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REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Systematic review on the association between calcification in carotid plaques and clinical ischemic symptoms

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Objective: **The association between carotid plaque calcification and clinical ischemic events is unclear. The aim of this study was to systematically review published studies comparing degree of calcification between clinically symptomatic and asymptomatic plaques.**

Methods: **A systematic search for relevant studies was performed in the PubMed/MEDLINE and Embase databases. For studies reporting a rating scale or a continuous measure of calcification, study-specific and pooled standardized mean differences (SMDs) between symptomatic and asymptomatic plaques were calculated. For studies reporting a dichotomous measure, study-specific and pooled odds ratios (ORs) were calculated. If no significant heterogeneity was present ($I^2 \leq 50\%$), a fixed-effects pooling model was used. If significant heterogeneity was present ($I^2 > 50\%$), a random-effects pooling model was used, and sources of heterogeneity were explored by subgroup analyses.**

Results: **The 24 studies included in this systematic review used a wide range of methodologies to quantify degree of calcification and a wide range of definitions to define clinically symptomatic and asymptomatic carotid plaques. Pooled fixed-effects SMD of calcification volume or weight between symptomatic and asymptomatic plaques was −0.425 (95% confidence interval [CI], −0.608 to −0.241); $I^2 = 39.3\%$. Pooled random-effects SMD of calcification percentage was −0.997 (95% CI, −1.793 to −0.200); $I^2 = 93.8$. Subgroup analyses did not reveal homogeneous subgroups. Pooled fixed-effects OR for the association between high degree of plaque calcification and symptoms was 0.696 (95% CI, 0.528 to 0.918); $I^2 = 21.1\%$.**

Conclusion: **The results of this systematic review suggest that clinically symptomatic plaques have a lower degree of calcification than asymptomatic plaques. Assessment of degree of carotid plaque calcification may be useful to predict which plaques will cause cerebrovascular ischemic events. (J Vasc Surg 2010;51:1015-25.)**

Carotid artery atherosclerosis is an important cause of stroke. Large randomized, controlled trials have demonstrated a benefit of carotid endarterectomy (CEA) in patients with high-grade stenosis of the carotid artery lumen.[1] However, many of these patients remain stroke-free even with medical therapy alone.[1] It is currently believed that plaque features may be more predictive for stroke than degree of luminal stenosis. Early identification of high-risk lesions that can cause thromboembolic events, so-called vulnerable plaques, may tailor and improve treatment strategies for individual patients, especially those without symptoms. Histopathologic studies suggest that vulnerable plaques are characterized by a large lipid-rich necrotic core (LRNC) with a thin overlying fibrous cap (FC), extensive macrophage infiltration, and paucity of smooth muscle cells.[2,3] Although calcifications are present in approximately 50% to 60% of carotid plaques, their association with cerebrovascular ischemic events is uncertain.[4] Some investigators stated that calcified plaques may be more biomechanically stable and less prone to disruption,[5] whereas others stated that degree of plaque calcification may predict stroke risk, independent of stenosis grade.[6] In addition, large prospective longitudinal ultrasonography (US) scan studies found conflicting results on the association between plaque echogenicity and the occurrence of stroke.[7,8] These conflicting results might be explained by differences in the methods for determining the degree of plaque calcification. Moreover, characterization of overall plaque echogenicity by standard B-mode US scan may not adequately reflect degree of plaque calcification.[9,10]

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Table I. Search strategy and results as of May 4, 2009

No.	*Search string*	*No. of articles*	
		PubMed/MEDLINE	*Embase*
1	Carotid	87,319	69,850
2	Atherosclerosis OR arteriosclerosis OR plaque OR atheroma	188,534	141,983
3	Calcif* OR calcium OR bone OR mineral	1,232,740	887,698
4	No. 1, 2, and 3	1118	1226

No., Number.

The present study systematically reviewed the literature to better determine the association between degree of calcification in carotid plaques and clinical ischemic events.

METHODS

Data sources. A computer-aided search of the PubMed/MEDLINE and Embase databases was conducted to find relevant publications on the relation between carotid plaque calcification and clinical cerebrovascular ischemic symptoms. The search strategy is presented in Table I. No beginning date limit was used. The search was updated until May 4, 2009. To expand the search, the reference lists of articles that finally remained after the selection process were screened for other potentially suitable articles.

