RESEARCH ARTICLE

Silent Myocardial Infarction and Subsequent Ischemic Stroke in the Cardiovascular Health Study

Alexander E. Merkler, MD, MS, Traci M. Bartz, MS, Hooman Kamel, MD, Elsayed Z. Soliman, MD, MSc, MS, Virginia Howard, PhD, Bruce M. Psaty, MD, PhD, Peter M. Okin, MD, Monika M. Safford, MD, Mitchell S.V. Elkind, MD, MS, and W.T. Longstreth, Jr., MD, MPH

Correspondence
Dr. Merkler
alm9097@med.cornell.edu

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Abstract

Objective

To test the hypothesis that silent myocardial infarction (MI) is a risk factor for ischemic stroke, we evaluated the association between silent MI and subsequent ischemic stroke in the Cardiovascular Health Study.

Methods

The Cardiovascular Health Study prospectively enrolled community-dwelling individuals ≥65 years of age. We included participants without prevalent stroke or baseline evidence of MI. Our exposures were silent and clinically apparent, overt MI. Silent MI was defined as new evidence of Q-wave MI, without clinical symptoms of MI, on ECGs performed during annual study visits from 1989 to 1999. The primary outcome was incident ischemic stroke. Secondary outcomes were ischemic stroke subtypes: nonlacunar, lacunar, and other/unknown. Cox proportional hazards analysis was used to model the association between time-varying MI status (silent, overt, or no MI) and stroke after adjustment for baseline demographics and vascular risk factors.

Results

Among 4,224 participants, 362 (8.6%) had an incident silent MI, 421 (10.0%) an incident overt MI, and 377 (8.9%) an incident ischemic stroke during a median follow-up of 9.8 years. After adjustment for demographics and comorbidities, silent MI was independently associated with subsequent ischemic stroke (hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.03–2.21). Overt MI was associated with ischemic stroke both in the short term (HR, 80; 95% CI, 53–119) and long term (HR, 1.60; 95% CI, 1.04–2.44). In secondary analyses, the association between silent MI and stroke was limited to nonlacunar ischemic stroke (HR, 2.40; 95% CI, 1.36–4.22).

Conclusion

In a community-based sample, we found an association between silent MI and ischemic stroke.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CHS = Cardiovascular Health Study; **CI** = confidence interval; **ECG** = electrocardiogram; **ESUS** = embolic strokes of undetermined source; **HR** = hazard ratio; **MI** = myocardial infarction.

Stroke is a leading cause of disability and the second-leading cause of death worldwide.[1] Most strokes are ischemic, of which up to one-quarter lack an identifiable cause and are considered cryptogenic.[2] Based on clinical and radiographic characteristics, many cryptogenic strokes appear to result from emboli from the heart, but this cannot be proven after a standard evaluation.[3] Clinically apparent (overt) myocardial infarction (MI) is a well-established risk factor for cardiac embolism and subsequent ischemic stroke.[4,5] The risk of stroke is highest in the first month after overt MI[5-7] and continues to remain elevated for years.[8] Silent MI is defined as pathologic Q waves on electrocardiogram (ECG), or evidence of MI on cardiac imaging, in the absence of clinical symptoms.[9] Silent MI accounts for up to one-half of all MIs[10-12] and is associated with an increased risk of clinically overt MI, heart failure, and death.[13-16] Similar to overt MI, silent MI leads to scar formation and ventricular dysfunction and may be capable of thrombus formation and subsequent cardiac embolism and stroke.[17] Cross-sectional studies have found associations between silent MI on cardiac MRI and cerebral infarction on brain MRI,[18,19] but whether silent MI is a risk factor for subsequent ischemic stroke remains uncertain. In this study, we examined in a longitudinal cohort study the association between silent MI and subsequent ischemic stroke.

