Comparison of Anticoagulation and Surgical Treatments of TIA. A Review and Consolidation of Recent Natural History and Treatment Studies

BY GILBERT FRANK, M.D.

Abstract: Comparison of Anticoagulation and Surgical Treatments of TIA. A Review and Consolidation of Recent Natural History and Treatment Studies

Combined results of selected studies of the natural history and therapeutic results in patients with TIA indicate that anticoagulation therapy is clearly worthwhile in the prevention of completed strokes during the first 40 months after onset. Surgery is somewhat less valuable, but preferable to nihilism, which is associated with new completed strokes in 19% of patients and death in 20% of patients followed for an average of 40 months from onset of TIA. The incidence of death from all causes is remarkably similar in both treated and untreated patients during this follow-up period, suggesting that fears of increased mortality in patients treated with anticoagulants are either unfounded or compensated by decreased mortality from occlusive strokes.

ADDITIONAL KEY WORDS stroke therapy combined studies stroke

Introduction

Interest in the syndrome of transient cerebral ischemic attacks (TIA) rests largely on the concern that TIA may be an early warning of impending completed stroke. The symptoms and signs of this disorder are generally attributed to reversible local cerebral ischemia in the carotid or basilar-vertebral systems subsequent to atherosclerosis of both cerebral and contributing extracerebral vessels. Superimposed systemic hypotension, cardiac arrhythmia, anemia, polycythemia, and other specific definable entities are often implicated in production of TIA.

Two major forms of therapy, anticoagulation and extracranial vascular surgery, have been used for about two decades—seemingly a sufficient time for thorough evaluation.

Yet, in a recent review, Browne and Poskanzer emphasize that there are "no data available affecting the decision . . . of whether to give anticoagulation or perform operation." This paper proposes to utilize and combine information from literature of the past ten years to provide a base for decisions regarding therapy of TIA.

Methods

Pertinent articles on the natural history, anticoagulation therapy and surgical treatment of TIA were selected for inclusion in this report on the basis of equivalent definitions of TIA, indication of numbers of new completed strokes and deaths, duration of follow-up, similar populations, and use of controlled experimental design. Age distributions appeared to be generally similar as might be expected in a population with atherosclerosis. Unusual study conditions were denoted where appropriate.

The occurrence of new completed strokes, as defined below, and deaths from all causes comprise the indicators of the natural history of TIA.
TIA and were utilized for comparison of anticoagulation and surgical treatment results. Diminution in severity or number of TIAs was not considered since these episodes are rarely disabling and since both anticoagulation and surgery are uniformly reported to decrease TIA symptoms markedly.

In addition to summary presentations of individual studies, simple arithmetic operations were used to adjust the incidences of new completed strokes and deaths to a common follow-up duration (40 months). Data from the selected studies were then pooled to obtain averaged resultant indicators of the natural history and effectiveness of therapy in TIA. All percentages in the text and tables are rounded to the nearest whole number.

Definitions
The following definitions, modified slightly from Millikan, are considered basic. Exceptions or further modifications in individual studies are noted where appropriate.

TRANSIENT ISCHEMIC ATTACK (TIA)
A transient episode of focal neurological deficit whose onset is rapid (few seconds) and duration is brief—usually a few minutes, but maximum 24 hours—with complete recovery.

COMPLETED STROKE (STROKE)
A stable focal neurological deficit present for more than 24 hours in carotid system lesions and 72 hours in vertebral-basilar lesions. The neurological deficit may be of any severity—only duration and stability are implied by the definition.

These two definitions leave an obvious gap which may be filled by defining the stroke in evolution (SIE), in which there has been progression or worsening of neurological signs within recent minutes—up to 24 hours in signs referable to carotid system lesions, and up to 72 hours in signs referable to basilar-vertebral lesions. Confusion between SIE and completed stroke in a given patient would be resolved in the chronic follow-up explicit in the studies reviewed here, and differentiation between TIA and SIE should be resolved by history and a few minutes to an hour of observation as symptoms progress in SIE or regress in TIA.

