JAMA Neurology | Original Investigation

Association Between Unrecognized Myocardial Infarction and Cerebral Infarction on Magnetic Resonance Imaging

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IMPORTANCE It is uncertain whether unrecognized myocardial infarction (MI) is a risk factor for cerebral infarction.

OBJECTIVE To determine whether unrecognized MI detected by cardiac magnetic resonance imaging (MRI) is associated with cerebral infarction.

DESIGN, SETTING, AND PARTICIPANTS This is a cross-sectional study of ICELAND MI, a cohort substudy of the Age, Gene/Environment Susceptibility–Reykjavik Study conducted in Iceland. Enrollment occurred from January 2004 to January 2007 from a community-dwelling cohort of older Icelandic individuals. Participants aged 67 to 93 years who underwent both brain MRI and late gadolinium enhancement cardiac MRI were included. Data analysis was performed from September 2018 to March 2019.

EXPOSURES Unrecognized MI identified by cardiac MRI.

MAIN OUTCOMES AND MEASURES Unrecognized MI was defined as cardiac MRI evidence of MI without a history of clinically evident MI. Recognized MI was defined as cardiac MRI evidence of MI with a history of clinically evident MI. Cerebral infarctions on brain MRI were included regardless of associated symptoms. Multiple logistic regression was used to evaluate the association between MI status (no MI, unrecognized MI, or recognized MI) and cerebral infarction after adjustment for demographic factors and vascular risk factors. In addition, we evaluated the association between unrecognized MI and embolic infarcts of undetermined source.

RESULTS Five enrolled participants had nondiagnostic brain MRI studies and were excluded. Among 925 participants, 480 (51.9%) were women; the mean (SD) age was 75.9 (5.3) years. There were 221 participants (23.9%) with cardiac MRI evidence of MI, of whom 68 had recognized MI and 153 unrecognized MI. There were 308 participants (33.3%) with brain MRI evidence of cerebral infarction; 93 (10.0%) had embolic infarcts of undetermined source. After adjustment for demographic factors and vascular risk factors, the likelihood (odds ratio) of having cerebral infarction was 2.0 (95% CI, 1.2-3.4; $P = .01$) for recognized MI and 1.5 (95% CI, 1.02-2.2; $P = .04$) for unrecognized MI. After adjustment for demographics and vascular risk factors, unrecognized MI was also associated with embolic infarcts of undetermined source (odds ratio, 2.0 [95% CI, 1.1-3.5]; $P = .02$).

CONCLUSIONS AND RELEVANCE In a population-based sample, we found an association between unrecognized MI and cerebral infarction. These findings suggest that unrecognized MI may be a novel risk factor for cardiac embolism and cerebral infarction.

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JAMA Neurol. 2019;76(8):956-961. doi:10.1001/jamaneurol.2019.1226
Published online May 20, 2019.

A substantial fraction of cerebral infarction is of unknown cause.[1] Clinically apparent myocardial infarction (MI) is an established risk factor for cerebral infarction,[2] but it is unknown whether unrecognized MI is also a risk factor for cerebral infarction. Unrecognized MI refers to electrocardiographic (ECG), echocardiographic, or cardiac magnetic resonance imaging (MRI) evidence of MI without clinical recognition of the event.[3,4] Unrecognized MIs make up one-third to one-half of all MIs[5-7] and are associated with an increased risk of clinically apparent MI, heart failure, and death.[8-11] The association between unrecognized MI and cerebral infarction is incompletely understood, because there are few studies on this topic and they have been inconclusive.[12-14] We therefore evaluated the association between unrecognized MI and cerebral infarction among participants of ICELAND MI, a substudy of the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik). We hypothesized that there is an association between unrecognized MI detected by cardiac MRI and cerebral infarction detected by brain MRI.

Key Points

Question Is unrecognized myocardial infarction associated with cerebral infarction?

Findings In a population-based sample, we found an association between unrecognized myocardial infarction detected by cardiac magnetic resonance imaging and cerebral infarction.

