Anticoagulant Therapy in Cerebrovascular Disease: Review and Meta-analysis

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Sixteen acceptably randomized studies of anticoagulant therapy after cerebral or retinal ischemia or infarction are reviewed and the results among 1,046 anticoagulated patients and 1,071 controls are analyzed. The following conclusions are derived. 1) Anticoagulant therapy has not been shown to be better than control management after transient ischemia or nonprogressing ischemic stroke; this is true whether the control management was deliberately ineffectual treatment (generally studies completed in 1974 or earlier) or platelet antiaggregant therapy (pooled results of three recent studies). 2) Although a study done 30 years ago demonstrated no benefit, a recent study showed benefit from anticoagulant therapy in patients who had had cerebral emboli of cardiac origin; additional controlled data are needed. 3) There is evidence that patients with thrombosis in evolution might benefit from anticoagulant therapy; additional controlled data are needed. (Stroke 1988;19:1043–1048)

Does anticoagulant therapy (ACT) improve stroke and death outcomes in patients who have suffered ischemia or infarction of the brain or retina? I review 17 controlled studies on the subject (Table 1).

Materials and Methods

Studies were found through computerized search, direct search of the cumulative Index Medicus, suggestions from colleagues, and review of references in articles already discovered. Being well aware that an analysis such as this, especially when the work of one person, can suffer from error, incompleteness, and bias,22 I solicit references to studies I have missed and alternative interpretations of the data I have summarized. I will, on request, provide more extensive notes on my own interpretations, as well as the various calculations.

Where possible, I have used the end points of stroke or death (S + D) occurring during observation. The overall expected S + D per patient-month of observation for a given (arm of a) study is the sum of S + D for the treated and control groups divided by the sum of the patient-months for the two groups. This overall expected S + D rate multiplied by the patient-months of observation for each group separately gives the expected S + D for each group. Significance is defined as p<0.05.

Where feasible, I have pooled the S + D results for meta-analysis. Certain studies present results in forms not suitable for S + D analysis and are therefore not amenable to meta-analytic pooling; the authors’ end points are given for these studies and the authors’ analyses of significance are recorded.

Results

Individual Studies

Table 2 summarizes the S + D results from 10 studies in which patients with stroke and transient ischemic attacks (TIAs) were randomized to ACT or to deliberately ineffectual treatment (placebo, no treatment, or deliberately ineffectual doses of anticoagulants). Among 20 identifiable groups or subgroups from these 10 studies there is one (the Cerebral Embolism Study20) in which the ACT outcome was significantly better than control. In three other instances (the completed stroke and embolism groups from the National Cooperative Study9,10 and the male stroke group from the Veterans Administration Cooperative Study11) the ACT results were significantly worse than control. In the other 16 groups or subgroups the difference between the ACT and control outcomes was not significant (in seven the ACT outcomes were a bit better, and in nine a bit worse, than control).

