Risk of Thromboembolism With Short-term Interruption of Warfarin Therapy

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Background: Significant uncertainty surrounds the treatment of patients who must discontinue warfarin sodium therapy before an invasive procedure. In part, the uncertainty results from the lack of published information about the risk of thromboembolism associated with short-term warfarin therapy interruption. We aimed to assess the frequency of thromboembolism and bleeding within a large cohort of patients whose warfarin therapy was temporarily withheld for an outpatient invasive procedure.

Methods: This prospective, observational cohort study was performed at 101 sites (primarily community-based physician office practices) in the United States. Enrollment was conducted from April 4, 2000, to March 6, 2002. The main outcome measures were thromboembolism or clinically significant hemorrhage within 30 days of warfarin therapy interruption.

Results: A total of 1293 episodes of warfarin therapy interruption in 1024 individuals were included. The mean (SD) patient age was 71.9 (10.6) years; 438 (42.8%) were female. The most common indications for anticoagulant therapy were atrial fibrillation (n = 550), venous thromboembolism (n = 144), and mechanical heart valve (n = 132). The most common procedures were colonoscopy and oral and ophthalmic surgery. Perioperative heparin or low-molecular-weight heparin was used in only 8.3% of cases overall. Seven patients (0.7%; 95% confidence interval [CI], 0.3%-1.4%) experienced postprocedural thromboembolism within 30 days. None of the 7 patients who experienced thromboembolism received periprocedural bridging therapy. Six patients (0.6%; 95% CI, 0.2%-1.3%) experienced major bleeding, whereas an additional 17 patients (1.7%; 95% CI, 1.0%-2.6%) experienced a clinically significant, nonmajor bleeding episode. Of these 23 patients who had bleeding episodes, 14 received periprocedural heparin or low-molecular-weight heparin. The duration of warfarin therapy interruption was variable; however, more than 80% of patients had warfarin therapy withheld for 5 days or fewer.

Conclusions: For many patients receiving long-term anticoagulation who need to undergo a minor outpatient intervention, a brief (≤5 days) periprocedural interruption of warfarin therapy is associated with a low risk of thromboembolism. The risk of clinically significant bleeding, even among outpatients undergoing minor procedures, should be weighed against the thromboembolic risk of an individual patient before the administration of bridging anticoagulant therapy.

Arch Intern Med. 2008;168(1):63-69

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Health care professionals face a dilemma when a warfarin sodium-treated patient needs to undergo an elective procedure or minor surgery. In these circumstances, the risk of bleeding, if the procedure is performed without stopping warfarin therapy, must be weighed against the risk of thrombosis associated with warfarin therapy interruption. The patient and physician have 3 options: (1) continue warfarin therapy, (2) withhold warfarin therapy for some time before (and after) the procedure, or (3) temporarily withhold warfarin therapy while also providing a short-acting (bridging) anticoagulant (such as unfractionated heparin or low-molecular-weight heparin) during the perioperative period. Current guidelines from the American College of Chest Physicians suggest that if the annual risk of thromboembolism is low, warfarin therapy may be held for 4 to 5 days before the procedure and restarted shortly thereafter. The 2006 guidelines for the treatment of patients with atrial fibrillation from the American College of Cardiology, American Heart Association, and European Society of Cardiology suggest an interval of up to 1 week without substituting heparin. The authors acknowledge that this level C recommendation is “based on extrapolation from the annual rate of thromboembolism” and is not evidence based because no studies are available to inform this question. For patients at higher risk for thromboembolism, several studies have described outcomes in patients treated with periprocedural low-molecular-weight heparin. However, since none of these studies included a control arm (ie, patients for whom bridging therapy was not prescribed), the risk of thromboembolism associated with short-term warfarin therapy interruption...
among experienced health care professionals who per-


terruption has led to significant practice variation, even

tment strategies for patients who require warfarin therapy


tive conclusion.


remains unknown. This represents a critical gap in cur-

t knowledge because the increased risk of hemor-

rhage associated with perioperative heparin is justified

by the theory that such bridging therapy will prevent

potentially devastating thromboembolic events (eg, stroke) that would otherwise occur. Without knowing the risk of thromboembolism associated with warfarin therapy interruption alone, an informed risk-benefit examination of bridging therapy cannot be performed. Three small observational studies7-9 of patients with venous thromboembolism within 4 weeks before warfarin interruption, and active malignancy.

Common examples from this category included prostate or breast biopsy, epidural injection, and dermatologic procedures such as removal of skin cancer.