Study selection. Studies that compared degree of calcification between clinically symptomatic and asymptomatic carotid plaques were eligible for inclusion. Only studies that assessed degree of plaque calcification by ex vivo x-ray, computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance (MR) spectroscopy, histologic or chemical analysis of CEA specimens,[11] or by in vivo CT, MRI, or B-mode US scan with pixel analysis (findings of all these in vivo imaging modalities strongly correlate with histologic measurements,[12-14] were included. Studies assessing overall plaque echogenicity by standard B-mode US scan were excluded, because it has been shown that characterization of overall plaque echogenicity may not adequately reflect degree of carotid plaque calcification.[9,10] No language restriction was applied. Review articles, meta-analyses, abstracts, editorials or letters, case reports, and studies performed on animals were excluded. Studies only assessing degree of calcification of the intracranial carotid artery were also excluded. Studies that provided a rating scale or continuous measure were included only if they provided sufficient data to calculate mean values and SDs of the measurements, both for symptomatic and asymptomatic plaques. Studies that provided dichotomous measures were included only if they provided sufficient data to construct a 2×2 contingency table to calculate the odds ratio (OR) of symptoms in relation to degree of carotid plaque calcification. When data were presented in more than one article, the article with the most details, or the most recent article, was chosen. Using the aforementioned inclusion and exclusion criteria, titles and abstracts of the retrieved articles were reviewed. Articles were rejected if they were clearly ineligible. Of each article that was potentially eligible for inclusion, the full-text version was retrieved. Full-text versions were then reviewed to determine study eligibility for inclusion.

Study analysis. For each included study, several study characteristics were recorded (Table II). For studies using a rating scale or continuous measure of degree of plaque calcification, the measurements were standardized on a uniform scale so that results of individual studies could be combined. This was done by calculating the standardized mean difference (SMD) for each study: first, mean values and SDs of calcification measurements for symptomatic and asymptomatic plaques were extracted. For studies providing SEs, the SD was recalculated by the following formula: $SD = SE * \sqrt{(\text{sample size})}$.[15] Subsequently, the SMD was calculated, which is the difference in mean calcification measurements between symptomatic and asymptomatic plaques, divided by an estimate of the within-group SD.[16,17] By expressing the outcome as SMD, the results of individual studies could be combined since they have no units.[16,17] Studies measuring calcification volume or weight were pooled, and studies measuring calcification percentage were pooled. The pooled SMD across studies was estimated by means of fixed and random-effects models.[16] The fixed-effects pooling model is based on the mathematical assumption that a single common (or "fixed") effect underlies every study in the meta-analysis, whereas the random-effects pooling model makes the assumption that individual studies are estimating different effects.[16] If the 95% confidence interval (CI) of the pooled SMD did not overlap the referent (0.0), it was considered to be statistically significant. Thus, if the pooled SMD was significantly greater than 0.0, symptomatic plaques had a higher degree of calcification than asymptomatic plaques. If the pooled SMD was significantly lower than 0.0, asymptomatic plaques had a higher degree of calcification. For studies using a dichotomous measure of degree of plaque calcification, the number of symptomatic and asymptomatic plaques containing a high and low degree of calcification were extracted. A standard correction of adding 0.5 to all cells of the 2×2 contingency table was applied if there were no plaques in one of the four cells. Study-specific ORs were calculated, and the pooled OR across studies was estimated by means of fixed and random-effects models.[16] The OR is the odds of the event (high degree of calcification) occurring in one group (symptomatic plaques) divided by the odds of the event occurring in the other group (asymptomatic plaques).[16,18] If the 95% CI of the pooled OR did not overlap the referent (1.0), it was considered to be statistically significant. Thus, if the pooled OR was significantly greater than one, symptomatic plaques were more likely to have a high degree of calcification than asymptomatic plaques. If the pooled OR was significantly lower than one, asymptomatic plaques were more likely to have a high degree of calcification. Results were graphically displayed in forest plots (Figs 1-3).[19] In these plots, bullets

represent each individual study's SMD or OR estimate. At the bottom of the plots, bullets represent the pooled estimate, both for the fixed and random-effects models. The lines extending from the bullets represent the 95% CI for the estimates. A vertical line through the referent (0.0 for the SMD and 1.0 for the OR) was also plotted. If the (pooled) 95% CI crosses this line, it indicates there is no significant difference in degree of calcification between symptomatic and asymptomatic plaques. Heterogeneity was tested by calculating the I^2 statistic.[20] The test seeks to determine whether there are genuine differences underlying the results of the studies (heterogeneity) or whether the variation in findings is compatible with chance alone (homogeneity). The I^2 ranges from 0 (no heterogeneity) to 100% (all variance due to heterogeneity). Significant heterogeneity was defined as $I^2 > 50\%$. If I^2 was $\leq 50\%$, emphasis was placed on the fixed-effects pooling model. If I^2 was $>50\%$, emphasis was placed on the random-effects pooling model, and potential sources for heterogeneity were explored by subgroup analysis. Covariates analyzed were: country of origin (USA vs other countries), primary study outcome (comparison of calcification in symptomatic and asymptomatic carotid plaques as primary outcome vs comparison of calcification in symptomatic and asymptomatic carotid plaques not as primary outcome), study design (reported prospective study design vs no or unreported prospective study design), way of patient recruitment (consecutive or random selection of patients vs nonconsecutive, nonrandom selection, or unreported way of recruitment), sample size (≥ 25 symptomatic and ≥ 25 asymptomatic plaques vs <25 symptomatic or <25 asymptomatic plaques), stenosis grade (no significant difference vs significant or unreported difference between symptomatic and asymptomatic plaques), method to analyze plaque calcification (ex vivo vs in vivo analysis), way of interpretation (blinding vs no or unreported blinding for symptomatic or asymptomatic status). Potential presence of publication bias was assessed by constructing funnel plots.[16,21] Publication bias arises from the tendency that studies with significant or "positive" results have a better chance of being published than those with nonsignificant or "negative" results. The subsequent overrepresentation of studies with significant or positive findings in a systematic review may mean that the review is biased toward a positive or significant result. In a funnel plot, the effect size (in this case the SMD or log OR) is plotted vs a measure of its precision, such as sample size (in this case represented by the SE). With increasing sample size, random variations of the effect are smaller. Thus, data from the included studies are expected to be symmetrically distributed in an inverted funnel-shaped area of the plot if there is a low likelihood of publication bias. Conversely, an asymmetrical funnel plot may indicate a biased study sample.[16,21] However, it should be kept in mind that a funnel plot is not a very reliable method of investigating publication bias.[16,22] Nevertheless, it does give some idea of whether the study results are scattered symmetrically around a central, more precise effect.[16]

