Restenosis after carotid interventions and its relationship with recurrent ipsilateral stroke: A systematic review and meta-analysis

Kumar R¹
Batchelder A¹
Saratzis A¹
AbuRahma AF²
Ringleb P³
Lal BK⁴
Mas JL⁵
Steinbauer M⁶
Naylor AR¹

¹The Department of Vascular Surgery at Leicester Royal Infirmary, Leicester UK
²Division of Vascular Surgery, West Virginia University USA
³Neurologische Klinik der Ruprecht-Karls-Universität, Heidelberg, Germany
⁴Division of Vascular Surgery, University of Maryland, Baltimore USA
⁵Hospital Sainte-Anne, Université Paris-Descartes, France
⁶Department of Vascular and Endovascular Surgery, Regensburg, Germany

Correspondence  Professor A. Ross Naylor MD, FRCS
Professor of Vascular Surgery
Vascular Research Group
Division of Cardiovascular Sciences
Clinical Sciences Building
Leicester Royal Infirmary
Leicester LE27LX, United Kingdom

Telephone  +44  116  2523252
Fax  +44  116  2523179
e-mail  ross.naylor@uhl-tr.nhs.uk

conflict of interest  none
Abstract

Objective
Do asymptomatic restenoses >70% after carotid endarterectomy (CEA) and carotid stenting (CAS) increase the risk of late ipsilateral stroke?

Methods
A systematic review identified 11 randomised controlled trials (RCTs) reporting rates of restenosis >70% and 9 reporting late ipsilateral stroke. Meta-analyses of proportions and Odds Ratios (OR) at the end of follow-up were performed.

Results
The weighted incidence of restenosis >70% was 5.8% after ‘any’ CEA at a median of 42 months (11 RCTs; 4249 patients); 4.1% after patched CEA at a median of 35 months (5 RCTs; 1078 patients) and 10% after CAS at a median of 39 months (5 RCTs; 2716 patients).

In 4 RCTs (2810 patients), 1/125 (0.8%) with a restenosis >70% after CAS suffered a late ipsilateral stroke over a median of 50 months, compared with 37/1839 (2.0%) in CAS patients with no significant restenosis (OR 0.87 (95%CI 0.24-3.21) p=0.8339).

In 7 RCTs (2810 patients), 13/141 (9.2%) with a restenosis >70% after CEA suffered a late ipsilateral stroke over a median of 44 months, compared with 33/2669 (1.2%) in patients with no significant restenoses (OR 9.01 (95%CI 4.70-17.28) p<0.0001. However, when the data were corrected to exclude patients whose surveillance scan showed no evidence of a restenosis >70% before stroke onset, the prevalence of stroke ipsilateral to an untreated asymptomatic >70% restenosis was 7/135 (5.2%) versus 40/2704 (1.5%) in CEA patients with no significant restenosis (OR 4.77 (95%CI 2.29-9.92).

Conclusions
CAS patients with an untreated asymptomatic >70% restenosis had an extremely low rate of late ipsilateral stroke (0.8% over 4 years). CEA patients with an untreated, asymptomatic >70% restenosis had a significantly higher risk of late ipsilateral stroke (compared to patients with no restenosis), but this was only 5% at 44 months. Overall, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients with no evidence of a significant restenosis.
What has this study added to the literature?

This meta-analysis of surveillance data derived from nine randomised controlled trials found that CAS patients with an untreated asymptomatic >70% restenosis had an extremely low rate of late ipsilateral stroke (0.8% over 4 years). While CEA patients with an untreated, asymptomatic >70% restenosis had a significantly higher risk of late ipsilateral stroke (compared to patients with no restenosis), the risk was only 5% at 44 months. Overall, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients with no evidence of a significant restenosis.
Introduction

