Optimal Timing of Resumption of Warfarin After Intracranial Hemorrhage

Ammar Majeed, MD; Yang-Ki Kim, MD; Robin S. Roberts, PhD; Margareta Holmström, MD, PhD; Sam Schulman, MD, PhD

Background and Purpose—The optimum timing of resumption of anticoagulation after warfarin-related intracranial hemorrhage in patients with indication for continued anticoagulation is uncertain. We performed a large retrospective cohort study to obtain more precise risk estimates.

Methods—We reviewed charts of 2869 consecutive patients with objectively verified intracranial hemorrhage over 6 years at 3 tertiary centers. We calculated the daily risk of intracranial hemorrhage or ischemic stroke with and without resumption of warfarin; we focused on patients who survived the first week and had cardiac indication for anticoagulation or previous stroke. Using a Cox model, we estimated rates for these 2 adverse events in relation to different time points of resumed anticoagulation. The combined risk of either a new intracranial hemorrhage or an ischemic stroke was calculated for a range of warfarin resumption times.

Results—We identified warfarin-associated intracranial hemorrhage in 234 patients (8.2%), of whom 177 patients (76%) survived the first week and had follow-up information available; the median follow-up time was 69 weeks (interquartile range [IQR] 19–144). Fifty-nine patients resumed warfarin after a median of 5.6 weeks (IQR 2.6–17). The hazard ratio for recurrent intracranial hemorrhage with resumption of warfarin was 5.6 (95% CI, 1.8–17.2), and for ischemic stroke it was 0.11 (95% CI, 0.014–0.89). The combined risk of recurrent intracranial hemorrhage or ischemic stroke reached a nadir if warfarin was resumed after approximately 10 to 30 weeks.

Conclusion—The optimal timing for resumption of warfarin therapy appears to be between 10 and 30 weeks after warfarin-related intracranial hemorrhage. (Stroke. 2010;41:2860-2866.)

Key Words: intracranial hemorrhage ■ anticoagulation ■ ischemic stroke ■ management

Intracranial hemorrhage is the most feared complication of treatment with vitamin K antagonists. The incidence of this hemorrhage is approximately 0.2% per year of treatment.1 Despite the underlying risk of a thromboembolic event in patients requiring long-term prophylaxis, an intracranial hemorrhage necessitates temporary discontinuation of a vitamin K antagonist. Depending on the indication for prophylaxis, the withdrawal of anticoagulation exposes the patient to a substantial risk of thromboembolic complications. Annual rates of 12% to 22% have been reported in patients with St. Jude’s Medical bileaflet heart valves,2 4% to 18% in patients with atrial fibrillation and additional risk factors for stroke,3 and 10% for patients with recurrent venous thromboembolism.4 The decision about when to resume anticoagulation requires the physician to balance the risk of an additional bleeding event (particularly of recurrent intracranial hemorrhage, the risk of which is likely high shortly after the index bleed, although poorly studied) with the risk of thromboembolism in the absence of anticoagulation.

A limited number of observational studies have addressed the question posed in this study.5–12 These studies generally included few patients who were followed at a single center and had limited follow-up. Several of the authors and the American Stroke Association13 suggest restarting anticoagulation after a period of 7 to 14 days following intracranial hemorrhage. A recent systematic review of studies in patients with mechanical heart valves reached the same conclusion based on only 2 recurrent hemorrhages and 4 strokes.14 Seven experts expressed the opinion that warfarin could be restarted in stable patients 3 to 10 days after intracranial hemorrhage.15

We performed this study to address the timing of resumption of warfarin after intracranial hemorrhage and assess the risks and benefits both in patients who restarted warfarin and those who did not. To our knowledge, this is the first

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S.S. planned and supervised the study. M.H. contributed to the implementation of the study at the Swedish sites. A.M. and Y.-K.K. performed the chart review. R.S.R. and S.S. performed the statistical analyses. A.M. and S.S. wrote the manuscript, and all the other authors critically reviewed the manuscript.

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multicenter study with analysis of the optimal timing of resumption of anticoagulation performed by calculating hazards of recurrent hemorrhage and of ischemic stroke, with or without warfarin.

