Restarting Anticoagulation Therapy After Warfarin-Associated Intracerebral Hemorrhage

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Background: Reinitiating warfarin sodium therapy in a patient with a recent warfarin-related intracerebral hemorrhage (WAICH) is a difficult clinical decision. Therefore, it is important to assess the outcome of resumption or discontinuation of warfarin therapy after WAICH.

Objective: To compare patients who survived an episode of WAICH and restarted warfarin therapy with a group of WAICH patients who did not resume warfarin therapy.

Design, Setting, and Patients: We conducted a follow-up study from November 1, 2001, through December 31, 2005, in a cohort from a single center. Long-term outcome was assessed at last clinical follow-up or via questionnaire.

Main Outcome Measures: Recurrent WAICH and thromboembolic events.

Results: Fifty-two patients were discharged from the hospital after a diagnosis of WAICH. Four patients were lost to follow-up. Mean follow-up among all patients was 43 (range, 1-108) months. Of the 23 patients who restarted warfarin therapy, 1 had a recurrent nontraumatic WAICH, 2 had traumatic intracerebral hemorrhages, and 2 had major extracranial hemorrhages. Of the 25 patients who did not restart warfarin therapy, 3 had a thromboembolic stroke, 1 had a pulmonary embolus, and 1 had a distal arterial embolus.

Conclusions: Restarting warfarin therapy in patients with a recent WAICH is associated with a low risk of recurrence, but patients are subjected to known, substantial risks of warfarin use. Withholding warfarin therapy is associated with a risk of thromboembolization.

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The use of warfarin sodium is rapidly increasing with the aging of the general population. Warfarin prevents thromboembolic events in patients with mechanical valve prostheses, atrial fibrillation, or venous thromboembolism, but its use increases the risk of intracerebral hemorrhage (ICH). As the incidence of warfarin-associated ICH (WAICH) also increases, the question of whether to restart warfarin therapy after WAICH is becoming more common in practice.

Reinitiating warfarin therapy in a patient with a recent WAICH is a difficult proposition, and the assessment of risks is a pertinent question for any physician. Competing risks include the risk of recurrent ICH if warfarin therapy is restarted vs the risk of recurrent thromboembolism without warfarin therapy. In addition, patients with residual neurological deficits from WAICH could be at increased risk of traumatic bleeding from falls. Very limited clinical data describe the long-term risk of recurrent ICH among patients with WAICH. Recent American Heart Association guidelines state that careful control of the anticoagulation level decreases the risk of ICH. However, no practical knowledge exists to address this important clinical problem.

To assess the risks of resumption or permanent discontinuation of warfarin therapy, we conducted a follow-up study on a cohort of patients with WAICH who restarted anticoagulation therapy. We compared their risk with that of a group of patients with prior WAICH who did not resume warfarin therapy.

Methods

We analyzed consecutive patients admitted to our hospital with a diagnosis of WAICH from November 1, 2001, through December 31, 2005. Our institutional review board approved the design of the study. We identified the patients retrospectively using a diagnosis-based electronic search engine and included them in the study after detailed analysis of medical records and

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Table 1. Clinical Characteristicsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restarted Group (n = 23)</th>
<th>Nonrestarted Group (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>70.8 (45-86)</td>
<td>75.3 (45-90)b</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>13/10</td>
<td>14/11</td>
</tr>
<tr>
<td>Reason for anticoagulation</td>
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<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9 (39)</td>
<td>14 (56)</td>
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<tr>
<td>Valve replacement</td>
<td>10 (44)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Thrombus/DVT</td>
<td>3 (13)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Otherc</td>
<td>1 (4)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hypertension treated with medication</td>
<td>19 (83)</td>
<td>18 (72)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>5 (22)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Coronary artery disease/CHF</td>
<td>5 (22)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>7 (30)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Concomitant neoplasm</td>
<td>1 (4)</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; DVT, deep venous thrombosis.

a Unless otherwise indicated, data are expressed as number (percentage) of patients.
b Differences between groups were significant (P = .02).
c Including vertebral basilar atherothrombotic disease and stroke history.

computed tomographic scans. Inclusion criteria were presentation to our hospital with radiologically documented ICH, an international normalized ratio of 1.5 or higher at admission, current treatment with warfarin, and discharge from the hospital. The ICH volumes were based on computed tomographic scans obtained at presentation and calculated using the formula (A×B×C)/2 described by Kothari et al.11

Follow-up data were obtained through a review of medical records and mailed questionnaires. The questionnaire included information on current disability, current use of warfarin or antiplatelet medications, and information about recurrent ICH, ischemic stroke, and other hemorrhagic or thromboembolic complications that occurred after the original ICH. A major hemorrhage or thromboembolic event was defined as an event requiring hospital admission or requiring a change in medical anticoagulation therapy. All hemorrhages were categorized as traumatic or nontraumatic. If the hemorrhage occurred in the setting of a fall or trauma, it was considered traumatic. When sufficient information was available, the ischemic stroke mechanism was determined.