In a 1997 systematic review, up to 8% of patients undergoing carotid endarterectomy (CEA) developed a significant restenosis of the operated internal carotid artery (ICA) during follow-up. However, very few (if any) contemporary practice guidelines provide specific advice as to how they should be managed, especially as most are asymptomatic at the point of detection after CEA or carotid artery stenting (CAS). The 2011 14-Society Guidelines on the management of extra-cranial carotid artery disease noted that “restenosis is generally benign and does not require revascularization, except when it leads to recurrent ischaemic symptoms or progresses to preocclusive severity. Under these circumstances, it may be justifiable to repeat revascularization, either by CEA in the hands of an experienced surgeon or by CAS”. However, this ‘comment’ was never promoted to become a formal recommendation and surgeons/interventionists have been left to manage patients on a case-by-case basis. No-one would dispute that most patients with a symptomatic restenosis >70% warrant reintervention, but what about patients with asymptomatic restenoses? Despite the informal advice provided in the 14-Society guidelines, meta-analyses suggest that two-thirds of patients undergoing reinterventions for restenoses after CEA are asymptomatic, suggesting that many surgeons and interventionists remain uncomfortable about not reintervening.

Data from individual multicentre randomised controlled trials (RCTs) have provided conflicting evidence as to whether restenoses after CEA/CAS are associated with an increased risk of recurrent ipsilateral stroke. Some have reported no statistically significant association between restenosis and recurrent ipsilateral stroke, while the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) reported that restenoses >70% after CEA were associated with a significantly higher prevalence of recurrent stroke after CEA, but not after CAS.

The aim of the current study was to perform a systematic review and meta-analysis of data derived from RCTs involving CEA and/or CAS, which published surveillance data on rates of restenosis >70% after CEA and CAS, with specific reference to whether an untreated asymptomatic restenosis >70% was associated with a higher risk of late ipsilateral stroke, compared to patients with no significant restenosis. RCTs were chosen (rather than
observational studies) because they are prospective, they tend to be conducted with greater scientific rigour and discipline, selection bias is reduced because of the randomisation process and independent physicians adjudicate most endpoints.
Materials and Methods

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. PubMed/Medline, Embase and the Cochrane databases were independently searched by two investigators (RK, AB) from January 1990 until July 2016 to identify RCTs involving CEA and/or CAS. Manual searches were also made of the following journals; Stroke, European Journal of Vascular and Endovascular Surgery, Journal of Vascular Surgery and the Annals of Vascular Surgery.

Demographic data retrieved from the constituent RCTs included mode of intervention (CEA, CAS), method of carotid endovascular intervention (CAS, balloon angioplasty, mixed cohort); method of CEA (traditional, eversion, mixed cohort), mode of CEA arteriotomy closure (primary, patched, mixed cohort), presence/absence of restenosis >70% and the median follow-up period. Studies considered for inclusion in the first meta-analysis (to determine the overall prevalence of restenosis >70% after CEA and CAS) had to report rates of restenosis >70% in the operated ICA during serial surveillance after CEA and/or CAS, but not whether these studies correlated rates of restenosis with recurrent ipsilateral stroke.

A second meta-analysis was undertaken to determine whether restenosis >70% after CEA and CAS was associated with higher rates of recurrent ipsilateral stroke. This required that the constituent RCTs reported rates of restenosis >70% and rates of recurrent late ipsilateral stroke. The threshold of 70% was chosen because few surgeons or interventionists would adopt a threshold of >50% or >60% for reintervening in asymptomatic patients, while very few RCTs published outcome data using a stenosis threshold of 80%. Data abstraction was performed independently and the results compared between investigators. If there was any disagreement between the two investigators (RK, AB), this was resolved by consensus discussion or referral to a third party (ARN).

