Cardiac Troponin I Associated with the Development of Unrecognized Myocardial Infarctions Detected with MRI

Charlotte Ebeling Barbier,1* Raquel Themudo,1 Tomas Bjerner,1 Lars Johansson,1,2 Bertil Lindahl,3 Per Venge,3 Lars Lind,3 and Håkan Ahlström1

BACKGROUND: Late enhancement MRI (LE-MRI) and cardiac troponin I (cTnI) are sensitive methods to detect subclinical myocardial injury. We sought to investigate the relation between plasma concentrations of cTnI measured with a high-sensitivity assay (hs-cTnI) and the development of unrecognized myocardial infarctions (UMIs) detected with LE-MRI.

METHODS: After approval from the ethics committee and written informed consent were obtained, LE-MRI was performed on 248 randomly selected community-living 70-year-old volunteers and hs-cTnI was determined with a highly sensitive premarket assay. Five years later these individuals were invited to a second LE-MRI, and 176 of them (82 women, 94 men), who did not have a hospital diagnosis of MI, constitute the present study population. LE-MRI images were analyzed by 2 radiologists independently and in a consensus reading, blinded to any information on previous disease or assessments.

RESULTS: New or larger UMIs were detected in 37 participants during follow-up. Plasma concentrations of hs-cTnI at 70 years of age, which were mainly within what is considered to be the reference interval, were related to new or larger UMIs at 75 years of age with an odds ratio of 1.98 per 1 unit increase in ln-transformed cTnI (95% CI, 1.17–3.35; *P* = 0.010). Plasma concentrations of hs-cTnI at 70 years of age were associated with the volumes of the UMIs detected at 75 years of age (*P* = 0.028).

CONCLUSIONS: hs-cTnI in 70-year-old community-living women and men was associated with the development of MRI-detected UMIs within 5 years. © 2014 American Association for Clinical Chemistry
subsampling from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (13). All individuals aged 70 years who resided in the municipality of Uppsala, Sweden, were eligible for the PIVUS study. The participants were randomly chosen from the register of municipality inhabitants. A total of 2025 individuals were invited to participate within weeks of their 70th birthday; 1016 agreed to participate in the study.

From the original cohort, 283 individuals were consecutively invited to undergo cardiac MRI, for which the number of participants was determined by the availability of MRI scan time, financial limitations, and a desire that the interval between the MR examination and the primary investigation should not be too long. A total of 259 of these individuals in whom the MRI was not contraindicated accepted the invitation and assessable images were obtained on 248 individuals as reported previously (8). Eleven individuals with recognized MI (i.e., scars on LE-MRI and a hospital diagnosis of MI) at baseline were excluded (for acquisition and assessment criteria, see below). Of the remaining 237 participants, 183 were reexamined 5 years later (10 had died, 44 declined to participate). One of these individuals, in whom plasma troponin was not analyzed, was excluded. To assure that the MI scars in this study were unrecognized, participants displaying MI scars at 75 who had acquired a hospital diagnosis of MI (n = 5) or who had been exposed to percutaneous coronary intervention (n = 1) during follow-up were excluded. The remaining 176 (83 women, 94 men) constitute the study population of the present study.

**IMAGE ACQUISITION**

Image acquisition and analysis have been described elsewhere (8). Briefly, imaging was performed on a 1.5-T MRI system (Gyroscan Intera; Philips Medical Systems) with a 33-mT/m gradient system, using the standard SENSE cardiac coil in the supine position and retrospectively gated vector ECG for cardiac triggering.

At 70 years of age, all participants were administered 40 ml gadolinium-diethylene triamine pentaaetic acid-bismethylamide (OmniscanTM; GE Healthcare) because whole-body MR angiography was performed before acquisition of the late enhancement images. When the participants were 75 years of age, the contrast dose was adjusted to body weight (0.2 mmol/kg). Late enhancement images were acquired using a 3-dimensional inversion recovery gradient echo sequence covering the entire heart in short- and long-axis views. The acquired slice thickness was 10 mm with a resolution of 1.56 × 2.81 mm and the inversion time was individually adjusted.

