Carotid Recurrent Stenosis and Risk of Ipsilateral Stroke
A Systematic Review of the Literature

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Background—The main goal of follow-up after carotid endarterectomy is to prevent new strokes caused by recurrent stenosis. To determine the most cost-effective follow-up schedule, it is necessary to know the incidence of recurrent stenosis and the risk of stroke it carries.

Methods—A systematic review of the literature was performed using standard meta-analytical techniques.

Results—Incidence of recurrent stenosis: The data were very heterogeneous. The risk of recurrent stenosis was 10% in the first year, 3% in the second, and 2% in the third. Long-term risk of recurrent stenosis is about 1% per year. Risk of stroke: The reported relative risks of stroke in patients with recurrent stenosis compared with patients without recurrent stenosis showed extreme heterogeneity and ranged from 10 to 0.10. The random effects summary estimator of relative risk was 1.88.

Conclusions—The data were very heterogeneous, and much better data are needed to arrive at truly reliable estimates of these important parameters of follow-up. It is clear, though, that the risk of recurrent stenosis is highest in the first few years after carotid endarterectomy and very low in later years. By use of general decision-analytic arguments, it can be argued that, given the test characteristics of carotid ultrasound, a small number of tests can be done in the first few years and that testing for restenosis should not be done after 4 years. (Stroke. 1998;29:244-250.)

Key Words: carotid artery ■ carotid endarterectomy ■ carotid stenosis ■ follow-up studies

Many vascular surgeons and neurologists prefer to follow up their patients after carotid endarterectomy because they assume that (1) a considerable number of patients will develop restenosis and (2) restenosis increases the risk of ipsilateral stroke. There is, however, little consensus on the best follow-up schedule, mainly because reported restenosis rates and associated ipsilateral stroke risks vary widely. Although there is little consensus as yet, we believe that important trends will require a more uniform follow-up policy in the future. First, the results of the ECST,1 the NASCET,2 and the ACAS3 will generate a steady inflow of patients into vascular follow-up programs, especially in the aging Western populations. Second, insurance companies and governments will demand more cost-effective health care and will take measures to cut spending while maintaining quality of care. These trends will sooner or later spur vascular surgeons and neurologists to develop cost-effective follow-up schedules that offer the greatest medical benefit at a reasonable cost. The most pivotal medical factors in determining a cost-effective follow-up schedule are the restenosis rate after carotid endarterectomy and its associated risk of ipsilateral stroke. In this article we present a systematic review of restenosis and ipsilateral stroke rates published since noninvasive diagnostic techniques became widely available.

Methods

Literature Search and Inclusion Criteria

We searched for articles by running the query “(carotid surgery or carotid endarterectomy)” and (restenosis or recurrent adj5 stenosis)” on the MEDLINE database.7 We purposely chose this highly specific query to minimize the risk of false-positive hits. To find any articles we might have missed, we ran the highly sensitive but less specific query “carotid surgery endarterectomy restenosis recurrent stenosis” on a MEDLINE implementation that uses fuzzy search algorithms.7 The abstract of each article was carefully studied, and if there was any suggestion of the data we looked for, the full text was retrieved. If an article contained data on restenosis and ipsilateral stroke risk, its reference section was checked for further leads.

Articles were included if (1) they were published in 1985 or later, (2) they reported on long-term follow-up of 100 patients or more, (3) the operation carried out was carotid endarterectomy with direct or patch closure, (4) restenosis was defined as a 50% stenosis of the operated artery, (5) patients were followed up with noninvasive diagnostic techniques, (6) follow-up was systematic and not just in case of symptoms, and (7) they were written in English. Articles were excluded if (1) they reported on asymptomatic patients only, (2) they reported on combined coronary and carotid surgery only, (3) only external carotid endarterectomies were performed, and (4) the carotid bifurcation was completely resected and replaced by a graft.

Four variables were considered essential for determining the incidence of restenosis: (1) the number of patients or arteries at risk, (2) the number of patients or arteries with restenosis, (3) the average follow-up time, and (4) the definition of restenosis. Articles that met the inclusion criteria, but in which one or more of these essential variables were missing, were coded as “not evaluable.” We carefully excluded articles that reported on patients whose data were already used in another article from the same institution, except when the methods sections made it absolutely clear that the patients did not overlap. In case of multiple publications, we chose the one most appropriate to this review, preferably the most recent. We included only recent articles because we wanted to make sure that modern noninvasive
Selected Abbreviations and Acronyms

