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# The Association Between Carotid Artery Atherosclerosis and Silent Brain Infarction: A Systematic Review and Meta-Analysis

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## Abstract

**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 two 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 MRI-defined SBI, excluding SBIs found after carotid intervention.

**Results—**We pooled 7 studies of carotid IMT reporting on 1,469 subjects with SBI and 5,102 subjects without SBI. Subjects with SBI had a larger mean IMT compared to subjects without SBI (pooled standardized mean difference, 0.37; 95% CI, 0.23 to 0.51; P<0.0001). We pooled 11 studies of carotid stenosis reporting on 12,347 subjects (2,110 subjects with and 10,237 subjects without carotid stenosis). We found a higher prevalence of SBI among subjects with carotid stenosis (30.4 vs. 17.4%). Our pooled random-effects analysis showed a significant positive relationship between carotid stenosis and SBI (OR, 2.78; 95% CI, 2.19 to 3.52; P<0.0001).

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**Disclosures**

None.

**Conclusions—**Two forms of atherosclerotic disease, carotid IMT and stenosis, are both are 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.

**Keywords**

carotid atherosclerosis; intima-media thickness; carotid stenosis; silent brain infarction; stroke

## 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 US[4]. However, the relationship between carotid stenosis and clinically asymptomatic ischemic events is less clear. Silent brain infarctions (SBI) are small, radiologically-detected infarctions that are associated with a two-fold increased risk of stroke[5]. SBI 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 non-eloquent location, it is difficult to assess which of several possible underlying mechanisms is responsible in a given patient.

Carotid atherosclerotic plaques represent one 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 non-stenosing 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 it 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.

While 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. 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 two distinct entities of intima-media thickening and plaque causing luminal stenosis.

## Methods

This study was designed and performed according to guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 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 12th, 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) measured SBI as lesions at least 3 mm in size with magnetic resonance imaging (MRI) and (2) reported mean IMT in subjects with and without SBI or (3) 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 one 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 was unclear, or if additional data was 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 study first author, 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 number of subjects, mean age, number of females, and number of subjects with risk factors (hyperlipidemia, diabetes mellitus, atrial fibrillation, coronary artery disease, hyperlipidemia, and smoking history). Data examining IMT, including definition of IMT, technique of measuring IMT, and mean IMT in subjects with and without SBI, were recorded. Additional data extracted included the number of subjects with and without carotid atherosclerosis, number of subjects with SBI in each group, the prevalence of SBI downstream of carotid stenosis, the relative risk estimate reported with 95% confidence interval, the technique of 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.

To assess the risk of bias of the selected studies, each article was evaluated with a set of nine questions adapted from a recently published meta-analysis focused on the association between atrial fibrillation and SBI[19]. These questions evaluated the potential for selection, detection, misclassification, reporting, and confounding bias in each study. The risk of bias questions were assessed by two researchers, with disagreements resolved by consensus.

### Data Synthesis and Analysis

The association between carotid atherosclerotic disease and SBI was measured separately for intima-media thickness (IMT) and carotid stenosis. First, the association between IMT and SBI was estimated using standardized mean difference (Cohen's d) of mean IMT in the presence and absence of SBI. Subgroup analysis was performed for (1) studies with subjects having at least one known stroke risk factor, (2) studies with stroke-free subjects, and (3) studies with the lowest risk of bias (low risk of bias in ≥6 of the 9 risk of bias questions assessed). Statistical significance was evaluated with a Z-test. Second, the association between carotid stenosis and SBI was estimated using crude odds ratios for the risk of SBI in the presence of carotid disease. Carotid atherosclerotic disease was defined as stenosis or plaque in the carotid artery causing measurable narrowing of the lumen. Subgroup analyses for carotid stenosis were performed stratified by the following characteristics: (1) subject type (without known risk factors, with at least one known risk factor, stroke-free); (2) relatively lower risk of bias as described above, and (3) categories of carotid plaque or stenosis (studies reporting >50% luminal stenosis, >70–75% luminal stenosis, and plaque score). Statistical significance was evaluated with a Chi-square test. Forest plots were generated to display the individual and pooled effect size and odds ratio for IMT and carotid stenosis, respectively. Data are presented as point estimates with a 95% confidence interval.