Methods

The study was conducted at 3 tertiary care hospitals: Karolinska University Hospital in Solna-Stockholm, and Karolinska University Hospital in Huddinge-Stockholm, both in Sweden; and at Hamilton Health Sciences-General Hospital, Ontario, Canada. One investigator in each country (A.M. in Sweden and Y.-K.K. in Canada) reviewed the charts of all patients admitted between January 2002 and December 2007 in Canada, and between January 2004 and December 2008 in Sweden, who had a diagnosis of intracranial hemorrhage (ICD-10 diagnosis code I600-I629). Data from patients with warfarin-associated intracranial hemorrhage underwent a final review by a third investigator (S.S.).

The Institutional Ethics Committees in both countries approved this retrospective study and waived the need for consent from patients. Patients who were being treated with warfarin at the time of diagnosis of intracranial hemorrhage, and who had an international normalized ratio of 1.5 at the time the bleeding occurred, were included in the study. The diagnosis had to be radiologically confirmed. Any combination of intracerebral hemorrhage with subdural or subarachnoid hemorrhage was classified as intracerebral. We excluded from our analysis patients with hemorrhage caused by severe accidents, with multi-trauma, or those with hemorrhagic transformation of ischemic stroke.

Data regarding patient characteristics, indication for warfarin treatment, risk score for stroke in patients with atrial fibrillation, additional antithrombotic treatment, international normalized ratio at presentation, cause of bleeding (spontaneous or traumatic), location of bleeding according to radiological investigations, and neurosurgical intervention were collected. From the follow-up period after intracranial hemorrhage, we collected data on resumption of warfarin, recurrent intracranial bleeding, ischemic stroke, systemic embolism, transitory ischemic attacks, heart valve thrombosis, venous thromboembolism, death, and the timing of these events in relation to the index intracranial hemorrhage. The data were retrieved from electronic hospital charts and by contacting each patient’s family physician.

Our aim was to describe the occurrences of recurrent bleeding, thromboembolic complications, and death in patients surviving the first week after the index intracranial hemorrhage. The reason for this focus was that resumption of anticoagulation with vitamin K antagonists during the first week has rarely been recommended. Furthermore, patients with such short survival are usually very ill and are not considered for anticoagulant therapy during this limited period. In addition, we focused the analysis on patients who were at a moderate-to-high risk of ischemic stroke, including those with atrial fibrillation, mechanical heart valves, left ventricle thrombus, or previous ischemic stroke.

Binomial data were analyzed with the chi-square test, and continuous variables were analyzed with Student t-test or Mann–Whitney for skewed distributions. Median value and interquartile range (IQR) were used to describe these skewed distributions. Cumulative risks were estimated with Kaplan–Meier analysis. A Cox model was fitted for recurrent intracranial hemorrhage and separately for ischemic cerebral events, with a time-dependent variable indicating the time at which warfarin was resumed (if at all). The assumption in the Cox model was that from the time of resumption, warfarin exerts a constant proportional effect on the risk of recurrent intracranial hemorrhage, and exerts a constant proportional reduction of the risk of ischemic events. The software for calculations was SAS7STAT 9 (SAS Institute Inc.). The results of the Cox models yielded estimates of the risks per day (hazards) of intracranial hemorrhage or of thromboembolic event, with and without warfarin treatment, over time since the qualifying event. Based on these estimates, we computed the cumulative risks over treatment horizons between 3 and 6 years, and with warfarin resumption commencing between 1 and 50 weeks after the index intracranial hemorrhage.

Results

Demographics

We identified and reviewed retrospectively the records of all 3287 admissions for 2869 consecutive patients diagnosed with intracranial hemorrhage at the 3 centers. Two hundred thirty-four patients (8.2%) fulfilled the criteria for inclusion in the study. The baseline characteristics of the patients are described in Table 1. Few patients were identified with intracranial pathology as secondary cause of intracerebral hemorrhage: 4 patients with aneurysms, 4 patients with amyloid angiopathy, 2 patients with tumors, and 1 patient with a ruptured colloid cyst. The number of patients who were reviewed, included in the study, and had resumption of anticoagulation at the 3 sites of investigation is shown in Table 2.

Mortality

We had access to follow-up information on the 234 patients regarding major clinical events for a median of 34 weeks (IQR 1–115). For the 177 patients who survived the first week, the median follow-up duration was 69 weeks (IQR 19–144). Overall, 113 patients (48%) died during the follow-up, corresponding to a median survival of 4.5 years. Fifty-seven patients (24%) died within the first week: 54 patients because of progression of bleeding and/or herniation (1 patient also had massive pulmonary embolism), 2 patients from ischemic stroke, and 1 patient from myocardial infarction. Fatal outcome within the first week occurred in 47 of all patients (36%) with intracerebral hemorrhage, 3 patients (14%) with subarachnoid hemorrhage, and 7 patients (8%) with subdural hematoma. During the entire follow-up, mortality among those with intracerebral hemorrhage was 59%, compared with 32% after subdural hematoma (Kaplan–Meier analysis, P<0.001). Recurrent intracranial hemorrhage was fatal in 4 of 18 patients (22%). In contrast, with the 21 patients (12%) who experienced a subsequent arterial thromboembolic event, none of those events were fatal.