The median length of withholding warfarin therapy was 3 days. Length of interruption was known for 886 patients (86.5%) and 1130 interruptions (87.4%).

For patients who had more than 1 interruption, bridging therapy during the first interruption is presented here.

The overall objective of the Anticoagulation Consortium to Im-

prove Outcomes Nationally (ACTION) study12 was to as-

semble a large prospective cohort of patients taking warfarin to identify practice variations in warfarin therapy management that might lead to improved drug safety. Specific areas to be studied included frequency of monitoring, response to out-of-range international normalized ratio values, periproce-

dural warfarin therapy management, and overall quality of anticoagulation control and related outcomes across the United States. At the time this study was planned, a software program designed to aid in warfarin therapy management had already been in use in the United States for many years. This program, called CoumaCare (Bristol-Myers Squibb [formerly DuPont Pharmaceuticals], Princeton, New Jersey), was available at no cost, and technological support was also provided without charge. CoumaCare was designed to help physicians manage warfarin therapy and was used for clinical purposes to aid in patient tracking, data entry, and record keeping. The program did not make dosing or follow-up interval recommendations. The study protocol was approved by the Western Institutional Review Board, Olympia, Washington, and local review boards where they existed.

SITE RECRUITMENT

Established physician practices that used CoumaCare as the pa-

tient anticoagulation medical record were invited to partici-

pate through a study Web site (www.ACTIONregistry.com). The only material incentive for participation in the project was an informational quarterly newsletter written by the investiga-

tors. An independent registry specialist, McKesson HBOC BioServices (Rockville, Maryland), was responsible for all op-

erational aspects of the study. McKesson is a health care ser-

vices company that provides biomedical support services to the US government, pharmaceutical and biotechnology industries, universities, institutions, and contract research organizations.

A total of 174 individual site registrations were received by McKesson. Of these, 101 sites had the technological capability and the institutional review board approval necessary to partici-

pate and were enrolled. All sites had at least 1 dedicated pro-

fessional managing warfarin therapy, usually within the setting of a community-based, physician group practice. McKesson provided individual on-site training related to all aspects of the research protocol, such as patient recruitment, informed consent procedures, data entry, and transmission. Adverse event reporting was mandatory, and study personnel were trained to perform such reporting with rigor sufficient to meet federal regu-
Patients were invited to participate by letter, by clinic flyer, or in person (at the time of a routine appointment). To be eligible, patients had to be 18 years or older and provide written informed consent. Enrollment was conducted from April 4, 2000, to March 6, 2002.

DATA MANAGEMENT

Encrypted data from each site were downloaded by modem and transmitted to the independent data coordinating center weekly. Missing data fields and questionable values were flagged and resolved directly with the sites before data were transferred to the study investigators. Study investigators were blinded to the identification and location of participating practices and patients.

PATIENTS AND OUTCOMES

Episodes of warfarin therapy interruption were identified by direct review of the 102,732 free-text patient treatment notes. For interruptions to be included, available documentation had to state that warfarin therapy was being interrupted because a procedure was planned, and subsequent documentation had to indicate that the planned procedure occurred (ie, was not canceled or postponed indefinitely). Surgical procedures (including cardiovasculat interventions) that required hospitalization were not eligible because responsibility for the management of anticoagulation would no longer be under the purview of the clinic and a reliable determination about heparin exposure could not be made.

The primary outcomes of interest were thromboembolism or hemorrhage within the 30-day period after the date of warfarin therapy interruption. Major hemorrhage was defined as bleeding that was fatal, led to hospitalization with transfusion of at least 2 U of packed red blood cells, or occurred at a critical site (eg, intracranial or retroperitoneal). Clinically significant, nonmajor hemorrhage was defined as other bleeding that led to an unplanned medical intervention (eg, subsequent operation or nasal packing). All primary outcome events were abstracted by an investigator (D.A.G. or E.M.H.) from patient treatment notes and validated by supporting information obtained by McKesson. For each patient with an identified interruption before a procedure, the following data were also subsequently abstracted: type of procedure, number of days warfarin therapy was withhold, presence or absence of bridging therapy (eg, low-molecular-weight heparin or unfractionated heparin), and the presence or absence of phytonadione use for warfarin reversal. Patients whose final study international normalized ratio was transmitted to the data coordinating center 30 days or fewer after a procedure/biopsy/minor surgery were included, since complete follow-up surveillance for bleeding or thromboembolic events could not be ensured.

