Cardiac Troponin I and Incident Stroke in European Cohorts. Insights From the BiomarCaRE Project

BiomarCaRE consortium (2020). Cardiac Troponin I and Incident Stroke in European Cohorts. Insights From the BiomarCaRE Project. Stroke, 51(9), 2770-2777. https://doi.org/10.1161/STROKEAHA.120.029452

Published in:
Stroke

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright 2020 the authors.
This is an open access article published under a Creative Commons Attribution-NonCommercial-NoDerivs License (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits distribution and reproduction for non-commercial purposes, provided the author and source are cited.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Download date: 27. Apr. 2021
Cardiac Troponin I and Incident Stroke in European Cohorts

Insights From the BiomarCaRE Project

Stephan Camen, MD; Tarja Palosaari, MSc; Jaakko Reinikainen, PhD; Ngoc Anh Sprünker, PhD; Teemu Niiranen, PhD; Francesco Gianfagna, MD; Julie K.K. Vihram-Nielsen, PhD; Simona Costanzo, PhD; Stefan Söderberg, PhD; Luigi Palmieri, PhD; Marco Ferrario, MD; Annette Peters, MD; Erkki Vartiainen, PhD; Maria Benedetta Donati, PhD; Chiara Donfrancesco, PhD; Rossana Borchini, MD; Christin Susanna Börschel, MD; Simona Giampaoli, MD; Augusto Di Castelnuovo, PhD; Christina Magnusson, MD; Frank Kee, MD; Wolfgang Koenig, MD; Stefan Blankenberg, MD; Giovanni de Gaetano, PhD; Hugh Tunstall-Pedoe, MD; Susanne Rospleszcz, PhD; Torben Jørgensen, DMSci; Tanja Zeller, PhD; Kari Kuulasmaa, MD; Allan Linneberg, PhD; Veikko Salomaa, MD; Licia Iacoviello, PhD; Renate B. Schnabel, MD; on behalf of the BiomarCaRE Consortium

BACKGROUND AND PURPOSE: Stroke is a common cause of death and a leading cause of disability and morbidity. Stroke risk assessment remains a challenge, but circulating biomarkers may improve risk prediction. Controversial evidence is available on the predictive ability of troponin concentrations and the risk of stroke in the community. Furthermore, reports on the predictive value of troponin concentrations for different stroke subtypes are scarce.

METHODS: High-sensitivity cardiac troponin I (hsTnI) concentrations were assessed in 82,881 individuals (median age, 50.7 years; 49.7% men) free of stroke or myocardial infarction at baseline from 9 prospective European community cohorts. We used Cox proportional hazards regression to determine relative risks, followed by measures of discrimination and reclassification using 10-fold cross-validation to control for overoptimism. Follow-up was based upon linkage with national hospitalization registries and causes of death registries.

RESULTS: Over a median follow-up of 12.7 years, 3033 individuals were diagnosed with incident nonfatal or fatal stroke (n=1654 ischemic strokes, n=612 hemorrhagic strokes, and n=767 indeterminate strokes). In multivariable regression models, hsTnI concentrations were associated with overall stroke (hazard ratio per 1-SD increase, 1.15 [95% CI, 1.10–1.21]), ischemic stroke (hazard ratio, 1.14 [95% CI, 1.09–1.21]), and hemorrhagic stroke (hazard ratio, 1.10 [95% CI, 1.01–1.20]). Adding hsTnI concentrations to classical cardiovascular risk factors (C indices, 0.809, 0.840, and 0.736 for overall, ischemic, and hemorrhagic stroke, respectively) increased the C index significantly but modestly. In individuals with an intermediate 10-year risk (5%–20%), the net reclassification improvement for overall stroke was 0.038 (P=0.021).

CONCLUSIONS: Elevated hsTnI concentrations are associated with an increased risk of incident stroke in the community, irrespective of stroke subtype. Adding hsTnI concentrations to classical risk factors only modestly improved estimation of 10-year risk of stroke in the overall cohort but might be of some value in individuals at an intermediate risk.

