Bleeding Risk Index in an Anticoagulation Clinic

Assessment by Indication and Implications for Care

Sherrie L. Aspinall, PharmD, BCPS,[1] Beth E. DeSanzo, PharmD,[2] Lauren E. Trilli, PharmD, BCPS,[3] Chester B. Good, MD, MPH[1]

[1]Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA; [2]Pharmacy Department, Butler Veterans Affairs Medical Center, Butler, PA, USA; [3]Pharmacy Department, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA.

BACKGROUND: The Outpatient Bleeding Risk Index (BRI) prospectively classified patients who were at high, intermediate, or low risk for warfarin-related major bleeding. However, there are only 2 published validation studies of the index and neither included veterans.

OBJECTIVE: To determine the accuracy of the BRI in patients attending a Veterans Affairs (VA) anticoagulation clinic and to specifically evaluate the accuracy of the BRI in patients with atrial fibrillation.

DESIGN: Retrospective cohort study.

PATIENTS AND MEASUREMENTS: Using the BRI, all patients managed by the Anticoagulation Clinic between January 1, 2001 and December 31, 2002 were classified as high, intermediate, or low risk for major bleeding. Bleeds were identified via quality-assurance reports. Poisson regression was used to determine whether there was an association between the index and the development of bleeding.

RESULTS: The rate of major bleeding was 10.6%, 2.5%, and 0.8% per patient-year of warfarin in the high-, intermediate-, and low-risk groups, respectively. Patients in the high-risk category had 14 times the rate of major bleeding of those in the low-risk group (incidence rate ratio (IRR) 14; 95% confidence interval (CI), 1.9 to 104.7). The rate of major bleeding was significantly different between the high- and intermediate-risk categories ($P<.001$). Among those with atrial fibrillation, patients in the high-risk category had 6 times the major bleeding rate of those in the intermediate- and low-risk groups combined (IRR=6; 95% CI, 2.4 to 15.3).

CONCLUSIONS: The BRI discriminates between high- and intermediate-risk patients in a VA anticoagulation clinic, including those with atrial fibrillation.

KEY WORDS: bleeding risk; warfarin; anticoagulation clinic.
DOI: 10.1111/j.1525-1497.2005.0229.x
J GEN INTERN MED 2005; 20:1008–1013.

Warfarin is effective for the prevention of thromboembolism in a variety of conditions, but hemorrhage is a major side effect. Physicians use their clinical judgment to estimate the risk of bleeding in an individual patient. However, in at least 1 study, these estimates did not correlate with the actual frequency of major bleeding.[1] Therefore, prediction rules can help physicians more accurately weigh the risks and benefits of warfarin therapy. Several prediction models have been developed based on independent risk factors for warfarin-related bleeding.[1–4] Of these, 2 were developed and validated in outpatients.[1,4] The prediction score constructed by Kuijer et al.[4] studied patients with established venous thromboembolism and identified those who were at high risk of developing a hemorrhagic event. The Outpatient Bleeding Risk Index (BRI) developed by Beyth et al.[1] included all patients initiating warfarin upon discharge from the hospital, regardless of their indication for therapy, and prospectively classified patients who were at high-, intermediate-, or low-risk for major bleeding. Wells et al.[5] published the only other prospective validation of the BRI. They found that the BRI discriminated between low- and moderate-risk patients who were anticoagulated for pulmonary embolism or deep vein thrombosis, but they could not determine the rate of major bleeding in the high-risk group because only 2 patients in their clinic were in this category.

Of the available prediction models, the BRI is the most applicable for a general medical population, is simple to perform, and has been validated in the literature. However, the studies by Beyth and Wells did not include a veteran population in their evaluation of the BRI. Therefore, we sought to determine the accuracy of the BRI in predicting major bleeds in all patients attending a Veterans Affairs (VA) anticoagulation clinic as a quality-improvement project. In addition, given the number of patients with atrial fibrillation, the emphasis on antithrombotic therapy for stroke prevention,[6] and a general lack of familiarity with objective methods for quantifying the risk of bleeding, we wanted to specifically evaluate the accuracy of the BRI in this group of patients.

