The Effect of Excessive Anticoagulation on Mortality and Morbidity in Hospitalized Patients With Anticoagulant-Related Major Hemorrhage

Sophia Koo, BS; Nils Kucher, MD; Paul L. Nguyen, AB; John Fanikos, RPh, MBA; Peter W. Marks, MD, PhD; Samuel Z. Goldhaber, MD

Background: We aimed to determine the effect of excessive anticoagulation on morbidity and mortality in hospitalized patients with major anticoagulant-associated hemorrhage.

Methods: We prospectively identified 101 consecutive inpatients admitted to Brigham and Women’s Hospital with major bleeding occurring during administration of warfarin sodium, unfractionated heparin (UFH), or low-molecular-weight heparin (LMWH).

Results: Fifty patients had excessive and 51 had nonexcessive anticoagulation. The overall mortality at 60 days was 26% (13/50) in the excessive group compared with 10% (5/51) in the nonexcessive group (P = .03). Excessive warfarin therapy was associated with an increased 60-day mortality (P = .049), in contrast to excessive anticoagulation with UFH or LMWH alone (P = .27) or UFH or LMWH as a “bridge” to warfarin therapy (P = .10). Multivariate regression identified excessive anticoagulation as an independent predictor of 60-day mortality (adjusted hazard ratio [HR], 4.17; 95% confidence interval [CI], 1.39-12.49; P = .01), along with intracranial hemorrhage (adjusted HR, 6.16; 95% CI, 1.75-21.67; P = .005) and active cancer (adjusted HR, 3.79; 95% CI, 1.13-12.70; P = .03). Excessive anticoagulation was also a significant predictor of the combined nonfatal end point of stroke, myocardial infarction, hypotension, critical anemia, and surgical or angiographic intervention at 30 days (HR, 2.17; 95% CI, 1.25-3.78; P = .006).

Conclusion: In a cohort of patients with anticoagulation-associated hemorrhage, excessive anticoagulation contributed independently to increased morbidity and mortality.

Arch Intern Med. 2004;164:1557-1560

ESPERTE THE EFFICACY OF anticoagulant medications in the prevention and treatment of arterial and venous thrombosis, hemorrhage continues to be a common and often serious complication of therapy.1,3 Studies of warfarin treatment have reported annual incidences of major hemorrhage between 1% and 12% and fatal hemorrhage between 0.5% and 1.1%.4,5 The incidence has been higher in cohort studies than in clinical trials with selected populations.6 Few prior studies have classified complications of anticoagulation according to whether they were related to excessive anticoagulation. In this prospective study, we examined the effect of excessive anticoagulation on morbidity and mortality in hospitalized patients with anticoagulant-related hemorrhage.

This study was approved by the Partners Human Research Committee. We prospectively identified 101 consecutive inpatients admitted to Brigham and Women’s Hospital, Boston, Mass, with major anticoagulation-related bleeding according to the Landefeld Bleeding Severity Index7 over a 2-month period. According to this index, major bleeding is defined as bleeding that is (1) fatal, (2) life-threatening, causing myocardial infarction, stroke, or surgical or angiographic intervention, or (3) potentially life-threatening, causing systolic hypotension (a ≥20% drop in systolic blood pressure to <90 mm Hg), critical anemia (a ≥20% decline in hematocrit to ≤20%), or reoperation. We defined anticoagulation-related bleeding as bleeding that occurred (1) during warfarin, unfractionated heparin (UFH), or low-molecular-weight heparin (LMWH) therapy, (2) following discontinuation of UFH or LMWH therapy within 24 hours prior to the hemorrhagic event, or (3) following discontinuation of warfarin therapy within 5 days prior to the hemorrhage.

Excessive anticoagulation was defined as administration of (1) warfarin with an international normalized ratio (INR) above the intended therapeutic range,6 (2) UFH with 2 or more consecutive partial thromboplastin time (aPTT) measurements greater than 2.5 times the upper limit of the normal range, or (3) full, weight-based dosing of LMWH in the presence of renal insufficiency (serum creatinine level >1.5 mg/dL [>132.6 µmol/L]). The non-

From the Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass. The authors have no relevant financial interest in this article.
The primary end point was all-cause mortality over 60 days. Our secondary end point was a combined nonfatal outcome of stroke, myocardial infarction, systolic hypotension (a 20% drop in systolic blood pressure to <90 mm Hg), critical anemia (a 20% decline in hematocrit to <20%), or the requirement of surgical or angiographic intervention to control hemorrhage during the hospital stay or up to 30 days after the initial hemorrhage.

