

2015

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Recommended Citation

Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambone A, Mtui E, Suri J, Sanelli P, Mushlin A, . Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. . 2015 Jan 01; 46(1):Article 1968 [p.]. Available from: <https://academicworks.medicine.hofstra.edu/articles/1968>. Free full text article.

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Published in final edited form as:

Stroke. 2015 January ; 46(1): 91–97. doi:10.1161/STROKEAHA.114.006091.

Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis: A Systematic Review and Meta-Analysis

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Abstract

Background and Purpose—Ultrasonographic plaque echolucency has been studied as a stroke risk marker in carotid atherosclerotic disease. We performed a systematic review and meta-analysis to summarize the association between ultrasound determined carotid plaque echolucency and future ipsilateral stroke risk.

Methods—We searched the medical literature for studies evaluating the association between carotid plaque echolucency and future stroke in asymptomatic patients. We included prospective observational studies with stroke outcome ascertainment after baseline carotid plaque echolucency assessment. We performed a meta-analysis and assessed study heterogeneity and publication bias. We also performed subgroup analyses limited to patients with stenosis $\geq 50\%$, studies in which plaque echolucency was determined via subjective visual interpretation, studies with a relatively lower risk of bias, and studies published after the year 2000.

Results—We analyzed data from 7 studies on 7557 subjects with a mean follow up of 37.2 months. We found a significant positive relationship between predominantly echolucent (compared to predominantly echogenic) plaques and the risk of future ipsilateral stroke across all stenosis severities (0-99%) (relative risk [RR], 2.31, 95% CI, 1.58-3.39, $P < .001$) and in subjects with $\geq 50\%$ stenosis (RR, 2.61 95% CI, 1.47-4.63, $P = .001$). A statistically significant increased RR for future stroke was preserved in all additional subgroup analyses. No statistically significant heterogeneity or publication bias was present in any of the meta-analyses.

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Disclosures

None.

Conclusions—The presence of ultrasound-determined carotid plaque echolucency provides predictive information in asymptomatic carotid artery stenosis beyond luminal stenosis. However, the magnitude of the increased risk is not sufficient on its own to identify patients likely to benefit from surgical revascularization.

Keywords

carotid stenosis; ultrasound; plaque; stroke; risk factor

Introduction

Two randomized controlled trials found that carotid endarterectomy can reduce the annual risk of stroke in asymptomatic patients with 50-99% carotid artery stenosis to 0.5-1.0%.^{1,2} However, the clinical relevance of these results has been questioned since progressive improvements in medical therapy have significantly reduced the annual stroke rate in asymptomatic carotid stenosis. For example, a meta-analysis³ demonstrated that when taking into account studies completing recruitment of asymptomatic carotid stenosis subjects between 2000 and 2010, the annual ipsilateral stroke rate is approximately 1%, and potentially even lower when only the most recent observational data included in this meta-analysis are considered. For this reason, and due to the marginal surgical stroke prevention benefit seen in the randomized trials, investigations have focused on improving risk stratification strategies beyond luminal stenosis measurements.

Ultrasound is an attractive potential tool for obtaining stroke risk information in carotid disease since it is widely available and has almost no contraindications. The use of carotid plaque echolucency as a potential marker for stroke risk is supported by histopathologic studies showing that plaque echolucency corresponds to lipid-rich necrotic core or intraplaque hemorrhage, more commonly found in symptom-associated carotid stenosis than in asymptomatic stenosis.^{4,5} However, there are conflicting data in the literature regarding the predictive value of carotid plaque echolucency in asymptomatic patients^{6,7} and the small study samples studied result in wide confidence intervals for risk estimates. For these reasons, we performed a systematic review and meta-analysis evaluating whether ultrasound characterization of carotid plaque echogenicity is a predictor of ipsilateral stroke in asymptomatic carotid atherosclerotic disease.