The Principle Investigators (PIs) of each RCT that were identified for potential inclusion in the second meta-analysis were contacted for additional information; eg. to clarify ipsilateral stroke rates where these had been combined with late ipsilateral TIA. All PIs were then specifically asked to review their surveillance data in patients with a ‘restenosis >70%’ who
suffered a late ipsilateral stroke. This was in order to determine the severity of the restenosis in the treated ICA in the Duplex ultrasound (DUS) surveillance study that immediately preceded stroke onset. In that way, it was possible to determine whether a diagnosis of ‘restenosis >70%’ was made before or after stroke onset. Additional data (regarding restenosis severity prior to stroke onset) were provided from eight RCTs including four RCTs with surveillance after different types of patch closure (AF AbuRahma, AR Naylor) and four RCTs comparing CEA with CAS including; CREST (BK Lal), The Endarterectomy Versus Stenting in patients with Severe Symptomatic Stenosis (EVA-3S) trial (J-L Mas), the Stent Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial (P Ringleb) and the Regensburg RCT on CEA vs CAS (M Steinbauer)).

The Jadad score was used to assess the quality of the individual randomised controlled trials, based on three questions: (i) was the study described as randomized?; (ii) was the study described as double blind? and (iii) was there a description of withdrawals and dropouts?. To receive a point, the manuscript had to report the number of withdrawals and dropouts in each study group and the underlying reasons. Additional points were given if the method of randomisation was described in the paper and was deemed appropriate and if the method of blinding was described and considered appropriate. Points were deducted if the method of randomisation was described, but deemed inappropriate and where the method of blinding was described, but considered inappropriate. Accordingly, the Jadad score could range from 0 (lowest quality) to 5 (highest quality).

Statistical analyses were performed using the R package for Windows (version 3.0). Random and fixed effects meta-analyses were performed using the proportions of patients who experienced a restenosis >70% as the outcome of interest. Furthermore, Odds Ratios (OR) with 95% confidence intervals (CI) were calculated for each study to assess the association between restenosis >70% and late ipsilateral stroke for the duration of follow-up. Studies where there were no late ipsilateral strokes at all (irrespective of restenosis severity) were excluded from the second meta-analysis. For those RCTs where one subgroup (eg no restenosis) reported no recurrent strokes, while another subgroup (eg restenosis >70%) reported at least one late ipsilateral stroke, a fixed factor of 0.5 was added to cells of study results with zero strokes in order to calculate an appropriate odds ratio. This type of
continuity correction is a well-established approach to incorporate zero event studies and 0.5 is the commonest choice of correction factor\textsuperscript{10}.

ORs were then combined using meta-analysis (fixed and random effects models, where appropriate). Inter-study heterogeneity was analysed using the $I^2$ statistic. This describes the percentage of total variation across studies due to heterogeneity, rather than chance or random error and is a recognised method of quantifying heterogeneity in literature synthesis. An $I^2$ value greater than 50\% reflects significant heterogeneity owing to real differences in study populations, protocols, interventions and outcomes. Based on the result of the $I^2$ statistic, a fixed effects model was used to combine studies if $I^2$ was <50\% and a random effects model if $I^2$ was $\geq$50\%. A $p$ value of <0.05 was considered to be statistically significant.
Results

A total of 1562 reports were identified during the preliminary search and a further 327 records identified through other sources. After exclusion of duplicates, 1306 records were screened and 1253 excluded (figure 1). Fifty-three full text articles were assessed for eligibility, following which 42 were excluded. The main reasons for study exclusion were; absence of relevant end-point data (no surveillance undertaken, restenosis >70% rates not reported separately, no data regarding late ipsilateral stroke) (n=41), the full text was either a systematic review or a meta-analysis (n=7), more relevant or greater information was available in a more recent paper by the same authors/study group (n=5) or the full text was not an RCT upon reviewing the methodology (n=2). This left 11 RCTs for qualitative and quantitative analyses.

Table 1 details the Jadad score for each RCT, case numbers, number and type of CEA/CAS procedure, Duplex ultrasound (DUS) surveillance strategies for each RCT, DUS criteria used for diagnosing >70% restenosis, studies which reported how many of the cohort were lost to DUS surveillance during follow-up and whether or not data were provided on late ipsilateral stroke rates and stenosis severity in the surveillance scan prior to stroke onset. The only RCT that did not define DUS criteria to be used for diagnosing restenosis >70% was SPACE. In this multicentre German/Swiss/Austrian RCT, randomising centres used locally validated DUS criteria. In three RCTs, MR angiography or digital subtraction angiography was used for corroboration whenever a restenosis >70% was suspected on DUS.

