Intracranial Hemorrhage Associated With Thrombolytic Therapy for Elderly Patients With Acute Myocardial Infarction

Results From the Cooperative Cardiovascular Project

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Background and Purpose—Intracranial hemorrhage is a serious complication of thrombolytic therapy for acute myocardial infarction, especially among the elderly, but little information exists on estimating risk. Better estimation of risk in individual patients may allow for withholding or using alternate therapies among those at highest risk.

Methods—To quantify the risk and identify predictors of intracranial hemorrhage associated with thrombolytic therapy, we performed a retrospective cohort study using data from medical charts. The study involved nearly all acute-care hospitals in the United States. All Medicare patients discharged with a principal diagnosis of acute myocardial infarction during a 9-month period in 1994 to 1995 were included. The main outcome measure was intracranial hemorrhage among those treated with thrombolytic therapy.

Results—The rate of intracranial hemorrhage was 1.43% (455 of 31 732). In a logistic model, age ≥75 years, female, black race, prior stroke, blood pressure ≥160 mm Hg, tissue plasminogen activator (versus other thrombolytic agent), excessive anticoagulation (international normalized ratio ≥4 or prothrombin time ≥24), and below median weight (≤65 kg for women; ≤80 kg for men) were independent predictors. A risk stratification scale was developed on the basis of these factors: with none or 1 of the factors (n=6651), the rate of intracranial hemorrhage was 0.69%; with 2 factors (n=10 509), 1.02%; with 3 factors (n=9074), 1.63%; with 4 factors (n=4298), 2.49%; and with ≥5 factors (n=1071), 4.11% (Mantel-Haenszel; P<0.001).

Conclusions—The rate of intracranial hemorrhage in older patients after treatment with thrombolytic therapy exceeds 1%. Readily available factors can identify elderly patients with acute myocardial infarction at high and low risk for intracranial hemorrhage associated with thrombolytic therapy. (Stroke. 2000;31:1802-1811.)

Key Words: intracranial hemorrhage • myocardial infarction • risk factors • thrombolytic therapy

