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ORIGINAL RESEARCH

Silent Myocardial Infarction and Risk of Stroke Recurrence: A Post Hoc Analysis of the IRIS Trial

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BACKGROUND: Unrecognized or silent myocardial infarction (MI) detected on an ECG is associated with first-ever stroke, but the impact on stroke recurrence is unknown. We aimed to determine the association of silent MI with stroke recurrence in patients with a recent ischemic stroke.

METHODS AND RESULTS: Subjects from the IRIS (Insulin Resistance Intervention After Stroke) trial with an available ECG were included. Clinical MI was defined as a history of hospitalization for MI. Silent MI was defined as ECG evidence of MI in the absence of clinical MI. The primary outcome was recurrent stroke. Ischemic stroke and subtype were assessed as secondary outcomes. Multivariable Cox regression analysis adjusted for demographics, pioglitazone, and vascular risk factors was used to examine the association between MI and stroke recurrence. A total of 2282 participants met the inclusion criteria. Clinical and silent MI were identified in 161 (7.1%) and 94 (4.1%) subjects, respectively. Over the study period, 209 recurrent strokes occurred, with 191 classified as ischemic. In the fully adjusted model, silent MI was significantly associated with any stroke (hazard ratio [HR], 2.29 [95% CI, 1.34–3.90]) and ischemic stroke (HR, 2.09 [95% CI, 1.18–3.70]) recurrence. Clinical MI was associated with stroke recurrence in the unadjusted analysis but not in the fully adjusted model (HR, 1.31 [95% CI, 0.81–2.11]). Silent MI was not associated with potential cardioembolic subtypes (HR, 1.50 [95% CI, 0.70–3.22]).

CONCLUSIONS: Among patients with a recent ischemic stroke, silent MI was associated with stroke recurrence. Tailored prevention strategies in this population warrant future investigation.

REGISTRATION: URL: https://clinicaltrials.gov. Unique Identifier: NCT00091949.

Key Words: cardioembolic ■ ECG ■ ischemic stroke

A history of clinically evident myocardial infarction (MI) is a known risk factor for stroke recurrence.[1–3] Although the risk of recurrent stroke may be the result of shared vascular risk factors, direct sequalae of myocardial injury, such as abnormal wall motion, depressed ejection fraction, or arrhythmia. are associated with an increased risk of future stroke.[4–6] A randomized-controlled trial, COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies), demonstrated a significant reduction in stroke using antithrombotic regimens in patients with a history of stable coronary artery disease, including a history of clinical MI.[7] However, up to 50% of MI may be devoid of clinical symptoms.[8] Silent or unrecognized MI is identified by the presence of pathologic Q waves on an ECG or evidence of infarction on cardiac imaging in the absence of clinical symptoms.[9] Multiple studies have demonstrated an increased risk of future major cardiovascular adverse events in patients with silent MI.[10–13] Recent data suggest that silent MI may be associated

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CLINICAL PERSPECTIVE

What Is New?

- Silent myocardial infarction is a risk factor for recurrent stroke, particularly ischemic, among patients with a recent ischemic stroke receiving secondary prevention therapy.

What Are the Clinical Implications?

- The identification of silent myocardial infarction after ischemic stroke may warrant more aggressive optimization of stroke risk factors and prolonged cardiac rhythm screening.
- Future randomized studies are necessary to investigate the potential benefit of tailored antithrombotic therapy in patients with silent myocardial infarction.

Nonstandard Abbreviations and Acronyms

HOMA	homeostasis model assessment of insulin resistance
IRIS	Insulin Resistance Intervention After Stroke
LAA	large-artery atherosclerosis

with an increased risk of stroke, but it is unknown whether silent MI is associated with an heightened risk of stroke recurrence in patients receiving secondary preventative therapies.[14,15]

Using the data from the IRIS (Insulin Resistance Intervention After Stroke) trial, we sought to determine if silent MI is a risk factor for stroke recurrence.

METHODS

The IRIS trial received local institutional review board approval at all study sites, and informed consent was received from all participants. This secondary analysis received institutional ethical board approval at Weill Cornell Medical Center. The Strengthening the Reporting of Observational Studies in Epidemiology guideline was completed.[16]

Patient Population

The IRIS trial was an international, randomized, double-blinded clinical trial conducted from 2005 to 2015 investigating the effect of pioglitazone on composite stroke and MI in insulin resistant, nondiabetic patients with a recent ischemic stroke or transient ischemic attack (TIA).[17] The study inclusion criteria required an age of at least 40 years, an ischemic stroke or TIA within 6 months before randomization, and evidence of insulin resistance using the homeostasis model assessment of insulin resistance (HOMA) index >3.0 measured at least 14 days after stroke.

A qualifying stroke required focal neurologic signs or symptoms for at least 24 hours. For events lasting <24 hours or events with nonfocal syndromes, radiographic evidence of acute infarction was required. Qualifying TIA included specified focal syndromes lasting for at least 10 minutes but <24 hours without imaging evidence of infarct. Ischemic stroke or TIA attributable to a structural cardiac lesion, head trauma, arterial dissection, or medical instrumentation was excluded.