Methods

This study followed guidelines presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.⁸

Study Eligibility Criteria

Studies with ultrasound characterization of carotid artery plaque echolucency in subjects subsequently followed for development of future ipsilateral stroke were eligible. Specific inclusion criteria were: (1) English language manuscripts; (2) studies with at least 30 subjects; (3) studies of asymptomatic patients without histories of prior ipsilateral stroke or TIA at the time of imaging; (4) ultrasound determination of the presence or absence of

carotid vessel plaque echolucency in subjects with carotid plaque (both stenosis-causing and non-stenosing plaques); (5) mean follow-up >12 months after plaque imaging; (6) clinical ascertainment of first time ipsilateral stroke during follow-up; and (7) non-surgical management of patients with follow-up information on greater than 85% of the initially asymptomatic cohort enrolled in the study. If a mixed cohort of previously symptomatic and asymptomatic patients or medically and surgically treated patients were presented, such a study was included if the ultrasound test and stroke outcome data for only the patients who were asymptomatic at baseline could be extracted from the manuscript. In cases where the ultrasound test result or outcome data were not clear in the manuscript, we attempted to contact the corresponding author for additional details. Furthermore, if ultrasound test data from a cohort was published more than once, only the originally published paper was used for the testing data and outcome results to avoid pooling duplicate results. Finally, if more than one method of echolucency determination was presented in a manuscript, the method with the greatest predictive ability was included in the meta-analysis.

Information Search and Data Collection

We performed systematic searches of multiple medical literature databases between January and March of 2014 to find all eligible articles without regard to when they were published. Major search terms for all databases included “carotid stenosis,” “plaque,” “atherosclerosis,” “ultrasound,” “sonography,” “doppler,” “stroke,” and “transient ischemic attack.” The search methodology details and data extraction process are provided in the Methods in the Online Supplement (please see <http://stroke.ahajournals.org>).

Assessment of Risk of Bias in Studies

We used the following bias assessment criteria which we adapted from published meta-analyses^{9,10} of imaging markers of stroke risk in carotid disease: (1) risk of outcome ascertainment bias, for which we assessed whether investigators were blinded to ultrasound testing results when stroke outcomes were assessed; (2) risk of confounding bias, for which we assessed whether potentially confounding stroke risk factors were collected and analyzed; (3) completeness of follow-up data, for which we assessed whether losses to follow-up were systematically recorded and reported.

Statistical Analyses

We performed a meta-analysis of studies meeting two criteria: (1) a relative risk (RR) was calculable from the raw data either as published or obtained via direct correspondence from the study author(s); (2) echolucency test results were presented in a dichotomized fashion (e.g., predominantly echolucent versus echogenic) or in a categorical fashion that could be dichotomized in the data extraction process. We used the Q statistic to determine study heterogeneity and the Begg test for publication bias. We performed all analyses using a random-effects model in which we made the conservative assumption that included studies did not have exactly the same effect size (relative risk). Given the potential for heterogeneity between studies in terms of sample size, patient characteristics, and testing methods, we did not employ a fixed-effects model since in this approach an identical effect size is assumed across all studies.

We performed 2 primary analyses from the studies in which ultrasound test data could be extracted, 1 including all patients (with all stenosis severities from 0 to 99%) and 1 limited to patients with $\geq 50\%$ stenosis. The analysis limited to patients with $\geq 50\%$ stenosis was performed by extracting this data from details provided in the manuscript or via direct correspondence with the author. We also performed 3 additional prespecified subgroup analyses limited to the following study characteristics: (1) studies in which authors were blinded to imaging test data during outcome ascertainment and analyzed potentially confounding vascular risk factors; (2) studies in which plaque echolucency determination was made by subjective visual interpretation without quantitative imaging postprocessing; (3) studies published since 2000. We also performed 3 post-hoc sensitivity analyses: (1) excluding Polak et al.¹¹ to evaluate the possibility that its cohort of 4,886 subjects could be significantly driving the effect size of the overall meta-analysis; (2) excluding Silvestrini et al.¹² given its use of an imaging-based (time-independent) definition of stroke, unlike the time-dependent, clinical definitions used in all other studies; and (3) excluding Topakian et al.⁷ given that a subset of its subjects developed TIAs prior to stroke outcome ascertainment.

