Risk of late stroke and survival following carotid endarterectomy procedures for symptomatic patients

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The long-term outcome following carotid endarterectomy for neurological symptoms was analyzed using a retrospective life-table approach in 212 patients who had undergone 243 endarterectomy procedures. The postoperative follow-up period averaged 38.9 ± 2.1 months (mean ± standard error of the mean). The endpoints of stroke and death were evaluated in these patients. Patient groups with the preoperative symptoms of amaurosis fugax, transient ischemic attack, and prior recovered stroke were similar in terms of life-table outcome over the follow-up period. Sixty-two percent of symptomatic patients were alive and free of stroke at 5 years. The late risk of stroke (after 30 days postoperatively) averaged 1.7% per year based on a linear approximation to the hazard at each life-table interval (1.3% per year for ipsilateral stroke). The trend of late stroke risk was clearly downward, however, and could be fitted more accurately by an exponential decay function with a half-life of 33 months. Thus, the risk of stroke following carotid endarterectomy for neurological symptoms was highest in the perioperative period, slowly declined with time, and occurred predominantly ipsilateral to the procedure.

The definition of a prospective medical control group remains crucial for a critical analysis of treatment modalities following the onset of premonitory neurological symptoms. In the absence of an adequate control group for this series, the calculated perioperative and postoperative stroke risk from this study was compared to data obtained from the literature on stroke risk in medically treated symptomatic patients. This uncontrolled comparison of treatment modalities suggests the combined perioperative and postoperative stroke risk associated with carotid endarterectomy to be modestly improved over medical treatment alone.

KEY WORDS • carotid endarterectomy • stroke • transient ischemic attack • amaurosis fugax • survival analysis

The incidence of stroke and death after a premonitory neurological symptom and the role of carotid endarterectomy in altering the subsequent risk of these events occurring remain highly controversial.1-9,12,13,15,16,19-21,23,24,26,28,31,33-35 Although the short-term (30-day perioperative or inpatient) risks following carotid endarterectomy have been well documented and highly debated, the long-term risks of stroke and death after surgery have been investigated less frequently, particularly with a life-table analysis.5,3,3,7,15,20,23,24,26,31,33-35 The hypothesis underlying carotid endarterectomy suggests that the procedure reduces the long-term risk of stroke by the physical removal of the offending plaque. However, the comparative risk of stroke and death in similar patients without surgery has been analyzed in only a few reports.4,9,26 In addition to the short-term risks from carotid endarterectomy, an analysis of the long-term benefits and risks may be very important in determining the overall advantage to be gained from carotid endarterectomy as an alternative to other medical therapies such as administration of aspirin. Thus, an improvement in prevention of either stroke or death over a period of years may be decisive in choosing one therapy over another.3,11,13,17,33,34,38

Whisnant, et al.,35 reported a yearly stroke risk after carotid endarterectomy of approximately 2% in patients presenting with transient ischemic attacks (TIA's), with the majority of the strokes occurring ipsilaterally. However, the patients in that series exhibited only a slightly higher mortality rate than what might be expected for a control population of the same age and sex: 80% survival at 6 years, compared to an expected normal 6-year survival rate of 84%. Other studies have also examined the late risk of stroke after carotid endarterectomy for neurological symptoms, but the results are often not clear in terms of the timing of stroke and the relative hazard of its occurrence at different time per-
iods after the procedure. Thus, it is of considerable interest to compare the results reported by Whisnant, et al., with those of a series of symptomatic patients followed at a Veterans Administration (VA) hospital, who demonstrate significantly higher systemic morbidity and mortality rates in general. Other series in which long-term outcome following carotid endarterectomy was studied were not as specific as to patient populations and thus are not as easy to interpret. The early joint study of extracranial arterial occlusion presented the risk of late stroke after carotid endarterectomy as approximately 1.15% per year, but the timing and laterality of these strokes were not well defined. Estimates of the yearly risk of stroke in the late postoperative period (after 30 days) have ranged from 1.15% to 4.5%. However, it is not clear from some of these reports how this risk varies as a function of time after surgery, and what other variables such as medical and neurological risks may be involved.