Enrolled subjects were randomly assigned to receive either pioglitazone titrated to 45 mg daily or placebo. The primary study outcomes were recurrent stroke or MI over a follow-up interval up to 5 years. Patients with a history of heart failure (New York Heart Association class 3–4 or class 2 with reduced ejection fraction) or diabetes were excluded. Diabetes was defined by the 2005 American Diabetes Association criteria or the use of medications for diabetes within 90 days of screening.[18] A full list of exclusionary criteria may be found in the original study protocol.[19]

Data Collection and Risk Factors

All subjects underwent screening and baseline interview to ascertain demographic information, medical history, cardiovascular risk factors, blood work, and medication inventory. This included age, sex, race (Black, White, all non-White and non-Black races, or unknown), blood pressure, fasting lipid profile, hemoglobin A1c, and HOMA. History of hypertension, previous stroke (before qualifying index stroke or TIA), dyslipidemia, atrial fibrillation, heart failure, and current cigarette use were self-reported. All prescribed medications were recorded, including statin, antiplatelet, and anticoagulation use.

ECG and Clinical Definition of MI

A history of MI was collected for all subjects during the baseline interview. Subjects were asked if they had ever received a diagnosis of MI by a health care provider. Respondents with a diagnosis of MI were asked to provide the number of hospitalizations for a heart attack lasting >1 day.[19] For the present study, clinical MI was ascribed to patients with any previous hospitalization for MI. All ECGs collected at the time of enrollment were reviewed by an independent board-certified cardiologist with specific expertise in electrocardiography (S.M.) to categorize ECG into definite, probable, possible, and no evidence of MI.[20] This cardiologist was blinded to the hypothesis and outcomes of the study. Electrocardiographic evidence

of prior MI was determined by the presence of Q waves or Q-wave equivalents. In the setting of left bundle-branch block, Wolff-Parkinson-White, and ventricular paced rhythms, prior MI cannot be ascertained and was excluded from analysis.[9] Standardized criteria were used to grade definite, probable, and possible evidence of MI of indeterminate age.[9,21] A detailed list of ECG criteria used for interpretation is found in Table S1. For this study, ECG evidence of MI was defined as those meeting criteria for definite or probable MI. Criteria used to define possible MI are considered less specific and were not categorized as ECG evidence of MI in the primary analysis. Silent MI was defined as the presence of ECG evidence of prior MI in the absence of a prior clinical MI.

Stroke Outcome

The original trial protocol defined stroke outcomes as an acute neurologic event with focal signs or symptoms and either an increase in baseline National Institutes of Health Stroke Scale by at least 1 point in a previously normal section or corresponding radiographic evidence of stroke.[19] In response to the updated American Heart Association/American Stroke Association definition of stroke in 2013, a secondary analysis was performed with readjudication of stroke outcomes to include any acute neurologic events with focal signs or symptoms persisting for at least 24 hours or events lasting <24 hours with radiographic evidence of infarction.[22,23] The present study used the updated stroke outcome criteria. Adjudication was performed by an external review committee of neurologists blinded to treatment assignment with a consensus opinion of 2 adjudicators required to confirm stroke event, stroke type (ischemic, primary intraparenchymal hemorrhage, subarachnoid hemorrhage, uncertain hemorrhage, or uncertain type), and ischemic stroke subtype. Epidural and subdural hematoma were not classified as stroke events. Categorization of ischemic stroke subtypes used the TOAST (Trial of Org 10172 in Acute Stroke Treatment) schema of large-artery atherosclerosis (LAA), cardioembolic, lacunar, other determined, cryptogenic, or multiple causes.[24] For this analysis, the primary outcome was stroke of any type. Ischemic stroke and ischemic stroke subtypes were assessed as secondary outcomes. In subjects with multiple recurrent ischemic strokes, subtype was categorized by the first event.

Statistical Analysis

The principal analysis aimed to examine the association of silent MI with risk of stroke recurrence. Because of the known difficulty in the accurate diagnosis of TIA, only subjects with index stroke events were included in the primary analysis.[25]

Baseline demographics and characteristics of subjects with clinical MI, silent MI, and no MI were evaluated with χ^2 test for categorical variables and Mann-Whitney *U* or Kruskal-Wallis test for continuous variables as appropriate. A Cox regression model estimated the hazard ratio (HR) of all stroke recurrence and specifically ischemic stroke recurrence for each MI category. The follow-up period for outcome ascertainment was 5 years or at conclusion of the trial in July 2015. The crude model was adjusted only for MI category and study drug assignment. Variables associated with stroke risk or with significant univariate association with stroke recurrence in the cohort were selected as adjusted covariates in multivariable analysis (age, sex, race, hypertension, history of prior stroke, hyperlipidemia, atrial fibrillation, anticoagulant use, antiplatelet use, statin therapy, and active smoking). Final HRs and 95% CIs were calculated using subjects without evidence of MI as reference. Models were performed including all stroke events and repeated with exclusion of hemorrhagic stroke events. Individuals were censored at the time of first stroke event, death, or final study follow-up. Cases with missing index event type, baseline ECG, uninterpretable ECG, MI hospitalization data, outcome data, or covariate data were excluded from the analytic cohort.