Results

Study Selection

We screened a total of 5,409 abstracts from which 8 manuscripts^{6,7,11-16} were ultimately deemed to meet all inclusion criteria for the systematic review. Study selection steps are summarized in Online Supplement Figure I (please see <http://stroke.ahajournals.org>)

Qualitative Assessment and Study Characteristics

Of the 8 articles meeting inclusion criteria for qualitative review and pooling (Table 1), all were prospective, longitudinal non-randomized observational studies with 2 conducted as international multicenter studies,^{7,15} 2 in the United States,^{11,16} and 1 each in Australia,¹³ Denmark,⁶ Italy,¹² and Norway.¹⁴ All evaluated patients with similar mean ages (range 64.0 to 72.6 years) and all except 1 study¹¹ had a preponderance of male subjects (range 43% to 84.2% male). We found considerable differences in the degree of extracranial carotid artery stenosis studied, with 5 studies^{11,13-16} including a combination of subjects with low (<50%), moderate (50-69%), and high-grade ($\geq 70\%$) stenosis. Of these 5 studies, 2 included a number of subjects who did not have stenosed carotid arteries^{13,14} and 1 study¹¹ included a number of subjects without carotid plaque (stenosing or non-stenosing). The remaining 3 studies^{6,7,12} were limited to moderate and high-grade carotid stenosis subjects. Subjects in all studies were followed for at least 21.8 months (range 21.8-52.8 months) for ascertainment of clinically-defined first-time stroke. The definition of asymptomatic carotid stenosis was not always explicitly given^{11, 14, 16} or sometimes included patients with remote ipsilateral symptoms (>12-24 months) as asymptomatic patients.^{7,13}

Ultrasound test results and outcomes in each test group are summarized in Tables 2 and 3 with additional details about the cohort with $\geq 50\%$ stenosis summarized in Online Supplement Table I (please see <http://stroke.ahajournals.org>). Seven studies^{6,7,11,13-16} defined stroke clinically as ipsilateral hemispheric neurologic deficit but only 3 of these 7 studies^{6,14,15} stipulated specifically that the deficit must be present for >24 hours to be

defined as a stroke. One study, Silvestrini et al.¹², utilized time-independent clinical features with brain imaging evidence of cerebral ischemia to define stroke. This meant that some transient events (most likely called TIAs in all the other studies we included) were classified as stroke in the study by Silvestrini et al. Of the 8 studies meeting inclusion criteria for the systematic review, 7 were amenable to the calculation of a RR of ipsilateral stroke in the presence of plaque echolucency. In the 1 other study¹³ the authors presented only a composite outcome measure of TIA plus stroke which prevented this study from being included in the pooled ipsilateral stroke RR calculation. In 6 of studies included in the systematic review, RR information for asymptomatic patients was either presented or could be calculated from the raw data provided in the manuscript. In the remaining 2 studies^{12,14} mixed cohorts of symptomatic and asymptomatic patients at baseline were presented for which we were able to obtain test and outcome data for the asymptomatic patients only after correspondence with the study authors.

Definitions of ultrasound testing methods, imaging equipment, abnormal test results, and outcome measures are provided in Table 4. For all studies we were able to dichotomize test results into positive or negative for echolucency, using definitions provided by the study authors. All studies used standard clinical ultrasound equipment. In addition, all studies except 2^{6,15} employed subjective observer interpretation of plaque echolucency as the definition of a positive test result.

Assessments of Study Methods

In 5 of the 8 studies^{6,7,11,12,14} the authors described a process of blinding of ultrasound results in the determination of clinical outcomes while in the remaining 3 studies blinding was not described. In 7 of the included studies, the authors recorded potentially confounding risk factors with only 1 study¹⁶ not including these data. Finally, in 2 studies there was a description of the exact numbers of subjects who were lost to follow-up (12 subjects in 1 study¹⁵ and 2 in another¹⁴) while in 1 study¹³ there was mention that some loss to follow-up had occurred without presenting the actual numbers. There was no mention of loss to follow-up in the remaining studies. Furthermore, in only 4 studies^{7,12,14,15} was the proportion of subjects undergoing surgical revascularization while asymptomatic provided. Finally, in 1 study⁷ patients who were asymptomatic at baseline were followed up until their first ipsilateral stroke, whether or not they had an ipsilateral TIA first. Therefore, in this study a mixture of asymptomatic and symptomatic patients were included in stroke event rates and correlations with plaque characteristics.