Thrombolytic therapy lowers the mortality rates for patients with suspected acute myocardial infarction (AMI) and ST-segment elevation or left bundle-branch block. It is the most widely used form of reperfusion therapy in the setting of an AMI and is part of standard emergency management.1,2 Many patients who are eligible for thrombolytic therapy may not be treated in part because of concern about specific patient characteristics associated with hemorrhagic complications, especially hemorrhagic stroke.3–6 Information about the risk of intracranial hemorrhage associated with thrombolytic therapy in clinical practice is limited, especially among the elderly,2 who are also at greater overall risk.7 Most of the information about the risk of hemorrhage comes from clinical trials or studies with small sample sizes, raising concerns about generalizability to routine clinical practice.
<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>n (%)</th>
<th>With Factor</th>
<th>Without Factor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male</td>
<td>18 054 (56.9)</td>
<td>1.21</td>
<td>1.73</td>
<td>0.001</td>
</tr>
<tr>
<td>Age 65–74 (vs ≥75) y</td>
<td>19 475 (61.4)</td>
<td>1.14</td>
<td>1.90</td>
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</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Black</td>
<td>1390 (4.4)</td>
<td>2.23</td>
<td></td>
<td>0.094</td>
</tr>
<tr>
<td>White</td>
<td>29 287 (92.3)</td>
<td>1.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1047 (3.3)</td>
<td>1.62</td>
<td></td>
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<tr>
<td>Medical history (PTA)</td>
<td></td>
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<tr>
<td>Atrial fibrillation/flutter</td>
<td>1713 (5.6)</td>
<td>1.58</td>
<td>1.44</td>
<td>0.636</td>
</tr>
<tr>
<td>Angina</td>
<td>13 185 (43.4)</td>
<td>1.41</td>
<td>1.43</td>
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<tr>
<td>CHF</td>
<td>2498 (7.9)</td>
<td>1.60</td>
<td>1.42</td>
<td>0.463</td>
</tr>
<tr>
<td>COPD</td>
<td>5253 (16.6)</td>
<td>1.33</td>
<td>1.45</td>
<td>0.499</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7690 (24.2)</td>
<td>1.26</td>
<td>1.49</td>
<td>0.144</td>
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<tr>
<td>Hypertension</td>
<td>18 070 (57.0)</td>
<td>1.59</td>
<td>1.22</td>
<td>0.006</td>
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<tr>
<td>Stroke</td>
<td>2332 (7.4)</td>
<td>2.14</td>
<td>1.38</td>
<td>0.003</td>
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<tr>
<td>Bleeding or bleeding disorder</td>
<td>2088 (6.6)</td>
<td>1.48</td>
<td>1.43</td>
<td>0.840</td>
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<tr>
<td>AMI</td>
<td>7325 (23.1)</td>
<td>1.61</td>
<td>1.38</td>
<td>0.146</td>
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<td>Current smoker</td>
<td>6401 (20.2)</td>
<td>1.28</td>
<td>1.47</td>
<td>0.250</td>
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<tr>
<td>PVD</td>
<td>2178 (7.2)</td>
<td>1.10</td>
<td>1.45</td>
<td>0.188</td>
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<tr>
<td>Ulcer</td>
<td>4212 (13.3)</td>
<td>1.47</td>
<td>1.43</td>
<td>0.823</td>
</tr>
<tr>
<td>Dementia</td>
<td>611 (1.9)</td>
<td>3.76</td>
<td>1.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Medications PTA</td>
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<tr>
<td>Aspirin</td>
<td>8600 (27.1%)</td>
<td>1.48</td>
<td>1.42</td>
<td>0.695</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1194 (3.8)</td>
<td>2.01</td>
<td>1.41</td>
<td>0.088</td>
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<tr>
<td>Insulin</td>
<td>2161 (6.8)</td>
<td>1.30</td>
<td>1.44</td>
<td>0.576</td>
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<tr>
<td>Oral hypoglycemics</td>
<td>3778 (11.9)</td>
<td>1.16</td>
<td>1.47</td>
<td>0.138</td>
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<td>Bronchodilators</td>
<td>2166 (6.8)</td>
<td>1.29</td>
<td>1.44</td>
<td>0.567</td>
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<tr>
<td>β-Blocker</td>
<td>5278 (16.6)</td>
<td>1.48</td>
<td>1.43</td>
<td>0.769</td>
</tr>
<tr>
<td>Ca-channel blocker</td>
<td>9453 (29.8)</td>
<td>1.44</td>
<td>1.43</td>
<td>0.963</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>4336 (13.7)</td>
<td>1.55</td>
<td>1.42</td>
<td>0.507</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>1687 (5.3)</td>
<td>1.54</td>
<td>1.43</td>
<td>0.703</td>
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<tr>
<td>Admission factors</td>
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<td></td>
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<tr>
<td>Diastolic BP ≥100</td>
<td>5084 (16.4)</td>
<td>1.81</td>
<td>1.36</td>
<td>0.014</td>
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<tr>
<td>Systolic BP ≥160</td>
<td>9091 (28.8)</td>
<td>2.06</td>
<td>1.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulse ≥100</td>
<td>4703 (14.9)</td>
<td>1.42</td>
<td>1.43</td>
<td>0.966</td>
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<tr>
<td>Weight (kg, sex-specific quartiles)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile I</td>
<td>7826 (26.4)</td>
<td>1.97</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Quartile II</td>
<td>7157 (24.1)</td>
<td>1.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile III</td>
<td>7459 (25.1)</td>
<td>1.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile IV</td>
<td>7247 (24.4)</td>
<td>0.84</td>
<td></td>
<td></td>
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<tr>
<td>Weight, kg, (sex-specific median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women ≤65 kg or men ≥80 kg</td>
<td>13 807 (46.5)</td>
<td>1.74</td>
<td>1.08</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index (vs lower)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>16 681 (61.7)</td>
<td>1.10</td>
<td>1.77</td>
<td>0.001</td>
</tr>
<tr>
<td>≥30</td>
<td>5426 (20.1)</td>
<td>0.85</td>
<td>1.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac arrest at or up to 6 h PTA</td>
<td>899 (2.8)</td>
<td>0.78</td>
<td>1.45</td>
<td>0.094</td>
</tr>
<tr>
<td>Shock at time of arrival</td>
<td>800 (2.5)</td>
<td>0.50</td>
<td>1.46</td>
<td>0.024</td>
</tr>
</tbody>
</table>
numbers of women and older patients; older patients in these trials tend to be highly selected. Given the poor prognosis for recovery, high mortality rate, and high health care costs associated with intracranial hemorrhage\(^7\) and the availability of alternate reperfusion strategies,\(^8\) identifying high-risk groups takes on special importance.