Meaning Unrecognized myocardial infarction may be a novel risk factor for cerebral infarction.

Methods

Study Design and Patient Population

The Icelandic Reykjavik Study was a longitudinal cohort study of 30 795 randomly selected Icelandic individuals born between 1907 and 1935. Serial cardiovascular measures were collected from this cohort between 1967 and 1996. Between 2002 and 2006, the 5764 surviving men and women of the Reykjavik Study underwent extensive physical, cognitive, and brain MRI examinations (in the AGES-Reykjavik Study).[15] All participants signed written informed consent, and the study was approved by the National Bioethics Committee in Iceland, which acts as the institutional review board for the Icelandic Heart Association, and by the intramural institutional review board of the National Institute on Aging. The ICELAND MI study was initiated to evaluate the prevalence of cardiovascular risk factors, including unrecognized MI via use of cardiac MRI with late gadolinium enhancement (LGE).[4] Patients were enrolled from January 2004 to January 2007 and were recruited from the AGES-Reykjavik study if they could provide written consent, safely undergo MRI, and receive intravenous gadolinium.[4] For this study, we included all patients enrolled in ICELAND MI who successfully underwent both cardiac MRI and brain MRI.

Measurements

Cardiac MRI scans were performed using a 1.5-T Sigma Twinspeed scanner with a 4-element cardiac phased-array coil (General Electric Medical Systems), as previously described.[16] Images were collected during breath hold and triggered to the ECG or pulse oximetry if ECG gating was suboptimal. Cardiac MRI with late gadolinium enhancement has been previously validated as an excellent technique to identify myocardial scarring.[17,18] Imaging to evaluate MI-associated scars was performed 6 to 15 minutes after injection of low-dose gadopentetate dimegulmine (0.1 mmol/kg; Magnevist [Schering AG]) using a phase-sensitive segmentation gradient echo inversion recovery sequence.[19] Myocardial infarction was defined as present if late gadolinium enhancement involved the subendocardium and was in the distribution of a coronary artery.[20] Late gadolinium enhancement patterns considered atypical for MI were not characterized as being consistent with MI, a strategy that yields sensitivities and specificities of greater than 90% for MI detection.[17,21,22] Presence of MI was established based on consensus of cardiologists (including A.E.A.) experienced in cardiac MRI and blinded to clinical history. For this analysis, recognized MI was defined as occurring when there was cardiac MRI evidence of MI in the presence of hospital records or surveillance records supporting a history of clinically evident MI.[15] Unrecognized MI was defined as occurring when there was cardiac MRI evidence of MI but no history supportive of clinical MI by hospital or surveillance records.[4]

All brain MRI studies were similarly performed using the same 1.5-T Sigma Twinspeed scanner.[16] The protocol included a 3-dimensional T1-weighted spoiled-gradient echo sequence, a proton-density/T2-weighted fast-spin echo sequence, a fluid-attenuated inversion recovery (FLAIR) sequence, and a T2*-weighted gradient echo-type planar sequence.[16] A parenchymal infarct was defined as a defect of the brain parenchyma with a signal intensity isointense to that of cerebrospinal fluid on all pulse sequences (FLAIR, T2-weighted, and proton density-weighted). Cortical infarcts were defined as parenchymal defects involving the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images. Subcortical infarcts were defined as brain parenchymal defects not extending into the cortex and surrounded by an area 4 mm or larger in diameter of high signal intensity on FLAIR images. For this analysis, we considered subcortical infarction to be present only if there was no evidence of cortical infarction. Similarly, we considered posterior fossa infarction to be present if there was a parenchymal defect in the posterior fossa and no evidence of anterior circulation infarction. The intraobserver and interobserver variability for determination of cerebral infarction in this cohort was assessed every 6 and 3 months, respectively, with resulting κ statistics of 0.92 and 0.66, respectively.[16]

Additional covariates recorded were demographic factors and vascular risk factors. These included age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation or flutter, heart failure, serum creatinine, alcohol use, and active tobacco use.