Key Words: cohort studies ◼ epidemiology ◼ risk assessment ◼ stroke ◼ troponin
S

Stro
to
erk

risk
assessment
in
the
community
remains
a
challenge.
Although
many
clinical
risk
factors
for
stroke
have
been
identified,
a
substantial
proportion
of
stroke
risk
remains
unexplained.1
Cardiac
troponin
is
a
structural
protein
released
into
the
blood
flow
as
a
consequence
of
myocardial
injury.2
Its
usefulness
as
a
sensitive
marker
for
myocardial
damage
has
been
widely
tested
and
become
a
routine
measurement
in
clinical
practice,
in
particular,
in
the
diagnosis
of
acute
ischemic
and
hemorrhagic
stroke.
However,
high-sensitivity
assays
have
led
to
a
significantly
enhanced
detection
of
troponin
concentrations,
considerably
broadening
its
clinical
application
and
interpretation.4
Mild
elevations
of
troponin
concentrations
are
associated
with
a
higher
risk
for
cardiovascular
disease
and
death
in
the
general
population.4–6
A
recent
meta-analysis
showed
an
association
between
elevated
troponin
concentrations
and
incident
stroke
in
the
general
population
but
also
revealed
large
heterogeneity
among
the
included
studies.7
While
the
additional
benefit
of
high-sensitivity
assayed
cardiac
troponins
to
predict
overall
cardiovascular
disease
has
been
repeatedly
demonstrated,
their
value
for
the
prediction
of
incident
stroke
in
primary
prevention
is
unknown.5,6,8,9
Furthermore,
reports
on
the
association
and
predictive
performance
of
troponin
in
relation
to
stroke
subtypes
are
scarce.7,9

Therefore,
based
on
cohorts
of
the
BiomarCaRE
(Biomarkers
for
Cardiovascular
Risk
Assessment
in
Europe)
consortium,10
our
primary
goal
was
to
further
investigate
the
relationship
of
high-sensitivity
cardiac
troponin
I
(hsTnI)
with
incident
stroke
in
Europe
and
to
examine
a
potential
difference
in
the
association
of
hsTnI
with
ischemic
and
hemorrhagic
stroke.
In
a
second
step,
we
aimed
to
determine
the
additional
predictive
value
of
hsTnI
beyond
classical
cardiovascular
risk
factors.

METHODS

Because
of
the
sensitive
nature
of
the
data
collected
for
this
study,
requests
to
access
the
dataset
from
qualified
researchers
trained
in
human
subject
confidentiality
protocols
may
be
sent
to
the
corresponding
author.

Study
Sample

We
pooled
participant-level
data
from
9
community
cohorts
of
the
BiomarCaRE
project
with
information
on
hsTnI
levels
and
stroke
status
at
baseline
and
follow-up
(http://www.biomincare.eu/),
the
MONICA
Brienza
Study,
the
KORA
study
(Cooperative
Health
Research
in
the
Region
of
Augsburg),
the
DanMONICA
study,
the
FINRISK
study,
the
MATISS
Rome
study,
the
Moli-sani
study,
the
Northern
Sweden
MONICA
study,
the
PRIME
(Prospective
Epidemiological
Study
of
Myocardial
Infarction)
from
Belfast,
and
the
SHHEC
(Scottish
Heart
Health
Extended
Cohort),
comprising
86,104
unique
individuals.10
Each
cohort
is
based
on
population
samples
with
baseline
examinations
between
1982
and
2010,
comprising
in
total
21
subcohorts
(please
see
the
Data
Supplement
for
details
on
the
enrollment
and
follow-up
procedures
of
each
cohort).
The
study
protocol
was
approved
by
the
local
ethics
review
boards
of
all
study
centers,
and
all
participants
provided
written
informed
consent.
The
protocol
adhered
to
the
principles
of
the
Declaration
of
Helsinki.
The
data
from
the
cohorts
were
harmonized
in
the
MONICA
Risk,
Genetics,
Archiving
and
Monograph
(MORGAM)
Project.11

Individuals
with
a
positive
history
of
stroke
or
myocardial
infarction
based
on
self-report
or
prior
physician’s
diagnosis
were
excluded
from
analyses,
including
individuals
in
whom
baseline
data
indicated
coronary
heart
disease,
but
separation
between
myocardial
infarction,
angina
pectoris,
and
possible
cardiac
revascularization
was
not
possible
(n=3223).
Therefore,
82,881
individuals
were
included
in
the
analysis.