Discrete variables were compared between the excessive and nonexcessive anticoagulation groups with a binomial test of proportions. We compared medians using the Mann-Whitney test. We used Cox multivariate analysis to determine the effect of excessive anticoagulation on the primary and secondary end points after accounting for baseline characteristics. Each potential cofactor was added to the model individually and was retained if it increased the hazard ratio (HR) by more than 10%. The Kaplan-Meier method was used to compare the end points between patients with and without excessive anticoagulation.

## RESULTS

Fifty-one patients had nonexcessive and 50 had excessive anticoagulation. Baseline characteristics, principal indications for anticoagulation, and anatomic sites of hemorrhage were similar between the 2 groups (Table).

Use of warfarin alone was more common in patients with excessive anticoagulation (P < .01) (Table). For patients receiving warfarin alone or UFH or LMWH as a "bridge" to warfarin therapy, the median INR (range) was 4.1 (1.2-30.0) in the excessive group, and 1.9 (1.0-2.9) in the nonexcessive group (P < .001). Thirteen (43%) of the (30%) patients receiving intravenous UFH had 2 or more consecutive excessively high aPTT measurements. Their mean±SD aPTT was 132±23 seconds. Of the 50 patients with excessive anticoagulation, 8 (16%) were receiving full, weight-based dosing of LMWH despite renal insufficiency.

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonexcessive Anticoagulation (n = 51)</th>
<th>Excessive Anticoagulation (n = 50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.3 (27.0-90.5)</td>
<td>70.4 (25.3-90.0)</td>
<td>.39</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>77.3 (45.7-136.4)</td>
<td>79.5 (46.4-124.1)</td>
<td>.67</td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>9 (2-118)</td>
<td>9 (1-70)</td>
<td>.76</td>
</tr>
<tr>
<td>Women</td>
<td>20 (39.2)</td>
<td>23 (46.0)</td>
<td>.49</td>
</tr>
<tr>
<td>Principal indication for anticoagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16 (31)</td>
<td>17 (34)</td>
<td>.74</td>
</tr>
<tr>
<td>Venous thromboembolism therapy</td>
<td>11 (22)</td>
<td>9 (18)</td>
<td>.43</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>14 (27)</td>
<td>6 (12)</td>
<td>.05</td>
</tr>
<tr>
<td>Mechanical heart valves</td>
<td>3 (6)</td>
<td>7 (14)</td>
<td>.18</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>2 (4)</td>
<td>7 (14)</td>
<td>.07</td>
</tr>
<tr>
<td>Venous thromboembolism prophylaxis</td>
<td>3 (6)</td>
<td>6 (12)</td>
<td>.29</td>
</tr>
<tr>
<td>Comorbid condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>33 (65)</td>
<td>29 (58)</td>
<td>.49</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (33)</td>
<td>11 (22)</td>
<td>.20</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (67)</td>
<td>37 (74)</td>
<td>.42</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>17 (33)</td>
<td>13 (26)</td>
<td>.42</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16 (31)</td>
<td>23 (46)</td>
<td>.13</td>
</tr>
<tr>
<td>Creatinine &gt;1.5 mg/dL [&gt;132.6 µmol/L]</td>
<td>22 (43)</td>
<td>27 (54)</td>
<td>.27</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>8 (16)</td>
<td>5 (10)</td>
<td>.39</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (16)</td>
<td>5 (10)</td>
<td>.39</td>
</tr>
<tr>
<td>History of gastrointestinal hemorrhage</td>
<td>9 (18)</td>
<td>15 (30)</td>
<td>.14</td>
</tr>
<tr>
<td>History of stroke</td>
<td>10 (20)</td>
<td>12 (24)</td>
<td>.59</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>.72</td>
</tr>
<tr>
<td>Other infection</td>
<td>8 (16)</td>
<td>13 (26)</td>
<td>.20</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>13 (26)</td>
<td>10 (20)</td>
<td>.51</td>
</tr>
<tr>
<td>Trauma</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>.63</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (24)</td>
<td>8 (16)</td>
<td>.34</td>
</tr>
<tr>
<td>Anticoagulant medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin alone</td>
<td>17 (33)</td>
<td>29 (58)</td>
<td>.01</td>
</tr>
<tr>
<td>UFH/LMWH as a bridge to warfarin</td>
<td>10 (20)</td>
<td>14 (28)</td>
<td>.32</td>
</tr>
<tr>
<td>UFH/LMWH alone</td>
<td>24 (47)</td>
<td>7 (14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Principal hemorrhage site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>24 (47)</td>
<td>24 (48)</td>
<td>.92</td>
</tr>
<tr>
<td>Intervention related</td>
<td>12 (24)</td>
<td>14 (28)</td>
<td>.61</td>
</tr>
<tr>
<td>Intracranial</td>
<td>9 (18)</td>
<td>4 (8)</td>
<td>.15</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2 (4)</td>
<td>0</td>
<td>.16</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>2 (4)</td>
<td>5 (10)</td>
<td>.23</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>.63</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

