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META-ANALYSIS

Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium

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Aims Our aims were to evaluate the distribution of troponin I concentrations in population cohorts across Europe, to characterize the association with cardiovascular outcomes, to determine the predictive value beyond the variables used in the ESC SCORE, to test a potentially clinically relevant cut-off value, and to evaluate the improved eligibility for statin therapy based on elevated troponin I concentrations retrospectively.

Methods and results Based on the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) project, we analysed individual level data from 10 prospective population-based studies including 74 738 participants. We investigated the value of adding troponin I levels to conventional risk factors for prediction of cardiovascular disease by calculating measures of discrimination (*C*-index) and net reclassification improvement (NRI). We further tested the clinical implication of statin therapy based on troponin concentration in 12 956 individuals free of cardiovascular disease in the JUPITER study. Troponin I remained an independent predictor with a hazard ratio of 1.37 for cardiovascular mortality, 1.23 for cardiovascular disease, and 1.24 for total mortality. The addition of troponin I information to a prognostic model for

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cardiovascular death constructed of ESC SCORE variables increased the C-index discrimination measure by 0.007 and yielded an NRI of 0.048, whereas the addition to prognostic models for cardiovascular disease and total mortality led to lesser C-index discrimination and NRI increment. In individuals above 6 ng/L of troponin I, a concentration near the upper quintile in BiomarCaRE (5.9 ng/L) and JUPITER (5.8 ng/L), rosuvastatin therapy resulted in higher absolute risk reduction compared with individuals <6 ng/L of troponin I, whereas the relative risk reduction was similar.

Conclusion In individuals free of cardiovascular disease, the addition of troponin I to variables of established risk score improves prediction of cardiovascular death and cardiovascular disease.

Keywords High-sensitivity assayed troponin I • Cardiovascular risk • Mortality • Biomarker for Cardiovascular Risk Assessment in Europe • MONICA Risk Genetics Archiving and Monograph

Introduction

Troponin is a cardiac-specific structural protein and guidelines recommend its use for the diagnosis and management of acute coronary syndrome.[1] Newly established technologies allow precise measurement of low circulating troponin concentrations in the general population.[2] These concentrations may directly reflect various pathophysiological processes including cardiac myocyte necrosis and apoptosis. They further correlate with the prevalence of cardiovascular risk factors, metabolic disorders, and cardiac hypertrophy or dysfunction.[3,4] Assessment of circulating troponin concentrations using a robust, highly sensitive assay might therefore be suitable to predict first and subsequent adverse events.[4–13] Broadly comparable scoring systems for risk assessment have been developed in Europe.[14,15] Whether the measurement of troponin in addition to those variables contained in the scores[14–16] is useful for cardiovascular risk assessment remains to be elucidated.

Using the harmonized database and biobank of the Biomarker for Cardiovascular Risk Assessment in Europe (BiomarCaRE) project (FP7/2007–2013),[17] we centrally analysed individual troponin I concentrations by a robust, highly sensitive assay in 74 738 individuals of 10 BiomarCaRE population-based cohorts to quantify the improvement in risk prediction in a prospective setting. We further measured troponin I concentrations in 12 956 participants from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)[8,18] trial to globally validate the findings and to evaluate retrospectively how the troponin I concentrations might better guide the eligibility for statin therapy.

Overall, we (1) evaluated the distribution of troponin I concentrations assayed by a highly sensitive method in population cohorts across Europe, (2) characterized the association with cardiovascular mortality, first non-fatal and fatal cardiovascular events, and overall mortality, (3) determined the predictive value beyond the variables used in the SCORE project developed by the European Society of Cardiology (ESC), (4) tested a potentially clinically relevant cut-off value, and (5) evaluated the improved eligibility for statin therapy based on elevated troponin I concentrations retrospectively.

Methods

Study overview

Details of the BiomarCaRE project have been described previously.[17] BiomarCaRE capitalizes on the MORGAM (MONICA Risk Genetics Archiving and Monograph) Project,[19] which harmonized data from almost 30 population-based studies in the MORGAM/BiomarCaRE Data Centre in Helsinki.

The current study was designed and analysed at the BiomarCaRE Coordinating Center in Hamburg. Troponin I had been centrally determined for all studies, including JUPITER, in the MORGAM/BiomarCaRE laboratory. All participating studies have been approved by local ethics review committees.

Study cohorts

Overall, the cohort consisted of 10 population-based studies involving 93 993 individuals, among them 74 738 participants with troponin I measurements from five European countries. The individual cohorts were the MONICA Brianza study, the Caerphilly Prospective study, the FINRISK study, the Gutenberg Health Study (GHS), the DanMONICA study, the Kooperative Gesundheitsforschung in der Region Augsburg (KORA) study, the Moli-Sani Project, the Prospective Epidemiological Study of Myocardial Infarction from Belfast (PRIME), the Scottish Heart Health Extended Cohort Study, and the Study of Health in Pomerania (SHIP). Each cohort is based on a well-defined population (Supplementary material online, *Table S1*). Full details of when the baseline data were collected are provided in Supplementary material online, *Figure S1*. Cohort descriptions are provided in Supplementary material online, *Box S1*. The final dataset to test the hypothesis that troponin I adds to risk prediction, comprised 74 738 participants. The harmonized variables included baseline information on smoking status, body mass index (BMI), systolic blood pressure, history of diabetes, total- and high-density lipoprotein cholesterol, history of myocardial infarction (MI), and history of stroke, and anti-hypertensive medication, as well as high-sensitivity C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR, CKD-EPI formula).[20] Subjects with a systolic blood pressure >140 mmHg and/or anti-hypertensive medication were classified as hypertensive.