Natural History
Knowledge of the natural history of a disorder is essential for evaluation of treatment. Three studies of natural history were selected to provide such background. The first is by Acheson and Hutchinson who studied 82 British patients (64 men, 18 women) with "repetitive attacks (TIA) of less than one hour's duration" unrelated to cardiac arrhythmias or head turning and excluding vertigo. Patients were followed for an average of 40 months and in this time 18 had completed strokes with significant disability or death and 14 died of all causes. Six of the original 82 were treated (anticoagulants, surgery, antipolychymic treatment) and are, therefore, excluded in our revision of the Acheson and Hutchinson figures (table 1): 76 patients were included; 16 (21%) had stroke with disability or death, and 13 (17%) died from all causes including stroke.

In 1968, Baker et al. reported on 79 male veterans with TIA, as defined above, followed for an average of 41 months. Seventeen developed completed strokes and 17 died, including two who succumbed to cerebral infarct. Six patients who were lost to follow-up are excluded from consideration for this review, so that table 1 indicates only 73 total cases with 17 patients (23%) having completed strokes and 17 (23%) dying from all causes. Baker and his co-workers found that about 5% of their patients at risk during each of the first four follow-up years had new completed strokes, and approximately 4% died

<table>
<thead>
<tr>
<th>Cases</th>
<th>Strokes</th>
<th>Death</th>
<th>Follow-up (ave. mos.)</th>
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<tbody>
<tr>
<td>Acheson &amp; Hutchinson⁴ (1964)</td>
<td>76</td>
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<td>Marshall⁷ (1964)</td>
<td>61</td>
<td>1 (2%)</td>
<td>7 (11%)</td>
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from all causes during each of these first four follow-up years. This study included only men, as might be expected in a veterans hospital population. This discrepancy was considered acceptable, but is noted here for the reader’s consideration.

The third study of natural history is a particularly controversial one by Marshall. TIA was defined as a “disturbance of neurological function of less than 24 hours’ duration . . . believed on clinical grounds to be associated with atherosclerotic disease in carotid or vertebralbasilar vessels or branches.” Sixty-one British patients of the author were considered, who when first seen had only “TIAs.” The 35 male and 26 female patients ranged in age from 35 to 85 years, and follow-up averaged 45 months. During the follow-up period, only one patient (2%), an 83-year-old, had a completed stroke (which was fatal) three years after the onset of TIAs. Seven patients (11%), including the aforementioned, died of all causes within the follow-up period. The results of this investigation are so different from others in the literature that Millikan comments, “this series is entirely different from those reported by other authors, and does not represent the natural history of transient ischemic attacks.” Nevertheless, Marshall’s report must be included in a consideration of natural history of TIA since it represents a large series by a reputable investigator, and no gross biases or errors are evident.

The natural history reports are summarized in table 1. These papers represent the largest and most objective-appearing studies of the natural history of TIA in the recent literature. The papers of Acheson and Hutchinson and Baker et al. show remarkable agreement despite significantly different patient sources, and separation by four years and the Atlantic Ocean. The third paper, by Marshall, indicates a considerably more benign course. This is especially interesting in light of a separate study by Marshall and Meadows of the natural history of amaurosis fugax (fleeting unilateral blindness), a not uncommon symptom of TIA. These attacks reportedly lasted only a few minutes except for a few which persisted up to four hours. This single symptom in 80 patients with no other neurological disorders was associated with permanent unilateral blindness in eight patients, hemiplegia in four, and both blindness and contralateral hemiplegia in one; an overall incidence of completed stroke in 13 patients (15%) and death in 19 patients (24%). The mean follow-up period was 24 months for patients with hemiplegia and 51 months for those with only uniocular blindness. These results are notably similar to those of patients with less-limited forms of TIA discussed earlier in this section. Another source of information on the natural history of TIA is the untreated control groups from treatment studies. These are considered in subsequent sections.