Our objectives were (1) to determine the rate of intracranial hemorrhage associated with thrombolytic therapy for elderly patients with AMI; (2) to identify independent predictive factors for intracranial hemorrhage; and (3) to develop an easily applied risk stratification scale for estimating the risk of intracranial hemorrhage among individual patients. To address these objectives, we analyzed data from 30,000 elderly patients treated with thrombolytic therapy included in the Cooperative Cardiovascular Project (CCP). The CCP is a geographically diverse, population-based cohort established as a collaborative project between the Health Care Financing Administration, healthcare professionals, and peer review organizations to examine patterns of care and stimulate improvements in the care and outcomes of Medicare beneficiaries with AMI.\(^3\)\(^,\)\(^9\)\(^–\)\(^11\)

### Subjects and Methods

The CCP is a Health Care Financing Administration quality-improvement initiative focusing on the treatment of AMI.\(^3\)\(^,\)\(^9\) The study sample includes Medicare patients ?65 years of age from nongovernmental acute-care hospitals with a principal discharge diagnosis of AMI, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 410, with those with a fifth digit of 2 (indicating subsequent episode of care) excluded. Patients were identified during an 8-month period (varying in each state) in 1994 and 1995 by means of hospital bills (UB-92 claims data) in the Medicare National Claims History File. Trained technicians abstracted predefined variables from copies of the hospital record and entered them directly into a computer database with use of interactive software. Data reliability was monitored by random reabstractions, with overall variable agreement averaging ?90%. The agreement for whether patients had been treated with thrombolytic therapy or not was 98.3%, and the \(k\) value was 0.93.\(^12\)

The outcome variable for the study was the occurrence of intracranial hemorrhage during the hospitalization (ICD-9-CM codes 430, 431, or 432). To assess the accuracy of our case ascertainment by using the discharge diagnoses, the outcome variable was compared with a separate variable abstracted from the medical record review that documented “any cerebrovascular accident” during the hospitalization (not specifically hemorrhagic). The agreement between the

### TABLE 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>Rate of Brain Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Hemorrhage 48 h PTA</td>
<td>513 (1.6)</td>
</tr>
<tr>
<td>Rales present at arrival</td>
<td>7877 (24.8)</td>
</tr>
<tr>
<td>Anteroseptal myocardial infarction</td>
<td>17 437 (55.0)</td>
</tr>
<tr>
<td>Able to walk PTA</td>
<td>30 705 (98.9)</td>
</tr>
<tr>
<td>Admit Killip class</td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>19 801 (62.4)</td>
</tr>
<tr>
<td>Class 2</td>
<td>4394 (13.9)</td>
</tr>
<tr>
<td>Class 3</td>
<td>6737 (21.2)</td>
</tr>
<tr>
<td>Class 4</td>
<td>800 (2.5)</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td></td>
</tr>
<tr>
<td>Time to therapy ≤3 h</td>
<td>26 163 (85.6)</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>6743 (21.3)</td>
</tr>
<tr>
<td>TPA</td>
<td>24 027 (75.7)</td>
</tr>
<tr>
<td>APSAC</td>
<td>234 (0.7)</td>
</tr>
<tr>
<td>Urokinase</td>
<td>681 (2.2)</td>
</tr>
<tr>
<td>Laboratory results</td>
<td></td>
</tr>
<tr>
<td>Albumin &lt;0.3 g/dL</td>
<td>1058 (4.5)</td>
</tr>
<tr>
<td>BUN &gt;40 mg/dL or Creatinine &gt;2.5 mg/dL</td>
<td>1020 (3.3)</td>
</tr>
<tr>
<td>INR &gt;4 or PT &gt;24</td>
<td>316 (1.1)</td>
</tr>
<tr>
<td>CKP &gt;4x normal</td>
<td>17 974 (58.4)</td>
</tr>
<tr>
<td>Glucose &gt;200 mg/dL</td>
<td>7820 (25.3)</td>
</tr>
<tr>
<td>Sodium &lt;130 mEq/L</td>
<td>405 (1.3)</td>
</tr>
<tr>
<td>Platelet ≤100 000/mm(^3)</td>
<td>154 (0.5)</td>
</tr>
</tbody>
</table>

PTA indicates before admission; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; APSAC, anisoylated plasminogen streptokinase activator complex; BUN, blood urea nitrogen; and CKP, creatine phosphokinase.
discharge diagnosis of a hemorrhagic stroke was >92%, indicating good accuracy for our method of case ascertainment.

