SUPPLEMENTAL MATERIAL

Cardiac Troponin I and Incident Stroke in European Cohorts– Insights from the BiomarCaRE Project

Supplemental Methods

Supplemental References

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Description of cohorts:

MONICA Brianza Cohort Study [1]:

The MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Brianza Cohort Study is a prospective observational study of three cohorts of 25-64 years old residents in Brianza, a highly-industrialized area located between Milan and the Swiss border, Northern Italy. Selection of individuals was bases on a two-stage sampling. First, a random sample of municipalities was selected with equal probabilities across the 73 municipalities of the area. Secondly, sex- and 10-year age group stratified samples were randomly drawn using the population registers of the selected municipalities. Cardiovascular risk factors were investigated at baseline following the procedures of the WHO MONICA Project. Baseline examinations were carried out in 1986-87 for cohort 1 (N=1,659), in 1989-1990 for cohort 2 (N=1599), and in 1993-1994 for cohort 3 (N=1674). Overall response rate was 69%. Follow-up was achieved by linkage to the municipality registers and to hospital discharge records and was completed up to the end of 2008.

https://epimed.uninsubria.eu

The WHO MONICA/ Cooperative Health Research in the Region of Augsburg (KORA) study [2]

The WHO MONICA/ Cooperative Health Research in the Region of Augsburg (KORA) cohorts comprise individuals from representative sample surveys from the city of Augsburg and the less urban Landkreis Augsburg and Landkreis Aichach-Friedberg regions in Bavaria, Southern Germany. List of municipalities and population registers were used as sampling frames for the first and the second stage of two-stage sampling, respectively. The second stage of sampling was stratified by sex and 10-year age group. The baseline examination (1994-1995) for survey 3 was carried out as part of the WHO MONICA project and included 4,480 men and women aged 25-74 years. The Survey 4 baseline examination (1999-2001) comprised 4,165 men and women aged 25-74 who were re-examined in 2006-2008 (3019 men and women, response rate of 72%). Only the baseline examinations for Surveys 3 and 4 were used in this study. Survey 4 baseline and follow-up examinations were conducted in the frame of the KORA [3]. Coronary events were identified through the MONICA/KORA Augsburg coronary event registry [4]. Coronary deaths were validated by autopsy reports, death certificates, and chart review from the last treating physician. Self-reported cases of incident stroke were validated by medical records. Mortality follow-up until 2009 was conducted through national death registers.

https://www.thl.fi/publications/morgam/cohorts/full/germany/ger-auga.htm

DanMONICA [5]

The three prospective DanMONICA cohorts from the Research Center for Prevention and Health in Glostrup are formed by randomly selected individuals from eleven municipalities from the western part of the suburbs of Copenhagen, Denmark. Random sampling was based on the national population register, stratified by sex and year of birth. For cohort 1 (baseline survey 1982-1984) and 3 (1991-1992) inhabitants with an age range from 30 to 70 years were invited, whereas invitations for participation in cohort 2 (1986-1987) were sent to individuals aged 30 to 60 years. Cohort 1 consists of 4,052 men and women. Cohort 2 and cohort 3 comprise 1,504 and 1,624 men and women, respectively. Follow-up was achieved by using a unique personal identification number to link each individual to the Civil Registration System, the National Hospital Discharge Register and to the National Cause of Death Register. At the present time, follow-up has been extended up to December 31st 2010.

https://www.thl.fi/publications/morgam/cohorts/full/denmark/den-gloa.htm

FINRISK [6]

FINRISK is a large Finnish population survey on cardiovascular risk factors carried out every five years since 1972 by the National Public Health Institute in Helsinki. The cohorts comprising individuals from up to six regions in eastern and south-western Finland were formed by random sampling based on the Nationwide Central Population Register, stratified by sex and 10-years age group. The cohort with baseline examination in 1997 (age range from 25 to 74 years) was included in this study (N=8,444). Follow-up is achieved through linkage to the National Register of Cause of Death, the National Hospital Discharge Register and the National Drug Reimbursement Register. Follow-up for the cohort is completed up to December 31st 2010.

https://www.thl.fi/publications/morgam/cohorts/full/finland/fin-fina.htm

The Malattie cardiovascolari Aterosclerotiche, Istituto Superiore di Sanità (MATISS) study [7]

The MATISS study started in 1984 as DiSCo - DIstretto Sezze controllo COmunitario - designed as demonstration project of non-communicable diseases in Central Italy. Four municipalities (Priverno, Sezze, Bassiano and Roccagorga) of the Region of Latina were involved, three at community treatment and one at control. Electoral rolls were used as sampling frames in the single stage sampling, which was stratified by municipality, sex and 5-year age group (age range 20-69 years at baseline). The project was then carried on as a prospective, observational study (MATISS), which included three cohorts. The first two cohorts were examined at baseline (1983-1984, N=3,648 and 1986-1987, N=2894) and in 4-year intervals. In 1993-96 the two cohorts were re-examined (N=2,519 persons) and a new random sample (third cohort), stratified by age and sex, was enrolled from the residence registry (N=1,970). The individuals of the first and second cohort who participated again in 1993-96 and those from the third cohort have biological samples preserved; they were included in the BiomarCaRE study as a combined sub-cohort. Follow-up is available for all cohorts until December 2004 for mortality and non-fatal coronary and stroke events, validated applying the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) criteria [8].

https://thl.fi/publications/morgam/cohorts/full/italy/ita-roma.htm

Moli-sani study [9, 10]

The cohort of the Moli-sani study was recruited from residents of the Molise region, Italy. Participants were recruited from city-hall registries by a multistage sampling. First, townships were sampled in two major areas by cluster sampling; then, within each township, individuals aged 35 years or older were selected by simple random sampling. Individuals, who were pregnant at the time of recruitment, who suffered from current polytrauma or coma, who had disturbances in understanding or willingness, or who refused to sign the informed consent form were excluded from the study. Baseline examinations were performed by trained staff; further trained personnel administered questionnaires to collect personal and clinical information. Overall, 24,325 individuals were included from 2005 to 2010. Median follow-up for the total cohort was 4.2 years (with a maximum of 6.5 years) from the baseline examination until death or December 31st 2011 for those individuals who remained alive. Follow-up was based on record linkage to national mortality registers and hospital discharge registers.

https://moli-sani.org

Northern Sweden MONICA project [11, 12]