Statistical Analyses

Baseline characteristics were stratified by MI status (ie, no MI, unrecognized MI, and recognized MI). The χ^2 or Fisher exact test were used to compare categorical variables and the *t* test or

Table 1. Characteristics of Participants, Stratified by Presence of Myocardial Infarction on Cardiac Magnetic Resonance Imaging

Characteristic	Myocardial Infarction, No. (%)			P Value
	None (n = 704)	Recognized (n = 68)	Unrecognized (n = 153)	
Age, mean (SD), y	75.6 (5.3)	76.4 (4.5)	76.8 (5.2)	.04
Female	400 (56.8)	24 (35.3)	56 (36.6)	<.001
Hypertension	564 (80.1)	66 (97.1)	138 (90.2)	<.001
Diabetes	230 (32.7)	31 (45.6)	70 (45.8)	.002
Hyperlipidemia	550 (78.1)	62 (91.2)	123 (80.4)	.04
Atrial fibrillation or flutter	44 (6.3)	9 (13.2)	22 (14.4)	.001
Congestive heart failure	1 (0.1)	8 (11.8)	6 (4.0)	<.001
Serum creatinine, mg/dL	1.0 (0.3)	1.1 (0.3)	1.0 (0.3)	<.001
Alcohol intake, mean (SD), g/wk	17.0 (34.4)	12.9 (24.5)	17.9 (34.4)	.58
Active tobacco use	72 (10.2)	8 (11.8)	21 (13.7)	.44
Antithrombotic medication use	40 (5.7)	8 (11.8)	19 (12.4)	.005

SI conversion factor: To convert serum creatinine to micromoles per liter, multiply by 76.25.

analysis of variance were used to compare continuous variables. Multiple logistic regression was used to evaluate the association between MI status and cerebral infarction after adjustment for the listed demographic and vascular risk factors. Since the goal of the study was to isolate the association between unrecognized MI and cerebral infarction rather than to build a parsimonious prediction model, all covariates were prespecified and included in the model regardless of statistical significance. In secondary analyses, we assessed the association between MI status and cortical vs subcortical infarction separately. In addition, we evaluated the association between unrecognized MI and embolic infarcts of undetermined source, defined as cortical infarcts in patients who lacked established stroke mechanisms, including significant carotid artery stenosis, atrial fibrillation, atrial flutter, or reduced ejection fraction (<30%).[23,24] In these secondary analyses, we restricted the analysis to cerebral infarctions involving the anterior circulation, because it is not well established whether posterior circulation infarctions should be considered cortical vs subcortical.

We performed 5 sensitivity analyses. First, since recent data suggest an association between left atrial size (independent of atrial arrhythmias) and cerebral infarction,[25] we additionally adjusted the multivariable model for left atrium size. In the second sensitivity analysis, we adjusted the multivariable model for left ventricular stroke volume. In the third sensitivity analysis, we adjusted the multivariable model for baseline systolic blood pressure and use of antihypertensive medication rather than just a history of hypertension. To account for baseline use of antithrombotic medications in the fourth sensitivity analysis, we additionally adjusted the model for use of antithrombotic medications. In the fifth sensitivity analysis, we excluded participants who were using antithrombotic medications. Finally, in an exploratory analysis, we evaluated the association between unrecognized MI detected by ECG and cerebral infarction. The threshold of statistical significance was set at an α of .05. Statistical analyses were performed using Stata/MP version 14 (StataCorp).

Results

We identified 930 participants who underwent both cardiac MRI and brain MRI, of whom 5 had nondiagnostic brain MRI studies and were excluded. Thus, the final cohort consisted of 925 participants (mean [SD] age 75.9 [5.3] years). The median interval between brain and cardiac MRI studies was 50 (interquartile range, 31-447) days.

A total of 221 participants (23.9%) had MRI evidence of MI, of whom 68 had a recognized MI and 153 an unrecognized MI (**Table 1**). We identified 308 participants (33.3%) who had MRI evidence of cerebral infarction, of whom 109 had cortical infarction, 76 had isolated subcortical infarction, and 123 had infarction restricted to the posterior fossa (**Table 2**).