Among those patients who received thrombolytic therapy, we examined bivariate associations between candidate clinical variables, selected on the basis of clinical judgment and prior reports, and intracranial hemorrhage. By using independent predictors from the bivariate analyses present in ≥5% of the cohort, we developed a multivariable logistic regression model by backward stepwise selection, with intracranial hemorrhage as the dependent variable. Because of its strong association with intracranial hemorrhage, we did make an exception and included excessive anticoagulation, which was present in ≤5% of the cohort in the regression model. Variables were dropped at a significance of $P<0.05$. The Hosmer and Lemeshow goodness-of-fit test was used to test the fit of the models.13 A risk stratification scale was developed on the basis of clinical factors and therapies, along with their associated rates of intracranial hemorrhage, are shown in Table 1. We examined the risk of hemorrhagic stroke associated with each 10–mm Hg increase in blood pressure (BP). On the basis of the results shown in Figure 1, a cutoff of ≥160 mm Hg ($\approx$29% of the sample) was used for subsequent analyses. The same strategy was used to establish the cutoff for diastolic BP ≥100 mm Hg (≈16% of the sample).

Data on an international normalized ratio (INR) or prothrombin time (PT) measurement were missing on 3882 patients. Of these, 98% (3798 of 3882) were not receiving anticoagulant therapy at the time of admission, so the comparison reported in Table 1 compares those with an elevated INR or PT with all other patients (ie, in the models, the variable was coded as either excessive anticoagulation being reported or not). To test for the effect of the missing values, a dummy variable for the missing values was included in the model. This variable was not significant, indicating that there is no association between the missing INR or PT values and the outcome of intracranial hemorrhage. The goodness-of-fit test was not significant ($P=0.21$), indicating a good fit for the model. Only the highest levels of anticoagulation were associated with an increased risk of intracranial hemorrhage. For those with an INR <2 (or a PT <15) (n=25 528), the rate of hemorrhage was 1.45%; for an INR ≥2 and <3 (or PT ≥15 and <20, n=1686), the rate of hemorrhage was 1.54%; for an INR ≥3 and <4 (or PT ≥20 and <24, n=320), the rate of hemorrhage was 1.25%; and for an INR ≥4 (or PT ≥24, n=316), the rate of hemorrhage was 2.85.

There was an increased hemorrhage rate associated with lower body weight (Figure 2). Given the consistent trend, the median weight was used for further analyses. The hemorrhage rate for weight below the median value (sex-specific values ≤65 kg for women and ≤80 kg for men) was 1.74% as compared with 1.08% for those above the median weight value ($P=0.001$). Similarly, the rates were higher for body mass index below the specified cutoff values (≥25 and ≥30) as compared with rates for body mass index above the cutoff values ($P=0.001$ for each).

Clinically relevant factors and variables selected from bivariate analyses were entered into a multiple logistic regression. Other factors that achieved statistical significance in bivariate analyses were not included because of low prevalence (eg, shock on admission, hemorrhage within 48
hours of admission, and dementia). We did make an exception and include excessive anticoagulation (INR $\geq 4$ or PT $\geq 24$) in the regression model because of the clear association of excessive anticoagulation with a greatly increased risk of intracranial hemorrhage$^{14,15}$ and the specific inclusion of excessive anticoagulation in the American College of Cardiology/American Heart Association guidelines on the management of AMI with thrombolytic therapy (Table 2).$^1$

From the multivariable logistic model (backward stepwise), the following factors were independent predictors of hemorrhagic stroke in this cohort: age $\geq 75$ years age (OR = 1.57 [95% CI 1.30 to 1.90]); female sex (OR = 1.39 [1.15 to 1.67]); black race compared with nonblack races (OR = 1.63 [1.13 to 2.37]); prior stroke (OR = 1.48 [1.10 to 2.00]); systolic BP $\geq 160$ mm Hg on admission (OR = 1.82 [1.51 to 2.21]); tissue plasminogen activator (TPA) (versus other thrombolytics) (OR = 1.57 [1.23 to 2.01]); and below median weight ($\leq 65$ kg for women and $\leq 80$ kg for men, OR = 1.47 [1.21 to 1.77]). The goodness-of-fit statistic for the final model had a probability value of 0.27, indicating a good fit for the model.

