**Carotid Endarterectomy: Does It Work?**

**CHARLES WARLOW, M.D., F.R.C.P.**

"Ah, don't say that you agree with me. When people agree with me I always feel that I must be wrong."

From, "The Critic as Artist" by Oscar Wilde.

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IF CAROTID ENDARTERECTOMY WAS A DRUG its efficacy would require scrutiny and licensure by the Committee on Safety of Medicines in the United Kingdom and by the Food and Drug Administration in the United States. Surgical procedures, unlike drugs, are exempt from the requirement that the risks of treatment be shown to be unequivocally less than the risks of no-treatment. That carotid endarterectomy can and does cause stroke and death is not in doubt and the main issue is whether this risk is greater or less than that of restricting therapy to medical treatment. While thousands of patients having the operation have been reported in the literature, and it is said to be "the most commonly performed vascular operation," and "one of the most commonly performed operations" in the United States, only one inconclusive randomised trial has been published.*

The theoretical basis for carotid endarterectomy is attractive but theories are vulnerable to new knowledge. Many fashionable medical and surgical treatments, the potentially useful as well as completely useless, have been abandoned when the theories supporting them collapsed without the solid support of convincing evidence of clinical efficacy. Carotid endarterectomy must not be rejected in error any more than its performance should be sustained in error. Unless the theoretical attractiveness of the procedure is supported by convincing clinical trials it may very easily fall out of fashion as a result of new theories to explain the pathophysiology of transient ischaemic attack (TIA) and stroke, new knowledge concerning atheroma and thromboembolism in the carotid circulation, or maybe just confusion between the currently correct view that "there is no convincing evidence that the operation does any good" and the incorrect view that "there is convincing evidence that the operation does no good".

This review will examine the logical basis for the operation (which is reasonable), the risk of not doing the operation (which we do not know very clearly), the risk of the operation itself (which depends on where it is done) and the evidence that the overall risk of surgery is less than the risk of no-surgery (which at the moment does not exist).

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The Rationale of Carotid Endarterectomy

Carotid endarterectomy is most often undertaken in patients who have had a TIA, retinal infarct, or mild stroke in the distribution of that artery; occasionally in patients with a more major stroke or stroke-in-evolution; in patients thought to be at high risk of stroke but who have had no cerebrovascular symptoms; in patients with ischaemic events in the distribution of the contralateral carotid artery; and rather rarely in patients with multi-infarct dementia. Complete carotid occlusion is usually regarded as inoperable although some surgeons disagree. This discussion will centre on the situation which is the most commonly encountered, for which the best data are available, and where the only randomised trial has been done; carotid endarterectomy after ipsilateral carotid distribution TIA.

The evidence that some, and perhaps most, carotid TIA are due to atherothromboembolism in relation to the origin of the internal carotid artery is reasonably good. An appreciable reduction in volume blood flow (which is only caused by more than about 70% stenosis on diameter measurements) may sometimes cause carotid TIA, particularly if associated with a sudden fall in blood pressure. In addition, carotid as well as other extra- and intra-cranial arterial stenoses may compromise collateral blood flow in the event of occlusion in another arterial territory, thus facilitating cerebral infarction. However, to put the matter into perspective it must be emphasized that only about 50% of carotid TIA patients actually have ipsilateral internal carotid disease, much more commonly stenosis than occlusion.

The justification for doing a carotid endarterectomy for carotid TIA depends on four judgements, which are seldom certain for an individual, but which need to be true in general:

1. A stenosing lesion at the origin of the internal carotid artery probably caused the preceding TIA, usually by embolism and occasionally by reduction in volume blood flow.
(2) No other lesion (arterial or cardiac), or general disorder (polycythaemia, arthritis, etc.), is as, or more likely to have been the cause of the focal neurological symptoms.

(3) The lesion is likely to cause further TIA and, more importantly, cerebral infarction.

(4) The longer term risk of stroke without surgery is greater than the longer term risk with surgery added to the risk of preceding angiography which is seldom, if ever required unless surgery is being considered.

What is “Significant” Carotid Stenosis?