Follow-Up
and
Definition
of
Outcomes

Follow-up
was
mainly
based
upon
linkage
with
national
hospitalization
registries
and
causes
of
death
registries.
In
addition,
some
cohorts
obtained
information
through
direct
contact
to
participants
or
general
practitioners
and
linkage
to
the
national
medication
registries.
Follow-up
for
mortality
was
obtained
from
central
death
registries.
The
follow-
up
for
the
different
cohorts
was
completed
between
2004
and
2012.12

Incident
strokes
and
identification
of
the
stroke
subtype
were
validated
according
to
MORGAM
criteria
(for
details
on
all
outcome
classifications,
please
see
https://www.ahajournals.org/journal/str).

Briefly,
a
stroke
was
categorized
as
an
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.
•
Typical
signs
of
infarct
in
the
brain
parenchyma
on
magnetic
resonance
imaging.
An event was also considered as ischemic stroke in the data analysis if there was no validation according to MORGAM criteria or validation was not possible due to insufficient data, but the routine clinical or death certificate diagnoses indicated cerebral infarction (International Classification of Diseases [ICD], Eighth Revision, code of 432, 433, or 434; ICD, Ninth Revision, code of 433 or 434; or ICD, Tenth Revision, code of I63).

Hemorrhagic stroke was defined as first fatal or nonfatal intracerebral or subarachnoid hemorrhage based on MORGAM criteria. To be classified as hemorrhagic stroke, at least one of the following criteria must be present:

- Validation of recent intracerebral hemorrhage or subarachnoid hemorrhage by necropsy.
- Typical signs of bleeding in the brain parenchyma (intracerebral hemorrhage) or signs of blood in the subarachnoid cisterns or in cerebral ventricles (subarachnoid hemorrhage) on computed tomography or magnetic resonance imaging.
- Bloody cerebrospinal fluid (liquor) in the presence of focal neurological signs at onset.

An event was also considered as hemorrhagic stroke in the data analysis if there was no validation according to MORGAM criteria or validation was not possible due to insufficient data but the routine clinical or death certificate diagnoses indicated hemorrhagic stroke (ICD, Eighth Revision, code of 430 or 431; ICD, Ninth Revision, code of 430 or 431; or ICD, Tenth Revision, code of I60 or I61).

Strokes that could be classified neither as ischemic nor hemorrhagic were called indeterminate. An incident coronary event was defined as a composite end point of any cardiac revascularization and acute coronary events including hospitalization for unstable angina pectoris. Incident atrial fibrillation (AF) was defined by date of the first documentation on ECG or assignment of the relevant ICD code (427.4 for ICD, Eighth Revision; 427.3 for ICD, Ninth Revision; and 148 for ICD, Tenth Revision).

### Laboratory Methods

All troponin I levels were measured by an hsTnl assay at the central BiomarCaRE laboratory in Hamburg (Abbott Diagnostics; ARCHITECT i2000SR). In line with previous studies, 1.9 pg/mL was considered the limit of detection (LoD).\(^6\)\(^8\) Observed values below this threshold were included for analyses in this study ( assay range, 0–50 000 pg/mL). The assay supported a 10% coefficient of variation at a concentration of 5.2 pg/mL.

### Statistical Analyses

Baseline characteristics are expressed as numbers and percentages for categorical variables, medians and interquartile ranges for continuous variables. To avoid possible problems caused by obvious outliers, hsTnl data were winsorized by replacing the 3 highest hsTnl values with the fourth highest value in each subcohort. We used multiple imputation to handle missing data in continuous variables.\(^13\) For the dichotomous variables, missing values were recoded to zero (no) to avoid incompleteness (please see https://www.ahajournals.org/journal/str for details on the multiple imputation).

### Association Analyses

To examine the association of hsTnl with incident stroke, we performed Cox proportional hazards regression models with overall stroke, ischemic stroke, and hemorrhagic stroke as the outcome. Age was used as the time scale. In these analyses, hsTnl was log-transformed (logarithm of hsTnl+1).

We performed incremental adjustment starting with a cohort-adjusted and sex-stratified model (model 1) and then added the variables of the Framingham risk score for estimating the 10-year risk of cardiovascular events in primary care (body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol level, antihypertensive medication, diabetes mellitus, and daily smoking; model 2).\(^14\) This set of risk factors was used for all analyses. Adjustment for region within studies was performed where available. In a third step, we calculated a Cox regression analysis with fatal and nonfatal coronary event as time-dependent covariates (model 3).

In a further analysis, we also accounted for incident AF as a time-dependent covariate (model 4). In a sensitivity analysis, we excluded individuals with prevalent AF or heart failure at baseline. MONICA Brianza, KORA, MATISS, and PRIME were excluded from the latter 2 analyses since data on AF were not available for these cohorts. Individuals were censored at the end of follow-up, death, or the time of their event in respective analyses.