Several sensitivity analyses were conducted: (1) inclusion of index events classified as TIA, (2) broadening the definition of silent MI to include ECG criteria for possible MI, (3) alternative adjustment for continuous measures of baseline systolic blood pressure, diastolic blood pressure, low-density lipoprotein, and HOMA in place of history of hypertension and hyperlipidemia in multivariable model, (4) competing risk analysis was performed to account for death over the follow up period, and (5) additional adjustment for baseline heart failure.

To test the hypothesis that silent MI increases the risk of stroke through a cardioembolic mechanism, we conducted a series of Cox regressions to estimate HR of potential cardiac (cardioembolic and cryptogenic), LAA, and lacunar ischemic stroke. Because of finite sample size within each category, models were adjusted for pioglitazone use alone to avoid overfitting. An additional secondary analysis was performed to assess the potential of Q waves on ECG as a potential biomarker for recurrent stroke risk. Multivariable Cox regression was performed with adjustment for self-reported MI history, Q-wave presence (using strict and broadened definitions), and identical adjustment covariates selected in the primary analysis. A sensitivity analysis of all participants with interpretable ECGs (including subjects with TIA as index event or missing MI history) was conducted with adjustment only for pioglitazone randomization.

The proportional hazards assumptions was confirmed in all Cox regression analysis. All reported *P*

values were 2 sided with the threshold of statistical significance set at $P<0.05$. Statistical analysis was performed using SPSS, version 29 (SPSS, Chicago, IL), the R Foundation for Statistical Computing, version 4.2.3, and Stata MP, version 15.1.

Data Availability

Clinical trial data are available through the National Institutes of Health/National Institute of Neurological Disorders and Stroke data archive.[26] Data specific to the analysis of this study are available on request to author A.E.

RESULTS

Of 3876 subjects, 2681 had ECG collected at enrollment. A total of 54 ECGs were uninterpretable (left bundle-branch block in 40 subjects, ventricular paced rhythms in 11 subjects, and Wolff-Parkinson-White in 3 subjects). Previous hospitalization for MI was missing in 3, and index cerebrovascular event type was missing in 8. TIA was the index event in 334 subjects. Thus, the analytic sample size was 2282. An additional 10 subjects were excluded in the multivariable adjusted model because of missing covariate data. Subjects without ECG at enrollment were less likely to be Black, and had more prevalent atrial fibrillation, higher HOMA, higher diastolic blood pressure, lower hemoglobin A1c, less recurrent stroke, and less recurrent ischemic stroke (Table S2). Among those with ECG data, excluded subjects were older and less likely to Black (Table S3). Inclusion and exclusion criteria are summarized in Figure 1. Criteria for definite, probable, or possible ECG evidence of MI were met in 65, 79, and 162 subjects, respectively.

History of clinical, silent, and no evidence of MI was present in 161 (7.1%), 94 (4.1%), and 2027 (88.8%) subjects, respectively. Baseline characteristics of each MI type are described in Table 1. Among subjects with clinical MI, a Q-wave pattern was present in 50 subjects and a non–Q-wave pattern was seen in 111 subjects. A total of 121 subjects were censored for death during the follow-up period, occurring in 102 with no MI (5.0%), 13 with clinical MI (8.1%), and 6 with silent MI (6.4%). There was no significant difference in mortality during the follow-up between MI types ($P=0.226$).

Recurrent Stroke in Silent MI and Clinical MI

Over a median follow-up period of 5.0 years (interquartile range, 4.0–5.0 years), 209 patients experienced recurrent stroke, of which 191 were ischemic stroke. Subjects with stroke recurrence were older, had more prevalent hypertension, prior stroke, atrial fibrillation, heart failure, active cigarette use, and MI of any type,