ACAS = Asymptomatic Carotid Atherosclerosis Study
ECST = European Carotid Surgery Trial
NASCET = North American Symptomatic Carotid Endarterectomy Trial

Data Extraction

Data were extracted by use of a predefined data sheet. If present, the following variables were extracted: (1) general—year of publication, number of patients, institution; (2) patient characteristics—sex and mean age; (3) risk indicators—hypertension, smoking, diabetes, hyperlipidemia, coronary artery disease; (4) indication for operation—asymptomatic, transient ischemic attack/amaurosis fugax stroke; (5) ipsilateral stroke events—fatal and nonfatal, perioperative and late; (6) restenosis events—number of patients or arteries at risk, number of patients or arteries with restenosis, average follow-up time, definition of restenosis; (7) risk of ipsilateral stroke in patients with restenosis—2x2 table of ipsilateral stroke by restenosis; (8) screening characteristics—diagnostic technique used; and (9) surgical technique—use of patch angioplasty. The data were extracted by the first author and checked by one of the other authors.

Data Analysis

Data analysis had two goals: (1) to construct a summary curve of the cumulative incidence of restenosis after carotid endarterectomy, and (2) to derive a summary value of the relative risk of ipsilateral stroke in patients with restenosis compared with patients without restenosis.

Because most studies report that the rate of restenosis is not constant over time, we tried to construct the summary incidence curve by combining data from life table analyses of restenosis rates. However, because only a few articles presented life table data in tabular form, we chose a different approach and plotted the proportion of patients or arteries who had developed restenosis against the average follow-up time. If the incidence rate is constant, these points should lie on a straight line through the origin with a slope equal to the incidence per time. If the incidence rate is constant over time, the points should lie on a curved line that is given (approximately) by the cumulative incidence (or hazard) with cumulative incidence proportional to time. If the incidence rate is not constant, these points should lie on a curved line that is given (approximately) by the cumulative incidence (or hazard) in more statistical terms. A generalization of the constant incidence (or hazard) with cumulative incidence proportional to time is given by the Weibull model, in which the cumulative incidence is modeled as \( \alpha t^\beta \). Despite the great heterogeneity, we fitted such a Weibull model to get an impression of the decreasing incidence rate over time. We used the nonlinear regression module of SPSS-7, taking the sample sizes at risk as weights. The summary value for the relative risk of ipsilateral stroke in patients with restenosis was determined by calculating the weighted sum of the relative risks of the individual studies using Mantel-Haenszel–type weights and maximum likelihood inverse variance weights. We used the odds ratio as an estimate of the relative risk because of computational advantages and low event rates. All results were tested for heterogeneity. If heterogeneity was present, we followed Greenland’s recommendations\(^7\) and carefully looked for variables that could “explain” the interstudy variation in a clinically plausible way. If we succeeded in constructing a homogeneous model, we used its resulting summary estimate. If no homogeneous model could be obtained, we calculated a random-effects summary estimator as described by DerSimonian and Laird.\(^8\) Calculations were done on a personal computer using Excel spreadsheet software,\(^9\) and SPSS,\(^10\) and Egret\(^11\) statistical software.

Results

The literature search resulted in 57 articles that met the inclusion criteria.\(^14–70\) Of these, 8 articles\(^43–50\) were excluded because they reported on patients already used in other publications from the same institution: Bandiyk et al\(^41\) was excluded in favor of Kinney et al\(^51\); Callow et al\(^44\) and O’Donnell et al\(^52\) were excluded in favor of Mackey et al\(^53\); De Letter et al\(^45\) and Eikelboom et al\(^54\) were excluded in favor of Ten Holter et al\(^51\); and Healy et al\(^57\) was excluded in favor of Healy et al.\(^24\)

Another 20 articles\(^51–70\) were excluded because one or more essential variables were missing: in 14 articles,\(^*\) the definition of restenosis was either not given or different from 50%; in 5 articles,\(^26,28,30,50\) the average follow-up time was not specified; and in 1 article,\(^32\) the number of restenoses was not clear. The main points of the remaining 29 articles\(^44–42\) that met all the requirements are summarized in Table 1.

Cumulative Incidence of Restenosis

The Figure shows a plot of the cumulative incidence of restenosis against average follow-up time. On inspection, the data show enormous heterogeneity, which is confirmed by formal statistical tests that show \( x^2 \) values in excess of 300 at 28 degrees of freedom.