Resumption of Warfarin

Fifty-nine patients (33%) resumed warfarin. The patients for whom warfarin was restarted were younger and had a longer follow-up than did the remainder (Table 1). Warfarin was restarted in 22 of the patients with atrial fibrillation (22%), 8 of the patients with venous thromboembolism (27%), 15 of the patients with mechanical aortic valve (79%), and 7 of the patients with mechanical mitral valve (77%). There was a highly significant difference between the proportions of restarted patients among those with mechanical valves compared with those of the remainder (P<0.001). Warfarin was resumed in 23 of all first-week survivors after intracerebral hemorrhage (28%), in 7 patients with subarachnoid hemorrhage (39%), and in 29 patients with subdural hematoma (38%). Resumption occurred after a median of 4.4 weeks (IQR 2.3–14) in patients with intracerebral hemorrhage, compared with 6.4 weeks (IQR 3.6–26) after subdural hematoma.
Finally, warfarin was restarted in 10 of those with previous stroke (31%) versus 49 of those without (34%). There were no statistically significant differences in any of those proportions.

Resumption of warfarin occurred after a median duration of 5.6 weeks (IQR 2.6–17) for all first-week survivors, after 9.2 weeks (IQR 5.6–34) for patients with atrial fibrillation, after 4.6 weeks (IQR 2.3–15) for patients with mechanical

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Patients</th>
<th>First-Week Survivors</th>
<th>With Cardiac Indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>Warfarin Resumed</td>
</tr>
<tr>
<td></td>
<td>234</td>
<td>177</td>
<td>45</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>76 (67–81)</td>
<td>75 (65–80)</td>
<td>70 (63–77)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>142 (61)</td>
<td>112 (63)</td>
<td>31 (69)</td>
</tr>
<tr>
<td>Indication for anticoagulation, n (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>135 (58)</td>
<td>102 (58)</td>
<td>22 (49)</td>
</tr>
<tr>
<td>Risk score CHADS₂=0</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Risk score CHADS₂=1</td>
<td>23 (17)</td>
<td>20 (20)</td>
<td>6 (27)</td>
</tr>
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<td>Risk score CHADS₂=2</td>
<td>44 (33)</td>
<td>34 (33)</td>
<td>6 (27)</td>
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<tr>
<td>Risk score CHADS₂=3</td>
<td>23 (17)</td>
<td>18 (18)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Risk score CHADS₂=4</td>
<td>25 (19)</td>
<td>19 (19)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Risk score CHADS₂=5</td>
<td>14 (11)</td>
<td>7 (7)</td>
<td>2 (9)</td>
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<tr>
<td>Risk score CHADS₂=6</td>
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<td>1 (1)</td>
<td>0 (0)</td>
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<td>Unknown</td>
<td>4 (3)</td>
<td>2 (2)</td>
<td>0 (0)</td>
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<tr>
<td>Venous thromboembolism</td>
<td>37 (16)</td>
<td>30 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mechanical aortic valve</td>
<td>24 (10)</td>
<td>19 (11)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Mechanical mitral valve</td>
<td>11 (5)</td>
<td>9 (5)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (11)</td>
<td>17 (10)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Additional antithrombotic treatment, n (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>205 (88)</td>
<td>158 (89)</td>
<td>40 (89)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>23 (10)</td>
<td>14 (8)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1 (0.4)</td>
<td>0.5</td>
<td>0</td>
</tr>
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<td>Aspirin and clopidogrel</td>
<td>5 (2)</td>
<td>4 (2)</td>
<td>2 (4)</td>
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<tr>
<td>Triggering factor, n (%)§</td>
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<tr>
<td>Spontaneous§</td>
<td>154 (66)</td>
<td>111 (63)</td>
<td>26 (58)</td>
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<tr>
<td>Fall or moderate trauma</td>
<td>51 (22)</td>
<td>44 (25)</td>
<td>13 (29)</td>
</tr>
<tr>
<td>Poorly controlled hypertension</td>
<td>11 (5)</td>
<td>10 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>4 (2)</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (6)</td>
<td>8 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>INR on admission, median (IQR)</td>
<td>2.65 (2.2–3.5)</td>
<td>2.6 (2.1–3.4)</td>
<td>2.5 (2.0–3.4)</td>
</tr>
<tr>
<td>Type of intracranial hemorrhage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral</td>
<td>130 (55)</td>
<td>83 (47)</td>
<td>18 (40)</td>
</tr>
<tr>
<td>Lobar</td>
<td>54 (22)</td>
<td>48 (58)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Deep hemispheric</td>
<td>53 (41)</td>
<td>29 (35)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>15 (12)</td>
<td>3 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Unclear</td>
<td>8 (6)</td>
<td>3 (4)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Subdural</td>
<td>83 (36)</td>
<td>76 (43)</td>
<td>22 (49)</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>21 (9)</td>
<td>18 (10)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Evacuation of hematoma, n (%)</td>
<td>81 (35)</td>
<td>73 (41)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>Follow-up, weeks, median (IQR)</td>
<td>34 (1–115)</td>
<td>69 (19–144)</td>
<td>140 (69–207)</td>
</tr>
</tbody>
</table>