Table 3 summarizes the results from three studies of ACT versus platelet antiaggregant therapy. ACT gave slightly better results in two and slightly worse results in the third study; in no study was the difference significant.
### TABLE 1. Controlled Studies of Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean [range] age (yr)</th>
<th>% male</th>
<th>Mean duration of study (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall and Shaw(^1^2) (begun 1956)</td>
<td>[30–59]</td>
<td>47</td>
<td>6</td>
<td>All: acute thrombosis; severe persistent disturbance 72 hr before admission. 15.7% ICA, 64.7% MCA, 5.9% ACA, 13.7% VB.</td>
</tr>
<tr>
<td>Carter(^3^4) (begun 1956)</td>
<td>[60–69]</td>
<td>58</td>
<td>6</td>
<td>All: thrombosis; 87% ICA, 13% VB.</td>
</tr>
<tr>
<td>McDowell et al(^5) (1956–1961)</td>
<td>[30–90]</td>
<td>~65</td>
<td>30</td>
<td>All: established stroke, not progressing, not TIA, not explicitly recent; blood pressure &lt;180/110 mm Hg. 79% CA, 21% VB.</td>
</tr>
<tr>
<td>Baker et al(^6) (1956–1964)</td>
<td>62</td>
<td>100</td>
<td>39.3</td>
<td>Stroke lasting &gt;24 hr, occurred ≥14 days earlier: 80.2% cerebral, 19.8% brainstem.</td>
</tr>
<tr>
<td>Hill et al(^7^8) (1957–1961)</td>
<td>57</td>
<td>73</td>
<td>29.5</td>
<td>TIA: 50% CA, 50% VB. None severely hypertensive.</td>
</tr>
<tr>
<td>Veterans Administration Cooperative Study(^9^10) (begun 1958)</td>
<td>Not given</td>
<td>100</td>
<td>11.1</td>
<td>Transient &quot;cerebral&quot; ischemia (deficit clearing in ≤12 hr) or &quot;completed infarction&quot; (deficit lasting &gt;12 hr); last episode ≥2 wk earlier in some. Mean follow-up: anticoagulant therapy 11.1 mo, control 15.5 mo.</td>
</tr>
<tr>
<td>Thygesen et al(^11) (begun ~1959)</td>
<td>62</td>
<td>~58</td>
<td>19</td>
<td>All: thrombosis ≥14 days earlier; mean diastolic blood pressure 102 mm Hg.</td>
</tr>
<tr>
<td>Wallace(^12)</td>
<td>76</td>
<td>75</td>
<td>9.7</td>
<td>68 patients with cerebral infarcts studied after hospital discharge.</td>
</tr>
<tr>
<td>Engerer and Boyesen(^13)</td>
<td>63</td>
<td>62</td>
<td>38.4</td>
<td>All: diastolic blood pressure &lt;120 mm Hg. 97% CA or VB thrombosis, 3% TIA; acute episode, deficit lasting &gt;24 hr. Mean follow-up: anticoagulant therapy 37.5 (22.8 on anticoagulant) mo, control 39.3 (22.6 on placebo) mo.</td>
</tr>
<tr>
<td>Pearce et al(^14) (begun 1962)</td>
<td>[55–64]</td>
<td>76</td>
<td>10.9</td>
<td>All: TIA; 19% diastolic blood pressure &gt;110 mm Hg. Anticoagulant therapy: 14 CA, 3 VB; control: 11 CA, 9 VB.</td>
</tr>
<tr>
<td>Bradshaw and Brennan(^16) (begun 1965, completed &lt;1974)</td>
<td>52</td>
<td>78</td>
<td>43.7</td>
<td>ICA TIA or minor stroke; no hypertension; normal appropriate carotid arteriogram. Randomization: method unspecified &lt;1970, by birth date &gt;1970. Mean follow-up: anticoagulant therapy 42.75 (18 on therapy) mo, control 44.64 mo.</td>
</tr>
<tr>
<td>Burren and Ygge(^17) (begun 1974)</td>
<td>67</td>
<td>55</td>
<td>24.1</td>
<td>All: TIA. 86% ICA, 14% VB. Computed tomography not mentioned. Randomization: by birth date.</td>
</tr>
<tr>
<td>Garde et al(^18) (begun 1976)</td>
<td>60</td>
<td>64</td>
<td>20</td>
<td>In the prior 14 days: cerebral or eye TIA (57% with incomplete recovery). Some had computed tomograms. 114 randomized to anticoagulant therapy, 127 to aspirin therapy.</td>
</tr>
<tr>
<td>Olsson et al(^19) (begun 1977)</td>
<td>66</td>
<td>69</td>
<td>12.6</td>
<td>TIA or RIND: 72% CA, 28% VB. Some had computed tomograms. All: anticoagulant therapy for 2 mo; 68 randomized for further anticoagulant therapy; 67 for aspirin + dipyridamole therapy.</td>
</tr>
<tr>
<td>Cerebral Embolism Study Group(^20) (1981–1982)</td>
<td>64</td>
<td>58</td>
<td>0.5</td>
<td>Cardiogenic embolic brain infarct (no hemorrhage on computed tomogram) ≤48 hr before entry. All: blood pressure &lt;180/115 mm Hg. Anticoagulant therapy stopped at 5 days in one and apparently at 10 days in some.</td>
</tr>
<tr>
<td>Duke et al(^21) (1980–1984)</td>
<td>67</td>
<td>63</td>
<td>0.25</td>
<td>Noncardiogenic stable partial stroke ≤48 hr before. No uncontrolled hypertension. All had computed tomograms, none had hemorrhage. Randomized to 7 days intravenous heparin or placebo.</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery territory; MCA, middle cerebral artery territory; ACA, anterior cerebral artery territory; VB, vertebrobasilar artery territory; TIA, transient ischemic attack; RIND, reversible ischemic neurologic deficit.

