Clinically Unrecognized Myocardial Infarction Detected at MR Imaging May Not Be Associated with Atherosclerosis

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Purpose:
To prospectively investigate whether there is support for the hypothesis that clinically unrecognized myocardial infarctions (UMIs) detected at magnetic resonance (MR) imaging have an atherosclerotic pathogenesis similar to that of recognized myocardial infarctions (RMIs).

Materials and Methods:
After ethics committee approval and informed consent were obtained, gadolinium-enhanced whole-body MR angiography and late-enhancement MR imaging were performed in 248 randomly chosen 70-year-old subjects (123 women, 125 men). Imaging included the aorta and the carotid, renal, and lower limb arteries to the ankle, but not the coronary arteries. Subjects with myocardial infarction (MI) scars at late-enhancement MR imaging were classified as having RMI (n = 110) (those with a diagnosis of MI at the hospital) or UMI (n = 49) (those without a diagnosis of MI at the hospital). The presence of 50% or higher luminal narrowing in any vessel at whole-body MR angiography was considered to represent significant atherosclerosis. Intima-media thickness of the common carotid artery was measured with ultrasonography. C-reactive protein level was measured, and coronary heart disease risk was estimated. Observers were blinded to any previous results. The χ² test, analysis of variance, and Bonferroni correction were used for statistical analyses.

Results:
None of the measured parameters differed significantly between the group without MI scars and the UMI group, but parameters were significantly increased in the RMI group (P < .05) compared with those in the group without MI scars. Forty-two of 49 UMIs and nine of 11 RMIs were located within inferolateral segments of the left ventricle.

Conclusion:
MR imaging–detected UMIs might have a different pathogenesis from that of RMIs or may have the same pathogenesis but may manifest at an earlier stage.
late-enhancement magnetic resonance (MR) imaging accurately depicts myocardial infarctions (MIs) and other myocardial scars as hyperintense areas (1–3). This technique depicts a larger number of clinically unrecognized MIs (UMIs) than does electrocardiography (4). The risk-factor profiles and mortality rates for subjects with UMIs detected at electrocardiography (ie, because of persistent Q waves) are similar to those for patients with recognized MIs (RMIs) (5), whereas the clinical effect and prognosis of UMIs detected at MR imaging are not yet established, to our knowledge.

It has recently been observed (6) that the presence and extent of unrecognized myocardial scars at MR imaging are strong predictors of major adverse cardiac events, including cardiac death, in patients suspected of having coronary artery disease but without a history of MI. An increased cardiovascular risk has also been found in a community-based population sample by the facts that subjects with UMIs had a higher frequency of chest pain symptoms, a lower ejection fraction, and a larger left ventricular mass than those without MI scars at MR imaging (4). MR imaging–detected UMIs are frequently distributed in the inferolateral segments of the left ventricle (4), which is a region where electrocardiography has low sensitivity (7,8).

There is evidence that atherosclerosis is a panarterial disease (9) and that atherosclerotic plaques in the aorta are associated with coronary artery disease (10), MI (11), and an increased risk of cardiac death (12) and coronary events (12,13). Furthermore, coronary atherosclerosis and related left ventricular dysfunction have been detected in subjects without a history of clinical cardiovascular disease, which indicates that myocardial damage induced by atherosclerosis can occur earlier than suspected (14).

The pathogenesis of MI includes three main components: the vulnerable atherosclerotic plaque, the vulnerable blood (prone to thrombosis), and the vulnerable myocardium (prone to arrhythmia) (15,16). The cardiovascularily vulnerable patient has one or several of these components and is thereby susceptible to an acute coronary syndrome or sudden cardiac death (15,16).

Whole-body MR angiography that includes the aorta and the carotid, renal, iliac, and lower limb arteries has been proved to have a high sensitivity and specificity for depiction of significant vascular stenoses compared with those of conventional digital subtraction angiography (17,18).

Increases in the thickness of the intima and media of the common carotid artery are associated with coronary atherosclerosis (19) and an increased risk of MI (20).