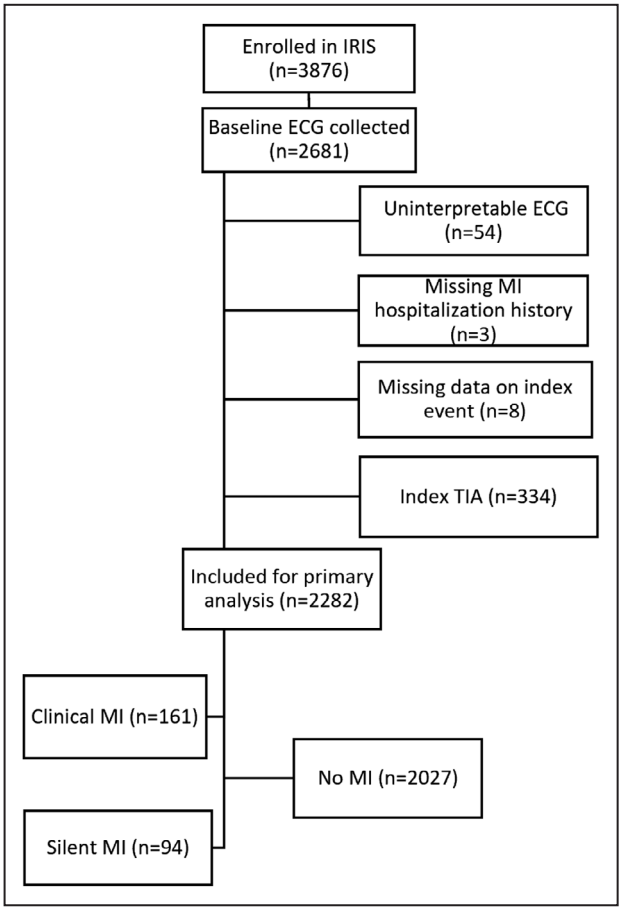

Figure 1. Flow diagram of exclusion and inclusion criteria. From the 3876 subjects enrolled in the IRIS (Insulin Resistance Intervention After Stroke) trial, baseline ECG was available for 2681. After exclusion of subjects with uninterpretable ECGs, missing data, and index transient ischemic attack (TIA) events, a total of 2282 were included in the primary analysis, with 161 clinical myocardial infarction (MI) and 94 silent MI.

and were less frequently randomized to pioglitazone use. Similar univariate associations were demonstrated in subjects with specifically ischemic stroke recurrence (Table 2).

Recurrent stroke occurred in 21 (13.0%) of patients with clinical MI, 15 (16.0%) of those with silent MI, and 173 (8.5%) of those without MI. Ischemic stroke occurred in 20 (12.4%), 13 (13.8%), and 158 (7.8%) subjects with clinical, silent, and no MI, respectively. The cumulative incidence rate of recurrent stroke was 3.2 per 100 person-years in clinical MI, 4.1 per 100 person-years in silent MI, and 2.0 per 100 person-years in no MI.

In the crude model adjusted only for pioglitazone treatment, a significant increased risk of recurrent stroke was demonstrated in subjects with silent MI (HR, 2.03 [95% CI, 1.20–3.44]; $P=0.009$) and clinical MI (HR, 1.58 [95% CI, 1.00–2.49]; $P=0.048$). The association with ischemic stroke recurrence was observed

Table 1. Baseline Characteristics of Subjects With Clinical, Silent, and No MI

Characteristic	No MI (n=2027)	Clinical MI (n=161)	Silent MI (n=94)	*P* value	Missing, n (%)
Age, mean±SD, y	62.64±10.8	65.04±10.5	60.47±10.2	0.003	0 (0)
Female sex, n (%)	719 (35.5)	33 (20.5)	30 (31.9)	<0.001	0 (0)
Black race, n (%)	279 (13.9)	13 (8.1)	12 (13.0)	0.117	27 (1.2)
Hypertension, n (%)	1419 (70.0)	126 (78.3)	74 (78.7)	0.020	0 (0.0)
Hyperlipidemia, n (%)	1343 (66.3)	144 (89.4)	51 (54.3)	<0.001	0 (0.0)
Prior stroke, n (%)	313 (15.4)	33 (20.5)	8 (8.5)	0.037	0 (0.0)
Atrial fibrillation, n (%)	113 (5.6)	16 (9.9)	7 (7.4)	0.066	1 (0.0)
Heart failure, n (%)	12 (0.6)	2 (1.3)	1 (1.1)	0.538	6 (0.3)
Current smoker, n (%)	310 (15.3)	33 (20.5)	20 (21.3)	0.077	0 (0.0)
Pioglitazone, n (%)	1016 (50.1)	84 (52.2)	55 (58.5)	0.260	0 (0)
Anticoagulation, n (%)	224 (11.1)	29 (18.0)	12 (12.8)	0.029	7 (0.3)
Antiplatelet, n (%)	1867 (92.2)	152 (95.0)	86 (91.5)	0.408	2 (0.1)
Statin, n (%)	1638 (81.1)	148 (91.9)	83 (88.3)	0.001	7 (0.3)
SBP, mean±SD, mm Hg	133.3±17.5	131.22±17.6	135.66±21.9	0.119	10 (0.4)
DBP, mean±SD, mm Hg	79.3±10.7	78.1±11.6	80.8±11.5	0.075	10 (0.4)
HbA1c, mean±SD	5.8±0.4	5.9±0.4	5.8±0.3	0.355	0 (0)
LDL, mean±SD, mg/dL	88.4±32.0	85.4±28.2	79.4±27.6	0.024	20 (0.9)
HOMA, median (IQR)	4.5 (3.7–6.1)	5.0 (3.8–6.6)	4.9 (3.9–5.9)	0.086	0 (0)

DBP indicates diastolic blood pressure; HbA1c, hemoglobin A1c; HOMA, homeostatic model assessment for insulin resistance; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; and SBP, systolic blood pressure.

for both silent (HR, 1.92 [95% CI, 1.09–3.37]; *P*=0.024) and clinical MI (HR, 1.65 [95% CI, 1.04–2.63]; *P*=0.034). In the fully adjusted model, silent MI remained significantly associated with a higher risk of recurrent stroke (HR, 2.29 [95% CI, 1.34–3.90]; *P*=0.002) and recurrent ischemic stroke (HR, 2.09 [95% CI, 1.18–3.70]; *P*=0.012). No significant association between clinical MI and recurrent stroke (HR, 1.31 [95% CI, 0.81–2.11]; *P*=0.266) or recurrent ischemic stroke (HR, 1.42 [95% CI, 0.87–2.32]; *P*=0.158) was detected in the final model (Table 3, Figures 2 and 3).