The prevalence of cerebral infarction was 29.4% (95% CI, 26.1%-32.9%) in patients without MRI evidence of MI, 43.8% (95% CI, 35.8%-52.0%) in patients with unrecognized MI, and 50.0% (95% CI, 37.6%-62.4%) in patients with recognized MI ($P < .001$ for comparison across groups). In univariate analyses, we found an increased likelihood of cerebral infarction in patients with recognized MI (odds ratio [OR], 2.4 [95% CI, 1.5-4.0]; $P = .001$) and unrecognized MI (OR, 1.9 [95% CI, 1.3-2.7]; $P = .001$). After adjustment for demographics and vascular risk factors, we found an increased likelihood of cerebral infarction in patients with recognized MI (OR, 2.0 [95% CI, 1.2-3.4]; $P = .01$) and unrecognized MI (OR, 1.5 [95% CI, 1.02-2.2]; $P = .04$) (**Table 3**). The results were essentially unchanged in the sensitivity analyses (Table 3).

In secondary analyses, there was a nonsignificant difference between unrecognized MI and cortical cerebral infarction; the same was true for unrecognized MI and subcortical cerebral infarction (**Table 4**). Ninety-three participants (10.0%) had embolic infarcts of undetermined source. After adjustment for demographic factors and vascular risk factors, unrecognized MI was associated with embolic infarcts of undetermined source (OR, 2.0 [95% CI, 1.1-3.5]; $P = .02$; Table 4).

Finally, in an exploratory analysis, we identified 42 participants with ECG evidence of unrecognized MI. We found no association between unrecognized MI detected by ECG and cerebral infarction (OR, 1.0 [95% CI, 0.4-2.6]).

Discussion

In a population-based sample of older adults, we found that cardiac MRI evidence of MI was associated with brain MRI evi-

Table 2. Characteristics of Participants, Stratified by Presence of Cerebral Infarction on Brain Magnetic Resonance Imaging

Characteristic	No. (%)		P Value
	No Cerebral Infarction (n = 617)	Cerebral Infarction (n = 308)	
Age, mean (SD), y	75.5 (5.2)	76.8 (5.3)	<.001
Female	348 (56.4)	132 (42.9)	<.001
Hypertension	497 (80.6)	271 (88.0)	.005
Diabetes	202 (32.7)	129 (41.9)	.006
Hyperlipidemia	496 (80.4)	239 (77.6)	.32
Atrial fibrillation or flutter	46 (7.5)	29 (9.4)	.31
Congestive heart failure	7 (1.1)	8 (2.6)	.10
Serum creatinine, mg/dL	1.0 (0.3)	1.1 (0.3)	<.001
Alcohol intake, mean (SD), g/wk	16.7 (33.7)	17.2 (34.0)	.83
Active tobacco use	68 (11.0)	33 (10.7)	.89
Use of antithrombotic medication	29 (4.7)	36 (11.7)	<.001

SI conversion factor: To convert serum creatinine to micromoles per liter, multiply by 76.25.

dence of cerebral infarction. The association was stronger in the case of recognized MI, but both recognized and unrecognized MI were associated with cerebral infarction. Additionally, we found that unrecognized MI was associated with embolic infarcts of undetermined source, suggesting that unrecognized MI may be a novel risk factor for cardiac embolism and cerebral infarction.

Prior studies have demonstrated that unrecognized MIs make up between one-third to one half of all MIs.[5-7] Clinically apparent MI causes myocardial scar formation, which leads to abnormal ventricular contraction and in turn thrombus formation.[26,27] Ventricular thrombi are associated with a high risk of cardiac embolism and cerebral infarction.[27-29] Unrecognized MI similarly leads to myocardial injury and scar formation,[8,30] but it is unknown whether this type or degree of scar can lead to thrombi formation and subsequent cardiac embolism and resultant cerebral infarction. Prior studies have found associations between unrecognized MI with future recognized MI, heart failure, and death,[8-11] but studies on the association between unrecognized MI and cerebral infarction have been inconclusive because they did not adjust for vascular risk factors or comorbidities[12] or were underpowered to look specifically at brain infarcts.[14] One previous study[13] evaluated the association between cardiac MRI evidence of MI and brain MRI evidence of cerebral infarction and found a nonsignificant association between MI and cortical infarction, but this study did not evaluate the association between MI and brain infarcts of any type. In this context, this study adds novel findings supporting the hypothesis that unrecognized MI is a risk factor for cardiac embolism and cerebral infarction.