Statistical analyses were performed by using Statistical Package for the Social Sciences software, version 11.5 (SPSS Inc, Chicago, Ill) and MedCalc software (MedCalc, Mariakerke, Belgium).

RESULTS

Literature search. The computer-aided search revealed 1118 articles from PubMed/MEDLINE and 1226 articles from Embase (Table I). Reviewing titles and abstracts from PubMed/MEDLINE revealed 35 articles potentially eligible for inclusion. Reviewing titles and abstracts from Embase revealed 34 articles, of which 32 were already identified by the PubMed/MEDLINE search. Thus, 37 articles remained for possible exclusion and were retrieved in full-text version. After reviewing the full article, 13 articles were excluded because they did not fulfill the selection criteria,[6,23-34] and one article[35] could not be retrieved and was not included in the analysis. Screening references of the remaining articles revealed one article, which was also included.[36] Eventually, 24 studies[9,14,36-57] were included in this systematic review (Table II).

Heterogeneity and pooled results. Wintermark et al[40] provided results for asymptomatic plaques from asymptomatic patients (n = 50) and for contralateral asymptomatic plaques from symptomatic patients (n = 40). Only results from the first group were used for meta-analysis and assessment of heterogeneity. There was no significant heterogeneity across studies measuring calcification volume or weight[40-44,46,51,55] (I^2 = 39.3%). Using a fixed-effects model, pooled SMD between symptomatic and asymptomatic plaques was −0.425 (95% CI, −0.608 to −0.241). The 95% CI of the pooled SMD did not cross the referent 0.0 (Fig 1), indicating that symptomatic plaques had lower calcification volume or weight than asymptomatic plaques. There was significant heterogeneity across studies measuring calcification percentage[14,42,45,47-50,53] (I^2 = 93.8%). Using a random-effects model, pooled SMD between symptomatic and asymptomatic plaques was −0.997 (95% CI, −1.793 to −0.200). The 95% CI of the pooled SMD did not cross the referent 0.0 (Fig 2), indicating that symptomatic plaques had a lower calcification percentage than asymptomatic plaques. Exploration of sources of heterogeneity did not reveal homogeneous subgroups (for all subgroups: $I^2 > 50.0\%$). There was no significant heterogeneity across studies using a dichotomous measure of degree of plaque calcification[9,36-39,52,54,56,57] (I^2 = 32.4%). Pooled OR, using a fixed-effects model, was 0.740 (95% CI, 0.565-0.969). The 95% CI of the pooled OR did not cross the referent 1.0 (Fig 3), indicating that plaques with a low degree of calcification were more likely to be clinically symptomatic. Visual assessment of the funnel plot on calcification volume or weight (Fig 4, *A*) shows that it is roughly symmetrical, which suggests a low likelihood of publication bias. The funnel plot on calcification percentage (Fig 4, *B*) is not symmetrical, although this impression is mainly caused by one small study to the left of the most common effect. This may indicate publication bias, but it may also be due to study factors. The funnel plot on dichotomous