Sensitivity Analysis

Inclusion of subjects with index TIA events demonstrated a persistent association between silent MI with stroke and ischemic stroke (stroke: HR, 2.04 [95% CI, 1.20–3.47]; *P*=0.008; ischemic stroke: HR, 1.92 [95% CI, 1.09–3.38]; *P*=0.025), whereas clinical MI still demonstrated no association with stroke or ischemic stroke recurrence (stroke: HR, 1.31 [95% CI, 0.84–2.05]; *P*=0.232; ischemic stroke: HR, 1.44 [95% CI, 0.91–2.26]; *P*=0.121).

Using a more inclusive definition of ECG evidence of MI, 147 subjects with no evidence of MI were reclassified to silent MI (Table S4). There was no significant association between silent MI or clinical MI with recurrent stroke or ischemic stroke with the broadened ECG criteria.

Adjustment for continuous baseline measures of blood pressure, low-density lipoprotein, and HOMA did not significantly impact the association between MI types and recurrent stroke. Neither adjustment for death over follow-up nor baseline heart failure significantly altered the association between MI types and recurrent stroke in the fully adjusted models (Table 4).

Ischemic Stroke Subtypes

Among subjects with recurrent ischemic stroke, cause was attributed to LAA in 32 (16.8%), cardioembolic in 23 (12.0%), lacunar in 26 (13.6%), other in 4 (2.1%), cryptogenic in 100 (52.4%), and multiple causes in 6 (3.1%) subjects. Neither silent nor clinical MI was associated with an increased risk of a definite or possible cardiac mechanism. Silent MI was associated with LAA (HR, 3.90 [95% CI, 1.35–11.25]; *P*=0.012), and clinical MI was associated with lacunar (HR, 4.18 [95% CI, 1.67–10.48]; *P*=0.002) (Table 5).

Q Wave Presence

Q wave was detected in 144 subjects using strict ECG criteria (definite and probable) and 305 subjects using broad criteria (definite, probable, and possible). Using the strict criteria, Q-wave detection was associated with both any recurrent stroke (HR, 1.95 [95% CI, 1.21–3.15]; *P*=0.006) and ischemic stroke (HR, 1.85 [95% CI, 1.12–3.05]; *P*=0.016) in the fully adjusted model. Sensitivity analysis of all subjects with interpretable ECG (n=2627) demonstrated a persistent association between Q-wave detection and stroke recurrence. The association attenuated using the broadened ECG

Table 2. Baseline Characteristics of Subjects With No Stroke, Any Stroke, and Ischemic Stroke

Characteristic	No recurrent stroke (n=2073)	Recurrent stroke (n=209)	*P* value*	Recurrent ischemic stroke (n=191)	*P* value*
Age, mean ±SD, y	62.5±10.6	65.1±11.6	0.006	64.7±11.5	0.033
Female sex, n (%)	711 (34.3)	71 (34.0)	0.924	66 (34.6)	0.930
Black race, n (%)	271 (13.2)	33 (15.9)	0.291	30 (15.8)	0.330
Hypertension, n (%)	1453 (70.1)	166 (79.4)	0.005	152 (79.6)	0.006
Hyperlipidemia, n (%)	1387 (66.9)	151 (72.2)	0.116	136 (71.2)	0.241
Prior stroke, n (%)	300 (14.5)	54 (25.8)	<0.001	47 (24.6)	<0.001
Atrial fibrillation, n (%)	117 (5.6)	19 (9.1)	0.043	17 (8.9)	0.070
Heart failure, n (%)	11 (0.5)	4 (1.9)	0.041	3 (1.6)	0.124
MI type, n (%)			0.011		0.019
No MI	1854 (89.4)	173 (82.8)		158 (82.7)	
Clinical MI	140 (6.8)	21 (10.0)		20 (10.5)	
Silent MI	79 (3.8)	15 (7.2)		13 (6.8)	
Current smoker, n (%)	311 (15.0)	52 (24.9)	<0.001	47 (24.6)	0.001
Pioglitazone, n (%)	1063 (51.3)	92 (44.0)	0.045	80 (41.9)	0.012
Anticoagulation, n (%)	238 (11.5)	27 (12.9)	0.548	26 (13.6)	0.377
Antiplatelet, n (%)	1913 (92.3)	192 (92.3)	0.992	174 (91.6)	0.687
Statin, n (%)	1703 (82.4)	166 (79.4)	0.280	150 (78.5)	0.172
SBP, mean ±SD, mmHg	133.1±17.6	134.4±18.4	0.321	134.6±18.2	0.238
DBP, mean ±SD, mmHg	79.3±10.7	78.5±11.9	0.366	78.6±11.7	0.559
HbA1c, mean ±SD	5.8±0.4	5.8±0.4	0.509	5.8±0.4	0.756
LDL, mean ±SD, mg/dL	87.7±31.7	88.3±31.6	0.857	89.1±31.2	0.589
HOMA, median (IQR)	4.6 (3.7–6.1)	4.5 (3.5–6.2)	0.194	4.5 (3.5–6.2)	0.214

DBP indicates diastolic blood pressure; HbA1c, hemoglobin A1c; HOMA, homeostatic model assessment for insulin resistance; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; and SBP, systolic blood pressure.
*P values refer to comparison to subjects with no recurrent stroke.

criteria with no significant association between Q-wave presence and stroke recurrence (Table S5).