The Northern Sweden MONICA project was initiated as part of the WHO MONICA study in 1985. The population-based surveys consist of individuals from the counties of Västerbotten and Norrbotten selected about every five years since 1986 Individuals were randomly selected from population registers, stratified for 10-years age group (with age range from 25 to 64 years in 1986 and 1990, and 25 to 74 years since 1994) and sex.
For every survey 250 men and 250 women were selected in each age group, totaling in 2,000 individuals for the first two surveys and 2,500 individuals from 1994 on, respectively. The participants of the 1986, 1990, and 1994 surveys were re-examined in 1999. The individuals that participated in

the baseline examinations in 1986, 1990, 1994, 1999 and 2004 were used in this study (8746 individuals, equaling a participation rate of 76.1%). Follow-up was achieved through linkage with the national death register and the National registers at the National Board of Health and Welfare (Cause of Death Register, Inpatient Diagnosis Register, Cancer Register, and Medication Register) as well as the MONICA stroke event and myocardial infarction registers, with endpoint diagnosis based on MORGAM criteria. Follow-up is completed until December 31st 2011.

https://www.thl.fi/publications/morgam/cohorts/full/sweden/swe-nswa.htm
https://snd.gu.se/en/catalogue/study/ext0042

Prospective Epidemiological Study of Myocardial Infarction (PRIME) study [13]:

The PRIME study examined the classic and putative cardiovascular risk factors to explain the large difference in heart disease incidence between Ireland and France. The study includes four cohorts of men aged 50-59; from Belfast, Northern Ireland and Lille, Toulouse, and Strasbourg in France. The current study only includes men from the Belfast cohort, which aimed to broadly match the social class structure of the background population. Therefore, recruitment was based firstly on industry and various employment groups, excluding those with more than 10% of their workforce of foreign origin. The recruitment was further based on general practice providing the opportunity to recruit unemployed or retired persons to the cohort. Baseline examination of this cohort took place from 1990 to 1994 (N=2745, response rate of 52%). Follow up until 2012 (18 years from the time of the inclusion of each individual) was achieved through annual follow up questionnaires with verification against national death registers, medical records, and hospital discharge diagnoses. Endpoints were validated by expert medical committee.

https://www.thl.fi/publications/morgam/cohorts/full/uk/unk-bela.htm

Scottish Heart Health Extended Cohort (SHHEC) [14]:

The Scottish Heart Health Extended Cohort consists of two overlapping studies which share a common protocol and methods: the Scottish Heart Health Study randomly recruited men and women aged 40-59 across 22 Scottish districts in 1984-1987; Scottish MONICA similarly recruited men and women aged 25-64 in Edinburgh and North Glasgow in 1986, and in North Glasgow again in 1989, 1992, and in 1995 as part of the WHO MONICA Project [14]. The cohorts comprise respondents of representative sample surveys of the respective area. As the first sampling stage, a random sample of general practitioners was selected based on a list of all general practitioners as the sampling frame. In the second stage, the lists of persons registered with the selected general practitioners were used as sampling frames. From each of these lists a sample of size proportional to the number of persons within the target age and sex groups in the list was selected. The second stage sampling was stratified by sex and 10-year age group. Follow-up was achieved by record linkage and extends through 2009. Of the original 18,107 individuals, complete data on 16,000 were transferred to Helsinki in 2000 for the MORGAM collaboration and available serum and plasma to the biomarker laboratory in Mainz/ Hamburg some years later, first for use in the MORGAM biomarker study and then for the Biomarker for Cardiovascular Risk Assessment across Europe (BiomarCaRE) project. A more detailed cohort description has been published elsewhere [15].
https://www.thl.fi/publications/morgam/cohorts/full/uk/unk-sco.htm

Assessment of risk factors at baseline

For each cohort the following cardiovascular risk factors were available at baseline: body mass index (BMI), systolic blood pressure, total and high-density lipoprotein cholesterol level, antihypertensive medication, diabetes mellitus, and daily smoking. Diabetes mellitus status at baseline was mainly based on self-report. Northern Sweden, FINRISK, and DANMONICA further assessed the prevalence of diabetes at baseline via linkage to national registries. General practitioners' notes and hospital discharge letters were additionally used for classification of diabetes status in KORA. The data from

the cohorts were harmonized in the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project [16].

Detailed outcome classification

Stroke was defined based on MORGAM criteria [8]. For an event to be classified as stroke there had to be rapidly developed clinical signs of focal disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery, other medical intervention or death) with no apparent cause other than a vascular origin. When no validation was done, the diagnosis was based on the clinical or death certificate diagnoses as specified for each cohort in the Description of MORGAM Cohorts [17].

According to MORGAM's data harmonization criteria, a stroke is further categorized as a *cerebral infarction* (ischemic stroke) if at least one of the following is present:

- Validation of recent brain infarction by necropsy.
- Circumscribed hypodensity changes of recent origin in the brain parenchyma on computed tomography (CT). Ischemic stroke was also diagnosed if localized changes of recent origin were absent on CT, but the criteria for definite stroke were fulfilled (rapidly developed clinical signs of focal disturbance of cerebral function lasting for more than 24 hours (unless interrupted by surgery, other medical intervention or death) with no apparent cause other than a vascular origin). Cases with small hematomas or diffuse bleedings occurring within a hypodense lesion were classified as hemorrhagic transformation and therefore coded as having cerebral infarction.
- Typical signs of infarct in the brain parenchyma on magnetic resonance imaging.

In addition, the event was also considered as cerebral infarction in the data analysis if there was no validation as described above or if there was insufficient data from the necessary diagnostic procedures to decide between "cerebral infarction" and "not cerebral infarction" but the routine clinical or death certificate diagnoses indicated cerebral infarction (ICD-8 code of 432, 433 or 434, ICD-9 code of 433 or 434 or ICD-10 code of I63). Strokes whose type could not be specified in this way were considered as "not cerebral infarction".

A stroke was further classified as a hemorrhagic stroke if MORGAM criteria for either intracerebral hemorrhage or subarachnoid hemorrhage were met.

For an event to be classified as *intracerebral hemorrhage*, at least one of the following criteria must be present:

- Validation of recent intracerebral hemorrhage by necropsy.
- Hyperdensity changes in the brain parenchyma on CT.
- Typical signs of bleeding in the brain parenchyma on magnetic resonance imaging.
- Bloody cerebrospinal fluid (liquor) in the presence of focal neurological signs at onset.