Table II. Characteristics of the 24 included studies

Study year	*Country*	*Comparison of calcification in symptomatic and asymptomatic carotid plaques as primary study outcome*	*Study design*	*Way of patient recruitment*
Romero, 2009	USA	Yes	Retrospective	NR
Peeters, 2009	The Netherlands	No	Prospective	Consecutive
Wahlgren, 2009	USA	No	NR	NR
Wintermark, 2008	USA	Yes	Retrospective	Consecutive
Raman, 2008	USA	No	Prospective	NR
Nandalur, 2007	USA	Yes	Retrospective	Consecutive
Uwatoko, 2007	Japan	Yes	NR	Consecutive
Miralles, 2006	Spain	Yes	NR	Consecutive
Baroncini, 2006	Brazil	No	NR	Non consecutive
Saam, 2006	USA	Yes	Retrospective	Consecutive
Lal, 2006	USA	Yes	Prospective	NR
Serfaty, 2006	France	Yes	Prospective	NR
Fisher, 2005	USA	Yes	NR	NR
Nandalur, 2005	USA	Yes	Retrospective	Consecutive
Shaalan, 2004	USA	Yes	Retrospective	Consecutive
Gonçalves, 2003	Sweden	Yes	NR	NR
Lal, 2002	USA	Yes	Prospective	NR
Tegos, 2000	UK	Yes	NR	NR
Kim, 2000	Korea	Yes	Retrospective	NR
Montauban, 1999	The Netherlands	No	NR	Consecutive
Carr, 1996	USA	Yes	Prospective	NR
Seeger, 1995	USA	Yes	NR	NR
Avril, 1991	France	Yes	Prospective	Consecutive
Bassiouny, 1989	USA	Yes	NR	NR

Study	*Definition of symptomatic carotid plaque*
Romero, 2009	Ipsilateral anterior circulation stroke or TIA <1 month of CTA
Peeters, 2009	According to ECST and NASCET criteria
Wahlgren, 2009	TIA, AFx, or nondisabling stroke <6 months before CEA
Wintermark, 2008	Ipsilateral acute infarct and the likely cause of stroke was large-artery atherosclerosis. Exclusion: atrial fibrillation
Raman, 2008	Ipsilateral stroke or TIA and absence of other source of embolism
Nandalur, 2007	Ipsilateral stroke, TIA, or AFx ≤7 days of undergoing CT. Exclusion: conflicting sources of neurological symptoms (cardiac emboli or lacunar infarcts)
Uwatoko, 2007	Ipsilateral symptomatic ischemic stroke, TIA, or AFx in the preceding 6 months
Miralles, 2006	Stroke, TIA, or AFx
Baroncini, 2006	Ipsilateral TIA, AFx, central retinal artery occlusion, CVA, silent infarcts, or lacunar symptomatology
Saam, 2006	Ipsilateral TIA, AFx, or stroke ≤4 months before MRI. Exclusion: other potential causes of symptoms, as assessed by additional diagnostic tests, including brain CT, MRI, echocardiography, and holter monitoring
Lal, 2006	According to NASCET criteria
Serfaty, 2006	A carotid artery was considered symptomatic only if the patient had contralateral symptoms
Fisher, 2005	According to NASCET criteria
Nandalur, 2005	AFx, TIA, or stroke <1 week of CTA. Exclusion: concomitant conflicting laterizing ischemic symptoms, such as those due to known cardiac thrombus or small vessel disease indicated by lacunar infarcts seen on CT and MRI
Shaalan, 2004	TIA, stroke, or AFx <6 months before CEA

Table II. Continued.

*Symptomatic/asymptomatic plaques**	*Method to assess stenosis grade Symptomatic vs asymptomatic# plaques*
37/38	CTA 82 ± 5% vs 80 ± 6% (*P* = .1093)
630/174	NR
9/21	NR
40/40 (all contralateral asymptomatic plaques in symptomatic patients) and 50	CTA 29.1 ± 4.9% vs 23.9 ± 4.3% (contralateral asymptomatic plaques) and 26.3 ± 4.1% (*P* = .647 and .386)
11/28	DSA or contrast-enhanced MRA, NR
35/67	CTA 82.0 ± 11.9% vs 79.4 ± 10.8% (*P* > .05)
37/47	DSA and DUS, NR
13/13	CTA >60% vs >60% (*P*: NR)
15/10	DUS ≥70% vs ≥80% (*P*: NR)
23/23 (all contralateral asymptomatic plaques)	MRI Mean lumen area: 26.6 ± 14.0 mm^2 vs 35.1 ± 13.9 mm^2 (*P* = .008)
18/27 (3 contralateral asymptomatic plaques)	DUS, NR
30/102 (including contralateral asymptomatic plaques)	CT >50% vs >50% (*P*: NR)
105/91	DSA Median: 64% (ipsilateral symptomatic plaques) and 67% (contralateral symptomatic plaques) vs 75% (*P*: NR)
15/21 (including contralateral asymptomatic plaques)	CT ≥60% vs ≥60% (*P*: NR)
25/23	DUS 76 ± 16% vs 82 ± 11% (*P* > .05)
14/16 (1 contralateral asymptomatic plaque)	DUS >70% vs >80% (*P*: NR)
7/13 (1 contralateral asymptomatic plaque)	DUS, NR
46/25	DUS Median: 90% vs 83% (*P* = .34)
38/17	DSA, NR
33/14	DSA and/or DUS >70% vs >70% (*P*: NR)
19/25	DSA or MRA 77 ± 15% vs 74 ± 17% (*P* = .57)
40/38	DSA and/or DUS 78.8 ± 15.1% vs 78.0 ± 12.1% (*P*: NR)
72/115	DUS and DSA NR (*P* = .084)
31/14	DSA 87 ± 2% vs 89 ± 2% (*P* > .05)