Methods

Design

The Cardiovascular Health Study (CHS) prospectively enrolled and follows a community-dwelling cohort of women and men ≥65 years of age. Four CHS field centers first recruited a cohort of 5,201 participants between 1989 and 1990 and then recruited another cohort of 687 predominantly Black participants between 1992 and 1993. These 5,888 participants were randomly selected from Medicare eligibility lists in 4 counties in California, Maryland, North Carolina, and Pennsylvania.[20] Participants were eligible to be enrolled in CHS regardless of whether they had existing cardiovascular disease at baseline. Until 1998–1999, and again in 2005–2006, participants returned annually for in-person study visits, which included a standard 12-lead ECG. In addition, participants were contacted via semiannual telephone calls throughout follow-up. At each encounter, participants were questioned about cardiovascular events and hospitalizations. For all hospitalizations, the CHS obtained discharge summaries and diagnoses. For all potential incident cardiovascular and cerebrovascular events, additional information including history, examination, laboratory findings, and findings from brain and cardiovascular imaging examinations were collected. The data for all potential MI and stroke events were reviewed and classified by the events adjudication committees.

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review boards at the University of Washington and each field center approved this study, and all participants provided written informed consent.

Participants

We included participants from only the first cohort of 5,201 participants because the second cohort underwent fewer years of annual ECGs and had fewer years of follow-up compared to the first cohort; in a sensitivity analysis, we included participants from the second cohort. We excluded participants with prevalent stroke, baseline ECG evidence of MI (silent or overt), or missing information on covariates.

Measurements

All suspected cardiovascular and cerebrovascular events and all deaths were reviewed by either the Cerebrovascular or Cardiovascular Adjudication Committees. The Cerebrovascular Adjudication Committee reviewed all events and deaths that were thought to be related to TIA or stroke. The Cardiovascular Adjudication Committee reviewed all other suspected events and deaths.[21]

The exposure variables were incident silent MI and incident overt MI. The algorithm for classifying overt MI vs silent MI in CHS has been previously published.[22,23] The Cardiovascular Adjudication Committee determined whether a participant had a definite incident overt MI on the basis of information about chest pain, ECG changes, and cardiac enzymes. Reliability between members of the Cardiovascular Adjudication Committee was excellent with a kappa of 0.86 for MI vs no MI.[24] Participants were determined to have an incident silent MI if they had new ECG evidence of MI in the absence of an adjudicated MI.[25] Standard 12-lead ECGs were obtained at the baseline examination (1989–1990) and annually thereafter through CHS visit 11 (1998–1999). ECGs were obtained on MAC PC ECG machines (Marquette Electronics) calibrated at 10 mm/mV with a speed of 25 mm/s. All ECGs were read centrally and manually inspected for technical errors or inadequate quality. ECG criteria for MI included the presence of Q-waves that were of sufficient duration and amplitude to meet the Minnesota Code (codes 1-1 or 1-2). Alternative criteria were the presence of smaller Q-waves (codes 1–3) in combination with significant abnormalities in the ST-segment or T-wave (codes 4-1 or 4-2, or 5-1 or 5-2).[26,27]

The primary outcome was incident ischemic stroke. The method for identification and adjudication of stroke has been previously published.[21] The Cerebrovascular Adjudication Committee was composed of study neurologists from each of the 4 study sites and a neuroradiologist from the MRI Reading Center. Neuroimaging was available in 86% of participants. The Cerebrovascular Adjudication Committee would decide whether a transient ischemic attack or stroke had occurred and, when appropriate, assign a stroke subtype: ischemic, hemorrhagic, or uncertain. Stroke was defined as a rapid onset of neurologic deficits lasting greater than 24 hours or until death, or a lesion on CT or MRI, without evidence that the symptoms were due to infection, tumor, or brain trauma. Ischemic stroke required a neurologic deficit without evidence of intracranial hemorrhage and evidence of brain ischemia referable to the presenting symptoms. Reliability between members of the Cerebrovascular Adjudication Committee was excellent, with a kappa of 0.86 for stroke vs no stroke, and among those with a stroke, a kappa of 1.0 for stroke subtype.

