Myocardial Infarction, Thrombolytic Therapy, and Stroke
A Community-Based Study

W.T. Longstreth Jr., MD, MPH; Paul E. Litwin, MS; W. Douglas Weaver, MD; and the MITI Project Group

Background: Thrombolytic therapy used in patients with acute myocardial infarction may increase the risk of stroke. Scant information is available from community-based studies.

Summary of Report: Among 5,635 consecutive patients admitted with acute myocardial infarction to hospitals in Seattle and surrounding suburban King County, Washington, 116 (2.1%) experienced strokes during hospitalization. Of these strokes, 82 (71%) were ischemic and 34 (29%) were hemorrhagic, defined by a patient's having had a computed tomographic scan of the head that showed blood. Thrombolytic therapy was given to 1,413 of these patients (25%) and was associated with increased risk of hemorrhagic stroke but reduced risk of ischemic stroke. The relative risk of stroke with thrombolytic therapy was estimated using multiple logistic regression to adjust for potential confounding factors. The adjusted relative risk for hemorrhagic stroke was 3.6 (95% confidence interval [CI], 1.7–8.0); for ischemic stroke, 0.4 (95% CI, 0.2–0.9); and for overall stroke, 1.0 (95% CI, 0.6–1.7). The adjusted risk for death from any cause following stroke was 3.0 (95% CI, 1.4–6.4).

Conclusions: Although thrombolytic therapy had little effect on the overall occurrence of stroke, thrombolytic therapy increased the risk of stroke death because more patients with hemorrhagic than ischemic strokes died during their hospitalization. The rates of hemorrhagic stroke with thrombolytic therapy reported in the present study are higher than those reported in clinical trials in which treatment is given to select patients under strict protocols. (Stroke 1993;24:587–590)

Keywords: cerebrovascular disorders • myocardial infarction • thrombolytic therapy

Information on the occurrence of stroke in patients with acute myocardial infarction who undergo thrombolytic therapy comes mostly from large randomized trials of select patients.1–5 This information may not be applicable to all patients with acute myocardial infarction or to the use of thrombolytic therapy outside strict study protocols. Thus, we examined the frequency of stroke and the influence of thrombolytic therapy using limited information collected as part of a community-based registry of all patients admitted with acute myocardial infarction.

Subjects and Methods
The Myocardial Infarction Triage and Intervention (MITI) Project encompasses a comprehensive registry of all patients admitted with an acute myocardial infarction and a series of clinical trials.6 This paper concentrates on information collected as part of the registry and not the randomized trials. The MITI registry includes all 19 acute care hospitals in Seattle and surrounding suburban King County, Washington. Since January 1988, admissions to coronary care units have been screened on a regular basis to identify those patients admitted with a possible acute myocardial infarction. Accredited medical record technicians reviewed the charts of those patients with evidence of an acute myocardial infarction at the time of discharge or death. The accuracy of this selection process has been reported previously.7 The information collected included demographics of the patients; clinical course during the hospitalization, including complications and treatments; and hospital outcomes.

For the purposes of this study, stroke was defined as an acute, focal neurological deficit occurring during the hospitalization, considered secondary to vascular disease (occlusion or rupture), and lasting more than 24 hours. If a computed tomographic (CT) scan of the head had been done and the radiology report described intracranial blood, the stroke was classified as hemorrhagic. No attempt was made on the basis of the information in the report to distinguish between intraparenchymal hemorrhage and hemorrhagic infarction. If a scan was not performed or if the scan failed to show blood, the stroke was classified as ischemic. Unfortu-
nately, no further information was collected on those classified as ischemic, so the exact number having had a CT scan of the head is unknown. In an unselected series of these patients with stroke, virtually all had been scanned.

Predictors of stroke were sought with both univariate and multivariate analyses. In analyses involving one stroke type (ischemic or hemorrhagic), patients with the other type were excluded. The univariate analysis consisted of comparisons between stroke and the potential predictors listed in Table 1. Multivariate analyses were done to control for potential confounding factors that might alter the associations between stroke and thrombolytic therapy. Stepwise multiple logistic regression was used and allowed the potential predictors of stroke in Table 1, with age and weight as continuous variables, to enter a model that always contained thrombolytic therapy. An estimate of the adjusted relative risk of stroke with thrombolytic therapy was calculated from the coefficient for thrombolytic therapy in the final model.