Patients were divided into those restarting (restarted group) and not restarting (nonrestarted group) warfarin therapy. Patients were included in the restarted group if they restarted warfarin therapy within 60 days of the primary ICH. This 2-month cutoff was intended to compensate for any other medical condition that would delay reinitiation of warfarin therapy and accounted for at least 1 outpatient hospital follow-up from the time of discharge, which is typically the time when the decision to reinitiate warfarin therapy is made. Patients who reinitiated warfarin therapy with an episode of recurrent thromboembolism, they were categorized in the restarted group for the remainder of their follow-up.

Follow-up time was calculated in months, from the presenting month of WAICH to the month of questionnaire response or the last neurological examination on file. End points included nontraumatic or traumatic recurrent ICH, abnormal bleeding requiring hospitalization, ischemic stroke, myocardial infarction, other thrombotic and thromboembolic events (pulmonary embolism, peripheral arterial embolism, and deep vein thrombosis), and the cause and time of death. Intracranial hemorrhage was subdivided into subdural or subarachnoid hemorrhage. Functional outcome was evaluated using the modified Rankin Scale score measured at hospital discharge and latest follow-up by reviewing physical examination results and questionnaire answers.12,13

Of the 88 consecutive patients identified with WAICH, only 52 (59%) were discharged from the hospital. The other 36 patients died in the hospital or in hospice care. Of the 52 discharged patients, 23 (44%) restarted warfarin therapy. Twenty-nine of the 52 patients (56%) did not restart warfarin therapy; 4 of these patients could not be reached to obtain follow-up information and were not included in the analysis. The clinical and radiological characteristics of our study population are detailed in Table 1 and Table 2. Mean age was higher in the nonrestarted group (75.3 vs 70.8 years). Most of the patients in the restarted group (10 patients [44%]) required warfarin for thromboembolic prevention owing to implantation of a prosthetic valve, a much higher proportion with this indication than among patients in the nonrestarted group. Of the 10 patients who reinstituted warfarin therapy because of mechanical valves, 8 had aortic valve replacements and 2 had both aortic and mitral valve replacements. Aortic valve replacements included 3 St Jude valves, 2 Star-Edwards valves, 1 caged-ball valve, 1 Brunwald-Cutter valve, and 1 Medtronic allograft valve. Both of the patients with aortic and mitral valve replacements had St Jude valves. Patients restarted warfarin therapy after a median of 10 (range, 7-28) days.

Fourteen of the 25 patients (56%) in the nonrestarted group originally received warfarin for atrial fibrillation. One of the 2 patients with a history of valve surgery who did not restart warfarin therapy had a Carpentier-Edwards valve and mitral valve repair. This patient did not restart warfarin therapy owing to concern about having another ICH. In the 34 months of follow-up, the patient reported a myocardial infarction but no other thromboembolic complications. The other patient had an aortic valve that had been replaced with a St Jude valve and did not restart warfarin therapy owing to comorbid medical concerns, specifically an abdominal aortic aneurysm, a right coronary artery aneurysm, and worsening congestive heart failure. The patient died 1 month after discharge from the hospital.

Locations of ICHs were generally similar between groups. In the restarted group, a slightly higher percentage of patients (10 vs 8 patients [43% vs 32%]) had lobar hemorrhage. Conversely, cerebellar hemorrhages (4 vs 2 patients [16% vs 9%]) and intraventricular hemorrhages (2 vs 1 patient [8% vs 4%]) were more common in the nonrestarted group (Table 2).
Mean follow-up among all patients was 43 months. Median follow-up was 36 (range, 1-100) months. At the time of last follow-up, mortality was high in both groups: 13 of the 23 patients in the restarted group and 12 of the 25 nonrestarted group had died. Survival outcomes were assessed using the log-rank outcome. Although the differences were not significant, there was a trend for those who restarted warfarin therapy to survive early after reinitiation of drug therapy. At 1 year, there was a 96% survival (SD, 4%) in the restarted group and a 76% survival (SD, 8.5%) in the nonrestarted group. At 2 years, the survival changed to 86% (SD, 14%) vs 68% (SD, 32%) in both groups. The average time to death appeared shorter in the nonrestarted group than in the restarted group (21.8 vs 55.6 months). The modified Rankin Scale scores were similar, and showed worsening of disability from time of discharge to current follow-up. Details of follow-up data are given in Table 3.