STATISTICAL ANALYSIS

Exact 95% confidence intervals (CIs) were calculated for the proportion of patients who sustained a thromboembolic or hemorrhagic event using the Poisson distribution.

RESULTS

In total, 1584 episodes of warfarin therapy interruption were identified. Of these, 1293 were included in our analysis (we did not include 228 inpatient vascular procedures, 62 major surgical procedures, or the 1 patient who was lost to follow-up). For the 1024 patients among whom the 1293 included procedures were performed, the mean (SD) age was 71.9 (10.6) years; 438 (42.8%) were female. The most common indications for warfarin use among the included patients were atrial fibrillation (n=550), venous thromboembolic disease (n=1+4), and mechanical heart valve (n=132) (Table 1). Of the valves, 54 (40.9%) were in the mitral position, 66 (50.0%) were aortic, and 12 (9.1%) were unspecified. Overall, 73 patients (7.1%) would have been considered high risk for thromboembolism because they had 1 or more of the following: prosthetic valve in the mitral position, venous thromboembolism within 4 weeks, or active malignancy. The most common reasons to interrupt warfarin therapy were colono-scopy (n=324), oral or dental surgery (n=323), and ophthalmic surgery (n=116). Among the remaining 530 interruptions classified as being due to “other procedure/biopsy/minor surgery,” the most common reasons for withholding warfarin therapy were epidural injection, prostate biopsy, breast biopsy, and dermatologic procedures.

PERIPROCEDURAL USE OF HEPARIN

Perioperative treatment with heparin, which was almost exclusively low-molecular-weight heparin, was documented for 88 of the 1024 patients undergoing their first elective interruption (8.6%) and for 108 of the 1293 total interruptions (8.3%) (Table 2). Among the 550 patients with atrial fibrillation, 15 (2.7%) received peri-procedural low-molecular-weight heparin. For patients with prosthetic valves, 38 of 132 (28.8%) received bridging therapy with low-molecular-weight heparin.

Table 2. Bridging Therapy by Indication

<table>
<thead>
<tr>
<th>Primary Indication</th>
<th>No. of Patients</th>
<th>Received Bridging Therapy (on First Interruption), No. (%)</th>
<th>No. of Total Interruptions</th>
<th>Received Bridging Therapy, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>550</td>
<td>15 (2.7)</td>
<td>650</td>
<td>17 (2.5)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>144</td>
<td>15 (10.4)</td>
<td>254</td>
<td>22 (10.9)</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>132</td>
<td>38 (28.8)</td>
<td>139</td>
<td>44 (27.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>93</td>
<td>7 (7.5)</td>
<td>117</td>
<td>10 (8.6)</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>34</td>
<td>2 (5.9)</td>
<td>43</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Other</td>
<td>71</td>
<td>11 (15.5)</td>
<td>83</td>
<td>13 (15.7)</td>
</tr>
<tr>
<td>Total</td>
<td>1024</td>
<td>88 (8.6)</td>
<td>1293</td>
<td>108 (8.4)</td>
</tr>
</tbody>
</table>
The duration of warfarin therapy interruption was available for 1130 episodes (87.4%). The frequency with which different interruption intervals were chosen is shown in Figure 1. In 947 of the 1130 interruptions (83.8%), warfarin therapy was withheld for 5 days or fewer; warfarin therapy was interrupted for more than 7 days in 71 instances (6.3%). Preprocedural use of phytonadione for reversal of anticoagulation was documented in only 13 cases (1.0%).

THROMBOEMBOLISM AND HEMORRHAGE

Of the 1024 patients, 7 (0.7%; 95% CI, 0.3%-1.4%) sustained a thromboembolic event during the 30-day follow-up period; 4 were arterial and 3 were venous (Table 1). None of the 7 patients with thrombosis received periprocedural bridging therapy; 2 would have been considered high risk (recent venous thromboembolism and active malignancy). If the patients who received no perioperative heparin are considered separately, the proportion of patients with an arterial thromboembolic event (3 strokes and 1 systemic embolism, probable ischemic bowel) was unchanged (7/936, 0.7%; 95% CI, 0.3%-1.5%). When all 1293 interruptions are considered, the proportion associated with thromboembolic events occurred after a bleeding episode and 10 of the 17 patients with clinically significant, nonmajor bleeding. Four of the 6 patients with major bleeding episodes and 10 of the 17 patients with clinically significant, nonmajor bleeding received periprocedural heparin. Figure 2A presents the bleeding and thromboembolic events according to whether the patients received bridging therapy. Although the patients who received periprocedural anticoagulation represented only 8.6% of the total population, 4 of the 6 major hemorrhagic events occurred in this group. Of note, none of the thromboembolic events occurred after a bleeding episode.