Rates of restenosis >70% after CEA

Eleven RCTs (4249 patients) reported restenosis rates >70% or occlusion (table 2) after any type of CEA (eversion, traditional, patched, primarily closed). Over a median of 42 months, the prevalence of restenosis >70% or occlusion was 5.8% (95%CI 4.1-8.2). Five RCTs (n=1078 patients) reported restenosis rates >70% or occlusion following patched CEA. Over a median of 35 months, the prevalence of restenosis >70% or occlusion was 4.1% (95%CI 2.0-8.4). There was insufficient data to perform a meta-analysis on restenosis >70% in CEA patients undergoing eversion CEA or primarily closed CEA.
Rates of restenosis >70% after CAS

Six RCTs (2916 patients)\(^4\) reported that over a median follow-up of 44 months, the prevalence of restenosis >70% or occlusion in patients undergoing any sort of endovascular intervention (CAS, balloon angioplasty) was 10.3% (95%CI 6.0-16.4). Five RCTs (2716 patients)\(^4\,5\,7\,11\,16\) reported that over a median follow-up of 39 months, the prevalence of restenosis >70% or occlusion was 10.0% (95%CI 6.0-16.3) in patients undergoing CAS.

Restenosis >70% and late ipsilateral stroke

(i) following CAS

Four RCTs (table 3) reported rates of restenosis >70% or occlusion and late ipsilateral stroke in 1964 patients undergoing CAS (ie not including balloon angioplasty)\(^4\,5\,7\,16\). Over a median of 50 months surveillance, 1/125 (0.8%) of CAS patients with a restenosis >70% or occlusion suffered a late ipsilateral stroke, compared with 37/1839 (2.0%) of CAS patients who did not have a restenosis >70%. Using a fixed effects model (\(I^2=0\%\)), the OR was 0.87 (95%CI 0.24-3.21), \(p<0.8529\), \(I^2=0\%\). The resulting forest plot is detailed in figure 2.

If the meta-analysis was restricted to the 1932 patients randomised within the three largest RCTs (CREST, SPACE, EVA-3S)\(^4\,5\,7\) (figure 3), 1/119 (0.8%) of patients with a restenosis >70% or occlusion after CAS suffered a late ipsilateral stroke, compared to 36/1813 (2.0%) of CAS patients with no restenosis >70% (OR 0.81 (95%CI 0.19-3.41), \(p=0.6845\)). These data suggest that there is no compelling evidence that a restenosis >70% or occlusion after CAS is associated with a significant increase in the risk of late ipsilateral stroke.

(i) following CEA

Eight RCTs reported rates of restenosis >70% and/or occlusion and late ipsilateral stroke in 2839 patients undergoing any type of CEA (eversion/traditional; primary/patched)\(^4\,5\,7\,13\)-\(^17\). Steinbauer's RCT reported no restenoses/occlusions and no late ipsilateral strokes in 29 CEA patients\(^16\). Accordingly, the data from this RCT were excluded from the meta-analysis. Table 3 and figure 4 detail rates of restenosis >70% and/or occlusion and whether this was
associated with late ipsilateral stroke in the seven remaining RCTs (2810 patients) undergoing any type of CEA (eversion/traditional; primary/patched)\textsuperscript{4,5,7,13-15,17}. Over a median of 37 months surveillance, 13/141 (9.2\%) of CEA patients with a restenosis >70\% or occlusion suffered a late ipsilateral stroke, compared with 33/2669 (1.2\%) patients who did not have a restenosis >70\% or occlusion. Using a fixed effects model ($I^2 = 0\%$), the OR was 9.01\% (95\%CI 4.70-17.28), $p<0.0001$, $I^2=0\%$).