From the variables selected by the logistic model, we developed a risk stratification scale to estimate the risk of intracranial hemorrhage in an individual patient. Since the odds ratios for the selected variables were similar in magnitude (range 1.4 to 1.8), each factor was given the same weight. Because of the small number of patients with 0 factors (n = 928) and the similar rate of hemorrhage for 0 or 1 factors, we combined these into a single group (n = 6721) with a rate of intracranial hemorrhage of 0.71%. Similarly, we combined those with $\geq 5$ factors into a single group (n = 1032) with a rate of intracranial hemorrhage of 4.07%. The trend in this model of increasing risk for intracranial hemorrhage with increasing number of factors was statistically significant (Mantel-Haenszel; $P < 0.001$). The median score for the cohort was 2 factors (mean of 2.4 ± 1.1 factors), indicating that more than half of all elderly patients have a low risk ($\leq 1\%$) for a hemorrhagic stroke.

Using patients with none or 1 factor as the referent group (21%), we determined the increase in risk associated with the cumulative number of the factors in the prediction scale (Table 3). Patients with 2 factors displayed odds similar to

| TABLE 2. Factors Associated With Intracranial Hemorrhage Based on Multiple Logistic Regression With Backward Stepwise Selection* |
|---------------------------------|------|---------|------|
| Factor                          | Adjusted OR | 95% CI  | $P$  |
| Age $\geq 75$ y                  | 1.57  | 1.30–1.90 | 0.0001 |
| Black                           | 1.63  | 1.13–2.37 | 0.0096 |
| Female                          | 1.39  | 1.15–1.67 | 0.0007 |
| History of stroke               | 1.48  | 1.10–2.00 | 0.0099 |
| Systolic BP $\geq 160$ mm Hg    | 1.82  | 1.51–2.21 | 0.0001 |
| Weight below median value (women $\leq 65$ kg; men $\leq 80$ kg) | 1.47  | 1.21–1.77 | 0.0001 |
| INR $> 4$ or PT $> 24$          | 2.15  | 1.10–4.22 | 0.0257 |
| TPA use (vs other thrombolytic agent) | 1.57  | 1.23–2.01 | 0.0003 |

*Adjusted odds ratios were derived from a multiple logistic regression analysis in which each OR was adjusted for all other factors listed. OR $> 1$ indicates that patients with the characteristic have a higher likelihood of having an intracranial hemorrhage than those without the characteristic.

<p>| TABLE 3. Risk of Hemorrhagic Stroke |
|-----------------------------------|-----------------|----------|--------|</p>
<table>
<thead>
<tr>
<th>No. of Factors</th>
<th>n*</th>
<th>% With Hemorrhagic Stroke</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1</td>
<td>6651</td>
<td>21.1</td>
<td>0.69%</td>
<td>1.00</td>
</tr>
<tr>
<td>(reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10509</td>
<td>33.3</td>
<td>1.02%</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.01–2.00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9074</td>
<td>28.7</td>
<td>1.63%</td>
<td>2.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.66–3.18</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4298</td>
<td>13.6</td>
<td>2.49%</td>
<td>3.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.51–4.97</td>
<td></td>
</tr>
<tr>
<td>$\geq 5$</td>
<td>1071</td>
<td>3.4</td>
<td>4.11%</td>
<td>5.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.89–8.89</td>
<td></td>
</tr>
</tbody>
</table>

*Missing data on 129 cases.
patients in the referent category (OR 1.41 [95% CI 1.01 to
2.00]). Patients with 3 factors had double the odds (OR = 2.28
[1.66 to 3.18]), patients with 4 factors had >3 times the odds
of having a hemorrhagic stroke (OR = 3.51 [2.51 to 4.97]),
and patients with ≥5 factors had almost 9 times the odds as
the referent group (OR = 5.89 [3.89 to 8.89]). The goodness-
of-fit statistic was not significant, which indicated a good fit
of the model.

Approximately 11% of all intracranial hemorrhages oc-
curred in the 21% of the sample with none or 1 factor, 23% of
hemorrhages occurred in the sample with 2 factors, and
≈66% of hemorrhages occurred in the 45% of the cohort that
had ≥3 risk factors. Among those 65 to 74 years of age, 74% (14
233 of 19 393) were at low risk with ≤2 risk factors for
intracranial hemorrhage. Even among those ≥75 years of
age, 25% (3021 of 12 210) had ≤2 risk factors for hemor-
rhage, even including age as 1 risk factor.

Comment

We found an overall rate of thrombolysis-related intracranial
hemorrhage in this elderly cohort 3 times higher than usually
cited in published clinical trials and treatment guide-
lines.1,16,17 Furthermore, the rate of hemorrhage is strongly
associated with easily determined clinical factors. Finally,
these same factors can identify the majority of elderly
patients who are at very low risk for thrombolysis-related
intracranial hemorrhage and a minority of patients who are at
greatly increased risk for intracranial hemorrhage.