To be accepted as a case of *subarachnoid hemorrhage* at least one of the following must be present:

- Validation of recent subarachnoid hemorrhage by necropsy.
- Signs of blood in the subarachnoid cisterns or in cerebral ventricles on CT.
- Magnetic resonance imaging - signs of blood in the subarachnoid cisterns or in cerebral ventricles.
- Bloody and/or xanthochromic cerebrospinal fluid (liquor) and the possibility of intracerebral haemorrhage excluded by necropsy or CT examination.

In addition, the event was also considered as a hemorrhagic stroke in the data analysis if there was no validation as described above or if there was insufficient data from the necessary diagnostic procedures to decide between "hemorrhagic stroke" and "not hemorrhagic stroke" but the routine clinical or death certificate diagnoses indicated hemorrhagic stroke (ICD-8 code of 430 or 431, ICD-9

code of 430 or 431 or ICD-10 code of I60 or I61). Strokes whose type could not be specified in this way were considered as "not hemorrhagic stroke".

Strokes which could be classified neither as a cerebral infarction nor hemorrhagic stroke were called *indeterminate*.

An *incident coronary event* was defined as a composite endpoint of any cardiac revascularization and acute coronary events including definite and possible myocardial infarction as well as hospitalization for unstable angina pectoris. Some of the studies included in this analysis did not follow-up all of the above-mentioned endpoints. In the KORA and the MONICA Brianza studies unstable angina pectoris was not assessed as an outcome but it is largely included in the category "possible myocardial infarction" of the WHO MONICA classification used in these studies. Furthermore, in the KORA study cardiac revascularization was not followed up. At last, the PRIME study (Belfast) did not include possible myocardial infarction as an outcome, which is likely to be compensated by the thorough assessment of unstable angina pectoris.

Atrial fibrillation was defined as atrial fibrillation of any kind or duration. Self-reported diagnosis as the only information source was considered insufficient during follow-up. Clinical and death certificate diagnosis were scanned and the relevant ICD codes are 427.4 for ICD-8, 427.3 for ICD-9 and I48 for ICD-10, respectively. These codes comprise atrial fibrillation as well as atrial flutter, so that some cases classified as atrial fibrillation in this study might have actually been considered as atrial flutter.

Overall mortality was defined as mortality due to any cause during the follow-up time.

Details of the follow-up and diagnostic procedures of each participating study have been published elsewhere [17].

Supplemental statistical methods

Since each variable has some amount of missing data, restriction of the multivariable adjusted models to complete cases would lead to a loss of information and reduced statistical power. Therefore, we used multiple imputation to handle missing data in continuous variables. Multiple imputation neither biases the results nor falsely decreases the standard errors of the estimates [18]. Dichotomous variables were not imputed but the missing values were recoded to 0 ("no") if missing, to avoid incompleteness. Amount of missing values are provided in Supplemental Table II.

The imputation model used included all relevant biomarkers available and classic cardiovascular risk factors. Nelson-Aalen estimators of cumulative baseline hazard on the all outcomes used in the analyses were included in the imputation model separately to avoid attenuation of the estimated effects [19, 20]. The imputation model used was multinormal Bayesian linear regression model estimated by chained equations [21]

Imputation is performed for each sub-cohort separately stratified by sex. The continuous variables in the imputation model were rank normalized to get normalized variables. The imputed values were transformed back to the original scale using inverse empirical cumulative distribution. We used 10 imputed datasets achieved after 30 iteration rounds in the chain of the imputed values. Several diagnostic plots and statistics of each imputed variable were calculated to assess the feasibility of the imputed values and the convergence of the imputation chains. Imputation was performed using R statistical software version 3.5.1 (The R Project for Statistical Computing).

When analyzing the multiple imputed datasets, the analysis was repeated for each imputed data separately. To get an overall estimate, the separate estimates and their standard errors that take into account the within- and between-imputation variance from each of the imputed dataset were combined using the Rubin's rules [18].

Supplemental Table I. Baseline characteristics of individuals included in the analyses by cohort

Cohort	**BRIANZA 01**	**BRIANZA 02**	**BRIANZA 03**
General characteristics	N=1,640	N=1,574	N=1,639
Years of baseline examinations	1986	1989	1993
Age at baseline examination, years	45.8 (19.2)	46.3 (18.7)	46.9 (19.1)
Men, No. (%)	801 (48.8)	786 (49.9)	787 (48.0)
Stroke risk factors			
Body mass index, kg/m²	24.6 (4.9)	25.0 (5.3)	25.1 (5.6)
Systolic blood pressure, mmHg	130 (24)	126 (25)	125 (25)
Total cholesterol, mmol/L	5.3 (1.4)	5.4 (1.5)	5.7 (1.5)
High-density lipoprotein cholesterol, mmol/l	1.4 (0.5)	1.4 (0.5)	1.4 (0.5)
Antihypertensive medication, No. (%)	144 (8.8)	181 (11.5)	166 (10.1)
Diabetes mellitus, No. (%)	39 (2.4)	47 (3.0)	33 (2.0)
Daily smoker, No. (%)	541 (33.0)	451 (28.7)	465 (28.4)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	756 (46.1)	391 (24.8)	1,089 (66.4)
Hs-TnI, pg/mL	1.7 (1.5)	0.5 (1.7)	2.3 (1.5)
Endpoints during follow-up			
Stroke (any type), No. (%)	50 (3.1)	42 (2.7)	30 (1.8)
Ischemic stroke, No. (%) *	37 (2.3)	31 (2.0)	20 (1.2)
Hemorrhagic stroke, No. (%) *	13 (0.8)	8 (0.5)	7 (0.4)
Death, No. (%)	266 (16.2)	193 (12.3)	104 (6.4)
Other events during follow-up			
Coronary events, No. (%)	95 (5.8)	85 (5.4)	48 (2.9)
Atrial fibrillation, No. (%)	n.a.	n.a.	n.a.