This study presents the long-term follow-up data on 212 patients who underwent carotid endarterectomy for neurological symptoms, including ipsilateral amaurosis fugax, TIA, or mild completed stroke with minimally disabling residual deficit. The patients were categorized by the time of late stroke and laterality, and the incidence of stroke and death is presented in terms of a series of life-tables of patient outcome. Calculation of interval hazards from the life-table outcome of patients who are alive and free of stroke permitted the estimation of the risk of late stroke as a function of time after surgery.

Clinical Material and Methods

Patient Review and Follow-Up Methods

The records of patients who had undergone a carotid endarterectomy procedure at the Minneapolis VA Hospital during the years 1978 through 1985 were analyzed retrospectively. These reviews included the preoperative medical, angiographic, and neurological risk factors, the clinical rationale for the procedure, and the immediate and late postoperative outcome. The usual indications for carotid endarterectomy included a preoperative neurological symptom (such as amaurosis fugax, TIA, or prolonged reversible ischemic neurological deficit (PRIND)) in combination with a stenosis of the ipsilateral internal carotid artery (ICA) greater than 75% to 80%. Ulceration or other irregularity of the internal lumen of the ICA on the angiogram was also considered as a factor in the surgical decision-making process, but mainly in concert with a luminal stenosis of high degree.

A few patients exhibited either progressive stenosis on serial angiography or a severe lesion contralateral to the symptomatic side. Carotid endarterectomy was also occasionally performed in this small group of asymptomatic patients, but this group is not considered in detail in this report.

The perioperative information on patients was updated by examination on subsequent clinic visits. If a question arose as to the presence or absence of a stroke, patients were subjected to repeat examination as part of their regular clinical follow-up monitoring, whenever possible.

The perioperative (within 30 days of the procedure) and late occurrence of stroke and/or death were evaluated in these patients. The cause of death was defined whenever possible and was known in 70% of cases. Patients with limited follow-up data were considered as censored for the life-table analysis, with the censored endpoint being the last known follow-up contact. All patients with signs or symptoms suggestive of completed stroke were subsequently examined and categorized as to the laterality of the stroke and etiology, whenever possible; this examination often included a repeat angiographic evaluation.

Anesthetic and Surgical Technique

The carotid endarterectomy procedures were supervised closely by the clinical staff, and the technical aspects of the surgery were fairly standardized. A majority (52%) of patients were operated on under regional anesthesia in an attempt to reduce the medical risks of the procedure, particularly cardiac sequelae. Neurological monitoring was greatly enhanced by the use of local anesthesia, especially in patients in unstable condition with fluctuating blood pressures or a tenuous cardiac status. Electroencephalographic monitoring was performed for many of the procedures carried out under general anesthesia. Arterial shunts and patch grafts were used selectively as required.

Data Analysis

Patients were initially separated on the basis of the clinical rationale for surgery into several groups; these included asymptomatic patients and those suffering from amaurosis fugax, hemispheric TIA’s, and prior completed stroke (PRIND) in whom recovery to an excellent functional grade was required before evaluation and surgery. The outcome in each patient was characterized with a series of life-table curves for each endpoint of stroke or death. Kaplan-Meier statistics were used for evaluation of the life-tables and for statistical comparison between subgroups. Confidence intervals around the Kaplan-Meier estimates were constructed from the standard errors of the mean (SEM) and the number of patients at risk for that time interval. The occurrence of late postoperative stroke was approximated both with a linear regression and an exponential regression of the stroke hazard at each life-table interval.