**Anticoagulant Therapy**

Four studies of anticoagulant therapy are included here. All investigators used oral anticoagulants to maintain 10% to 25% prothrombin concentration (two to two and one-half times control level in seconds) in treated patients. The earliest report is from a national cooperative study involving seven general hospitals throughout the United States. Forty-four cases with “single or multiple episodes of cerebral ischemia lasting no longer than one hour and clearing without significant residuum” were studied. There were 20 controls (12 males, eight females) and 24 treated patients (20 males, four females). “Progress or recurrence of infarction” (completed stroke) occurred in four (25%) control patients and one (4%) treated patient. Two (10%) control patients died while five (21%) treated patients died during the 20 average months of follow-up. These findings are summarized in table 2. Two (8%) treated patients died of cerebral hemorrhage after 26 months of therapy, and the authors conclude that short-term (four to six months) anticoagulation may be worthwhile for TIA.

In a second independent study, Baker et al. reported on 30 controls followed for an average of 31 months and 30 treated patients followed for an average of 38 months. Four (13%) control patients and two (7%) treated patients developed new completed strokes. Five (17%) of the controls and six (20%) of the treated patients died during the period of follow-up (see table 2). One patient died of cerebral hemorrhage 22 months after anticoagulants were discontinued. This randomized study from a VA hospital included only males, and excluded patients who were poor risks for anticoagulation, patients with potentially fatal illnesses, and persons over 80.
In 1965 Pearce and associates, in England, reported an investigation of 37 patients. All were less than 70 years old and considered "sound candidates for anticoagulation." Seventeen, including 14 males and three females, were treated with therapeutic doses (50 mg) of the oral anticoagulant, Phenindione. Twenty (14 males, six females) patients were given one-fiftieth of the therapeutic dose and considered "controls." The patients were followed for an average of only 11 months. Two (10%) of the controls and one (6%) of the treated patients had new strokes, while three (15%) of the control patients and none of the treated patients died in this brief observation period (table 2). The authors conclude that "anticoagulant drugs do not show any significant effect on the outcome of transient ischemic attacks."

The largest single study on this subject is by Siekert et al., from the Mayo Clinic, involving 335 patients with "incipient stroke" or episodes of focal ischemia with symptoms and signs lasting up to 60 minutes with complete recovery between attacks. Of these patients, 175 were anticoagulated to therapeutic levels and followed for an average of 60 months. Seven (4%) developed signs and symptoms of cerebral infarction and 40 patients (23%) died of all causes. There were 160 patients as controls; 51 (32%) had completed strokes and 44 (28%) died. The control group is quite different from the other studies. Several patients were initially treated "briefly" with anticoagulants and transferred to the control group when anticoagulants were discontinued. Others had immediate contraindications for anticoagulation, and, therefore, may have been at greater risk of morbidity and death than were those in the treated group. Distribution of men and women was not reported.

A notable number of cases in the Mayo study died of intracranial hemorrhage—13 (7%) in the treated group and seven (4%) in the control group. Of the other studies reviewed here, only Baker et al. reported any intracranial hemorrhages with or without death; two (8%) treated patients died after 26 months of therapy, and one died 22 months after therapy was discontinued. Table 2 demonstrates the notable variability in (completed) strokes and deaths among the several studies reviewed. Some of this variability may
be attributed to the differences in average follow-up. One feature is consistently evident: The treated patients in each study have significantly fewer completed strokes than do the controls.

**Surgical Treatment of TIA**

Surgery for extracranial vascular disease has become an increasingly popular form of treatment for cerebrovascular disease in the past 20 years, but few objective reports are available for comparison with the studies on anticoagulation therapy. Siekert et al.² and Bauer et al.¹² have such publications, but Siekert’s article presents somewhat early data in the rapidly evolving field of extracerebral vascular surgery, and Bauer’s patients are incorporated in a larger, more recent study by Fields et al.,¹ which seems to represent optimal results of modern surgical treatment in TIA, and was selected as the prime source of information for this section. This report¹ is from a national cooperative study involving 316 patients with “recurrent transient attacks of brief duration with spontaneous resolution of neurological deficit,” whose major impairment was usually present for some minutes to a few hours, and rarely up to 72 hours. Patients were randomly allocated to surgical or “nonsurgical” treatment (control) categories.