Continued

Cohort	KORA S3	KORA S4	DANMONICA 01
General characteristics	N=4,462	N=4,077	N=3,925
Years of baseline examinations	1994	1999	1982-1985
Age at baseline examination, years	50.6 (23.5)	49.0 (23.9)	50.5 (20.1)
Men, No. (%)	2,220 (49.8)	1,961 (48.1)	1,998 (50.9)
Stroke risk factors			
Body mass index, kg/m²	26.4 (5.6)	26.5 (5.9)	24.2 (5.0)
Systolic blood pressure, mmHg	131 (27)	128 (26)	122 (23)
Total cholesterol, mmol/L	5.9 (1.5)	5.8 (1.5)	5.7 (1.5)
High-density lipoprotein cholesterol, mmol/l	1.3 (0.5)	1.4 (0.6)	1.4 (0.6)
Antihypertensive medication, No. (%)	549 (12.3)	579 (14.2)	230 (5.9)
Diabetes mellitus, No. (%)	204 (4.6)	193 (4.7)	86 (2.2)
Daily smoker, No. (%)	1,006 (22.5)	937 (23.0)	1,828 (46.6)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	2,609 (58.5)	2,029 (49.8)	2,761 (70.3)
Hs-TnI, pg/mL	2 (1.7)	1.8 (1.8)	2.7 (2.5)
Endpoints during follow-up			
Stroke (any type), No. (%)	167 (3.7)	79 (1.9)	443 (11.3)
Ischemic stroke, No. (%) *	122 (2.7)	58 (1.4)	123 (3.1)
Hemorrhagic stroke, No. (%) *	28 (0.6)	15 (0.4)	86 (2.2)
Death, No. (%)	568 (12.7)	221 (5.4)	1,470 (37.5)
Other endpoints during follow-up			
Coronary events, No. (%)	121 (2.7)	72 (1.8)	352 (9.0)
Atrial fibrillation, No. (%)	n.a.	n.a.	356 (9.1)

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Cohort	**DANMONICA 02**	**DANMONICA 03**
General characteristics	N=1,471	N=1,945
Years of baseline examinations	1986-1987	1991-1992
Age at baseline examination, years	41.0 (11.2)	49.9 (20.2)
Men, No. (%)	727 (49.4)	951 (48.9)
Stroke risk factors		
Body mass index, kg/m²	24.3 (4.7)	24.7 (5.3)
Systolic blood pressure, mmHg	119 (22)	122 (24)
Total cholesterol, mmol/L	5.8 (1.5)	5.7 (1.6)
High-density lipoprotein cholesterol, mmol/l	1.4 (0.5)	1.4 (0.5)
Antihypertensive medication, No. (%)	67 (4.6)	151 (7.76)
Diabetes mellitus, No. (%)	17 (1.2)	57 (2.9)
Daily smoker, No. (%)	625 (42.5)	821 (42.2)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	1,270 (86.3)	1,383 (71.1)
Hs-TnI, pg/mL	3.1 (2.2)	2.8 (2.7)
Endpoints during follow-up		
Stroke (any type), No. (%)	129 (8.8)	175 (9.0)
Ischemic stroke, No. (%) *	43 (2.9)	58 (3.0)
Hemorrhagic stroke, No. (%) *	20 (1.4)	29 (1.5)
Death, No. (%)	345 (23.5)	495 (25.4)
Other events during follow-up		
Coronary events, No. (%)	122 (8.3)	133 (6.8)
Atrial fibrillation, No. (%)	99 (6.7)	149 (7.7)

Continued

Cohort	**FINRISK 1997**	**MATISS**	**MOLI-SANI**
General characteristics	N=7,909	N=4,363	N=23,658
Years of baseline examinations	1997	1993-1996	2005-2010
Age at baseline examination, years	47.6 (22.0)	49.7 (23.1)	54.2 (18.3)
Men, No. (%)	3,868 (48.9)	1,688 (38.7)	11,201 (47.3)
Stroke risk factors			
Body mass index, kg/m²	26.1 (5.6)	27.4 (6.0)	27.5 (6.1)
Systolic blood pressure, mmHg	133 (27)	136 (30)	138 (28)
Total cholesterol, mmol/L	5.4 (1.4)	5.6 (1.5)	5.5 (1.4)
High-density lipoprotein cholesterol, mmol/l	1.4 (0.5)	1.3 (0.4)	1.4 (0.5)
Antihypertensive medication, No. (%)	949 (12.0)	741 (17.0)	6,416 (27.1)
Diabetes mellitus, No. (%)	400 (5.1)	184 (4.2)	1,433 (6.1)
Daily smoker, No. (%)	1,711 (21.6)	1,008 (23.1)	4,872 (20.6)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	6,432 (81.3)	2,421 (55.5)	14,187 (60.0)
Hs-TnI, pg/mL	3 (2.6)	2 (1.9)	2.2 (2)
Endpoints during follow-up			
Stroke (any type), No. (%)	303 (3.8)	82 (1.9)	86 (0.4)
Ischemic stroke, No. (%) *	244 (3.1)	36 (0.8)	52 (0.2)
Hemorrhagic stroke, No. (%) *	66 (0.8)	20 (0.5)	28 (0.2)
Death, No. (%)	814 (10.3)	306 (7.0)	498 (2.1)
Other events during follow-up			
Coronary events, No. (%)	369 (4.7)	60 (1.4)	305 (1.3)
Atrial fibrillation, No. (%)	379 (4.8)	n.a.	374 (1.6)

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Cohort	**NORTHERN SWEDEN 01**	**NORTHERN SWEDEN 02**
General characteristics	N=1,547	N=1,537
Years of baseline examinations	1986	1990
Age at baseline examination, years	45.3 (18.3)	44.7 (18.8)
Men, No. (%)	774 (50.0)	745 (48.5)
Stroke risk factors		
Body mass index, kg/m²	24.7 (4.9)	24.8 (4.8)
Systolic blood pressure, mmHg	125 (23)	125 (22)
Total cholesterol, mmol/L	5.9 (1.7)	6.1 (1.7)
High-density lipoprotein cholesterol, mmol/l	1.2 (0.4)	1.4 (0.4)
Antihypertensive medication, No. (%)	122 (7.9)	108 (7.03)
Diabetes mellitus, No. (%)	40 (2.6)	40 (2.6)
Daily smoker, No. (%)	382 (24.7)	379 (24.7)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	633 (40.9)	473 (30.8)
Hs-TnI, pg/mL	1.6 (1.6)	1.2 (1.6)
Endpoints during follow-up		
Stroke (any type), No. (%)	144 (9.3)	102 (6.6)
Ischemic stroke, No. (%) *	109 (7.0)	80 (5.2)
Hemorrhagic stroke, No. (%) *	32 (2.1)	24 (1.6)
Death, No. (%)	361 (23.3)	219 (14.2)
Other events during follow-up		
Coronary events, No. (%)	187 (12.1)	149 (9.7)
Atrial fibrillation, No. (%)	139 (9.0)	100 (6.5)

