Medical Treatment of Transient Ischemic Attacks: Does It Influence Mortality?

Manuel Ramirez-Lassepas, MD, and Robert J. Cipolle, PharmD

All randomized studies published on the medical treatment of transient ischemic attacks in which controls received no treatment or placebo and in which mortality was reported were reviewed. Using the odds ratio method, we analyzed the results to determine if treatment had an effect on expected mortality. Studies were analyzed separately according to the treatment modality used. Chronic anticoagulation was used in four studies and platelet inhibitors in 12 (14 trials). This meta-analysis showed that neither treatment modality significantly reduces mortality. Chronic anticoagulation may have an adverse effect, and even though platelet inhibitors appeared to reduce mortality, no significance can be demonstrated, and the 95% confidence intervals did not allow us to rule out the possibility, albeit small, of an adverse effect or no effect at all. (Stroke 1988;19:397–400)

The medical treatment of transient ischemic attacks (TIAs) continues to be controversial. Two types of medical treatment aimed at interfering with intra-arterial clot formation have been studied: chronic anticoagulation and platelet inhibition. Reviews have scrutinized the studies of both treatment modalities and have exposed their methodologic weaknesses. However, the main questions regarding the efficacy of these different treatment modalities remains unanswered: does either treatment modality decrease the risk of stroke or recurrent TIAs and/or reduce mortality?

The difficulty in answering these questions resides in the fact that the majority of studies did not include enough patients in their trials. Most of those that did include enough patients failed to show significant results. The studies were so heterogeneous in their methodologies that any conclusions derived from direct comparisons between studies and/or pooling of the data are highly questionable.

A statistical method of analysis that avoids direct comparisons between patients in different studies — the proverbial apples and oranges — by analyzing exclusively the observed occurrence of end points (results) would provide the appropriate means to look at the above-posed questions. Yusuf et al used such a method in studying the effect of beta blockers in myocardial infarction. Using this method, called the estimated odds ratio, we analyzed the results of the published studies on the medical treatment of TIAs to determine whether risk of death was reduced by treatment.

Materials and Methods

All 56 studies on the medical treatment of TIAs published as of June 1986 were reviewed. The 15 studies in which randomized controls received either no treatment or placebo and in which mortality results were given were selected for analysis so that an expected mortality could be calculated for each treatment modality. Studies were then classified according to the treatment modality used in the trials: chronic anticoagulation in 4, aspirin in 6, sulfinpyrazone in 3, dipyridamole in 2, clofibrate in 1, and aspirin plus sulfinpyrazone in 1 study.

Statistical Methods

Standard methods for 2 × 2 comparison of treatment/placebo vs. lived/died analyses were used. The observed number of deaths among the treatment group (O) in each study was contrasted with the expected number of deaths for all patients (E) in the same study. Assuming no effect of drug treatment, E was calculated as $E = nd/N$, where $n$ is the number of patients treated with active drug, $d$ is the total number of deaths observed in the study, and $N$ is the total number of patients studied. If treatment with chronic anticoagulation and/or platelet inhibitors had no effect on mortality, the difference between observed and expected deaths $(O - E)$ would differ only ran-

