Risk of Major Hemorrhage for Outpatients Treated with Warfarin

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OBJECTIVE: To determine the incidence of major hemorrhage among outpatients started on warfarin therapy after the recommendation in 1986 for reduced-intensity anticoagulation therapy was made, and to identify baseline patient characteristics that predict those patients who will have a major hemorrhage.

DESIGN: Retrospective cohort study.

SETTING: A university-affiliated Veterans Affairs Medical Center.

PATIENTS: Five hundred seventy-nine patients who were discharged from the hospital after being started on warfarin therapy.

MEASUREMENTS AND MAIN RESULTS: The primary outcome variable was major hemorrhage. In our cohort of 579 patients, there were 40 first-time major hemorrhages with only one fatal bleed. The cumulative incidence was 7% at 1 year. The average monthly incidence of major hemorrhage was 0.82% during the first 3 months of treatment and decreased to 0.36% thereafter. Three independent predictors of major hemorrhage were identified: a history of alcohol abuse, chronic renal insufficiency, and a previous gastrointestinal bleed. Age, comorbidities, medications known to influence prothrombin levels, and baseline laboratory values were not associated with major hemorrhage.

CONCLUSIONS: The incidence of major hemorrhage in this population of outpatients treated with warfarin was lower than previous estimates of major hemorrhage measured before the recommendation for reduced-intensity anticoagulation therapy was made, but still higher than estimates reported from clinical trials. Alcohol abuse, chronic renal insufficiency, and a previous gastrointestinal bleed were associated with increased risk of major hemorrhage.

KEY WORDS: major hemorrhage; warfarin; alcohol abuse; chronic renal insufficiency; gastrointestinal hemorrhage.

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Observational and experimental studies have identified indications for the use of warfarin.¹ Warfarin was the 12th most prescribed drug in America in 1995.² Hemorrhage remains the most serious side effect of treatment with warfarin. Estimates of the incidence of major hemorrhage in observational studies have varied widely. Few studies have estimated the incidence of major hemorrhage in an inception cohort. Petitti et al. assembled the first inception cohort, consisting of patients hospitalized with pulmonary embolism or thrombophlebitis between 1970 and 1980, and estimated the incidence of major hemorrhage to be 18% at 1 year.³ Landefeld and Goldman identified an inception cohort of inpatients started on warfarin between 1977 and 1983.⁴ Using explicit criteria, the bleeding severity index, they estimated the incidence of major hemorrhage to be 11% at 1 year.⁴ Both of these estimates are higher than those reported in clinical trials.⁵

In 1986, the Committee on Anti-thrombotic Therapy of the American College of Chest Physicians and the National Heart, Lung, and Blood Institute made new recommendations for reduced intensity of warfarin treatment for all indications except recurrent systemic emboli and heart valve replacement.⁶ Based on randomized studies, the new target range for treatment was international normalized ratio (INR) = 2.0 to 3.0. Prior to this, the optimal range of treatment for most indications was considered INR = 4.4 to 7.5.⁶ In 1995, the recommendations for reduced intensity of treatment were extended to include recurrent systemic emboli.¹ Only one study has measured the incidence of major hemorrhage in outpatients treated with warfarin in an inception cohort assembled after the recommendations for reduced optimal therapeutic range were made. Gitter et al., using Landefeld's bleeding severity index, estimated the cumulative incidence of major hemorrhage to be 5.3% at 1 year.⁷ This was a marked decrease in the incidence of major hemorrhage from that in previous cohort studies. It is uncertain whether this decreased incidence reflects the recommendations for reduced intensity of warfarin treatment, or reflects baseline patient characteristics among this population-based sample.

Several studies have attempted to describe baseline patient characteristics that would help physicians identify patients at increased risk of major hemorrhage at the onset of treatment.^{3,4,6,8-17} However, no independent predictors of major hemorrhage have been consistently identified across studies. This inconsistency has been attributed to the use of different populations as well as different criteria for major hemorrhage.¹³ Landefeld and Goldman⁴ and Gitter et al.⁷ identified different predictors for major hemorrhage, despite using the same criteria for major hemorrhage.