We carefully studied each article for medical and epidemiological factors that might explain heterogeneity, but unfortunately only five variables were present in 20 or more of the 29 studies: publication year, mean age, percentage men, percentage asymptomatic patients, and percentage patch closure. Of these, only mean age and percentage patch closure were statistically significant (\( P<.001 \)); increasing mean age was associated with a higher risk of ipsilateral stroke, and increasing percentage patch closure with a lower risk. Although they were statistically significant, these two variables did not have an appreciable impact on \( x^2 \) scores for heterogeneity. Outside of the five variables present in 20 or more studies, no other variables were tested because there would have been too many missing cases.

The cumulative Weibull incidence curve (CI(t)) fitted to the data in Fig 1 is given by CI(t) = 0.0864x^0.03. The corresponding risk of restenosis in a certain year for somebody who has not experienced restenosis before is given by 1 – exp(-CI(t)), with CI equal to the increase in CI during that year. Numerical results are given in Table 2.

The curve rises steeply to a cumulative incidence of about 10% at 1 year and then gradually flattens to about 20% at 10 years. The yearly risk of restenosis is by far the greatest in the first year: about 10%. After the first year the risk is much lower, about 3% in the second year, 2% in the third and fourth years, and then gradually diminishing further until in the long run it stabilizes at about 1% per year. When the five most extreme outliers, Healy et al,\(^24\) Keagy et al,\(^56\) Rosenthal et al,\(^57\) Kierry et

\(*\)References 51, 53–58, 60, 61, 64, 65, 67–69.
Relative Risk of Ipsilateral Stroke in Patients With Restenosis

Of the 57 articles, 12 provided ipsilateral stroke rates for both patients with and without restenosis, allowing calculation of within-study relative risks. The studies by Nicholls et al. and O’Donnell et al. were excluded because their data were already used in Healy et al. and Mackey et al., respectively. The main points of the remaining 10 articles are summarized in Table 3.

It is clear from Table 3 that there are only very few ipsilateral strokes. In the restenosis group, only one study has more than five events, and no less than three studies have no events at all. In the no restenosis group, only three studies have more than 10 events, and five studied have fewer than 5 events. Only the study by Hansen et al. has a reasonable number of events in both groups.

The odds ratios vary widely, roughly ranging from 1:10 to 10:1, again showing extreme heterogeneity. There are only two studies, Healy et al. and Kinney et al., in which the 95% confidence interval does not include 1. All other studies have wide confidence intervals including 1.

We calculated several commonly used summary estimators of relative risk. The standard Mantel-Haenszel exact summary odds ratio is 0.95 (95% confidence interval, 0.54–1.61). The associated $\chi^2$ test for heterogeneity is 37.2 ($8 \text{ df}, P<0.001$), which confirms the impression of extreme heterogeneity gained from the table. We also calculated a summary estimator using maximum likelihood estimates of variance. Its value is 1.61 (95% confidence interval, 0.95–2.72), and the associated $\chi^2$ test for heterogeneity is 23.8 ($8 \text{ df}, P<0.01$). The DerSimonian-Laird random effects estimator is 1.88 (95% confidence interval, 1.33–2.61).

### Table 3. Main Points of 29 Studies Reporting Incidence of Restenosis After Carotid Endarterectomy

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*References 17, 18, 22, 24, 28, 29, 32, 33, 37, 42, 49, 50.
interval, 0.71–4.98). χ² tests for heterogeneity are not done when this method is used because heterogeneity is already accounted for in the summary estimate and its confidence interval.

### Discussion

Three state-of-the-art, large-scale clinical trials have now clearly established the value of carotid endarterectomy in both symptomatic and asymptomatic patients. Although some debate on the indications for operation will continue, especially in asymptomatic patients, it is certain that carotid endarterectomy will take its place as a widely accepted surgical procedure for a number of indications. It is equally certain that the number of carotid endarterectomies carried out will be considerable, although it is hard to make exact predictions. This acceptance will raise the question of what to do with the patient after the operation: intensive follow-up, limited follow-up, or no follow-up at all? So far, there seems to be a tacit consensus that some form of follow-up is necessary, motivated by the assumptions that patients may develop restenosis and that restenosis increases the risk of ipsilateral stroke. There were, however, only very few articles that directly study both assumptions, most notably Healy et al., Mackey et al., and Mattos et al. Of these three, only Mackey and Mattos study the effectiveness of follow-up, both raising doubts about its value. Most other authors in this review were primarily interested in the occurrence of restenosis and its relation to surgical technique, intraoperative detection of residual disease, cardiovascular risk indicators, and medical treatment.

