High-Sensitivity C-Reactive Protein, Lipoprotein-Associated Phospholipase A2, and Outcome After Ischemic Stroke

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Background: Inflammatory markers have been associated with ischemic stroke risk and prognosis after cardiac events. Their relationship to prognosis after stroke is unsettled.

Methods: A population-based study of stroke risk factors in 467 patients with first ischemic stroke was undertaken to determine whether levels of high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2) predict risk of stroke recurrence, other vascular events, and death.

Results: Levels of Lp-PLA2 and hs-CRP were weakly correlated \( (r=0.09; P=0.045) \). High-sensitivity CRP, but not Lp-PLA2, was associated with stroke severity. After adjusting for age, sex, race and ethnicity, history of coronary artery disease, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, smoking, and hs-CRP level, compared with the lowest quartile of Lp-PLA2, those in the highest quartile had an increased risk of recurrent stroke (adjusted hazard ratio, 2.08; 95% confidence interval, 1.04-4.18) and of the combined outcome of recurrent stroke, MI, or vascular death (adjusted hazard ratio, 1.86; 95% confidence interval, 1.01-3.42). After adjusting for confounders, hs-CRP was not associated with risk of recurrent stroke or recurrent stroke, myocardial infarction, or vascular death but was associated with risk of death (adjusted hazard ratio, 2.11; 95% confidence interval, 1.18-3.75).

Conclusions: Inflammatory markers are associated with prognosis after first ischemic stroke and may offer complementary information. Lipoprotein-associated phospholipase A2 may be a stronger predictor of recurrent stroke risk. Levels of hs-CRP, an acute-phase reactant, increase with stroke severity and may be associated with mortality to a greater degree than recurrence.

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INDEX EVALUATION OF PATIENTS

Data were collected through interviews by trained research assistants, and physical and neurologic examinations were conducted by study neurologists. When possible, data were obtained directly from patients using the standardized data collection instruments. When the patient was unable to provide answers, a proxy knowledgeable about the patient’s history was interviewed. Race and ethnicity was based on self-identification.

Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System.17 Standard techniques were used to measure blood pressure, height, weight, and fasting glucose and lipid panels as described previously.18 Hypertension and hyperlipidemia were defined as a history of the disorder or taking medication for it. Diabetes mellitus was defined as the patient’s self-report of such a history or insulin or oral hypoglycemic drug use.

Stroke severity was assessed using the NIHSS and was categorized as mild (NIHSS score <6), moderate (NIHSS score of 6–13), or severe (NIHSS score ≥14).13,18,19 Assessment of stroke subtype using modified TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria20 was determined by a consensus of stroke neurologists using all available information, as described previously.21

ASSESSMENT OF hs-CRP AND Lp-PLA2

Blood samples collected at the time of hospitalization or the clinic visit in 5-mL serum separator tubes by a trained phlebotomist were centrifuged at 3000g for 15 minutes and then aliquotted into 2-mL tubes (Eppendorf, Westbury, NY). Samples were stored at ~80°C until assays were run. Serum samples were assayed for Lp-PLA2 mass using a microplate-based enzyme-linked immunosorbent assay (PLAC assay; DiaDexus Inc, South San Francisco, Calif) as previously described22 and for hs-CRP using an enzyme-linked immunosorbant assay (BioCheck Inc, Foster City, Calif). Assays were run at a central laboratory at DiaDexus Inc, and laboratory personnel were masked to all patient clinical data and outcomes.

Quality control was maintained using standard procedures. Twenty percent of the samples tested for Lp-PLA2 and

Table 1. Characteristics of the 467 Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>68.9 ± 12.7</td>
</tr>
<tr>
<td>Male</td>
<td>212 (45.4)</td>
</tr>
<tr>
<td>High school education (n = 456)</td>
<td>160 (34.9)</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>83 (17.8)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>127 (27.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>249 (53.3)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td><strong>Risk factors and medical history</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>317 (67.9)</td>
</tr>
<tr>
<td>Diabetes mellitus (n = 466)‡</td>
<td>150 (32.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>74 (15.9)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>160 (34.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>62 (13.3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>50 (10.7)</td>
</tr>
<tr>
<td>Peripheral arterial disease (n = 465)</td>
<td>108 (23.2)</td>
</tr>
<tr>
<td>Current smoking (n = 446)</td>
<td>101 (22.7)</td>
</tr>
<tr>
<td>Ever smoked (n = 465)</td>
<td>250 (53.8)</td>
</tr>
<tr>
<td>History of hypercholesterolemia (n = 464)</td>
<td>171 (36.9)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL (n = 461)</td>
<td>192.2 (45.0)</td>
</tr>
<tr>
<td>LDL cholesterol, mean (SD), mg/dL (n = 452)</td>
<td>121.3 (39.3)</td>
</tr>
<tr>
<td>HDL cholesterol, mean (SD), mg/dL (n = 459)</td>
<td>39.7 (12.9)</td>
</tr>
<tr>
<td>LDL cholesterol &gt;130 mg/dL (n = 452)</td>
<td>170 (37.6)</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dL (n = 459)</td>
<td>274 (59.7)</td>
</tr>
<tr>
<td>Creatinine, mean (SD), mg/dL (n = 238)</td>
<td>1.2 (1.1)</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; cholesterol to millimoles per liter, multiply by 0.02586.