In this context the meaning of “significant” has never been satisfactorily defined because, in a sense, it depends on the risk-benefit equation for carotid endarterectomy. It could be taken to mean the point at which stenosis of the internal carotid artery begins to interfere with blood flow, but lesser degrees of stenosis can be associated with ulceration and thromboembolism. Consequently, “significant” should really only be used to describe a lesion which has caused the preceding TIA and, more importantly, is likely to cause subsequent stroke by embolism, occlusive thrombosis, or interference with blood flow. There is not much doubt that more than about 25% diameter stenosis is associated with a past TIA. Unfortunately there is very scanty data to answer the more relevant question, “does the degree of carotid disease influence the subsequent risk of stroke, and how much greater is this risk compared with a patient without a TIA?”

Patients with TIA in the carotid territory and with a normal angiogram of the symptomatic artery do not necessarily have a completely benign prognosis, although subsequent stroke is not always caused by ipsilateral cerebral infarction, and sometimes may be due to embolism from the heart.

The Risk of Stroke without Surgery

There has been no completely “natural” history study of TIA patients since there are always some, and probably many, who are “treated” in some way or another and this intervention may have reduced, or increased the risk of stroke or death. The only certain conclusion to be drawn from the many studies is that the risk of stroke or death (usually due to vascular disease but more often cardiovascular than cerebrovascular) depends on which study is quoted. It is difficult to disentangle all the possible reasons for the variation between studies: but possibilities include: differing age structures of the populations studied; different periods of follow-up; variation in the temporal boundary between TIA and stroke which has ranged from 30 minutes to 72 hours; inclusion of patients with isolated vertigo which is often a symptom of more benign disorders; inclusion of patients with a previous stroke or residual deficit; differences in the prevalence of risk factors for stroke, particularly hypertension; whether or not the study was community or hospital based, and prospective or retrospective; different referral patterns and selection biases; and possibly the extent of the underlying arterial disease.

The most informative way to present the natural history of TIA patients is by a life-table with an estimate of the probability of surviving free of stroke at various intervals after the first TIA, the most recent TIA, or the date of presentation. The only series re-
ported in this way comes from the Mayo Clinic.\textsuperscript{35, 41–43} Unfortunately, an unspecified number of the TIA patients had come to medical attention as a result of a stroke rather than only a TIA and yet were included in the study. This series must, therefore, contain an unrepresentatively small proportion of TIA patients with a benign prognosis. The often-quoted finding that of the TIA patients who did develop a stroke, 51% did so in the first year after the first TIA\textsuperscript{41} was probably inflated by the fact that those TIA patients who were identified because they came to attention with a stroke would have been more likely to remember a recent TIA rather than a distant one. Not surprisingly the figure of 51% fell to 41% when the same patients were followed up for longer.\textsuperscript{35} This is an important issue to resolve since if the risk of stroke is particularly high soon after the onset of TIA and treatment is effective, then the condition becomes something of a medical emergency.

A reasonable estimate of the probability of stroke and/or death, at least among men, is based on the 91 men taking placebo in the Canadian Cooperative Study Group trial of aspirin and sulphinpyrazone in threatened stroke,\textsuperscript{44} about 10%/annum in each of the three years after randomisation. One must, however, remember that 39% of these patients had some residual neurological deficit and that patients entering clinical trials usually have a better prognosis than expected. Moreover, early stroke after the qualifying TIA would have disqualified patients from randomisation and, therefore, from analysis.

The Risk of Surgery

It is ironic that the most feared and tragic complication of carotid endarterectomy is stroke, the very event which the operation is designed to prevent. Peri-operative stroke may be due to occlusive thrombosis at, or embolism from the endarterectomy site during or in the first few days after surgery, impaired cerebral blood flow during clamping of the carotid arteries, or ipsilateral intracerebral haemorrhage. Death is almost always due to stroke or myocardial infarction. Complications related to the wound are more often a nuisance than serious and include haematoma, infection, and damage to the hypoglossal and superior laryngeal nerves. These issues have been extensively reviewed by others.\textsuperscript{4, 12, 45}

Dozens of surgical series covering thousands of patients have been reported. Unfortunately, in rather few it is possible to extract the figures for patients being operated on with carotid TIA ipsilateral to an arterial lesion, since they are often buried among the results of patients with cerebral infarction, asymptomatic bruit, etc. Table 1 includes 18 series pertaining to patients most of whom probably have carotid TIA in the distribution of the operated artery. Although it is not always possible to determine exactly how many deaths were caused by stroke and whether the quoted number of strokes included fatal strokes, the risk of stroke and/or death is tabulated as accurately as the data allow. This is probably the most acceptable figure for comparing the surgical series with each other, and with the so-called natural history series since it is obviously directly related to the most relevant clinical question which is, "what is the probability of surviving free of stroke at various points in time after surgery?". A treatment which prevents fatal and non-fatal strokes is of little importance if it often causes death from other causes. Since comparisons have been confused in the past by quoting either the patient risk or the procedure risk, figures for both are given when available.