Meta-Analysis Results for all Subjects including those with and without Stenosis

In this primary analysis we studied 7,557 subjects with a mean follow up of approximately 37.2 months yielding a total of 23,410.2 person-years of follow-up. No significant heterogeneity ($Q=9.438$, $P=0.150$) or publication bias (Kendall's score=7, $P=0.293$) was present in this primary analysis. We found a significant positive relationship between plaque echolucency and the risk of future ipsilateral stroke with a random effects RR of 2.31 (95% confidence interval [CI], 1.58-3.39, $P<.001$) (Figure 1). Of the total study sample, 1,741 subjects (23.0%) had a positive ultrasound test for echolucency while 5,816 (77.0%) had a negative test for echolucency. In the echolucent positive test group, 100 ipsilateral strokes

occurred compared to 141 ipsilateral strokes in the echolucent negative test group. The cumulative incidence of ipsilateral stroke in the echolucent plaque cohort was 5.7% compared to 2.4% in the non-echolucent plaque cohort.

Meta-Analysis Results for Moderate and High-Grade Carotid Stenosis

In our analysis limited to subjects with $\geq 50\%$ extracranial carotid stenosis,^{6,7,12,15,16} we accumulated 2,095 subjects with a mean follow up of approximately 29.7 months yielding a total of 5,185.1 person-years of follow-up (Figure 2). No significant heterogeneity ($I^2=8.216$, $P=0.084$) or publication bias (Kendall's score=0, $P=1.000$) was present in this subgroup analysis. In patients with $\geq 50\%$ carotid stenosis, we found a significant positive relationship between plaque echolucency and the risk of future ipsilateral stroke with a random effects RR of 2.61 (95% CI, 1.47-4.63, $P=.001$) (Figure 2). Of the moderate to high-grade stenosis patient sample, 649 subjects (31.0%) had a positive ultrasound test for echolucency while 1,446 (69.0%) had negative test for echolucency. In the echolucent positive test group, 67 ipsilateral strokes occurred compared to 59 ipsilateral strokes in the echolucent negative test group. The cumulative incidence of ipsilateral stroke in the moderate and high-grade stenosis echolucent plaque cohort was 10.3% compared to 4.1% in the non-echolucent plaque cohort.

Subgroup Meta-analysis Results

No significant heterogeneity or publication bias was found in any of the subgroup or sensitivity analyses (Table 4). A statistically significant random-effects RR was preserved in subgroup analyses involving: (1) only those studies where test result blinding and analysis of confounding stroke risk factors occurred (RR 2.03, 95% CI 1.26-3.27), (2) only those studies in which echolucency was determined by subjective visual interpretation (RR 2.73, 95% CI 1.76-4.22), (3) only those studies which were published after 2000 (RR 2.14, 95% CI 1.28-3.59). Likewise, a statistically significant random-effects RR was also preserved in the 3 post-hoc sensitivity analyses performed and the magnitude of the RR was not sizably different.

Discussion

The degree of carotid stenosis criteria alone within the 50-99% range provides only a relatively weak means for clinically stratifying the risk for ipsilateral stroke in asymptomatic patients.^{18,19} In this systematic review and meta-analysis of over 7,500 patients, we studied plaque echogenicity as an additional marker of stroke risk. We found that patients with predominantly echolucent plaques had an approximately 2.3 fold higher risk of future ipsilateral stroke than those with predominantly echogenic plaques. In patients with 50-99% carotid stenosis, we also found an approximately 2.6-fold higher risk of ipsilateral stroke if the plaques were predominantly echolucent compared to plaques which were not predominantly echolucent.

Furthermore, in 3 additional prespecified subgroup analyses we showed that the increased risk of ipsilateral stroke noted in patients with echolucent plaques was robust to differences in patient samples, study methodology, and study era. Specifically, we showed that the