Results

Perioperative Outcome and Risk Factors

This study incorporated data on 212 symptomatic patients who had undergone 243 carotid endarterectomy procedures. All patients except one were men,
Long-term outcome after carotid endarterectomy

TABLE 1
Preoperative risk factors in 212 symptomatic patients

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>active or previous hypertension</td>
<td>59</td>
</tr>
<tr>
<td>organic heart disease (history, examination, or test)</td>
<td>76</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>28</td>
</tr>
<tr>
<td>advanced age (&gt; 70 yrs)</td>
<td>15</td>
</tr>
<tr>
<td>cerebral hemisphere insult (history, examination, or test)</td>
<td>49</td>
</tr>
</tbody>
</table>

and the mean age was 63 years. Neither immediate nor late follow-up data were available on an additional 22 patients identified from operating-room records, because their charts were permanently lost or the patients had moved to another VA region. None of these 22 patients required an immediate second carotid endarterectomy or embolectomy, and none was known to have died in the perioperative period; however, further information on the outcome of this group was not available. An additional 23 patients without preoperative neurological symptoms also underwent carotid endarterectomy during the study period, but these asymptomatic patients are not considered further. Table 1 defines the preoperative risk factors for the 212 symptomatic patients.

The perioperative complications (within 30 days following surgery) showed a stroke risk rate of 4.9% related to the procedure and a 2.1% procedure mortality rate. The perioperative complication rate declined over the years 1978 through 1985, with audits for 1984 and 1985 showing a 4% total stroke morbidity and death rate. A multiplicity of medical, angiographic, and surgical risk factors was often present. The patients were grouped according to the risk factor elements presented by Sundt, et al., with the majority of patients in either Grades III or IV.

Table 2 shows the preoperative indications for carotid endarterectomy in the 212 symptomatic patients. Patients experiencing a stroke typically underwent carotid endarterectomy after a 6- to 8-week delay while receiving anticoagulation therapy, and then only if their neurological status improved to significant functional use of the involved extremity. Table 2 also shows the time elapsed for 50% of the patients to reach an endpoint of either stroke or death and the combined estimate for all symptomatic patients together as a group.

Late Postoperative Outcome

Table 3 shows the early and late postoperative outcome of the 212 neurologically symptomatic patients. The follow-up period was 38.9 ± 2.1 months (mean ± SEM, median 33 months), with a range from 1 to 115 months. However, the distribution of stroke and death (the rate of occurrence per year) was not uniform over the follow-up period and thus the occurrence of late stroke (as an isolated endpoint) was also calculated using life-table methods (see below). A total of 48 deaths were recorded over the perioperative and the late postoperative periods. However, four patients had experienced a nonfatal stroke in the perioperative period and eventually died of causes unrelated to stroke during the follow-up period. Since these patients were counted in the stroke group initially as having reached one of the endpoints, their death was not included in the late-death group. The majority of the strokes that occurred were ipsilateral to the side of surgery: 94% of the immediate and 79% of the late postoperative strokes were ipsilateral.

Table 4 lists the cause of death when known, both in the perioperative and late postoperative periods. The high incidence of cardiovascular-related deaths and those due to malignant neoplasia occurred mainly in the late postoperative period, whereas known stroke-related death was not recorded in the late category. None of the late deaths from unknown causes could be directly related to earlier strokes, since death super-

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I, 0.5 0.6 0.4

Fig. 1. Separate life-table curves for patients with preoperative indications of amaurosis fugax (AF, 46 cases), transient ischemic attacks (TIA, 98 cases), and prolonged reversible ischemic neurological deficit (PRIND, 68 cases). The endpoints for these curves include both stroke occurrence and death due to any cause. These three individual groups were not significantly different and thus were lumped into one larger symptomatic group.

Sixty-two percent of the symptomatic patients remained alive and free of stroke at 5 years, considering the endpoints of either stroke or death occurrence. This proportion is considerably less than that reported in the study by Whisnant, et al., of patients with TIA's using similar endpoints, in which approximately 85% of the study patients remained alive and free of stroke at 5 years. However, our proportion of patients who were alive and free of stroke at 5 years was similar to data from other reports of patients with TIA's undergoing carotid endarterectomy and also to the outcome determined for patients with previous neurological deficit undergoing carotid endarterectomy. The increased risk of reaching one of these two endpoints may reflect the multiplicity of medical risk factors in the general VA population (Tables 1 and 4), particularly the high incidence of late mortality due to either neoplasia or cardiac problems.