The results of this study may have therapeutic implications. Currently, one-third of all ischemic strokes have no known stroke causative mechanism and are classified as cryptogenic.[24,31] Most of these cryptogenic strokes appear to arise from distant emboli and are classified as embolic strokes of undetermined source (ESUS).[24] The lack of identification of an underlying stroke causative mechanism in patients with ESUS precludes targeted secondary stroke preventive strategies aimed at reducing stroke recurrence and mortality. The association found between unrecognized MI and embolic infarcts of undetermined source suggests that unrecognized MI may be a novel risk factor for cardiac embolism and cerebral infarction and may explain some proportion of ESUS cases. Although recent trials have found that anticoagulation does not benefit the overall population of patients with

Table 3. Associations Between Myocardial Infarction and Cerebral Infarction on Magnetic Resonance Imaging

Analysis of Myocardial Infarction	Cerebral Infarction, Odds Ratio (95% CI)	P Value
Unadjusted		
Recognized	2.4 (1.5-4.0)	.001
Unrecognized	1.9 (1.3-2.7)	.001
Primary analysis[a]		
Recognized	2.0 (1.2-3.4)	.01
Unrecognized	1.5 (1.02-2.2)	.04
Sensitivity analysis 1[b]		
Recognized	2.0 (1.2-3.4)	.01
Unrecognized	1.5 (1.02-2.2)	.04
Sensitivity analysis 2[c]		
Recognized	2.0 (1.2-3.4)	.01
Unrecognized	1.5 (1.03-2.2)	.04
Sensitivity analysis 3[d]		
Recognized	1.9 (1.1-3.3)	.02
Unrecognized	1.5 (1.02-2.2)	.04
Sensitivity Analysis 4[e]		
Recognized	2.0 (1.2-3.4)	.01
Unrecognized	1.5 (1.0-2.2)	.047
Sensitivity analysis 5[f]		
Recognized	2.1 (1.2-3.7)	.01
Unrecognized	1.5 (1.0-2.2)	.07

[a] Adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation or flutter, heart failure, serum creatinine, weekly alcohol use, and active tobacco use.

[b] Additionally adjusted for left atrial size.

[c] Additionally adjusted for left ventricular stroke volume.

[d] Adjusted for systolic blood pressure and use of antihypertensive medication.

[e] Adjusted for antithrombotic medication use.

[f] Excludes participants who were using antithrombotic medications.

Table 4. Associations Between Myocardial Infarction and Cerebral Infarction Type on Magnetic Resonance Imaging

Type of Myocardial Infarction[a]	Cortical Cerebral Infarction		Subcortical Cerebral Infarction		Embolic Infarct of Undetermined Source	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Recognized	1.8 (0.8-3.7)	.14	1.3 (0.5-3.2)	.91	NA	NA
Unrecognized	1.6 (1.0-2.7)	.08	1.0 (0.5-2.0)	.57	2.0 (1.1-3.5)	.02

Abbreviation: NA, not applicable.

[a] All models are adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation or flutter, heart failure, serum creatinine, weekly alcohol use, and active tobacco use.

ESUS,[32,33] given the findings of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, which found that anticoagulation reduced ischemic stroke risk in patients with clinically apparent myocardial disease,[34] future trials could test whether anticoagulation is superior to antiplatelet therapy at reducing recurrent stroke among patients with ESUS and evidence of unrecognized MI.