Cine images were acquired during breath-holding by using a steady-state free precession sequence covering the left ventricular myocardium in 8-mm-thick short axis slices with a 2.5-mm slice gap, an acquired in-plane resolution of 2.27 × 1.81 mm, 18 phases/cardiac cycle, and 2 slices/breath hold. The temporal resolution varied between the participants depending on their heart rates.

**IMAGE ANALYSIS**

All LE-MR images were analyzed by 2 radiologists independently and in a consensus reading, using subendocardial involvement as a criterion for identifying MI scars (14, 15). Each observer was blinded to the other observer’s assessments and to information on any previous disease, as described elsewhere (8, 16). The radiologists who analyzed the images acquired when the participants were 75 years old were blinded to the analysis results from images acquired when they were 70 years old. To avoid overreporting the prevalence of MI scars, an additional consensus reading was performed in which images displaying MI scars at either 70 or 75 years of age were compared side by side with the images from the individual’s other MR examination and viability was assessed taking information from the cine images into consideration.

Left ventricular mass (LVM) and function were established via images from both examinations using a workstation with commercially available analysis software (ViewForum R4.1 V1L2; Philips Medical Systems). Quantification was performed by 1 observer on short-axis images, using a semiautomated method with papillary muscles included in the LVM. Ejection fraction (EF) and LVM were computed assuming a myocardial density of 1.05 g/mL (17), and LVM was adjusted for body surface area (18).

The myocardium displaying LE, representing MI scars, was manually outlined by 1 observer in all slices where it was present, as described elsewhere (8). The same observer performed the outlining in the images from the examinations at 70 and 75 years of age in a blinded setup.

Images were assessed for new UMIs at 75 years in individuals without MI scars at age 70 years. In individuals displaying UMIs at 70 years, images were assessed for enlarged scars in the same location and for scars in a new location at age 75 years. An increase in total scar volume of 0.2 g or more was considered to represent an enlargement of the UMI. This level was estimated considering the spatial resolution of the images.

Participants who had not acquired any new or larger UMI were classified into 3 groups: those who did not display any areas of nonviable myocardium (NoLE), those who displayed LE that did not represent any MI scar (i.e., not involving the subendocardial layer) (Other LE), and those who displayed a UMI that had not increased in size between 70 and 75 (Old UMI).
The interobserver variability in assessing the LE-MRI images was determined as the percentage of time that the observers agreed on the presence or absence of UMI.

**PARTICIPANT DATA AND LABORATORY ANALYSES**

At the time of inclusion in the study, the participants answered a questionnaire about their medical and drug histories, and then they were weighed and measured, blood pressures were measured, and a 12-lead ECG was performed using standard techniques (13). A venous blood sample was taken in the morning after an overnight fast. No medication or smoking was allowed after midnight. There was a mean delay of 16 months (range 3–22 months) between these investigations and the MRI examination at 70 years of age. Another venous blood sample was taken at the time of the second MRI examination after an overnight fast, with no medication or smoking allowed after midnight.

Fasting blood glucose, LDL cholesterol, and HDL cholesterol were measured using standard techniques. The following definitions were applied: hypertension, blood pressure ≥140/90 mmHg or antihypertensive treatment; diabetes, fasting blood glucose ≥6.2 mmol/L or receiving antidiabetic treatment.

cTnI, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and creatinine were measured in EDTA plasma samples that were collected and frozen at the time of the primary investigation in the PIVUS study.

cTnI was analyzed on an ARCHITECT i2000SR platform using the ARCHITECT STAT hs-TnI assay (Abbott Laboratories). The limits of the blank and of detection for this assay have been reported as 0.9 ng/L and 1.2–1.5 ng/L, respectively, and the 99th percentile among healthy individuals has been reported in the range of 14–23 ng/L (19, 20). The imprecision profile of 250 duplicate samples in our internal validation showed a 10% CV at 8 ng/L and a 20% CV at <2 ng/L.

NT-proBNP was measured using the Elecsys proBNP sandwich immunoassay on an Elecsys 2010 instrument (Roche Diagnostics). According to the manufacturer the imprecision is <4% CV within the measuring range of 59–6552 ng/L.

Plasma creatinine was measured using the modified kinetic Jaffe reaction. The MDRD (Modification of Diet in Renal Disease) formula (21) was used to calculate the glomerular filtration rate (GFR).