METHODS

The Anticoagulation Clinic at the VA Pittsburgh Healthcare System (VAPHS) is a pharmacist-run clinic that was established in 1987 to coordinate outpatient warfarin management. As part of a long-standing quality-assurance program, BRI is recorded on all patients. All thromboembolic events and major and minor bleeds are identified, and the event rate per patient-year of warfarin is reported to the Pharmacy and Therapeutics (P&T) Committee. The event rates are consistently below published results for routine medical care and comparable with other anticoagulation clinics.

Data Collection

This analysis includes all patients managed by the Anticoagulation Clinic between January 1, 2001 and December 31, 2002. Patients include those newly started on warfarin, as well as those who had been anticoagulated for varying lengths of time. No patients were lost to follow-up as clinic providers call or automatically reschedule every patient who misses an appointment.

The BRI was collected using the administrative database for the clinic. Patients enrolled in clinic prior to January 1,

The authors have no conflicts of interest to declare for this article or this research.

Address correspondence and requests for reprints to Dr. Aspinall: VA Pittsburgh Healthcare System, Center for Health Equity Research and Promotion (151C-CU), University Drive C, Pittsburgh, PA 15240 (e-mail: sherrie.aspinall@med.va.gov).

Accepted for publication July 5, 2005

2001 had the BRI determined by retrospective chart review; all others had the BRI applied prospectively. As per the BRI (Table 1), patients received 1 point for each of the following risk factors that was documented by a provider in the electronic medical record: (1) age $\geq$65 years, (2) history of stroke, (3) history of gastrointestinal (GI) bleed, and (4) the presence of 1 or more serious comorbid conditions, namely recent myocardial infarction, hematocrit $<$30%, serum creatinine $>$1.5 mg/dL, or diabetes mellitus. Based on their total number of points, or risk factors, patients were classified as low- (0 points), intermediate- (1 or 2 points), or high-risk (3 or 4 points) for major bleeding.[1] No data were missing for the BRI.

Next, we retrospectively reviewed the quality-assurance reports for the clinic and identified patients who experienced a major or minor bleed between January 1, 2001 and December 31, 2002. A bleed was defined as major when the patient was hemodynamically unstable, required a transfusion, had an intracranial hemorrhage, or died (e.g., GI bleed in a hypotensive patient, subdural hematoma). A bleed was defined as minor when the patient was hemodynamically stable, but required hospitalization or a physician visit for evaluation. Minor bleeds ranged from epistaxis or gingival bleeding to those requiring admission for clinically stable hematochezia or hematuria, not requiring a blood transfusion. Bleeding episodes are identified via several mechanisms. Providers in the Anticoagulation Clinic query patients about major and minor bleeds at every visit. Reported bleeds are reviewed, compiled quarterly, and reported to the P&T Committee. The inpatient anticoagulation service identifies all bleeds that occur among patients on warfarin who are hospitalized at our medical center. Finally, when providers contact patients who miss clinic appointments, they capture bleeding episodes, including those requiring hospitalization outside VAPHS.

Using the administrative database for the clinic, we identified the date warfarin was initiated and indication for therapy. We determined the total patient-years of warfarin by indication and BRI using the date of clinic enrollment and discharge, if applicable. The categories for indications were grouped as follows: atrial fibrillation (atrial fibrillation and flutter), heart valve replacement (mechanical, bioprosthetic, and patients with a valve replacement in addition to other indications for warfarin), venous thromboembolism (deep vein thrombosis, pulmonary embolism, or both), cerebrovascular accidents and transient ischemic attacks, hypercoagulable states, cardiomyopathy, myocardial infarction, peripheral vascular disease, and other (patients with less common indications such as an arterial bypass graft). Patients with more than 1 indication for anticoagulation (e.g., stroke and atrial fibrillation) were also placed in the "other" group, except for individuals with mechanical valves, who are always categorized as a valve replacement.