Definition of asymptomatic carotid plaque	*Method, calcification measure*	*Blinding*
No stroke or TIA, or stroke or TIA >1 month old, not referable to the target artery	In vivo CT Calcified vs noncalcified (calcified: density >130 HU and >50% of the plaque volume)	NR
According to ACST criteria	Histologic analysis Moderate/heavy vs none/minor calcification	Yes
NR	Histologic analysis Calcified vs noncalcified	NR
No stroke or stroke in a distribution not consistent with a carotid origin	In vivo CT Calcification volume and percentage	Yes
NR	Chemical analysis of CEA specimens Calcium mg/g dry weight	NR
No history of symptoms, neither remote or at the time of examination	In vivo CT Calcification volume and percentage	Yes
Ipsilateral small-artery territory infarct or hemodynamic failure on SPECT	In vivo CT Calcification volume	Yes
NR	In vivo CT Calcification volume	NR
No history of recent neurologic symptoms or nonspecific, nonhemispheric symptoms such as dizziness and vertigo	Histologic analysis Percentage calcification of the total plaque area	NR
NR	In vivo MRI Calcification volume	Yes
According to ACAS criteria	B-mode US with pixel segmentation with tissue mapping Percentage calcium of the total area of the plaque in longitudinal view	Yes
NR	In vivo CT Calcified vs noncalcified (calcified: % soft plaque tissue/calcification <40%)	Yes
According to ACAS criteria	X-ray of CEA specimens Percentage calcification of total plaque area	NR
No history of ischemic neurologic symptoms, either remote or current	In vivo CT Percentage calcification, median density ≤50 HU, 51-130 HU, or >130 HU	Yes
NR	Ex vivo CT Percentage calcification of total plaque area	Yes

Table II. Continued.

Study	*Definition of symptomatic carotid plaque*
Gonçalves, 2003	Ipsilateral AFx, TIA, or stroke <6 months. Exclusion: atrial fibrillation, aortic valve disease, mechanical heart valves
Lal, 2002	According to NASCET criteria
Tegos, 2000	Ipsilateral AFx, TIA, or stroke ≤3 months. Exclusion: cardioembolic conditions, lacunar symptomatology, or cerebral hematoma
Kim, 2000	NR
Montauban, 1999	TIA, stroke, or AFx 1-6 weeks before CEA
Carr, 1996	Ipsilateral stroke, TIA, or AFx
Seeger, 1995	Ipsilateral TIA, AFx, or embolic CVA, and no other source of embolic material
Avril, 1991	TIA, reversible ischemic neurologic deficits, minor stroke
Bassiouny, 1989	Ipsilateral TIA or reversible ischemic neurologic deficit, AFx, stroke

ACAS, Asymptomatic carotid atherosclerosis study; *ACST,* Asymptomatic Carotid Surgery Trial; *AFx,* amaurosis fugax; *CEA,* carotid endarterectomy; *CT,* computed tomography; *CTA,* computed tomography angiography; *CVA,* cerebrovascular accident; *DSA,* digital subtraction angiography; *DUS,* duplex ultrasonography; *ECST,* European Carotid Surgery Trial; *HU,* Hounsfield units; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *NR,* not reported; *SPECT,* single photon emission computed tomography; *TIA,* transient ischemic attack; *US,* ultrasound scan.

*Unless otherwise indicated, data indicate number of asymptomatic plaques in asymptomatic patients.

#Unless otherwise indicated, data indicate mean degree of stenosis ± SD.

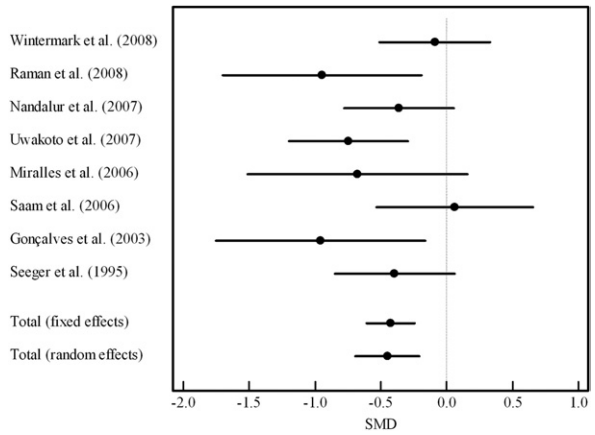

Fig 1. Forest plot of the association between plaque calcification volume or weight and clinical ischemic symptoms; study-specific and pooled standardized mean differences (SMDs) for studies using a rating scale or continuous measure of calcification volume or weight. Bullets represent each individual study's SMD estimate. At the bottom of the plot, bullets represent the pooled estimate, both for the fixed and random-effects models. The lines extending from the bullets represent the 95% confidence interval (CI) for the estimates. A vertical line through the referent (0.0) has also been plotted.