In results of a previous study (4), among 248 70-year-old subjects, 188 had no MI scars at cardiac MR imaging (ie, no MI), 49 had MI scars but no diagnosis of MI at the hospital (ie, a UMI), and 11 had both an MI scar and a diagnosis of MI at the hospital (ie, an RMI). Given these observations, the purpose of our study was to prospectively investigate whether there is support for the hypothesis that MR imaging–detected UMIs have a pathogenesis similar to that of RMIs.

**Materials and Methods**

Three authors (L.J., L.L., and J.H.) are employed by AstraZeneca (Gothengburg, Sweden). Gadodiamide (Omniscan) was provided by GE Healthcare (Oslo, Norway). The authors who are not employees of AstraZeneca had full control of the data and the information published.

**Study Population**

Whole-body MR angiography and cardiac MR imaging were prospectively performed in a sample of subjects from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (21), who were recruited at age 70 years. The PIVUS study and our current study were approved by the ethics committee of Uppsala University Hospital, and all participants gave written informed consent. Eligible for the PIVUS study were all subjects who were 70 years of age and residents of the municipality of Uppsala, Sweden. The subjects were chosen in a randomized manner from the register of municipality inhabitants, and 2025 subjects were invited to participate.

**Implications for Patient Care**

- If our observations indicate that unrecognized myocardial infarctions (UMIs) have a different pathogenesis from that of recognized myocardial infarctions (RMIs), subjects with UMI and those with RMI may require different care and treatment.
- If UMIs are caused by atherosclerosis but manifest at an earlier stage of disease than conventional methods are able to depict, MR imaging then could be useful as a method for depicting early atherosclerosis.

**Abbreviations:**
- MI = myocardial infarction
- PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors
- RMI = recognized MI
- UMI = unrecognized MI

**Author contributions:**
Guarantors of integrity of entire study, C.E.B., H.A.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, C.E.B., L.J., H.A.; clinical studies, C.E.B., T.B., L.L., L.J., H.A.; statistical analysis, C.E.B., T.B., L.L., L.J., H.A.; and manuscript editing, C.E.B., T.B., L.L., L.J., H.A.

See Materials and Methods for pertinent disclosures.
participate within weeks of their 70th birthday; 1016 agreed.

From the original cohort, 283 subjects were consecutively invited to undergo cardiac MR imaging, which was ultimately performed in 259 subjects, with a mean delay of 16 months (range, 3–22 months) after the primary investigations. Their mean age was 71 years 6 months (age range, 70 years 5 months to 71 years 10 months) when MR imaging was performed. The number of subjects invited was preset; it was determined by financial limitations and the availability of MR imaging time. Eleven examinations were not assessable because of poor image quality, which left assessable data from 248 subjects (123 women, 125 men). The subjects were grouped on the basis of late-enhancement MR imaging findings: 188 had no MI scar, 49 had a UMI, and 11 had an RMI. This has been described elsewhere (4). All parameters described below were measured in all 248 subjects, except the intima-media thickness of the carotid artery, for which measurements were assessable in only 239 subjects (183 of 188 of those without MI scars at MR imaging, 46 of 49 of those with UMI, and 10 of 11 of those with RMI).

At the time of inclusion in the study, which was, on average 16 months (range, 3–22 months), before the MR imaging examination, the participants answered a questionnaire about their medical and drug histories, and their blood pressures were measured. A venous blood sample was taken in the morning after an overnight fast. No medication or smoking was allowed after midnight. Fasting blood glucose and low- and high-density lipoprotein cholesterol levels were measured by using standard techniques. Subjects were considered to have diabetes mellitus if their fasting blood glucose level was 6.2 mmol/L or higher or if they were undergoing antidiabetic treatment. High-sensitive C-reactive protein level was assessed by using a particle-enhanced immunoturbidimetric assay (Konelab autoanalyzer; Orion Diagnostica, Espoo, Finland). The coefficient of variation for this method is 3.25%, with a detection limit of 0.25 mg/L.

The risk of coronary heart disease was estimated by one observer (L.L.) by using the Framingham risk score (which estimates total coronary heart disease risk by using the following factors: age, low- and high-density lipoprotein cholesterol levels, blood pressure, cigarette smoking habits, and diabetes mellitus) (22).

