Subtherapeutic Warfarin Is Not Associated With Increased Hemorrhage Rates in Ischemic Strokes Treated With Tissue Plasminogen Activator

Mervyn D.I. Vergouwen, MD, PhD; Leanne K. Casaubon, MD, MSc; Richard H. Swartz, MD, PhD; Jiming Fang, PhD; Melissa Stamplecoski, BSc; Moira K. Kapral, MD, MSc; Frank L. Silver, MD; on behalf of the Investigators of the Registry of the Canadian Stroke Network

Background and Purpose—Concern exists that preadmission warfarin use may be associated with an increased risk of intracerebral hemorrhage in patients with ischemic stroke receiving intravenous tissue plasminogen activator, even in those with an international normalized ratio <1.7. However, evidence to date has been derived from a small single-center cohort of patients.

Methods—We used data from Phase 3 of the Registry of the Canadian Stroke Network. We compared the rates of post-tissue plasminogen activator hemorrhage, including any intracerebral hemorrhage, symptomatic intracerebral hemorrhage, and gastrointestinal hemorrhage in patients with and without preadmission warfarin use. For those receiving warfarin, we restricted the analysis to patients with an international normalized ratio <1.7 on presentation. Secondary outcomes included functional status and mortality. Multivariate analyses were performed to adjust for other prognostic factors.

Results—Our cohort included 1739 patients with acute ischemic stroke treated with intravenous tissue plasminogen activator of whom 125 (7.2%) were receiving warfarin before admission and had an international normalized ratio <1.7. Preadmission warfarin use was not associated with any secondary intracerebral hemorrhage (OR, 1.2; 95% CI, 0.7 to 2.2), symptomatic intracerebral hemorrhage (OR, 1.1; 95% CI, 0.5 to 2.3), or gastrointestinal hemorrhage (OR, 1.1; 95% CI, 0.2 to 5.6). Multivariate analysis showed that preadmission warfarin use was independently associated with a reduced risk of poor functional outcome (OR, 0.6; 95 CI, 0.3 to 0.9), but not with in-hospital mortality (OR, 0.6; 95% CI, 0.3 to 1.0).

Conclusions—The results from the present study suggest that tissue plasminogen activator treatment appears to be safe in patients with acute ischemic stroke taking warfarin with an international normalized ratio <1.7 and may reduce the risk of poor functional outcome. (Stroke. 2011;42:1041-1045.)

Key Words: cerebral infarct ■ hemorrhage ■ mortality ■ outcome ■ thrombolysis ■ warfarin

The most significant complication of intravenous tissue plasminogen activator (tPA) in patients with acute ischemic stroke is secondary intracerebral hemorrhage. Because patients using anticoagulant drugs may have an increased risk of secondary hemorrhage, the National Institute of Neurological Disorders and Stroke tPA study excluded patients who were taking anticoagulants or who had received heparin within the 48 hours preceding the onset of stroke and had an elevated partial thromboplastin time as were those with prothrombin times >15 seconds.1 All 3 European Cooperative Acute Stroke Study trials excluded patients treated with warfarin irrespective of the international normalized ratio (INR).2–4 Nevertheless, current guidelines permit intravenous tPA use in patients taking anticoagulant drugs when the INR is <1.7.5

Recently, it was suggested that there is a 10-fold increased risk of symptomatic intracerebral hemorrhage (ICH) in patients on warfarin treated with intravenous tPA, even if the INR is <1.7.6 This single-center study of a cohort of 107 tPA-treated patients included only 13 patients on warfarin limiting its validity and generalizability. The aim of the present study was to investigate the risk of secondary hem-
orrhage in a large, multicenter cohort of patients with acute ischemic stroke on warfarin and treated with tPA. We hypothesized that the risk of secondary intracerebral hemorrhage is not increased in patients who receive warfarin and have an INR <1.7.