The main conclusion to be drawn from table 1 is that the risk of carotid surgery varies widely from a stroke and/or death rate of 2.5% to 24.4% (in patients rather than procedures). The many other series which are not quoted merely confirm this variation although there may well be a literature bias in that surgeons, or physicians, experiencing poor results are unlikely to submit them for publication and, if they do, editors may be less than enthusiastic about publishing them rather than more interesting "positive" results. It may be no coincidence that the worst results of all were published by a group of neurologists rather than surgeons and if these results really are at all representative of what is happening in many centres there is cause for alarm since they are at odds with the rest of the literature and highly unlikely to be an improvement on the natural history of the disease itself.

The variation in surgical risk must of course depend to some extent on surgical and anaesthetic skill but this cannot explain all the variation. Patients with uncontrolled hypertension,\textsuperscript{45} 61 severe ischaemic heart disease,\textsuperscript{45, 62} 63 and unstable or progressing neurological signs\textsuperscript{64, 65} do particularly badly. Whether cerebral protection (e.g. with a shunt) is helpful is vigorously debated but no randomised trials have been reported. By selecting low surgical risk patients, surgery can be made safer but it is not inconceivable that such a group contains the very patients who will do particularly well without surgery — relatively young patients with a normal blood pressure, normal heart, and no neurological signs.

Is the Risk of Stroke without Surgery greater than the Risk of Stroke with Surgery?

Non-random Comparisons

It is fashionable, with some exceptions,\textsuperscript{66, 67} to discount treatment effects which are based on a comparison with historical controls, or on concurrent controls which are not selected at random. This disciplined approach with its emphasis on randomisation to minimize systematic errors and large numbers to reduce random errors, is considered correct when the effect of treatment is likely to be modest rather than spectacular, and it is supported by convincing arguments,\textsuperscript{68–72} as well as practical examples.\textsuperscript{73–75} Not only do non-random trials usually exaggerate treatment effects when compared to the results of randomised trials,\textsuperscript{70, 76} but some real though modest treatment effects may be obscured and then discarded in error.

Despite these doubts about non-random comparisions it is interesting to examine the long-term outcome of patients submitted to operation and to compare it
CAROTID ENDAVERECTOMY: DOES IT WORK? / Warlow

Table 1 Stroke and Death Complicating Carotid Endarterectomy in Patients with TIA

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Procedures</th>
<th>Number</th>
<th>Patient risk %</th>
<th>Peri-operative stroke</th>
<th>Number</th>
<th>Patient risk %</th>
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Legend to comments: (a) definitely excluded patients with only vertebrobasilar TIA; (b) definitely excluded patients with carotid occlusion; (c) defined the boundary, in time, between TIA and stroke; (d) described how carotid and vertebrobasilar TIA were distinguished; (e) stated the extent of carotid disease which was operated on.

with what one might expect without surgery. The results are somewhat surprising and are presented in table 2; the series from table 1 which are missing did not report follow-up data on stroke or death. The average period of follow-up was often only an approximation and was never presented as a life table. The number of strokes and/or deaths are utilized for reasons already discussed and all strokes (symptoms for 24 hours or more) were counted. In many surgical series there is a tendency to dismiss and then exclude from analysis strokes which are 'transient', 'transient-temporary', 'transient-temporary' and 'prolonged-temporary', caused 'weakness which cleared before discharge,' or were not 'permanent'. Some exclusions will introduce bias in favour of surgery since comparisons have to be made with the so-called natural history studies in which all strokes are counted.