There were 5 cases of recurrent major hemorrhage in the restarted group, including 1 recurrent WAICH, 2 traumatic ICHs, and 2 extracranial bleedings. Three of the 5 events were fatal. The patient with the recurrent nontraumatic WAICH had a fatal deep hematoma contralateral to the side of the original bleeding that occurred 35 months after reinitiating warfarin therapy (Figure 1). Of the traumatic ICHs, one was primarily subarachnoid and resulted in death, whereas the other was a nonfatal small subdural hemorrhage. Of the 2 extracranial hemorrhages, one was a fatal pulmonary hemorrhage and the other was a soft tissue abdominal wall hematoma requiring hospital admission. In the cases of the fatal recurrent nontraumatic WAICH and traumatic subarachnoid hemorrhage, the international normalized ratios at presentation were 2.5 and 4.1, respectively.

Among the patients who did not restart warfarin therapy, there were 5 cases of thromboembolic events, including 3 thromboembolic strokes (all attributed to atrial fibrillation), 1 pulmonary embolus, and 1 distal arterial embolus resulting in leg ischemia. Only 1 case was fatal. All thromboembolic events occurred in patients who originally received warfarin for secondary prevention of thromboembolism. Among the patients with thromboembolic strokes, the mean time to the event was 5.7 (range, 3-7) months; 2 of these patients reinitiated warfarin therapy at the time of the stroke, and in 1 patient the stroke was fatal. The 2 patients who restarted warfarin therapy after an embolic stroke had no subsequent hemorrhagic complications. Categorizing these 2 patients in the restarted group after reinitiation of warfarin therapy did not change the results of the survival analysis or outcome between the groups.

Other complications were noted in both groups. There were 2 ischemic strokes in the nonrestarted group that were not attributed to thromboembolism. One was ascribed to penetrating artery disease and the other to infectious endocarditis. Two patients who did not restart warfarin therapy had gastrointestinal tract bleeding. One case occurred 1 month after the WAICH and was fatal; the other required hospital admission and was related to aspirin use.

Although examination of the Kaplan-Meier curves suggests that an adverse event (major hemorrhage or thromboembolic event) occurred sooner in the nonrestarted group than in the restarted group (21.8 vs 55.6 months). The modified Rankin Scale scores were similar, and showed worsening of disability from time of discharge to current follow-up. Details of follow-up data are given in Table 3.

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tistically significant ($P = .62$), with a hazard ratio of 1.4 (95% confidence interval, 0.4-4.9) for the nonrestarted vs restarted groups. Furthermore, when all hemorrhagic and thromboembolic events were considered as a combined end point, there was no significant difference between the groups.

Survival analysis showed that 86.1% of the patients in the nonrestarted group were free of thromboembolic complication after 1 year, whereas 73.6% were free of thromboembolic event after 3 years. When all ICH events were accounted for, 100% of the patients who restarted warfarin therapy were free of ICH after 1 year, whereas 92.9% of the patients were free of ICH at 3 years (95% confidence interval, 80.3%-100.0%).

**COMMENT**

This study provides the longest clinical follow-up of patients presenting with WAICH and for the first time, to our knowledge, compares the outcome of patients who restarted warfarin therapy with those of patients who did not restart therapy after a WAICH. Although there were no statistically significant differences, the observational results of our study suggest that recurrent primary ICH after reinitiation of warfarin therapy occurs less frequently than does recurrent thromboembolic events in patients who do not restart warfarin therapy. However, reinitiating anticoagulation therapy was also associated with an increased risk of traumatic ICH and extracranial hemorrhagic complications.

Two previous studies addressed the outcomes of patients who reinitiated warfarin therapy after ICH. One study followed up 13 patients with ICH and prosthetic heart valves for 2 years and reported no cases of recurrent nontraumatic ICH. Another study described 25 patients who restarted warfarin therapy after ICH with no episodes of recurrent ICH after anticoagulation was reinitiated, but the length of follow-up after reinitiating anticoagulation therapy was not provided. A recent analysis of estimated ICH recurrence, not restricted to WAICH, concluded that the risk would be 2.3% per patient per year. In our series, recurrent primary WAICH was uncommon (1 of 23 patients) after reinitiation of anticoagulation therapy, whereas ICH occurred in 3 of 23 patients.