INR, international normalized ratio.

*These 132 patients are the basis for the risk modeling.
†P<0.001 (Mann–Whitney test) in the comparison of those who resumed warfarin or did not.
‡P<0.001 (Pearson χ² test for multiple groups, followed by 2-group comparison of mechanical valves vs other indications using Fisher exact test) in the comparison of those who resumed warfarin or did not.
§In this subset, there are 4 patients with aneurysm/arterio-venous malformation, 2 with tumors, and 1 with ruptured colloid cyst.
those without (8.6%); (0.004). The cumulative risk of P-lism in patients with previous stroke (28%) compared with
showed a significantly higher risk of arterial thromboembo-
with another indication for warfarin. Kaplan–Meier analysis
in 4 patients (14%) with mechanical heart valves, in 1 patient
Strokes occurred in 12 patients (12%) with atrial fibrillation,
for patients with venous thromboembolism.

Recurrent Intracranial Hemorrhage
Recurrent intracranial hemorrhage was observed in 18 pa-
tients (10%); 8 of those patients restarted warfarin and 10 of
those patients did not, although 2 of the latter patients
subsequently resumed warfarin treatment. Twelve patients
with subdural hematoma (16%; 4 had resumed warfarin and 8
patients had not) and 6 patients with intracerebral hemorrhage
(7%; 4 had resumed warfarin and 2 patients had not) developed recurrent intracranial hemorrhage, versus none of
those with subarachnoid hemorrhage (P=0.1). Kaplan–Meier
analysis showed a trend toward higher risk of recurrence in
patients with subdural hematoma (16%) compared with those
with intracerebral hemorrhage (8.4%); (P=0.07). Among the
patients with intracerebral hemorrhage, it recurred in 4 patients
with lobar localization and in 1 patient each with deep hemispheric or brainstem localization. The type of
recurrence was generally the same as it was in the index
bleeding, except for 1 patient with initial intracerebral hem-
orrhage, which it recurred as subdural, and another patient
with the opposite sequence. The cumulative risk of recurrent
intracranial hemorrhage without restarted anticoagulation or
from the time point of resumption of anticoagulation is shown
in Figure 1A and 1B, respectively.

Thromboembolic Events
Among the 21 patients who suffered a subsequent arterial
thromboembolic event, 2 patients had systemic embolism
(brachial artery and femoral artery), 1 patient had a transient
ischemic attack, and 18 patients suffered an ischemic stroke.
Strokes occurred in 12 patients (12%) with atrial fibrillation,
in 4 patients (14%) with mechanical heart valves, in 1 patient
(3%) with venous thromboembolism, and in 1 patient (6%)
with another indication for warfarin. Kaplan–Meier analysis
showed a significantly higher risk of arterial thromboembo-
lism in patients with previous stroke (28%) compared with
those without (8.6%; (P=0.004). The cumulative risk of ischemic events without restarted anticoagulation or from the
time point of resumption of anticoagulation is shown
in Figure 1A and 1B, respectively.

Eleven patients (5%) developed symptomatic venous
thromboembolism following warfarin cessation, after a me-
dian of 2 weeks (IQR, 1.5–5) from the intracranial hemorrhage;
in 4 of these patients, the initial indication for warfarin
was venous thromboembolism.