Study outcome

The outcome measures in our analysis were (1) cardiovascular mortality, (2) the first occurrence of a major cardiovascular event, and (3) overall mortality. The definition of cardiovascular mortality was similar to that of the ESC described by Conroy *et al.*[14] but based in the data harmonized in the MORGAM Project.[15] First major cardiovascular events include the first fatal or non-fatal definite or possible MI or coronary death, unstable angina, cardiac revascularization, ischaemic stroke, and unclassifiable death. Overall mortality was defined as mortality due to any cause during the follow-up time. More details of the event classification are provided in Supplementary material online and the MORGAM Manual.[15]

The risk of cardiovascular mortality, cardiovascular disease, and total mortality was calculated using variables of the Systematic COronary Risk Evaluation—SCORE developed by the ESC. Applicability of this score is described by Perk *et al.*[15] and Conroy *et al.*[14]

To predict non-fatal or fatal cardiovascular events, we included only those participants in the analyses who did not have a prior history of major cardiovascular disease such as MI, hospitalized unstable angina, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or ischaemic or haemorrhagic stroke.

To enable potential translation into the clinical situation, we recommend establishing a troponin I cut-off. We selected a cut-off value of 6 ng/L as it approximates the upper quintile of 5.9 ng/L of the overall distribution in the aggregated BiomarCaRE population. To examine how the cut-off >6 ng/L improves risk prediction, we computed HRs, *C*-statistics, and net reclassification improvement for all endpoints.

To validate our findings and test a more individualized eligibility for statin therapy, we estimated the effects of statin therapy among individuals with high (>6 ng/L) and lower (≤6 ng/L) troponin I concentrations using the database of the globally conducted JUPITER trial. The selection of 6 ng/L was justified as it approximates the upper quintile in BiomarCaRE (5.9 ng/L) and JUPITER (5.8 ng/L). The design and results of the JUPITER trial are described in Supplementary material online, *Box S1*, and in detail elsewhere.[8,18]

Laboratory procedures

Serum troponin I was determined in the BiomarCaRE core laboratory using a highly sensitive troponin I immunoassay (Abbott Diagnostics, USA, ARCHITECT i2000SR). The limit of detection for the assay was 1.9 ng/L (range 0–50 000 ng/L). The assay had a 10% coefficient of variation at a concentration of 5.2 ng/L. The high-sensitivity assayed troponin I is denoted as 'troponin I' during the course of the manuscript. The study-specific intra- and inter-assay coefficients of variation are described in Supplementary material online, *Table S2*. N-terminal pro-B-type natriuretic peptide levels were measured on the ELECSYS 2010 and the Cobas e411 using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics). The analytical range is 5–35.000 ng/L. C-reactive proteins were measured with the routine laboratory using an Abbott Architect c8000 system and the CRP Vario immunoassay.

Statistical methods

Initial descriptive associations between baseline variables and troponin I were assessed using linear mixed models or ordinary linear models with the cubic root of troponin I as the dependent variable depending on whether the association was being examined in the overall BiomarCaRE cohort or in a single cohort. To measure a standardized association between troponin I and other baseline variables, we used a partial correlation coefficient.[21] To visualize these associations, an effect plot of a model including linear, quadratic terms, and sex interactions was produced using the methods of Fox.[22]

Survival curves for cardiovascular disease events, cardiovascular mortality, and overall mortality were computed according to fifths of the troponin distribution. Quintiles were computed in the overall BiomarCaRE cohort using linear quantile mixed models[23,24] with troponin I as the dependent variable. These models contained no predictors, just an intercept, fixed, and random. The latter was allowed to vary between cohorts. The upper quintile was 5.9 ng/L.

Sex- and cohort-stratified Cox proportional hazards models for cardiovascular disease events, cardiovascular mortality, and overall mortality were computed using the individual-level data from the available cohorts. For these analyses, troponin I was used after applying the cubic root transformation, categorized using quintiles as defined in the overall BiomarCaRE cohort, and using the cut-off of 6 ng/L which approximates the upper quintile of 5.9 ng/L. The Cox models for all three considered endpoints were adjusted for the SCORE[14,15] variables (systolic blood pressure, total cholesterol, smoking status, sex as strata, and age as time scale). Additional models exchanging troponin I with CRP, NT-proBNP, and eGFR were also computed. C-reactive protein and NT-proBNP were log-transformed for these analyses.

The C-index[25,26] and the net reclassification improvement (NRI)[27–29] were used to quantify the added predictive value of troponin I beyond that from a model including the variables in SCORE. This was repeated exchanging troponin I with CRP, NT-proBNP, and eGFR. For these analyses, the 10-year event probabilities were computed using a Weibull curve fitted over age and adjusted by the linear predictor of the estimated Cox model. For the computation of C-indices and NRI, the follow-up times were censored at 10 years. Ten-fold cross validation was used to control for the over-optimism of calculating performance measures on the same dataset from which the models were computed. The risk categories used for the NRI analysis were <1%, 1 to <5%, 5 to <10%, and ≥10%[15] for cardiovascular mortality, cardiovascular disease, and overall mortality. A version of NRI appropriate for survival analyses was computed using the Kaplan–Meier method.[28] The overall NRI does not represent a proportion and is therefore reported as a decimal number between −2 and 2 rather than a percentage, as recommended by Leening *et al.*[29] Differences in *C*-statistics (with 95% CIs) after the addition of troponin I to the model consisting of cardiovascular risk factors were computed using the method described by Antolini *et al.*[30] Cox regressions, *C*-indices, and NRIs described above were also computed for the age groups <45, 45–54, 55–64, and ≥65 years at baseline.