Continued

Cohort	**NORTHERN SWEDEN 03**	**NORTHERN SWEDEN 24**
General characteristics	N=1,797	N= 1,682
Years of baseline examinations	1994	1999
Age at baseline examination, years	48.6 (23.6)	49.7 (23.8)
Men, No. (%)	859 (47.8)	805 (47.9)
Stroke risk factors		
Body mass index, kg/m²	25.3 (5.2)	25.9 (5.0)
Systolic blood pressure, mmHg	126 (28)	130 (28)
Total cholesterol, mmol/L	6 (1.7)	5.8 (1.6)
High-density lipoprotein cholesterol, mmol/l	1.3 (0.5)	1.5 (0.6)
Antihypertensive medication, No. (%)	165 (9.18)	192 (11.4)
Diabetes mellitus, No. (%)	54 (3.0)	49 (2.9)
Daily smoker, No. (%)	383 (21.3)	267 (15.9)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	762 (42.4)	954 (56.7)
Hs-TnI, pg/mL	1.6 (2)	2.1 (2.5)
Endpoints during follow-up		
Stroke (any type), No. (%)	131 (7.3)	67 (4.0)
Ischemic stroke, No. (%) *	97 (5.4)	53 (3.2)
Hemorrhagic stroke, No. (%) *	28 (1.6)	14 (0.8)
Death, No. (%)	299 (16.6)	148 (8.8)
Other events during follow-up		
Coronary events, No. (%)	165 (9.2)	96 (5.7)
Atrial fibrillation, No. (%)	136 (7.6)	83 (4.9)

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Cohort	NORTHERN SWEDEN 25	PRIME	SHHEC 01
General characteristics	N=1,755	N=2,560	N=11,166
Years of baseline examinations	2004	1991-1994	1984-1987
Age at baseline examination, years	49.3 (24.1)	54.6 (5.1)	49.8 (11.1)
Men, No. (%)	837 (47.7)	2,560 (100)	5,626 (50.4)
Stroke risk factors			
Body mass index, kg/m²	30.9 (6.3)	26.0 (4.1)	25.3 (4.8)
Systolic blood pressure, mmHg	126 (25)	131 (25)	130 (25)
Total cholesterol, mmol/L	5.7 (1.7)	5.8 (1.3)	6.3 (1.6)
High-density lipoprotein cholesterol, mmol/l	1.1 (0.4)	1.2 (0.4)	1.5 (0.5)
Antihypertensive medication, No. (%)	245 (14.0)	222 (8.7)	684 (6.1)
Diabetes mellitus, No. (%)	66 (3.8)	54 (2.1)	152 (1.4)
Daily smoker, No. (%)	237 (13.5)	596 (23.3)	4,147 (37.1)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	1,150 (65.5)	2,532 (98.9)	8,792 (78.7)
Hs-TnI, pg/mL	2.3 (2)	5.2 (2.6)	4.2 (4.1)
Endpoints during follow-up			
Stroke (any type), No. (%)	32 (1.8)	102 (4.0)	659 (5.9)
Ischemic stroke, No. (%) *	29 (1.7)	84 (3.3)	275 (2.5)
Hemorrhagic stroke, No. (%) *	4 (0.2)	19 (0.7)	126 (1.1)
Death, No. (%)	68 (3.9)	476 (18.6)	2,974 (26.6)
Other events during follow-up			
Coronary events, No. (%)	52 (3.0)	298 (11.6)	1,214 (10.9)
Atrial fibrillation, No. (%)	58 (3.3)	n.a.	788 (7.1)

Continued

Cohort	**SHHEC 02**	**SHHEC 03**	**SHHEC 21**
General characteristics	N=1,633	N=1,565	N=976
Years of baseline examinations	1992	1995	1988-1989
Age at baseline examination, years	51.7 (25.2)	45.1 (19.3)	46.8 (18.5)
Men, No. (%)	768 (47.0)	736 (47.0)	468 (48.0)
Stroke risk factors			
Body mass index, kg/m²	25.4 (5.6)	25.7 (5.7)	25.1 (4.8)
Systolic blood pressure, mmHg	130 (32)	125 (25)	127 (26)
Total cholesterol, mmol/L	5.9 (1.6)	5.8 (1.6)	5.7 (1.6)
High-density lipoprotein cholesterol, mmol/l	1.4 (0.5)	1.3 (0.5)	1.1 (0.4)
Antihypertensive medication, No. (%)	156 (9.6)	118 (7.5)	68 (7.0)
Diabetes mellitus, No. (%)	28 (1.7)	33 (2.1)	22 (2.3)
Daily smoker, No. (%)	686 (42.0)	608 (38.8)	421 (43.1)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	874 (53.5)	757 (48.4)	648 (66.4)
Hs-TnI, pg/mL	2 (2.7)	1.8 (2.4)	2.2 (2.3)
Endpoints during follow-up			
Stroke (any type), No. (%)	111 (6.8)	45 (2.9)	54 (5.5)
Ischemic stroke, No. (%) *	58 (3.6)	22 (1.4)	23 (2.4)
Hemorrhagic stroke, No. (%) *	20 (1.2)	10 (0.6)	15 (1.5)
Death, No. (%)	502 (30.7)	197 (12.6)	229 (23.5)
Other events during follow-up			
Coronary events, No. (%)	128 (7.8)	73 (4.7)	76 (7.8)
Atrial fibrillation, No. (%)	116 (7.1)	52 (3.3)	59 (6.1)

Characteristics are presented as absolute and relative frequencies for categorical variables and median and interquartile range for continuous variables; *In some cases stroke could not be further subdivided into ischemic or hemorrhagic stroke; n.a. indicates not available.