Results

Between January 1988 and April 1991, 5,635 patients were admitted with their first acute myocardial infarction. A hundred sixteen of these patients (2.1%) experienced a stroke during hospitalization: 82 (71%) were ischemic and 34 (29%) were hemorrhagic. In the univariate analyses (Table 1), many factors were significantly related to the occurrence of ischemic stroke. Few were related to the occurrence of hemorrhagic stroke, in part because of the smaller numbers of patients who had such strokes. Patients who had no chest pain at the time of admission were at increased risk for both ischemic and hemorrhagic strokes. Such patients either had resolution of chest pain before admission, or their presenting symptoms were predominantly breathlessness due to congestive heart failure. Advanced age was also a risk factor for both stroke types. Patients treated with aspirin during their hospitalization were only half as likely to have a hemorrhagic stroke as those not treated with aspirin (relative risk, 0.48). This apparent protective effect of aspirin for hemorrhagic strokes was spurious because patients with intracranial bleeding were not treated with aspirin during their subsequent hospitalization, whereas those without bleeding were likely to be treated with aspirin. A similar argument likely explains the paradoxical association between heparin therapy and stroke types listed in Table 1.

One quarter of the patients (1,413) received thrombolytic therapy. For 1,137 (80.5%) this consisted of recombinant tissue plasminogen activator (alteplase), which was almost always given intravenously. For 222 (15.7%) streptokinase was used, given by intravenous means in 75 (34%) and intracoronary means in 147 (66%). Other thrombolytic agents were used in 54 patients (3.8%).

The frequencies of stroke and death among those experiencing a stroke are presented in Figure 1 for the patients receiving or not receiving thrombolytic therapy. With thrombolytic therapy most of the strokes were hemorrhagic, whereas without thrombolytic therapy most were ischemic. Patients with a hemorrhagic stroke were more likely to die than those with an ischemic stroke (53% versus 28%). Eight patients suffered a stroke with thrombolytic therapy and survived to discharge. One patient with a hemorrhagic stroke was discharged to a nursing home; the others were discharged home. Twenty-six patients suffered a stroke without thrombolytic therapy and survived to discharge. Seven of 11 surviving patients with a hemorrhagic stroke

### Table 1. Potential Predictors of Stroke in Patients With Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Ischemic (n=82)</th>
<th>Hemorrhagic (n=34)</th>
<th>Overall (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR*</td>
<td>95% CI</td>
<td>RR*</td>
</tr>
<tr>
<td>70 years or older</td>
<td>3.0†</td>
<td>1.9-4.8</td>
<td>2.0†</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.9†</td>
<td>1.2-2.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Weight of ≤69 kg</td>
<td>1.4</td>
<td>0.91-2.2</td>
<td>2.0</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.9†</td>
<td>1.2-3.0</td>
<td>1.1</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>1.7</td>
<td>0.95-2.9</td>
<td>0.72</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>0.73</td>
<td>0.41-1.3</td>
<td>0.47</td>
</tr>
<tr>
<td>No chest pain on admission</td>
<td>5.0†</td>
<td>3.1-8.0</td>
<td>2.8†</td>
</tr>
<tr>
<td>Syncope on admission</td>
<td>5.6†</td>
<td>3.2-10.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Shock on admission</td>
<td>4.2†</td>
<td>2.0-9.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Heart failure after admission</td>
<td>3.0†</td>
<td>1.9-4.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Extension of myocardial infarct</td>
<td>2.8†</td>
<td>1.4-5.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>0.45†</td>
<td>0.22-0.89</td>
<td>0.62</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>1.8†</td>
<td>1.0-3.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Aspirin therapy</td>
<td>0.55†</td>
<td>0.35-0.86</td>
<td>0.48†</td>
</tr>
<tr>
<td>Heparin therapy</td>
<td>1.5</td>
<td>0.53-4.0</td>
<td>0.55</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>0.28†</td>
<td>0.13-0.61</td>
<td>2.3†</td>
</tr>
</tbody>
</table>

*Relative risk (RR) calculated by dividing frequency of stroke in those with attribute by frequency of stroke in those without attribute. An RR of >1 indicates an increased risk of stroke; <1, a reduced risk. If the 95% confidence interval (CI) does not include one, the finding is statistically significant at a p<0.05 level.

†Significant at p<0.05 level.
and 19 of 56 with an ischemic stroke were discharged to a nursing home.

Table 2 summarizes the information on stroke occurrence and stroke death with estimates of unadjusted and adjusted relative risks. Thrombolytic therapy was associated with a reduced risk of ischemic stroke and an increased risk of hemorrhagic stroke and hemorrhagic stroke death. Thrombolytic therapy did not affect overall stroke occurrence, but it did increase the risk of overall stroke death.