As this was a quality improvement project, exempt status was requested from the Institutional Review Board at the VAPHS.

Table 1. The Outpatient Bleeding Risk Index (Beyth RJ, 1998 58/id)

1. Bleeding Risk Factors (Check all that apply)	Points Assigned
☐ Age $\geq$65 y	1
☐ History of stroke	1
☐ History of GIB	1
☐ Recent MI ☐ Hct $<$30% ☐ SCr $>$1.5 mg/dL ☐ Diabetes mellitus	1 point maximum if any are checked
2. Bleeding Risk Group	**Total Points Assigned**
Low	0
Intermediate	1 to 2
High	3 to 4

GIB, gastrointestinal bleed; MI, myocardial infarction; Hct, hematocrit; SCr, serum creatinine.

Analysis

We describe the incidence of major and minor bleeding by BRI group in all patients followed by the Anticoagulation Clinic at the VAPHS and in the subgroup with atrial fibrillation. Poisson regression was used to determine whether there was an association between the BRI and the development of major and minor bleeding. The results are reported as the incidence rate ratio (IRR) with the corresponding 95% confidence intervals (CIs). Finally, we compare the incidence of bleeding in patients who were newly started on warfarin between January 1, 2001 and December 31, 2002 with those who were on warfarin at the start of the project.

RESULTS

Table 2 describes the baseline characteristics of all patients enrolled in the Anticoagulation Clinic between January 1, 2001 and December 31, 2002, as well as the subgroup that experienced a major bleed. In general, the baseline characteristics of patients who had a major bleed were similar to those who did not have a hemorrhagic event, with the exception of age and BRI category. Patients who experienced a major bleed were slightly older, and more were in the high-risk BRI group. Increased age, history of a GI bleed, and a hematocrit $<$30% were more prevalent in those who bled and led to the high-risk classification. Table 3 summarizes the patient-years of warfarin by indication and BRI. There were 1308 patient-years of warfarin therapy among the 1269 patients in clinic during this time period. Atrial fibrillation was the most common indication (556 patient-years), and the majority of patients were in the intermediate-risk BRI category (997 patient-years).

In 2001 and 2002, there were 45 major bleeds in 42 patients. Of the 34 patients with an INR at the time of the major bleed, the median value was 3.5 (Table 4). Nineteen INRs (55.9%) were supratherapeutic (e.g., INR$>$3 in a patient with atrial fibrillation, INR$>$3.5 in a patient with a mitral valve replacement). Of the 45 major bleeds, 26 were GI, and 4 involved the central nervous system. Three of these 4 patients experienced a fall, which contributed to the event. Most patients had been on warfarin for $>$1 year prior to their major bleed (71.5%). No patients died as result of warfarin-related bleeding.

The number of bleeds in each BRI category by type of bleed is summarized in Table 5 for all patients and the subgroup with atrial fibrillation. The overall rate of minor bleeding was 5.6% (95% CI, 4.4–7.0) per patient-year of warfarin, while the rate of major bleeding was 3.4% (95% CI, 2.5–4.6) per patient-year of warfarin. The rate of major bleeding was the greatest in the high-risk BRI group (10.6% per patient-year of

Table 2. Baseline Patient Characteristics: All Patients and Subgroup with a Major Bleed

