner KJ, Diemert P, Munzel T, Blankenberg S, Wild PS. Association of high-sensitivity assayed troponin I with cardiovascular phenotypes in the general population: the population-based Gutenberg health study. *Clin Res Cardiol*. 2014;103:211–222.
 16. Kavsak PA, Xu L, Yusuf S, McQueen MJ. High-sensitivity cardiac troponin I measurement for risk stratification in a stable high-risk population. *Clin Chem*. 2011;57:1146–1153.
 17. Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Rosjo H, Saltyte Benth J, Maggioni A, Domanski MJ, Rouleau JL, Sabatine MS, Braunwald E. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2013;61:1240–1249.
 18. Lewis J, Lim W, Wong G, Abbs S, Zhu K, Lim E, Thompson P, Prince R. Association between high-sensitivity cardiac troponin I and cardiac events in elderly women. *J Am Heart Assoc*. 2017;6:e004174. DOI: 10.1161/JAHA.116.004174.
 19. Norman P, Flicker L, Almeida O, Hankey G, Hyde Z, Jamrozik K. Cohort profile: the Health in Men Study (HIMS). *Int J Epidemiol*. 2009;38:48–52.
 20. Yeap B, Alfonso H, Chubb S, Handelsman D, Hankey G, Almeida O, Gollidge J, Norman P, Flicker L. In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. *J Clin Endocrinol Metab*. 2013;99:E9–E18.
 21. Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
 22. Sawyer N, Blennerhassett J, Lambert R, Sheehan P, Vasikaran S. Outliers affecting cardiac troponin I measurement: comparison of a new high sensitivity assay with a contemporary assay on the Abbott ARCHITECT analyser. *Ann Clin Biochem*. 2014;51:476–484.
 23. Holman C, Bass A, Rosman D, Smith M, Semmens J, Glasson E, Brook E, Trutwein B, Rouse I, Watson C, de Klerk N, Stanley FJ. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. *Aust Health Rev*. 2008;32:766–777.
 24. Steyerberg EW, Vedder MM, Leening MJ, Postmus D, D'Agostino RB Sr, Van Calster B, Pencina MJ. Graphical assessment of incremental value of novel markers in prediction models: from statistical to decision analytical perspectives. *Biom J*. 2015;57:556–570.
 25. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+ year olds. *Age Ageing*. 2010;39:674–680.
 26. Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, Pressel SL, Blaum CS. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial. *JAMA Intern Med*. 2017;177:955–965.
 27. Koerbin G, Abhayaratna WP, Potter JM, Apple FS, Jaffe AS, Ravalico TH, Hickman PE. Effect of population selection on 99th percentile values for a high sensitivity cardiac troponin I and T assays. *Clin Biochem*. 2013;46:1636–1643.
 28. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, Wild P, Genth-Zotz S, Warnholtz A, Giannitsis E, Mockel M, Bickel C, Peetz D, Lackner K, Baldus S, Munzel T, Blankenberg S. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA*. 2011;306:2684–2693.
 29. Sandoval Y, Apple FS. The global need to define normality: the 99th percentile value of cardiac troponin. *Clin Chem*. 2014;60:455–462.
 30. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem*. 2012;58:1574–1581.
 31. Krintus M, Kozinski M, Boudry P, Lackner K, Lefevre G, Lennartz L, Lotz J, Manyasiak S, Shih J, Skadberg O, Chargui AT, Sypniewska G. Defining normality in a European multinational cohort: critical factors influencing the 99th percentile upper reference limit for high sensitivity cardiac troponin I. *Int J Cardiol*. 2015;187:256–263.
 32. Aw TC, Phua SK, Tan SP. Measurement of cardiac troponin I in serum with a new high-sensitivity assay in a large multi-ethnic Asian cohort and the impact of gender. *Clin Chim Acta*. 2013;422:26–28.
 33. Omland T, de Lemos J, Holmen O, Dalen H, Benth J, Nygård S, Hveem K, Røsjø 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.
 34. Webb I, Yam S, Cooke R, Aitken A, Larsen P, Harding S. Elevated baseline cardiac troponin levels in the elderly—another variable to consider? *Heart Lung Circ*. 2014;24:142–148.
 35. Rains M, Laney C, Bailey A, Campbell C. Biomarkers of acute myocardial infarction in the elderly: troponin and beyond. *Clin Interv Aging*. 2014;9:1081–1090.
 36. Korley F, Jaffe A. Preparing the United States for high-sensitivity cardiac troponin assays. *J Am Coll Cardiol*. 2013;61:1753–1758.
 37. Lyngbakken MN, Skranes JB, de Lemos JA, Nygård S, Dalen H, Hveem K, Rosjo H, Omland T. Impact of smoking on circulating cardiac troponin I concentrations and cardiovascular events in the general population: the HUNT Study (Nord-Trøndelag Health Study). *Circulation*. 2016;134:1962–1972.
 38. McEvoy J, Chen Y, Ndumele C, Solomon S, Nambi V, Ballantyne C, Blumenthal R, Coresh J, Selvin E. Six-year change in high-sensitivity cardiac troponin T and risk of subsequent coronary heart disease, heart failure, and death. *JAMA Cardiol*. 2016;1:519–528.