Discussion

In this large community-based study of consecutive patients with acute myocardial infarction, 2.1% of the patients experienced a stroke. Ischemic strokes were more than twice as common as hemorrhagic strokes. Many risk factors for ischemic stroke, including age and history of hypertension, were identified. In general, those variables indicating a more extensive myocardial infarction were associated with an increased risk of ischemic stroke, probably because of emboli from the heart. Interestingly, thrombolytic therapy was associated with a reduced risk of ischemic stroke. The apparent protection persisted after controlling for potential confounding factors in a multivariate model. Thrombolytic therapy could reduce the risk of embolic stroke by reducing the extent of myocardial damage and thus the occurrence of left ventricular thrombi. On the other hand, the major predictor of hemorrhagic stroke was the use of thrombolytic therapy. This increased risk persisted after controlling for potential confounding factors in a multivariate model.

The outcomes from the stroke types were markedly different. Twenty-eight percent of patients with ischemic stroke died during the hospitalization, compared with 53% of those with hemorrhagic stroke. Thus, although thrombolytic therapy had little effect on overall stroke occurrence (a greater number of patients with hemorrhagic strokes being balanced by fewer with ischemic strokes), it increased the risk of stroke death. After controlling for potential confounding factors in a multivariate model, we found that thrombolytic therapy tripled the risk of stroke death.

The major strength of the study is its being community based, with large numbers of consecutive patients. These results are more likely to reflect general practice than results from clinical trials in which thrombolytic therapy is given to a narrower spectrum of patients under stricter protocols. Weaknesses in the study include its having scant information about the stroke types, considering outcomes that occurred only during the hospitalization, and having too few patients with strokes to perform subgroup analyses among those receiving different agents or combinations of antithrombotic therapies.

Nonetheless, the frequency of stroke in this community-based study is higher than that reported in randomized trials but not as high as has been reported in some hospital-based series. For instance, following thrombolytic therapy, the frequency of hemorrhagic stroke in randomized trials has been 3.0–0.7%, compared with 1.1% in the current study and 2.8–5.0% in some hospital-based reports. One previous randomized trial suggested a differential effect of thrombolytic therapy, as found in this study, increasing the risk of hemorrhagic stroke while reducing the risk of ischemic stroke. Despite these balancing effects on stroke occurrence, overall thrombolytic therapy seems to increase the risk of stroke death because of an excess of deaths among patients who develop hemorrhagic stroke.

Acknowledgments

This study was possible because of the cooperation of the hospitals and cardiologists in King County, Washington, and the dedicated staff members who helped to collect these data.

**Figure 1. Diagram showing use of thrombolytic therapy and occurrence of stroke among 5,635 consecutive patients admitted to hospitals in King County, Washington, with their neurological deficits developing during the hospitalization, considered to be due to vascular disease, and lasting more than 24 hours. Stroke was classified as hemorrhagic if computed tomographic scan showed blood or ischemic if scan showed no blood or was not done. Outcome from hospitalization was indicated as either died or discharged alive.**

**Table 2. Relative Risk of Stroke and Stroke Death With Thrombolytic Therapy**

<table>
<thead>
<tr>
<th>Stroke type*</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke rate</td>
<td>RR† 95% CI</td>
<td>RR† 95% CI</td>
<td>RR† 95% CI</td>
<td>RR† 95% CI</td>
</tr>
<tr>
<td>Ischemic</td>
<td>0.3 0.1–0.6</td>
<td>0.4 0.2–0.9</td>
<td>0.6 0.2–1.9</td>
<td>1.5 0.4–5.3</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>2.3 1.2–4.6</td>
<td>3.6 1.7–8.0</td>
<td>3.6 1.5–9.3</td>
<td>5.2 1.9–14</td>
</tr>
<tr>
<td>Overall</td>
<td>0.7 0.4–1.1</td>
<td>1.0 0.6–1.7</td>
<td>1.5 0.8–3.0</td>
<td>3.0 1.4–6.4</td>
</tr>
</tbody>
</table>

*Stroke defined by acute focal neurological deficits developing during the hospitalization, considered to be due to vascular disease, and lasting more than 24 hours. Stroke classified as hemorrhagic if computed tomographic scan showed blood or ischemic if scan showed no blood or was not done. Stroke death defined by death from whatever cause during the hospitalization of a patient who had suffered a stroke.

†Unadjusted relative risks (RR) and 95% confidence intervals (CI) calculated as in Table 1. Estimates of relative risk adjusted for potential confounding factors listed in Table 1 derived from stepwise multiple logistic regression.
References


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