Rate of Hemorrhage

The rate of intracranial hemorrhage associated with
thrombolytic therapy is generally considered to be about half
a percent.18–23 This low rate has been derived largely from
clinical trials. The generalizability of this low rate of intra-
cranial hemorrhage to a broader population is limited by the
highly selected nature of patients enrolled in clinical trials.24
Trials enrolled healthier subjects compared with the patients
in the community;35 older patients and women are particu-
larly underrepresented.26 Higher rates of intracranial hemor-
grahve have been reported in community-based studies; the
Second National Registry of Myocardial Infarction (NRMI-2)
reported a rate of intracranial hemorrhage of 0.95%.7

Risk Factors

This large, national, community-based sample of elderly
patients with AMI treated with thrombolytic therapy is well
suited to identify characteristics associated with hemorrhagic
stroke. The CCP database is rich in clinical information, and
our cohort contains the biggest group of patients ≥75 years of
age reported to date. Among the clinical trials, there were
often exclusions for those beyond age 7077.28 or 75 years.29–33

Blacks have higher rates of both ischemic and hemorrhagic
stroke compared with whites.34 They are also at higher risk
for intracranial hemorrhage after thrombolysis in our cohort
and others.7,35 The reasons for this are unclear; however, race
remained an independent predictor in our study. Factors not
included in our analyses might account for at least part of this
association. For example, blacks have higher rates of chronic
hypertension and poorer rates of BP control.36 This may
render the intracranial vessels more susceptible to most forms
of stroke, including hemorrhage associated with thrombolytic
therapy.

Many studies report a higher rate of hemorrhagic stroke
associated with thrombolytic therapy among women35,37–39;
however, this effect may not remain significant after adjust-
ing for other factors. Women treated with thrombolytic
therapy tend to be older, more often have a history of
hypertension, smoking, and diabetes, and take longer to
present for treatment.38,40 Our report suggests that women are
at higher risk for intracranial hemorrhage even after correct-
ing for other common risk factors.7,35,41

Similarly, prior stroke was often an exclusion criterion for
trials of thrombolytic therapy, so information on the preva-
ience of prior stroke and the associated risk for hemorrhagic
stroke is limited.42 Where data are available, prior cerebro-
vascular events were associated with an increased risk of
thrombolysis-related intracranial hemorrhage;7,18,21,38,43–45;
however, the increased risk has also been attributed to the
older age and less favorable risk profile among patients with
prior cerebrovascular events.45 Our multivariate model con-
firms an earlier report by Gurwitz et al7 that prior stroke is an
independent predictor of intracranial hemorrhage.

In our model, we used systolic BP. In other studies,
diastolic BP appeared to be more significant.38 The Throm-
bolytic Predictive Instrument Project46 found that excessive
pulse pressure predicted intracranial hemorrhage better than
systolic, diastolic, or mean BP, although this was based on a
small number of cases. We did not find an advantage of using
the pulse pressure, nor did Gore and colleagues.38

Weight has been reported to have an inverse relation with
the risk of intracranial hemorrhage with thrombolytic ther-
apy.7,35,38,43 Recommendation for weight-based dosing became
widespread several years before the start of this study, based
on results such as the TIMI-II.29 A lower body weight may
result in higher serum concentration of medication, resulting
in a greater degree of fibrinolytic activity25 and an increased
risk for hemorrhage. It has been suggested that this effect may
be seen with TPA but not streptokinase.43 Our results corrobo-
rate those of Gurwitz and colleagues,7 who suggested an
inverse relation between body weight and intracranial hemor-
grahve.

Our results suggest that a nonlinear, weight-based dosing
schedule with a lower (mg/kg) dose for lighter patients may
be appropriate. This effect could help explain differences
among TPA trials for acute ischemic stroke and may provide
valuable insight for planning future trials.47–49

Most patients were treated with TPA. Nearly all of the
remainder was treated with streptokinase. TPA has been
associated with a higher rate (3 per 1000 treated patients) of
intracranial hemorrhage than streptokinase.19,20,43 The differ-
ence may be more prominent among the elderly.29 Other
studies have demonstrated that higher doses of TPA appear
further increase the rate of intracranial hemorrhage, as does
the accelerated TPA regimen with intravenous heparin or
combination thrombolytic therapy.7,29,35,38,42 The use of TPA,
higher doses, and accelerated administration of thrombolytic
agents, however, may achieve greater efficacy.42 Future
studies may be able to more safely explore the best use of
these more aggressive regiments by selecting subjects to minimize risk factors for intracranial hemorrhage.