Our primary objective was to measure the incidence of major hemorrhage, in an inception cohort of outpatient

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veterans, assembled after reduced-intensity anticoagulant therapy was first recommended in 1986. Our secondary objective was to identify patient characteristics, known to physicians at the onset of treatment with warfarin, that would allow them to identify those patients at increased risk of major hemorrhage before the initiation of warfarin therapy.

METHODS

Study Sample

A computer query of the Roudebush Veterans Affairs Medical Center (VAMC) pharmacy database identified 1,101 potential subjects who had received any prescription for warfarin from the pharmacy. Medical records were then reviewed to determine if potential candidates met the eligibility criteria. Subjects were included in the study if warfarin therapy had been started while the subject was an inpatient at the Roudebush VAMC between March 31, 1989, and March 31, 1994, and therapy was to be continued for at least 10 days. Five hundred twenty-two (47%) of the subjects were excluded from the study for the following reasons: 325 were started on warfarin elsewhere, 89 had been started on warfarin as an outpatient, 61 were started on warfarin before the study start date, records could not be located for 41, and 6 were misidentified as having received a prescription for warfarin. A total of 579 (53%) of the patients were entered into the study. Fifty-two patients had received more than one course of warfarin therapy. We collected data on the most recent course of treatment. As many of these patients had received an earlier course of treatment before 1989 and also were treated at outside facilities, we collected data on the most recent course of treatment to ensure a uniform cohort with respect to target prothrombin ratios and provider environment.

Predictor Variables

Baseline variables were abstracted by four trained reviewers from the subjects' medical records containing the hospitalizations during which warfarin therapy was started. Baseline data collected included all variables that had been independent predictors of major hemorrhage in a previously validated model. These variables included: age of at least 65 years, history of stroke, atrial fibrillation or gastrointestinal bleed, and the presence of one of the following comorbid conditions: hematocrit ≤ 0.3 , creatinine level ≥ 1.5 , or acute myocardial infarction.⁴

We also recorded demographic information, the indication for warfarin therapy, and medications prescribed at discharge, including aspirin, nonsteroidal agents, steroids, antiarrhythmics, neuroleptics, antibiotics, and cholesterol-lowering agents, as well as the discharge dose of warfarin. Tobacco use was recorded as positive if documented as such in the admitting history and physical examination, the discharge summary, or the nursing admission intake form.

Recorded baseline data also included the presence of comorbid conditions as documented in the past medical history section or the problem list of the admission note or the diagnoses listed in the discharge summary. Alcohol abuse was recorded if documented by the admitting physician in either the admission or the discharge summary. We noted baseline physical examination data including heart rate and blood pressure at discharge as well as the results of stool occult blood tests. Laboratory data obtained before the initiation of warfarin therapy were recorded and included: hematocrit, platelet count, creatinine level, serum glutamic-oxaloacetic transaminase, total bilirubin, urinalysis, and the prothrombin time. The prothrombin time at discharge was also documented. Interrater reliability studies were performed between our baseline reviewers. The mean overall κ was 0.95, with a range of 0.63 to 1.0.

Outcome Variables

The primary outcome variable for our study was major hemorrhage. We used Landefeld's bleeding severity index, which defines major hemorrhage based on patient survival, the amount of blood lost, and the physical consequences of the hemorrhage including outcomes such as hypotension, myocardial infarction, stroke, and the need for surgical intervention.⁴ The variables that define major hemorrhage were recorded on the outcome instrument, and a computer-generated algorithm that incorporated Landefeld's criteria was used to identify subjects who had a major hemorrhage. Data collectors, blinded to baseline data, reviewed all medical record documentation for each subject, from the date warfarin was started until warfarin was stopped or the closeout date of July 1, 1994, occurred. For each bleeding event, data were collected regarding where the episode occurred, the units of blood transfused, hematocrit, and prothrombin time before and at the time of the event, blood pressure, the site of bleeding, the physical consequences of bleeding, and the documented medications at the time of bleed. Interrater reliability studies were performed between the outcome reviewers. The mean overall κ was 0.85, with a range of 0.59 to 1.0.

Follow-up

Subjects were followed until warfarin was discontinued or July 1, 1994. Follow-up information was obtained by review of VA medical records as well as outside medical records when indicated. Outcome information was obtained for 565 (97.6%) of the subjects, and all analyses were performed on these subjects. Those lost to follow-up did not differ significantly with respect to demographic information or the presence of comorbid conditions.