The Cerebrovascular Adjudication Committee further subdivided ischemic stroke into 4 subtypes: lacunar, large-artery atherosclerosis, cardioembolic, and other/unknown. The Cerebrovascular Adjudication Committee had access to and reviewed information regarding the hospitalization record, neurologic evaluation, brain imaging, echocardiography, and ECG to determine the ischemic stroke subtype. A diagnosis of cardioembolic stroke required a well-established cardiac source of embolism, including atrial fibrillation/flutter or sick sinus syndrome, overt MI within 6 weeks of stroke, akinetic myocardial segment or ventricular aneurysm, intracardiac thrombus, valvular vegetations, prosthetic heart valve, dilated cardiomyopathy, right to left intracardiac shunt, presence of concomitant systemic embolism, or autopsy evidence of embolus to the brain. A diagnosis of stroke from large-artery atherosclerosis required a >70% stenosis or occlusion by angiography in the vessel appropriate to the infarct. A diagnosis of lacunar stroke required lack of evidence of large-artery atherosclerosis and a clinical presentation and imaging consistent with a lacunar infarct, defined as <2 cm of infarction on CT or MRI. As per prior CHS analyses, participants with strokes of multiple subtypes were classified as follows: the combination of cardioembolic and other determined were classified as cardioembolic; the combination of lacunar and large-artery atherosclerosis were classified as lacunar; the combination of lacunar and other determined were classified as lacunar; and the combination of large-artery atherosclerosis and other determined were classified as large-artery atherosclerosis.[21] Reliability of ischemic stroke subtypes among members of the Cerebrovascular Adjudication Committee was very good, with a kappa of 0.77.

Because our hypothesis was that silent MI leads to thrombus formation and subsequent cardiac embolism, our secondary analyses examined nonlacunar (in which we combined cardioembolic and large-artery atherosclerosis stroke subtypes), lacunar, and other/unknown stroke subtypes separately, reasoning that cardioembolic mechanisms would be enhanced in the nonlacunar subtype and diminished in the lacunar subtype, which are unlikely to have a cardioembolic mechanism.

We adjusted our models for the following baseline confounders: age, sex, race (black vs other race), education level (<high school vs high school or more), CHS clinic, body mass index, diabetes, atrial fibrillation, heart failure, systolic blood pressure, use of antihypertensive medication, high- and low-density lipoprotein and triglyceride levels, and smoking status (never, past, or current).

Statistical Analysis

Baseline characteristics were reported as mean and SD for continuous variables and number and percent for categorical variables. Cox proportional hazards analysis was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for the association between MI status (silent, overt, no MI) and ischemic stroke. The reference group was no MI. Participants were censored at the time of any stroke, death, removal of consent to participate in the study, or at CHS visit 12 (1999–2000). We tested the validity of the proportional hazards assumption using Schoenfeld residuals. Missing visit dates were filled in with prior visit date plus 1 year. Silent MI and overt MI were modeled as time-varying exposures. Participants' MI status was re-assessed and updated throughout follow-up. Overt MI was updated continuously and silent MI was updated at each clinic visit. As the date of silent MI is unknown, in our primary analysis, we conservatively used the date of the ECG showing evidence of MI as the onset date of silent MI. Thus, for example, a participant who had a normal ECG at CHS visit 1, then stroke, and then an ECG on CHS visit 2 showing silent MI was determined as having a stroke prior to development of silent MI.

A participant's MI status could transition from no MI to silent MI, from no MI to overt MI, and from silent MI to overt MI, but not from overt MI to silent MI, from overt MI to no MI, or from silent MI to no MI. Participants who had an overt MI and stroke on the same day were coded to have MI prior to stroke as MI is a well-established short-term risk factor for stroke.[5-7] Because the proportional hazards assumption was violated with the overt MI exposure, we split this exposure into short-term (within 30 days following the MI) and long-term (beyond 30 days following the MI) periods based on prior data suggesting that the risk of stroke is highest within the first month after overt MI.[5-7]