We did not find a clearly increased risk associated with the overall use of warfarin; however, those excessively anticoagulated did have a higher rate of intracranial hemorrhage. Excessive anticoagulation was included in our model despite its low frequency. Excessive anticoagulation in the setting of AMI has been associated with an increased risk for intracranial hemorrhage with agents such as heparin or hirudin.23 Because of the exclusion of patients with a prolonged PT or significantly elevated INR, little information on the risk of thrombolytic therapy and anticoagulation with warfarin is available from clinical trial data sets. Observational studies have not had sufficient power to achieve statistical significance despite at least 1 study with a suggestive trend.25 Because excessive anticoagulation with warfarin is strongly and consistently related to intracranial hemorrhage and because it is specifically mentioned as a relative contraindication in national guidelines, we believed that its inclusion in the scale was justified.

Other contraindications for thrombolytic therapy associated with hemorrhagic risk were not included in the stratification scale because of concern of significant ascertainment bias or a low reported frequency in the cohort. For example, we did find an association between the documentation of dementia in the medical record and the occurrence of hemorrhage but did not include this in the model because of the low frequency of documentation and the potential for reporting bias.50 It would be of great interest to include dementia or cognitive dysfunction in a prospective evaluation. Among the elderly, amyloid angiopathy is associated with both intracerebral hemorrhages and cognitive decline. It has been reported as a risk factor for thrombolyis-related intracranial hemorrhage and deserves further study.51

Risk Stratification

Our findings extend the results of others reporting risk stratification scales or models for intracranial hemorrhage27,28,52 by including more cases and a geographically diverse, population-based cohort. Simoons and colleagues43 used pooled data derived mostly from clinical trials. There were 150 patients with intracranial hemorrhage and 294 matched control subjects. The overall risk for intracranial hemorrhage in their cohort was 0.75%. Four factors independently contributed to the risk for hemorrhage: age >65 years, body weight <70 kg, hypertension on admission (systolic BP ≥170 mm Hg, diastolic BP ≥95 mm Hg, or both), and the use of TPA. The probability of hemorrhage ranged from 0.26% to 2.17%. In older age groups, the range of hemorrhage was shifted upward.

The rate of intracranial bleeding in our lowest-risk group (age 65 to 74 years with no other risk factors) is 0.66%, which is very close to that predicted by Simmons’s model for 1 risk factor (ie, age >65 years with no other risk factors): 0.64%. Because we were able to include additional risk factors (7 in total), our model has a wider range of values, being able to identify those at high risk. At these higher risks, the net benefit for thrombolytic therapy may be lost.53

Selker and colleagues52 derived a model for intracranial hemorrhage by using pooled data from clinical trials and registries. It was based on 2 factors: age and pulse pressure. The range among 4 strata was 0.0% to 4.4% (mean 0.6±0.8%). Their instrument also predicts major bleeding, cardiac arrest, and death. For intracranial hemorrhage, however, the instrument was based on only a few events (n=18). Only a very small portion of patients in their database was >75 years of age or had significantly elevated acute BPs (ie, systolic BP >190 mm Hg). This observation may account for the low overall rate of intracranial hemorrhage of 0.6%.

Their predictive instrument is complicated, and it is not intended for a clinician to calculate a specific risk. The instrument was intended to be computed by a software program integrated into an ECG machine used in the emergency medical setting. The system also does not take into account other factors that have been shown in this and other studies to be predictive of hemorrhagic stroke.

Gurwitz and colleagues7 presented the relation between age and intracranial hemorrhage in men and women according to history of stroke. These results were adjusted for race, BP, and dose of TPA. They found an overall incidence of intracranial hemorrhage of 0.95%. Although this cohort included a broader range of patients than in most clinical trials and hence should be more reflective of the rate of intracranial hemorrhage in practice, the participating hospitals and the patients in this registry were selected, their study was restricted to TPA and included fewer elderly patients. Our risk stratification included all risk factors used in the previous instrument.

Low Risk

Concern for a possible stroke adversely influences both patient and physician preferences for thrombolysis in the setting of AMI.54,55 A disabling stroke is a feared complication among patients, and it is often rated as the least desirable outcome, even when death is included.56,57 Physicians appear to avoid the use of thrombolytic therapy for patients with an increased risk of bleeding, especially among the elderly.3

The availability of a widely applicable, simple system to stratify the risk of hemorrhagic stroke may assist those devising thrombolytic strategies by identifying patients at low risk for hemorrhagic stroke. On the basis of our results, half of all elderly patients are at low risk for intracranial hemorrhage. The risk of patients with ≤2 risk factors is comparable to that seen in the randomized controlled trials. This result points to a potent opportunity to enhance the care of older patients with AMI by increasing the appropriate use of thrombolytic therapy among those at low risk for hemorrhage.