Of the 17 studies in Table 1, three presented data in forms that do not permit S + D analysis. The authors' conclusions are summarized in the text, along with additional results of Duke et al\(^21\) whose S + D results are given in Table 2.

Marshall and Shaw\(^1^2\) randomized 25 acute stroke patients to ACT and 26 to control management. ACT was gradually withdrawn after 21 days. By 6 weeks there had been six deaths in the ACT group and three ischemic episodes among the controls. By 6 months there had been another six deaths (two in the ACT group) and another three ischemic episodes (all in the ACT group). Whether the five ischemic episodes were TIA s or strokes is not stated; S + D analysis therefore cannot be performed. Marshall and Shaw analyzed survival to 6 weeks; they found ACT "not of value."

Carter\(^3^4\) assigned by alternation to ACT or to control management 76 patients who had had a stroke within the 48 hours preceding entry and who had shown progression for at least 2 hours before or after admission to the hospital. ACT was given for 1 month...
### Table 2. Results During and After Anticoagulant Therapy Compared With Control (Deliberately Ineffectual Treatment)

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant Stroke or death</th>
<th>Control Stroke or death</th>
<th>$\chi^2$</th>
<th>Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDowell et al‡†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke (stable)</td>
<td>90</td>
<td>51</td>
<td>51.4</td>
<td>100</td>
<td>58</td>
</tr>
<tr>
<td>Baker et al§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male TIA</td>
<td>30</td>
<td>14</td>
<td>11.1</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Hill et al‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male stroke‡</td>
<td>49</td>
<td>22</td>
<td>18.9</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>Female stroke‡</td>
<td>17</td>
<td>7</td>
<td>5.5</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>National Cooperative Study³⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TIA</td>
<td>24</td>
<td>6</td>
<td>6.2</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Thrombosis in evolution‡</td>
<td>61</td>
<td>21</td>
<td>25.7</td>
<td>67</td>
<td>39</td>
</tr>
<tr>
<td>Completed stroke (stable)</td>
<td>72</td>
<td>30</td>
<td>22.2</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Thrombosis or embolism‡</td>
<td>53</td>
<td>19</td>
<td>15.3</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>Embolism</td>
<td>12</td>
<td>11</td>
<td>6.4</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Veterans Administration Cooperative Study⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male TIA</td>
<td>22</td>
<td>2</td>
<td>0.9</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Male stroke (stable)</td>
<td>56</td>
<td>15</td>
<td>9.9</td>
<td>62</td>
<td>10</td>
</tr>
<tr>
<td>Enger and Boyesen (97% stroke)⁶</td>
<td></td>
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<tr>
<td>Male‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During therapy*</td>
<td>28</td>
<td>6</td>
<td>7.2</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>During and after therapy</td>
<td>28</td>
<td>16</td>
<td>14.1</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Female‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During therapy*</td>
<td>23</td>
<td>4</td>
<td>3.0</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>During and after therapy</td>
<td>23</td>
<td>7</td>
<td>7.1</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Pearce et al⁷</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male TIA</td>
<td>14</td>
<td>0</td>
<td>1.0</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Female TIA</td>
<td>3</td>
<td>1</td>
<td>1.0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Bradshaw and Brennan⁸</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>TIA + minor stroke</td>
<td>24</td>
<td>5</td>
<td>4.8</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral Embolism Study⁹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain infarct (embolism)</td>
<td>24</td>
<td>0</td>
<td>2.1</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Duke et alⁱ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute partial stable stroke</td>
<td>112</td>
<td>2</td>
<td>1.5</td>
<td>113</td>
<td>1</td>
</tr>
<tr>
<td>Overall total</td>
<td>714</td>
<td>229</td>
<td>205.1</td>
<td>723</td>
<td>235</td>
</tr>
<tr>
<td>By sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>199</td>
<td>69</td>
<td>55.9</td>
<td>206</td>
<td>54</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>15</td>
<td>13.6</td>
<td>39</td>
<td>12</td>
</tr>
<tr>
<td>By ischemic event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All TIA</td>
<td>93</td>
<td>23</td>
<td>20.2</td>
<td>89</td>
<td>19</td>
</tr>
<tr>
<td>All TIA + minor stroke‡</td>
<td>117</td>
<td>28</td>
<td>25.0</td>
<td>114</td>
<td>24</td>
</tr>
<tr>
<td>All embolism</td>
<td>36</td>
<td>11</td>
<td>8.5</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>All stable stroke</td>
<td>330</td>
<td>98</td>
<td>85.0</td>
<td>335</td>
<td>89</td>
</tr>
<tr>
<td>All strokes</td>
<td>546</td>
<td>178</td>
<td>158.9</td>
<td>560</td>
<td>190</td>
</tr>
</tbody>
</table>