All analysis was performed using a pooled random-effects model (DerSimonian-Laird) due to the presence of heterogeneity in the studies. The combinability of the studies was assessed statistically with the Cochran Q test of statistical heterogeneity. Finally, the possibility of publication bias was assessed with the Begg-Mazumdar (BM) rank-correlation test, and funnel plots were created as a visual aid to assess publication bias. In the event of possible publication bias based on our statistical testing (BM $p<0.05$), we also created a contour funnel plot[20] to investigate the hypothetical possibility that unpublished non-significant studies may exist. All statistical analysis was performed using StatsDirect statistical software (Version 2.7.9; 7/9/2012 StatsDirect Ltd, Cheshire, England) and R 3.0.2. The significance level was defined as $P < 0.05$ for all statistical analysis.

## Results

### Study Selection

We screened the titles and abstracts of 1853 articles and identified 64 articles for full text review. Our review and subsequent contact with authors yielded 16 studies that met our inclusion criteria[21–36] (Supplemental Figure I). Seven articles provided data for the mean IMT in subjects with and without SBI, and eleven articles provided the prevalence of SBI in subjects with and without carotid stenosis. Three articles provided the prevalence of SBI in vascular distributions downstream of areas of carotid stenosis.

### Qualitative Study Characteristics

The 16 studies identified for analysis were published between 1998 and 2016 (Supplemental Table I). Ten were cross-sectional, non-prospective studies[21, 22, 24, 28–3335], four were cross-sectional analyses of a prospective cohort[23, 25–27], one was a case-control study[36], and one was a retrospective study[34]. Eight studies were from Japan[21, 24, 27, 28, 30, 32, 33, 36]; three

from the United States[22, 2535]; and one each from the Netherlands[26], Taiwan[29], Republic of Korea[31], France[23], and China[34]. All of the studies except two[26, 34] focused on subjects without a history of stroke or TIA. Eight studies included subjects who were asymptomatic, randomly sampled, or lacking known stroke risk factors[21–25, 29, 3236], while eight studies included subjects with at least one known stroke risk factor[26–28, 30, 31, 33–35].

### Definition of SBI and Carotid Atherosclerotic Disease

The majority of studies defined SBI as lesions ≥3 mm that are hypointense on T1 weighted imaging and hyperintense on T2 weighted imaging (Supplemental Table II). Several studies differentiated SBI from dilated perivascular spaces with FLAIR sequences[24, 27, 28, 33], subtraction imaging[25], multiplanar reformatting[23], and lesion morphology and location[26].

Of the seven studies that provided data for IMT, all except one[27] measured the IMT at the common carotid artery (Supplemental Table III). The remaining study averaged the IMT measurements at the common carotid artery, carotid bulb, and internal carotid artery[27]. Four studies measured IMT at more than one location and averaged the measurements to calculate mean IMT for each subject[26, 27, 30, 33]. The most common definition of IMT was the distance between the lumina-intima and media-adventitia interfaces[23, 27].

The definition and measurement of carotid stenosis varied widely between the nine studies that reported an association between carotid stenosis and SBI (Supplemental Table III). However, all studies except one used ultrasound-based measures of extracranial plaque and stenosis. Only one study used magnetic resonance angiography or computed tomographic angiography to assess carotid stenosis[35]. Seven studies recorded the number of subjects with carotid stenosis ≥50%[22, 25, 26, 3134–36], two of these measuring stenosis using the Doppler peak flow velocity during ultrasonography[22, 25]. One study only included stenosis of ≤50%, measuring lesions protruding into the arterial lumen[24]. The four remaining studies reported the presence of detectable plaque in the carotid arteries[21, 23, 29, 32]. One study computed a plaque score by assigning a grade to the level of plaque in each segment of the artery, summing to assess the overall level of plaque[29]. Another defined atherosclerotic lesions as plaques when IMT >1 mm and calculated a plaque score by summing the maximum thickness of the intima-media complex at different sites[32]. Still another study defined plaque as structures encroaching into the vessel lumen where the IMT ≥1 mm[23].

### Association between Intima-Media Thickness and SBI

Seven studies reported an association between IMT and SBI[22, 23, 26–28, 30, 33] (Figure 1A). These studies report the mean IMT for a total of 1,469 subjects with MRI evidence of SBI and 5,102 subjects without SBI. The weighted mean IMT was 1.06 mm for subjects with SBI and 0.91 mm for subjects without SBI. We compared the two groups using a pooled random-effects effect size (Cohen's d) to evaluate the effect of SBI on mean IMT. Subjects with SBI had a larger mean IMT compared to subjects without SBI (pooled random-effects standardized mean difference=0.37; 95% CI, 0.23 to 0.51; P<0.0001) (Figure 1A). There was statistically significant heterogeneity ($Q$=18.65, $P$=0.0048) but no significant publication bias (Kendall's tau score=0.05, $P$>0.99) present in this analysis (Supplemental Figure II). Restricting the analysis to studies examining subjects with at least one stroke risk

factor[26–28, 30, 33], stroke-free subjects[22, 23, 27, 28, 30, 33], or studies with a low risk of bias[22, 23, 27] did not significantly alter the results (Supplemental Table IV).