**METHODS**

SELECTION OF STROKE COHORT

The Northern Manhattan Stroke Study includes a population-based incident ischemic stroke follow-up study designed to determine predictors of stroke recurrence and prognosis in a multiethnic, urban population. The methods of patient identification and enrollment of this cohort (n = 655) have been described previously.13,16 Briefly, patients with stroke were enrolled if they (1) were diagnosed as having a first stroke; (2) were 40 years and older; and (3) resided in northern Manhattan for 3 months or longer in a household with a telephone. For this analysis, only patients with ischemic stroke were included. Patient evaluation was performed at Columbia University Medical Center hospital; individuals either not hospital-ized or hospitalized elsewhere were evaluated in the outpatient research clinic. This study was approved by the institutional review board at Columbia University Medical Center. All the participants gave consent directly or through a surrogate when appropriate.

Measurements of hs-CRP and Lp-PLA2 levels were available for this analysis in 467 participants. The distribution of sociodemographic factors, comorbid vascular diseases, and conventional atherosclerotic risk factors is given in Table 1. Patients for whom these measurements were available were slightly younger (mean ± SD age, 68.9 ± 12.7 years) than those who did not undergo these measurements (mean ± SD age, 71.9 ± 12.4 years; P = .006). There were also fewer patients with severe stroke: 64 (14.1%) of 455 analyzed patients had severe stroke (National Institutes of Health Stroke Scale [NIHSS] score ≥14) compared with 23.0% in the nonanalyzed group (P = .02). There were no statistically significant differences between groups in sex, race or ethnicity, or any risk factors. Participants were followed up for up to 6.2 years. Using logistic modeling, the probability of selection was shown to be independent of recurrent stroke, conditional on other covariates (age, sex, race and ethnicity, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, current smoking, and coronary artery disease).
hs-CRP assay were run in duplicate, with 97% producing coefficients of variation of 10% or less between duplicates. All the samples had coefficients of variation less than 15% for Lp-PLA2. For hs-CRP, 3% had coefficients of variation greater than 15%. All of these samples quantitated in the very low range of the assay and were repeated to meet acceptance criteria.

FOLLOW-UP AND OUTCOMES ASSESSMENT

Follow-up evaluations were conducted at 6 months by telephone and annually in person for 5 years. Information on vital status, functional status, and intercurrent symptoms, illness, or hospitalization was collected. Evaluation was conducted at home or in an alternative place of residence (eg, nursing home) for patients unable or unwilling to come to the medical center. Ongoing surveillance of admissions to Columbia University Medical Center and other local hospitals, described previously,22 was also used to identify study participants who experienced recurrent stroke, MI, hospitalization, or death. When available, medical records were reviewed for all outcome events, including death. Myocardial infarction was validated by review by a study cardiologist, and stroke by a study neurologist. Deaths were also validated by a study physician.