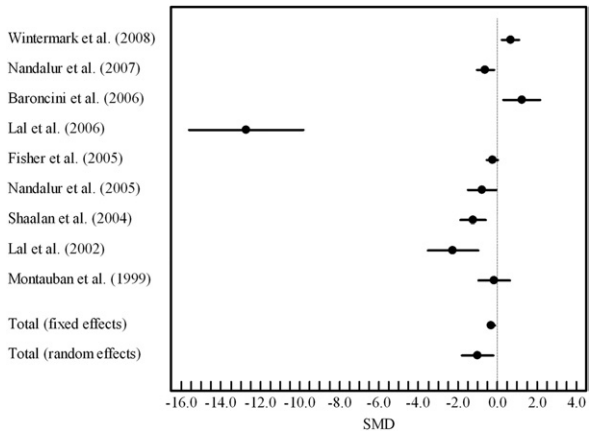

Fig 2. Forest plot of the association between plaque calcification percentage and clinical ischemic symptoms; study-specific and pooled standardized mean differences (SMDs) for studies using a rating scale or continuous measure of calcification percentage. Bullets represent each individual study's SMD estimate. At the bottom of the plot, bullets represent the pooled estimate, both for the fixed and random-effects models. The lines extending from the bullets represent the 95% confidence interval (CI) for the estimates. A vertical line through the referent (0.0) has also been plotted.

calcification measure (Fig 4, *C*) is roughly symmetrical, suggesting a low likelihood of publication bias.

DISCUSSION

The results of this systematic review show that carotid plaques which have lower calcification volume, weight, or percentage, are more likely to be clinically symptomatic. Results of studies measuring calcification volume or weight, and studies using a dichotomous measure of degree of plaque calcification, were homogeneous. Results of studies measuring calcification percentage were heterogeneous,

Table II. Continued.

Definition of asymptomatic carotid plaque	*Method, calcification measure*	*Blinding*
NR	Chemical analysis of CEA specimens Calcium hydroxyapatite mg/g wet weight	NR
According to ACAS criteria	B-mode US with pixel segmentation with tissue mapping Percentage calcium of the total area of the plaque in longitudinal view	NR
No history of symptoms on the side of interest	Histologic analysis Calcification vs no calcification at the level of the largest plaque area	Yes
NR	Histologic analysis Calcium deposit vs no calcium deposit	NR
No cerebral ischemic symptoms	Histologic analysis Percentage calcification of total plaque volume	Yes
NR	Histologic analysis Predominantly calcific vs predominantly noncalcific	Yes
Absence of ipsilateral TIA, AFx, or embolic CVA	Chemical analysis of CEA specimens Calcium mg/mg dry weight	NR
NR	Histologic analysis Calcification vs no calcification	NR
NR	Histologic analysis Calcification vs no calcification	Yes

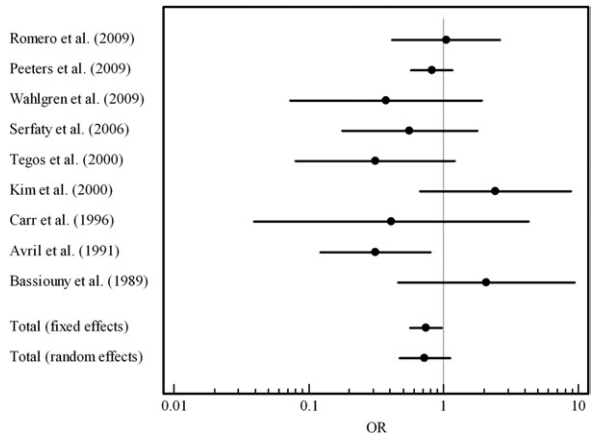

Fig 3. Forest plot of the association between degree of plaque calcification and plaque clinical ischemic symptoms; study-specific and pooled odds ratios (ORs) for studies using a dichotomous measure of degree of plaque calcification. Bullets represent each individual study's standardized mean difference (SMD) estimate. At the bottom of the plot, bullets represent the pooled estimate, both for the fixed and random-effects models. The lines extending from the bullets represent the 95% confidence interval (CI) for the estimates. A vertical line through the referent (1.0) has also been plotted.

and sources of heterogeneity could not be identified by subgroup analyses.