DISCUSSION

In this reanalysis of the IRIS trial, silent MI was associated with an elevated risk of recurrent stroke, ischemic stroke in particular.

Our findings add to the existing literature supporting silent MI as a risk factor for ischemic stroke. Previous large, population-based studies report an increased incidence of first-ever stroke, first-ever ischemic stroke, radiographic infarcts, and future cognitive impairment among individuals with silent MI.[14,27–30] Mechanisms underlying the relationship of silent MI with cerebrovascular disease remain unclear. The novelty of the present study is that all participants underwent evaluation of stroke cause, risk factor optimization, and secondary stroke prevention. Thus, it is unlikely that untreated risk factors alone provide an adequate explanation for the elevated risk of stroke. A potential explanatory hypothesis is silent MI may be an occult source of cardioemboli

Table 3. Association of Silent MI and Clinical MI With All Stroke and Ischemic Stroke Recurrence

Outcome	No MI	Silent MI HR (95% CI)	*P* value	Clinical MI HR (95% CI)	*P* value
Model 1*					
All stroke	Reference	2.03 (1.20–3.44)	0.009	1.58 (1.00–2.49)	0.048
Ischemic stroke	Reference	1.92 (1.09–3.37)	0.024	1.65 (1.04–2.63)	0.034
Model 2†					
All stroke	Reference	2.29 (1.34–3.90)	0.002	1.31 (0.81–2.11)	0.266
Ischemic stroke	Reference	2.09 (1.18–3.70)	0.012	1.42 (0.87–2.32)	0.158

HR indicates hazard ratio; and MI, myocardial infarction.
*Adjusted for pioglitazone alone.
†Adjusted for age, sex, race, pioglitazone, atrial fibrillation, prior stroke, smoking, hypertension, hyperlipidemia, anticoagulation, antiplatelet, statin.

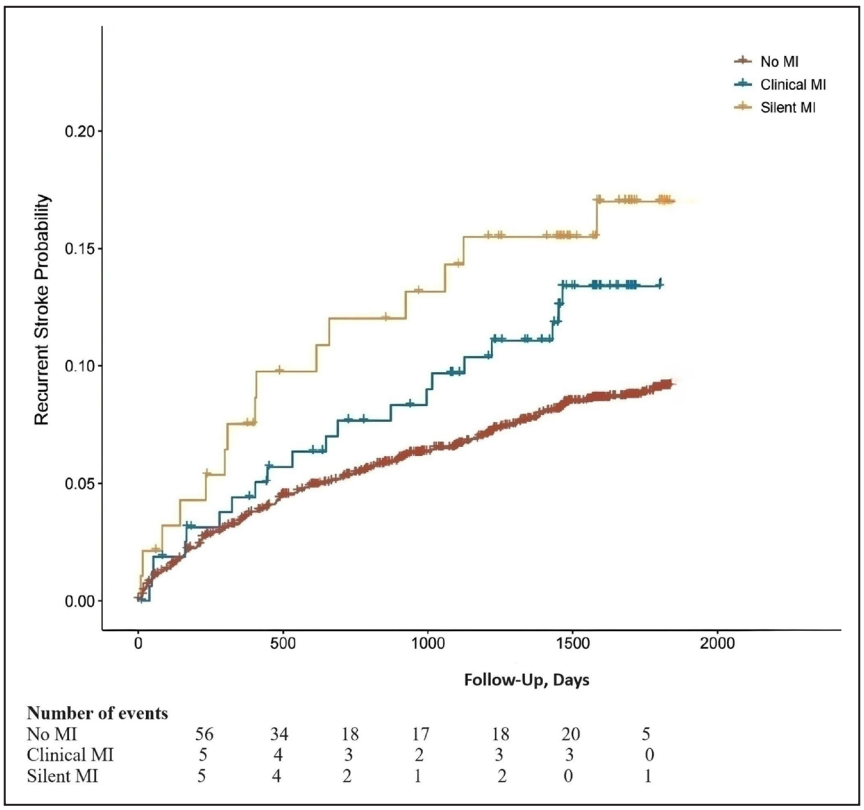

Figure 2. Stroke recurrence rates. Cumulative incidence rate of stroke recurrence per 100 person-years was 4.1, 3.2, and 2.0 for silent myocardial infarction (MI), clinical MI, and no MI, respectively.
Adjusted hazard ratios for recurrent stroke among silent and clinical MI were 2.29 (95% CI, 1.34–3.90) and 1.31 (95% CI, 0.81–2.11), respectively.

because of ventricular wall motion dysfunction and depressed ejection fraction with resultant turbulent blood flow and coagulation cascade activation. In prior studies, silent MI has the strongest association with stroke attributed to cortical infarcts, embolism of unknown source, and nonlacunar infarcts.[14,15,27] With ≈30% of all ischemic stroke lacking an identifiable cause, this may constitute a subset of embolic-appearing cryptogenic stroke.[31] Although not reaching statistical significance, subjects with silent MI demonstrated a trend toward increased risk of recurrent ischemic stroke secondary to definite or potential cardiac sources or emboli. Alternatively, because atherosclerosis is the primary cause of coronary artery disease, silent MI may serve as a biomarker for concomitant intracranial atherosclerotic disease, which carries a high rate of recurrent ischemic stroke.[32] Although sample size was limited, silent, but not clinical, MI was associated with an increased risk of ischemic stroke attributed to LAA in the IRIS trial cohort. The COMPASS trial demonstrated low-dose rivaroxaban combined with aspirin to be superior to aspirin monotherapy in the composite outcome of cardiovascular death, stroke, or MI in subjects with stable atherosclerotic disease.[7] Patients with silent MI may benefit from a similar regimen for secondary stroke prevention.