subjective visual interpretation of echolucency also identified higher risk subgroups in our pooled analysis without the use of quantitative gray-scale median analysis of plaque⁶ or post processing image normalization.¹⁵ However, the relative performance of subjective, visually-determined echolucency versus quantitative, computer-based methods requires further investigation since only 2 studies^{6,15} in our meta-analysis used computer-aided methods thereby preventing a meaningful comparison of the techniques. In addition, after excluding studies with a relatively higher risk of outcome ascertainment and confounding bias, there was a preserved statistically significant RR. Moreover, we found that the risk of stroke was increased with echolucent plaque even when the analysis was limited to publications after the year 2000, an era in which improvements to medical therapy for stroke risk prevention have been more widely implemented.³ Finally, our post-hoc sensitivity analyses demonstrated that our results were robust to the following: (1) the exclusion of the largest cohort¹¹ in our study; (2) the exclusion of a study¹⁶ with imaging-based (time-independent) definition of stroke which has the possibility of over-classifying TIAs as strokes which would not be done in all other studies using the time-dependent, clinical definitions; and 3) the exclusion of a study⁷ in which a subset of patients were followed for first-time stroke whether or not they had an ipsilateral TIA that preceded the stroke.

The mechanism underlying increased stroke risk in echolucent carotid artery plaque is not entirely understood but is likely related to the echolucent appearance of high-risk elements of atherosclerosis including lipid-rich necrotic core and intraplaque hemorrhage.⁴ The relative proportion of these tissues is also uncertain though most histopathologic studies suggest that lipid may be the largest plaque element by volume in echolucent plaque.⁵ However, the precise differentiation of tissues in echolucent plaque may be of limited clinical significance, since most of these presumed tissue-types are features of more advanced atherosclerotic lesions.¹⁰

There are limitations of the ultrasonographic imaging methods used by the studies included in this meta-analysis. First, we found a lack of consistency in the methods used to determine plaque echolucency. More work is needed standardize the definitions of echolucency and provide inter- and intra-observer variability measures of echolucency assessment. The role of quantitative methods such as the use of gray-scale median values as well as the impact of differences in ultrasound equipment on diagnostic accuracy and prediction of outcome also requires additional study. In addition, future work is needed to understand how risk from plaque echolucency could be incorporated in a multi-factorial risk assessment strategy in which other presumptive stroke risk markers such as plaque ulceration are synthesized to produce a composite risk score.¹⁸ It is important to remember that even assuming a 0.5 to 1% annual stroke risk in asymptomatic carotid stenosis $\geq 50\%$, that a 2.6 times higher RR of stroke as seen with predominantly echolucent plaque will still require additional risk factors to be taken into account to inform decisions with regard to a carotid procedure supplementing modern medical therapy. The most meaningful improvements in risk stratification in asymptomatic carotid stenosis may only occur when plaque echolucency is combined with other risk markers such as clinical features, the degree of stenosis and other imaging measures.¹⁸

Several additional limitations of our study are important to consider. First, we noted that most studies did not make clear what systematic efforts were used to assure complete subject follow-up and thus it is unclear to what extent losses to follow-up may have contributed to bias in our estimation of the relative risk associated with echolucent plaques. Second, in the studies where blinding to test results was not performed, we believe that the possibility of outcome ascertainment bias exists. Third, we studied only medically managed asymptomatic patients and it is therefore unclear to what extent selection bias may have influenced the risk profile of this group compared to asymptomatic patients undergoing surgical revascularization. Fourth, we calculated unadjusted RRs. Since the covariate risk factors, individual patient follow-up times, and medical therapies used varied so widely across studies, the existing data is not amenable to the calculation of covariate-adjusted RRs or annualized stroke risks. Fifth, most studies included patients with a wide range of carotid stenosis including 2 studies in which carotid stenosis was not present in all subjects^{13,16} and 1 study¹¹ in which a number of patients did not have any carotid plaque (stenosing or non-stenosing). However, specific breakdowns of subjects with and without stenosis were not provided. Since some studies focused only on stenosis $\geq 50\%$ or presented these data separately, we were able to estimate a pooled RR for this group. However, the total study data were not amenable to similar calculation of RR for only patients with low-grade carotid stenosis ($<50\%$) or non-stenosing carotid plaque. Finally, additional heterogeneity of the studies in this meta-analysis arise from lack of clarity in reporting on asymptomatic carotid disease including variability in the definition of stroke and symptomatic status, inconsistent reporting of the nature of medical therapy received by subjects, and imprecision about the classification of first-time versus recurrent ischemic events. Future studies in carotid disease should rely on standardized definitions for these basic clinical features and outcome measures so that studies can be understood, analyzed, and interpreted in a transparent and clear fashion.