Model 1 was adjusted for age, sex, and race. Model 2 included covariates from model 1 plus education level, CHS clinic, body mass index, diabetes, atrial fibrillation, congestive heart failure, systolic blood pressure, use of antihypertensive medication, high- and low-density lipoprotein and triglyceride levels, and smoking status. In a secondary analysis, we evaluated the association between MI status and ischemic stroke subtypes (nonlacunar, lacunar, and unknown/other) separately. Because the actual date of silent MI is unknown, and some strokes may have occurred prior to the date on which

evidence of silent MI was newly captured by annual study ECG, we performed a secondary analysis using the date of the last ECG without evidence of MI as the onset date of silent MI among those with new ECG evidence of silent MI. We also tested the interaction between sex and MI in relation to incident ischemic stroke, as prior studies have noted sex differences in the association between silent MI and vascular brain injury.[19,28] We performed 3 sensitivity analyses. First, for patients who had MI and stroke on the same day, we assumed that the stroke occurred prior to MI. Second, we adjusted our final model for the use of statins and anticoagulants as time-varying covariates. Finally, we repeated the primary analysis among participants enrolled in both CHS cohorts. The threshold of statistical significance was a 2-tailed $\alpha = 0.05$.

Data Availability

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

Results

Description of the Cohort

Of the 5,201 participants in the first CHS cohort, 199 were excluded because of prevalent stroke at baseline, 474 were excluded because of prevalent overt MI at baseline, 161 were excluded because of prevalent silent MI at baseline, and 143 were excluded for missing covariates, leaving 4,224 participants who were included in our analysis. Participants excluded from the analysis more often were male, more often had not completed high school, and had a greater burden of vascular risk factors and comorbidities compared to included participants (table 1). The mean number of ECGs per participant was 7.7. Among the 4,224 participants in this analysis, during a median 9.8 years of follow-up, 362 (8.6%) had an incident silent MI; 421 (10.0%) had an incident overt MI, of whom 23 (0.5%) had first had an incident silent MI; and 377 (8.9%) had an incident ischemic stroke. Among the 377 participants with an incident ischemic stroke, 136 (36.1%) were nonlacunar (108 cardioembolic, 19 large-artery atherosclerosis, 9 listed as both cardioembolic and large-artery atherosclerosis), 57 (15.1%) were lacunar, and 184 (48.8%) were other/unknown subtype (9 were other determined, 174 were of indeterminate etiology, and 1 was missing a subtype). Twenty-seven (0.6%) participants had a stroke that occurred on the same day as MI. The raw numbers of participants with no MI, silent MI, and overt MI stratified by ischemic stroke subtype are available in table 2.

Association Between Silent MI and Ischemic Stroke

After adjustment for baseline demographics and vascular risk factors, a significant association remained between silent MI and incident ischemic stroke (HR, 1.51; 95% CI, 1.03–2.21). Our results were similar in secondary and sensitivity analyses of the primary outcome of any incident ischemic stroke (table 3). In secondary analyses of specific ischemic stroke subtypes, silent MI was significantly associated with nonlacunar ischemic stroke after adjustment for demographics and risk factors (HR, 2.40; 95% CI, 1.36–4.22), but not with other/unknown ischemic stroke subtypes (HR, 1.29; 95% CI, 0.73–2.31) (table 4). As there were only 2 participants with silent MI prior to ischemic stroke, we could not reliably evaluate the association been silent MI and lacunar stroke (table 2).

Association Between Overt MI and Ischemic Stroke

After adjustment for baseline demographics and vascular risk factors, a significant association remained between overt MI and incident ischemic stroke, especially in the short term (HR, 80; 95% CI, 53–119), but also in the long term (HR, 1.60; CI, 1.04–2.44) (table 3). In the secondary analysis of specific ischemic stroke subtypes, only the association of overt MI with nonlacunar ischemic stroke violated the proportional hazards assumption. Overt MI was associated with nonlacunar ischemic stroke in both the short term (HR, 210; CI, 127–348) and the long term (HR, 2.21; CI, 1.16–4.22). Overt MI was also associated with other/unknown stroke in the short term (HR, 29; 95% CI, 12–72), but not in the long term (HR, 1.57; CI, 0.84–2.94) (table 4). As there were only 2 participants with overt MI prior to lacunar ischemic stroke, we could not reliably evaluate the association been silent MI and lacunar stroke (table 2).