To assess the calibration of the models, we used an extension of the Hosmer–Lemeshow test for survival analyses proposed by Demler *et al.*[31] Tenths of the risk distribution were used.

A two-sided *P*-value of <0.05 was considered statistically significant. All statistical methods were implemented in R statistical software version 3.2.1[32] (www.R-project.org). For more detailed statistical description, please see Supplementary material online, Statistical methods.

Results

Demographic characteristics of the study population

The characteristics of the BiomarCaRE study participants are provided in *Table 1*. Overall, the study comprised 49 104 (52.2%) men and 44 889 (47.8%) women. Mean age at baseline was 52.2 (interquartile range 17.8) years, the age-range was 20–99 years. The median follow-up time was 13.8 years for cardiovascular mortality and cardiovascular disease events and 12.1 years for overall mortality (maximum of 28 years of follow-up). Of the participants, 4516 (5.7%) died of cardiovascular causes, 7722 (10.3%) had their first cardiovascular event, and 12 688 (13.5%) died from any cause. The prevalence of daily smokers at baseline was 26.7%. 42.1% had hypertension and 5% diabetes.

Distribution of troponin I and its association with cardiovascular risk factors and subclinical phenotypes

Troponin I was determined in 74 738 participants. Comparative information among individuals with and without troponin I measurements is provided in Supplementary material online, *Table S3*. The

Table 1 Baseline characteristics of the study population

Characteristics	
Number of cohorts, *n*	10
Number of individuals, *n*	93 993
Years of baseline examinations (years)	1982–2012
Men, *n* (%)	49 104 (52.2)
Women, *n* (%)	44 889 (47.8)
Age at baseline examination (years)	52.2 (42.9, 60.7)
Cardiovascular risk factors	
Daily smoker, *n* (%)	24 828 (26.7)
Diabetes, *n* (%)	4655 (5.0)
Hypertension[a], *n* (%)	39 227 (42.1)
Body-mass-index (kg/m^2)	26.3 (23.6, 29.4)
Systolic blood pressure (mmHg)	132.0 (120.0, 147.0)
Total cholesterol (mmol/L)	5.7 (5.0, 6.5)
HDL cholesterol (mmol/L)	1.4 (1.2, 1.7)
Medication	
Anti-hypertensive, *n* (%)	17 682 (19.0)
Troponin	
Information on troponin I, *n* (%)	74 738 (79.5)
Troponin I (ng/L)	2.7 (1.5, 4.6)
Other biomarkers	
CRP (mg/L)	1.5 (0.7, 3.1)
NT-proBNP (pg/mL)	49.7 (25.8, 93.9)
eGFR (Crea) (mL/min/1.73 m^2)	93.7 (82.4, 103.5)
Endpoints	
Cardiovascular mortality, *n* (%)	4516 (5.7)
Cardiovascular disease, *n* (%)	7722 (10.3)
Total mortality, *n* (%)	12 688 (13.5)

Baseline characteristics are presented as absolute and relative frequencies for categorical variables, and quartiles for continuous variables as well as ranges in years for years of baseline examinations.
Troponin I measured by a high-sensitivity assay.
[a]Hypertension was defined as anti-hypertensive medication and/or systolic RR > 140 mmHg.

median value of troponin I was 2.7 ng/L, the upper quintile limit was calculated at 5.9 ng/L. The distribution of troponin I concentrations among the overall population is displayed in Supplementary material online, *Figure S2*. Detailed distributions of troponin I for each cohort are outlined in Supplementary material online, *Figure S3* and *Table S1*.

In age-adjusted models the cube root of troponin I was higher in males than in females (regression coefficient 0.213, $P < 0.001$) and in individuals with diabetes than in those without diabetes (coefficient 0.106, $P < 0.001$). It increased in a non-linear fashion with systolic blood pressure in the overall BiomarCaRE cohort, and—as assessed in GHS only—with left ventricular mass and the extent of carotid atherosclerosis (each $P < 0.001$). Furthermore, troponin I decreased with eGFR, assessed in the overall BiomarCaRE cohort (Supplementary material online, *Figure S4*). Overall, associations of troponin I with cardiovascular risk factors and phenotypes are only moderate, with the highest partial correlations observed for left ventricular mass (females $r = 0.13$, males $r = 0.24$), carotid plaque (females $r = 0.10$, males $r = 0.11$), and eGFR (females $r = 0.08$, males $r = 0.14$) (Supplementary material online, *Figure S4* and in 'Measuring and definition of phenotypes in Gutenberg Health Study').

Troponin I concentrations and association with cardiovascular outcomes and all-cause mortality

Figures 1 and *2* display unadjusted survival curves and fully adjusted hazard ratios across fifths of the troponin I distribution indicating strong associations with cardiovascular mortality, first cardiovascular event, and overall mortality. An approximately doubling of risk was observed across increasing fifths. Individuals in the top fifths of the troponin I distribution compared with the bottom fifth had a 160% increase in mortality from cardiovascular causes (HR 2.60, 95% CI 2.29–2.94; $P < 0.001$), 92% increase in risk for a first cardiovascular event (HR 1.92, 95% CI 1.76–2.10; $P < 0.001$), and a 63% increase in the risk of overall mortality (HR 1.63, 95% CI 1.53–1.75; $P < 0.001$). Hazard ratios for cardiovascular mortality, cardiovascular disease, and overall mortality were broadly similar in all subgroups (Supplementary material online, *Figure S5*). The association between troponin I (treated as continuous variable) and the three outcome measures according to each cohort is displayed in Supplementary material online, *Figure S6*.