Control was ineffectual dose of anticoagulant for Hill et al⁷,⁸ and for Pearce et al⁷; in other studies control was placebo or no treatment. Shorter follow-up for anticoagulant-treated patients in National Cooperative Study and Veterans Administration Cooperative Study explains high value for control expected stroke or death. Thyesen et al¹² not included in Table 2 because authors did not specify randomization of patients to treatment. ACT, anticoagulant therapy; C, control; >, better than; <, worse than; NS, difference not significant; TIA, transient ischemic attack.

*Not included in overall total.
†Not included by sex.
‡Not included in all strokes.
and then tapered off. All patients were followed until 6 months, when outcome was assessed for two sub-
groups. Among the 22 ACT patients whose deficits were "incomplete but progressing" when treatment
was begun, 17 recovered or improved and five were unimproved or had died; among the 20 similar con-
trols the division was 10 and 10 (p<0.05). Among 16
ACT patients whose deficits were "clinically com-
plete when treatment was begun" nine recovered or
improved and seven were unimproved or had died;
the division was nine and nine among 18 similar
controls (p>0.05). Since the numbers of S + D are not
given, S + D analysis cannot be performed.

Wallace randomized 52 patients who had had a
thrombosis at least 14 days before entry and who had "lasting evidence of neurologic deficit" (51
cerebral, one brainstem, 27 to ACT and 25 to
control management. Mean follow-up was 9.5
months for the ACT group (time spent on ACT is
not given) and 10 months for the controls. There
were three strokes in the ACT group and 10 among
the controls. According to Wallace, p was <0.05 for
this favorable ACT result. There were five or six
ACT and seven or eight control deaths. It was not
stated whether any death accompanied or followed
any of the 13 strokes; therefore, these data are not
suitable for S + D analysis.

Duke et al randomized 112 patients with acute
but stable and nonprogressing partial stroke to 7
days of continuous intravenous heparin therapy
(activated partial thromboplastin time maintained
between 50 and 70 seconds) (ACT) and 113 patients
to 7 days of intravenous placebo treatment (control).
At 0.25, 3, and 12 months (no mention was made of
therapies that might have been given during the
year of follow-up) there was no difference between
the two groups in daily activity level. By 12 months
there was an excess of deaths in the heparin group
(17 vs. 8 among the controls); the authors' life table
analysis gives p<0.01 for this undesirable ACT out-
come. Since stroke data are not given for the later
follow-up periods, S + D analysis for these periods is
not possible.