The basic characteristics and major cardiovascular risk factors of our subjects (Table) did not differ significantly from those of the entire PIVUS population (determined by using the chi-squared test for dichotomous variables and two-way analysis of variance for continuous variables, with the significance level set at .05) (21), except that there were fewer current smokers among the subjects in our study (7.7% compared with 11%; \( P < .05 \), binomial probability test). The cardiac morbidity of the PIVUS study participants did not differ significantly from that of the background population at a significance level of .05 (21).

### Carotid Artery Intima-Media Thickness

The intima-media thickness of the common carotid artery was measured by one observer (J.A., 3 years of experience). Measurements were made bilaterally in diastole 1 cm proximal to the bifurcation by using a cardiac ultrasonographic (US) unit (XP124; Acuson, Mountain View, Calif) with a 10-MHz transducer. The mean measurement of the two arteries was used as the measurement of intima-media thickness.

### Image Acquisition

Imaging was performed with a 1.5-T MR system (Gyroscan Intera; Philips Medical Systems, Best, the Netherlands) with a maximum gradient amplitude of 33 mT/m by using the standard quadrature body coil for MR angiography and the standard sensitivity-encoding cardiac coil for cardiac imaging, with retrospectively gated vector electrocardiography for cardiac triggering.

The whole body was imaged in the supine position by using a three-di-dimensional radiofrequency spoiled T1-weighted gradient-echo sequence during the first pass of 40 mL of gadodiamide (Omniscan; GE Healthcare), which was injected intravenously at a rate of 0.6 mL/sec (23). Imaging was performed in four stations, with 3-cm overlap between the stations. The acquired section thickness was 4 mm, with a resolution of 1.76 \( \times \) 1.76 mm. Imaging included the aorta and the carotid, renal, and lower limb arteries to the ankle. The coronary arteries were not imaged.
After whole-body MR angiography, cardiac late-enhancement images were acquired by using a three-dimensional inversion-recovery gradient-echo sequence that covered the entire heart in short- and long-axis views. The acquired section thickness was 10 mm, with a resolution of 1.56 × 2.81 mm, and the inversion time was individually adjusted. This has been described previously (4).

**Image Analysis**

Whole-body MR angiographic images were assessed by one observer (T.H., 4 years of experience). Measurements were made in the narrowest part of the vessel and were compared with the normal vessel diameter by using the source and maximum intensity projection images. The presence of luminal narrowing of 50% or greater in any assessable vessel was considered to represent significant atherosclerosis.

Late-enhancement images were analyzed by two observers (C.E.B., 3 years of experience; T.B., 8 years of experience) independently and in a consensus reading by using subendocardial involvement as a criterion for identification of MI scars (24,25). The analysis of cardiac MR images and interobserver variability have been described elsewhere (4). The proportion of MI scars at an inferolateral location (including segments 4, 5, 10, and 11 of the American Heart Association segmentation system [26]) was established by the same two observers in consensus (C.E.B. and T.B.) (4).

**Statistical Analysis**

Software (StatView, version 5.0.1; SAS Institute, Cary, NC) was used for statistical analyses. For the estimation of differences in the prevalence of atherosclerosis between the groups, the χ² test was used. Variance analysis of intima-media thickness, C-reactive protein level, and Framingham risk score was performed by using two-way analysis of variance, with Bonferroni correction for post hoc analysis. The significance level was set at .05 in all analyses (ie, P < .05).

**Results**

Forty-two (86%) of 49 UMIs and eight (73%) of 11 RMIs were located within one to four inferolateral segments of the left ventricle (segments 4, 5, 10, and 11) (Fig 1). One of the UMIs included all four of these segments, three included three segments, 21 included two segments, and 17 included only one segment.

Neither the prevalence of significant atherosclerosis at whole-body MR angiography nor the intima-media thickness, C-reactive protein level, or Framingham risk score differed significantly between the group without MI scars and the UMI group (P > .0167 [ie, .05 with Bonferroni correction]), but these prevalence rates were all significantly increased in the RMI group compared with those in the group without MI scars (P < .0167 [ie, .05 with Bonferroni correction]) (Figs 2–4).