In most Western countries, governments, insurance companies, and Health Maintenance Organizations are expected to demand more cost-effective health care. We believe that only two retrospective studies on follow-up after carotid endarterectomy will be insufficient evidence to meet these demands. For this reason, we did a systematic review of the literature, hoping to obtain good estimates of the two most important medical factors involved in follow-up: the rate of restenosis and the risk of ipsilateral stroke once restenosis has developed. Of some 500 articles studied, only 29 contained evaluable data on the rate of restenosis in 100 or more patients. Because the risk of restenosis varies with time, we plotted the cumulative incidence of restenosis against the average follow-up time. Several authors, in comparing restenosis rates from various studies, have failed to do this, thereby introducing an important bias in their conclusions.

We preferred not to use the person-years of follow-up method because it leaves valuable information in the data unused. The person-years method is the ratio of the number of events and the total number of follow-up years. The resulting number is a uniform value for the entire follow-up period and so does not indicate whether the risk varies with time. If we plot the number of events against the average follow-up time, variations of the risk over time become immediately clear. The resulting graph shows discouraging heterogeneity: for studies with an average follow-up time between 2 and 3 years, for example, the reported cumulative incidence ranges between 1.9% and 22.1%. Formal statistical tests showed χ² values in excess of 300 at 2 df. In general, most data analysts will consider 1 to 2 χ² points per df a good indication of homogeneity. Ten points per df is extreme and usually means that it will not be possible to deal with heterogeneity in a satisfactory way. When we tried to explain heterogeneity, we were greatly impeded by the scarcity of relevant study characteristics. Only five characteristics were present in 20 or more studies. Moreover, important characteristics such as average number of follow-up investigations per patient, definition of stroke, stroke ascertainment, exact technical definition of 50% stenosis, etc., were often absent altogether. Nevertheless, we believe the Weibull summary curve we constructed is reasonably accurate. First, it agrees with the common clinical observation that the rate of restenosis is much higher in the first few years and decreases over time. Second, the shape of the curve coincides remarkably with five of the largest studies in which graphical curves were published. Third, the curve is unaffected by outlier removal. Fourth, the heterogeneity in the first few years may well be caused by commonly observed regression of intimal hyperplasia. Because this lesion may quickly develop and regress, the exact timing of noninvasive testing may to a large extent determine the observed rate of

### TABLE 2. Life Table of Cumulative Incidence of Carotid Restenosis Associated With the Fitted Weibull Curve in the Figure

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<td>.152</td>
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</table>

CI indicates confidence interval.

*Limited to first 100 cases.
Table 3. Summary of 10 Studies Reporting Incidence of Ipsilateral and Contralateral Stroke in Relation to Restenosis After Carotid Endarterectomy*

<table>
<thead>
<tr>
<th>Study (1st author)</th>
<th>Year of Publication</th>
<th>Ipsilateral Stroke</th>
<th>No Ipsilateral Stroke</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
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<tr>
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<td>12</td>
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<tr>
<td>Cuming18</td>
<td>1993</td>
<td>0</td>
<td>18</td>
<td>ND</td>
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<tr>
<td>Hansen22</td>
<td>1993</td>
<td>8</td>
<td>85</td>
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<td>Healy14</td>
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<td>76</td>
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<td>Kinney15</td>
<td>1993</td>
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<td>32</td>
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<td>1.68-101.4</td>
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<td>Mackey29</td>
<td>1992</td>
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<td>Mattos32</td>
<td>1993</td>
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<td>Ouriel33</td>
<td>1987</td>
<td>0</td>
<td>17</td>
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<td>Rosenthal37</td>
<td>1990</td>
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<td>22</td>
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<tr>
<td>Zbornikova42</td>
<td>1986</td>
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<td>24</td>
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Mantel-Haenszel summary estimator (95% CI) 0.95 0.54-1.61
Maximum likelihood summary estimator (95% CI) 1.61 0.95-2.72
DerSimonian-Laird random effects summary estimator (95% CI) 1.88 0.71-4.98

* ND, not determined; CI, confidence interval.

Carotid Restenosis and Risk of Stroke

Restenosis. We therefore see the summary curve as a useful instrument in thinking about follow-up schedules. However, we are well aware that the incidence of stroke after carotid endarterectomy is low and that restenosis in itself is only one of the factors that influence the odds of stroke as patients may suffer stroke from other causes than restenosis.