The 'expected' number of strokes and/or deaths in table 2 has been calculated on the basis of an approximate knowledge of the duration of follow-up and an annual risk without surgery of either 10% (based on the natural history evidence referred to earlier), or 7.4% (based on the medically treated patients in the American Joint Study — see below). As is almost always the case in randomised trials, the control group in the trial fared better than expected, i.e. 7.4% per annum stroke and/or death compared with 10%. From table 2 it can be seen that in every series, apart from one, in which there was complete follow-up information on strokes and deaths the patients fared worse than expected (on the expectation of 7.4% per annum risk), and the only other series in which the patients fared better than 10% per annum was the randomised trial for which the randomised control group obviously provides the more acceptable comparison. Therefore, even by the unacceptable standards of non-randomised comparisons, the surgically treated patients did worse than expected.

If one includes the risk of angiography, which need seldom be undertaken unless a surgical policy is being pursued, then the patients in surgical series will have fared even worse.

The authors of most surgical series concluded that surgery is of value because they (1) often excluded from their analysis relatively minor strokes in the surgical group, (2) tended to select the gloomiest natural history studies against which to compare their operated patients and (3) failed to account for the complications of angiography. Non-stroke deaths are included in this analysis because the patient is more interested in the probability of survival free of stroke than the proba-
TABLE 2  Stroke and/or Death after Carotid Endarterectomy: Operative Risk and Long-term Follow-up

<table>
<thead>
<tr>
<th>Author(s)</th>
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<th>Average follow-up (months)</th>
<th>Operative stroke and/or death</th>
<th>Follow-up stroke and/or death</th>
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*Excludes strokes since number not stated.
†Excludes deaths since number not stated.
1Expectation based on the medically treated patients in the Joint Study.37
2Excludes strokes since number not stated.
3Expectation based on the natural history of TIA in the literature.
4Expectation based on the medically treated patients in the Joint Study.37

bility of fatal and non-fatal stroke. This should not introduce bias against surgery since presumably the long-term non-cerebrovascular mortality of operated patients is likely to be relatively low because patients tend to be selected for operation if they are reasonably fit and not too old. However, it must be emphasized that follow-up in the surgical series has usually been fairly short and it is conceivable that had the patients been followed for longer an advantage for surgery might have appeared.

The analysis presented so far is inherently fallacious because the surgical and non-surgical patients have not been matched for the important prognostic variables affecting outcome (particularly age), and any retrospective matching is impossible because the relevant data are unavailable. Furthermore, the surgical series seldom involve only patients with TIA in carotid territory, and often are "contaminated" by patients with vertebrobasilar TIA; the natural history series include patients with normal angiograms as well as those with "surgical" lesions. Finally, poor risk patients are less likely to be operated on than good risk patients and so surgical series may be biased towards a favourable outcome even if surgery had not been undertaken.

Randomised Comparisons

The Joint Study of Extracranial Arterial Occlusion is the only published randomised trial of carotid endarterectomy.37 Between 1962 and 1968, in 24 centres, 316 patients with carotid stenosis who had experienced a TIA were randomly allocated to surgery or no-surgery (fig. 1). Over a mean follow-up of 42 months the 169 patients allocated to surgery experienced a stroke rate of 12% (20 patients) and a stroke and/or death rate of 27% (45 patients). The comparable figures for the 147 non-surgical patients were 13% (19 patients) and 26% (38 patients). Even if one excludes the operative risk of stroke and death the difference between the two groups remains statistically insignificant (15% versus 24% stroke and/or death during follow-up) although it is of interest that any advantage to surgery was almost entirely with respect to strokes in the operated or previously symptomatic side (2 versus 11). The frequency of continuing carotid TIA was less in the surgical patients but not statistically significant. However, in general continuing TIA are neither frequent nor prolonged enough to be a clinical problem for the majority of patients. They would need to represent a considerable disability to justify an operative risk of stroke and/or death of even 5%, let alone the 11% of the Joint Study. Therefore it was far too small to have detected reliably a modest but clinically worthwhile surgical advantage.
of 25% in the risk of stroke attributable to surgery. The 95% confidence limits of the American Joint Study would certainly include the possibility of a 25% risk reduction attributable to surgery, as well as a 25% risk increase.

Another important point is that the trial may have been inconclusive because the follow-up was too short to allow any long-term benefit to emerge. This is illustrated in figure 2 which is a series of very approximate survival curves based on the available data. Line “E” represents the course of events in the non-surgical group who had a risk of stroke and/or death of about 7.4% per annum. The exact shape of the line is unknown but a straight line has been used for convenience and illustrative purposes. Line “B” represents the course of events in the surgically treated patients with an operative risk of stroke and/or death of 11%, and a total risk at a mean of 42 months of 27% (again a straight line is used for illustrative purposes). These two lines intersect at about 4 years. Thus surgery might have been shown to be beneficial if follow-up had been longer.