The absence of increased stroke recurrence risk in subjects with prior clinical MI merits discussion. The existing literature comparing the incidence of stroke between silent and clinical MI has shown mixed results. An analysis of the CHS (Cardiovascular Health Study) cohort described a similar increased incidence of first-ever stroke in both silent and clinical MI, whereas the Rotterdam study demonstrated only silent MI was associated with an increased risk for first-ever stroke.[14,27] A potential confounder is the time-dependent nature of the stroke risk after an overt MI. The risk of ischemic stroke is elevated during the first 3 months after a clinical MI, with a gradual decline thereafter.[2,3,33] Because the date of clinical MI was unavailable, we were unable account for time-variable nature of stroke risk after a clinical MI. The IRIS trial excluded individuals with more severe heart failure attributable to risk of exacerbation with pioglitazone use; thus, the MI cohort likely underrepresents more severe infarcts with subsequent ischemic cardiomyopathy. Furthermore, it is plausible that stroke recurrence risk may be attributed to residual confounding in secondary stroke prevention by

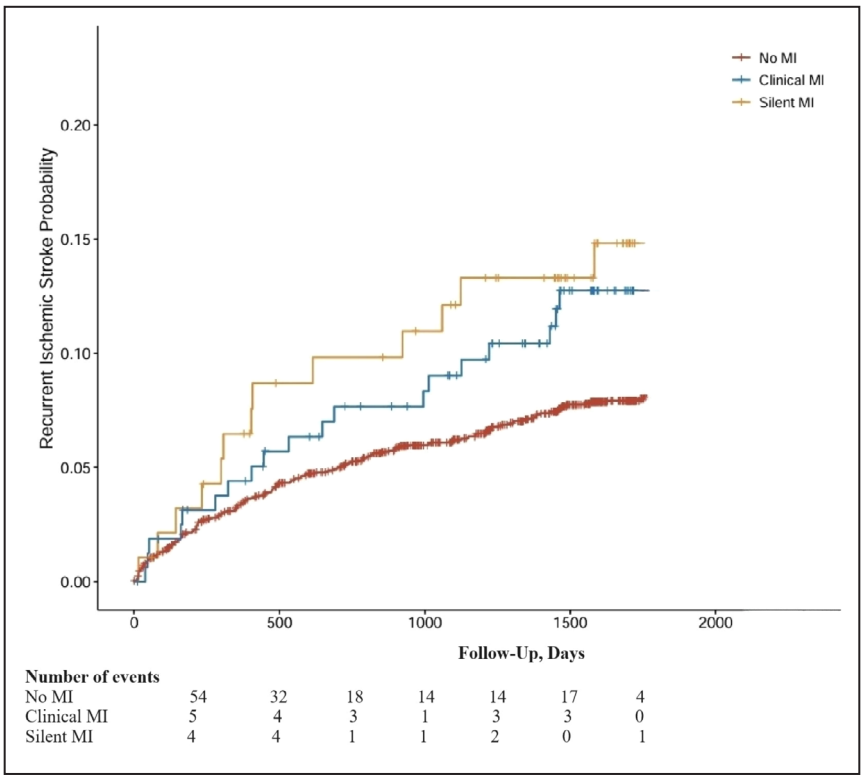

Figure 3. Ischemic stroke recurrence rates.
Adjusted hazard ratios for recurrent ischemic stroke among silent and clinical myocardial infarction (MI) were 2.09 (95% CI, 1.18–3.70) and 1.42 (95% CI, 0.87–2.32), respectively.

providers when caring for patients with previous overt MI. This may include more aggressive antithrombotic and statin regimens, greater emphasis on dietary and lifestyle interventions, and more extensive search for treatment-modifying comorbidities, such as atrial fibrillation. In the IRIS trial cohort, patients with clinical MI