The risk of coronary heart disease (CHD) was estimated using the Framingham Risk Score (FRS) (which estimates total CHD risk using the factors age, LDL and HDL cholesterol, blood pressure, cigarette smoking, and diabetes mellitus) (22). Within days from the MR examination at 75 years of age, a new 12-lead ECG was performed.

Medical records of the entire baseline cohort (n = 248) from all divisions of Uppsala University Hospital and from all general practitioners in the county were scrutinized, and data on cardiac and atherosclerotic symptoms, morbidity, and mortality that occurred before and between the MRI examinations were collected. In cases in which the participant was listed as deceased in the medical records, death certificates were obtained and reviewed. A major adverse cardiac event (MACE) was defined as cardiac death (i.e., cardiac arrest being registered as the primary cause of death in the death certificate), nonfatal MI (i.e., a hospital diagnosis of MI set using the criteria defined by the Joint European Society of Cardiology/American College of Cardiology Committee (23)), or symptom-driven coronary artery revascularization.

**STATISTICAL METHODS**

STATA 11 (STATA Inc.) was used for statistical analyses.

Nonnormally distributed variables, such as cTnI measured with the hs-cTnI assay and NT-proBNP, were ln-transformed before analysis to obtain a normal distribution.

To estimate differences between groups in baseline characteristics, a χ² test was used for nominal parameters and a 2-sample Wilcoxon rank-sum (Mann–Whitney) test was used for continuous parameters. To estimate differences in hs-cTnI between participants with and without new or larger UMI, an unpaired Student t-test was used, and to estimate differences in hs-cTnI between baseline and follow-up within each group a paired Student t-test was used.

The predictive power of hs-cTnI was evaluated with logistic regression models using hs-cTnI as a continuous variable and adjusting first for sex only and then for sex, GFR, LVM, EF, NT-proBNP, and the Framingham risk score. The relationship between hs-cTnI and the change in scar volume was evaluated by Spearman rank correlation in those who developed a new or larger UMI. The relationship between hs-cTnI and risk of new or larger UMI was visualized by plotting the predictive margins, allowing for nonlinear relationships by including a squared term for hs-cTnI in the model. The statistical significance level was set at 0.05 in all analyses.

**Results**

The incidence rate of new or larger UMIs at 75 years of age was 21% (n = 37/176) in the entire cohort, 20% (n = 16/82) in women, and 22% (21/94) in men. At baseline (i.e., at 70 years of age) 33 participants displayed UMIs. At 75 years of age, 13 of these displayed an increased scar volume. Twenty-four participants...
who were free from scars at baseline displayed new UMIs at follow-up (i.e., at 75 years of age). Baseline characteristics and cardiac function parameters are displayed in Table 1.

There was an interobserver agreement of 81% in the primary LE-MR image assessments. The agreement between the 2 observers and the final consensus was 87% and 91% respectively.

hs-cTnI was measurable in all participants. The median plasma concentration of hs-cTnI at follow-up was 5.9 ng/L (interquartile range, 4.1–8.7 ng/L) in individuals who had acquired a new or larger UMI during follow-up, and 4.8 ng/L (interquartile range 3.6–6.4 ng/L) in individuals who had not (P = 0.037). The median plasma concentration of hs-cTnI at baseline was 4.1 ng/L (interquartile range 3.1–7.0 ng/L) in individuals who had acquired a new or larger UMI during follow-up and 3.3 ng/L (interquartile range 2.5–4.2 ng/L) in those who had not (P = 0.004) (Table 1). There was a significant difference in the median plasma hs-cTnI concentrations at follow-up compared with baseline in individuals with (P = 0.04) and without (P < 0.0001) new or larger UMI.

Among the 139 participants who had not acquired any new or larger UMI, 98 displayed no areas of nonviable myocardium (NoLE), 21 displayed LE not involving the subendocardial layer (Other LE), and 20 displayed a UMI that had not increased in size during follow-up (Old UMI). The median plasma concentrations of hs-cTnI did not differ significantly between these 3 groups at baseline or at follow-up (Table 2). However, baseline hs-cTnI concentrations differed from follow-up hs-cTnI concentrations within each group (Table 2). There was a significant difference in median hs-cTnI between individuals with NoLE and those with new or larger UMI, both at baseline (P = 0.009) and at follow-up (P = 0.017) (Table 3).

