Subtherapeutic International Normalized Ratio in Warfarin-Treated Patients Increases the Risk for Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis

Raymond C.S. Seet, MD; Yi Zhang, MD; S. Arthur Moore, MD; Eelco F. Wijdicks, MD, PhD; Alejandro A. Rabinstein, MD

**Background and Purpose**—There is uncertainty whether warfarin-treated patients (despite international normalized ratio \(<1.7\)) have increased risks of symptomatic intracerebral hemorrhage after intravenous thrombolysis.

**Methods**—Vascular risk factors, stroke subtype, and outcome measures were compared between warfarin- and nonwarfarin-treated patients undergoing acute thrombolysis within 3 hours of symptom onset.

**Results**—From 212 patients (mean age, 74±14 years; 50% men) studied, 14 (6.5%) had prior warfarin use. After adjusting for age, baseline National Institutes of Health Stroke Scale, and stroke subtype, warfarin-treated patients had significantly increased risks of developing symptomatic intracerebral hemorrhage (adjusted OR, 14.7; 95% CI, 1.3 to 54.3). A trend for poorer stroke recovery and increased mortality was observed in warfarin-treated patients on univariate, but not on multivariable, analyses.

**Conclusions**—Warfarin-treated patients with stroke have increased risks of symptomatic intracerebral hemorrhage after thrombolytic treatment. These data raise safety concerns of thrombolytic treatment in warfarin-treated patients with subtherapeutic international normalized ratio. *(Stroke. 2011;42:2333-2335.)*

**Key Words:** INR ■ intracerebral hemorrhage ■ ischemic stroke ■ warfarin

A pproximately 1 in 10 patients eligible for recombinant tissue-type plasminogen activator (rtPA) treatment had prior warfarin use.\(^1\)\(^2\) However, clinical trials and treatment guidelines differ in their enrollment of warfarin-treated patients for rtPA treatment. The National Institute of Neurological Disorders and Stroke and all 3 European Cooperative Acute Stroke Study (ECAS) trials excluded warfarin-treated patients from study enrollment, whereas the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study and the postmarketing study of rtPA (Standard Treatment With Alteplase to Reverse Stroke Study [STAR]) included such patients. The current American Heart Association guidelines consider warfarin-treated patients eligible for rtPA treatment if they present within 3 hours of symptom onset with international normalized ratio (INR) \(\leq 1.7\). In Europe, patients with prior warfarin use are excluded from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).

Current data on the safety of warfarin-treated patients with subtherapeutic INR undergoing rtPA treatment are conflicting. One study indicated increased symptomatic intracerebral hemorrhage (ICH) risks,\(^1\) whereas another suggested the risks to be unchanged.\(^2\) These studies, however, did not assess the confounding effects of blood pressure control after rtPA treatment and stroke subtype. The purpose of this study is to evaluate the frequency of symptomatic ICH among rtPA-treated patients with stroke prior warfarin use and to investigate whether blood pressure control (before and after rtPA treatment) may account for the differences in hemorrhagic risks.

**Methods and Materials**

Between April 2006 and September 2010, consecutive rtPA-treated patients with acute ischemic stroke who presented within 3 hours of symptom onset at St Marys Hospital, Mayo Clinic, Rochester, MN, were studied. Patients who underwent primary or adjunctive endovascular treatments due to contraindication to or after intravenous rtPA were excluded. Warfarin use was defined as the consumption of warfarin 5 days before stroke onset. Several indices of BP variability were derived for each systolic and diastolic BP measurement, which included maximum, minimum, and differences between maximum
and minimum BP.3 Antihypertensive treatment was recorded. The presence of ICH was classified according to the European–Australian Acute Stroke Study (ECASS) criteria and symptomatic ICH was defined by hemorrhagic transformation with at least a 4-point increment in National Institutes of Health Stroke Scale score. Poor functional recovery was considered when 3-month modified Rankin scale score was ≥3. The study protocol was approved by the Mayo Clinic Institutional Review Board.