This systematic review has some potential limitations. Due to the large methodologic differences among the studies, the pooled results should be interpreted with caution. There was large between-study variation in methodologies used to analyze plaque calcification. However, there is no single gold standard reference and measurement method for quantifying plaque calcification. The ex vivo methods used by the included studies (histologic analysis, CT, x-ray, and chemical analysis) are accepted methods to quantify vascular calcification,[11] and the in vivo methods (CT, MRI, and B-mode US scan with pixel analysis) have shown to strongly correlate to histologic measurements.[12-14] Still, differences in methodologies may account for heterogeneity across studies. Furthermore, there were considerable differences in the definition of symptomatic and asymptomatic plaques across studies. Regarding symptomatic status, only four studies[14,38,47,48] stated that they applied North American Symptomatic Carotid Endarterectomy Trial (NASCET)[58] or European Carotid Surgery Trial (ECST)[59] selection criteria. According to these criteria, patients with cardiac disease likely to cause embolism were excluded, because in these cases, symptoms may not be attributable to carotid atherosclerosis. Of the remaining 20 studies, only 8 explicitly stated that they excluded patients with a possible cardiac source of embolism.[9,40-42,46,49,51,55] Ten studies did not report whether they excluded patients with a possible cardiac source of embolism,[37,39,43-45,50,52-54,56,57] whereas one study reported to also include patients with atrial fibrillation.[37] It is debatable whether carotid plaques of patients with ipsilateral lacunar infarcts should be defined as symptomatic. The NASCET[58] and ECST[59] criteria do not specify this. Although it is believed that lacunar infarcts are mainly caused by small-vessel disease occluding a small perforating ar-

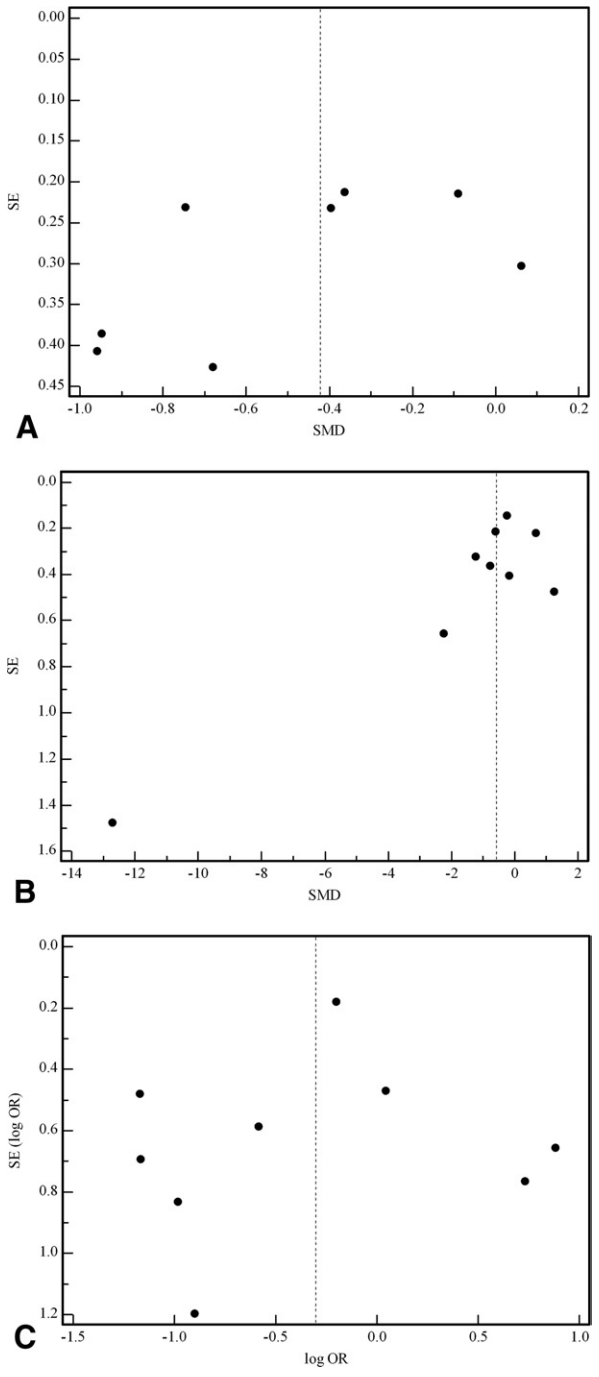

Fig 4. A, Funnel plots on studies using calcification volume or weight, **(B)** calcification percentage, **(C)** and dichotomous calcification measure. The vertical axis is a measure of the precision of the effect size of a study, in this case represented by the SE of the standardized mean difference (SMD) or log odds ratio (OR) (the log OR was used, because it can take any value and has an approximately normal distribution). The horizontal axis measures the study's effect size, in this case, the SMD or log OR. The point estimate from each study has been plotted, and a vertical line has been added where the pooled estimate from the meta-analysis lies.