Ten studies provided evaluable data on the relative risk of ipsilateral stroke in patients with restenosis compared with patients without restenosis. Because of the heterogeneity between results of studies, it is imperative that ipsilateral stroke rates for patients with and without restenosis are compared only within studies. Several authors have compared stroke rates between studies, but we believe this introduces biases that make the resulting figures uninterpretable. These ten studies, too, showed great heterogeneity, their odds ratios ranging from roughly 1:10 to 10:1. The small numbers of events complicate matters further because they destabilize the odds ratios—a few events more or less may cause dramatic changes—and are associated with wide confidence intervals and low statistical power. In addition, they make heterogeneity much harder to deal with, because they may be the single cause of it or there may be other causes involved. Unfortunately, the other causes cannot be dealt with until more events are available. Under these circumstances, the results of any statistical analysis of these data must be approached with caution, and we felt uncomfortable in presenting overall summary estimators. We did so only for the benefit of the reader who wishes to know them. We do not encourage that they be used in patient care. In theory, the Mantel-Haenszel and inverse variance weighted estimators should not be too far apart. The abnormal difference found here, 0.95 versus 1.61, should be attributed to extreme heterogeneity. The DerSimonian-Laird random effects summary estimator, which in recent years has become a popular method to deal with “unexplained” heterogeneity, showed a moderately increased overall odds ratio of 1.88. But considering the extreme heterogeneity and low event rates, we think it is better to accept the simple fact that, as yet, there is no scientific evidence for any conclusion about the relative risk. In the absence of harder evidence, the literature shows that many vascular surgeons reason by analogy. They assume that the secondary lesions of intimal hyperplasia and recurrent atherosclerosis carry the same increased risk of obstructive and thromboembolic ischemia as primary obstructive and atherosclerotic lesions. Until more reliable data are available, this reasoning by analogy is probably a safe way to go.

If this review has shown one thing, it is that to develop better follow-up schedules, better data are needed. First of all, a clear and uniform definition of restenosis is necessary, both for angiographic and ultrasound examination. Second, if restenosis rates are to be compared between studies, identical follow-up schedules should be used to prevent timing biases caused by benign hyperplastic lesions that quickly develop and regress. Third, it is absolutely necessary that studies use identical definitions and detection methods for ipsilateral stroke. Fourth, more ipsilateral stroke events are needed for a reliable estimate of the relative risk of stroke in patients with restenosis. For example, assuming a relative risk of 2 and using the event rates from Table 3, a series of 1500 patients or more is needed to obtain numerically stable and statistically significant estimates of relative risk. Fifth, and last, uniform standards for the pathological classification of restenosis are necessary to assess whether early hyperplasia and late atherosclerosis have different risks of ipsilateral stroke. Despite the weaknesses in the data, it is possible to make a few important points on follow-up using general decision analytic principles. In doing this we have made five assumptions: (1) the incidence curve constructed in this review is reasonably accurate; (2) the relative risk of ipsilateral stroke in patients with restenosis is moderately increased, say 2.0; (3) in the first 2 years restenosis is caused by largely benign, obstructive intimal hyperplasia that...
may quickly develop and regress; (4) in later years restenosis is caused by recurrent atherosclerosis that may give rise to thromboembolic ischemia; and (5) the sensitivity and specificity of ultrasound examination for a 50% stenosis of the carotid artery are 91% and 87%, respectively.

In the first 2 years, then, approximately 10% of patients develop restenosis. If one ultrasound test is done at the end of this period, 9% of all patients will be true-positive and 12% will be false-positive. If more tests are done in between, the prevalence of restenosis and the number of true-positives will be lower and the number of false-positives will be higher. In short, more frequent testing will cause larger numbers of false-positive patients and not necessarily increase the number of true-positives. Given the benign nature of the stenotic lesion in this period and the possibility of regression, we have decided to test only twice at our institution: after 1 year and after 2 years. In later years, recurrent atherosclerosis will occur in 1% to 2% of patients per year. Because this lesion is more dangerous, it may be more important to detect it. Unfortunately, the low prevalence makes for even higher numbers of false-positive tests than in the first 2 years. Without a full cost-effectiveness study, it is hard to find a balance between the harm done by missing dangerous restenoses and the discomfort caused by false-positive tests. Untill such a study is available, we recommend that ultrasound testing for restenosis be done sparingly.

**Acknowledgments**

The authors thank Prof Hans van Houwelingen and Dr Koos Zwinderman for statistical guidance.

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Carotid Restenosis and Risk of Stroke


Carotid Recurrent Stenosis and Risk of Ipsilateral Stroke: A Systematic Review of the Literature

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Stroke. 1998;29:244-250
doi: 10.1161/01.STR.29.1.244
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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