Thus, among the five results (two from Carter)
not suitable for S + D analysis, two were signifi-
cantly favorable and one was significantly unfavor-
able for ACT. Combining these results for variously
defined outcomes with the S + D outcomes listed in
Tables 2 and 3, there are three significantly favor-
able and four significantly unfavorable results among
1,046 ACT patients and 1,071 controls from 27
groups and subgroups of 16 randomized studies.

The results of Thygesen et al (ACT worse but
not significantly so) have not been included in the
above discussion because Thygesen et al did not
explicitly state that their patients were randomized.

Pooled Results

In addition to reviewing results in the individual
cohorts, one can also look at pooled S + D results.

Table 2 shows that 714 ACT patients did signifi-
cantly worse than 723 controls who received delib-
erately ineffectual treatment.

Table 3 shows no significant benefit of ACT in 128
patients compared with 132 controls who received
aspirin + dipyridamole (ASA + DP). The addition of
a third study (114 ACT patients, 127 controls who
received ASA) to the pool on the assumption that
the use of ASA + DP resulted in a response no
different from that seen with ASA alone does not
change the result of the original pooling.

Table 2 also summarizes outcome by sex. Out-
come was worse among 199 men on ACT than
among 206 men on deliberately ineffectual treat-
ment (p<0.02). Outcome was slightly worse among
43 treated women than among 39 control women
(p>0.05).

Table 2 also summarizes outcome by type and
stability of ischemic event: TIA; TIA or minor
stroke (the minor stroke cases of Bradshaw and
Brennan cannot be separated from their TIA cases);
embolism; stable stroke; and all strokes thrombotic
or embolic, stable or evolving. For each type of ischemic event ACT gives results no better than control; for all strokes ACT is significantly worse (whether the results of Enger and Boyesen, who do not separate their three TIA case outcomes from their 97 stroke case outcomes, are included or not).

Table 4 shows that results of ACT in studies completed in 1974 or earlier were unfavorable ($p<0.02$). For studies begun in 1974 or later, no significant advantage from ACT was demonstrable.

**Other**

Table 2 also gives data for acute but stable partial stroke (Duke et al, no benefit from ACT) and for thrombosis in evolution (National Cooperative Study, suggesting that a larger series might have demonstrated ACT to be valuable). In this regard it should be recalled that Carter and Boyesen, who do not separate their three TIA case outcomes from their 97 stroke case outcomes, are included or not).

For stable stroke it should be recalled that Carter had noted a significant benefit from ACT. However, a contrary result was seen in the embolism arm of the study of 1957-1961: the National Cooperative Study showed significant benefit from ACT. However, a much heavier evidence of a lack of S+D benefit occurred; these are discussed below.

Wallace noted a significantly lower occurrence of new stroke among 27 stroke patients with persisting deficits who were treated with ACT than among 25 controls. However, this suggestion of benefit in a small study is strongly negated by the much heavier evidence of a lack of S+D benefit among the stable stroke patients (330 ACT, 335 control) of four studies pooled in Table 2.

Carter showed a significant benefit from ACT among patients with thrombosis in evolution in a nonpoolable study. The National Cooperative Study showed a nonsignificantly better result among ACT than among control patients with thrombosis in evolution. On the basis of these two outcomes, one could suggest that additional controlled study of stroke in evolution is warranted.

The Cerebral Embolism Study of 1981-1982 showed significant benefit from ACT. However, a contrary result was seen in the embolism arm of the National Cooperative Study of 1957-1961: the

**Discussion**

There is no evidence of significant benefit from ACT in various poolings of patients with brain or retinal ischemia or infarction. With respect to individual studies, in four groups the results were significantly unfavorable. In three groups, however, significant benefit occurred; these are discussed below.