Risk Modeling
The modeling of risk for recurrent intracranial hemorrhage
versus ischemic stroke in patients with or without resumption
of warfarin therapy is based on the population with cardiac
indication for anticoagulation and/or with previous ischemic
stroke and who had survived the first week without a
recurrent event (n=132; Table 1).

As might be expected, fitting separate Cox models with a
time-dependent variable to indicate the point at which war-
farin was restarted revealed strong effects of anticoagulation
resumption. Restarting warfarin increased the risk of recur-
rent intracranial hemorrhage by more than a factor of 5 (HR
5.57; 95% CI, 1.80–17.25; P=0.0029), whereas the risk of a
thromboembolic event was reduced by almost 90% (HR 0.11;
95% CI, 0.14–0.87; P=0.036). These model-based estimates
are apparent in the raw data displayed in the top panel of
Table 3. There, time is divided into periods with reasonably
constant risk, which differ somewhat among recurrent hem-
orrhage and ischemic stroke, as these have independent
natural courses. Within each time period, we show the
observed number of events and the number of days at risk,
separately for days when patients are receiving versus not

<table>
<thead>
<tr>
<th>Table 2. Distribution of Patients at the 3 Sites of Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Health Sciences, General Site</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Admissions* for intracranial hemorrhage, n</td>
</tr>
<tr>
<td>Patients with intracranial hemorrhage, n</td>
</tr>
<tr>
<td>Warfarin-associated intracranial hemorrhage, n (%)</td>
</tr>
<tr>
<td>Patients restarted on warfarin, n (%)</td>
</tr>
</tbody>
</table>

*Some patients had >1 admission.
receiving warfarin. For example, in the first 35 days there were 7 recurrent intracranial hemorrhages in 3829 patient-days while not on warfarin, equating a daily rate of 0.18%; this is compared with 2 events in 265 patient-days while on warfarin, equating a daily rate of 0.75%. The ratio of these two rates is 4.13, which is the estimated hazard ratio associated with starting warfarin on or before day 35. The corresponding hazard ratio in the 36- to 93-day period is 4.46, and then becomes infinite in later periods because there are no subsequent intracranial bleeds in patients not on warfarin. The Cox model hazard ratio estimate of 5.57 is essentially a weighted average of these individual estimates from the separate time intervals. The data in Table 3 clearly suggest a pattern of reducing risk of recurrent intracranial hemorrhage with time since the index bleed, both in the presence and absence of warfarin. Despite the lack of observed events beyond 63 days in the absence of warfarin, the data are quite consistent with a constant hazard ratio over time; thus, whatever the time of warfarin resumption, it would be anticipated that retreatment would multiply the background risk of an intracranial bleed by a factor of 5.57.

The risk of a subsequent thromboembolic event is also much higher immediately following the index intracranial bleed and then declines with time (Table 3). Only 1 thromboembolic event was observed in a patient receiving warfarin, in keeping with its antithrombotic efficacy. The assumption of a constant proportional risk reduction of approximately 90% is hard to verify in this data set, but the results of warfarin trials, for example in atrial fibrillation, tend to show diverging cumulative risk curves consistent with an ongoing constant proportional effect.\[^{16}\]

Resumption of warfarin at any given time point will increase the subsequent risk of recurrent intracranial hemorrhage and reduce the risk of a thromboembolic event. The optimal restart time must balance these 2 competing cumulative risks over the entire warfarin “treatment horizon.” Because the underlying need for prophylaxis will continue indefinitely and the median survival rate in our data was 4.5 years, we evaluated a range of treatment horizons from 3 to 6 years in our modeling. To determine the optimal restart time, we varied warfarin resumption between 1 and 50 weeks after the index intracranial bleed and calculated the “total” risk (ie, before plus after the selected time point of resumption) of recurrent intracranial hemorrhage, and of a thromboembolic event through to the end of treatment. The calculation of cumulative risks used the rates displayed in the bottom panel of Table 3. Given that it is implausible that the actual risk of intracranial bleed or thromboembolic event is 0, we have not used the observed daily risks directly, but instead we have blended the observed rates and Cox model hazard ratios as indicated in the footnote to Table 3.