In spite of these challenges and limitations, we believe that there is sufficient evidence to conclude that ultrasound carotid plaque echolucency is a predictive risk factor for ipsilateral stroke in patients across a wide range of carotid stenosis severity. Despite the limitations of available research results, to our knowledge, our study is the best quality, most comprehensive analysis of the predictive value of detecting plaque echolucency. Ultimately, the validation of plaque echolucency and other risk markers to inform treatment decisions in patients with asymptomatic carotid stenosis will require examination in high quality, prospective longitudinal studies of patients receiving current optimal medical treatment. Finally, although nearly 30% of subjects with $\geq 50\%$ stenosis demonstrated plaque echolucency, given the low absolute stroke risk in these patients, plaque echolucency alone is not a powerful enough risk factor to select asymptomatic stenosis patients likely to benefit from carotid endarterectomy or stenting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding Dr. Gupta's effort was supported by an Association of University Radiologists-General Electric Radiology Research Award Fellowship and the Foundation of the American Society of Neuroradiology Scholar Award. Dr. Mushlin received funding from an NIH Clinical and Translational Science Award to Weill Cornell Medical College.

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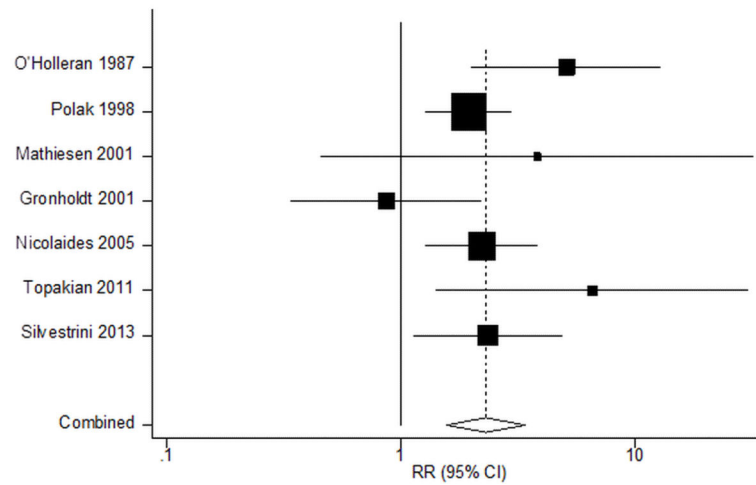


Figure 1.

Forest plot of the association between ultrasound-determined plaque echolucency and future ipsilateral stroke. Meta-analysis calculated using a random-effects model. Squares represent point estimates for the effect size expressed as a relative risk. The size of the squares is proportional to the inverse of the variance of the estimate. Diamond represents the pooled estimate and the horizontal lines represent the 95% confidence intervals.

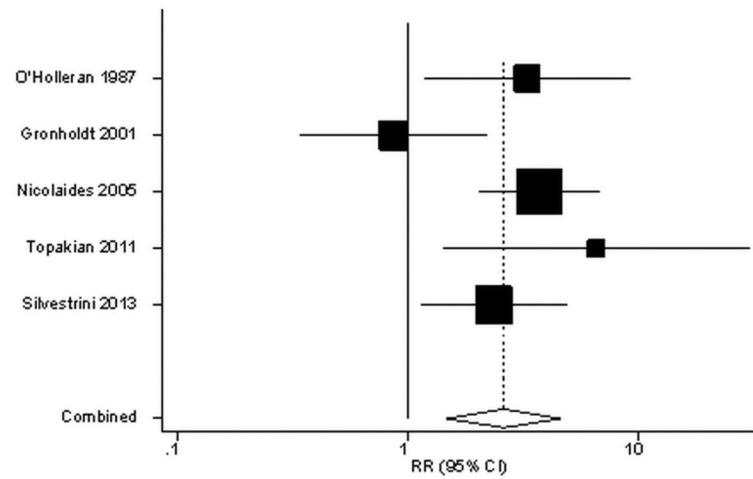


Figure 2.