Characteristic	Total (*N*=1,269) *N* (%)	Major Bleed (*N*=42) *N* (%)	No Bleed (*N*=1,227) *N* (%)	*P* Value*
Age (mean, SD)	67.9 (11.4)	72.0 (9.6)	67.8 (11.4)	.02
Gender				.45
Male	1167 (92.0)	42 (100.0)	1125 (91.7)	
Female	22 (1.7)	0	22 (1.8)	
Missing	80 (6.3)	0	80 (6.5)	
Race†				1.00
White	1040 (82.0)	37 (88.1)	1003 (81.7)	
African American	139 (11.0)	5 (11.9)	134 (10.9)	
Missing	90 (7.1)	0	90 (7.3)	
Indication for warfarin				.21
A. fib.	543 (42.8)	18 (42.9)	525 (42.8)	
Valve	138 (10.9)	9 (21.4)	129 (10.5)	
VTE	253 (19.9)	5 (11.9)	248 (20.2)	
CVA/TIA	86 (6.8)	2 (4.8)	84 (6.8)	
Hypercoagulable	14 (1.1)	2 (4.8)	12 (1.0)	
CMP	47 (3.7)	1 (2.4)	46 (3.7)	
MI	17 (1.3)	0	17 (1.4)	
PVD	7 (0.6)	0	7 (0.6)	
Other	164 (12.9)	5 (11.9)	159 (13)	
Duration of warfarin therapy†‡				.38
<1 mo	70 (5.5)	1 (2.4)	69 (5.6)	
≥ 1 mo to <1 y	397 (31.3)	10 (23.8)	387 (31.5)	
≥ 1 to <3 y	271 (21.4)	13 (31.0)	258 (21.0)	
≥ 3 y	531 (41.8)	18 (42.9)	513 (41.8)	
BRI category†				$<.001$
High	196 (15.4)	22 (52.4)	174 (14.2)	
Intermediate	943 (74.3)	18 (42.9)	925 (75.4)	
Low	130 (10.2)	2 (4.8)	128 (10.4)	
BRI risk factors§				
Age ≥ 65 y	834 (65.7)	34 (81.0)	800 (65.2)	.05
h/o Stroke	267 (21.0)	10 (23.8)	257 (21.0)	.70
h/o Gastrointestinal bleed	94 (7.4)	15 (35.7)	79 (6.4)	$<.001$
h/o MI	266 (21.0)	9 (21.4)	257 (21.0)	1.00
Hematocrit $<30\%$	169 (13.3)	13 (31.0)	156 (12.7)	.002
Serum creatinine >1.5 mg/dL	310 (24.4)	14 (33.3)	296 (24.1)	.20
Diabetes mellitus	421 (33.2)	13 (31.0)	408 (33.2)	.87

**Patients with a major bleed versus those without a major bleed.*
†Percentages may not equal 100 because of rounding.
‡Total duration of warfarin therapy from initiation through December 31, 2002.
§Percentages do not equal 100 because patients may have multiple risk factors.
BRI, outpatient bleeding risk index; A. fib., atrial fibrillation; valve, heart valve replacement; VTE, venous thromboembolism; CVA/TIA, cerebrovascular accident/transient ischemic attack; hypercoagulable, hypercoagulable state (e.g., antiphospholipid antibody syndrome); CMP, cardiomyopathy; MI, myocardial infarction; PVD, peripheral vascular disease; Other, patients with multiple indications for warfarin (e.g., MI/CMP).

Table 3. Patient-Years (%) of Warfarin by Indication and BRI

Indication	Patient-years	BRI		
		Low	Intermediate	High
A. fib.	556	32 (5.8)	459 (82.5)	65 (11.7)
Valve	180	24 (13.3)	131 (72.8)	25 (13.9)
VTE	203	53 (26.1)	139 (68.5)	11 (5.4)
CVA/TIA	102	1 (1)	57 (55.9)	44 (43.1)
Hypercoagulable	17	6 (35.3)	9 (52.9)	2 (11.8)
CMP	50	5 (10)	42 (84)	3 (6)
MI	20	0	20 (100)	0
PVD	8	0	6 (75)	2 (25)
Other	172	11 (6.4)	134 (77.9)	27 (15.7)
Total	1,308	132 (10.1)	997 (76.2)	179 (13.7)