**Discussion**

The results of our study suggest that MR imaging–detected UMIs are not associated with manifestations of significant atherosclerosis in the rest of the body or with traditional risk factors for coronary heart disease, whereas RMIs are. This is consistent with the findings of a recent study (27) of previously unrecognized MR imaging–detected MI scars in 30% of patients with acute chest pain and elevated troponin I level but with no or minimal coronary artery disease detected at coronary angiography. Furthermore, changes in coronary vascular reactivity have been detected in subjects without symptomatic coronary heart disease who did, however, display risk factors (28).

The MI scars that were found in the patients without coronary artery disease detected at coronary angiography were located mainly in the inferolateral region of the left ventricle (27), which is the same region where the majority of the MI scars in our study were seen (segments 4, 5, 10, and 11). Myocarditis also occurs predominantly in the lateral segments (5,11, 16,25,29) but originates from the epicardial quartile of the ventricular wall and not from the subendocardium (29), which is typical for MI (24,25). Subendocardial involvement was used as a criterion for the identification of MI scars in our study. The distribution of myocarditic lesions is thus typically subepicardial or midwall, even though transmurality can occur (25).

It is possible that some of the lesions assessed as transmural UMIs in our study could be myocarditis scars, but far from all cases of myocarditis leave...
myocardial scars (29) and none of these subjects had a myocarditis diagnosis in their medical records (4). However, the fact that myocarditis occurs mainly in the lateral segments indicates that this region may have a generally increased vulnerability.

The inferolateral segments where the MI scars were predominantly distributed belong to different vascular territories; segments 4 and 10 are generally supported by the right coronary artery, and segments 5 and 11 are generally supported by the left circumflex artery (26), even though there is an interindividual anatomic variation of the dominance of the right or left coronary artery (30). Many of the MI scars extended into both territories. The lack of significant atherosclerosis in the rest of the body suggests that the classical atherosclerotic pathogenetic features, including plaque rupture and occlusion of a large supporting vessel, may not be the cause of these UMIs. This location would, however, indicate that the cause could be ischemic. Because the MI scars were distributed around a border between two vascular territories (26), it is conceivable that this border constitutes a watershed area that is supported by small end arteries and is thus more vulnerable to ischemia than other areas, like the watershed areas of the brain (31,32). This hypothesis is supported by a previous observation that perfusion from the neighboring artery in a watershed area of the heart is significantly poorer in the lateral segments indicates that this region may have a generally increased vulnerability.

In our study cohort, none of the factors contributing to the Framingham risk score were increased in the UMI group, whereas the prevalence rates of hypertension, hypercholesterolemia, and diabetes were significantly increased in the RMI group compared with those in the group without MI scars (4). Because all subjects in our study population were the same age, it is possible that only two factors were responsible for the increased Framingham risk score in the RMI group: the increased prevalence of diabetes and the overrepresentation of male sex (nine of 11 subjects were men). The Framingham risk score was created to estimate total coronary heart disease risk during the course of 10 years, and the observations made by Nicholls et al (36) demonstrate that it does not provide information on the severity of coronary atherosclerosis.

Unrecognized myocardial scars at MR imaging have been observed to have important prognostic implications in patients suspected of having coronary artery disease (6). However, the clinical effect and prognosis of MR imaging–detected UMIs in a community-based population have not been established, to our knowledge. In our community-based study population, the total risk of coronary heart disease during the course of 10 years, which was estimated with the Framingham risk score (22), was not increased in the subjects with UMI. There also was no increase in the C-reactive protein level, which is known to predict cardiovascular events (34,35).