### Association between Carotid Atherosclerosis and SBI

Eleven studies reported an association between carotid atherosclerosis and SBI[21–26, 29, 31, 323436] (Figure 1B). A total of 12,347 subjects were included in the analysis, 2,110 subjects with carotid atherosclerosis and 10,237 subjects without carotid atherosclerosis. In total, 641 (30.4%) of the subjects with carotid atherosclerosis had SBI, while 1,781 (17.4%) of the subjects lacking carotid atherosclerosis had SBI. Our pooled random-effects analysis shows a significant positive relationship between carotid atherosclerosis and SBI (OR, 2.78; 95% CI, 2.19 to 3.52; P < 0.0001) (Figure 1B). There was statistically significant heterogeneity ($Q$=26.2, $P$=0.0035) and the possibility of significant publication bias (Kendall's tau score=0.53, $P$=0.0264) present in this analysis (Supplemental Figure III). However, subgroup analysis of publication bias limited to the highest quality studies showed no significant publication bias (Supplemental Table V).

Subgroup analysis restricting the examination to studies that included subjects without known risk factors[21–25, 29, 32, 36], with at least one known risk factor[26, 31, 34], and stroke-free subjects[21–25, 29, 31, 32, 34, 36] did not significantly change the results (Supplemental Table V). Restricting the analysis to studies with an overall low risk of bias[22, 23, 25] lowered the risk estimate (OR, 1.96; 95% CI, 1.62 to 2.38; P < 0.0001). Studies reporting stenosis ≥50%[22, 25, 26, 31, 34, 36] had a similar risk estimate to studies reporting ≥70–75% stenosis[22, 26], but studies reporting carotid plaque or plaque score had a higher risk estimate[21, 23, 29, 32].

### Prevalence of SBI Downstream of Carotid Stenosis

Three studies reported the presence of SBI in brain tissue downstream of areas of >50% carotid stenosis (Table 1)[22, 35, 36]. Manolio et al. found little evidence of increased SBI ipsilateral to sites of carotid stenosis[22]. Takahashi et al. also found no difference in prevalence of carotid stenosis contralateral and ipsilateral to SBI in a population of subjects with unilateral SBI[36]. Conversely, Baradaran et al. found that subjects with asymptomatic, unilateral internal carotid artery stenosis had a higher prevalence of SBI in the vascular distribution of the stenotic artery, using the contralateral hemisphere as a within-subject comparison[35].

### Assessment of Quality of the Included Studies

Supplemental Table VI shows the results from our assessment of potential selection, detection, misclassification, reporting, and confounding bias in each study. First, five studies drew their population from a randomly selected or community-dwelling sample to minimize selection bias[22, 23, 25, 29, 32]. In general, these studies were larger than studies drawing from a more targeted population. Second, the primary objective of ten of the studies was to assess whether carotid atherosclerotic disease is predictive of SBI[21–25, 27, 28, 34–36]. The other studies primarily viewed carotid atherosclerotic disease as a covariate in their study population. As mentioned, only three studies examined the prevalence of infarcts downstream of the site of stenosis[22, 35, 36]. Third, studies were heterogeneous regarding the

quality of outcome ascertainment and SBI definitions. Nine studies used blinding when assessing SBI[22, 25–27, 29–31, 35, 36] with seven of these studies using more than one independent investigator to assess outcome[22, 25, 26, 29–31, 35]. Finally, seven studies described a method to differentiate SBI from dilated perivascular spaces[22, 23, 25–28, 33]. In general, the results of the risk of bias assessment were heterogeneous. Despite the fact that only four studies had a relatively low risk of bias, limiting analysis to only these studies did not change the overall results. Additionally, a subgroup analysis of publication bias limited to the high quality studies showed no significant publication bias.