Forest plot of the association between ultrasound-determined plaque echolucency and future ipsilateral stroke in the subgroup of patients with 50% stenosis. Meta-analysis calculated using a random-effects model. Squares represent point estimates for the effect size expressed as a relative risk. The size of the squares is proportional to the inverse of the variance of the estimate. Diamond represents the pooled estimate and the horizontal lines represent the 95% confidence intervals.

Table 1
Overview of Patient Characteristics in Studies Evaluating Risk of Stroke in Patients with Carotid Ultrasound Plaque Echolucency

Study Number	Study First Author and Year	Number of Medically Managed Subjects	Medical Therapy Received by Cohort	Number of Carotid Arteries with follow-up outcome data	Mean Age	Male (%)	Stenosis Severity Range (%)	Mean Follow-Up (Months)	Number of Subjects undergoing Carotid Endarterectomy of Asymptomatic Carotid Artery During Follow-up (%)
1	O'Holleran 1987 ¹⁶	293	none	296	N/A	N/A	0-100	46	NA
2	Langsfield 1989 ¹³	319	not described	436	67.9	84.2	0-100	22	NA
3	Polak 1998 ¹¹ from the Cardiovascular Health Study	4886	not described	N/A	72.6	43	0-100	39.6	NA
4	Mathiesen 2001 ¹⁴ from the Tromso Study	177	antiplatelet therapy	177	67.8	58.7	35-99	36	3 (1.7)
5	Gronholdt 2001 ⁶	111	Not described	111	64.0	59	50-99	52.8	NA
6	Nicolaides 2005 ¹⁵ from the Asymptomatic Carotid Stenosis and Risk of Stroke Study	1092	antiplatelet, antihypertensives, and lipid lower agents as per local standard of care	1092	70.0*	61*	12-99	37.1	116 (10.6)
7	Topakian 2011 ⁷ from the Asymptomatic Carotid Emboli Study	435	antiplatelet, antihypertensives, and statins as per local standard of care	435	71.4	74.7	70	21.84	16 (3.7)
8	Silvestrini 2013 ¹²	621	antiplatelet, antihypertensives, and statins as per local standard of care	621	72.2	56	60	27 (median)	0 (0)

N/A, data not available.

* indicates demographic data derived from a subsequent publication¹⁷ of the same cohort

Table 2
Overview of Ultrasound Plaque Testing Characteristics and Risk of Ipsilateral Ischemic Events

Study Number	Study First Author and Year	Ultrasound plaque measure (echolucency)	Mean Follow-Up (Mo)	Number of Tests with Predominantly Echolucent Plaque (percentages in parenthesis)	Ipsilateral Ischemic Strokes in Predominantly Echolucent Plaque Group	Percent Predominantly Echolucent Subjects with Future Ipsilateral Stroke	Ipsilateral Ischemic Strokes in Predominantly Echogenic Plaque	Percent of Predominantly Echogenic Subjects with Future Ipsilateral Stroke	Ipsilateral Stroke RR	Ipsilateral Stroke RR 95% CI
1	O'Holleran 1987 ¹⁶	echolucency	46	88 (29.7)	13	14.8	6	2.9	5.12	2.01-13.04
2	Langsfeld 1989 ¹³	echolucency	22	98 (22.4)	N/A	N/A	N/A	N/A	N/A	N/A
3	Polak 1998 ¹¹	hypoechogenicity	39.6	856 (17.8)	30	3.5	73	1.8	1.96	1.25-2.90
4	Mathiesen 2001 ¹⁴	echolucency	36	100 (56.4)	5*	5.0	1*	1.3	3.85	0.46-32.28
5	Gronholdt 2001 ⁶	echolucency (gray-scale median <74)	52.8	63 (56.8)	8	12.7	7	14.6	0.87	0.34-2.23
6	Nicolaides 2005 ¹⁵	echolucency (type 1 or 2)	37.1	409 (37.5)	28	6.8	21	3.1	2.23	1.28-3.87
7	Topakian 2011 ⁷	echolucency (type 1 or 2)	21.8	164 (37.7)	8	4.9	2	0.7	6.61	1.42-30.75
8	Silvestrini 2013 ¹²	echolucency	27 (median)	61 (9.8)	8*	13.1	31*	5.5	2.37	1.14-4.92

CI indicates confidence interval; RR, relative risk;