Troponin I and prediction of cardiovascular mortality, cardiovascular disease, and overall mortality

The addition of troponin I to variables of the ESC SCORE for prediction of cardiovascular mortality (*C*-index of 0.84 with 95% CI 0.82–0.86) led to an increment in the *C*-index of 0.007 with 95% CI 0.005–0.009. The addition of troponin I in the overall cohort to a prognostic model for first cardiovascular events and total mortality (*C*-index of 0.80 with 95% CI 0.79–0.81 for both events) increased the *C*-index by 0.004 with 95% CI 0.003–0.005 for cardiovascular disease and the *C*-index by 0.003 with 95% CI 0.002–0.004 for total mortality (*Table 2*). After stratification according to decades of age, the addition of troponin I led to a greater incremental risk prediction with rising age for all three investigated endpoints: 0.010 with 95% CI 0.006–0.014 for cardiovascular mortality and even 0.010 with 95% CI 0.008–0.013 for total mortality, and 0.018 with 95% CI 0.012, 0.024 for first cardiovascular events (*Table 2*). Most interestingly, baseline *C*-indices decreased with increasing age suggesting that the inclusion of additional variables such as troponin I become more valuable over the life time.

The magnitude of an incremental effect achieved by the inclusion of troponin I into the models is comparable with that obtained from the separate addition of established cardiovascular risk factors, although this varies between prediction of cardiovascular death and CVD risk prediction (Supplementary material online, *Table S4*).

The *C*-statistics for each biomarker including troponin I, CRP, NT-proBNP, and eGFR (CKD-EPI formula) when added to the

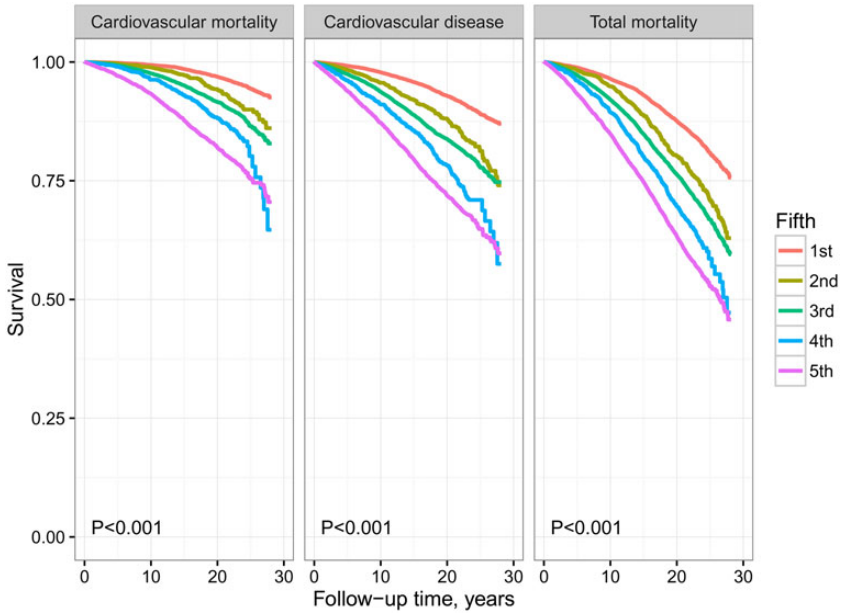

Figure 1 Survival curves according to fifths of the troponin I distribution in the study population. The *P*-value given in the survival curves is for the log-rank test. The troponin I quintiles, computed in the overall population via linear quantile mixed models, are 2.5, 2.8, 5.4, and 5.9 ng/L. The number of cohorts contributing to the figure decreases gradually over the 28 years, and includes only the Glostrup cohort at the end of follow-up. The number of persons at risk at 27 years of the follow-up according to troponin I fifths in increasing order is 1288, 162, 669, 30, 155 for cardiovascular mortality and total mortality, and 1201, 145, 601, 26, 136 for cardiovascular disease.