TABLE 1. Published Reports on the Medical Treatment of Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Pts</th>
<th>O</th>
<th>%</th>
<th>E</th>
<th>E-O</th>
<th>Variance of E-O</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baker et al¹⁸</td>
<td>1962</td>
<td>24</td>
<td>5</td>
<td>20.83</td>
<td>20</td>
<td>2</td>
<td>10.00</td>
<td>3.82</td>
</tr>
<tr>
<td>Pierce et al¹⁹</td>
<td>1965</td>
<td>17</td>
<td>0</td>
<td>0.00</td>
<td>20</td>
<td>2</td>
<td>10.00</td>
<td>0.92</td>
</tr>
<tr>
<td>Baker et al²⁰</td>
<td>1966</td>
<td>30</td>
<td>6</td>
<td>20.00</td>
<td>20</td>
<td>30</td>
<td>15.67</td>
<td>5.50</td>
</tr>
<tr>
<td>Bradshaw and Brennan²¹</td>
<td>1975</td>
<td>24</td>
<td>2</td>
<td>8.33</td>
<td>25</td>
<td>1</td>
<td>4.00</td>
<td>1.47</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>95</td>
<td>13</td>
<td>13.68</td>
<td>95</td>
<td>10</td>
<td>10.53</td>
<td>11.71</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fields et al²²</td>
<td>1977</td>
<td>68*</td>
<td>3</td>
<td>4.41</td>
<td>60*</td>
<td>4</td>
<td>6.67</td>
<td>3.72</td>
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<tr>
<td>Fields et al²³</td>
<td>1978</td>
<td>48*</td>
<td>2</td>
<td>4.17</td>
<td>41*</td>
<td>1</td>
<td>2.44</td>
<td>1.62</td>
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<tr>
<td>Canadian Cooperative Study Group²⁴</td>
<td>1978</td>
<td>144</td>
<td>4</td>
<td>2.78</td>
<td>139</td>
<td>10</td>
<td>7.19</td>
<td>7.12</td>
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<tr>
<td>Reuther and Dorndorf²⁵</td>
<td>1978</td>
<td>29</td>
<td>0</td>
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<td>0</td>
<td>0.00</td>
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<tr>
<td>Jessico et al²⁶</td>
<td>1978</td>
<td>9</td>
<td>0</td>
<td>0.00</td>
<td>9</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Sorensen et al²⁷</td>
<td>1983</td>
<td>101</td>
<td>7</td>
<td>6.93</td>
<td>102</td>
<td>2</td>
<td>6.86</td>
<td>6.97</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>399</td>
<td>16</td>
<td>4.01</td>
<td>380</td>
<td>22</td>
<td>5.79</td>
<td>19.46</td>
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<tr>
<td><strong>Platelet inhibitors other than aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acheson et al²⁸ᵗ</td>
<td>1969</td>
<td>85</td>
<td>13</td>
<td>15.29</td>
<td>84</td>
<td>14</td>
<td>16.67</td>
<td>13.58</td>
</tr>
<tr>
<td>Acheson and Hutchinson²⁹ᵗ</td>
<td>1972</td>
<td>47</td>
<td>23</td>
<td>48.94</td>
<td>48</td>
<td>20</td>
<td>41.67</td>
<td>21.27</td>
</tr>
<tr>
<td>Veterans Administration Cooperative Study Group³⁰ᵗ</td>
<td>1973</td>
<td>268</td>
<td>22</td>
<td>8.21</td>
<td>264</td>
<td>30</td>
<td>11.36</td>
<td>26.20</td>
</tr>
<tr>
<td>Canadian Cooperative Study Group³¹ᵗ</td>
<td>1978</td>
<td>156</td>
<td>9</td>
<td>5.77</td>
<td>139</td>
<td>10</td>
<td>7.19</td>
<td>10.05</td>
</tr>
<tr>
<td>Robertson³²ᵗ</td>
<td>1979</td>
<td>76</td>
<td>1</td>
<td>1.32</td>
<td>71</td>
<td>5</td>
<td>7.04</td>
<td>3.10</td>
</tr>
<tr>
<td>Roden et al³³ᵗ</td>
<td>1981</td>
<td>39</td>
<td>0</td>
<td>0.00</td>
<td>39</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>671</td>
<td>68</td>
<td>10.13</td>
<td>645</td>
<td>79</td>
<td>12.25</td>
<td>74.20</td>
</tr>
</tbody>
</table>

Pts, patients; O, observed deaths; E, expected deaths; E-O, expected minus observed deaths.

For anticoagulants, pooled odds ratio = 1.30 (95% confidence interval = 3.12–0.54). For aspirin, pooled odds ratio = 0.68 (95% confidence interval = 1.31–0.36). For platelet inhibitors other than aspirin, pooled odds ratio = 0.81 (95% confidence interval = 1.16–0.56).

*Data at 6 months into study.
†Dipyridamole as platelet inhibitor.
‡Clofibrate as platelet inhibitor.
§Sulfinpyrazone as platelet inhibitor.

randomly from 0 and have a variance (V) calculated as

\[ V = E(1 - n/N) (N - d)/(N - 1) \]

If the results of a single study indicated that drug treatment was beneficial, O - E would be negative. \( \chi^2 \) statistics for all individual studies had one degree of freedom, and, therefore, a value of \( \geq 3.84 \) was considered significant at \( p \leq 0.05 \).

In our analysis, direct comparison of patients in one study with patients in another was avoided by considering the results (O - E) of each trial as an independent, randomly fluctuating estimate of the true effect of drug therapy on the relative risk of mortality. The grand total (GT) of O - E from several similar studies was examined; any overall beneficial effect from drug therapy yielded a negative GT. Similarly, if therapy were without effect, GT would differ only randomly from 0 with V equal to the sum of the individual variances (SIV). An estimate of the pooled odds ratio of death among treated patients relative to placebo and no-treatment controls was calculated as \( e^{\text{SIV}} \). A pooled odds ratio of <1.0 represented a beneficial effect of drug treatment. Pooled odds ratios were calculated separately for classes of studies employing chronic anticoagulation, aspirin, and nonaspirin platelet inhibitors. The pooled odds ratio for all randomized, placebo-controlled studies employing any antiplatelet agent, including aspirin and aspirin plus sulfinpyrazone, was also calculated. In studies in which a single placebo group was used for comparison with multiple drug treatment groups, the placebo group data were used only once in the pooled analyses. The 95% confidence intervals of the pooled odds ratios were calculated as \( e^{\text{SI(NV)}} \). A beneficial effect of drug therapy was considered significant if the pooled odds ratio was <1.0 and the 95% confidence intervals did not encompass 1.0.