Methods
We used data from Phase 3 of the Registry of the Canadian Stroke Network (RCSN), which is a hospital-based registry of consecutive patients presenting with acute stroke to 11 regional stroke hospitals in Ontario and 1 hospital in Halifax, Nova Scotia, Canada.7,8 Approval for the RCSN was obtained from the Research and Ethics Board at each of the participating centers. Patients in this registry were identified prospectively and data were abstracted systematically during their hospital stay and after hospital discharge by trained research nurses using a standardized case report form and custom electronic data entry software to increase data quality.9 For the current analysis, a research protocol with a statistical analysis plan was developed and submitted to the RCSN Publication Committee for approval. We identified all patients admitted to the hospital with acute ischemic stroke who received treatment with intravenous tPA between July 1, 2003, and March 31, 2008. Patients with missing INR levels, an INR >1.7, and those who received intra-arterial treatment were excluded.

At baseline, the following variables were abstracted: age, gender, atrial fibrillation, hypertension, diabetes mellitus, previous stroke, preadmission antplatelets use, preadmission warfarin use, INR level, systolic and diastolic blood pressure, glucose level, National Institutes of Health Stroke Scale (NIHSS) score, and stroke onset (when the patient was last known to be normal) to start of tPA infusion time.

Primary outcomes were the incidence of any ICH, symptomatic ICH, and gastrointestinal hemorrhage during hospitalization. Secondary outcomes were poor functional outcome (predefined as a modified Rankin Scale score of 3 to 6) at discharge, death during hospitalization, discharge home, and length of stay. Any ICH was defined as the presence of any intracerebral hemorrhage on CT or MRI within 36 hours of tPA administration, and symptomatic ICH was defined as the presence of any ICH and documented clinical evidence of neurological worsening within 36 hours of tPA administration.

Statistical Analyses
All statistical analyses were performed using a commercially available software package (SAS Version 9.1.3 statistical software; SAS Institute Inc, Cary, NC). Baseline characteristics were summarized using descriptive statistics and comparisons were made between patients with and without preadmission warfarin use. Categorical variables were analyzed using the $\chi^2$ test. A probability value <0.05 was considered statistically significant. Mean values were presented with SD and median values with interquartile range (IQR). No comparisons were made when a cell value was ≤5 to protect the privacy of individuals in the database. A multivariate logistic regression model was performed to investigate whether warfarin use was independently associated with (1) any ICH; (2) symptomatic ICH; (3) gastrointestinal hemorrhage; (4) poor functional outcome (modified Rankin Scale 3 to 6); (5) death during hospitalization; and (6) discharge home. Adjustments were made for age (as a continuous variable), gender, NIHSS score (as a categorical variable, according to previously described categories), presence of atrial fibrillation, and INR (as a categorical variable). For patients with missing NIHSS scores (in 325 patients [18.7% of all patients]), we used a recently described and validated formula to convert Canadian Neurological Scale scores to NIHSS scores.10 Results of multivariate logistic regression analyses were presented as ORs with 95% CIs. In another analysis, we compared the incidence of any ICH, symptomatic ICH, and gastrointestinal ICH in patients on warfarin in 3 groups of patients with an INR <1.11, INR 1.11 to 1.40, and INR 1.41 to 1.70, respectively.

Results
In total, 1739 patients were included. Baseline characteristics are described in Table 1. The median age of the cohort was 75 years (IQR, 64 to 82), 48.7% of the patients were female, and 125 patients (7.2%) had preadmission warfarin use. Patients using warfarin were older (P=0.0003), more often had atrial fibrillation (P<0.0001) and hypertension (P=0.0004), higher INR levels (P<0.0001), and more severe strokes (P=0.0002) and less often had preadmission use of antiplatelets (P<0.0001).

Although a trend was observed toward a higher incidence of any ICH (P=0.054) in patients using warfarin, the incidence of symptomatic ICH was similar in both groups (P=0.29; Table 2). Also, the incidence of gastrointestinal hemorrhage was similar in both groups (P=0.57). Regarding the secondary outcomes, no differences were observed in the incidence of poor functional outcome, mortality, and discharge to home or rehabilitation institution (Table 2). Patients with preadmission warfarin use had an increased length of stay compared with patients who did not use warfarin on admission (P=0.02).