BRI, outpatient bleeding risk index; A. fib., atrial fibrillation; valve, heart valve replacement; VTE, venous thromboembolism; CVA/TIA, cerebrovascular accident/transient ischemic attack; hypercoagulable, hypercoagulable state (e.g., antiphospholipid antibody syndrome); CMP, cardiomyopathy; MI, myocardial infarction; PVD, peripheral vascular disease; Other, patients with multiple indications for warfarin (e.g., MI/CMP).

warfarin), followed by the intermediate- (2.5% per patient-year) and low-risk (0.8% per patient-year) groups. Patients in the intermediate-risk category had approximately 3 times the rate of major bleeding of those in the low-risk group (IRR 3.3; 95% CI, 0.5–24.4). Patients in the high-risk BRI category had 14 times the rate of major bleeding of those in the low-risk group (IRR 14; 95% CI, 1.9–104.7). The rate of major bleeding was significantly different between the high- and intermediate-risk BRI categories ($P<.001$). The BRI did not predict minor bleeding ($P=.28$).

Among the subgroup with atrial fibrillation, there were no major bleeds among patients in the low-risk category (Table 5). The rate of major bleeding was 2.2% (95% CI, 1.0–4.0) per patient-year of warfarin in the intermediate-risk group, and 12.3% (95% CI, 5.3–24.3) in the high-risk group. As there were no major bleeds in the low-risk BRI category, we combined the low- and intermediate-risk groups. Patients in the high-risk category had 6 times the major bleeding rate of those in the intermediate- and low-risk groups (IRR 6; 95% CI, 2.4–15.3). The rate of major bleeding was significantly differ-

Table 4. Description of Major Bleeds (*N*=45)

Descriptor	*N* (%)
INR (*N*=34)	
Median (range)*	3.5 (1.3–16.3)
Subtherapeutic	6 (17.6)
Therapeutic	9 (26.5)
Supratherapeutic	19 (55.9)
Location of hemorrhage	
GI	26 (57.8)
HEENT	7 (15.6)
Soft tissue	4 (8.9)
CNS	4 (8.9)
GU	2 (4.4)
Unknown†	2 (4.4)
Duration of warfarin therapy prior to bleed‡	
<1 mo	3 (7.1)
≥1 mo to <1 y	9 (21.4)
≥1 to <3 y	13 (31.0)
≥3 y	17 (40.5)
Outcomes	
Bleed resolved–warfarin continued	16 (35.6)
Bleed resolved–warfarin discontinued	29 (64.4)
Death	0

**INRs were unavailable for 11 patients who presented to a facility outside of the VA.*
†These patients were hospitalized outside of the VA and required a transfusion, but records were unavailable to identify the source of the major bleed.
‡Forty-five major bleeds occurred in 42 patients.
HEENT, head, eyes, ears, nose, and throat (e.g., epistaxis, hemoptysis); CNS, central nervous system (e.g., subdural, intracranial); GU, genitourinary tract.

ent between the high- and intermediate-risk categories ($P<.001$). The BRI did not predict minor bleeding in patients with atrial fibrillation ($P=.29$).

Patients who started warfarin between January 1, 2001 and December 31, 2002 did not have a significantly higher percentage of major and minor bleeds (Table 6). Compared with patients who were on warfarin prior to January 1, 2001, a higher percentage of the patients who were just starting warfarin during the study period were in the intermediate- and low-risk BRI groups.

Table 5. Minor and Major Bleeds by BRI Category in All Patients and in the Subgroup with Atrial Fibrillation