* indicates data not present in the original manuscript but provided via direct author correspondence

Table 3

Ultrasound Plaque Testing and Outcome Characteristics

Study Number	Study First Author and Year	Ultrasound equipment (machine type)	Stenosis Severity Measurement Technique	Definition of Abnormal Plaque Echolucency	Definition of Stroke
1	O'Hollerhan 1987 ¹⁶	N/A	cross sectional area and spectrum analysis	Qualitative; low-level echo pattern	No specific definition given. New symptoms ascertained through communication with referring physicians or patient questionnaire.
2	Langsfeld 1989 ¹³	Hoffrel model 518 (7.5 MHz probe); Medasonics model SPA.25	cross sectional area and spectrum analysis	Qualitative; type 1: predominantly echolucency; type 2: echogenic lesions with substantial areas of echolucency	No specific definition given. Symptoms referable to the carotid artery territory considered to be ischemic event.
3	Polak 1998 ¹¹	linear array probes (6.7 MHz); pulsed Doppler ultrasound scanner	pulsed Doppler spectrum defined velocities	Qualitative; same or less echogenicity as vessel lumen	Stroke defined clinically by an adjudication committee, excluding patients with hemorrhage or cardioembolic process.
4	Mathiesen 2001 ¹⁴	linear array probes (5 - 7 MHz); B-mode and Doppler ultrasound scanner	Doppler velocity criteria	Qualitative (type 1 or 2); vessel lumen used as reference for echolucency and media-adventitia interface of the far wall used as reference for echogenicity	Ipsilateral hemispheric neurologic deficit lasting >24 hours.
5	Gronholdt 2001 ⁶	high-resolution B-mode ultrasound with computer-assisted image processing	Doppler velocity criteria	Quantitative; gray-scale median <74	Focal ipsilateral neurological symptoms >24 hours.
6	Nicolaides 2005 ¹⁵	high frequency linear array transducer (4-7MHz)	ECST and NASCET methods derived from velocity and cross sectional areas	Qualitative after image normalization; type 1: uniformly echolucient, <15% of plaque occupied by bright echoes; type 2: mainly echolucient, 15-50% occupied by bright echoes	Ipsilateral hemispheric neurologic deficit lasting >24 hrs. Classification made by committee.
7	Topakian 2011 ⁷	standard clinical equipment according to multi-center ACES protocol	criteria of the local ultrasound laboratories	Qualitative; type 1: uniformly echolucient, >50% of plaque	Stroke defined clinically but without more specific details about exact definition
8	Silvestrini 2013 ¹²	Doppler and color flow B-mode ultrasound (Phillips iU22)	standardized methods using NASCET criteria	Qualitative; uniformly hypoechogenic	Ipsilateral hemispheric neurologic deficit with MRI or CT confirmation.

ACES indicates Asymptomatic Carotid Emboli Study; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial;

Table 4
Meta-analysis Summary for Subgroups Analyses and Sensitivity Analysis Evaluating Relative Risk of Ipsilateral Stroke in Patients with Carotid Ultrasound Plaque Echolucency

Subgroup	No. of Studies	RR (95% CI)	RR P-value	Test of Heterogeneity P-value	Publication Bias P-value
Studies with blinding and analysis of confounding stroke risk factors ^{6,7,11,12,14}	5	2.03 (1.26-3.27)	0.004	0.206	0.327
Studies with qualitative echolucency determination ^{7,11,12,14,16}	5	2.73 (1.76-4.22)	<0.0001	0.263	0.327
Studies published since 2000 ^{6,7,12,14,15}	5	2.14 (1.28-3.59)	0.004	0.201	0.327
Sensitivity analysis with all studies except the largest single cohort (Polak et al ¹¹)	6	2.52 (1.50-4.24)	0.001	0.112	0.573
Sensitivity analysis excluding Silvestrini et al ¹² which used a time-independent imaging-based definition of stroke	6	2.39 (1.46-3.76)	<0.0001	0.094	0.143
Sensitivity analysis excluding Topakian et al ⁷ in which a subset of strokes occurred after TIA	6	2.17 (1.50-3.14)	<0.0001	0.191	0.07

CI indicates confidence interval; RR, relative risk.