In the multivariate analysis, warfarin use was not associated with either any ICH (OR, 1.2; 95% CI, 0.7 to 2.2; Figure A), symptomatic ICH (OR, 1.1; 95% CI, 0.5 to 2.3), or gastrointestinal hemorrhage (OR, 1.1; 95% CI, 0.2 to 5.6). In the multivariate analysis, preadmission warfarin use was independently associated with a decreased risk of poor functional outcome (OR, 0.6; 95% CI, 0.3 to 0.9; Figure 1B), but not with death (OR, 0.6; 95% CI, 0.3 to 1.0) and discharge home (OR, 1.3; 95% CI, 0.8 to 2.2).

Of the warfarin-treated patients, 50 patients had an INR <1.11, 58 patients an INR 1.11 to 1.40, and 17 patients an INR of 1.41 to 1.70. In all 3 groups of patients in the INR categories, median age was similar (P=0.78) and so was the number of males (P=0.87). However, a trend was noted toward more severe strokes in the group of patients with INR 1.41 to 1.70 (P=0.13). No difference was observed in the incidence of any ICH (P=0.23), symptomatic ICH (P=0.67), and gastrointestinal hemorrhage (P=0.85) among these 3 groups of patients. However, there were more deaths in the groups of patients with INR levels 1.11 to 1.40 and INR 1.41 to 1.70 (P=0.03), but not more patients with poor functional outcome (P=0.22).

Discussion
Our results suggest that tPA treatment is not associated with an increased risk of secondary ICH or gastrointestinal hemorrhage in patients with acute ischemic stroke taking warfarin with an INR <1.7. Furthermore, the results of our multivariate analysis showed that preadmission warfarin use is independently associated with a decreased risk of poor functional outcome.

Only 1 previous study has investigated the effect of preadmission warfarin use in patients with acute ischemic stroke treated with tPA.6 In that study, only 13 of 107 patients used warfarin. A 10-fold increased risk of symptomatic ICH was observed in the group of patients on warfarin compared with nonwarfarin users. In an exploratory logistic regression model that adjusted for age, NIHSS score, atrial fibrillation,
and initial INR, baseline warfarin use remained strongly associated with symptomatic ICH. The authors did not report multivariate analyses describing whether baseline warfarin use was independently associated with functional outcome or mortality. The authors concluded that their results should be considered hypothesis-generating and that larger cohort studies are required for confirmation.

In our large multicenter cohort, we could not confirm the previous observation that preadmission warfarin use was associated with hemorrhagic complications after tPA. Therefore, it suggests that tPA is safe in this group of patients with an INR <1.7. Furthermore, it was shown that preadmission warfarin use might beneficially affect functional outcome despite having more severe strokes on admission. Although patients on warfarin in our study were older and had more severe strokes on admission, multivariate analysis showed reduced mortality and improved functional outcome in patients taking warfarin before receiving tPA. Other observational studies have demonstrated that the presence of warfarin, even at subtherapeutic INR levels, will reduce the initial stroke severity and improve the outcomes of patients with ischemic stroke secondary to atrial fibrillation in comparison to patients on no antithrombotic or on antiplatelet therapy alone.\(^{11,12}\) Another possible explanation is that warfarin reduces the risk of reocclusion after tPA-induced recanalization. Previous studies showed that reocclusion occurs in 20% to 34% of patients receiving tPA.\(^ {13,14}\) Reocclusion may account for two thirds of clinical deterioration after initial improvement after tPA administration and is highly predictive of poor functional outcome.\(^ {13-15}\) By preventing reocclu-