BRI	Patients *N*	Patient-Years of Warfarin	Minor *N* (% per patient) (% per patient-year; 95% CI)	Major *N* (% per patient) (% per patient-year; 95% CI)
All patients				
High	196	179	12 (6.1) (6.7; 3.4–11.7)	19 (9.7) (10.6; 6.4–16.6)
Intermediate	943	997	50 (5.3) (5.0; 3.7–6.6)	25 (2.6) (2.5; 1.6–3.7)
Low	130	132	11 (8.5) (8.3; 4.2–14.9)	1 (0.8) (0.8; 0–4.2)
Total	1269	1308	73 (5.8) (5.6; 4.4–7.0)	45 (3.5) (3.4; 2.5–4.6)
Atrial fibrillation				
High	72	65	5 (6.9) (7.7; 2.5–18.0)	8 (11.1) (12.3; 5.3–24.3)
Intermediate	435	459	19 (4.4) (4.1; 2.5–6.5)	10 (2.3) (2.2; 1.0–4.0)
Low	36	32	3 (8.3) (9.4; 1.9–27.3)	0 (0) (0; 0–9.4)
Total	543	556	27 (5.0) (4.9; 3.2–7.1)	18 (3.3) (3.2; 1.9–5.1)

BRI, outpatient bleeding risk index; 95% CI, 95% confidence interval.

Table 6. Comparison of Bleeding and BRI in New Patients Versus All Others

Characteristic	New Patients* (*N*=502) *N* (%)	All Others (*N*=767) *N* (%)	*P* Value
Bleeds			
Minor	28 (5.6)	43 (5.6)	1.00
Major	11 (2.2)	31 (4.0)	.08
BRI†			
High	59 (11.8)	137 (17.9)	.009
Intermediate	385 (76.7)	558 (72.8)	
Low	58 (11.6)	72 (9.4)	

**Patients who were newly started on warfarin between January 1, 2001 and December 31, 2002.*
†Percentages not equal to 100 because of rounding.
BRI, outpatient bleeding risk index.

DISCUSSION

These are the first published results validating the use of the BRI in a large, pharmacist-run anticoagulation clinic. In addition, it is the first to evaluate the BRI in patients by indication, and in particular, those with atrial fibrillation. We believe the project adds important information regarding the risk of bleeding with chronic warfarin in an unselected patient population. In addition, our findings should help clinicians assess the risk-to-benefit ratio with warfarin when they are considering the most appropriate antithrombotic agent in their patients with atrial fibrillation.

Overall, the rate of major bleeding was 3.4% per patient-year of warfarin. This is comparable with other anticoagulation clinics (e.g., average 2.8%) and below-published results for routine medical care (e.g., average 10.9%).[7] Among the 3 groups defined prospectively by the BRI, the risk of a major hemorrhage was 0.8%, 2.5%, and 10.6% per patient-year of warfarin in low-, intermediate-, and high-risk patients, respectively. This is lower than the rates reported by Beyth et al.[1] (cumulative risk at 12 months was 3% in low-risk, 8% in intermediate-risk, and 30% in high-risk patients) and comparable with those published by Wells et al.[5] (0% per patient-year of warfarin in low-risk patients and 4.3% in the intermediate-risk group). Our anticoagulation clinic uses a slightly different definition for a major hemorrhage. Beyth and Wells both defined a major bleed as the loss of 2 U of blood within 7 days, or one that is life-threatening. In addition to the patients captured by this definition, we classified patients who were hemodynamically unstable secondary to a bleeding event, or those who required any transfusion of blood, as having experienced a major bleed.

The most common site for major bleeding was the GI tract (57.8%). In the study by Beyth et al.,[1] 9 of the 22 major bleeds (40.9%) were GI, and 2 of these patients died. By comparison, all of the major bleeds involved the GI tract in the study by Wells.[5] Although none of our patients died, the mortality rate from acute GI hemorrhage is not inconsequential. Epidemiologic studies have reported a mortality rate of 3.5% to 7% for upper GI bleeds and 3.6% for those involving the lower GI tract.[8,9]

The BRI did not predict minor bleeds, but it was not developed for that purpose. Although the BRI did not discriminate between the intermediate- and low-risk patients because of the low rate of major bleeding, there was a difference between the high- and intermediate-risk groups. This may be more clinically useful because the patients at greatest risk for a major bleed are likely to benefit the most from closer monitoring.