STATISTICAL ANALYSES

Descriptive statistics were calculated for the cohort with stroke. Means for continuous variables and proportions for dichotomous variables were compared using t tests and χ² tests as appropriate. Values for hs-CRP were log transformed as needed for correlational analyses. Correlations between inflammatory marker values and other prognostic factors were also calculated. After examining the distributions, inflammatory marker values were categorized by quartile for further analyses. Preliminary analyses indicated a differential effect of markers on recurrent stroke and death as independent outcomes. Cox proportional hazard models were then constructed to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the effect of these markers on independent risks of recurrent stroke, death, and the combined event cluster of recurrent stroke, MI, or vascular death. Time to first event was analyzed with censoring at the time to either nonvascular death or last follow-up. Unadjusted models and models adjusted for demographic characteristics (age, sex, and race and ethnicity) and risk factors (coronary artery disease, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, and smoking) were calculated. Interaction terms were included to satisfy assumptions of proportionality, and there was no evidence of overfitting or collinearity. Analyses including death were additionally adjusted by stroke severity. Analyses stratified by LDL cholesterol were not associated with stroke severity. The proportion of participants with Lp-PLA2 levels in the highest quartile among patients with mild stroke (24.1%, n=37) did not differ significantly from those with moderate (23.4%, n=40) or severe (37.5%, n=46; χ²=0.03; P=.89) stroke. Levels of hs-CRP were also inversely correlated with history of current smoking, with 96 nonsmokers (27.8%) and 15 current smokers (14.9%) having hs-CRP levels in the fourth quartile (P=.03). Levels of Hs-CRP were not associated with other risk factors. Levels of Lp-PLA2 after stroke were associated with age (Table 2). Of patients 70 years and older, 67 (29.9%) had Lp-PLA2 levels in the highest quartile (≥388.6 mg/mL) vs 50 (20.6%) of those younger than 70 years (P=.001). Levels of Lp-PLA2 were not associated with stroke severity. The proportion of participants with Lp-PLA2 levels in the highest quartile among patients with mild stroke (24.1%, n=57) did not differ significantly from those with moderate (23.4%, n=36) or severe (37.5%, n=24) stroke (P=.13). Proportions of patients with Lp-PLA2 levels in the highest quartile did not differ by other vascular risk factors, including smoking and diabetes mellitus.

Hs-CRP AND Lp-PLA2 AS PREDICTORS OF OUTCOME

Median follow-up was 4.0 years. Outcomes included 80 recurrent strokes (15 fatal), 18 MIs, 53 vascular deaths, and 159 deaths. Unadjusted HRs for the association of hs-CRP and Lp-PLA2 with several outcomes across quartiles of these markers are given in Table 3. The cumulative risk of a recurrent stroke among individuals in the highest quartile of hs-CRP was 17.9% (95% CI, 9.2%-26.7%) compared with a risk of 20.4% (95% CI, 12.8%-28.1%) among those in the lowest quartile. Using as a referent group the lowest quartile, those in the highest hs-CRP quartile were not at increased risk for recurrent stroke (adjusted HR, 0.73; 95% CI, 0.37-1.44) (Table 4). In separate models adjusting for risk factors and stroke severity, a well-recognized predictor of mortality after stroke, individuals in the highest quartile of hs-CRP had twice the risk of death (adjusted HR, 2.04; 95% CI, 1.18-3.53) but no increase in risk of stroke, MI, or vascular death (adjusted HR, 1.04; 95% CI, 0.57-1.88). There was little change after further adjusting for Lp-PLA2 level.
Cumulative risk of recurrent stroke among patients in the highest quartile of Lp-PLA2 was 27.1% (95% CI, 18.3%-36.0%) compared with a risk of 13.2% (95% CI, 6.7%-19.6%) among those in the lowest quartile. Levels of Lp-PLA2 were associated with recurrent stroke and the combined vascular event outcome of recurrent stroke, Ml, or vascular death. Compared with the lowest quartile of Lp-PLA2, those in the highest quartile were at increased risk for recurrent stroke (HR, 2.30; 95% CI, 1.21-4.36). After adjusting for demographics, hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation, and coronary disease, this effect attenuated slightly (adjusted HR, 2.17; 95% CI, 1.08-4.39). Further adjusting for quartile of hs-CRP had little effect (adjusted HR, 2.08; 95% CI, 1.04-4.18) (Table 4). Those in the highest quartile of Lp-PLA2, after fully adjusting for hs-CRP and other risk factors, were at increased risk for the combined outcome of recurrent stroke, MI, or vascular death.
Inflammatory markers predict incident ischemic events, including MI and stroke, but their ability to predict prognosis after ischemic stroke is unsettled. A recent summary statement from the European CRP Pooling Project concluded that there were insufficient data to recommend testing for hs-CRP in patients with stroke. In the present population-based study of patients with a first ischemic stroke, levels of hs-CRP and Lp-PLA2 measured shortly after stroke predicted complementary aspects of prognosis. During approximately 4 years of follow-up, hs-CRP levels were associated with increased mortality but not recurrent stroke or combined ischemic events. Levels of Lp-PLA2, however, were a stronger predictor of recurrent stroke risk than mortality in this population, and they also predicted recurrent stroke, MI, and vascular death.