*Data are median (range) value or number (percentage) of patients.
hemorrhage compared with patients who developed hemorrhage in the hospital (62% vs 37%; \( P = .01 \)).

At 60 days, the overall mortality was 18% (n = 18): 10% (n = 9) in the nonexcessive and 26% (n = 13) in the excessive anticoagulation group (Figure, A; \( P = .03 \)). The difference in mortality between the 2 groups emerged within a few days following the hemorrhage. Twelve of the 13 deaths in the excessive anticoagulation group and 4 of the 5 deaths in the nonexcessive anticoagulation group were clearly caused by or related to hemorrhage. Excessive warfarin therapy was associated with an increased 60-day mortality (6 patients [21%] with excessive vs none with nonexcessive anticoagulation; \( P = .049 \)), in contrast to excessive anticoagulation with UFH or LMWH alone (4 patients [29%] with excessive vs 1 [10%] with nonexcessive anticoagulation; \( P = .27 \)) or UFH or LMWH as a “bridge” to warfarin therapy (3 patients [43%] with excessive vs 4 [17%] with nonexcessive anticoagulation; \( P = .10 \)).

Excessive anticoagulation was a significant univariate predictor of mortality (unadjusted HR, 2.93; 95% confidence interval [CI], 1.05-8.23; \( P = .04 \)) and remained a significant predictor of mortality after controlling for other clinical factors (adjusted HR, 4.17; 95% CI, 1.39-12.49; \( P = .01 \)). Intracranial hemorrhage (HR, 6.16; 95% CI, 1.75-21.67; \( P = .005 \)), and active malignancy (HR, 3.79; 95% CI, 1.13-12.70; \( P = .03 \)) were also independent predictors of mortality. Age, sex, and all other recorded clinical factors did not contribute significantly to mortality on multivariate analysis.

There was a higher rate of the nonfatal end point in the excessive anticoagulation group at 30 days (72% vs 39%; \( P = .001 \); Figure, B). Only excessive anticoagulation contributed significantly to the nonfatal end point (HR, 2.17; 95% CI, 1.25-3.78; \( P = .006 \)).

Twenty (39%) patients with nonexcessive and 32 (64%) patients with excessive anticoagulation received phytonadione (vitamin K\(_1\)) (\( P = .01 \)). The median (range) of administered blood products, including packed red blood cell units, fresh frozen plasma, and platelet units transfused over the course of the hemorrhage was 2 (0-13), 0 (0-12), and 0 (0-5) units, respectively, in the nonexcessive and 3 (0-27), 3 (0-15), and 0 (0-12) units, respectively, in the excessive anticoagulation group (\( P = .15, .01, .21 \), respectively). The administration of vitamin K\(_1\), or blood products did not contribute to 30-day mortality or the nonfatal end point.

Sixteen patients (31%) with nonexcessive and 28 (56%) with excessive anticoagulation developed new or worsening pulmonary congestion following the transfusion of blood products (\( P = .01 \)). The development of pulmonary congestion did not contribute to mortality or the nonfatal end point on multivariate analysis. Five patients (10%) with nonexcessive anticoagulation levels and 4 (8%) with excessive anticoagulation developed a thrombotic event during 60-day follow-up (\( P = .75 \)).

**COMMENT**

Our principal and most provocative finding was that the mortality of patients with major hemorrhage and excessive anticoagulation was greater than that of patients with major hemorrhage and nonexcessive anticoagulation. Most adverse clinical outcomes occurred in patients receiving warfarin alone or UFH or LMWH as a bridge to warfarin therapy. After adjusting for clinical covariates, excessive anticoagulation remained a strong independent predictor of mortality and the nonfatal end point.