For categorical analysis, we defined 3 cut points for hsTnl at 1.9 pg/mL (LoD) as the lowest cut point and by further subdividing individuals with observed hsTnl values above the LoD into thirds (resulting in cut points of 2.9 and 4.8 pg/mL, respectively). \(P\) trend was calculated for linear increase in log relative hazards with increasing categories. Kaplan-Meier curves for incident overall stroke, ischemic stroke, and hemorrhagic stroke were produced using categorized troponin concentrations. The score log-rank test was used to test for potential survival difference between hsTnl categories. Proportional hazards assumption was tested by plotting scaled Schoenfeld residuals against follow-up time for each covariate separately and using \(\chi^2\) test to test for a nonzero slope.

### Prediction Analyses

In prediction analyses, 10-year absolute risks were estimated by a Weibull curve fitted over age for the baseline hazard and adjusted by the linear predictor of the estimated Cox model with and without hsTnl. Ten-fold cross-validation was used to control for overoptimism. The additional value of hsTnl concentrations to the Framingham risk factors was assessed by calculating C-index improvement, integrated discrimination improvement, as well as categorical and continuous net reclassification improvement (NRI).\(^15\) The risk categories used for the categorical NRI analysis were 0% to 5%, 5% to 10%, 10% to 20%, and >20%. We further determined the clinical NRI, which refers to individuals with an intermediate 10-year risk of cardiovascular events (5%–20%). For the calculation of \(C\) indices and NRI, the follow-up time was censored at 10 years.

A 2-sided value of \(P\leq0.05\) was considered statistically significant. All statistical analyses were conducted with R statistical software, version 3.6.0 (the R project for statistical computing).
RESULTS

Population Characteristics

Eighty-two thousand eight hundred eighty-one individuals were included for analyses in this study, 49.7% being men. The median age at baseline was 50.7 (interquartile range, 18.0) years (Table 1). The prevalence of diabetes mellitus at baseline was 3.9%, 14.8% were treated with antihypertensive medication, and about every fourth was a daily smoker. Over a median follow-up of 12.7 years, 3033 (3.7%) individuals were diagnosed with stroke. Of these, 1654 (2.0% of the overall cohort) had an ischemic stroke, 612 (0.7%) had a hemorrhagic stroke, and stroke subtype could not be specified in 767 (0.9%) individuals.

hsTnI Concentrations and Their Association With Incident Stroke

The median hsTnI value in the overall cohort was 2.4 pg/mL (interquartile range, 2.7 pg/mL). Values above the LoD were observed in 52 902 (63.8%) individuals. HsTnI was associated with a significantly increased risk for overall (hazard ratio [HR], 1.15 per 1-SD increase [95% CI, 1.10–1.21]; P<0.001), ischemic (HR per SD, 1.14 [95% CI, 1.09–1.21]; P<0.001), and hemorrhagic stroke (HR per SD, 1.10 [95% CI, 1.01–1.20]; P=0.032). The inclusion of incident coronary events and AF as time-dependent covariates did not markedly alter the results (Table 2). The multivariable adjusted HRs for incident stroke increased with increasing hsTnI categories, and individuals in the highest category had a 42% increased risk for overall stroke compared with individuals with hsTnI levels below the LoD (HR, 1.42 [95% CI, 1.24–1.61]; P<0.001; Figure 1). The HRs for ischemic and hemorrhagic stroke were 1.45 ([95% CI, 1.22–1.74] P<0.001) and 1.39 ([95% CI, 1.07–1.80] P<0.001) for individuals in the highest compared with the lowest category, respectively. Figure 2 displays survival curves according to categories of hsTnI for overall, ischemic, and hemorrhagic stroke. The association of hsTnI with incident overall stroke was observed in all cohorts (Figure 3).