Levels of hs-CRP, an acute-phase reactant, were strongly associated with stroke severity in this population. Because stroke severity is also strongly associated with mortality after stroke, it is not surprising that hs-CRP is also associated with mortality. Because hs-CRP remained independently associated with mortality even after adjusting for stroke severity, however, it seems that this marker may provide additional general prog-

Table 4. High-Sensitivity C-Reactive Protein (hs-CRP) and Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) Levels as Predictors of Outcomes After First Ischemic Stroke, Stratified by Marker*†

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>hs-CRP</th>
<th>Lp-PLA2</th>
</tr>
</thead>
</table>
| Recurrent stroke (n = 80 events) | Hazard ratios represent risk for highest quartile vs lowest quartile. Hazard ratios are adjusted for age, sex, race and ethnicity, history of hypertension, diabetes mellitus, atrial fibrillation, current smoking, hypercholesterolemia, and coronary artery disease. Hazard ratios represent risk for highest quartile vs lowest quartile. Hazard ratios are adjusted for age, sex, race and ethnicity, history of hypertension, diabetes mellitus, atrial fibrillation, current smoking, hypercholesterolemia, and coronary artery disease.

Table 5. High-Sensitivity C-Reactive Protein (hs-CRP) and Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) Levels as Predictors of Outcomes After First Ischemic Stroke, Stratified by LDL Cholesterol Level

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>LDL Cholesterol &lt;130 mg/dL</th>
<th>LDL Cholesterol ≥130 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke†</td>
<td>0.87 (0.36-2.11)</td>
<td>0.42 (0.11-1.60)</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>2.80 (0.97-8.10)</td>
<td>0.93 (0.34-2.50)</td>
</tr>
<tr>
<td>Recurrent stroke, MI, or vascular death‡</td>
<td>hs-CRP</td>
<td>1.37 (0.63-2.96)</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>2.80 (1.10-7.16)</td>
<td>0.75 (0.31-1.78)</td>
</tr>
<tr>
<td>Death§</td>
<td>hs-CRP</td>
<td>2.67 (1.27-5.64)</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>2.02 (1.06-3.86)</td>
<td>1.15 (0.38-3.45)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; LDL, low-density lipoprotein; MI, myocardial infarction.

SI conversion factors: To convert LDL cholesterol to millimoles per liter, multiply by 0.02586.

*Models adjusted for age, sex, race and ethnicity, history of hypertension, diabetes mellitus, atrial fibrillation, current smoking, hypercholesterolemia, and coronary artery disease.

†This model included interaction terms between current cigarette smoking and risk factors, and stroke severity.

‡This model included interaction terms between hs-CRP and Lp-PLA2 and age to satisfy proportionality assumptions.
nastic information. High-sensitivity CRP was less valuable as a predictor of vascular events alone, however, providing evidence that some of its prognostic value may relate to its role as an acute-phase reactant and its potential association with other causes of mortality in patients after stroke, such as infections or general medical decline.

Other studies have suggested that hs-CRP is associated with prognosis in patients with established coronary artery disease. There is evidence that hs-CRP and other markers predict mortality after unstable angina and MI, and in patients with stable angiographic evidence of disease. The prognostic value of inflammatory markers in patients with stroke is less clear, however. Among patients with stroke, interleukin 6, but not tumor necrosis factor α, measured at baseline was an independent predictor of worsening in the first 24 hours after stroke in one study. Other researchers found similar results with interleukin 6 and interleukin 1 receptor antagonist. An hs-CRP level greater than 10.1 mg/L measured within 72 hours of stroke predicted increased mortality during follow-up of up to 4 years. Other researchers found that the measurement of CRP at 24 or 48 hours, but not at hospital admission, predicted outcome. An hs-CRP level greater than 15 mg/L at hospital discharge was significantly associated with the occurrence of a new vascular event or death at 1 year in another study, with an HR of 9.4. Other investigators measured hs-CRP levels at least 3 months after a first ischemic stroke or transient ischemic attack and found that patients in the highest quintile had significantly increased risk of subsequent stroke or MI. Relatively few studies have examined hs-CRP in relation to recurrent stroke independent of an effect on mortality, and those have been limited to specific subtypes of stroke and hospitalized recurrences. Further limitations in these studies include a hospital-based design and post hoc determination of threshold levels. The present data provide evidence that hs-CRP predicts mortality but not recurrent stroke.

Lipoprotein-associated phospholipase A₂ is a recently discovered enzyme derived from leukocytes, particularly macrophages, that is responsible for the metabolism of LDL cholesterol to the pro-inflammatory mediators lysophosphatidylcholine and oxidized fatty acids. Lysophosphatidylcholine increases the expression of vascular adhesion molecules, up-regulates cytokines and CD40 ligand, and stimulates macrophage proliferation. Lipoprotein-associated phospholipase A₂ has been associated with increased risk of incident ischemic cardiac and cerebrovascular events in epidemiologic studies. To our knowledge, no previous data are available on the relationship of Lp-PLA₂ to outcome after stroke, however. The present study provides evidence that this novel marker of vascular inflammatory activity is associated with risk of recurrent stroke and other vascular events after first stroke. Because the effect of Lp-PLA₂ on risk of recurrent stroke and combined vascular events was greater than the effect on risk of mortality alone, Lp-PLA₂ may provide a more specific marker of the risk associated with vascular disease than hs-CRP. Levels of Lp-PLA₂ were not markedly affected by stroke severity in this population, probably because it is not an acute-phase reactant, unlike CRP.