Subgroup and Sensitivity Analyses

Interactions between sex and silent or overt MI in relation to incident ischemic stroke were not significant. Our results were similar in our sensitivity analyses, in which we (1) assumed that stroke occurred prior to MI in participants with stroke and MI on the same day, (2) adjusted our final model for the use of statins and anticoagulants as time-varying covariates, and (3) repeated the primary analysis in participants enrolled in both CHS cohorts (table 3).

Discussion

In a large, prospective, longitudinal cohort study, we found that silent MI was associated with incident ischemic stroke. Our findings were broadly similar across sensitivity and subgroup analyses.

Our results should be considered in the context of other recent studies on silent MI and cardiovascular outcomes. A recent meta-analysis found that silent MI is associated with future mortality, cardiovascular events, and heart failure, but associations with stroke were inconclusive because of too few studies.[16] Individual studies on the association between silent MI and stroke have been inconclusive because they did not adjust for vascular risk factors[26,29] or did not specifically assess ischemic stroke.[28,30,31] Recent data suggest that silent MI is associated with brain infarcts, specifically embolic-appearing

Table 1 Baseline Characteristics of Cardiovascular Health Study Participants, Stratified by Inclusion in Analysis of Silent Myocardial Infarction (MI) and Ischemic Stroke

Characteristics	Included (n = 4,224)	Excluded[a] (n = 977)
Age, y	72.6 (5.6)	73.6 (5.7)
Male	1,694 (40.1)	545 (55.8)
Black	193 (4.6)	53 (5.4)
Did not complete high school	1,131 (26.8)	307 (31.9)
Body mass index, kg/m^2	26.4 (4.5)	26.7 (4.5)
Systolic blood pressure, mm Hg	136 (21)	137 (23)
Diastolic blood pressure, mm Hg	70 (11)	69 (12)
High-density lipoprotein, mg/dL	55 (16)	48 (15)
Low-density lipoprotein, mg/dL	130 (36)	129 (36)
Triglycerides, mg/dL	135 (59)	177 (129)
Antihypertensive medication use	1,711 (40.5)	637 (65.9)
Diabetes	539 (12.8)	224 (24.6)
Atrial fibrillation	109 (2.6)	39 (4.0)
Heart failure	98 (2.3)	132 (13.5)
Smoking status		
Never smoked	2008 (47.5)	389 (39.9)
Past smoker	1738 (41.1)	462 (47.4)
Current smoker	478 (11.3)	123 (12.6)
Anticoagulant use	35 (0.8)	53 (5.5)
Statin use	60 (1.4)	37 (3.8)

Data are presented as mean (SD) or n (%).
[a] Reasons for exclusion were prevalent stroke at baseline (n = 199), prevalent overt MI at baseline (n = 474), prevalent silent MI at baseline (n = 161), and missing baseline covariates (n = 143).

brain infarcts,[18,19] but these studies were cross-sectional and evaluated MRI-defined brain infarcts, not clinically overt ischemic stroke; in one of these studies, the association between silent MI and cortical brain infarcts was limited to women.[19] In this context, our study adds novel findings supporting the hypothesis that silent MI is a risk factor for ischemic stroke. While there may be residual confounding as we could not adjust for vascular risk factors that occurred subsequent to baseline and we could not account for the potential contribution of systemic inflammation on stroke as a result of silent MI, the association between silent MI and incident ischemic stroke is consistent with the hypothesis that silent MI may lead to thrombus formation and subsequent cardiac embolism, as also seen in overt MI (figure).[32-34] Thus, although the MI is silent or unrecognized, it should not be considered benign, but rather a covert risk factor for many adverse outcomes.