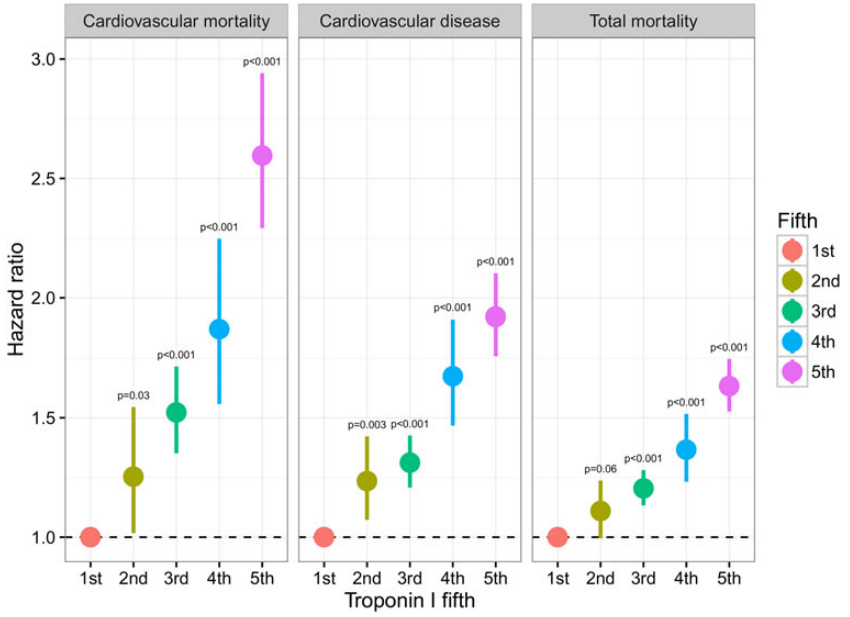

Figure 2 Hazard ratios according to fifths of the troponin I distribution in the study population. The troponin I quintiles, computed in the overall population via linear quantile mixed models, are 2.5, 2.8, 5.4, and 5.9 ng/L. The hazard ratios come from Cox models adjusted for variables of the ESC SCORE (cardiovascular mortality, total mortality) and ACC/AHA score (cardiovascular disease). Age was used as the time scale. The models were stratified by sex and cohort. ns stands for non-significant ($P \geq 0.05$), *$0.01 \leq P < 0.05$, **$0.001 \leq P < 0.01$, ***$0.0001 \leq P < 0.001$, and ****$P < 0.0001$.

Table 2 Changes in *C*-statistics for 10-year risk prediction of cardiovascular mortality and cardiovascular disease and total mortality endpoints after adding of continuous troponin I to established risk scores in the overall cohort and according to age groups

	ESC SCORE *C*-index (95% CI)	ESC SCORE *C*-index difference (95% CI)	*P*-value
Cardiovascular mortality			
All	0.84 (0.82, 0.86)	0.007 (0.005, 0.009)	<0.001
<45	0.83 (0.75, 0.91)	0.002 (−0.003, 0.007)	0.50
45–54	0.75 (0.71, 0.79)	0.014 (0.006, 0.021)	<0.001
55–64	0.75 (0.72, 0.77)	0.010 (0.005, 0.015)	<0.001
≥65	0.72 (0.69, 0.75)	0.010 (0.006, 0.014)	<0.001
Cardiovascular disease			
All	0.80 (0.79, 0.81)	0.004 (0.003, 0.005)	<0.001
<45	0.83 (0.79, 0.87)	0.001 (−0.002, 0.004)	0.66
45–54	0.74 (0.72, 0.77)	0.006 (0.002, 0.009)	<0.001
55–64	0.69 (0.67, 0.71)	0.007 (0.004, 0.009)	<0.001
≥65	0.64 (0.62, 0.67)	0.018 (0.012, 0.024)	<0.001
Total mortality			
All	0.80 (0.79, 0.81)	0.003 (0.002, 0.004)	<0.001
<45	0.73 (0.69, 0.76)	0.000 (−0.001, 0.000)	0.32
45–54	0.70 (0.67, 0.72)	0.004 (0.001, 0.007)	<0.0024
55–64	0.68 (0.66, 0.70)	0.008 (0.005, 0.011)	<0.001
≥65	0.67 (0.66, 0.69)	0.010 (0.008, 0.013)	<0.001

The ESC SCORE variables were used to adjust the models. *C*-index difference means the difference to the 'base model' where troponin I was not used. Age is used as the time scale of the Cox models (so they are implicitly adjusted for age). A Weibull baseline hazard was used to compute the event probabilities (from the Cox models). These (10 years) event probabilities are used to compute the *C*-indices.

ESC SCORE are shown in Supplementary material online, *Table S4*. We observed similar performance of each biomarker.

Examining C-statistics for prediction at 1, 5, and 10 years of the follow-up, the decrease in *C*-indices regarding cardiovascular disease endpoint could be noticed for each biomarker (Supplementary material online, *Figure S7*).

Calibration of the Cox models including troponin I is shown in the Supplementary material online, *Figure S8*. No major miscalibration could be observed in the plots and the Hosmer–Lemeshow test for cardiovascular mortality showed no significant deviation between predicted and observed cardiovascular mortality ($P = 0.094$, $\chi^2 = 13.6$), whereas the test was formally significant for cardiovascular disease ($P < 0.001$, $\chi^2 = 31.2$ and overall mortality ($P < 0.001$, $\chi^2 = 34.3$).

Reclassification analyses for the addition of troponin I to a model consisting of ESC SCORE variables are presented in *Figure 3* and *Table 3*. The addition of troponin I to the ESC score for cardiovascular mortality led to an NRI of 0.048 (95% CI 0.030–0.066), 0.038 (95% CI 0.020–0.056) for cases and 0.010 (95% CI 0.008–0.012) for non-cases. In particular, in individuals above the age of 65 years, the NRI was 0.039 (95% CI from 0.020–0.059). The addition of troponin I to the ESC SCORE algorithm produced an NRI of 0.017 (95% CI from 0.008–0.025), 0.010 (95% CI 0.002–0.018) for cases and 0.006 (95% CI 0.005–0.008) for non-cases for cardiovascular disease and an NRI of 0.013 (95% CI from 0.007–0.020), 0.005 (95% CI −0.001 to 0.011) for cases, and 0.008 (95% CI 0.007–0.010) for non-cases for total mortality. Reclassification tables showing estimates of the expected number of reclassifications per risk category for cases and non-cases are provided in *Table 3*.