Supplemental Table II. Comparison of multiple imputed and non-imputed baseline characteristics of the study population (N=82,881)

	Multiple imputed data	Non-imputed data	Missing values, No. (%) *
Body mass index, kg/m²	26.2 (5.7)	26.2 (5.8)	212 (0.3)
Systolic blood pressure, mmHg	131 (28)	131 (28)	91 (0.1)
Total cholesterol, mmol/l	5.7 (1.5)	5.7 (1.5)	297 (0.4)
High-density lipoprotein cholesterol, mmol/l	1.4 (0.5)	1.4 (0.5)	1212 (1.5)
Antihypertensive medication, No. (%)	12,253 (14.8)	12,253 (15.0)	999 (1.2)
Diabetes mellitus, No. (%)	3,231 (3.9)	3,231 (3.9)	362 (0.4)
Daily smoker, No. (%)	22,371 (27.0)	22,371 (27.1)	439 (0.5)
hs-TnI ≥ 1.9 pg/mL, No. (%)	52,902 (63.8)	46,949 (63.5)	8,938 (11.0)
hs-TnI, pg/mL	2.4 (2.7)	2.4 (2.7)	8,938 (11.0)

*Before performing multiple imputations. Numbers are absolute and relative frequencies for categorical variables, and medians and interquartile ranges for continuous variables.

Supplemental Table III. Intra- and inter-assay variation of troponin I measured by a high sensitivity assay in the different studies

Study	Intra-assay variation (%)	Inter-assay variation (%)
Cooperative Health Research in the Region of Augsburg (KORA)	4.50	3.50
DanMONICA studies	4.71	5.00
FINRISK study	2.36	4.80
Malattie cardiovascolari ATerosclerotiche, Istituto Superiore di Sanità (MATISS) study	1.97	5.10
Moli-Sani study	7.52	6.25
MONICA Brianza Study	6.13	5.56
Northern Sweden MONICA study	3.96	6.15
Prospective Epidemiological Study of Myocardial Infarction (PRIME) Belfast	2.14	4.30
Scottish Heart Health Extended Cohort (SHHEC)	4.26	6.29

Supplemental Table IV. Baseline characteristics of individuals restricted to cohorts with available information on atrial fibrillation at baseline and follow-up

General characteristics	**N=62,566**
Years of baseline examinations	1982−2010
Age at baseline examination, years	50.6 (17.8)
Men, No. (%)	30,363 (48.5)
Prevalent atrial fibrillation	429 (0.7)
Prevalent heart failure	348 (0.6)
Stroke risk factors	
Body mass index, kg/m²	26.2 (5.81)
Systolic blood pressure, mmHg	132 (28)
Total cholesterol, mmol/L	5.7 (1.5)
High-density lipoprotein cholesterol, mmol/l	1.4 (0.5)
Antihypertensive medication, No. (%)	9,671 (15.5)
Diabetes mellitus, No. (%)	2,477 (4.0)
Daily smoker, No. (%)	17,367 (27.8)
Hs-TnI ≥ 1.9 pg/mL, No. (%)	41,075 (65.7)
Hs-TnI, pg/mL	2.5 (2.7)
Endpoints during follow-up	
Stroke (any type), No. (%)	2,481 (4.0)
Ischemic stroke, No. (%) *	1,266 (2.0)
Hemorrhagic stroke, No. (%) *	502 (0.8)
Death, No. (%)	8,619 (13.8)
Other events during follow-up	
Coronary events, No. (%)	5,016 (8.0)
Atrial fibrillation, No. (%)	2,888 (4.6)

Numbers are absolute and relative frequencies for categorical variables and median and interquartile range for continuous variables; *In some cases stroke could not be further subdivided into ischemic or hemorrhagic stroke.

Supplemental Table V. Hazard ratios for high-sensitivity troponin I (hsTnI) in relation to stroke excluding individuals with prevalent atrial fibrillation and heart failure (sensitivity analysis)

	Continuous hsTnI*		Categorical hsTnI†		N events
	HR per SD (95% CI)	p-value	HR (95% CI)	p-value	
Overall stroke					
All individuals	1.15 (1.09-1.20)	<0.001	1.39 (1.22-1.60)	<0.001	2481
Sensitivity analysis	1.15 (1.09-1.20)	<0.001	1.39 (1.21-1.60)	<0.001	2436
Ischemic stroke					
All individuals	1.14 (1.07-1.21)	<0.001	1.41 (1.16-1.72)	0.001	1266
Sensitivity analysis	1.14 (1.07-1.21)	<0.001	1.41 (1.16-1.71)	0.001	1231
Hemorrhagic stroke					
All individuals	1.11 (1.00-1.22)	0.042	1.37 (1.02-1.83)	0.036	502
Sensitivity analysis	1.10 (0.99-1.22)	0.077	1.34 (1.01-1.79)	0.046	494

Cox regression analyses were stratified by sex and adjusted for age, cohort, body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol level, antihypertensive medication, diabetes mellitus, and daily smoking (model 2).
For sensitivity analyses individuals with prevalent atrial fibrillation (N=429) and heart failure (N=348) at baseline were excluded.
Age was used as the time scale in all models.
* hsTnI concentrations were log-transformed for this analysis.
†Results presented here are from individuals with hsTnI values in the highest category (hsTnI ≥4.8 pg/ml) compared to individuals with hsTnI values below the limit of detection (hsTnI <1.9 pg/ml).
HR, hazard ratio; hsTnI, troponin I measured by a high-sensitivity assay; SD, standard deviation

Supplemental Table VI. Adjusted hazard ratios for incident events by increasing categories of high-sensitivity assayed troponin I