High Risk

Identifying those at high risk for intracranial hemorrhage may assist in selecting those for alternate therapies for acute reperfusion such as primary percutaneous transluminal coronary angioplasty, which is associated with a lower rate of intracranial hemorrhage.8

Our highest-risk group has a rate of intracranial hemorrhage exceeding 4%. A decision analysis has shown that thrombolytic therapy is favored for the treatment of suspected...
myocardial infarction in the elderly over a wide range of estimates; however, as the rate of a serious adverse event approaches 4%, the therapy has greater harm than benefit.\textsuperscript{58} Even if the therapy is beneficial on average, many patients and their physicians may not want to take a risk at a level as high as 2% of a catastrophic stroke. Others physicians, recognizing the high mortality rate of myocardial infarction in the elderly, may be willing to take a higher risk. Our study provides the best estimate of the risk of intracranial hemorrhage for older patients treated with thrombolytic therapy and should provide practical evidence for decisions made by patients and their physicians.

Our study does have several important limitations. Some relate to observation data\textsuperscript{59,60} and others are specific to this cohort.\textsuperscript{3,61} In observational studies there is the risk of a chance association (type I error). Although this is a possibility for some of the variables included in our scale, we limited our selection to variables that were clinically sensible to consider. In addition, each of the factors that remained in our multivariate model have been reported to be associated with intracranial hemorrhage in at least 1 previous report and were highly significant in the model.

Limitations of the CCP cohort have been reviewed in previous publications\textsuperscript{3,61,62}; however, several items are worth reiterating for this report. The data were based on a retrospective chart review. Medical records are sometimes illegible or poorly organized. Although the reliability of abstracted data for this cohort has been reported to be high,\textsuperscript{61} patient characteristics may not have been documented in the medical record. This could limit our ability to identify important contraindications to therapy. Other potential risk factors, such as cholesterol, were not abstracted. We also did not have a record of the BP immediately before treatment; only the admission BP was recorded.

Age <65 years may be associated with a lower rate of hemorrhage.\textsuperscript{43} Our cohort was limited to those ≥65 years of age.

The existence of intracranial hemorrhage was based on diagnosis. Concern has been raised about the use of ICD-9-CM coding for ischemic stroke\textsuperscript{63}; however, the diagnosis of hemorrhagic stroke has a greater specificity.\textsuperscript{34,64} Cases could have been missed if the clinical syndrome was not recognized. Most patients who have neurological signs or symptoms suggestive of a stroke do receive either a CT scan or MRI of the brain.\textsuperscript{7} We did not, however, have the specific results of brain imaging. We also did not have detailed information on the type of hemorrhage. Although most thrombolytic-associated hemorraghes are parenchymal and are readily identifiable on brain imaging, other types do occur.\textsuperscript{38,64}

Finally, the risk stratification scale devised in the report remains to be externally validated and quantitatively compared with other risk stratification scales in an independent cohort.

Our study also has several strengths. Reports from clinical trials or voluntary registries may not reflect care provided across the United States. Our results are based on a broad, population-based cohort that reflects actual practice patterns. It represents the most comprehensive evaluation of the risk of intracranial hemorrhage associated with thrombolytic therapy. In addition, the data were based on chart abstractions by trained professionals using standardized definitions with high reliability.

Conclusions

Our report extends previous reports on the rate and risk factors for intracranial hemorrhage. Although we demonstrated that the overall rate of intracranial hemorrhage is significantly higher than usually quoted in trials and treatment guidelines, our risk stratification scale can estimate the risk of hemorrhage in an individual patient with the use of easily identifiable factors. Withholding thrombolytic therapy or the selection of alternate reperfusion strategies for the minority of elderly patients at high risk may help avoid some cases of intracranial hemorrhage.\textsuperscript{37,65} The use of our risk stratification scale may help clinical decision-making and improve the care of elderly by encouraging the appropriate use of thrombolytic therapy.

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Intracranial Hemorrhage Associated With Thrombolytic Therapy for Elderly Patients With Acute Myocardial Infarction: Results From the Cooperative Cardiovascular Project
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