However, results of a recent study (36) showed no correlation between atherosclerotic plaque burden measured with intravascular US in patients with coronary disease and the traditional risk factors of hypertension, hypercholesterolemia, C-reactive protein level, and current smoking habit. Diabetes and male sex were, however, strong predictors for disease severity (36). Except for C-reactive protein level, these parameters are, together with age, used to calculate the Framingham risk score (22). In our study cohort, none of the factors contributing to the Framingham risk score were increased in the UMI group, whereas the prevalence rates of hypertension, hypercholesterolemia, and diabetes were significantly increased in the RMI group compared with those in the group without MI scars (4). Because all subjects in our study population were the same age, it is possible that only two factors were responsible for the increased Framingham risk score in the RMI group: the increased prevalence of diabetes and the overrepresentation of male sex (nine of 11 subjects were men). The Framingham risk score was created to estimate total coronary heart disease risk during the course of 10 years, and the observations made by Nicholls et al (36) demonstrate that it does not provide information on the severity of coronary atherosclerosis.

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Furthermore, only luminal narrowing exceeding 50% at whole-body MR angiography, which corresponds to a rather advanced stage of atherosclerosis, was registered. Furthermore, it has been advocated that it is not lumen size but the tendency of the plaque to rupture that constitutes the risk for future cardiovascular events (37). Hence, estimation of the total plaque burden may not be an adequate tool to evaluate atherosclerotic risk.

Intima-media thickness of the common carotid artery—which was measured in our study—correlates only weakly with the extent and severity of coronary artery disease (38), whereas intima-media thickness of the carotid bifurcation and plaques are associated with ischemic heart disease (39), and an intima-media thickness score of the common and internal carotid artery, carotid bifurcation, and femoral artery correlates well with the extent of coronary atherosclerosis (19).

C-reactive protein elevation is not specific for atherosclerosis and was, as mentioned above, not related to coronary plaque burden in the study by Nicholls et al (36).

The prognostic importance of MR imaging–detected UMIs is suggested by several recent observations. Christiansen et al (27) showed that, among patients with minimal coronary artery disease detected at coronary angiography, subsequent cardiac events during 14 months of follow-up were more frequent in those with MI scars than in those without. Ingkanisorn et al (40) observed the presence of an MI scar on MR images to be predictive of future coronary artery disease, MI, or death, despite the fact that 43% of the scars were smaller than 10 g. The UMIs in our study were significantly smaller than RMIs (mean of 1.9% of left ventricular myocardial mass compared with mean of 4.8% of left ventricular myocardial mass) (4). However, in patients suspected of having coronary artery disease, even small myocardial scars on MR images (mean of 1.4% of left ventricular myocardial mass) were associated with a more than sevenfold increase in major adverse cardiac events, including cardiac death (6).

Among the three components contributing to the concept of the vulnerable patient (15,16), the watershed hypothesis could provide the vulnerable myocardium. A subclinical atherosclerotic plaque might then be sufficient to cause ischemic injury in such an area. The UMIs of our study may thus represent an early stage of atherosclerosis that has not yet manifested itself in any other detectable way, similar to or even earlier than the coronary atherosclerosis detected by Edvardsen et al (14) in subjects without a history of clinical cardiovascular disease.

Our study was limited by the fact that the parameters selected to indicate an atherosclerotic pathogenesis of MR imaging–detected UMIs may have been too coarse compared with the sensitivity of late-enhancement MR imaging. Other limitations were that imaging did not include the coronary arteries and that the RMI group consisted of only 11 subjects. The rather long time between the blood sampling and the MR imaging examination should not matter, because neither the biochemical nor the myocardial status was likely to have changed dramatically in this community-based population sample.

In conclusion, MR imaging–detected UMIs were not associated with manifestations of significant atherosclerosis, increased intima-media thickness, C-reactive protein elevation, or traditional risk factors for coronary heart disease, which suggests that UMIs might have a different pathogenesis from that of RMIs or have the same pathogenesis but manifest at an earlier stage. If the pathogenesis is different, the prognosis will probably differ, too. This needs to be further investigated. We are currently performing a 5-year

**Figure 4**

![Graphs of differences in (a) intima-media thickness (IMT), (b) C-reactive protein level (CRP), and (c) Framingham risk score between subjects without MI scars on cardiac MR images (No MI), those with UMI, and those with RMI. ∗ = P < .0167 (i.e., .05 with Bonferroni correction).](image-url)
follow-up study of the same cohort that will provide information on the prognosis of UMs and on whether UMs and RMs have the same pathogenesis.

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