The Association between Carotid Artery Atherosclerosis and Silent Brain Infarction: A Systematic Review and Meta-analysis

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Background: Carotid atherosclerosis is responsible for ~20% of ischemic strokes, but it is unclear whether carotid disease is associated with the presence of downstream silent brain infarction (SBI). We performed a systematic review and meta-analysis to study the relationship between SBI and 2 separate manifestations of carotid atherosclerosis, carotid intima–media thickening (IMT) and luminal stenosis. *Methods:* Ovid MEDLINE, Ovid Embase, and the Cochrane Library Database were searched with an additional search of references and citing articles of target studies. Articles were included if they reported an association between carotid IMT or stenosis and magnetic resonance imaging-defined SBI, excluding SBIs found after carotid intervention. *Results:* We pooled 7 studies of carotid IMT reporting on 1469 subjects with SBI and 5102 subjects without SBI. Subjects with SBI had a larger mean IMT than subjects without SBI (pooled standardized mean difference, .37; 95% confidence interval [CI], .23-.51; $P < .0001$). We pooled 11 studies of carotid stenosis reporting on 12,347 subjects (2110 subjects with carotid stenosis and 10,237 subjects without carotid stenosis). We found a higher prevalence of SBI among subjects with carotid stenosis (30.4% versus 17.4%). Our pooled random-effects analysis showed a significant positive relationship between carotid stenosis and SBI (odds ratio, 2.78; 95% CI, 2.19-3.52; $P < .0001$). *Conclusions:* Two forms of atherosclerotic disease, carotid IMT and stenosis, are both significantly associated with SBI. This review highlights a lack of consistent definitions for carotid disease measures and little evidence evaluating SBI prevalence downstream from carotid stenosis. **Key Words:** Carotid atherosclerosis—intima–media thickness—carotid stenosis—silent brain infarction—stroke.

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Introduction

Carotid atherosclerotic disease is a major cause of cerebral ischemic events, accounting for approximately 10%-20% of ischemic strokes[1-3] or an estimated 150,000 strokes annually in the United States.[4] However, the relationship between carotid stenosis and clinically asymptomatic ischemic events is less clear. Silent brain infarctions (SBIs) are small, radiologically detected infarctions that are associated with a 2-fold increased risk of stroke.[5] SBIs are found in 20% of stroke-free older adults[6-10] with an annual incidence of 3%-4% in older populations.[11,12] Given their incidental discovery, small size, and noneloquent location, it is difficult to assess which of several possible underlying mechanisms is responsible in a given patient.

Carotid atherosclerotic plaques represent 1 possible source of cerebral emboli, causing SBI in vascular territories downstream of sites of stenosis. It is also possible that any association between carotid atherosclerosis and SBI results from the shared cardiovascular risk factors underlying both processes. If cardiovascular risk confounds the relationship between carotid stenosis and SBI, then one might expect to see an association between SBI and nonstenosing forms of atherosclerosis, such as increased intima–media thickness (IMT), but not necessarily a greater prevalence of SBI specifically downstream of a carotid stenosis. IMT is accepted as an early and quantifiable marker for incident stroke[13,14] and cardiovascular events,[15] but is unlikely to directly cause ischemic events. An understanding of carotid atherosclerosis as a *direct* cause of SBI could aid in identifying the most effective stroke prevention measures.

Although several existing studies have examined the relationship between carotid stenosis and SBI, the extent to which carotid stenosis is responsible for SBI remains poorly understood. Studies of SBI in territories downstream of carotid stenosis have shown conflicting results, and studies of IMT in patients with SBI have yielded variable results with wide confidence intervals (CIs). For these reasons, we have conducted a systematic review and meta-analysis of the existing literature to evaluate the relationship between SBI and carotid atherosclerotic disease, focusing on the 2 distinct entities of intima–media thickening and plaque causing luminal stenosis.

Methods

The present study was designed and performed according to guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[16,17] and meta-analysis of observational studies in epidemiology guidelines.[18] The search and methodology were specified in advance but not publicly registered.

Data Sources and Searches

Relevant articles were identified through a comprehensive search of Ovid MEDLINE, Ovid Embase, and the Cochrane Library performed by a research librarian on May 12, 2016. Additional articles were identified through a search of the references and citing articles of each selected article using the "View References" and "Cited by" tools in Scopus. No language restriction was applied. The search methodology is detailed in the Supplemental Methods.

Study Selection

Studies were eligible for inclusion in this meta-analysis if they met the following criteria: (1) the studies measured SBI as lesions at least 3 mm in size with magnetic resonance imaging (MRI); (2) the studies reported mean IMT in subjects with and without SBI; or (3) the studies reported the prevalence of SBI in patients with carotid atherosclerosis or a risk estimate for the association between SBI and carotid atherosclerosis. If articles reported only mean IMT or carotid stenosis, they were included in the respective analysis. Articles were excluded if they (1) were not written in English; (2) evaluated SBI after a procedure, such as carotid artery stenting or carotid endarterectomy; or (3) reported data for a subject sample studied in another included paper. For subject samples that were published in more than 1 article, the article that was more recently published or had more readily accessible data was selected. Finally, the corresponding author was contacted if the data were unclear or if additional data were required.

Data Extraction and Quality Assessment

A single researcher screened the titles and abstracts of all relevant articles. Two independent readers assessed whether the articles met inclusion and exclusion criteria and evaluated the full text of selected articles. Two researchers extracted data with discrepancies resolved by consensus. The data extracted included the first author of the study, the study design, major inclusion criteria and study population, study name, country, and characteristics of the study population in total and stratified by SBI status, including the number of subjects, mean age, number of women, and number of subjects with risk factors (hyperlipidemia, diabetes mellitus, atrial fibrillation, coronary artery disease, hyperlipidemia, and smoking history). Data examining IMT, including the definition of IMT, techniques in measuring IMT, and the mean IMT in subjects with and without SBI, were recorded. Additional data extracted included the number of subjects with and without carotid atherosclerosis, the number of subjects with SBI in each group, the prevalence of SBI downstream of carotid stenosis, the relative risk estimate reported with 95% CI, techniques in measuring carotid stenosis, and the definition of stenosis. Finally, the definitions of SBI were also recorded, including the magnet field strength, section thickness, section gap, signal characteristics, and means of differentiating SBI from perivascular spaces.