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. 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. 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 NIHSS 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 antiplatelets 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 chi² 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 categories9, 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,
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>Preadmission antiplatelets use (n/N [%])</td>
<td>712/1739 (40.9)</td>
<td>689/1614 (42.7)</td>
<td>23/125 (18.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INR on admission (median±IQR) (no.)</td>
<td>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 ≥1.10 (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></td>
</tr>
<tr>
<td>INR 1.41–1.70 (n/N [%])</td>
<td>20/1739 (1.2)</td>
<td>3/1614 (0.2)</td>
<td>17/125 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure on admission (mean±SD) (no.)</td>
<td>157.8±28.9 (1733)</td>
<td>157.8±28.7 (1608)</td>
<td>157.6±31.4 (125)</td>
<td>0.93</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>276/1728 (16.0)</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></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></td>
</tr>
<tr>
<td>Last seen normal time to start tPA treatment in minutes (median±IQR] (no.N)</td>
<td>145 (120–175) (1738)</td>
<td>146 (120–175) (1613)</td>
<td>145 (117–170) (125)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

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 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 (4–18) (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 reoclusion.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


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조직플라스미노겐활성제 치료를 받은 허혈뇌출혈 환자에서 치료 용량보다 저용량의 와파린 사용은 출혈 발생을 증가시키지 않는다

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

배경과 목적
입원 전 와파린(warfarin) 사용이 정맥내 조직플라스미노겐활성계(intravenous tissue plasminogen activator) 치료를 받는 허혈뇌출혈(ischemic stroke) 환자에서 뇌내출혈(intracerebral hemorrhage)의 위험을 높일 수 있다고, 심지어는 국제 표준화비율(international normalized ratio, INR)이 1.7 미만인 경우에도 비슷한 위험이 있을 수 있다는 것이 알려져 있다. 그러나 현재까지의 증거는 작은 단일 기관 환자 코호트 연구 결과에 불과하다.

방법
저자들은 3단계 캐나다 뇌졸중 네트워크의 등록 사업(Registry of the Canadian Stroke Network)으로부터 데이터를 얻었고, 입원 전 와파린 사용 여부에 따른 조직플라스미노겐활성계 사용 후 뇌내출혈, 중상성 뇌내출혈, 위장출혈(gastrointestinal hemorrhage)을 포함한 출혈 발생률을 비교하였다. 저자들은 와파린을 복용하고 있는 사람들을 중에서 병원 당시 INR이 1.7 미만인 환자들로 근본하여 분석하였다. 이차 임상 결과는 기능 변화 및 사망률로 정하였다. 다양한 예후 인자를 보정하기 위하여 다변량 분석이 함께 시행되었다.

결과
본 연구 코호트는 급성 허혈뇌졸중으로 정맥내 조직플라스미노겐활성계 치료를 받은 1,739명을 포함하였고, 이들 중 125명(7.2%)은 입원 전에 와파린을 복용하고 있었으며 INR이 1.7 미만이었다. 입원 전 와파린 사용은 뇌내출혈(교차비[OR], 1.2, 95% 신뢰구간[CI]: 0.7~2.2), 중상성 뇌내출혈(OR, 1.1, 95% CI: 0.5~2.3), 위장출혈 발생(OR, 1.1, 95% CI: 0.2~5.6)과 유의한 연관성을 가지지 못하였다. 다변량 분석은 입원 전 와파린 사용이 심한 기능 손상의 감소(OR, 0.6, 95% CI: 0.3~0.9)와 독립적으로 연관되어 있음을 보여 주었다. 그러나 병원 내 사망률의 변화와는 유의한 연관성이 없었다(OR, 0.6, 95% CI: 0.3~1.0).

결론
본 연구 결과는 1.7 미만의 INR 목표를 가지고 와파린을 복용 중인 급성 허혈뇌졸중 환자에서 조직플라스미노겐활성계 치료가 안전하고, 봉방한 예후 위험을 감소시킬 수 있다는 것을 제시한다.