Our findings are consistent with those of Odén and Fahlen, who investigated the relationship of 1250000 INR values and mortality in 42451 patients. They reported a 2.2-fold increase in the hazard of mortality per unit INR elevation greater than 2.5. These results underscore the importance of adhering as closely as possible to recommended therapeutic INR ranges for patients taking warfarin and following standard heparin dosing and monitoring guidelines. Suboptimal use and monitoring of UFH persist in clinical practice despite the availability of validated weight-based nomograms developed to optimize therapy. Patients with renal insufficiency who receive LMWH are at increased risk of hemorrhage; reduced-dose regimens with monitoring of anti-factor Xa levels may maximize safety.

Although the risk of intracranial hemorrhage increases with the level of anticoagulation, it may occur with nonexcessive anticoagulation. In a study of 121 patients with warfarin-related intracranial hemorrhage, more than half had a prothrombin time ratio of 2.0 or less at the time of diagnosis. In our study, 9 (69%) of the 13 pa-
tients with nonexcessive anticoagulation had intracra-
nial hemorrhage.

Excessive anticoagulation may occur, in part, be-
cause of errors in physicians orders, transcription of or-
ders, pharmacy dispensing, nursing administration, and
drug monitoring.14 Our study findings confirm that er-
rors in drug monitoring are the main cause of excessive
anticoagulation. Preventive interventions, including com-
puterized anticoagulant dosing adjustments,15,16 special-
ized anticoagulation clinics,17,18 “bridging” protocols,19
and multicomponent strategies20 may decrease the fre-
cquency of excessive anticoagulation and possibly re-
duce the morbidity and mortality associated with an-
ticoagulant-related hemorrhage. Anticoagulation
management in specialized clinics needs to be popular-
ized, especially for patients at increased risk of both bleed-
ing and clotting complications.

Because our study was performed in a single cen-
ter, the results may not be generalizable to other popu-
lations with different clinical characteristics. Neverthe-
less, the strengths of our study include the prospective
design, the recruitment of consecutive hospitalized pa-
tients with major anticoagulation-related bleeding, and
accurate identification of patients receiving excessive an-
ticoagulation prior to the bleeding event.

Future research should focus on detailed investiga-
tions of anticoagulant medication errors. Development
and implementation of preventive measures will reduce
the number of excessively anticoagulated patients and the
magnitude of adverse clinical outcomes.

Accepted for publication December 15, 2003.

Correspondence: Samuel Z. Goldhaber, MD, Cardio-
vascular Division, Brigham and Women’s Hospital, 75 Francis
St, Boston, MA 02115 (sgoldhaber@partners.org).

REFERENCES

1. Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE. Prospective study of
the outcomes of ambulatory patients with excessive warfarin anticoagulation.

2. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and
preliminary validation of predictors of major bleeding in hospitalized patients start-

3. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients tak-

4. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology,

5. Fihn SD, McDonell M, Martin D, et al. Warfarin Optimized Outpatient Follow-up
Study Group. Risk factors for complications of chronic anticoagulation: a mul-

6. Schulman S. Care of patients receiving long-term anticoagulant therapy. N Engl

7. Landefeld CS, Anderson PA, Goodnough LT, et al. The bleeding severity index:
validation and comparison to other methods for classifying bleeding complica-

8. Ode´n A, Fahlen M. Oral anticoagulation and risk of death: a medical record link-
age study. BMJ. 2002;325:1073-1075.


10. Hirsh J, Warkentin, TE, Shaughnessy, SG. Heparin and low-molecular-weight he-
parin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and

11. Hylek EM, Regan S, Henriult LE, et al. Challenges to the effective use of unfraction-
ted heparin in the hospitalized management of acute thrombosis. Arch Intern

12. Raschke R, Hirsh J, Guidry JR. Suboptimal monitoring and dosing of unfrac-
tionated heparin in comparative studies with low-molecular-weight heparin. Ann

13. Busby LT, Weyman A, Rodgers GM. Excessive anticoagulation in patients with
mild renal insufficiency receiving long-term therapeutic enoxaparin. Am J Hem-
atol. 2001;67:54-56.

drug events among older persons in the ambulatory setting. JAMA. 2003;289:
1107-1116.

system for hospitalized patients starting on oral anticoagulant therapy. Thromb

16. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order en-
try and clinical decision support systems on medication safety: a systematic re-

17. Grasso-Correnti N, Goldszer RC, Goldhaber SZ. The critical pathways of antico-

18. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with
usual medical care: anticoagulation control, patient outcomes, and health care

19. Piazza G, Goldhaber SZ. Periprocedural management of the chronically antico-

20. Beyth, RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent ma-
2000;133:687-695.