In clinical practice, if a policy of surgery is to be compared with a policy of no-surgery one has to decide how long an individual patient is likely to survive and be exposed to the risk of stroke without surgery (i.e. the natural history), and balance this against the immediate risk of surgery itself and what might happen after surviving surgery without a stroke which is presumably rather similar in all such survivors. From figure 2 it can be seen that an institution with a surgical risk of stroke and/or death of 5% (Line “A”) would start benefiting patients after about two years, whereas an institution with a surgical risk of 20% (Line “C”) would not start benefiting patients even after five years. Knowing the surgical risks in an institution (which should be quite easy to find out) and the difference between the slope of the no-surgery and post-surgical stroke and/or death rates (which should emerge from well-conducted randomised trials), a physician can work out whether surgery should be done in a similar patient to those in the randomised trial.

By itself the American Joint Study does not give us enough reliable information to allow the above calculation to be made. The reasons are as follows:

1. The sample size was too small leading to wide confidence limits and uncertainty.
2. Follow-up was too short.
3. No life table analysis is available.
4. No attempt at “blind” evaluation of the major end-point of stroke was attempted. Mortality-only comparison, which would be unbiased by either patient or observer, would need a trial so much larger that it would probably be impossible to organize.
5. About 43% of the patients had experienced only vertebrobasilar TIA before randomisation and the full results for those with only carotid TIA are unknown. It is this latter group which is more likely to benefit by the removal of an embolic source to the ipsilateral cerebral hemisphere.
6. Modern medical treatment, particularly the control of hypertension, is almost certainly more effective than in the 1960s when the American Joint Study was in progress. It is conceivable that any advantage of surgery in addition to medical treatment may now be less than it was. On the other hand, surgical risk is also less than it was.
7. It is not clear whether the patients were analysed in the groups to which they were originally randomised. We do not know that patients randomised to surgery were analysed from that point onwards nor how many received surgery, nor do we know if any of the patients randomised to no-surgery actually had surgery.
8. It is unknown how many patients in each group were lost to follow-up and whether the reasons were similar in the two groups. Major differences in the number of, or reasons for withdrawals might have affected the conclusions.

**Variation in Surgical Policy**

Neurologists vary in their policy on angiography for TIA patients and, by implication, their policy on carotid endarterectomy. This variation is extremely large and is worth reviewing since it is a reflection of the uncertainty and confusion surrounding the usefulness of the operation.

**Comparison between England and Wales, and Canada**

In England and Wales the number of carotid endarterectomies can be roughly estimated from Hospital In-patient Enquiry (HIPE) statistics using category 082
which includes operations on arteries in the neck, not elsewhere classified. This category includes "ligation, embolectomy, resection with graft, bypass graft, implantation of graft, resection with re-anastomosis, suture of vessel and carotid endarterectomy" and will, therefore, somewhat over-estimate the endarterectomy rate. However, since the other operations are rarely performed any over-estimate will be small. In figure 3 the operation rates by year are shown from 1968 to 1978 for persons aged 45–64, and 65 or over (1969 data are unavailable). There has been a modest increase from a total of 143 to 560 operations in a year, most of this increase being in the 45–64 age group. In Canada carotid endarterectomy is included in category 261 of "Surgical Procedures and Treatments" which is designated "endarterectomy, head and neck, base of brain." The rates are also shown in figure 3 and it is immediately clear they have been rising rapidly, both in the 45–64 age group and 65 or over age group.

The difference between the rates in Canada and England and Wales is striking. For the last year in which direct comparison is possible (1977) the Canadian rate was 8.6 times the rate in England and Wales for persons aged 45–64, and 16.9 times for persons aged 65 or over. Not all the operations on either side of the Atlantic would have been for carotid TIA and some of the difference may be accounted for by a more aggressive Canadian policy with respect to asymptomatic bruit, vertebrobasilar TIA, or completed strokes. Some of the difference might also be explained by the greater share of the G.N.P. devoted to health care in Canada. However, it appears more probable that it represents a marked difference in opinion as to whether carotid endarterectomy is useful in general and for carotid TIA in particular. To explore the last point further one needs to examine more detailed statistics published by cooperative groups within a single country.