## Discussion

In this systematic review and meta-analysis, we found that two distinct manifestations of carotid atherosclerotic disease, increased carotid IMT and carotid stenosis, are associated with the presence of SBI. A recent meta-analysis of four studies showed an association between SBI and carotid stenosis,[37] but did not synthesize the relationship between carotid atherosclerosis and directly downstream SBI. Our pooled findings of an association between carotid disease and ipsilateral SBI support a direct relationship rather than mediation via systemic vascular risk factors.

Patients with SBI had a significantly greater mean IMT compared to those without SBI, suggesting an association between subclinical atherosclerosis and silent brain ischemic events in stroke-free individuals. Furthermore, stroke-free individuals with carotid stenosis are significantly more likely to harbor SBI compared to those with no carotid stenosis. This relationship was preserved whether or not patients had additional known stroke risk factors and across the various measures of carotid stenosis reported in the literature. The association between SBI and carotid atherosclerosis has face validity given the known increased risk of incident symptomatic stroke in patients with increased carotid IMT[38] and hemodynamically significant internal carotid artery stenosis[39].

The presence of increased SBI in patients with carotid stenosis may be the result of increased generalized cardiovascular risk in these patients, or carotid stenosis may be a direct source of emboli that cause SBI. If carotid stenosis were causally associated with SBI, one would expect to see a greater prevalence of SBI in the cerebral hemisphere downstream from the diseased carotid artery compared to the contralateral hemisphere. Early studies using far less sensitive computed tomographic methods of SBI detection have shown conflicting results about whether carotid atherosclerosis is specifically associated with an increased burden of SBI downstream from the side of stenosis[40–43]. Our analysis of more modern, MRI-based studies showed similarly mixed results. One study of patients with unilateral carotid stenosis showed a higher prevalence of SBI in downstream tissue compared with the contralateral hemisphere[35]. Two older studies showed no differences between the ipsilateral and contralateral hemispheres[22, 36]. Whether carotid stenosis simply represents a marker of generalized, elevated cardiovascular risk or rather is mechanistically related to an increased likelihood of plaque rupture and downstream silent infarction is unclear from the current literature and requires further investigation.

The results of this study are particularly relevant to stroke-free patients with asymptomatic carotid stenosis. Though carotid revascularization procedures, such as endarterectomy or stenting, are indicated for those with over 70% stenosis who have clinical symptoms of stroke or transient ischemic attack (TIA)[39, 44], it less clear whether revascularization procedures benefit patients with asymptomatic carotid stenosis[45–47]. Plaque characteristics, including ultrasound echolucency[48] and MRI features[49], have been used to identify those atherosclerotic plaques most at risk of causing ischemic stroke. The presence of SBI in patients with asymptomatic carotid atherosclerosis may be a useful clinical marker to identify the subset of patients at highest risk of stroke.

Our study highlighted important limitations in the existing literature. First, the definitions of SBI, IMT, and carotid stenosis varied widely between studies. Though all studies measured IMT and carotid stenosis with ultrasound, each used different slightly different diagnostic features, including location of the measurement, use of flow parameters, and metrics reported. The variation in definitions between studies may have contributed to the statistically significant heterogeneity in the primary pooled analyses of IMT and stenosis. However, significant heterogeneity was not present when we restricted our analysis to the highest quality studies nor was present in subgroup analysis of studies reporting ≥50% and ≥70–75% stenosis. Ultimately, our study highlights the need for more standardized definitions of SBI, IMT, and carotid stenosis in both research and clinical practice. Second, due to variability in measurement and lack of individual patient level covariate risk factors, the data were not amenable to the calculation a pooled adjusted effect size for carotid IMT or stenosis. Third, our analysis of carotid stenosis showed statistically significant publication bias. Though calculations of publication bias have limited reliability when examining a relatively small number of studies, it is possible that small, non-significant studies were unpublished and therefore not included in our analysis. Despite the possibility of publication bias in our overall study of carotid stenosis, when we restricted our analysis to the highest quality studies, there was no significant publication bias. The absence of publication bias in the higher quality studies improves our confidence in the overall association between carotid stenosis and SBI.