Results
From 248 patients who received thrombolysis, 36 patients (who underwent endovascular procedures) were excluded. Mean age (SD) of the remaining 212 patients was 74.1 (14.1) years; median baseline National Institutes of Health Stroke Scale score, 13.4 (interquartile range, 10.2 to 16.4), and mean onset-to-treatment time with rtPA 142 (56) minutes (Table 1). BP measurements and antihypertensive use (at baseline and 24 hours post-rtPA) did not differ between warfarin and nonwarfarin patients (data not shown). Fourteen patients (6.5%) had consumed warfarin before rtPA treatment, of whom 5 (36%) had baseline INR <1.1. Among warfarin-treated patients, baseline INR levels did not differ between those with and without symptomatic ICH (median INR, 1.1 versus 1.2; \( P=0.937 \)).

Sixteen patients developed symptomatic ICH. Symptomatic ICH occurred in 36% of warfarin-treated patients and 6% of nonwarfarin patients. After adjusting for baseline National Institutes of Health Stroke Scale, mean arterial pressure, and stroke subtype, warfarin-treated patients had 5-fold increased incidence of symptomatic ICH compared with nonwarfarin patients (adjusted OR, 14.7; 95% CI, 1.3 to 54.3; Table 2).

Among patients with atrial fibrillation, the incidence of symptomatic ICH was higher in warfarin-treated compared with nonwarfarin patients (40% versus 8%, \( P=0.034 \)). Similarly, patients with cardioembolic stroke on warfarin treatment had a higher incidence of symptomatic ICH compared with those without (39% versus 4%, \( P<0.001 \)).

Discussion
We observed a significant increase in the incidence of symptomatic ICH among rtPA-treated patients with prior warfarin use, an association that is independent of BP control and stroke etiology. Our findings are in agreement with those of a previous study1 but differed from another study that included younger patients and those undergoing endovascular treatments.2

Consistent with previous observations, symptomatic ICH occurred in warfarin-treated patients who presented with normal or near-normal baseline INR and these INR levels did not differ between those who developed symptomatic ICH and those who did not.1,2 It is not known whether baseline INR accurately reflects the subsequent anticoagulant effects of warfarin in the presence of exogenous rtPA and whether warfarin could interact with other hemostatic factors, resulting in an excess of hemorrhagic events. In warfarin-treated patients with subtherapeutic INR, caution should be exercised when making treatment decisions based on baseline INR alone. Future studies should consider serial measurements of

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tr>
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<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>Male, no. (%)</td>
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<tr>
<td>Whites, no. (%)</td>
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<td>Current smoking, no. (%)</td>
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<tr>
<td>NIHSS indicates National Institutes of Health Stroke Scale; INR, international normalized ratio; IQR, interquartile range; APTT, activated partial thromboplastin time; ICH, intracranial hemorrhage; SD, standard deviation.</td>
</tr>
</tbody>
</table>
INR, tPA antigen, and endogenous fibrinolysis inhibitors (e.g., plasminogen activator inhibitor) to elucidate the excess in hemorrhagic risks.

Despite including a relatively small number of patients from a single referral center, we highlight serious safety concerns of rtPA in warfarin-treated patients with stroke.

Disclosures

None.

Table 2. Odds Ratios (95% CIs)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Unadjusted</th>
<th>P</th>
<th>Adjusted*</th>
<th>P</th>
<th>Adjusted†</th>
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<td>Any intracerebral hemorrhage</td>
<td>4.61 (1.49–14.3)</td>
<td>0.004</td>
<td>5.29 (0.98–19.5)</td>
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<td>In-hospital mortality</td>
<td>2.37 (0.75–7.46)</td>
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NIHSS indicates National Institutes of Health Stroke Scale; CI, confidence interval.

*Adjusted for age and baseline NIHSS.
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Abstract 11

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