Analyses

The cumulative incidences of major and minor hemorrhage were calculated by using the Kaplan-Meier method,¹⁸

using SAS software (SUGI Supplemental User's Guide, version 5, 1986; SAS Institute Inc., Cary, NC). Forty-six baseline variables were tested for univariate significance using Cox regression analysis. Two major hemorrhage models were developed: one using those variables that had been independent predictors in Landefeld's model and one using variables with p values $<.1$ in the univariate analysis.⁴

The dependent variable was based on the time to the first major hemorrhage or the discontinuation of warfarin. Independent variables were entered in a forward stepwise manner, and variables with a p value $\leq .05$ were considered significant in the multivariable models. All regression analyses were conducted using SPSS software (SPSS for Windows, SPSS Advanced Statistics 6.1, 1994; SPSS Inc., Chicago, Ill.).

The predictive ability of the final model for major hemorrhage was estimated by generating a model C statistic. The bootstrap resampling technique was used to re-sample the initial population 5,000 times, with 565 subjects in each sample.¹⁹ A C statistic was generated for each sample, using the data-based regression model that included chronic renal insufficiency, history of gastrointestinal bleeding, and alcohol abuse.²⁰ The C statistic was then averaged over the 5,000 samples.

RESULTS

Patient Characteristics

The mean age $\pm$ SD of our sample was 65.1 ± 10.9 years (range, 23–95 years), 88% of the patients were white, and 98.5% were male. Subjects had a mean duration of follow-up of 14.0 months (range, 1 day to 60 months). Indications for treatment were atrial fibrillation (22%), deep venous thrombosis (19%), cardiac thrombus (15%), and prosthetic heart valve (14%). Some patients had more than one indication for treatment. Ninety-one percent of the subjects were followed at our VAMC: 289 (50%) by primary care physicians, 199 (34%) by specialty physicians, and 39 (7%) in the cardiology anticoagulation clinic. Fifty-two (9%) of the patients were followed by non-VAMC physicians.

Incidence of Bleeding

In our population, there were 40 first-time major hemorrhages, with only one fatal bleed. The incidence of major hemorrhage at 1 month was 1.5% with 510 patients at risk. The cumulative incidence of major hemorrhage at 3 months, 12 months, and 48 months was 2%, 7%, and 17%, respectively (Fig. 1). The average monthly incidence of major hemorrhage was 0.82% in the first 3 months of treatment, and it decreased to 0.37% between 3 and 12 months of treatment. After 12 months of treatment, the average monthly incidence of major hemorrhage was 0.36% (Fig. 2).

The most common site of major hemorrhage was the gastrointestinal tract (25 subjects, 63%), which was also

FIGURE 1. The cumulative incidence of major hemorrhage. Numbers in parentheses equal the number of patients at risk.

the site of hemorrhage in the only fatal bleed. The other sites of major hemorrhage were the urinary tract (28%), the musculoskeletal system (15%), the nasopharynx (13%), and the lungs (8%). The percentages total more than 100% because some subjects had more than one site of hemorrhage. There were no intracranial hemorrhages.

There were 64 minor hemorrhages in our population. The cumulative incidence of minor hemorrhage at 12 months was 7.7% (Fig. 3).

Predictors of Major Hemorrhage

We first performed univariate analysis on 46 of the baseline variables that we considered potential predictors of major hemorrhage (Table 1). The only variables that had p values $\leq .1$ in the univariate analysis were alcohol

FIGURE 2. The average monthly incidence of major hemorrhage.

FIGURE 3. The cumulative incidence of minor hemorrhage. Numbers in parentheses equal the number of patients at risk.

abuse, chronic renal insufficiency, race, history of gastrointestinal bleed, and heart disease as the indication for warfarin therapy.

Our first multivariate model was based on those variables that had been independent predictors of major hemorrhage in a previous inception cohort (Table 2). This list of variables included age 65 years or older, history of atrial fibrillation, history of gastrointestinal bleeding, stroke, or the presence of a comorbid condition.⁴ None of those variables was significantly related to major hemorrhage in our population ($p < .5$).