There was insufficient data to perform meaningful meta-analyses regarding the relationship between restenosis >70\% (or occlusion) and recurrent ipsilateral stroke in CEA patients undergoing patched repair, primary closure or eversion endarterectomy.

**How many CEA patients suffering a late ipsilateral stroke had a restenosis >70\% prior to stroke onset?**

The data in table 3 and figure 4 suggest that the presence of an untreated, asymptomatic restenosis >70\% (or occlusion) was associated with a significant increase in late ipsilateral stroke after CEA. However, the key question to be answered is exactly when the diagnosis of restenosis >70\% (or occlusion) was made. If it was made after stroke onset, then DUS surveillance could never prevent them. If, however, the asymptomatic >70\% restenosis was present before stroke onset, that would support a move towards DUS surveillance and reintervention after CEA.

Eight RCTs reported 13 late ipsilateral strokes in 141 patients with a restenosis >70\% or occlusion\textsuperscript{4,5,7,13-17} (table 4). The PIs were asked to review their surveillance data and indicate whether the diagnosis of restenosis >70\% or occlusion was made after stroke onset, or whether it was present at the DUS surveillance scan preceding stroke onset. The findings are detailed in table 4. In four RCTs\textsuperscript{4,5,13,14}, 0/S patients who suffered a late ipsilateral stroke had evidence of a restenosis >70\% in the DUS surveillance scan preceding stroke onset. In the Leicester patch trial, one of two patients destined to suffer a stroke had no evidence of a restenosis >70\% at the DUS surveillance scan preceding stroke onset\textsuperscript{15}. The remaining patient did. Paradoxically, his stroke followed a CAS procedure that was performed because he had very low middle cerebral artery velocities during carotid clamping (at the original
CEA), suggesting that he would not tolerate progression to occlusion. All of the six CREST patients who suffered a late ipsilateral stroke had an untreated, asymptomatic restenosis >70% at the DUS surveillance scan preceding stroke onset.

Accordingly, six of the thirteen patients who suffered a late ipsilateral stroke (and who were initially reported to have a restenosis >70% or occlusion at stroke onset) had NO evidence of any restenosis >70% at the last DUS scan preceding stroke onset (table 4); ie the diagnosis of restenosis >70% (or occlusion) was made after stroke onset in these six patients and not before. Accordingly, 7/135 patients (5.3%) with a previously asymptomatic, untreated restenosis >70% suffered a late ipsilateral stroke, compared with 40/2704 (1.5%) who did not have a restenosis >70% prior to stroke onset. When these data are factored into a revised meta-analysis (figure 5), the presence of an untreated asymptomatic restenosis >70% after CEA was still associated with a significant increase in the risk of late ipsilateral stroke (OR 4.77 (95%CI 2.29-9.92), p<0.0004).
**Discussion**

The management of symptomatic and asymptomatic carotid artery disease is one of the most scientifically scrutinised areas of modern vascular practice, aided greatly by the performance of numerous RCTs which have underpinned practice guidelines around the world. However, while it is accepted that patients developing a symptomatic 70-99% restenosis following CEA (or CAS) should be considered for reintervention, there is no consensus regarding the optimal management of asymptomatic 70-99% restenoses.

Restenoses tend to develop in the first 6-12 months after CEA and are usually due to neointimal hyperplasia. Lesions developing after 24-36 months have elapsed tend to represent a recurrence of the atherosclerotic process. Several European RCTs comparing CEA with CAS observed no statistically significant association between restenosis >70% after either CEA/CAS with an increased risk of late ipsilateral stroke. However, CREST reported that while a restenosis >70% after CAS was not associated with an increased risk of late ipsilateral stroke, a restenosis >70% after CEA was associated with a significantly higher risk of late ipsilateral stroke.