Among the 550 patients with atrial fibrillation, 4 (0.7%; 95% CI, 0.2%-1.9%) experienced an arterial thromboembolic event (3 strokes and 1 systemic embolism, probable ischemic bowel). One of the stroke events occurred 30 days after a 7-day warfarin therapy interruption. Of the 550 patients, 15 received heparin. If the patients with atrial fibrillation who received no perioperative bridging therapy are considered separately, the proportion of patients with an arterial thromboembolic event is unchanged (4/535, 0.7%). For each patient with atrial fibrillation, the number of risk factors for stroke13 was determined. Use of transition therapy stratified by stroke risk factors is indicated in Table 4. Our data suggest that patients with a prior stroke may be at heightened risk, but the number of events is too small to draw any definitive conclusion.

Two patients sustained a major hemorrhage and 4 patients experienced clinically significant, nonmajor bleeding during the 30 days after their procedure. One of these 6 patients had received heparin therapy. Outcome data for this subgroup of patients with atrial fibrillation, stratified by whether bridging therapy was used, are displayed in Figure 2B.
Among 6761 prospectively enrolled patients, we identified 1293 episodes of warfarin therapy interruption for elective outpatient procedures in 1024 patients. Of the 1293 interruptions, 108 (8.4%) were bridged with heparin or low-molecular-weight heparin. Most patients in our study would be considered to be at low to intermediate thromboembolic risk, which likely explains the infrequent use of heparin therapy. Patients at highest risk for thromboembolism composed only 7% of our cohort. The overall proportion of interruptions associated with thromboembolism within the 30-day follow-up period was 0.5% (7/1293). None of these patients had received heparin; 2 would have been considered high risk (recent venous thromboembolism and active malignancy). Among patients whose warfarin therapy was interrupted for 5 days or fewer, the proportion with thromboembolism was 4 (0.6%) arterial (3 CVA, 1 SE) and 1 (0.1%) venous (PE).

Figure 2. Thirty-day outcome events by bridging status for interruptions. A, Events for all patients. B, Events for patients with atrial fibrillation. CVA indicates cerebrovascular accident; DVT, deep venous thrombosis; GI, gastrointestinal; PE, pulmonary embolism; SDH, subdural hematoma; SE, systemic embolism; and TE, thromboembolism.

Table 4. Proportion of Patients With Atrial Fibrillation Who Received Bridging Therapy According to Stroke Risk Factors

<table>
<thead>
<tr>
<th>Stroke Risk Factor</th>
<th>No. of Patients (n=550)</th>
<th>Received Bridging Therapy, No. (%)</th>
<th>Arterial Events, No. (%) (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 y</td>
<td>285</td>
<td>4 (1.4)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>60</td>
<td>6 (9.8)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>277</td>
<td>9 (3.2)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>104</td>
<td>1 (0.96)</td>
<td>1 (0.96)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>139</td>
<td>7 (5)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>No. of risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>75</td>
<td>2 (2.7)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>191</td>
<td>5 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>194</td>
<td>4 (2.0)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>2 (2.7)</td>
<td>0</td>
</tr>
<tr>
<td>≥4</td>
<td>15</td>
<td>2 (13.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*None of these patients received bridging therapy.*
boembolism was 0.4% (4/984). No thromboembolic events occurred among the 108 interruptions bridged with heparin. Major hemorrhage was uncommon but was higher among patients receiving heparin (4/108, 3.7%) than among those patients who did not receive heparin (2/1185, 0.2%). The proportion of patients with clinically significant, nonmajor bleeding was also higher in those who received periprocedural heparin (9% vs 0.6%, respectively).

Our study demonstrates that thromboembolism is uncommon among low- to intermediate-risk outpatients who undergo elective periprocedural warfarin therapy interruption for a brief period (≤5 days). Our findings support a previous proposal that perioperative anticoagulation may be unnecessary for a significant proportion of patients who have undergone long-term anticoagulation whose warfarin therapy must be interrupted.15 Our results are consistent with current guidelines, proposed by the American College of Chest Physicians, suggesting that low-risk patients may undergo 4 to 5 days of warfarin therapy interruption without bridging therapy.1

The evidence from our study (and others15) that bridging therapy may result in significant and potentially avoidable perioperative hemorrhage emphasizes the need for a randomized controlled trial of heparin vs placebo among warfarin-treated patients who need procedures. The principal challenge of such a trial will be to enroll a large number of participants while avoiding selection bias during the screening process.