Association and prediction above the upper quintile

The strong improvement of risk prediction for troponin I concentration above 6 ng/L could be demonstrated for cardiovascular mortality, yielding an HR of 1.87 (95% CI 1.72–2.03; $P < 0.001$), *C*-index difference of 0.010 (95% CI 0.007–0.012; $P < 0.001$), and NRI of 0.0743 (95% CI 0.0487–0.0999), 0.061 (95% CI from 0.036–0.086), for cases and 0.013 (95% CI 0.011–0.016) for non-cases. Detailed results for cardiovascular disease and overall mortality endpoints are also displayed in Supplementary material online, *Table S5*.

Troponin I, statin therapy, and outcome

To identify subjects with potentially improved eligibility for statin therapy based on elevated troponin I, we assessed the risk reduction by rosuvastatin in the JUPITER trial according to troponin I levels below and above 6 ng/L, a level, which is near the upper troponin I quintile of 5.8 ng/L achieved in this trial.

Similar to the BiomarCaRE population, individuals with troponin I concentrations above that level had an increased risk of cardiovascular disease (HR = 1.93, 95% CI 1.31–2.84; $P < 0.0008$) and overall mortality (HR = 2.25, 95% CI 1.60–3.15; $P < 0.001$). A formal

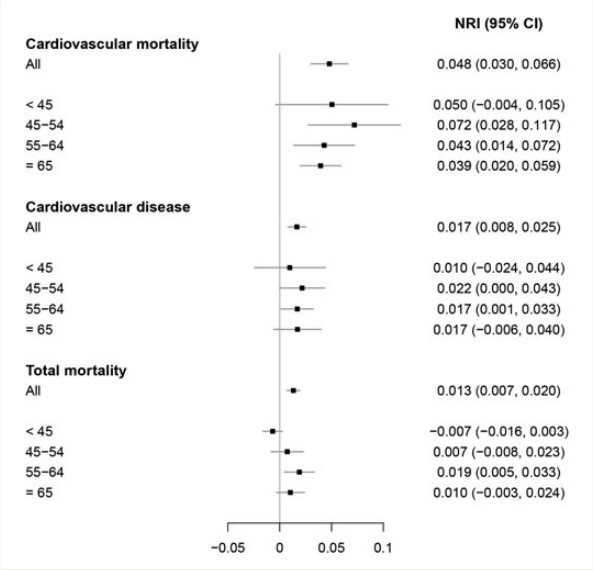

Figure 3 Net reclassification improvement of 10-year risk prediction by troponin I over model with variables used in the ESC SCORE (cardiovascular mortality, total mortality, and cardiovascular disease) in the overall cohort and according to age groups. The risk categories used are <1%, 1 to <5%, 5 to <10%, and ≥10%. Net reclassification improvement is presented as a number with a theoretical range between −2 and 2.

test for interaction showed that the relative risk reduction for cardiovascular events and overall mortality in those receiving rosuvastatin was similar in both groups, whereas the absolute risk reduction for cardiovascular events and mortality was higher in those individuals with troponin I concentration >6 ng/L (*Table 4*).

Discussion

Based upon harmonized individual level data and a centrally standardized troponin I measurement in 74 738 individuals from population-based studies, our analyses suggest that the addition of troponin I to conventional risk factors improves risk prediction in particular for cardiovascular death as well as any first cardiovascular event and overall mortality in the general population. The upper quintile of troponin I in the study population corresponding to 6 ng/L might provide a clinically applicable concentration to identify individuals at high risk for cardiovascular death.

Clinical implications of troponin I measurements in apparently healthy subjects at risk for cardiovascular disease

The current study has several important implications. First, our results indicate that troponin I concentrations in apparently healthy subjects are continuously associated with fatal cardiovascular events and to a lesser extent with incident cardiovascular disease as well as overall mortality.

Comparing the improvement by troponin I in risk prediction with other biomarkers such as CRP, NT-proBNP, and eGFR, we observed the following trends: CRP concentration showed continuous associations of similar magnitude with risk of coronary heart disease, ischaemic stroke, vascular mortality, and death from several cancers and lung disease. Associations with ischaemic vascular disease depend considerably on conventional risk factors and other markers of inflammation.[33] Everett *et al.*[34] demonstrated within the Women's Health Initiative the relationship between NT-proBNP and incident cardiovascular events. Several features suggest that these findings are significant: there was a linear relationship between risk and NT-proBNP values; the hazard ratios were consistent across several methods of adjustment; NT-proBNP levels predicted each individual component of the composite endpoint; and there were no interactions with any other cardiac risk factor or patient descriptor.[34,35] Ledwidge *et al.*[36] and Huelsmann *et al.*[37] also demonstrated the efficacy of primary prevention strategies in patients with elevated NT-proBNP levels highlighting its potential utility for risk prediction. Recent studies suggest that targeting intensified cardiovascular care on the basis of NT-proBNP levels may reduce events, but this was seen in populations at higher risk than in those from observational studies. An exponential increase in risk for all-cause and cardiovascular mortality was observed at low eGFR.[38] The pattern of an increased risk for all-cause and cardiovascular mortality for lower eGFR in high-risk cohorts[38] is comparable with that observed in general population cohorts.[39] Thus, we cannot show which biomarker performs better for risk prediction of cardiovascular events. But we could prove with our additional analyses, as displayed in Supplementary material online, *Figure S7*, that troponin I presents itself a roughly comparable predictor for cardiovascular events.