Risk of Late Stroke

Figure 3 illustrates the life-table estimate of the proportion of patients who were free of stroke as a function of time, assuming that causes of mortality other than stroke were not specifically considered as endpoints. For this analysis all nonstroke-related deaths were considered as censored endpoints, similar to the theoretical discussions presented by Barnett, Warlow, and Whisnant, et al. Since in this series most perioperative deaths were related to stroke and none of the known late deaths was attributable to stroke, this analysis closely approximates the theoretical data by including both the early and late risks associated with carotid endarterectomy. The immediate limitation of this graphic life-table estimate lies in the exclusion of a possible increased risk of nonstroke-related death due to the procedure from both the postoperative and the late periods. For example, if the procedure contributed in an indirect way to a late death due to myocardial infarction, this information would be excluded. Examined in this way, the data approximate the isolated effect of endarterectomy on subsequent stroke risk.

Stroke Risk Approximation

The carotid endarterectomy outcome curve in Fig. 3 (solid line) demonstrates an immediate drop with the perioperative risk of stroke, and then a lesser slope that is not clearly defined due to the multiple intervals. The changing slope and irregular intervals of the life-table curve as a function of time suggest that the risk of vened a minimum of 26 months later. The exact cause of death could not be identified in the “unknown” group because either the death occurred outside the VA medical system or there were no autopsy and/or clinical data to corroborate the cause of sudden death.

Graphic Life-Table Estimates of Stroke and Death Occurrence

Figure 1 shows the proportion of patients who were alive and free of stroke as a function of time after the carotid endarterectomy procedure, grouped according to the different types of preoperative neurological symptoms. The life-table curves were not statistically different for the three main groups of patients with amaurosis fugax, TIA’s, and PRIND, according to a comparison of the mean time values to reach the two endpoints of stroke and death (Table 2). Thus, these three groups were subsequently lumped into one symptomatic curve (Fig. 2), with the 99% confidence intervals around the Kaplan-Meier life-table estimate for the neurologically symptomatic patients.

Figure 2. Plot showing the life-table curve for the combined group of 212 symptomatic patients including those with amaurosis fugax (AF), transient ischemic attacks (TIA), and prolonged reversible ischemic neurological deficit (PRIND), considering the endpoints of both stroke and death. The dotted lines indicate the 99% confidence intervals around the life-table estimate. At 5 years postoperatively, 62% of the original patient group remained alive and free of stroke.

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stroke following carotid endarterectomy may be better estimated using a smooth approximation or a model function rather than the actual data. Two different types of approximations were fitted to the data: a linear model for the late postoperative period (after 30 days), which assumes a stable risk of stroke for the entire late period, and an exponential model, which would indicate a continually declining stroke risk as a function of time after surgery. Previous reports on the risk of late stroke after carotid endarterectomy have assumed the linear model, particularly those using lumped data as shown in Table 3. The model with the better fit may indicate how the risk of stroke changes with time after surgery.

The possibilities for the direction of change in the stroke risk include the following: 1) The protective effects of the carotid endarterectomy procedure may lessen with time, or the beneficial effect of the procedure may wear off. The slope and stroke risk of these data should be increasing as a function of time. 2) The risk may be stable from the early to the late postoperative period (as assumed in previous studies) and be well approximated by a linear model with a constant slope. 3) The risk of stroke may decrease with time after both the initial premonitory neurological symptom and the carotid endarterectomy procedure, which would be better modeled by an exponential function with a declining slope. These possibilities were assessed by fitting the interval risk for subsequent stroke at each step on the graph (from immediately to 8 years postoperatively) with either a linear (Fig. 3, dashed line) or an exponential least-squares regression line (Fig. 3, dotted line).