Comparison Within Countries

In the Co-operative Study of Hospital Frequency and Character of Transient Ischaemic Attacks conducted in the United States, there were six participating centres and 400 patients with carotid TIA were collected. The proportion undergoing angiography ranged from 33% to 91%, and the proportion undergoing extra-cranial arterial surgery (usually carotid endarterectomy) ranged from 6% to 35%. Some of these differences might have been due to differing age structures between the centres but this was not thought to be the entire explanation. Variation within the United Kingdom seems to be even more extreme. During the UK-TIA Aspirin trial, of the 515 patients under the age of 70 who had experienced carotid TIA the proportion undergoing angiography ranged from 5% to 85%, and the proportion undergoing surgery ranged from 0% to 29%. These variations within countries suggest that the variation is not due to differences in resources devoted to health care which, amongst neurological centres in the UK at least, are fairly uniform.

Conclusions: The Need for Another Trial

Having reviewed the evidence, the conclusion is drawn that there is not sufficient data available to allow a rational decision as to whether carotid endarterectomy does or does not increase the duration of survival free of stroke after TIA have developed in the carotid artery territory. The non-randomised studies are unacceptable as evidence and the only available randomised trial was inconclusive. However, the fact that the trial was done at all remains a remarkable achievement, particularly when one remembers that at the time the climate of opinion towards randomised trials was not so favorable as it is today. The uncertainty on this matter is reflected in the enormous variation between neurologists in their routine practice. The concern is that this state of confusion will lead either to an excess of possibly unnecessary surgery, or to the abandoning of a potentially useful but unproven procedure when some more promising therapy becomes available.

If carotid endarterectomy does turn out to be useful in the prevention of stroke after carotid TIA then, in England and Wales, the number of procedures would need to increase from about 600 per annum to about 3,000 per annum, assuming that surgery is inappropriate over the age of 75 (table 3). Similar calculations for the 1977 Canadian population show that about 1,500 patients would have had symptomatic and operable carotid lesions. In actual fact 1,531 carotid endarterectomies were done although many of these may have been in patients with completed stroke or asymptomatic carotid disease. Is carotid endarterectomy overrated in Canada or underused in the United Kingdom? There are no data to help us decide which of these two possibilities is correct or whether there is a middle way.

### Table 3: Potential Number of TIA Patients Available for Carotid Endarterectomy — England and Wales 1978

<table>
<thead>
<tr>
<th>Age</th>
<th>Population</th>
<th>TIA incidence*</th>
<th>No. TIA</th>
<th>No. &quot;operable&quot; ‡</th>
<th>Cumulative no. &quot;operable&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>30,670,800</td>
<td>1</td>
<td>306</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>45–54</td>
<td>5,702,900</td>
<td>16</td>
<td>912</td>
<td>192</td>
<td>256</td>
</tr>
<tr>
<td>55–64</td>
<td>5,559,900</td>
<td>69</td>
<td>3,836</td>
<td>806</td>
<td>1,062</td>
</tr>
<tr>
<td>65–74</td>
<td>4,568,700</td>
<td>220</td>
<td>10,051</td>
<td>2,111</td>
<td>3,173</td>
</tr>
<tr>
<td>75+</td>
<td>2,672,400</td>
<td>293</td>
<td>7,830</td>
<td>1,644</td>
<td>4,817</td>
</tr>
<tr>
<td>All ages</td>
<td>49,174,700</td>
<td>22,935</td>
<td>4,817</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on Winshant et al (1973) number/100,000 population.
‡21% of all TIA, since about 60% of TIA are carotid in distribution, and about 35% of carotid TIA have ipsilateral carotid stenosis.
The value of carotid endarterectomy after carotid TIA (or any other possible indication) will only be established by more well-conducted randomised trials. One trial has started in the United Kingdom, France, England & Wales in two age strata: 45-64, and 65 or more years old.

In the meantime a good philosophy might be to confess to being "delightfully surprised when any treatment at all is effective, and always assume that a treatment is ineffective until there is evidence to the contrary".

Acknowledgments

I would like to thank Richard Peto, Klim McPherson and Stephen Haines for helpful discussions and also Dr. Haines for his help in compiling the endarterectomy rates in Canada, and the Office of Population Censuses and Surveys for supplying HIEP data.

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