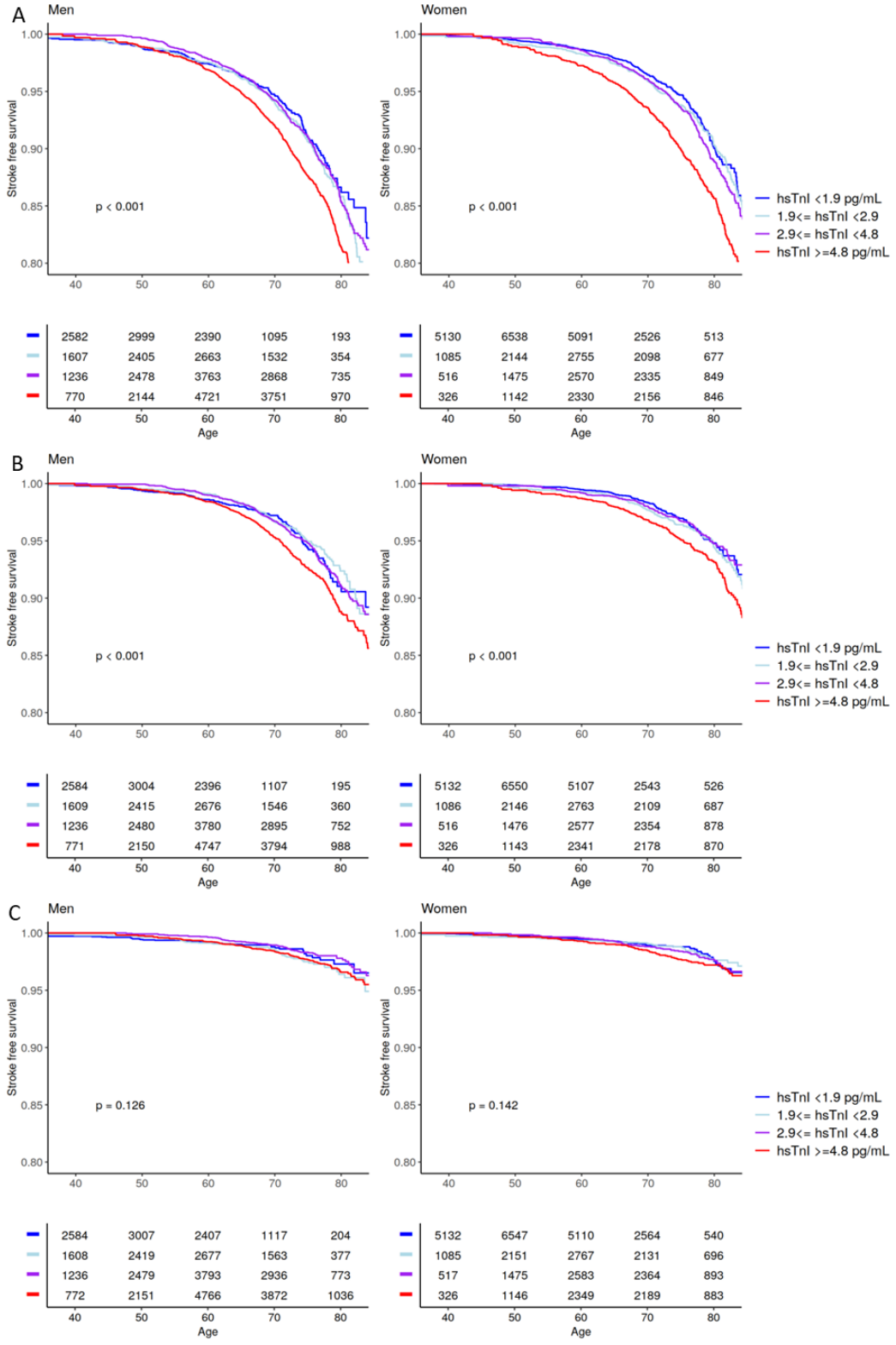
	High-sensitivity assayed troponin I (pg/ml)				p-value*
	<1.9	1.9-2.9	2.9-4.8	≥4.8	
Overall stroke					
Model 1	Reference	1.12 (0.98-1.27)	1.19 (1.05-1.34)	1.68 (1.48-1.90)	<0.001
Model 2	Reference	1.06 (0.93-1.21)	1.07 (0.94-1.21)	1.42 (1.24-1.61)	<0.001
Ischemic stroke					
Model 1	Reference	1.09 (0.90-1.32)	1.20 (1.01-1.42)	1.73 (1.46-2.06)	<0.001
Model 2	Reference	1.03 (0.84-1.25)	1.07 (0.89-1.28)	1.45 (1.22-1.74)	<0.001
Hemorrhagic stroke					
Model 1	Reference	1.18 (0.92-1.53)	1.16 (0.90-1.51)	1.53 (1.18-1.97)	0.002
Model 2	Reference	1.16 (0.90-1.50)	1.10 (0.84-1.43)	1.39 (1.07-1.80)	0.024

Model 1: stratified by sex, adjusted for age and cohort.
Model 2: Adjustment as in model 1 + adjustment for cardiovascular risk factors at baseline (body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol level, antihypertensive medication, diabetes mellitus, and daily smoking).
Data presented as hazard ratios (95% confidence interval).
Age was used as the time scale in all models.
*P-trend was calculated for linear increase in log relative hazards with increasing categories.

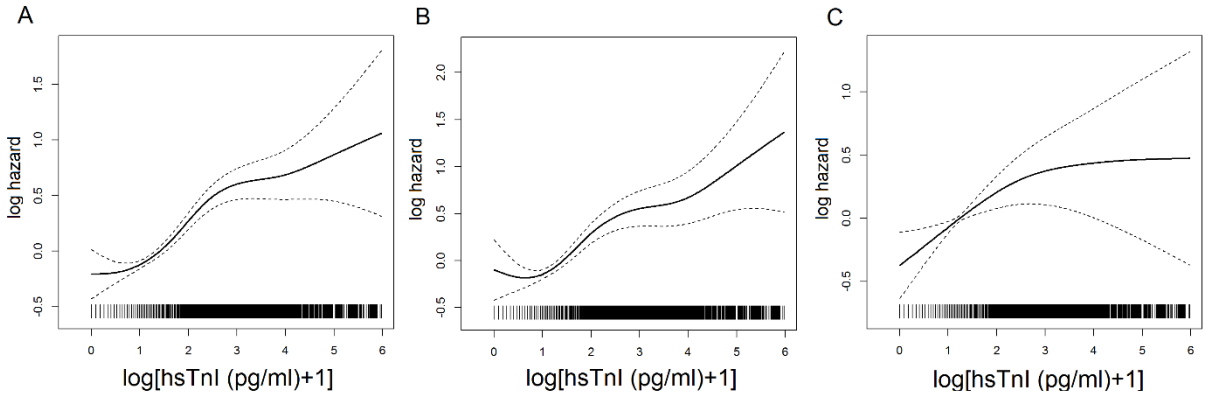
Supplemental Table VII. Detailed results on the improvement of 10-year risk prediction using troponin I measured by high-sensitivity assay for overall, ischemic and hemorrhagic stroke over the first 10 years of follow-up