The exponential line (assuming an asymptote of 80% of patients free of stroke) demonstrated a better regression coefficient than a linear fit ($R = 0.98$ for the exponential fit vs. $R = 0.95$ for a linear fit). The slope of the linear fit implied a constant 1.7% yearly risk of stroke (in those patients who were susceptible). The exponential approximation started with an initial risk of 4.38% per year (beginning in the postoperative period) and declined to nearly 1% per year by the 6th year postoperatively (Table 5). The exponential line was also calculated to have a half-life of 33 months.

The best approximation to the carotid endarterectomy outcome data was the exponential model, which suggested that Possibility No. 3 (a decreasing stroke risk over time) may be the most accurate. This conclusion is similar to estimates of the risk of stroke associated with medical treatment of TIA's, which show a declining risk of stroke after the initial event. Because of the changing risk, a constant per-year figure for stroke risk may be misleading over a prolonged follow-up period, and the hazard calculated using the smoothed exponential approximation may be more accurate (as shown in Table 5).

**Comparison of CEA Outcome and Predicted Medical Risk**

Figure 4 shows the perioperative and postoperative risks of stroke (and stroke-related death) superimposed on a presumed best medical treatment regimen, defined by a summary report of medical treatment data. This plot represents an approximation for many reasons. Nonstroke-related mortality is not included in the carotid endarterectomy outcome line, but stroke-related morbidity and death comprise more than 90% of the total perioperative risk (Table 3). The 99% confidence limits were calculated from the life-table analysis, but are fairly wide due to the small numbers. The initial perioperative stroke and death risk for the medically treated patients were not known, although the stroke rate in the first month after a neurological event has been reported as high as 8%. The medical treatment

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**TABLE 5**

<table>
<thead>
<tr>
<th>Yearly Time Interval (Starting Point)</th>
<th>Yearly Risk of Stroke after CEA (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1 (1 mo)</td>
<td>1.7</td>
</tr>
<tr>
<td>Year 2 (12 mos)</td>
<td>1.7</td>
</tr>
<tr>
<td>Year 3 (24 mos)</td>
<td>1.7</td>
</tr>
<tr>
<td>Year 4 (36 mos)</td>
<td>1.7</td>
</tr>
<tr>
<td>Year 5 (48 mos)</td>
<td>1.7</td>
</tr>
<tr>
<td>Year 6 (60 mos)</td>
<td>1.7</td>
</tr>
<tr>
<td>Year 7 (72 mos)</td>
<td>1.7</td>
</tr>
<tr>
<td>Year 8 (84 mos)</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Linear Model</strong></td>
<td><strong>Exponential Model</strong></td>
</tr>
</tbody>
</table>

* CEA = carotid endarterectomy.
The main goal of this study was to define the risk of late stroke following carotid endarterectomy, in a fairly uniform VA population. The follow-up percentage available in this patient population was generally high over the period of this study. Additionally, the two endpoints of stroke (with a permanent neurological deficit) and death were relatively unambiguous and usually involved inpatient documentation of the altered status. Thus, the combination of inpatient records, outpatient visits, telephone inquiries, and follow-up letters allowed a firm delineation of outcome within the confines of the patient seeking continued care within the VA medical system. Likewise, the use of the Kaplan-Meier life-table method circumvented the highly variable follow-up data inherent in a retrospective series. However, there are clear limitations on the available information, such as the unknown cause of death in 30% of the patients who died during the follow-up period (Table 4).

The risk of late stroke presented in Table 5 is clearly a lower limit, with an upper limit bracketed by the possibility of some of the deaths with unknown causation really being due to stroke. The maximum for this upper limit appears to be approximately 10% of the deaths with known etiology attributable to stroke (from Table 4), which would indicate that possibly up to two additional patients may have experienced a stroke leading to death during the period of the study (10% of 17 patients). This change in numbers would not significantly affect the curves representing survival free of stroke, but could slightly affect the stroke risk definition. However, this is not likely to be a significant change and would average out over the multiple time periods that were used for the stroke risk predictions.