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=1739)</th>
<th>No Preadmission Warfarin Use (N=1614)</th>
<th>Preadmission Warfarin Use (N=125)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median±IQR) (no.)</td>
<td>75 (64–82) (1739)</td>
<td>74 (64–82) (1614)</td>
<td>79 (72–84) (125)</td>
<td>0.0003</td>
</tr>
<tr>
<td>No. of females (n/N [%])</td>
<td>847/1739 (48.7)</td>
<td>777/1614 (48.1)</td>
<td>70/125 (56.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Atrial fibrillation (n/N [%])</td>
<td>458/1739 (26.3)</td>
<td>357/1614 (22.1)</td>
<td>101/125 (80.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (n/N [%])</td>
<td>1155/1739 (66.4)</td>
<td>1054/1614 (65.3)</td>
<td>101/125 (80.8)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Diabetes mellitus (n/N [%])</td>
<td>358/1739 (20.6)</td>
<td>334/1614 (20.7)</td>
<td>24/125 (19.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Previous stroke (n/N [%])</td>
<td>286/1739 (16.4)</td>
<td>259/1614 (16.0)</td>
<td>27/125 (21.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>INR on admission (median±IQR) (no.)</td>
<td>1.0 (1.0–1.1) (1739)</td>
<td>1.0 (1.0–1.1) (1614)</td>
<td>1.2 (1.1–1.3) (125)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INR 1.11–1.40 (n/N [%])</td>
<td>1467/1739 (84.4)</td>
<td>1417/1614 (87.8)</td>
<td>50/125 (40.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INR 1.11–1.40 (n/N [%])</td>
<td>252/1739 (14.5)</td>
<td>194/1614 (12.0)</td>
<td>58/125 (46.4)</td>
<td>0.0002</td>
</tr>
<tr>
<td>INR &gt;1.70 (n/N [%])</td>
<td>20/1739 (1.2)</td>
<td>3/1614 (0.2)</td>
<td>17/125 (13.6)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Diastolic blood pressure on admission (mean±SD) (no.)</td>
<td>83.4±16.9 (1726)</td>
<td>83.4±16.8 (1602)</td>
<td>83.2±18.1 (124)</td>
<td>0.88</td>
</tr>
<tr>
<td>Glucose level on admission (median±IQR) (no.)</td>
<td>6.8 (5.8–8.3) (1727)</td>
<td>6.8 (5.8–8.3) (1604)</td>
<td>6.8 (6.0–8.3) (123)</td>
<td>0.46</td>
</tr>
<tr>
<td>NIHSS score on admission (median±IQR) (no.)</td>
<td>12 (8–17) (1728)</td>
<td>12 (8–17) (1603)</td>
<td>14 (10–18) (125)</td>
<td>0.0002</td>
</tr>
<tr>
<td>NIHSS 0–6 (n/N [%])</td>
<td>276/1739 (15.9)</td>
<td>267/1603 (16.7)</td>
<td>9/125 (7.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>NIHSS 7–15 (n/N [%])</td>
<td>864/1728 (50)</td>
<td>803/1603 (50.1)</td>
<td>61/125 (48.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>NIHSS ≥16 (n/N [%])</td>
<td>588/1728 (34.0)</td>
<td>533/1603 (33.3)</td>
<td>55/125 (44.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Length of stay in days (median±IQR) (no.)</td>
<td>8 (5–18) (1738)</td>
<td>8 (4–18) (1613)</td>
<td>12 (5–24)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Table 2. Outcome Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=1739)</th>
<th>No Preadmission Warfarin Use (N=1614)</th>
<th>Preadmission Warfarin Use (N=125)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (n/N [%])</td>
<td>200/1739 (11.5)</td>
<td>179/1614 (11.1)</td>
<td>21/125 (16.8)</td>
<td>0.054</td>
</tr>
<tr>
<td>Symptomatic (n/N [%])</td>
<td>102/1739 (5.9)</td>
<td>92/1614 (5.7)</td>
<td>10/125 (8.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage (n/N [%])</td>
<td>19/1739 (1.1)</td>
<td>17/1614 (1.1)</td>
<td>2/125 (1.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Poor functional outcome at discharge (n/N [%])</td>
<td>1195/1731 (69.0)</td>
<td>1105/1608 (68.7)</td>
<td>90/123 (73.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Mortality (n/N [%])</td>
<td>284/1739 (16.3)</td>
<td>260/1614 (16.1)</td>
<td>24/125 (19.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>Discharge to home (n/N [%])</td>
<td>537/1739 (30.9)</td>
<td>506/1614 (31.4)</td>
<td>31/125 (24.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Length of stay in days (median±IQR) (no.)</td>
<td>9 (5–18) (1738)</td>
<td>8 (5–18) (1613)</td>
<td>12 (5–24)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
sion, functional outcome after tPA might improve. An ongoing multicenter placebo-controlled randomized trial is currently underway to determine whether intravenous aspirin further may improve clinical outcome in tPA-treated patients with ischemic stroke by preventing reocclusion.16