Plasma concentrations of hs-cTnI at baseline were associated with new or larger UMIs at 75 years of age with an odds ratio (OR) of 1.98 (95% CI, 1.17–3.35; Table 3).

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### Table 1. Baseline characteristics in 70-year-old participants with and without new or larger UMI on LE-MRI at 75 years of age.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study population (n = 176)</th>
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<tr>
<td></td>
<td>No new MI (n = 139)</td>
<td>P value</td>
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<tr>
<td>Female sex, n (%)</td>
<td>66 (48)</td>
<td>0.62</td>
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<tr>
<td>hs-cTnI, median (interquartile range), ng/L</td>
<td>3.2 (2.5–4.2)</td>
<td>0.004</td>
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<tr>
<td>GFR, median (interquartile range), mL/min</td>
<td>89.4 (81.6–99.5)</td>
<td>0.94</td>
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<tr>
<td>LVM, median(interquartile range), g/m²</td>
<td>58 (49–65)</td>
<td>0.07</td>
</tr>
<tr>
<td>EF, median(interquartile range), %</td>
<td>72 (68–76)</td>
<td>0.21</td>
</tr>
<tr>
<td>NT-proBNP, median(interquartile range), ng/L</td>
<td>90.9 (55.2–145)</td>
<td>0.09</td>
</tr>
<tr>
<td>FRS, median (interquartile range)</td>
<td>11 (9–13)</td>
<td>0.91</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>40 (29)</td>
<td>0.61</td>
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<tr>
<td>Diabetes, n (%)</td>
<td>9 (6.5)</td>
<td>0.72</td>
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<tr>
<td>Statin use, n (%)</td>
<td>16 (11)</td>
<td>0.23</td>
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<tr>
<td>Current smoking, n (%)</td>
<td>8 (5.8)</td>
<td>0.36</td>
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### Table 2. hs-cTnI in community-living individuals at 70 (baseline) and at 75 (follow-up) years of age grouped according to the findings on LE-MRI at 75 years of age.

<table>
<thead>
<tr>
<th>hs-cTnI</th>
<th>No new MI (n = 139)</th>
<th>Other LE (n = 21)</th>
<th>Old UMI (n = 20)</th>
<th>Comparison: no new MI vs new or larger UMI</th>
<th>New or larger UMI (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, median, ng/L</td>
<td>3.2</td>
<td>3.3</td>
<td>3.8</td>
<td>P = 0.004</td>
<td>4.1</td>
</tr>
<tr>
<td>Comparison baseline vs follow-up hs-cTnI</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P = 0.008</td>
<td></td>
<td>P = 0.042</td>
</tr>
<tr>
<td>Follow-up hs-cTnI, median, ng/L</td>
<td>4.6</td>
<td>5.0</td>
<td>5.1</td>
<td>P = 0.037</td>
<td>5.9</td>
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</table>
P = 0.010) per 1 unit increase in ln-transformed cTnI in a model using hs-cTnI as a continuous variable when adjusted for sex, and an OR of 1.81 (95% CI, 1.04–3.13; P = 0.035) when adjusted for sex, GFR, LVM, EF, NT-proBNP, and FRS. There was a linear relationship between baseline hs-cTnI concentrations and the incidence of new or larger UMI (P = 0.010) (Fig. 1).

The median size of the UMIs (i.e., the median of the volumes of the new UMIs and of the volumes of the additional MI scar tissue at 75 years of age) was 1.07 g (interquartile range, 0.68–1.59 g). In the 37 individuals who experienced a new UMI or an enlargement of a UMI during follow-up, the baseline hs-cTnI plasma concentrations were associated with the new or additional myocardial scar volumes (Spearman ρ = 0.36, P = 0.028) (Fig. 2). Examples of UMIs are displayed in Fig. 3 with the associated scar volumes and the hs-cTnI concentrations.

Sex, LVM, EF, NT-proBNP, and FRS were all individually associated with hs-cTnI plasma concentrations at baseline, but GFR was not.