Why is this an important issue to resolve? In a recent meta-analysis on the management of restenosis after CEA, Fokkema observed that two-thirds of reinterventions were undertaken in patients with an asymptomatic restenosis after CEA, suggesting that many surgeons and interventionists were reluctant not to reintervene on asymptomatic stenoses. Notwithstanding the lack of corroborative evidence from the European RCTs, it is likely that the CREST data will lead to a more pro-active position (especially in North America) regarding reintervening in patients with >70% asymptomatic restenoses in the future.

The aim of the current systematic review and meta-analysis was to determine whether there was a significant association between restenosis >70% and late ipsilateral stroke. The advantage of using a meta-analysis of surveillance data derived from RCTs (as opposed to retrospective, observational studies) is that RCTs are prospective, they tend to be conducted with greater scientific rigour, selection bias is reduced because of the randomisation process and most endpoints tend to be adjudicated by independent physicians.
There were several important findings from the two meta-analyses. Firstly, the overall prevalence of ‘restenosis >70%’ was relatively low (6% for any type of CEA, 4% for patched CEA and 10% following CAS).

Second, the presence of an asymptomatic restenosis >70% following CAS did not appear to be associated with an increased risk of late ipsilateral stroke (table 3, figure 2). This lack of any association with increased stroke risk persisted when only the largest multi-centre RCTs (EVA-=3S, SPACE, CREST) were included in the meta-analysis (figure 3). This suggests that few (if any) CAS patients with significant asymptomatic restenoses will benefit from surveillance and reintervention, especially as emerging evidence suggests that reinterventions using CAS may confer no additional benefit over non-intervention. This is an important finding, as there has been much debate about how best to diagnose the severity of restenosis after CAS, as DUS criteria are quite different to those used to diagnose restenoses after CEA. This is because of the effect of the stented ICA on ultrasound haemodynamics. However, in the absence of any clear evidence that restenoses >70% after CAS are associated with an increased risk of late ipsilateral stroke, the debate about which criteria should be used to diagnose 70-99% restenoses after CAS becomes less clinically important.

The third important finding was that the presence of a ‘restenosis >70%’ or occlusion (after CEA) was associated with a significant increase in the risk of late ipsilateral stroke (OR 9.01 (95%CI 4.70-17.28). Figure 4 shows that each of the constituent RCTs were reporting broadly similar findings. However, the key issue to be determined (before advocating a more aggressive approach towards surveillance and reintervention after CEA), was to establish exactly when the diagnosis of ‘restenosis >70%’ was made. If the diagnosis was made before the patient suffered their ipsilateral stroke, the findings of the current meta-analysis assume considerable importance and will greatly influence future recommendations regarding imaging surveillance and treatment strategies after CEA. If, however, the diagnosis of restenosis >70% was usually made after the patient had suffered their ipsilateral stroke (ie it was not present at the preceding surveillance study), the evidence for surveillance and reintervention would become much less compelling. It has previously been shown in asymptomatic patients (with primary atherosclerotic disease) who were in DUS surveillance,
that while disease progression was often associated with onset of TIA or stroke, in at least 50% of cases, this happened at the time of the event, rather than being evident at the surveillance scan preceding stroke onset.

Accordingly, the PIs of the eight RCTs provided additional information on the status of the operated ICA prior to stroke onset. Out of 13 strokes associated with a ‘restenosis >70%’ or occlusion at the time of stroke onset (table 4), six (46%) did not have DUS evidence of a restenosis >70% at the surveillance scan prior to the patient suffering their stroke (i.e., no DUS surveillance programme could have prevented their stroke). However, even after excluding these patients, a further meta-analysis (figure 5) still found that the presence of an untreated, asymptomatic restenosis >70% after CEA was associated with a significant increase in the risk of late ipsilateral stroke (OR 4.77 (95%CI 2.29-9.92).