Table 1. Characteristics of the Study Population

| General Characteristics | n=82,881 |
|-------------------------|---------|
| Years of baseline examinations, range in years | 1982–2010 |
| Age at baseline examination, y | 50.7 (18.0) |
| Men, n (%) | 41,166 (49.7) |
| Stroke risk factors | |
| Body mass index, kg/m² | 26.2 (5.7) |
| Systolic blood pressure, mm Hg | 131 (28) |
| Total cholesterol, mmol/L | 5.7 (1.5) |
| High-density lipoprotein cholesterol, mmol/L | 1.4 (0.5) |
| Antihypertensive medication, n (%) | 12,253 (14.8) |
| Diabetes mellitus, n (%) | 3,231 (3.9) |
| Daily smoker, n (%) | 22,371 (27.0) |
| hsTnI ≥1.9 pg/mL, n (%) | 52,902 (63.8) |
| HsTnI, pg/mL | 2.4 (2.7) |
| End points during follow-up | |
| Stroke (any type), n (%) | 3,033 (3.7) |
| Ischemic stroke, n (%) | 1,664 (2.0) |
| Hemorrhagic stroke, n (%) | 612 (0.7) |
| Death, n (%) | 10,753 (13.0) |
| Other events during follow-up | |
| Coronary event, n (%) | 6102 (7.4) |
| AF, n (%) | 2888/62566† (4.6) |

Table 1. Characteristics of the Study Population

Pooled characteristics of the 9 cohorts are presented as absolute and relative frequencies for categorical variables and medians and interquartile ranges for continuous variables. AF indicates atrial fibrillation; and hsTnI indicates high-sensitivity cardiac troponin I.

DISCUSSION

In our pooled analysis of 9 European community-based cohorts, we demonstrate an association of hsTnI concentrations with incident stroke, independent of stroke subtype. The addition of hsTnI to the variables of the Framingham risk score hardly improved stroke risk prediction among all subjects. Focusing on individuals with an intermediate 10-year risk (5%–20%), we found a clinical NRI for overall, ischemic, and hemorrhagic stroke of 0.038 ([95% CI, 0.006–0.070] P=0.021), 0.036 ([95% CI, −0.014 to 0.087] P=0.159), and 0.150 ([95% CI, 0.068–0.232] P<0.001), respectively. Details on all risk prediction analyses are provided in Table 3.

hsTnI as a Stroke Risk Factor

A recent meta-analysis of 12 studies conducted in the general population demonstrated an association of
However, the authors reported a great heterogeneity in the included studies, and no information on stroke subtype was provided. A report from the ARIC study (Atherosclerosis Risk in Communities) revealed an association of high-sensitivity assayed troponin T with incident ischemic stroke with the highest HRs for cardioembolic stroke but did not show a significant association with hemorrhagic stroke. In a more recent analysis, an association of hsTnI with incident ischemic stroke of similar strength compared with the present study was demonstrated using the same hsTnI assay, but they did not report on hemorrhagic stroke. In the present study, we found an association of hsTnI with ischemic and hemorrhagic stroke. A possible explanation for the observed association between hsTnI and ischemic stroke is that these events might be related to asymptomatic arrhythmias, in particular, AF. Although, in some cases of a (cardio)embolic stroke, a secondary hemorrhagic transformation might have led to a misclassification of stroke subtype, this concept does not sufficiently explain the association of hsTnI with hemorrhagic stroke. Hypertension and increasing age constitute major risk factors for both stroke subtypes, but etiology and further risk factors differ significantly. Elevated hsTnI values reflect a subclinical manifestation of cardiac injury, likely as a consequence of cardiac stress due to the presence of cardiovascular risk factors, for example, arterial hypertension. Therefore, the association of hsTnI with incident stroke might be an indicator of an underlying systemic (vascular) disease, considering the overlap of cardiovascular and cerebrovascular risk factors.

### Table 2. HRs for hsTnI in Relation to Stroke

|                       | Continuous hsTnI* | Categorical hsTn† |
|-----------------------|-------------------|------------------|
|                       | HR per SD (95% CI) | P Value | HR (95% CI) | P Value | No. of Events |
| Overall stroke        |                   |         |             |         |               |
| Model 1               | 1.21 (1.16–1.26)  | <0.001  | 1.68 (1.48–1.90) | <0.001  | 3033          |
| Model 2               | 1.15 (1.10–1.21)  | <0.001  | 1.42 (1.24–1.61) | <0.001  | 3033          |
| Model 3               | 1.14 (1.10–1.18)  | <0.001  | 1.42 (1.28–1.55) | <0.001  | 2994          |
| Model 4               | 1.14 (1.10–1.18)  | <0.001  | 1.40 (1.26–1.54) | <0.001  | 2391          |
| Ischemic stroke       |                   |         |             |         |               |
| Model 1               | 1.20 (1.14–1.26)  | <0.001  | 1.73 (1.46–2.06) | <0.001  | 1654          |
| Model 2               | 1.14 (1.09–1.21)  | <0.001  | 1.45 (1.22–1.74) | <0.001  | 1654          |
| Model 3               | 1.14 (1.09–1.19)  | <0.001  | 1.47 (1.28–1.65) | <0.001  | 1633          |
| Model 4               | 1.13 (1.07–1.18)  | <0.001  | 1.41 (1.21–1.61) | <0.001  | 1210          |
| Hemorrhagic stroke    |                   |         |             |         |               |
| Model 1               | 1.14 (1.05–1.24)  | 0.003   | 1.53 (1.18–1.97) | 0.001   | 612           |
| Model 2               | 1.10 (1.01–1.20)  | 0.032   | 1.39 (1.07–1.80) | 0.013   | 612           |
| Model 3               | 1.10 (1.01–1.18)  | 0.030   | 1.39 (1.12–1.66) | 0.016   | 607           |
| Model 4               | 1.10 (1.01–1.20)  | 0.037   | 1.39 (1.09–1.69) | 0.033   | 496           |