Second, the level of troponin I is moderately related to the extent of other cardiovascular risk phenotypes for vascular atherosclerosis and cardiac function. Third, as a specific marker of myocardial necrosis, troponin I adds information on risk prediction beyond variables of the European SCORE. According to age-stratified analyses, the troponin I-based risk prediction information is particularly useful among individuals aged >65 years. Below the age of 45, assessment of troponin I is apparently not useful in improving risk prediction. Fourth, 6 ng/L of troponin I correspond to the upper quintile of the general population and might offer a reasonable cut-off value for direct clinical application. This population potentially benefits most from preventive therapy strategies such as statin therapy in terms of absolute risk reduction. Whether or not the same intervention threshold might maximize benefit from aspirin or other preventive therapies needs to be tested in appropriate trial populations.[40] Finally, we used a commercially available assay which easily and reliably detects very low levels of troponin I and thus opens the possibility of stratifying risk by use of a cardiac-specific biomarker. Importantly, the technical imprecision value of 5.2 ng/L—the so-called 10% coefficient of variation—is below the proposed cut-off value of 6 ng/L, which allows a precise detection of troponin I for clinical decision-making.

Troponin I, cardiovascular phenotypes, and prognosis

Troponin I is mainly released by cardiac myocytes and correlates with subclinical risk phenotypes such as the degree of

Table 3 Net reclassification improvement by endpoint with estimates of the expected number of reclassifications per risk category for cases and non-cases

	ESC SCORE and troponin I				Reclassified up, *n* (%)	Reclassified down, *n* (%)	NRI (95% CI)
	<1%	1 to <5%	5 to <10%	≥10%			
Pattern A (for cardiovascular mortality)							
Cases							
<1%	107	12	0	0	91 (6.4)	37 (2.6)	0.038 (0.020, 0.056)
1 to <5%	8	433	36	2			
5 to <10%	0	15	283	41			
≥10%	0	0	14	408			
Non-cases							
<1%	37 029	392	3	3	993 (1.6)	1625 (2.6)	0.010 (0.008, 0.012)
1 to <5%	856	17 354	368	41			
5 to <10%	0	521	4047	186			
≥10%	0	0	248	2159			
Overall							0.048 (0.030, 0.066)
Pattern B (for cardiovascular disease)							
Cases							
<1%	44	2	0	0	96 (3.0)	65 (1.9)	0.010 (0.002, 0.018)
1 to <5%	4	482	30	2			
5 to <10%	0	30	823	62			
≥10%	0	0	31	1668			
Non-cases							
<1%	15 099	277	1	0	1013 (1.8%)	1377 (2.4%)	0.006 (0.005, 0.008)
1 to <5%	373	21 383	373	12			
5 to <10%	0	543	10 078	350			
≥10%	0	0	461	8316			
Overall							0.017 (0.008, 0.025)
Pattern C (for total mortality)							
Cases							
<1%	140	5	0	0	96 (2.1)	77 (1.6)	0.005 (−0.001, 0.011)
1 to <5%	5	613	26	1			
5 to <10%	0	20	778	64			
≥10%	0	0	52	2896			
Non-cases							
<1%	18 299	303	3	0	1035 (1.6)	1565 (2.5)	0.008 (0.007, 0.010)
1 to <5%	399	21 741	355	14			
5 to <10%	0	661	10 067	360			
≥10%	0	0	505	11 232			
Overall							0.013 (0.007, 0.020)

Net reclassification improvement is presented as a number with a theoretical range between −2 and 2.

atherosclerosis, ventricular hypertrophy, and vascular stiffness. Consequently, the detection of very low circulating levels provides additional information on risk beyond that obtained from modifiable cardiovascular risk factors, which already explain a substantial proportion of cardiovascular risk.[15,41] The addition of this biomarker to models including traditional risk factors adds similar predictive information in all cardiovascular risk subgroups. When addressing fatal cardiovascular outcome, the magnitude of additional risk prediction achieved by inclusion of troponin I into the risk models is similar to that obtained from any single accepted risk factor. Elevated troponin I at baseline is most probably due to subclinical cardiac pathology which increases the risk of cardiovascular death or major CVD events years later. Therefore, the predictive value of troponin I is stronger in populations at higher cardiovascular risk, and becomes more evident with increasing age. The clinical significance of this is that elevated troponin I should trigger careful examinations to

Table 4 Association of troponin I with selected endpoints in the JUPITER trial

Endpoint	*N* events/*N* at risk for individuals with troponin I >6	Adjusted[a] HR in the placebo group					
Pattern A (association of troponin I > 6 with selected endpoints)							
Cardiovascular disease	45/1204	1.93					
Total mortality	64/1204	2.25					
Troponin I category	**Rosuvastatin**		**Placebo**		**Absolute risk reduction**	**HR[a] (95% CI)**	***P*-value[†]**
	***N* events**	**Incidence rate**	***N* events**	**Incidence rate**			
Pattern B (cardiovascular disease as an endpoint)							
≤6 ng/L	36	0.31	73	0.65	0.34	0.47 (0.32–0.71)	<0.0003
>6 ng/L	22	0.87	45	1.61	0.74	0.54 (0.32–0.90)	0.018
Pattern C (total mortality as an endpoint)							
≤6 ng/L	79	0.64	88	0.74	0.10	0.89 (0.66–1.21)	0.46
>6 ng/L	41	1.49	64	2.11	0.62	0.70 (0.47–1.03)	0.07

[a]Adjusted for age, sex, race, hypertension, cigarette smoking, BMI, total and HDL cholesterol, family history of coronary heart disease, and Ln(hsCRP).
[†]*P*-value for interaction between troponin I category and active rosuvastatin for cardiovascular disease = 0.80 and for overall mortality = 0.78. The model testing for interaction adjusts for the covariates noted above and including terms for the main effects of drug and troponin I category. The incidence rates are per 100 person-years of observation. The median follow-up time in this sample was 2 years.

precisely diagnose the underlying cardiac problem, and to treat it appropriately, which may prevent or postpone the future adverse events.