Lipoprotein-associated phospholipase A₂ was an independent and significant predictor of recurrent stroke in patients with levels of LDL cholesterol less than 130 mg/dL (<3.36 mmol/L) but not in those with levels of 130 mg/dL or greater (≥3.36 mmol/L), although we found marginal evidence of a statistical interaction. This result is similar to that found in the Atherosclerosis Risk in Communities study of incident cardiovascular disease, in which Lp-PLA₂ was associated with incident heart disease in patients with LDL cholesterol levels less than 130 mg/dL (<3.36 mmol/L) but not among those with LDL cholesterol levels of 130 mg/dL or greater (≥3.36 mmol/L). In other studies, however, there was no interaction between Lp-PLA₂ and LDL cholesterol levels. Measurements of LDL cholesterol immediately after stroke, moreover, similar to measurements of blood pressure, may not accurately reflect long-term levels, and their role in secondary prevention after stroke remains uncertain.

The strengths of this study include the ability to study hs-CRP and Lp-PLA₂ simultaneously in a well-characterized first stroke cohort followed up for several years. We also had outcome data on several types of outcomes, including not only death but also recurrent stroke, MI, and vascular death specifically. We thus provide some evidence that Lp-PLA₂ may have more of an effect on vascular outcomes (stroke and combined vascular events), whereas hs-CRP may be more predictive of fatal events not limited to vascular mechanisms. Proof of this hypothesis awaits confirmation from other studies.

This study also has limitations. Blood samples were not available from all patients with stroke, but there were minimal differences between the entire cohort and the sample analyzed in this study, and an analysis for selection bias did not show significant bias. This was a post hoc analysis in a previously assembled cohort. The number of participants, moreover, was relatively small, and so we cannot exclude the possibility that the lack of association between hs-CRP and recurrent ischemic events was due to low power to detect these associations. Systematic information on infections or other complications, such as deep venous thrombosis, which might increase hs-CRP levels, was not available, and neither were blood samples at multiple points. It is possible that samples collected at later points, after resolution of such complications, would have produced different associations with outcome. Studies that have found associations of hs-CRP with recurrent stroke and other vascular events, as opposed to mortality alone, have used measurements made at least 115 to 336 months after stroke. Levels of hs-CRP and Lp-PLA₂ 30 days after MI, but not at baseline, were also found to be predictive of recurrent cardiac events in a large clinical trial of statins. Further studies are needed to assess how hs-CRP and Lp-PLA₂ levels change across time after stroke and whether levels drawn at later points provide improved prognostic information. These studies need to be large, involve multiple centers, and provide statistical confirmation of incremental value of these markers beyond that provided by potential confounding risk factors before inflammatory biomarkers could be considered as part of the routine clinical evaluation of patients with stroke.
Ongoing clinical trials are testing whether the risk of atherosclerotic disease may be modified by the use of inhibitors of Lp-PLA2.43 In addition, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, may reduce levels of hs-CRP4 and Lp-PLA245 although whether this effect contributes to the vasoprotective effects of statins remains uncertain.

In summary, these data support an association between serum inflammatory markers and prognosis after stroke. These markers seem to provide complementary information, with hs-CRP providing information about mortality and Lp-PLA2 providing information about the risk of recurrent stroke and other vascular events. The use of both markers together may provide more information than the use of either alone. Corroboration from other prospective studies of stroke prognosis is needed to clarify the potential role of hs-CRP, Lp-PLA2, and other inflammatory markers in risk stratification and in clinical trials with novel anti-inflammatory or other therapies to prevent recurrent stroke and its attendant disability.

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Author Contributions: Dr Elkind had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Elkind and Sacco. Acquisition of data: Elkind, Coates, and Sacco. Analysis and interpretation of data: Elkind, Tai, and Paik. Drafting of the manuscript: Elkind and Coates. Critical revision of the manuscript for important intellectual content: Elkind, Tai, Paik, and Sacco. Statistical analysis: Tai and Paik. Obtained funding: Elkind and Sacco. Administrative, technical, and material support: Elkind, Coates, and Sacco. Study supervision: Elkind and Sacco.

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REFERENCES