Higher frequencies of bleeding have been reported early in the course of warfarin therapy. In 1 study, the frequency of major bleeding was 3% in the first month, 0.8% per month during the remainder of the first year, and 0.3% per month thereafter.[10] However, in our study, there was no difference in the duration of warfarin therapy between those who experienced a major bleed and the rest of the group. Patients who initiated warfarin during the period reviewed did not have a higher incidence of bleeding than those on chronic therapy (Table 6).

Numerous well-done, randomized clinical trials have demonstrated the efficacy of warfarin in preventing thromboembolic events related to atrial fibrillation. Consequently, the American College of Chest Physicians recommends warfarin therapy for all patients at high-risk for thromboembolic events, as well as for patients with more than 1 moderate risk factor.[11] More recently, a review of the literature found that evidence strongly supports the use of warfarin in patients with atrial fibrillation who have an average or high risk for stroke, unless there is an increased risk of bleeding.[12]

Although oral anticoagulation is recommended for these moderate- to high-risk patients with atrial fibrillation, results from clinical trials suggest that many do not receive warfarin.[13,14] In a physician survey using clinical vignettes, warfarin was not recommended in half of patients for whom it was judged appropriate by the authors.[15] In particular, warfarin was prescribed less often for patients aged 75 or older.[15] A systematic review of the literature suggests that physicians' concerns about warfarin-related bleeding in older persons with atrial fibrillation might be unfounded.[16] However, Byeth et al.[1] found physicians usually underestimate the risk of serious bleeding in patients prescribed warfarin. Thus, physicians caring for patients with atrial fibrillation who have a moderate or high risk of stroke must carefully weigh the benefits and risks and determine the most appropriate antithrombotic therapy.

The recommendations for which patients benefit from aspirin and warfarin are relatively objective,[11] but the caveat to avoid warfarin when there is an increased risk of bleeding is problematic as methods to quantify the risk may not be clear to clinicians. Several analyses of randomized controlled trials of antithrombotic therapy in atrial fibrillation have helped to quantify the benefits. Pooling the results of 5 trials in an intention-to-treat analysis found an annual stroke rate of 4.5% with placebo and 1.4% with warfarin.[11] A meta-analysis of 6 studies of warfarin versus aspirin in patients with nonvalvular atrial fibrillation reported ischemic stroke rates of 4.3% per patient-year of aspirin therapy and 2% per patient-year of warfarin.[17] The presence of other risk factors may increase or decrease the risk of stroke. In this same meta-analysis, the major bleeding rate overall in patients on warfarin was 2.2% per patient-year (1.3% in those on aspirin).[17] In our population, the rate of major bleeding was 3.2% per patient-year of warfarin in individuals with atrial fibrillation, which is comparable. However, in our high-risk BRI group, the rate of major bleeding was about 12% per patient-year of warfarin, compared with no bleeds in our low-risk group. Thus, the simple use of the BRI may objectively quantify the risk for major hemorrhage with warfarin therapy.

There are several limitations in our study. First, data were collected for quality-assurance purposes. Therefore, we were unable to determine the reliability of data collection measures. Data were not readily available on potential confounders that may have influenced the rate of major bleeding such as concomitant use of drugs that interfere with hemostasis. Patients in the Anticoagulation Clinic are not permitted to use nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen). Nonacetylated salicylates, acetaminophen, and opioids are most commonly prescribed for pain. Cyclooxygenase-2 selective agents were only used in a small number of patients due to the presence of stringent prescribing guidelines. However, low-dose aspirin may have been used. Second, we had a limited number of patients in the low-risk BRI group, which may have affected our ability to detect a difference in the rate of major bleeding between the intermediate- and low-risk BRI categories. Third, we identified bleeds from the quality-assurance reports for the clinic, so we may have missed some events even though bleeds are captured via several mechanisms. Our rate of major bleeding is consistent with the results published by Wells et al. and other anticoagulation clinics. Fourth, we included patients with different indications for warfarin and therefore, different intensities of anticoagulation. However, among patients on warfarin for hypercoagulable states or mechanical valve replacements (i.e., patients maintained at a higher target INR), approximately the same numbers of patient-years of warfarin were in the high- and low-risk groups (27 vs 30 patient-years, respectively). Finally, although our results are likely to be generalizable to other VA anticoagulation clinics, they are from a single site and may not apply to females or a younger, healthier population as most of our patients are elderly males.