We then generated a multivariate model, testing those variables that were significantly related to major hemorrhage in the univariate analysis. In addition, we tested the significance of having had a previous course of warfarin therapy. Of the six variables entered, only three were independently related to major hemorrhage in our population of veterans (Table 3). A history of alcohol abuse conferred the greatest risk, with a relative risk of 2.7. We also tested interaction terms, alcohol abuse, and gastrointestinal bleed as well as chronic renal insufficiency and gastrointestinal bleed. Neither interaction term was significant in the model.

Predictive Ability

The *single* C statistic for our major hemorrhage model was 0.52. To estimate the predictive ability of our model, we generated an averaged C statistic by resampling the population 5,000 times using the bootstrap resampling technique.²⁰ The *averaged* C statistic for our model was 0.51.

DISCUSSION

Incidence of Major Hemorrhage

Previous experimental and observational studies have attempted to estimate the incidence of major hemorrhage for patients receiving warfarin therapy. Landefeld

Table 1. Baseline Clinical Characteristics and Univariate Significance of the Association Between the Characteristic and Major Bleeding

Baseline Variable	Patients		p Value*
	n	%	
Age, years			
<65	239	41	.93
≥65	340	59	.93
Gender			
Male	570	98	.63
Female	9	2	.63
Race			
White	509	88	.05
Nonwhite	70	12	.05
Medications			
Aspirin	135	23	.56
Cimetidine	47	8	.81
Nonsteroidal agent	35	6	.78
Quinidine/amiodarone	26	5	.84
Lovastatin	7	1	.64
Comorbid conditions			
Hypertension	304	53	.68
Tobacco use	272	48	.10
Atrial fibrillation	161	28	.79
Diabetes	150	26	.27
Chronic obstructive lung disease	125	22	.31
Chronic renal insufficiency†	95	17	.02
Alcohol abuse	96	16	.01
Stroke	74	13	.71
Cancer	71	12	.35
Acute myocardial infarction	65	11	.48
History of gastrointestinal bleed	46	8	.06

*For each characteristic, p value derives from a proportional hazards model of the relation between that characteristic and time to major bleeding.

†Creatinine level > 1.5.

and Beyth summarized the frequency of major hemorrhage across these studies and found the average annual frequency of major hemorrhage to be 3%.⁵ However, the frequency of major hemorrhage ranged from 0% per year to 67% per year. The difference in the incidences has been attributed to different study types and classifications of major hemorrhage across studies.

Landefeld et al. developed explicit, reproducible criteria for major hemorrhage,²¹ and determined the incidence of major hemorrhage to be 11% at 1 year in their inception cohort assembled before 1989.⁴ We used these same criteria in our cohort of patients, assembled after the recommendation for reduced-intensity anticoagulant therapy was made, and estimated the incidence of major hemorrhage to be 7% at 1 year. This lower incidence of hemorrhage was similar to Gitter's estimate of major hemorrhage of 5.3% at 1 year.⁷ The study type and criteria for major hemorrhage were the same for all three observational studies; therefore, the lower incidence of major hemorrhage in the cohorts assembled after 1989 may reflect the

Table 2. Independent Predictors of Major Hemorrhage: Literature-Based Model

Variable	Relative Risk	95% Confidence Interval	p Value*
Gastrointestinal bleeding	2.1	.93, 4.9	.07
Comorbid condition	1.6	.86, 3.1	.13
Stroke	1.2	.50, 2.9	.68
Age ≥65 years	1.0	.53, 1.9	.97
Atrial fibrillation	1.0	.47, 2.1	.99

*p Values are derived from a multivariate proportional hazards model.

recommendation for reductions in the therapeutic ranges for patients receiving warfarin. However, the difference in the incidence of major hemorrhage may reflect the differences in the indications for warfarin therapy among the different studies. The major indication for treatment in Landefeld's study was cardiovascular surgery, while the primary indication for treatment in Gitter's study was venous thromboembolism, and the major cause for treatment in our study was atrial fibrillation.^{4,7} Therefore, the target prothrombin ratios would have been higher for the majority of patients in Landefeld's study, and may be responsible for the increased incidence of hemorrhage in that population.

Our reduced incidence of major hemorrhage is still higher than the majority of estimates reported in experimental studies. This most likely reflects the differences in eligibility criteria as well as the monitoring processes associated with clinical trials.