There were no significant differences in EF or in LVM between the ages of 70 and 75.

Among the 37 individuals displaying a new or larger UMI, 2 developed an ST-segment depression on ECG between the age of 70 and 75 years, whereas 4 with Q-wave or T-wave abnormalities at 70 years of age had normal ECGs at age 75 years. Among the 139 participants without MI scars on LE-MRI, 1 developed an ST segment depression and 1 developed a T-wave abnormality, whereas there were no new Q waves in this group. Thus, development of a new or larger UMI on

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<th>hs-cTnI, median (interquartile range), ng/L</th>
<th>NoLE (n = 98)</th>
<th>Comparison NoLE vs new or larger UMI</th>
<th>New or larger UMI (n = 37)</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>3.2 (2.3–4.2)</td>
<td>P = 0.009</td>
<td>4.1 (3.1–7.0)</td>
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<tr>
<td>Follow-up</td>
<td>4.6 (3.5–6.0)</td>
<td>P = 0.017</td>
<td>5.9 (4.3–8.7)</td>
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Fig. 1. Relationship between hs-cTnI concentrations and a new or larger UMI.

The proportion of community-living participants displaying a new or larger unrecognized myocardial infarction at 75 years of age in relation to their hs-cTnI concentrations at 70 years of age estimated with a logistic regression model (P = 0.010). The proportion (and 95% CI) of a new or larger UMI is given on the y axis. The ln-value corresponding to the 99th percentile would be 2.5–3 and is not included in the figure.
LE-MRI was not associated with the development of signs of ischemia on the ECG.

During follow-up, 5 MACEs occurred in participants without MI scars on MRI (1 hospital diagnosis of MI and 4 symptom-driven coronary artery revascularizations). There were no MACEs in the participants with new or larger UMIs (because participants displaying MI scars at 75 who had acquired a hospital diagnosis of MI or who had been exposed to percutaneous coronary intervention were excluded, as described in Materials and Methods). Among the 72 participants who were excluded from the baseline cohort, 8 MACEs occurred during follow-up (1 cardiac death, 4 hospital diagnoses of MI, and 3 symptom-driven coronary artery revascularizations). The other 9 participants who were excluded because they had died between the MRI examinations had died from noncardiac causes.

Discussion

Plasma hs-cTnI concentrations at 70 years of age were associated with the development of new or larger MRI-detected UMIs within 5 years, and the sizes of the UMIs were associated with these baseline concentrations of cTnI. The proportion of community-living participants developing a new or larger UMI within 5 years increased with increasing baseline cTnI concentrations. This suggests that the risk of developing a UMI increases with increasing cTnI, even within what is considered to be the reference interval, i.e., below the 99th percentile of a healthy reference population (24).

Others have reported that even minimally increased cardiac troponin may represent subclinical myocardial injury (1). This notion is supported by the results of the present study. Moreover, our results emphasize that LE-MRI (8, 9) and cardiac troponin (1, 2) may be the 2 most sensitive methods available to detect myocardial injury.

The spatial resolution of LE-MRI should be sufficient for detection of the smallest UMIs in the present study. Because infarct size normally decreases during healing (25–27), an increase in MI scar volume was considered to represent an active process similar to the one generating a new UMI. A linear relation between MI size determined with LE-MRI and cTnI concentrations has been reported in 7 patients with acute coronary syndrome (28). A relation between UMI size and hs-cTnI was observed in the present study as well. However, in the present study cTnI concentrations were measured before the UMI had developed or become enlarged, suggesting that cTnI concentrations might predict not only the development of a UMI but also its size.

Several pathophysiological processes may cause cardiac troponin release (29). Cardiac troponin might reflect reversible as well as irreversible myocyte damage (29), whereas MRI-detected UMIs represent irreversibly damaged myocytes. The pathophysiological process or processes causing MRI-detected UMIs are unknown. The observed association between cTnI and the development of UMI in the present study do not necessarily indicate causality but could represent a co-variation of parameters reflecting the same pathophysiological process or vulnerability.