Table 5 shows that results of ACT in studies completed in 1974 or earlier were unfavorable ($p<0.02$). For studies begun in 1974 or later, no significant advantage from ACT was demonstrable.

**Other**

Table 2 also gives data for acute but stable partial stroke (Duke et al, no benefit from ACT) and for thrombosis in evolution (National Cooperative Study, suggesting that a larger series might have demonstrated ACT to be valuable). In this regard it should be recalled that Carter had noted a significant benefit from ACT in a recovery-improvement-death analysis in incomplete but progressing stroke. For stable stroke it should be recalled that the studies not suited for pooling showed varying results by a variety of outcome criteria: worsening, Duke et al; benefit, Wallace; or no significant difference, Marshall and Shaw, and Duke et al.

Table 2 also summarizes outcome during 23 months of ACT versus outcome when 15 months of post-ACT follow-up were added (Enger and Boyesen). Neither analysis demonstrates benefit. It should be recalled that the patients of Duke et al received no S+D benefit during 1 week of ACT; at 1 year their death rate was worse than control, and their activity level was no better.

There is no evidence of significant benefit from ACT in various poolings of patients with brain or retinal ischemia or infarction. With respect to individual studies, in four groups the results were significantly unfavorable. In three groups, however, significant benefit occurred; these are discussed below.

Wallace noted a significantly lower occurrence of new stroke among 27 stroke patients with persisting deficits who were treated with ACT than among 25 controls. However, this suggestion of benefit in a small study is strongly negated by the much heavier evidence of a lack of S+D benefit among the stable stroke patients (330 ACT, 335 control) of four studies pooled in Table 2.

Carter showed a significant benefit from ACT among patients with thrombosis in evolution in a nonpoolable study. The National Cooperative Study showed a nonsignificantly better result among ACT than among control patients with thrombosis in evolution. On the basis of these two outcomes, one could suggest that additional controlled study of stroke in evolution is warranted.

The Cerebral Embolism Study of 1981-1982 showed significant benefit from ACT. However, a contrary result was seen in the embolism arm of the National Cooperative Study of 1957-1961: the
ACT outcome was significantly bad. Could the disparity between these two outcomes be due to intracranial hemorrhage among the earlier patients? In this regard the Cerebral Embolism Study had two possible advantages: computed tomography to rule out intracerebral hemorrhage before treatment and the availability of effective antihypertensive therapy to minimize the chance of such hemorrhage during treatment (the National Cooperative Study did not exclude hypertensive patients and the Cerebral Embolism Study excluded only those with blood pressures of >180/115 mm Hg; see Table 1).

Table 5 attempts to evaluate the possible contribution of intracerebral hemorrhage to the outcome of the earlier study. Although Baker et al9 and Fisher10 considered all observed strokes to have been infarcts, only nonstroke deaths are used as ACT end points to eliminate the chance that some end-point strokes might actually have been unrecognized hemorrhages. Despite this adjustment, which is very generous to ACT, significant benefit from ACT cannot be demonstrated in the 1957–1961 cohort or in the pooling of this cohort with the 1981–1982 patients. Still, the finding of apparent benefit from ACT after cardioembolic cerebral embolism in the Cerebral Embolism Study warrants careful attention; further controlled investigation is needed.

With regard to the issue of avoiding intracerebral hemorrhage regardless of the cause of the presenting ischemic event, it can be presumed that effective antihypertensive treatment was available to the patients of Duke et al21 and the three studies in which the controls received aspirin17–19 since all four studies were begun in 1974 or later. Furthermore, all patients of Duke et al21 and some patients of Garde et al18 and Olsson et al19 had computed tomograms (see Table 1). Nevertheless, these studies did not demonstrate a benefit from ACT.

Thus, while it is possible that the unfavorable results of the older studies (Table 4) reflected in part the existence or occurrence of intracerebral hemorrhages avoidable now, there is no demonstration from the more recent pooled results that ACT currently offers an advantage over placebo or platelet antiaggregant treatment.

References


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