Importantly, the addition of troponin I improves overall risk estimation particularly among individuals above the age of 65, in whom the traditional risk prediction scores are apparently less informative. Overall, the predictive strength of troponin I becomes more evident with increasing age.

Strengths and limitations of the study

Our study has several strengths and limitations. Since 1998, we have harmonized data from population-based cohort studies in the MORGAM Data Centre in Helsinki providing the best possible endpoint validation consistent with and supported by the European Union framework programmes. Furthermore, we performed all troponin I measurements of the cohorts and JUPITER participants in one central laboratory within the frame of the EU-FP7 programme BiomarCaRE. Standardized epidemiological and laboratory procedures based on individual level data allow for the best possible risk stratification analyses. Additionally, we compared prediction analyses in different European regions and demonstrated generalizability across all participating regions. The association with outcomes showed consistently increasing risk with increasing troponin I concentrations—far below the so-called 99th percentile. Using a validation strategy, individuals above a specific cut-off level near the upper quintile benefit with greater absolute risk reduction from preventive therapies such as statin therapy. This value is still above the technical imprecision value of 5.2 ng/L. These results are also in line with those observed in the LIPID trial. Here, patients receiving pravastatin demonstrated a slightly greater reduction in troponin I with treatment and the delta of troponin I (from baseline pre-treatment concentrations) was an independent predictor of cardiovascular risk and mortality among patients receiving pravastatin.[42]

Several limitations merit consideration. In total, >93 000 individuals were investigated in 10 cohorts. We encountered missing information concerning important variables in some cohorts. For example, the GHS study and the SHIP study did not include information on cardiovascular disease as an endpoint, the Caerphilly study did not include information on low- and high-density cholesterol.

Additional limitation is hidden in what could be interpreted as inconsistent results, when regarding the association between troponin I and the three outcomes according to each cohort as displayed in Supplementary material online, *Figure S6*. The results presented by the Brianza and the FINRISK studies are less strong than in most other cohorts. Age, sex, and careful exclusion of people with prevalent cardiac disease might have contributed to such differences. FINRISK, Brianza, and KORA are three cohorts with a high percentage of young people. The proportion of women is about the same in FINRISK compared with the other cohorts. Finnish women tend to have relatively little CHD[43,44] in international comparisons, clearly differing from Finnish men. Furthermore, in FINRISK the exclusion of people with prevalent CVD was based on hospital discharge register diagnoses, whereas in most other cohorts exclusions were based on self-reported history of CVD. On the contrary, according to *Figure S5*, risk factors for CVD (like diabetes and hypertension) do not seem to influence endpoints. Since troponin I is very specific for heart problems and even minor elevations most likely reflect subclinical heart disease, all of these points may play a role in explaining the weaker associations. Moreover, a measurement error could be possible. Earlier studies showed that evaporation could be a problem giving rise to higher concentrations in older samples.

A further limitation is that we cannot be sure that our proposed cut-off value of 6 ng/L, when applied in an everyday clinical setting, would improve the outcome of preventive strategies. While data driven approaches such as ours for threshold estimation are known to be over-optimistic, the bias is minimal with large sample size.[45] In addition, troponin concentrations vary according to population. Net reclassification improvement results depend on the number and the level of the thresholds used to define the risk categories, and for this reason we adopted the widely recommended clinically meaningful categories appropriate for the prediction of cardiovascular disease.[28] Finally, some degree of miscalibration was detected when addressing overall mortality and CVD outcome. However, given the large sample size and the consistency of predictions for cardiovascular mortality, this effect appears rather small.

Conclusion

In conclusion, the addition of troponin I to established risk models consistently improved risk prediction in apparently healthy individuals drawn from the general population. As established risk models provide less information with increasing age, the addition of troponin I might be particularly helpful in those >65 years. Troponin I determination might support the selection of those individuals, who would benefit most from preventive strategies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

F.O., S.B., V.S., B.M.E., J.K., W.K., F.K., T.Z., K.K., T.J. performed statistical analysis; S.B. handled funding and supervision; F.O., N.M. acquired the data; S.B., V.S., N.M., F.O., P.W., K.J.L., T.J., B.T., A.P., M.N., A.P., E.V., G.V., P.B., S.C., L.I., G.L., J.Y., C.C.P., B.M.E., P.M.R., J.K., R.B.S., W.K., F.K., T.Z., K.K. conceived and designed the research; N.M., F.O., S.B., V.S., B.M.E., W.K., F.K., T.Z., K.K., T.J., B.T., J.Y. drafted the manuscript; N.M., F.O., S.B., V.S., W.K., T.Z., K.K. made critical revision of the manuscript for key intellectual content.

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Ethical statement

Our study complies with the Declaration of Helsinki that the locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from the subjects (or their legally authorized representative).

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