Results

No individual study employing anticoagulants, aspirin, or other antiplatelet agents significantly reduced mortality when compared with placebo or no-treatment controls. The most common cause of death observed was cardiac.
Table 1 depicts the data of the chronic anticoagulation studies, which provide no good evidence for any effect of anticoagulant therapy on mortality. Only 190 patients have been evaluated, 95 treated with chronic anticoagulation versus 95 no-treatment controls in four studies. The pooled odds ratio of 1.3 indicates that an adverse effect from chronic anticoagulation on mortality is likely. However, the 95% confidence intervals were wide and included values from 0.54 to 3.12. Thus, we could not rule out a substantial beneficial or adverse effect.

In 1970, the data of the aspirin studies are presented. A total of 779 patients have been evaluated in aspirin versus placebo studies. From these results, our best estimate of the effect of aspirin on mortality is a 32% reduction (pooled odds ratio of 0.68). This estimate, however, is not significant since the 95% confidence interval ranges from 0.36 to 1.31 so we cannot rule out no effect or adverse effect of treatment.

Also in Table 1, the data of 1,316 patients evaluated in studies employing a single platelet inhibitor other than aspirin are presented. The pooled odds ratio was 0.81, with a 95% confidence interval of 0.56 to 1.16. The results of these studies indicate that the best estimate of the overall effect of nonaspirin platelet inhibitors is a reduction in the relative risk of mortality of 19% when compared with placebo controls. This estimate, again, was not significant and we could not rule out, although less likely, an absence of effect or an adverse effect on mortality.

**Discussion**

By using the odds ratio method, or meta-analysis, we avoided direct comparisons between studies and concentrated only on their results. We specifically avoided comparing results from the chronic anticoagulation studies with those of the different platelet inhibitors. Their methodologies were, in general, quite different; the older chronic anticoagulation studies had multiple flaws in their designs; other than the small number of patients studied. Baker et al., for instance, eliminated from their study as misdiagnosed those patients in the control group who suffered intracerebral hemorrhage. However, they kept as complications of therapy those cases suffering intracerebral hemorrhage who were in the treatment group. This, no doubt, is reflected in their mortality results. In the latest of the chronic anticoagulation studies, published in 1975, Bradshaw and Brennan did not prospectively randomize all patients, and even though they did not have deaths due to intracerebral hemorrhage, their treatment group experienced a higher incidence of myocardial infarction, which accounted for their higher mortality.

The studies in which platelet inhibitors were used to treat TIA's had, in general, better methodologies, and, except for those of Acheson et al and Acheson and Hutchinson and the Veterans Administration Cooperative Study, all were published within the last decade. These studies included more patients, and their designs were more in keeping with sounder statistical methods; nevertheless, flaws can be found in all of them.

Because of the similar trend in the results of the aspirin and nonaspirin platelet inhibitors classes, we combined them to express the mortality risk reduction for all platelet inhibitor studies. Although these studies employed different drugs, their methodologies are comparable, and the effect of the treatment is similar; therefore, we thought it justified to pool their results. Additionally, we found similarities between the pooled odds ratios and confidence intervals for the aspirin (0.68, 0.36–1.31) and the nonaspirin platelet inhibitor classes (0.81, 0.56–1.16). The observed G O – E is – 8.56, indicating that there were eight fewer deaths in the treatment groups than would have been expected if the platelet inhibitor therapy had no effect on mortality and, therefore, eight more deaths in the placebo control groups. These data indicate that a total of 16 deaths might have been prevented during the studies if all enrolled patients had received antiplatelet therapy. The pooled odds ratio was 0.79, a value that would suggest a 21% reduction in the risk of death associated with antiplatelet therapy, three fewer deaths for every 100 patients treated. This difference, however, did not reach significance. The 95% confidence interval included 0.57 to 1.09. Although our best estimate is that antiplatelet therapy reduced the risk of mortality by 21%, we cannot rule out, although less likely, no effect or a mildly detrimental effect. None of the studies by themselves demonstrated a significant reduction in mortality. However, as a class, the platelet inhibitor studies show that it may be more likely than not that mortality was reduced.

In only two studies were results for men and women reported separately, and in neither was there a difference in mortality between the sexes.

Failure of chronic anticoagulation, aspirin, and other platelet inhibitors to protect against mortality in the reviewed studies may reflect their failure to prevent cardiac complications in these patients, and it may be independent of their effectiveness in reducing the incidence of ischemic stroke in patients with TIAs.

**References**

15. Dyken ML: Transient ischemic attacks and aspirin, stroke, and death; negative studies and Type II error (editorial). *Stroke* 1983;14:2-4

**KEY WORDS** • anticoagulants • drug therapy • mortality • platelet inhibitors • transient ischemic attacks
Medical treatment of transient ischemic attacks: does it influence mortality?
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Stroke. 1988;19:397-400
doi: 10.1161/01.STR.19.3.397

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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