The results of our study may have clinical implications. One-fifth of ischemic strokes have no known etiology, but have clinical and radiographic characteristics that suggest they arise from a distant source, and thus are considered to be embolic strokes of undetermined source (ESUS).[3] Failure to identify the mechanism of these strokes precludes targeted secondary

Table 2 Number of Participants With Myocardial Infarction (MI) Stratified by Ischemic Stroke Subtype

MI type	Nonlacunar	Lacunar	Other/unknown
None	87	53	155
Silent	16	2	13
Overt (short term)[a]	22	0	5
Overt (long term)[b]	11	2	11

[a] As there was a violation in the proportional hazards assumption in this model, overt MI was split into short and long term. Short term refers to the risk of ischemic stroke within 30 days of the MI.
[b] Long term refers to the risk of ischemic stroke beyond 30 days following the MI.

Table 3 Associations Between Myocardial Infarction (MI) and Ischemic Stroke in the Cardiovascular Health Study[a]

Exposure variable	Model 1[d]	Model 2[e]	Secondary analysis[e,f]	Sensitivity analysis 1[e,g]	Sensitivity analysis 2[e,h]	Sensitivity analysis 3[e,i]
Overt MI (short term)[b]	92 (61–137)	80 (53–119)	74 (48–113)	NA	80 (53–120)	74 (49–110)
Overt MI (long term)[c]	1.85 (1.21–2.83)	1.60 (1.04–2.44)	1.68 (1.10–2.58)	1.54 (1.02–2.32)	1.61 (1.05–2.47)	1.54 (1.02–2.34)
Silent MI	1.83 (1.03–2.21)	1.51 (1.03–2.21)	1.55 (1.10–2.17)	1.44 (0.99–2.08)	1.48 (1.01–2.17)	1.47 (1.02–2.14)

[a] Data represent hazard ratio (95% confidence interval) with the reference group being no MI.
[b] As there was a violation in the proportional hazards assumption in this model, overt MI was split into short and long term. Short term refers to the risk of ischemic stroke within 30 days of the MI.
[c] Long term refers to the risk of ischemic stroke beyond 30 days following the MI.
[d] Adjusted for age, sex, race.
[e] Adjusted for age, sex, race, education level, study site, body mass index, diabetes, atrial fibrillation, congestive heart failure, systolic blood pressure, use of antihypertensive medication, high- and low-density lipoprotein and triglyceride levels, and smoking status (never, past, or current).
[f] Silent MI was defined as occurring on the date of electrocardiogram (ECG) prior to the ECG on which MI was identified.
[g] This sensitivity analysis assumed that stroke occurred prior to MI for patients who had MI and stroke on the same day. As there was no violation in the proportional hazards assumption in this model, overt MI was not split between short and long term.
[h] This sensitivity analysis adjusted model 2 for the use of statins and anticoagulants as time-varying covariates.
[i] This sensitivity analysis included all participants enrolled in both study cohorts and was adjusted for the covariates listed in model 2.

stroke preventive strategies, and there is a high risk of recurrent stroke with standard antiplatelet therapy. Some ESUS cases may therefore be explained by preceding silent MIs. Although 2 recent randomized trials found that anticoagulation is not superior to antiplatelet therapy among all patients with ESUS,[35,36] the etiology of ESUS in these trials is likely heterogenous, with some stroke originating from the heart, and others originating from pathologies that would not respond to anticoagulation, such as nonstenosing atherosclerosis. Our findings suggest that silent MI may predispose to cardiac embolism and subsequent stroke and therefore represents a novel therapeutic target for secondary stroke prevention that is currently inadequately treated with standard antiplatelet regimens. The COMPASS trial found that the combination of low-dose anticoagulant and antiplatelet therapy was superior to antiplatelet therapy alone for reducing ischemic stroke among patients with stable, clinically apparent cardiovascular disease,[37] including the subgroup of patients with prior stroke.[38] In addition, meta-analyses of randomized controlled studies have found that long-term anticoagulation is superior to antiplatelet therapy in reducing ischemic stroke after overt MI. In this context, our findings suggest the need for secondary analyses of existing trials and dedicated randomized trials to determine whether anticoagulation is superior to the current standard antiplatelet therapy among patients with ischemic stroke and evidence of silent MI.