In summary, our systematic review and meta-analysis suggests that SBI is strongly associated with two forms of carotid atherosclerosis, elevated IMT and luminal stenosis. Further studies appear warranted to examine the mechanisms of SBI in subjects with carotid atherosclerosis and whether SBI in the presence of carotid atherosclerosis may be a clinically useful risk factor to identify those most at risk of future stroke.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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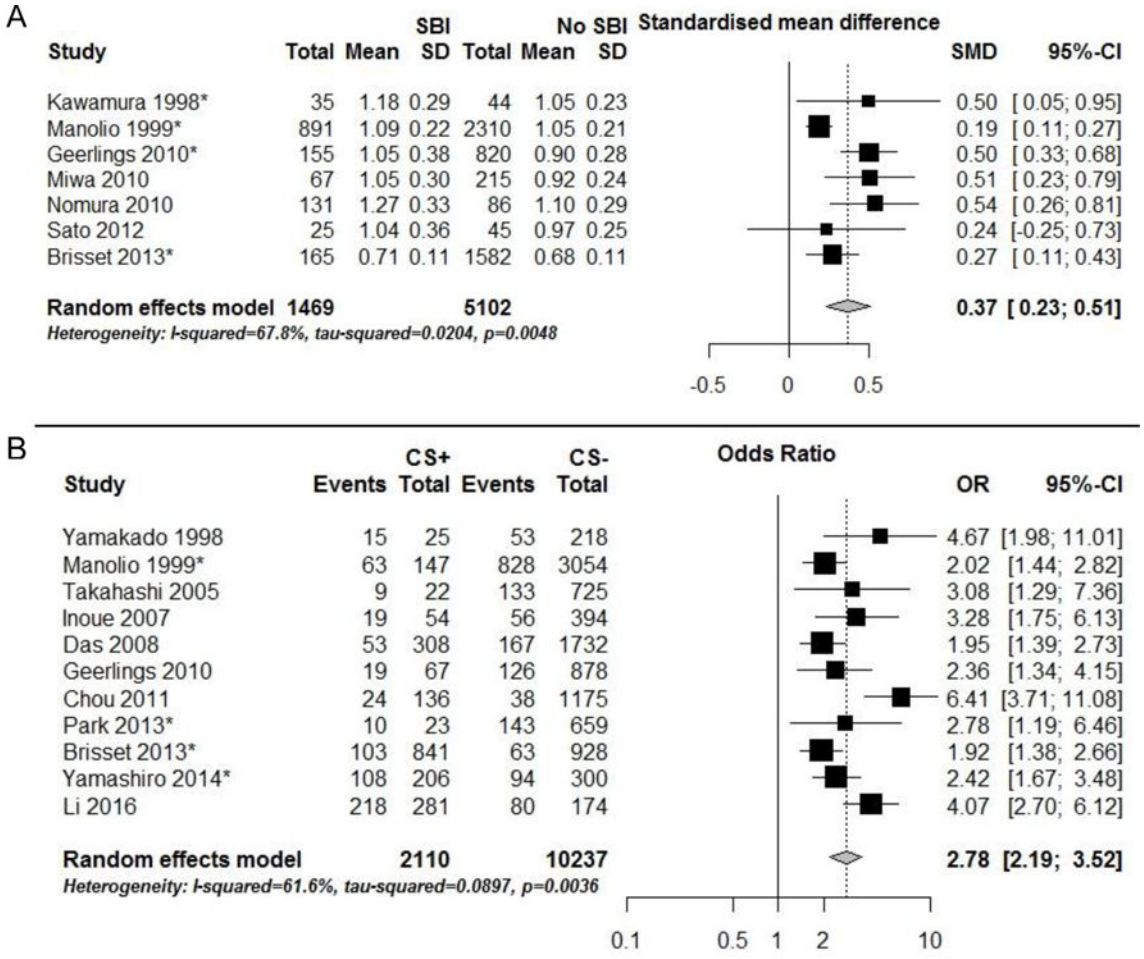


**Figure 1. Association between carotid atherosclerotic disease and SBI**

**A. Association between Intima-media thickness and SBI** IMT = intima-media thickness; SBI = silent brain infarction; SD = standard deviation; SMD = standardized mean difference; CI = confidence interval

**B. Association between carotid stenosis and SBI** CS = carotid stenosis; OR = odds ratio; CI = confidence interval

**Table 1**

Studies evaluating the prevalence of silent brain infarction (SBI) downstream of carotid stenosis

| Study First Author and Year | Number of Participants | SBI Ipsilateral to Carotid Stenosis (%) | SBI Contralateral to Carotid Stenosis (%) | P Value |
|---|---|---|---|---|
| Manolio 1999 | 178 | 31.2 | 29.3 | – |
| Takahashi 2005 | 4 | 75 | 25 | – |
| Baradaran 2016 | 102 | 33.3 | 20.8 | 0.0067 |