The life-table approach treats patients with unknown outcome as censored data, and the censored time points were uniformly spread over all intervals. Likewise, the confidence limits from the survival curve data showed a fairly narrow spread. However, the lack of significant difference between the three symptomatic groups in stroke-free survival suggests that larger numbers may be required for further stratification of subgroups.

Mortality

The group of patients in our study demonstrated a decreased rate of remaining alive and free of stroke compared to the operative series (for TIA’s) of Whisnant, et al. Most of the defined deaths appeared due to either cardiac or neoplastic sources (Table 4). The main reasons for the decreased survival in the symptomatic VA population may be the high percentage of patients undergoing surgery with prior neurological deficit and the frequent coexistence or later onset of comorbid factors, such as hypertension, diabetes, and neoplasia. The risk of immediate or late stroke and also the mortality rate are similar to those of the Group

**Discussion**

**Limitations of Clinical Methods**

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Long-term outcome after carotid endarterectomy

IV patients described by Sundt, et al.29,30 The survival in this operative series is also similar to long-term follow-up reports on patients presenting with TIA but not undergoing carotid endarterectomy.36 However, this current series of symptomatic patients demonstrated improved survival data compared with a group of patients followed after completed strokes,16 whose median survival time was less than 4 years.

Late Postoperative Outcome

As shown by Figs. 3 and 4, the risk of stroke continued to decline as a function of time after surgery. The half-life for this decay was calculated to be approximately 33 months. The linear estimate of the yearly stroke risk averaged 1.7% per year, in close agreement with the previous estimate of 2% per year from the Mayo Clinic series.35 The preponderance of these strokes appeared to be ipsilateral to the carotid endarterectomy procedure, also similar to the Mayo Clinic data. However, the substantial difference appeared to be in the medical comorbidity present in the VA patients included in this series and their greatly decreased rate of survival over time. This difference was largely due to the high incidence of neoplasia in the VA population.

Clearly, the best manner in which to approximate the risk of late stroke was as a slowly declining exponential function, which takes into account both the early and the late stroke risk. The pattern of a slowly declining function would also fit the three-stage medical risk, as described by reviews of the currently available medical data.3,11,16,27,33,34,38 The present postoperative series demonstrates a modest improvement over this predicted composite medical risk but, clearly, significance cannot be assigned to this difference without a comparable control series. The risk of late stroke does clearly decline with time, however, presumably reaching some asymptotic level, here presumed to be a plateau of 80% free of stroke. Thus, the clinical effects of carotid endarterectomy in terms of lowering the stroke risk do not appear to lessen with time, and the main consideration is the comparison of the operative and postoperative risk with the total management risk of nonoperative treatment.

In comparison to other series with long follow-up periods, the present data on survival free of stroke in symptomatic patients are similar to those in patients with a preoperative neurological deficit. However, the analysis of the stroke risk has usually been presented as a composite of total risk divided by the follow-up period, similar to those presented in Table 3. This format does not permit assessment of the underlying time distribution of stroke risk and the relative hazard to the patient at different time periods after carotid endarterectomy. Thus, the data from this report can be compared directly to either the presumed composite medical risk (Fig. 4, dashed line) or to reported series of medical risk if presented in a life-table format.16,27,36 This form of comparison does not allow matching of related variables in the populations under study, however, and underscores the limitations of currently available control data and conclusions generated from these data.

The finding of a decreased stroke risk with time indicates that a patient is probably not returned to a high-risk group after carotid endarterectomy. Alternatively, the increased risk of stroke after a symptom occurrence also is likely declining with time, whether or not carotid endarterectomy is performed. A careful comparison with a matched control group is critical to identifying benefit from the surgical procedure, and particularly in delineating the significance of the decline in stroke as a function of time after the carotid endarterectomy procedure. The demonstration of a modest surgical benefit in Fig. 4 is thus tentative and requires confirmation from additional (prospective) patient data.

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