*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 with individuals with hsTnI values below the LoD (hsTnI, <1.9 pg/mL).

Figure 1. Hazard ratios (HRs) and 95% CIs for high-sensitivity cardiac troponin I (hsTnI) categories.

The presented HRs are based on a sex-stratified Cox regression analyses with adjustment for cohort, body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol level, antihypertensive medication, diabetes mellitus, and daily smoking (model 2).
studies demonstrated a potential benefit in global cardiovascular risk prediction by addition of hsTnI, but reports focusing on incident stroke are rare.\textsuperscript{5,6,8} Two prior studies found no significant improvement in stroke risk prediction by adding high-sensitivity troponin T or hsTnI.\textsuperscript{8,9} It is difficult to improve discrimination beyond classical risk factors, in particular, when risk indicators such as hsTnI are partially correlated with the other variables.\textsuperscript{6,15} In the setting of primary prevention, individuals with an estimated intermediate risk for incident disease are most likely to benefit from additional guidance on potential therapy initiation/modification, since guideline recommendations for these individuals are often less clear.\textsuperscript{1} Considering the observed clinical NRI in our study, the assessment of hsTnI might be of help in selected individuals at intermediate cardiovascular risk in whom standard stroke risk classification yields inconclusive results.

Limitations and Strengths

Several limitations merit consideration. Stroke diagnosis was based on medical records rather than on standard neurological examination or review of brain imaging. Despite the systematic and detailed validation of stroke events, residual misclassification cannot be ruled out. Furthermore, due to the comparatively small number of events, we did not perform separate analyses for subarachnoid and intracerebral hemorrhages, although their pathophysiology differs significantly.

HsTnI was measured only once at the time of inclusion of the individuals in the specific cohort. Therefore, information on possible changes of hsTnI and how these might be related to incident stroke was not available.

Considering that NT-proBNP (N-terminal pro-B-type natriuretic peptide) has been shown to be associated with both ischemic and hemorrhagic stroke,\textsuperscript{19} it would have been preferable to include NT-proBNP into our analysis and to assess potential interaction of both factors.
biomarkers in their association with incident stroke. However, NT-proBNP measurements were not available for all cohorts, and, therefore, the number of incident stroke events would have decreased significantly. Further, earlier studies suggest that the association of troponin with stroke is independent of NT-proBNP levels.\(^4,5,9\)

Our results are based on European cohorts and cannot be extrapolated to other populations, in particular, since an interaction by race for the association of hsTnI and stroke has been suggested.\(^5\)

The strength of our study is the large sample from several countries with a long follow-up and carefully harmonized data in which we can provide results with good power, in particular, with regard to the less common outcome of hemorrhagic stroke.

**Conclusions**

Elevated hsTnI concentrations are associated with an increased risk of incident stroke in the general population, irrespective of stroke subtype. A possible explanation may be underlying systemic cardiovascular disease. However, adjustment for interim cardiovascular disease did not alter the results substantially. Adding hsTnI concentrations to classical cardiovascular risk factors only modestly improved the prediction of 10-year risk of stroke in the overall cohort but might be of some value in intermediate-risk groups. More importantly, the pathophysiological relationship between the cardiac biomarker hsTnI and stroke needs to be further elucidated.

**ACKNOWLEDGMENTS**

We thank the participants and the staff of the cohorts for their continuing dedication and efforts.