The results, as shown in Figure 2, demonstrate how the total risk of intracranial hemorrhage and an ischemic event for the whole treatment period varies according to when warfarin is restarted. Based on this combined risk, the optimal period of resumption of warfarin seems to be between 10 and 30 weeks from the index intracranial hemorrhage over a survival- and treatment-horizon of 3 years. This total risk did not change when the treatment horizon was expanded to 4, 5, or 6 years (data not shown). Resumption of anticoagulation within the first month results in a much higher “total” risk, which is driven by the high risk of recurrent intracranial hemorrhage. Inclusion of patients with a noncardiac indica-

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**Table 3. Cox Proportional Hazards Model for Recurrent Intracranial Hemorrhage or for Ischemic Event at Different Time Intervals With and Without Resumption of Warfarin**

<table>
<thead>
<tr>
<th>Warfarin Status</th>
<th>Risk of Intracranial Hemorrhage per Day</th>
<th>Risk of Ischemic Stroke per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed rate n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7/3829 (0.18%)</td>
<td>1/2250 (0.044%)</td>
</tr>
<tr>
<td>Yes</td>
<td>2/265 (0.75%)</td>
<td>1/504 (0.20%)</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>4.13</td>
<td>4.46</td>
</tr>
<tr>
<td><strong>Rate used in prediction model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.18%</td>
<td>0.044%</td>
</tr>
<tr>
<td>Yes</td>
<td>1.02%f</td>
<td>0.25%f</td>
</tr>
</tbody>
</table>

\[^{*}\]The Cox proportional hazard model provided a Warfarin Hazard Ratio for recurrent intracranial hemorrhage of 5.57 (95% CI, 1.80–17.25; \(P=0.0029\)) and for ischemic stroke of 0.11 (95% CI, 0.0139–0.868; \(P=0.036\)). The rates used in the prediction model were based on the following hazard ratios:

\[^{†}\]Observed rate on warfarin/5.57.

\[^{‡}\]Observed rate without warfarin.

\[^{§}\]Observed rate without warfarin \times 5.57.

\[^{§}\]Observed rate without warfarin \times 0.11. The remaining proposed rates are those actually observed.
tion for warfarin or without previous stroke in this analysis did not change the outcome (data not shown).

**Discussion**

We are reporting results from a large cohort of patients with warfarin-induced intracranial hemorrhage. Our analysis of patients with a high risk for arterial thromboembolic complications and the extended follow-up enabled us to estimate the optimal time interval for resumption of warfarin, taking into account the risk for recurrent intracranial hemorrhage as well as for ischemic stroke. In contradiction to previous studies, our data suggest that warfarin resumption should be delayed at least a month from the index event. With 100 patients resuming anticoagulation 2 weeks, 5 weeks, or 10 weeks after warfarin-associated hemorrhage, there would, according to our modeling, be during a 3-year treatment horizon 36, 24, or 19 recurrent intracranial hemorrhages versus 4, 5, or 7 ischemic events, respectively.

The ideal design would have been a randomization between early and late resumption of anticoagulation, but this poses substantial logistical challenges. We needed approximately 5 years of consecutive cases from 3 tertiary referral centers to collect sufficient data for our analysis. We chose to analyze only recurrent major bleeds that were intracranial because of the clinical burden and the high risk of chronic sequel and death. The only thromboembolic complication of similar severity is ischemic stroke, and we therefore excluded transitory ischemic attacks and systemic embolism from our analysis. Our hazards model was focused on patients with a cardiac indication for anticoagulation or with previous stroke because when untreated, these conditions confer a moderate-to-high risk of ischemic stroke. Clinicians are usually less hesitant about permanent discontinuation of anticoagulation if the initial indication was venous thromboembolism.

In a systematic review of 6 retrospective studies, which included 120 patients with mechanical heart valves and intracranial hemorrhage, the authors concluded that it was safe to resume warfarin within 2 weeks. All 6 studies were either small or had a very limited follow-up, and only 2 recurrent intracranial hemorrhages and 4 ischemic strokes were reported. These studies did not include patients with atrial fibrillation and additional risk factors for stroke, or patients with myocardial infarction and intramural thrombus; both groups are also of interest due to high risk of stroke. A recently published systematic review with 492 patients concluded that anticoagulation may be resumed after 72 hours. This review included a large number of single-case reports with a high risk for bias toward successful cases, and the authors considered all anticoagulants of any dose together. The hitherto largest cohort included 141 patients, of whom 35 patients resumed warfarin; however, the follow-up was only 30 days, which may explain why no recurrent intracranial hemorrhage was observed. The second-largest cohort had 52 patients, of whom 23 patients resumed warfarin, reported 3 recurrent intracranial hemorrhages and 3 ischemic strokes during a mean follow-up of 43 months. These small numbers of events do not allow statistical analysis of the optimal time of resumption of anticoagulation. Eckman et al addressed this question by using a Markov model, and concluded that patients with deep hemispheric location of the hemorrhage (which had a reported low risk of recurrence) would qualify for resumption of anticoagulation, provided that the risk of ischemic stroke was high. Conversely, patients with lobar hemorrhage, which appears to carry a higher risk of recurrence, should never be restarted on anticoagulation. This analysis focused on patients who had atrial fibrillation and an average risk of stroke of 4.5% per year. We had too-small numbers of each of the subtypes of intracerebral hemorrhage with recurrence to confirm those assumptions. Furthermore, the risk for ischemic stroke varies widely, and for a patient with a previous stroke, the risk of recurrence (28% in our material) may justify resumption of anticoagulation for a patient with lobar hemorrhage as well.