tery,[60] a pooled posthoc analysis of individual patient data from NASCET and ECST showed that CEA was also beneficial in a subgroup of patients with a lacunar infarct on CT.[61] This indirectly suggests that there may also be a causative relation between carotid stenosis (70%-99%) and ipsilateral lacunar infarcts. In this systematic review, four of the included studies[9,40,42,49] reported to exclude patients with lacunar infarcts, whereas one study did consider plaques ipsilateral to lacunar infarcts as symptomatic.[45] Of the included studies, only Baroncini et al[45] stated how plaques of patients with silent infarcts were categorized. In their study,[45] these plaques were defined as symptomatic. However, according to NASCET[58] and ECST[59] criteria, patients must have experienced clinical symptoms to define a plaque as symptomatic. On the other hand, it has recently been shown that patients with asymptomatic carotid stenosis and an ipsilateral silent infarct on CT have a higher risk of ipsilateral hemispheric neurologic events and stroke.[62] Thus, the topic whether or not to define carotid plaques ipsilateral to silent infarcts as symptomatic, is also controversial. Remarkably, Serfaty et al[36] classified carotid plaques as symptomatic if there were contralateral symptoms. Furthermore, vascular calcification is a dynamic process,[63] and degree of calcification of individual plaques may change over time. There was a large variation in reported maximum time interval between last symptoms and inclusion, which varied from 1 week[42,49] up to 6 months.[14,38,39,43,47,48,50,51] Ten studies did not report the maximum time interval.[36,40,41,44,45,52,54-57]

Regarding asymptomatic status, one study[38] stated that it applied Asymptomatic Carotid Surgery Trial (ACST) selection criteria.[8] According to these criteria,[8] a carotid plaque is considered to be asymptomatic if it had not caused any stroke, transient cerebral ischemia, or other relevant neurologic symptoms in the past 6 months. Three studies[14,47,48] used Asymptomatic Carotid Atherosclerosis Study (ACAS) methodology.[64] However, in ACAS,[64] the definition of an asymptomatic carotid plaque is vague. Eleven studies also did not specify how asymptomatic plaques were defined.[36,39,41,44,46,50-52,54,56,57] Seven studies defined carotid plaques as asymptomatic when there was no history of ipsilateral ischemic symptoms.[9,37,40,42,49,53,55] One study considered plaques of patients without any history of recent neurologic symptoms as asymptomatic but did not specify the time criterion they applied.[45] Another study defined plaques as asymptomatic even when there was an ipsilateral small artery territory infarct or ipsilateral ischemic event and hemodynamic failure on single photon emission CT.[43] Aforementioned differences in definition of symptomatic and asymptomatic plaques may have been important sources of heterogeneity and may have influenced the pooled results. However, due to the large variation and relatively small number of studies, these effects could not be explored by meaningful subgroup analyses. Furthermore, when there is a difference in degree of stenosis between symptomatic and asymptomatic plaques, the presence or absence of symptoms may be attributed to this parameter rather than degree of plaque

calcification. However, only eight studies reported that there was no significant difference in degree of luminal stenosis caused by symptomatic and asymptomatic plaques.[9,37,40,42,50,54,56,57] In addition, one study reported that symptomatic plaques caused a higher degree of luminal narrowing,[46] which may explain why the SMD in that study was higher than 0.0. Finally, 11 studies did not report whether they assessed degree of plaque calcification blinded to clinical information,[14,37,39,41,44,45,48,51,52,55,56] which may have biased their results.

In the present systematic review, pooled SMD for calcification volume or weight between symptomatic and asymptomatic plaques was −0.425, whereas pooled SMD for calcification percentage was −0.997, suggesting that calcification percentage may be a stronger prognostic parameter for plaque stability. Plaques that have a higher calcification percentage may have smaller LRNC size, which could decrease plaque vulnerability. Abedin et al[63] hypothesized that the relationship between calcification and clinical events likely relates to mechanical instability introduced by calcified plaque at its interface with softer, noncalcified plaque and that larger interface area would make plaques more prone to rupture. They also hypothesized that as calcification proceeds, interface surface area initially increases, but eventually decreases as plaques coalesce.[63] This could explain why plaques with a high degree of calcification are less likely to produce clinical symptoms compared with plaques that are moderately calcified. In addition, it has also been reported that noncalcified carotid plaques harbor a greater degree of FC inflammation, a key process in FC disruption.[39,50] Li et al[65] suggested that the location of calcification may be a critical factor in plaque stability. Using a computational simulation, they showed that the presence of calcification at the thin FC, close to the lumen, may result in high stress concentrations, which could increase the risk of plaque rupture. Calcification of the FC at other locations further away from the lumen or calcification deposits in the LRNC would have no or little impact on plaque stress.[65] This theory could not be confirmed by the present systematic review, because none of the included studies assessed the frequency of calcification located at the FC.

In conclusion, the studies included in this systematic review used a wide range of methodologies to quantify degree of calcification and a wide range of definitions to define clinically symptomatic and asymptomatic carotid plaques. Pooled results suggest that symptomatic carotid plaques have a lower degree of calcification. Future studies should use standardized methods and definitions and investigate whether in vivo assessment of degree of plaque calcification is useful to predict which plaques will cause future cerebrovascular ischemic events.

AUTHOR CONTRIBUTIONS

Conception and design: RK
Analysis and interpretation: RK
Data collection: RK
Writing the article: RK
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