CONCLUSIONS

The BRI discriminates between high- and intermediate-risk patients in a VA anticoagulation clinic, including those patients with atrial fibrillation. Although warfarin is reportedly underutilized in eligible patients with atrial fibrillation, it is important to objectively consider the trade off between the benefits and risks of oral anticoagulation, especially among individuals prospectively scored as high-risk for major bleeding by the Index.

At the time of the study, Dr. DeSanzo was a pharmacy practice resident at the VA Pittsburgh Healthcare System.

We appreciate the statistical support provided by Mary Kelley, PhD. At the time of the research, Dr. Kelley was a statistician with the Center for Health Equity Research and Promotion, VAPHS, Pittsburgh, PA. She is now at Emory University, Atlanta, GA. No funding was obtained for this research project. Dr. Aspinall is a VA Health Services Research and Development (HSR&D) Research Career Development Awardee.

REFERENCES

1. **Beyth RJ, Quinn LM, Landefeld CS.** Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105:91–9.
2. **Landefeld CS, McGuire E, Rosenblatt MW.** A bleeding risk index for estimating the probability of major bleeding in hospitalized

patients starting anticoagulant therapy. Am J Med. 1990;89: 569–78.
3. **Landefeld CS, Goldman L.** Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient thereapy. Am J Med. 1989;87:144–52.
4. **Kuijer PMM, Hutten BA, Prins MH, Buller HR.** Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med. 1999;159:457–60.
5. **Wells PS, Forgie MA, Simms M**, **et al**. The outpatient bleeding risk index: validation of a tool for predicting bleeding rates in patients treated for deep venous thrombosis and pulmonary embolism. Arch Intern Med. 2003;163:917–20.
6. **Hart RG, Halpern JL, Pearce LA**, **et al**. Lessons from the stoke prevention in atrial fibrillation trials. Ann Intern Med. 2003;138:831–8.
7. **Ansell JE, Hughes R.** Evolving models of warfarin management: anticoagulation clinics, patient self-monitoring, and patient self-management. Am Heart J. 1996;132:1095–100.
8. **Longstreth GF.** Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol. 1995;90:206–10.
9. **Longstreth GF.** Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol. 1997;92:419–24.
10. **Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S.** Hemorrhagic complications of anticoagulant treatment. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004; 126:287S–310S.
11. **Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE.** Antithrombotic therapy in atrial fibrillation. Chest. 2001;119:194S–206S.
12. **McNamara RL, Tamariz LJ, Segal JB, Bass EB.** Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiograpy. Ann Intern Med. 2003; 139:1018–33.
13. **Antani MR, Beyth RJ, Covinsky KE**, **et al**. Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. J Gen Intern Med. 1996;11:713–20.
14. **Sudlow M, Rodgers H, Kenny RA, Thomson R.** Population based study of use of anticoagulants among patients with atrial fibrillation in the community. BMJ. 1997;314:1529–30.
15. **Beyth RJ, Antani MR, Covinsky KE**, **et al**. Why isn't warfarin prescribed to patients with nonrheumatic atrial fibrillation? J Gen Intern Med. 1996;11:721–8.
16. **Man-Son-Hing M, Laupacis A.** Anticoagulant-related bleeding in older persons with atrial fibrillation: physicians' fears often unfounded. Arch Intern Med. 2003;163:1580–6.
17. **Van Walraven C, Hart RG, Singer DE**, **et al**. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA. 2002;288:2441–8.