There are a number of limitations with this meta-analysis. First; is the lack of standardisation regarding what is considered to be a significant restenosis. A threshold of 70% was selected as few surgeons and interventionists would recommend reintervening in patients with asymptomatic 50-69% restenoses and few RCTs provide any data on the outcome of patients with untreated restenoses >80%. Second; are the criteria for making a diagnosis of ‘restenosis >70%’. Most (if not all) will have been made by ultrasound (rather than angiography), and ultrasound-based criteria differ between CEA and CAS. Table 1 details the various DUS criteria used in the constituent RCTs for diagnosing a ‘restenosis >70%’. In only one RCT (SPACE) was there no guidance on what criteria should be used. In this study, randomising centres were instructed to use locally validated DUS criteria. In three of nine RCTs, anyone suspected of having a ‘restenosis >70%’ on DUS surveillance underwent corroborative MRA or digital subtraction angiography. For the purposes of this meta-analysis, it had to be assumed that any diagnosis of ‘restenosis >70%’ was correct. Third; a number of other RCTs did not provide additional data regarding restenosis rates and recurrent ipsilateral stroke, despite communication with the various PIs. Had these been available for inclusion, the meta-analyses would have contained more patients. Fourth; it was not possible to determine whether the method of CEA (eversion vs traditional) or the mode of arteriotomy closure (primary vs patched) influenced restenosis rates and late
ipsilateral stroke rates, as this was rarely provided as separate data. Most of the large RCTs combined all CEA patients together.

So what is the clinical relevance of the findings from this meta-analysis? First, there appears to be no compelling evidence that CAS patients benefit from entering a post-procedure DUS surveillance programme, as the risk of late ipsilateral stroke is extremely low (<1%) in CAS patients with a restenosis >70%. In the meta-analysis, 97% of all late ipsilateral strokes occurred in the cohort of 1839 CAS patients who had no evidence of a significant restenosis (table 3).

Using data from table 2, about 4% of patients undergoing a patched CEA will develop a restenosis >70% over about 36 months follow-up. This means that approximately 2500 patched CEA patients would need to undergo serial DUS surveillance in order to identify 100 patients with an asymptomatic restenosis >70%. Using the revised data from table 4, the presence of an untreated, asymptomatic restenosis >70% would be associated with a 5% risk of late ipsilateral stroke. If one assumes that all would benefit from reintervention, 5 strokes might be prevented by redo CEA or CAS. However, 95 would ultimately undergo an unnecessary reintervention and two of the 100 would suffer a peri-operative stroke following either CAS or redo CEA and about 5% would suffer a cranial nerve injury after redo CEA. In effect, such a strategy could only ever prevent about 3 ipsilateral strokes in the long-term. Moreover, despite DUS surveillance, 85% of all late ipsilateral strokes would still occur in patients with no evidence of a restenosis >70% (table 4).

In summary, this meta-analysis found no evidence that a restenosis >70% after CAS was associated with an increased risk of late ipsilateral stroke, suggesting that DUS surveillance offers little additional benefit to the patient. While the presence of a restenosis >70% after CEA was associated with a significant increase in late ipsilateral stroke, the actual benefits from reintervening (in terms of strokes prevented) were relatively modest and would not prevent the vast majority of late ipsilateral strokes from occurring, again casting doubt on the potential benefit of any DUS surveillance programme in CEA patients.
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Captions to figures

Figure 1
PRISMA Flow Diagram

Figure 2
Forest plot depicting the relationship between restenosis >70% (or occlusion) or no restenosis >70% after carotid artery stenting and the risk of late ipsilateral stroke in all RCTs.

Figure 3
Forest plot depicting the relationship between restenosis >70% (or occlusion) or no restenosis >70% after carotid artery stenting and the risk of late ipsilateral stroke in CREST, ICSS and EVA-3S.

Figure 4
Forest plot depicting the relationship between restenosis >70% (or occlusion) or no restenosis >70% after carotid endarterectomy and the risk of late ipsilateral stroke all RCTs.

Figure 5
Forest plot depicting the relationship between restenosis >70% (or occlusion) or no restenosis >70% after carotid endarterectomy and the risk of late ipsilateral stroke in patients who did (or did not) have an untreated asymptomatic restenosis >70% or occlusion prior to stroke onset.
References