Table 4. Sensitivity Analyses Results

Outcome	No MI	Silent MI HR (95% CI)	*P* value	Clinical MI HR (95% CI)	*P* value
Sensitivity 1: inclusion of subjects with TIA index event					
All stroke	Reference	2.04 (1.20–3.47)	0.008	1.31 (0.84–2.05)	0.232
Ischemic stroke	Reference	1.92 (1.09–3.38)	0.025	1.44 (0.91–2.26)	0.121
Sensitivity 2: broadened ECG criteria of MI to include possible MI					
All stroke	Reference	1.33 (0.88–2.01)	0.210	1.30 (0.81–2.10)	0.279
Ischemic stroke	Reference	1.22 (0.78–1.91)	0.373	1.40 (0.86–2.30)	0.177
Sensitivity 3: adjustment for systolic blood pressure, diastolic blood pressure, LDL, and HOMA in replacement of hypertension and hyperlipidemia history					
All stroke	Reference	2.27 (1.33–3.87)	0.003	1.21 (0.74–1.99)	0.452
Ischemic stroke	Reference	2.07 (1.17–3.67)	0.013	1.30 (0.78–2.18)	0.310
Sensitivity 4: competing risk analysis to adjust for death over follow up					
All stroke	Reference	2.29 (1.35–3.90)	0.002	1.30 (0.80–2.12)	0.296
Ischemic stroke	Reference	2.09 (1.19–3.68)	0.010	1.41 (0.85–2.32)	0.179
Sensitivity 5: additional adjustment for heart failure					
All stroke	Reference	2.31 (1.35–3.94)	0.002	1.32 (0.82–2.13)	0.251
Ischemic stroke	Reference	2.07 (1.17–3.67)	0.013	1.44 (0.88–2.34)	0.148

Sensitivity models adjusted for age, sex, race, pioglitazone, atrial fibrillation, prior stroke, smoking, hypertension, hyperlipidemia, anticoagulation, antiplatelet, and statin. HOMA indicates homeostasis model assessment of insulin resistance; HR, hazard ratio; LDL, low-density lipoprotein; MI, myocardial infarction; and TIA, transient ischemic attack.

Table 5. Association of Silent MI and Clinical MI With Ischemic Stroke Subtype

Outcome	No MI	Silent MI HR (95% CI)	*P* value	Clinical MI HR (95% CI)	*P* value
Definite or potential cardiac source	Reference	1.50 (0.70–3.22)	0.298	0.97 (0.47–1.99)	0.932
Large-artery atherosclerosis	Reference	3.90 (1.35–11.25)	0.012	2.16 (0.75–6.21)	0.155
Lacunar	Reference	1.28 (0.17–9.56)	0.811	4.18 (1.67–10.48)	0.002

All models adjusted for pioglitazone use. HR indicates hazard ratio; and MI, myocardial infarction.

were prescribed anticoagulation and statin therapy more frequently. The association of increased recurrent ischemic stroke and clinical MI in the minimally adjusted model disappeared after controlling for these factors, supporting this possibility. Although no overall association was demonstrated between clinical MI and stroke recurrence in the fully adjusted model, the exploratory association between clinical MI and lacunar stroke possibly reflects overlapping risk factors in the pathogenesis of both atherosclerosis and cerebral small-vessel disease.[34]

Limitations

One of the challenges in the study of silent MI is inconsistency in ECG criteria of prior MI.[35] Previous population-based cohorts have implemented standardized ECG coding systems, such as the Minnesota criteria, to preserve interrater and intrarater reliability with reasonable sensitivity and specificity for MI detection.[36] The inclusion of a broadened criteria to define silent MI in our sensitivity analysis highlights this issue as the number of silent MI more than doubled and nullified the association with stroke recurrence. Significant effort was made to minimize measurement bias of ECG interpretation via independent interpretation of all ECGs by a blinded cardiologist using standardized classification criterion. The emerging use of cardiac magnetic resonance imaging may improve diagnostic accuracy of silent MI in future studies.[37] The IRIS trial was performed in a cohort of patients with insulin resistance who have been demonstrated to have an elevated risk of atherosclerotic disease and cerebral ischemic events.[38,39] Although our findings were unchanged with adjustment for baseline heart failure, the IRIS trial did not enroll patients with severe heart failure. Thus, the generalizability of the impact of silent MI on recurrent stroke risk to the remainder of the stroke population may be uncertain and requires validation in other cohorts. The definition of clinical MI used in the IRIS trial relied on self-reported hospitalization; however, it is possible that some patients with silent MI may have failed to report previous hospitalizations. Secondary stroke prevention strategies were left to the discretion of treating physicians and not enforced uniformly in the trial. Thus, residual confounders may be unaccounted for in this analysis. Overlap in effective medical treatments for both coronary artery disease and ischemic stroke introduces the possibility of collider bias and potential spurious multivariable analysis results. However, the consistent directionality of effect size between the minimally and fully adjusted analysis is reassuring. Other unaccounted shared risk factors, such as inflammation, diet, lifestyle, socioeconomic status, and genetics, may also contribute to the association between stroke and silent MI. Although the IRIS trial had well-characterized ischemic stroke mechanisms, sample size within individual stroke subtype categories was limited and underpowered to account for all potential confounders. Last, the use of a time-based definition of TIA introduces misclassification bias because of potential inclusion of stroke mimics or mild strokes. Although the inclusion of TIA events in our sensitivity analysis did not nullify the association of silent MI with stroke recurrence, the application of a tissue-based definition of TIA may improve fidelity of future investigations.

Conclusions

Silent MI was significantly associated with stroke recurrence in patients with a recent ischemic stroke, whereas clinical MI was not found to be associated with stroke recurrence. Future studies exploring the pathophysiology of the association and potential individualized secondary stroke prevention strategies are warranted.

ARTICLE INFORMATION

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Supplemental Material

Tables S1-S5

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