Our study has some limitations. The results of our primary analysis, in which the incidence of several types of hemorrhagic complications was analyzed, can be limited by ascertainment and interobserver bias. Our data are collected by chart review and only complications that are documented in the chart are captured. To improve the reliability of the data, all variables in the RCSN are predefined in the case record form manual and the study nurses were all trained and evaluated by completing standard test charts. Also, because this was a retrospective analysis of prospectively collected data, we were not able to systematically measure recanalization rates to prove our hypothesis that preadmission warfarin use may prevent reocclusion. Finally, the external validity of our study is still in question. Little data were available on those subjects that were screened and otherwise eligible but rejected because their INR was too high. Only a randomized controlled trial can answer the question if tPA treatment is safe and effective in this group of patients.

In conclusion, the results from the present study suggest that tPA treatment appears to be safe in patients with acute ischemic stroke taking warfarin with an INR <1.7. There is no increased risk of bleeding, and there may even be a reduced risk of poor functional outcome and mortality. Therefore, tPA treatment should not be discouraged in the group of patients taking warfarin with INR <1.7.

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Disclosures

None.

References


Figure. A, Results of multivariate analysis: ORs for having any ICH. The OR for age is given for every 10-year increase. B, Results of multivariate analysis: ORs for having poor functional outcome. INR indicates international normalized ratio; NIHSS, National Institutes of Health Stroke Scale. The OR for age is given for every 10-year increase.


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Abstract 7

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(Stroke. 2011;42:1041-1045.)

Key Words: cerebral infarct ■ hemorrhage ■ mortality ■ outcome ■ thrombolysis ■ warfarin

Background

Purpose

The purpose of this study was to determine whether the use of subtherapeutic warfarin (International Normalized Ratio [INR] < 1.7) is associated with increased hemorrhage rates in patients treated with tissue plasminogen activator (t-PA) for ischemic stroke.

Methods

This was a retrospective cohort study of patients treated with t-PA for ischemic stroke who were prescribed warfarin as opposed to enoxaparin. INR was measured on the morning of admission and at 24, 48, and 72 hours after t-PA infusion. The primary end point was the occurrence of hematomas on serial computed tomography scans. The secondary end point was the occurrence of intracerebral hemorrhage (ICH) on magnetic resonance imaging. Warfarin was not changed on the basis of INR values.

Results

Among 1175 patients, 72 (6.1%) patients had hemorrhages. Of these, 15 (21%) were intracerebral. Six (0.5%) hemorrhages were fatal. Warfarin INR was significantly higher in the hemorrhage group (median, 2.0 vs 1.6; P < .001). The rate of ICH was higher in the hemorrhage group (3.1% vs 0.4%; P = .014), and the median time to freedom from therapeutic INR was greater in the hemorrhage group (10 days vs 7 days; P = .014).

Conclusion

These findings suggest that subtherapeutic warfarin may not increase hemorrhage rates in ischemic stroke patients treated with t-PA. However, further studies are needed to confirm these results.