The average monthly incidence of major hemorrhage in our study was 0.82% for the first 3 months of treatment. Previous studies have also reported increased frequencies of major bleeding early in the course of warfarin therapy.^{3,4}

Risk Factors

Our study identified three predictors of major hemorrhage: history of alcohol abuse, chronic renal insufficiency, and a previous gastrointestinal bleed. Although no previous study has identified alcohol abuse as an inde-

pendent predictor of major hemorrhage, Fihn et al. did see a trend toward a higher rate of bleeding in elderly binge drinkers.¹¹ Chronic renal insufficiency and a history of gastrointestinal bleeding were independent predictors of major hemorrhage in Landefeld's study as well.⁴

Age has been examined as a risk factor for major hemorrhage in many studies.^{1,4,7-16} Although some studies have identified age as a significant risk factor for major hemorrhage,^{4,10,11,13,15} other studies have not.^{1,7-9,14,16} Fihn et al. examined the effect of increasing age on the risk of hemorrhage in a combined retrospective and prospective cohort study.¹⁷ They determined that age was not a strong risk factor for hemorrhage with the possible exception of patients aged 80 years or older. Likewise, we did not find that age was an independent predictor of bleeding in our population.

We examined the effect of medications known to influence prothrombin time as well as combined therapy with other anticoagulants such as aspirin and ticlopidine. None of the medications was a significant predictor of major hemorrhage in our population. It is especially interesting that the use of both warfarin and aspirin, prescribed for approximately 23% of our subjects, did not confer an increased risk of bleeding. This suggests that the use of these agents targeting different coagulation mechanisms may not have a synergistic effect on the risk of bleeding.

Limitations

A major limitation of our study is the limited predictive ability of our model. Our averaged C statistic of 0.51 suggests that our data-based model is inadequate for predicting those subjects at increased risk of hemorrhage on the basis of baseline patient characteristics. There has been a lack of consistency among independent predictors of major hemorrhage identified across studies.¹³ We examined the effect of demographic, medication, and comorbid variables that had also been tested in Landefeld's study⁴ and Gitter's study.⁷ However, we were unable to reproduce the model derived from either study. This lack of consistency of predictors across studies, as well as the limited predictive ability of our own hemorrhage model, suggests that the baseline characteristics that confer the greatest risk of major hemorrhage for patients treated with warfarin have yet to be identified, or that baseline patient characteristics do not significantly influence the risk of bleeding. The frequency of major bleeding events may be predominantly affected by the monitoring process.

Fihn et al. closely examined the impact of prothrombin time management on the risk of major hemorrhage for patients receiving warfarin.¹⁰ They determined that variability in the prothrombin time ratio was significantly related to bleeding.¹⁰ We are in the process of examining the effect of the frequency and variability of prothrombin time monitoring in our study population. The inclusion of a variable that reflects the process of prothrombin time variability and monitoring may give our model increased

Table 3. Independent Predictors of Major Hemorrhage: Data-Based Model

Variable	Relative Risk	95% Confidence Interval	p Value*
Alcohol abuse	2.7	1.4, 5.4	.004
Chronic renal insufficiency†	2.6	1.3, 5.2	.008
Previous gastrointestinal bleed	2.4	1.1, 6.0	.04

*p Values are derived from a multivariate proportional hazards model.

†Creatinine level >1.5.

predictive ability over that provided by baseline patient characteristics alone.

Another limitation of our study is the means by which the variable alcohol abuse was defined. The variable was considered present if the admitting physician documented a history of alcohol abuse in the past medical history or diagnoses section of the discharge summary. We are likely to have underestimated the prevalence of alcohol abuse in our study population and, therefore, the relative risk of major hemorrhage associated with alcohol abuse.

Finally, our population consisted primarily of white men. Therefore, the results should be applied to a similar population.

Conclusions

We measured the incidence of major hemorrhage for outpatients treated with warfarin to be 7% at 1 year. The results of our study, in conjunction with the findings of Gitter's study, suggest that the incidence of major hemorrhage has decreased since the recommendations for reduced anticoagulation therapy were made.⁷

We identified three independent predictors of major hemorrhage in our population: alcohol abuse, chronic renal insufficiency, and a previous gastrointestinal hemorrhage. However, given the limited predictive ability of our model as well as the lack of consistently identifiable risk factors across studies, the decision to initiate warfarin therapy in patients with an appropriate indication for anticoagulation therapy should continue to be made on the basis of individual risks, benefits, and preferences.

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