SUPPLEMENTAL MATERIAL

Table S1. CVD Model Scoring Matrix.

| Points | Age | Total Cholesterol | HDL | Current Smoker | Prior Diabetes | SBP Not Treated | SBP Treated |
|---------------|------------|--------------------------|------------|-----------------------|-----------------------|------------------------|--------------------|
| -5 | | | | | | | <120 |
| -4 | | | | | | 160+ | |
| -3 | | | 60+ | | | | |
| -2 | | | | | | 140-159 | 120-129 |
| -1 | | | 50-59 | | | 130-139 | |
| 0 | 70-74 | <160 | 45-49 | No | No | 120-129 | 130-139 |
| 1 | | | 35-44 | | | <120 | |
| 2 | | | <35 | | | | |
| 3 | | 160-199 | | | Yes | | 140-159 |
| 4 | | | | | | | |
| 5 | 74-79 | | | Yes | | | |
| 6 | | 200-239 | | | | | |
| 7 | | | | | | | |
| 8 | | | | | | | |
| 9 | | 240-279 | | | | | 160+ |
| 10 | 80+ | 280+ | | | | | |
| 11 | | | | | | | |

Table S2. CVD plus Troponin Scoring Matrix.

| Points | Age | Total Cholesterol | HDL | Current Smoker | Prior Diabetes | SBP Not Treated | SBP Treated | Troponin |
|--------|-------|-------------------|-------|----------------|----------------|-----------------|-------------|----------|
| -12 | | | | | | | <120 | |
| -11 | | | | | | | | |
| -10 | | | | | | 160+ | | |
| -9 | | | | | | | | |
| -8 | | | | | | | 120-129 | |
| -7 | | | | | | | | |
| -6 | | | | | | | | |
| -5 | | | 60+ | | | 140-159 | | |
| -4 | | | | | | | 130-139 | |
| -3 | | | | | | | | |
| -2 | | | | | | 130-139 | | |
| -1 | | | 50-59 | | | | | |
| 0 | 70-74 | <160 | 45-49 | No | No | 120-129 | | <2 |
| 1 | | | | | | | | |
| 2 | | | 35-44 | | Yes | <120 | 140-159 | |
| 3 | | | | | | | | |
| 4 | | | <35 | | | | | |
| 5 | 74-79 | 160-199 | | | | | | |
| 6 | | | | Yes | | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | 2-2.9 |
| 9 | | 200-239 | | | | | | |
| 10 | 80+ | | | | | | | |
| 11 | | | | | | | | |
| 12 | | 240-279 | | | | | 160+ | |
| 13 | | | | | | | | 3-3.9 |
| 14 | | 280+ | | | | | | |
| 15 | | | | | | | | |
| 16 | | | | | | | | |
| 17 | | | | | | | | 4-4.9 |
| 20 | | | | | | | | 5-5.9 |
| 22 | | | | | | | | 6-6.9 |
| 24 | | | | | | | | 7-7.9 |
| 26 | | | | | | | | 8-8.9 |
| 28 | | | | | | | | 9-9.9 |
| 39 | | | | | | | | 10+ |

Table S3. CVD Model Scores and associated risk estimates.

| CVD Model Score | 10-year Risk |
|-----------------|--------------|
| -7 | 0.09 |
| -5 | 0.10 |
| -4 | 0.11 |
| -3 | 0.12 |
| -2 | 0.12 |
| -1 | 0.13 |
| 0 | 0.14 |
| 1 | 0.15 |
| 2 | 0.16 |
| 3 | 0.17 |
| 4 | 0.18 |
| 5 | 0.19 |
| 6 | 0.21 |
| 7 | 0.22 |
| 8 | 0.23 |
| 9 | 0.25 |
| 10 | 0.26 |
| 11 | 0.28 |
| 12 | 0.29 |
| 13 | 0.31 |
| 14 | 0.33 |
| 15 | 0.35 |
| 16 | 0.37 |
| 17 | 0.39 |
| 18 | 0.41 |
| 19 | 0.43 |
| 20 | 0.45 |
| 21 | 0.48 |
| 22 | 0.50 |
| 24 | 0.55 |

Table S4. CVD plus Troponin Model Scores and associated risk estimates.

| CVD plus Troponin Model Score | 10-Year Risk |
|-------------------------------|--------------|
| -3 | 0.07 |
| -2 | 0.07 |
| 0 | 0.08 |
| 1 | 0.08 |
| 2 | 0.08 |
| 3 | 0.09 |
| 4 | 0.09 |
| 5 | 0.09 |
| 6 | 0.10 |
| 7 | 0.10 |
| 8 | 0.11 |
| 9 | 0.11 |
| 10 | 0.11 |
| 11 | 0.12 |
| 12 | 0.12 |
| 13 | 0.13 |
| 14 | 0.13 |
| 15 | 0.14 |
| 16 | 0.14 |
| 17 | 0.15 |
| 18 | 0.15 |
| 19 | 0.16 |
| 20 | 0.17 |
| 21 | 0.17 |
| 22 | 0.18 |
| 23 | 0.19 |
| 24 | 0.19 |
| 25 | 0.20 |
| 26 | 0.21 |
| 27 | 0.22 |
| 28 | 0.22 |
| 29 | 0.23 |
| 30 | 0.24 |
| 31 | 0.25 |
| 32 | 0.26 |
| 33 | 0.27 |
| 34 | 0.28 |
| 35 | 0.29 |
| 36 | 0.30 |
| 37 | 0.31 |
| 38 | 0.32 |
| 39 | 0.33 |
| 40 | 0.34 |
| 41 | 0.35 |
| 42 | 0.36 |
| 43 | 0.37 |
| 44 | 0.38 |
| 45 | 0.40 |

| | |
|----|------|
| 46 | 0.41 |
| 47 | 0.42 |
| 48 | 0.44 |
| 49 | 0.45 |
| 50 | 0.46 |
| 51 | 0.48 |
| 52 | 0.49 |
| 53 | 0.50 |
| 55 | 0.53 |
| 56 | 0.55 |
| 58 | 0.58 |
| 59 | 0.59 |
| 60 | 0.61 |
| 62 | 0.64 |
| 63 | 0.65 |
| 65 | 0.68 |
| 67 | 0.71 |