Although we found an association between unrecognized MI detected on cardiac MRI and cerebral infarction, no association was found between unrecognized MI detected on ECG and cerebral infarction. This lack of association between ECG-detected MI may be a result of the lower sensitivity of ECG to detect MI.[4,7] In addition, although ECG is a widely used, low-risk, cost-effective tool to evaluate coronary health, cardiac MRI represents a promising application of a contemporary diagnostic tool in the field of stroke research. Cardiac MRI, however, remains costly and detection of unrecognized MI requires use of intravenous gadolinium, which may pose risk in certain patients with kidney disease.[35]

Limitations

This study should be considered in light of its limitations. First, although this was a population-based study using adjudicated measures of MI and cerebral infarction, we used a cross-sectional design, and thus we could not precisely date the MIs and cerebral infarctions. Second, we lacked data on potentially important covariates, such as sleep apnea and history of drug abuse. Third, there were too few clinically symptomatic strokes to reliably evaluate the association between unrecognized MI and clinical ischemic stroke, but existing data strongly indicate that silent cerebral infarctions are associated with future clinical strokes and dementia,[36,37] highlighting the importance of MRI-detected cerebral infarction as an important endpoint. Fourth, all participants in ICELAND MI were older Icelandic individuals, and thus the results of this study may not be generalizable to patients with other demographic profiles.

Conclusions

In a population-based sample, we found an association between unrecognized MI and cerebral infarcts, and in particular, embolic infarcts of undetermined source. These results suggest that unrecognized MI may be a novel risk factor for cerebral infarction and may explain some proportion of ESUS cases. Because 2 recent trials found no benefit of anticoagulation in the overall ESUS population, a more personalized secondary stroke preventive strategy is warranted. Given the results of the COMPASS trial, which found that anticoagulation reduced ischemic stroke risk in patients with clinically apparent myocardial disease,[34] it may be worthwhile to evaluate whether anticoagulation could be beneficial at reducing recurrent stroke in patients with ESUS who also have evidence of unrecognized MI.

ARTICLE INFORMATION

Accepted for Publication: March 29, 2019.

Published Online: May 20, 2019. doi:10.1001/jamaneurol.2019.1226

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Author Contributions: Dr Launer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Merkler.
Obtained funding: Safford, Gudnason, Arai, Launer.
Administrative, technical, or material support: Eiriksdottir, Safford, Phillips, Iadecola, Gudnason, Weinsaft, Arai.
Supervision: Safford, Iadecola, Gudnason, Weinsaft, Kamel, Arai, Launer.

Conflict of Interest Disclosures: Dr Arai reports US Government Cooperative Research and Development Agreements with Siemens Bayer outside the submitted work; in addition, Dr Arai has a patent on analyzing cardiac MR images pending and licensed. Dr Iadecola reports personal fees for scientific advisory board participation from Broadview Ventures, outside the submitted work. Dr Kamel serves on the steering committee for Medtronic's Stroke AF trial and has served on an advisory board for Roivant Sciences on anticoagulant therapy. He receives indirect research support from the BMS-Pfizer alliance (in the form of an in-kind study drug) and Roche (in the form of N-terminal pro b-type natriuretic peptide assay kits) for the ARCADIA trial. Dr Safford reports support from Amgen outside the submitted work. No other disclosures were reported.

Funding/Support: The Age, Gene/Environment Susceptibility–Reykjavik Study was supported by the National Institutes of Health (grants N01-AG-12100; KL2TR000238 5 [Dr Merkler]; R01HL128278 [Dr Weinsaft]; R01HL80477 [Dr Safford]; and K23NS082367, R01NS097443, and U01NS095869 [Dr Kamel]), the Intramural Research Program of the National Institute on Aging, the Icelandic Heart Association and Icelandic Parliament, the American Heart Association (grant 18CDA34110419 [Dr Merkler]), the Leon Levy Fellowship in Neuroscience (Dr Merkler), a Rubicon

fellowship of the Netherlands Organization for Scientific Research (Mr Sigurdsson), and the Michael Goldberg Research Fund (Dr Kamel).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The authors are grateful to Monica Chen, BA, Weill Cornell Medicine, for her editing and clerical assistance. She was not compensated for her contribution.

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