**Sources of Funding**

The BiomarCaRE (Biomarkers for Cardiovascular Risk Assessment in Europe) Project is funded by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No. HEALTH-F2-2011-278913. Dr Schnabel has received funding from the European Research Council under the European Union’s Horizon 2020 research and innovation programme (grant agreement No. 648131), from the European Union’s Horizon 2020 research and innovation programme (grant agreement No. 847770; AFFECT-EU), and the German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103). German Federal Ministry of Research and Education (BMBF; 01ZX1408A) and ERA-COSysMed3 (031L0599). The activities of the MONICA Risk, Genetics, Archiving and Monograph (MORGAM) Data Center have been sustained by recent funding from the European Union FP 7 project CHANCES (HEALTH-F3-2010-242244). The MORGAM Biomarker Study (Serum Biomarkers in the MORGAM Populations) has further received funding from the Medical Research Council London (G0601463, No. 80983). The KORA study (Cooperative Health Research in the Region of Augsburg) was initiated and financed by the German Heart Foundation Munich, Technical University of Munich, Germany (W.K.). German Centre for Cardiovascular Research, Partner Site Munich Heart Alliance (WK, A.P., AP). Institute of Epidemiology and Medical Biometry, University of Ulm, Germany (W.K.). Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, United Kingdom (HT-P). Faculty of Medicine, Aalborg University, Denmark (T.J.).

**ARTICLE INFORMATION**

Received: February 21, 2020; final revision received: June 18, 2020; accepted: July 9, 2020.

**Affiliations**

University Heart and Vascular Center Hamburg, Clinic for Cardiology, Germany (S.C., N.A.S., C.B., C.M., S.B., T.Z., R.B.S.). German Center for Cardiovascular Research, Partner Site Hamburg/Kiel/Luebeck (S.C., S.C., C.M., S.B., T.Z., R.B.S.). Finnish Institute for Health and Welfare, Helsinki, Finland (T.P., J.R., T.N., E.V., K.K., S.G.). Department of Medicine, Turku University Hospital and University of Turku, Finland (T.N.). Research Center in Epidemiology and Preventive Medicine, Department of Medicine and Surgery, University of Insibria, Varese, Italy (F.G., M.F., R.B., L.I.). Mediterranean Cardiocentro, Napoli, Italy (F.G., A.D.C.). Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Capital Region of Denmark, Copenhagen (J.K.K.V.-N., T.J., A.L.). Department of Cardiology, Rigshospitalet (J.K.K.V.-N.), Department of Public Health, Faculty of Health and Medical Sciences (T.J.), and Department of Clinical Medicine, Faculty of Health and Medical Sciences (A.L.), University of Copenhagen, Denmark, Department of Epidemiology and Prevention, IRCSS Neuromed, Pozzilli, Italy (S. Costanzo, M.B.D., G.d.G., L.I.). Department of Public Health and Medicine and Health Centre, Umeå University, Sweden (S.S.). Department of Cardiovascular, Endocrine-Metabolic Diseases and Aging, Istituto Superiore di Sanità-ISS, Rome, Italy (L.P., C.D., S.G.). Institute of Epidemiology, Helmholtz Zentrum München–German Research Center for Environmental Health, Neuherberg (A.P., S.R.). Institute for Medical Information Sciences, Biometry and Epidemiology, Ludwig Maximilians University, Munich, Germany (A.P., S.R.). Centre for Public Health, Queens University of Belfast, United Kingdom (F.K.). German Heart Center Munich, Technical University of Munich, Germany (W.K.). German Centre for Cardiovascular Research, Partner Site Munich Heart Alliance (WK, A.P.). Institute of Epidemiology and Medical Biometry, University of Ulm, Germany (W.K.). Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, United Kingdom (HT-P). Faculty of Medicine, Aalborg University, Denmark (T.J.).
Camen et al Cardiac Troponin I and Incident Stroke in Europe

5. Jia X, Sun W, Hoogeveen RC, Nambi V, Matsuhashi K, Folsom AR, Heiss G, Couper DJ, Solomon SD, Boerwinkle E, et al. High-sensitivity troponin I and incident coronary events, stroke, heart failure hospitalization, and mortality in the ARIC Study. Circulation. 2019;139:2642–2653. doi: 10.1161/CIRCULATIONAHA.118.038772

6. Blankenberg S, Salomaa V, Makarova N, Ojeda F, Wild P, Lackner KJ, Jürgensen T, Thordar B, Peters A, Nauck M, et al; BiomarCaRE Investigators. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. Eur Heart J. 2016;37:2428–2437. doi: 10.1093/eurheartj/ehw172

3. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Adams JE III, Bodor GS, Dávila-Román VG, Delmez JA, Apple FS, Ladenson PW, Huxley RR, Ballantyne CM, Troponin T. N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. Stroke. 2013;44:961–967. doi: 10.1161/STROKEAHA.111.000173

2. Adams JE III, Bodor GS, Dávila-Román VG, Delmez JA, Apple FS, Ladenson PW, Huxley RR, Ballantyne CM, Troponin T. N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. Stroke. 2013;44:961–967. doi: 10.1161/STROKEAHA.111.000173

REFERENCES

1. Meschia JF, Bushnell C, Boden-Alba B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Ekild MS, Fornage M, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension; Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:3754–3832. doi: 10.1161/STROKEAHA.113.000052

2. Adams JE III, Bodor GS, Dávila-Román VG, Delmez JA, Apple FS, Ladenson JH, Jaffe AS. Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation. 1993;88:101–106. doi: 10.1161/01.cir.88.1.101

3. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Föhrlich M, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med. 2009;361:668–677. doi: 10.1056/NEJMoa090315

4. Willeit P, Welch P, Evans JD, Tischder L, Boachie C, Jukema JW, Ford I, Trumpet S, Stott DJ, Kearney PM, et al. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. J Am Coll Cardiol. 2017;70:558–568. doi: 10.1016/j.jacc.2017.05.062

The Academy of Finland (321351). The DanMONICA cohorts at the Research Center for Prevention and Health were established over a period of 10 years and have been funded by numerous sources, which have been acknowledged, where appropriate, in the original articles. The MATISS Project was partly supported by the National Research Council, by the Istituto Superiore di Sanità-ISS (1984, 1987, 1993-1996) and by the Ministry of Health (1998). The Mol-sani Project was partially supported by research grants from Pfizer Foundation (Rome, Italy), the National Society of Italian Research (Rome, Italy)—Programma Tien- nale di Ricerca, Decreto n.1568, and Instrumentation Laboratory, Milan, Italy. The Northern Sweden MONICA project was supported by the Norrbotten and Västerbotten County councils. Dr Söderberg has been supported by the Swedish Heart-Lung Foundation (20140799, 20120631, and 20100635), the County Council of Västerbotten (ALF, VLL-548791), and Umeå University. The SHReC (Scottish Heart Health Extended Cohort) received funding from the Scottish Health Department Chief Scientist Organization, the British Heart Foundation, and the FP Fleming Trust.

Disclosures

Dr Di Castelnuovo reports grants from the European Foundation for Alcohol Research as the coapplicant of the ongoing study supported by a research grant (id. EA1767) unrelated to the current study. Dr Kee reports funding from grants of the UK Clinical Research Collaboration and from the Wellcome Trust unrelated to the current work. Dr Schnabel reports personal fees from BMS/Pfizer and lecture and advisory board fees unrelated to the current study. Dr Blankenberg reports research funding from Abbott Diagnostics, Bayer, SIE- MENS, Singulex, and Thermo Fisher. He further received honoraria for lectures from Abbott, Abbott Diagnostics, AstraZeneca, Bayer, AMGEN, Medtronic, Pfizer, Roche, SIEMENS Diagnostics, SIEMENS, and Thermo Fisher as a member of Advisory Boards and for consulting for Bayer, Novartis, and Thermo Fisher. Dr Costanzo reports funding from an ERAB grant (id. EA1767) and personal fees as a member of the Organizing Committee and speaker for the Ninth European Beer and Health Symposium (Bruxelles 2019) and for given lecture at the 13th European Nutrition Conference (FENS 2019, Dublin), all unrelated to the current work. Dr Söderberg reports personal fees from Acte- lium, Ltd. Dr Salomaa has received honoraria from Novo Nordisk and Sanofi for consultations. He also has ongoing research collaboration with Bayer AG (all unrelated to the present study). Dr Koenig reports personal fees from AstraZeneca, Novartis, Pfizer, The Medicines Company, DaCoR, Kowa, Amgen, Corvidia, Berlin-Chemie, Sanofi, Bristol-Myers Squibb, and Daichii-Sankyo and nonfinancial support by grants from Abbott, Roche Diagnostics, Beckmann, and Singulex, all unrelated to the current study. The other authors report no conflicts.