The main limitation of our study is the retrospective design with resumption of anticoagulation occurring at different time points. The choice of time point might have been biased by the fear of the clinician of recurrent bleeding or of ischemic stroke, that seems to have been the case for patients with mechanical valves who were restarted on warfarin more frequently than for other subsets. However, those with previous stroke were treated in a similar manner to those without, despite higher risk for new ischemic events. Among patients with subdural hematoma and a high risk for recurrent hemorrhage, the rate of resumption was as high as it was for other patients. Although warfarin was resumed more frequently in younger patients, we did not observe a difference in the risk for recurrent intracranial hemorrhage or ischemic events depending on age (data not shown). Another limitation of our study is the significantly shorter follow-up of patients who were not restarted on warfarin. However, with a median of 39 weeks of observation in this subset, the period with the highest event rate should have been covered.

We acknowledge that our conclusions are based on relatively few clinical events. However, our study includes more events than does any previous study or systematic review. We have shown that the initial risk for recurrent intracranial hemorrhage increases 5-fold when warfarin is resumed, and that the risk of recurrent bleeding with resumed warfarin is higher than is the risk of ischemic events without anticoagulation. Resumption of warfarin can therefore be delayed by more than 1 month after the index event. In fact, the optimal period for resumption of anticoagulation seems to occur between week 10 and week 30 after warfarin-associated intracranial hemorrhage, when the risk for recurrent intracranial hemorrhage and the risk for ischemic stroke are taken into account. Our findings contradict the recommendations made in previous studies and expert opinion. The larger number of patients included in this study, the longer follow-up, and the modeling we performed have allowed for a more precise description of the total risk for serious events in relation to the timing of resumed anticoagulation. The span of this interval of 20 weeks may be helpful to select when patients with a perceived high risk for bleeding versus high risk for stroke should be restarted.

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Abstract 14

두개내출혈 이후 와파린을 다시 복용하는 적절한 시점

Optimal Timing of Resumption of Warfarin After Intracranial Hemorrhage

Ammar Majeed, MD; Yang-Ki Kim, MD; Robin S. Roberts, PhD; Margareta Holmström, MD, PhD; Sam Schulman, MD, PhD

(Stroke. 2010;41:2860-2866.)

Key Words: intracranial hemorrhage ■ anticoagulation ■ ischemic stroke ■ management

배경과 목적
항응고 치료를 지속해야 하는 적응증을 가지고 있는 환자에서, 와파린-warfarin과 관련하여 발생한 두개내출혈(intracranial hemorrhage) 이후 언제부터 와파린을 다시 복용해야 하는지에 대하여는 아직 분명하지 않다. 저자들은 보다 정확한 위험 예측을 위해 대규모의 후향적 코호트 연구를 하였다.

방법
세 개의 3차 의료 기관에서 6년 동안 두개내출혈로 확진받은 환자 2,869명의 의무 기록을 조사하였다. 저자들은 와파린은 다시 복용하였던지의 여부에 따른 두개내출혈 또는 혈협 뇌졸중(ischemic stroke)의 일일 병병 위험도를 계산하였다. 일주일 이상 생존하였고 항응고 치료에 적용되는 심장 질환을 가지고 있거나 뇌졸중 병력이 있는 환자들에 점수를 주었다. 저자들은 Cox 모형을 이용하여 항응고 치료를 다시 시작한 다양한 시점에 따른 이 두 가지 합병증에 대한 발병률을 계산하였다. 와파린을 다시 복용한 시점에 따른 새로운 두개내출혈이나 혈협뇌졸중이 발생한 위험도를 계산하였다.