	Overall stroke	**Ischemic stroke**	**Hemorrhagic stroke**
Addition of high-sensitivity assayed troponin I as a continuous variable			
C-index increment	0.00259 (95% CI 0.001-0.004; p<0.001)	0.00191 (95% CI 0.001-0.003; p=0.008)	0.00567 (95% CI 0.002-0.010; p=0.004)
Categorical NRI (cases)	0.0008 (95% CI -0.0122 - 0.0138; p=0.900)	0.0101 (95% CI -0.0072 - 0.0275; p=0.253)	0.0000 *
Categorical NRI (non-cases)	0.0001 (95% CI -0.0008 -0.0010; p=0.884)	-0.0004 (95% CI -0.0011 - 0.0003; p=0.212)	-0.0002 (95% CI -0.0004 - (-0.00004); p= 0.014)
Categorical NRI (overall)	0.0009 (95% CI -0.0121 -0.0139; p=0.893)	0.0097 (95% CI -0.0077 - 0.0270; p=0.274)	-0.0003 (95% CI -0.0004 - (-0.00004; p=0.014) *
Clinical NRI (cases)	-0.0212 (95% CI -0.0524 - 0.0100; p=0.183)	-0.0339 (95% CI -0.0827 - 0.0150; p= 0.174)	0.0000 *
Clinical NRI (non-cases)	0.0593 (95% CI 0.0508 - 0.0678; p<0.001)	0.0702 (95% CI 0.0571-0.0834; p<0.001)	0.1501 (95% CI 0.0679 - 0.2324; p<0.001)
Clinical NRI (overall)	0.0381 (95% CI 0.0057 - 0.0705; p=0.021)	0.0364 (95% CI -0.0142 - 0.0870; p=0.159)	0.1501 (95% CI 0.0679 - 0.2324; p<0.001) *
Continuous NRI (cases)	-0.1094 [95% CI -0.1640 – (-0.0548); p<0.001]	-0.1413 [95% CI -0.2139 – (-0.0687); p<0.001]	-0.0686 (95% CI -0.1864 - 0.0492; p=0.254)
Continuous NRI (non-cases)	0.1764 (95% CI 0.1695 – 0.1832; p<0.001)	0.1771 (95% CI 0.1702 – 0.1839; p<0.001)	0.2028 (95% CI 0.1960 - 0.2096; p<0.001)
Continuous NRI (overall)	0.0670 (95% CI 0.0120 – 0.1220; p=0.017)	0.0358 (95% CI -0.0371 – 0.1087; p=0.336)	0.1342 (95% CI 0.0163 - 0.252; p=0.026)
IDI	0.0006 (95% CI 0.0000-0.0013; p=0.050)	0.0004 (95% CI -0.0004 - 0.0011; p=0.363)	0.0002 (95% CI -0.0001 - 0.0004; p=0.168)
Addition of high-sensitivity assayed troponin I as a categorical variable			
C-index increment	0.00184 (95% CI 0.001 – 0.003; p=0.006)	0.00193 (95% CI 0.000 – 0.004; p=0.026)	0.00482 (95% CI 0.000 – 0.010; p=0.074)
Categorical NRI (cases)	0.0020 (95% CI -0.0122 - 0.0162; p=0.785)	0.0137 (95% CI -0.0065 – 0.0338; p=0.184)	0.0035 (95% CI -0.0026 - 0.0096; p=0.259)
Categorical NRI (non-cases)	-0.0005 (95% CI -0.0016 - 0.0005; p=0.318)	-0.0004 (95% CI -0.0013 – 0.0004; p=0.305)	-0.00007 (95% CI -0.0002 - 0.0001; 0.443)
Categorical NRI (overall)	0.0015 (95% CI -0.0128 - 0.0157; p=0.841)	0.0132 (95% CI -0.0070 – 0.0334; p=0.199)	0.0034 (95% CI -0.0027 - 0.0095; p=0.269)
Clinical NRI (cases)	-0.0156 (95% CI -0.0490 -0.0177; p=0.359)	-0.0668 (95% CI -0.1210 – (-0.0127); p=0.016)	0.0000 *
Clinical NRI (non-cases)	0.0698 (95% CI 0.0600 - 0.0796; p<0.001)	0.1096 (95% CI 0.0935 - 0.1258; p<0.001)	0.1770 (95% CI 0.0881 - 0.2660; p<0.001)
Clinical NRI (overall)	0.0542 (95% CI 0.0194 - 0.0889; p=0.002)	0.0428 (95% CI -0.0137 - 0.0993; p=0.138)	0.1770 (95% CI 0.0881 - 0.2660; p<0.001) *
Continuous NRI (cases)	-0.1171 (95% CI -0.1717 – (-0.0626); p<0.001)	-0.1358 (95% CI -0.2084 – (-0.0632); p<0.001)	0.0469 (95% CI -0.0708 – 0.1647; p=0.435)
Continuous NRI (non-cases)	0.1952 (95% CI 0.1883 – 0.2021; p<0.001)	0.2086 (95% CI 0.2018 – 0.2155; p<0.001)	0.0728 (95% CI 0.0660 – 0.0796; p<0.001)
Continuous NRI (overall)	0.0780 (95% CI 0.0230 – 0.1331; p=0.005)	0.0728 (95% CI 0.000 – 0.146; p=0.050)	0.1198 (95% CI 0.0018 – 0.2377; p=0.047)
IDI	0.0006 (95% CI 0.00000 -0.00122; p=0.049)	0.0008 (95% CI 0.00005 - 0.00165; p=0.038)	0.00004 (95% CI -0.0002-0.0003; p=0.725)

All models were sex-stratified and adjusted for cohort and cardiovascular risk factors at baseline (model 2). IDI, integrated discrimination improvement; NRI, net reclassification improvement. * The addition of hsTnI did not lead to a change in the event classification regarding the cases. Therefore, the NRI for cases is zero and the total NRI is equal to the NRI for non-cases.



Supplemental Figure I. Stroke-free survival according to high-sensitivity assayed troponin I (hsTnI) categories stratified by sex for overall stroke (A), ischemic stroke (B), and hemorrhagic stroke (C). Numbers below the curves represent individuals at risk at a certain age for the different hsTnI categories. Note that the y-axes are truncated at 0.8. Given p-values are for the comparison of the highest and lowest hsTnI categories.



Supplemental Figure II. Spline plots displaying the relative risk for the development of overall stroke (A), ischemic stroke (B) and hemorrhagic stroke (C) according to levels of high-sensitivity assayed troponin I (hsTnI). Individuals with log (hsTnI) > 6 pg/ml were dropped from these analyses. No fixed knots were used in order to allow for an optimal degree of freedom.

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