Table 4 Associations Between Myocardial Infarction (MI) and Ischemic Stroke Subtype in the Cardiovascular Health Study

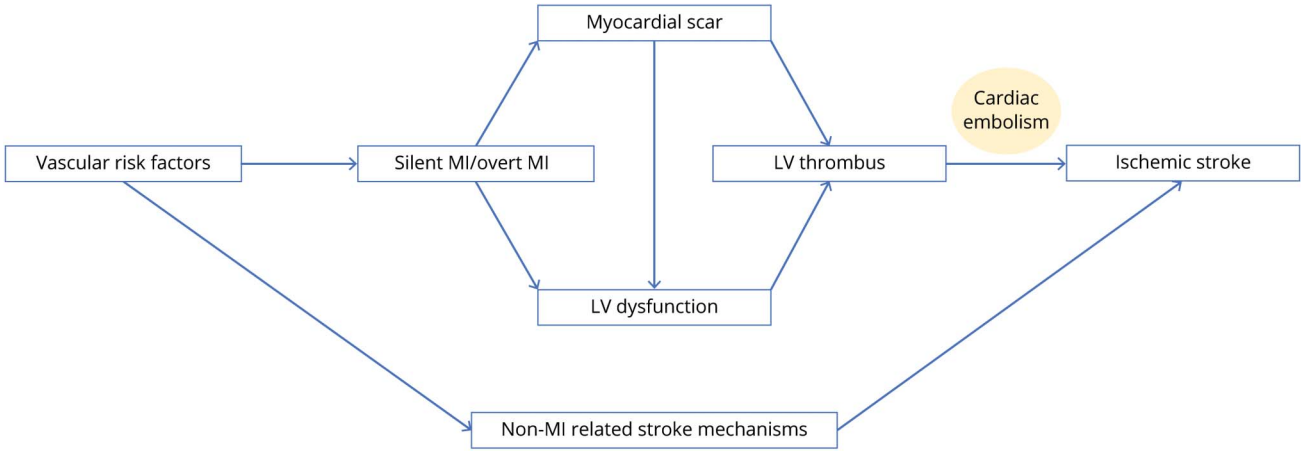
Model[a]	Nonlacunar	Other/unknown
Overt MI (short term)[b]	210 (127–348)	29 (12–72)
Overt MI (long term)[c]	2.21 (1.16–4.22)	1.57 (0.84–2.94)
Silent MI	2.40 (1.36–4.22)	1.29 (0.73–2.31)

[a] Data represent hazard ratio (95% confidence interval) with the reference group being those with no MI. Models were adjusted for age, sex, race, education level, study site, body mass index, diabetes, atrial fibrillation, congestive heart failure, systolic blood pressure, use of antihypertensive medication, high- and low-density lipoprotein and triglyceride levels, and smoking status (never, past, or current).
[b] As there was a violation in the proportional hazards assumption in this model, overt MI was split into short and long term. Short term refers to the risk of ischemic stroke within 30 days of the MI.
[c] Long term refers to the risk of ischemic stroke beyond 30 days following the MI.

The strengths of our study include its longitudinal prospective design, large sample size, availability of annual study ECGs, and adjudication of both incident MI and ischemic stroke. However, limitations exist. First, we lacked granular details regarding the degree of left ventricular dysfunction or severity of myocardial scar resulting from the MI. Second, we were unable to determine the exact date of silent MI and thus could not evaluate whether the risk of stroke attenuated over time after silent MI. Third, participants did not undergo continuous heart-rhythm monitoring to ascertain subclinical atrial fibrillation. Thus, we could not explore the degrees to which the association between silent MI and stroke was mediated by myocardial scar, left ventricular dysfunction, subclinical atrial fibrillation, or some combination. Fourth, we lacked detailed information on vascular risk factors that accrued subsequent to baseline and thus could not adjust for new or changing risk factors that may have affected the relationship between silent MI and stroke. Fifth, as intracranial imaging was not widely available, the number of undetermined strokes was high and the number of large-artery atherosclerosis strokes was low. Sixth, our findings must be interpreted in light of the wide CIs in our adjusted analyses, especially with regard to ischemic stroke subtype, in which there were few cases and fewer still with silent or overt MI prior to stroke. Lastly, all patients in CHS were ≥65 years of age and thus our findings may not be generalizable to younger patients.