The percentage of thromboembolic complications in patients who did not restart warfarin therapy was substantial, despite a lower incidence of patients with mechanical prosthetic valves. All patients with thromboembolic events after WAICH had originally started warfarin therapy after a thromboembolic event. This suggests that patients requiring warfarin for secondary (as opposed to primary) prevention of thromboembolic events may be more likely to benefit from reinitiation of warfarin therapy after WAICH. Recurrent thromboembolic strokes occurred mostly within 6 months of the WAICH,
suggesting that early reinitiation of warfarin therapy may be advantageous. In our population, most patients re-started warfarin therapy within 2 weeks of the WAICH. This practice was guided by previous data indicating that there is a low probability of thromboembolic events in patients with mechanical valves within the first 2 weeks after an ICH.17

Our study results confirm the poor outcomes of patients with WAICH and the frequent adverse effects attributable to warfarin. A recent study of patients with atrial fibrillation who were hospitalized for ICH and extracranial hemorrhage attributed to warfarin use had a mean follow-up of 2.4 years.18 It concluded that mortality and long-term disability were high in patients with ICH, whereas those with extracranial hemorrhage survived with minor or no disability. In our patients, mortality during follow-up was high (48%), and functional scores worsened over time. The average time to death was much shorter in the nonrestarted group. One possible explanation is that these patients were older than those in the restarted group. However, there may have been other medical problems that could have contributed to this difference and likely influenced the decision to discontinue warfarin therapy permanently after the ICH.

Hemorrhage risk is well described in patients taking warfarin. Aside from ICH, extracranial sites such as the gastrointestinal tract, genitourinary tract, and soft tissue are common sites for hemorrhage.19-21 Patients who have had previous hemorrhagic events while receiving warfarin are at increased bleeding risk. Other risk factors include liver and renal disease, hypertension, cancer, and stroke.19,22-25 Among our patients who restarted warfarin therapy, recurrent hemorrhages were fatal in 3 of 5 cases, thus confirming the severity of recurrent hemorrhagic complications in patients receiving anticoagulation therapy.

The data often cited to guide clinicians on the risks and benefits of restarting anticoagulation therapy after WAICH are derived from a computer model based on hypothetical strategies and a decision analysis that made predictions based on certain assumptions of risk.26 Underlying assumptions used in this model include that the risk of recurrent ICH is constant over a patient's lifetime, and that any ICH should result in permanent discontinuation of anticoagulation therapy. Although this model is helpful in conceptualizing this difficult clinical problem, its conclusions need to be interpreted with caution because it was built using assumptions not confirmed by actual clinical data. For instance, the model recommends that, in patients with deep hemorrhage, anticoagulation therapy should be permanently withheld owing to concern about recurrent hemorrhage unless there is a high risk of ischemic stroke.

The main limitation of this retrospective study is that we could not control for the clinical differences and time of follow-up between the 2 groups. For instance, the restarted group was younger and included a higher proportion of patients with a mechanical valve prosthesis. Although patients with prosthetic valves are at greater risk of thromboembolic events, our data indicated that they had fewer thromboembolic events than patients who did not restart warfarin therapy. This observation reinforces the benefit of anticoagulation therapy in patients with mechanical valves. Unfortunately, a randomized controlled study addressing the clinical decision of re-starting warfarin therapy after a WAICH is unlikely to be conducted. The decision for randomization would probably be deemed unsafe in certain patients; for example, a patient with a prosthetic valve is more likely to have warfarin therapy restarted than is a patient with atrial fibrillation and severe neurological deficits after a stroke. Therefore, we have to rely on observational data to evaluate this clinical problem. In addition, 4 patients were lost to follow-up. All of these patients were in the nonrestarted group, and this discrepancy could have generated a bias.

This is, to our knowledge, the first long-term clinical study comparing the outcomes in patients with or without reinitiation of warfarin therapy after a WAICH. Our clinical data indicate that recurrent WAICH is uncommon when anticoagulation therapy is resumed, whereas the risk of thromboembolic events may be comparatively greater in patients who do not reinitiate warfarin therapy. However, the clinician deciding whether to re-start anticoagulation therapy after an episode of WAICH should weigh other factors, including the patient’s risk of falls, general medical condition, and other risk factors for systemic hemorrhage. Patients without these risks may benefit from reinstitution of warfarin therapy. Failure to do so might unnecessarily subject them to thromboembolic complications.

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REFERENCES


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