In the present study, cTnI was measured at a random point of time when no chest pain or other possible symptoms of myocardial ischemia were present and the participants had no MI scar on LE-MRI. Hence, increased concentrations might reflect an ongoing low-grade consumption of myocytes, also presenting as areas of nonviable myocardium, i.e., UMIs. The observation that cTnI increased between baseline and follow-up suggests such a process, first detectable with slightly higher cTnI concentrations at 70 years of age, and 5 years later with even higher cTnI concentrations and myocardial damage large enough to be detected as a scar on MRI. Both the actual cTnI concentration and the UMI size could indicate to what extent myocytes are consumed, a concept supported by the observation that there was an association between these 2 parameters.

The positive association between cTnI and FRS that was observed in the present study might indicate that these UMIs and the cTnI concentrations reflect an early stage of atherosclerosis. This theory is supported by the observation that progressively increasing cTnT...
concentrations are found in patients with mild, moderate, and multivessel coronary artery disease on computed tomography angiography compared with patients without coronary artery disease (30). It has been suggested that increases in troponin might be caused by silent rupture of noncalcified plaques, with subsequent microembolization (31). The theory that MRI-detected UMIs reflect an early stage of atherosclerosis is supported by the association between such UMIs and atherosclerosis risk factors, coronary calcium, and treatment for atherosclerosis that was observed in a large population-based sample (9).

Myocardial injury can also arise from an ischemic imbalance between myocardial oxygen supply and demand (24). Such an imbalance might have generated the UMIs and the cTnl increases detected in the present study, a notion supported by the observed positive association between cTnl and LVM. Increased cTnl in patients with a large LVM has been observed by others (32). Furthermore, changes in coronary vascular reac-

![Fig. 3. UMIs in 75-year-old community-living individuals.](image)

Examples of short-axis late enhancement MRIs displaying UMIs (with and without the infarct area delineated) constituting 4% of the LVM in an individual with a cTnl 4.5 ng/L at 70 years of age (A) and constituting 0.6% of the LVM in an individual with cTnl 2.5 ng/L at 70 years of age (B).
Activity can occur in individuals without symptomatic CHD (33), and MI can be caused by coronary vasospasm (34) and endothelial dysfunction (35, 36).

Irrespective of the underlying pathophysiological process, MRI-detected UMIs (9) and cTnI (2, 37) both predict death in population-based samples. In addition, low concentrations of cTnI (2, 38) and small MRI-detected UMIs (11, 39) have proven prognostic significance. The observation that cTnI concentrations below the 99th percentile were associated with the development of an MRI-detected UMI suggests that even cTnI concentrations within the reference interval may provide prognostic information, because having such a UMI is associated with increased mortality (9).

Hence, these highly sensitive methods to detect myocardial damage enable us to identify individuals with a formerly unknown increased cardiovascular risk. In the present study there was an overlap between the range of cTnI concentrations that predicted UMI and the range of cTnI concentrations that did not. Thus, from only these data it is not possible to determine a cutoff concentration at which cTnI would necessitate preventive measures for the individual. Furthermore, any cutoff concentration would be greatly influenced by the age of the patient, because cTnI concentrations in the present study differed more between baseline and follow-up than between individuals with and without UMI.

Nevertheless, cTnI concentrations might contribute to the identification of risk groups. The associations between cTnI concentration and sex, LVM, EF, NT-proBNP, and FRS that were observed in the present study suggest that these parameters may be part of the same risk profile. Furthermore, NT-proBNP (40), sex, LVM, EF and atherosclerosis risk factors (10) are all individually associated with MRI-detected UMIs. Thus, considering cTnI concentrations in relation to these parameters might give additional information when estimating cardiovascular risk. Still, it remains to be investigated at what level this risk becomes substantial and who would benefit from primary prevention or treatment.

The present study was limited by the fact that only elderly white individuals were studied. Thus, results may not be applicable to other ethnic or age groups. Owing to a rather small sample size, analysis of sex-specific data was considered to be statistically unreliable and adjustment for sex was preferred.

In conclusion, increased hs-cTnI plasma concentrations in 70-year-old community-living individuals were associated with the development of new or larger MRI-detected UMIs within 5 years. The sizes of the new UMIs were associated with the baseline concentrations of cTnI. The clinical impact of these UMIs has yet to be determined.

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