Surgical treatment consisted of unilateral carotid endarterectomy in a majority of treated patients; bilateral endarterectomy was done in 35 patients, and unilateral carotid endarterectomy with vertebral endarterectomy in two patients. “Nonsurgical treatment” consisted of the “best available medical management in the participating institution,” which in some institutions included anticoagulant therapy. This may be reflected in the reduced incidence of new completed strokes among surgical controls (table 3) compared with natural history cases in table 1 and anticoagulant controls in table 2. Another point relevant to this difference may be that the 316 patients in this study had no previous completed strokes, while some of the patients in the other (natural history and anticoagulant) reports considered herein had a history of previous completed strokes.

Fields et al.¹ chose to exclude from their analysis all patients who died or had strokes in the immediate postoperative period and those nonsurgically treated patients who died or had strokes in the first 30 days after hospitalization. The results are summarized in table 3: 18 (12%) of 145 control patients had a new completed stroke with neurological deficit or death, and 27 (19%) died. In the treated group of 150, only six (4%) developed a new completed stroke and 23 (15%) died of all causes. This analysis is clearly biased. A number of patients (19) initially selected for the study were subsequently excluded because of completed stroke or death in the immediate postoperative period. Two nonsurgically treated patients were excluded because of stroke or death during the first 30 days of hospitalization. This obviously modifies the apparent results of surgical therapy considerably, and really represents an idealized situation devoid of postsurgical complications.

Re-analysis of the data including patients who died or had stroke in the immediate postoperative period or during the initial 30 days’ hospitalization produces quite a different result from the author’s analysis. Nineteen (13%) of 147 control patients had new completed strokes, and 28 (19%) died. In the operated group, 19 (11%) of 169 patients had new strokes and 29 (17%) died. The results of these two approaches are summarized in table 3: In Fields¹ analysis, the results of surgical therapy appear clearly better than in the controls. However, when these idealized condi-

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<td>Surgical Treatment of TIA—Incidence of Completed Strokes and Deaths From All Causes</td>
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tions are eliminated there is no statistical difference between surgical and "nonsurgical" therapy. Death rates are similar in both groups despite modes of analysis.

**Combining Results From Several Studies**

Review of the aforementioned studies and tables 1, 2, and 3 provides some idea of the incidence of new completed strokes and death in TIA with and without therapy. Those treated with anticoagulants seem to have fewer completed strokes than do controls, and surgical therapy promises fewer strokes (compared with controls) after the immediate postoperative period. The incidence of death is often (usually) similar in treated, control, and natural history reports. Such a review is unsatisfying and leaves the reader wishing for a sensible combination of the data to provide more singular and distinct indications of the natural history and results of therapy. Pooling of data from the several studies is an obvious approach to this goal. Ideally, all the treatment controls could be combined with natural history studies to yield a very large group, and all anticoagulated patients might be lumped to produce meaningful figures equivalent to a single large study. The single surgical treatment study used here needs no such manipulation, but is in reality already a pooled (cooperative) investigation.

Studies were selected for this review based on similarities which might allow pooling of data for summarization. Populations are broadly similar, as are definitions and experimental designs. Exceptions and limitations are noted; for instance, two of the control groups have limitations which must exclude them from the Natural History pool.

The controls of Siekert et al. include some patients who had been treated with anticoagulants, and many who had medical and unspecified contraindications to anticoagulation. This might result in a higher risk of death and/or completed stroke among these controls than among randomized control patients.

The control ("nonsurgical") group from Fields et al. is likely to have a lower incidence of new completed strokes than others because patients are included who were anticoagulated or otherwise given the "best medical treatment" in the cooperating institutions.