결과
와파린과 관련이 있는 두개내출혈은 234명(8.2%)의 환자에서 발견되었고, 그 중 177명(76%)은 일주일 이상 생존하여 추적 관찰 정보가 존재하였다. 추적 관찰 기간의 중앙값은 69주 (interquartile range [IQR] 19~144)였다. 59명이 중앙값으로 5.6주(IQR 2.6~17)가 지난 후에 와파린을 다시 복용하였 다. 와파린을 다시 복용하였을 때 두개내출혈은 재발 위험도는 5.6 (95% CI, 1.8~17.2)이었고, 혈협뇌졸중의 위험도는 0.11 (95% CI, 0.014~0.89)이었다. 두개내출혈이 재발과 혈협뇌졸 중 발생을 결합한 위험도는 와파린을 다시 복용한 뒤 약 10~30주가 되었을 때에 최저점에 도달하였다.

결론
와파린을 다시 복용하는 가장 적절한 시점은 와파린과 관련한 두개내출혈이 발생한 후 10~30주 사이이다.
Figure 2. The "total" risk for a treatment horizon of 3 years of recurrent intracranial hemorrhage and of ischemic stroke according to the time point of resumption of anticoagulation.

Table 3. Cox Proportional Hazards Model for Recurrent Intracranial Hemorrhage or for Ischemic Event at Different Time Intervals With and Without Resumption of Warfarin

<table>
<thead>
<tr>
<th>Warfarin Status</th>
<th>Risk of Intracranial Hemorrhage per Day</th>
<th>Risk of Ischemic Stroke per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed rate n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7/3829 (0.18%)</td>
<td>1/2250 (0.044%)</td>
</tr>
<tr>
<td>Yes</td>
<td>2/265 (0.75%)</td>
<td>1/504 (0.20%)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>4.13</td>
<td>4.46</td>
</tr>
<tr>
<td>Rate used in prediction model*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.18%</td>
<td>0.044%</td>
</tr>
<tr>
<td>Yes</td>
<td>1.02%‡</td>
<td>0.25%‡</td>
</tr>
</tbody>
</table>

*The Cox proportional hazard model provided a Warfarin Hazard Ratio for recurrent intracranial hemorrhage of 5.57 (95% CI, 1.80–17.25; P=0.0029) and for ischemic stroke of 0.11 (95% CI, 0.0139–0.866; P=0.036). The rates used in the prediction model were based on the following hazard ratios:
‡Observed rate on warfarin×5.57.
§Observed rate without warfarin×0.11. The remaining proposed rates are those actually observed.
背後の物語および目的：抗凝固療法の適応患者がワルファリン投与に伴い頭蓋内出血を発症した場合の、出血後の抗凝固療法再開の最適時期は明確ではない。より正確なリスク推定値を得るために、大規模な後ろ向きコホート研究を実施した。

方法：3つの三次医療施設において、6年間に頭蓋内出血が診断された2,869例の病歴を連結的に検討した。ワルファリンを再開とした場合と再開しなかった場合の1日あたりの頭蓋内出血または虚血性脳卒中のリスクを算出した。本研究では、最初の頭蓋内出血から1週間以上生存し、心疾患により抗凝固療法が適応であるか、または脳卒中の既往のある患者に焦点をあてた。Coxモデルを用い、抗凝固療法再開（または非再開）後の各時点における頭蓋内出血と虚血性脳卒中の発現率を推定した。ある一定のワルファリン再開時期範囲における新たな頭蓋内出血または虚血性脳卒中の複合リスクを算出した。

結果：ワルファリンに伴う頭蓋内出血が234例（8.2%）に認められ、このうち1週間以上生存した177例（76%）から追跡調査データが得られた。追跡調査期間の中央値は69週であった（四分位範囲IQR：19～144）。59例が5.6週（中央値、IQR：2.6～17）後にワルファリンを再開した。ワルファリン再開による頭蓋内出血再発のハザード比は5.6（95% CI：1.8～17.2）、虚血性脳卒中のハザード比は0.11（95% CI：0.014～0.89）であった。頭蓋内出血再発または虚血性脳卒中の複合リスクが最も低かったのは、約10～30週後にワルファリンを再開した場合であった。

結論：ワルファリン治療再開の最適時期は、ワルファリン投与に伴う頭蓋内出血から10～30週後であると思われる。

注：177例の内訳は脳内出血83例、硬膜下脳血76例、くも膜下出血18例であり、全体の44例で転倒または中等度の外傷が誘因とされた（詳細は英文誌表1を参照）。