Our study has several limitations. First, the observational nature of our study leaves open the possibility of selection bias, whereby only the patients at high risk for thromboembolism may have received heparin. However, because less than 10% of the overall cohort underwent transition with heparin, we do not believe that such a selection bias would substantively change our results. For example, among patients with atrial fibrillation, there were 690 interruptions; 17 (2.5%) were bridged. Even if one conservatively assumes that, in the absence of bridging therapy, 2 of these 17 patients (11.8%) would have experienced thrombosis, the overall proportion experiencing an arterial thromboembolism would increase from 0.6% (4/690) to 0.9% (6/690). In contrast, among patients with mechanical prosthetic heart valves, bridging therapy was administered in 28.8% of cases. Thus, we acknowledge that for patients with mechanical heart valves, our analysis may, because of selection bias, underestimate the risk of thromboembolism associated with warfarin therapy interruption in this subpopulation. Similarly, patients with a history of stroke constituted only 10.9% of our atrial fibrillation cohort. Because this subgroup is known to be at higher risk for stroke, further study of such patients is warranted.

We are confident that our study has captured all important events because our database was constructed by directly downloading patients' anticoagulation records. Because data were collected prospectively, the consecutive patients included in this study constitute an inception cohort established at the time warfarin therapy was discontinued. Since documentation is central to medical care (and of particular clinical importance in the hazard-prone area of anticoagulation), we highly doubt that health care professionals would neglect to enter information about prescribed warfarin therapy interruptions, major hemorrhage, thrombotic events, or the use of heparin. Of the 1024 patients identified in our study, only 1 patient was lost to follow-up.

It is possible that selection bias may have been introduced by voluntary participation and the requirement for written informed consent. However, the distribution of stroke risk factors in our overall cohort is similar to that seen in other published studies. The overall comparability provides reassurance that the patient population in our study is representative of patients with atrial fibrillation treated with warfarin.

Despite the unprecedented size of our study, the small number of thromboembolic events limits our ability to draw definitive conclusions about the risk of periprocedural anticoagulation interruption for any individual patient. The risk of perioperative thromboembolism is influenced by multiple patient-specific, procedure-specific, and physician-specific factors that collectively influence thrombogenicity. Quantifying the effect of independent factors (eg, indication for warfarin) with any degree of precision would require substantially more data. Our results, however, do not apply to patients undergoing major surgery or other more invasive procedures that require hospitalization. Compared with the procedures included in our study, more invasive surgical procedures would almost certainly be associated with a greater risk of bleeding. More invasive operations would also increase exposure of tissue factor to circulating plasma. Because this has the potential to increase coagulation activation16 while reducing fibrinolytic capacity,17 it is possible that such major surgical procedures would also confer a higher risk of thromboembolism.

We conclude that for many patients receiving long-term anticoagulation who need to undergo a minor outpatient procedure, a brief (≤5 days) periprocedural interruption of warfarin therapy is associated with a low risk of thromboembolism. Because our study and others4 indicate that bridging anticoagulant therapy may be associated with a significantly increased risk of hemorrhage, a prospective randomized trial of bridging vs no bridging is needed to assess the risks and benefits of providing periprocedural anticoagulation. Until such a trial is completed, our results provide valuable information to physicians who must weigh the risks and benefits of different periprocedural treatment strategies for patients taking warfarin.

Accepted for Publication: August 18, 2007.
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Author Contributions: Dr Hylek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Garcia and Hylek. Acquisition of data: Garcia, Henault, Upadhyay, and Othman. Analysis and interpretation of data: Garcia, Regan, Henault, Upadhyay, Baker, Othman, and Hylek. Drafting of the manuscript: Garcia, Henault, Baker, Othman, and Hylek. Critical revision of the manuscript for important intellec-

Financial Disclosure: Dr Garcia has received consulting honoraria and research support from Bristol-Myers Squibb, AstraZeneca, and Sanofi-Aventis. Dr Hylek has served on advisory boards for Bristol-Myers Squibb and has received research support from Astra Zeneca and Bristol-Myers Squibb.

Funding/Support: This study was funded by Bristol-Myers Squibb (formerly Dupont Pharmaceuticals).

Role of the Sponsors: The sponsor had no role in any of the following: design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to publish the findings.

Additional Contributions: Mark A. Crowther, MD, performed a helpful review of the manuscript.

REFERENCES