Another obstacle to pooling is the error accrued in combining data from studies with average follow-ups ranging from 11 months to 60 months. Logic and clinical experience suggest that morbidity and mortality would increase with prolongation of follow-up. Support for this concept is provided by Baker et al. who noted that the incidence of stroke and of death in persons at risk (having had TIA) was fairly linear, with about 5% having new strokes each year and 4% deaths per year in patients whom they followed for an average of 41 months. This suggests that individual studies of different follow-up duration might be adjusted to some theoretical average follow-up period by simply multiplying the number of strokes (or deaths) by the theoretical average follow-up time (months) and dividing by the number of months of actual average follow-up. Forty months was chosen as the theoretical follow-up period since patients in a majority of studies were followed for approximately this duration. As an example, Baker et al. reported on 20 control cases of which four (20%) had completed strokes and two (10%) died in a 20-month average follow-up (table 2). To adjust for a theoretical 40-month average follow-up, the actual number of strokes (four) is multiplied by 40 (months theoretical average follow-up) and divided by 20 (months actual follow-up), giving a projected value of eight (40%) strokes in a 40-month projected follow-up period. Similar calculations indicate four (20%) deaths in the same projected follow-up period.

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<tr>
<th>TABLE 4</th>
<th>Natural History (Adjusted to 40 Months' Average Follow-up with Pooled Results)</th>
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period. Tables 4, 5 and 6 summarize the adjustment to a 40-month average follow-up for all studies considered; in addition, pooled resultants are shown. The combined studies of natural history of TIA indicate (table 4) 16% new completed strokes and 17% deaths in the 210 total patients of these three studies. The work of Marshall obviously contributes markedly to the lowering of morbidity and mortality in the pooled resultant.

Pooling of anticoagulant therapy results is considered in two parts. Since the Mayo Clinic study is the largest, it exerts a dominant influence on the pooled results. To indicate the relative effect of this influence, the three smaller studies were combined as a separate group for comparison with the total pool (table 5). Both groupings indicate a significant reduction of completed stroke incidence in treated patients compared with controls.

Since the surgical therapy results are dependent on a single cooperative study, no pooling was necessary. However, the adjustment to a 40-month follow-up was made and it can be seen in table 6 that the numbers of patients in the strokes and deaths categories are reduced slightly, though the percentages of these categories are unchanged since all percentages are rounded off to the nearest whole number.

**Discussion and Conclusions**

Table 7 summarizes the data for comparison. The natural history group (pool) includes all three natural history studies and three anticoagulant control studies. Sickert's anticoagulant controls and the Fields "nonsurgical" controls were excluded for reasons noted earlier. The anticoagulant therapy group (pool) includes all studies reviewed, and the surgical therapy group (pool) includes all patients studied by Fields (i.e., the "reanalysis" of table 6), including those who died or had strokes in the immediate postoperative period. The numbers of patients are not large, yet they represent investigations over many years in several institutions. This table suggests strongly that either anticoagulation or surgery is preferable to no therapy, but anticoagulant therapy appears the better at this time. In patients with contraindications to anticoagulation, surgery should certainly be considered, since this almost halves the likelihood of completed stroke in three and one-half years'
follow-up. In order to assure surgical morbidity results at least as good as reported by Fields et al.,1 decisions on surgical therapy must depend ultimately on the availability of surgeons and others with interest and experience in this form of therapy.

**Summary**

Combined results of selected studies of the natural history and therapeutic results in patients with TIA indicate that anticoagulant therapy is clearly worthwhile in the prevention of completed strokes during the first 40 months after onset. Surgery is somewhat less valuable, but preferable to nihilism, which is associated with new completed strokes in 19% of patients and death in 20% of patients followed for an average of 40 months from onset of TIAs. The incidence of death from all causes is remarkably similar in both treated and untreated patients during this follow-up period, suggesting that fears of increased mortality in patients treated with anticoagulants are either unfounded or compensated by decreased mortality from occlusive strokes.

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