In a population-based cohort, we found an association between silent MI and incident ischemic stroke. These results suggest that silent MI may be a novel stroke risk factor that may explain some proportion of ischemic strokes that

Figure Conceptual Model Shows the Proposed Pathway Between Silent Myocardial Infarction (MI) and Ischemic Stroke



LV = left ventricular.

currently lack an identifiable source. A trial of stronger antithrombotic therapy in patients with stroke and evidence of previously unrecognized MI may identify better therapeutic strategies to prevent recurrent stroke, thus reducing the public health burden from a previously unappreciated interaction between heart disease and stroke, the first and second leading causes of death worldwide.

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Disclosure

Dr. Merkler has performed medicolegal expert consulting on stroke. Dr. Bartz reports no disclosures relevant to the manuscript. Dr. Kamel serves as co-PI for the NIH-funded ARCADIA trial (NINDS U01NS095869), which receives in-kind study drug from the BMS-Pfizer Alliance for Eliquis and ancillary study support from Roche Diagnostics, serves as Deputy Editor for *JAMA Neurology*, serves as a steering committee member of Medtronic's Stroke AF trial (uncompensated), serves on an endpoint adjudication committee for a trial of empagliflozin for Boehringer-Ingelheim, and has served on an advisory board for Roivant Sciences related to Factor XI inhibition. Dr. Soliman and Dr. Howard report no disclosures relevant to the manuscript. Dr. Psaty serves on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. Dr. Okin serves as an Editorial Advisory Board Member of the *American Heart Journal* and *Journal of Hypertension*. Dr. Safford receives funding from Amgen on work unrelated to this topic. Dr. Elkind receives honoraria from UpToDate for a chapter on cryptogenic stroke and receives research support from the BMS-Pfizer Alliance for Eliquis (in-kind study drug) and Roche (ancillary funding) for the NINDS-funded ARCADIA trial. Dr. Longstreth is a co-investigator for CHS. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Contribution
Alexander E. Merkler, MD	Weill Cornell Medical College, New York, NY	Contributed to the conception and design of the study, interpreted data for the work, drafted and revised the manuscript for content, prepared final format for submission
Traci M. Bartz, MS	University of Washington, Seattle	Contributed to the conception and design of the study, drafted and revised the manuscript for content, performed statistical analysis and critical revision of the manuscript, provided final approval of the version to be submitted

Appendix *(continued)*

Name	Location	Contribution
Hooman Kamel, MD	Weill Cornell Medical College, New York, NY	Contributed to the conception and design of the study, performed critical revision of the manuscript, provided final approval of the version to be submitted
Elsayed Z. Soliman, MD, MSc, MS	Wake Forest University School of Medicine, Winston-Salem, NC	Performed critical revision of the manuscript, provided final approval of the version to be submitted
Virginia Howard, PhD	University of Alabama at Birmingham	Performed critical revision of the manuscript, provided final approval of the version to be submitted
Bruse M. Psaty, MD, PhD	University of Washington, Seattle	Performed critical revision of the manuscript, provided final approval of the version to be submitted
Peter M. Okin, MD	Weill Cornell Medical College, New York, NY	Performed critical revision of the manuscript, provided final approval of the version to be submitted
Monika M. Safford, MD	Weill Cornell Medical College, New York, NY	Performed critical revision of the manuscript, provided final approval of the version to be submitted
Mitchell S.V. Elkind, MD, MS	Columbia University, New York, NY	Performed critical revision of the manuscript, provided final approval of the version to be submitted
W.T. Longstreth, Jr., MD, MPH	University of Washington, Seattle	Contributed to the conception and design of the study, interpreted data for the work, performed critical revision of the manuscript, provided final approval of the version to be submitted

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