Original Work

Assessment of Bleeding Risk in Patients on Warfarin in an Ambulatory Care Setting

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Abstract

Objective: Warfarin is an effective oral anticoagulant used to prevent thromboembolic events, but has significant bleeding risks. Estimation of bleeding risk for patients on warfarin is an important factor in determining the clinical value of this treatment option. HAS-BLED, ATRIA, and OBRI are bleeding risk assessment tools used in clinical practice. The purpose of this study was to evaluate the predictive performance of the HAS-BLED, ATRIA, and OBRI risk assessment tools in patients on warfarin in an ambulatory care setting.

Methods: Electronic health records from patients on warfarin enrolled in an anticoagulation service between March 1, 2011 and September 30, 2014 were retrospectively analyzed for bleeding risk using HAS-BLED, ATRIA, and OBRI scoring methods. HAS-BLED, ATRIA, and OBRI scores were calculated using laboratory results, ICD-9 diagnosis codes, and patient medication lists. Anatomical site of bleeds, INR on the bleeding event date, and blood transfusion data were manually collected. Primary analyses of bleeding risk were based on proportional hazards time-to-event models, and model discrimination was determined via the C-index.

Results: The C-indices for the HAS-BLED, ATRIA, and OBRI bleeding risk assessment tools were 0.72 (0.69–0.75), 0.75 (0.73–0.77), and 0.71 (0.68–0.74), respectively. The HAS-BLED, ATRIA, and OBRI tools performed substantially better than chance at predicting bleeds with similar overall performance.

Conclusions: Combining criteria of these risk assessment tools with the volume of diagnostic information available from electronic health records could improve the predictive ability of risk assessment tools for bleeding events.

Warfarin is a commonly prescribed oral anticoagulant used to prevent thromboembolic events. Although warfarin is highly effective, it is also associated with significant bleeding risks.[1] Numerous comorbidities such as age, kidney function, and hypertension have been identified as risk factors for bleeding and are used in a number of clinical tools to assist practitioners in determining bleeding risk for individual patients.[2-8] Risk assessment tools for bleeding events differ from one another based on how the scores are derived, the clinical factors included in the risk analysis, and whether or not there is a weighting scale with respect to certain comorbidities (Table 1). These differences make identifying the proper risk assessment tool to use for a given patient difficult. Multiple studies have been conducted comparing the predictive performance of bleeding risk assessment tools.[9-13] These studies are limited by small number of bleeding events,[9,12,13] short follow up periods,[9-11,13] and the inclusion of only patients with atrial fibrillation.[10-12] Study conclusions conflict regarding which tool best predicts bleeding. How these results should be applied to the care of patients on warfarin in the ambulatory care setting is unclear. The primary objective of this study was to assess the predictive performance of the HAS-BLED, ATRIA, and OBRI bleeding risk assessment tools in the Clinic's Anticoagulation Service patient population on warfarin.

Methods

This retrospective study was approved by the Institutional Review Board. Patients ≥ 18 years-of-age on warfarin who were enrolled in the Clinic's Anticoagulation Service at any time between March 1, 2011 and September 1, 2014 were included in the study. Patients who did not have a primary care provider within the health system were excluded. Patient data was abstracted from the electronic health record to calculate HAS-BLED, ATRIA, and OBRI scores. Definitions of the clinical risk factors included in the bleeding risk assessment tools have been previously described in detail.[2,6,8] Bleeding risk scores were calculated at 3-month intervals throughout the study period by utilizing laboratory results, ICD-9 diagnosis codes, and patient medication lists. The definitions used in this study for each risk category are described in detail in Box 1 at the end of the article. Anatomical site of bleeds, International Normalized Ratio (INR) on the bleeding event date, and blood transfusion information were manually collected.

The Clinic's Anticoagulation Service definition of a major bleed is any bleed that results in blood transfusion, hospitalization, or death. Major bleeding events matching this definition are prospectively identified by Anticoagulation Service staff and

recorded in a database. All major bleeding events entered from March 1, 2011 to September 1, 2014 were retrospectively reviewed and validated per an approved protocol. If an individual had multiple major bleeding events entered, all events entered after a valid event were censored.

For the purposes of this study, the Clinic's Anticoagulation Service definition of major bleed was divided into two separate categories: clinically relevant non-major (CRNM) bleeds and major bleeds. CRNM bleeds were defined as any bleed resulting in an outpatient blood transfusion or a hospitalization that did not require a blood transfusion. Major bleeds were defined as any bleed resulting in hospitalization requiring a blood transfusion, bleeding into a critical site, or death. Bleeding into a critical site was defined as any intracranial, intra-spinal, intra-ocular, retroperitoneal, pericardial, intra-articular, or visceral bleed.

Standard descriptive statistics were used to summarize important characteristics of the patient cohort. For each patient, one or more observation periods within the overall study time frame were determined using warfarin dosing information and INR laboratory results from the electronic health record. Individuals could contribute multiple time periods of follow-up if warfarin therapy was discontinued and subsequently resumed. The risk assessment tools were calculated as time-varying covariates within these observation periods, and observation times were accumulated to directly determine event rates. Primary analyses of bleeding risk were based on proportional hazards time-to-event models for the assessment tools and for the individual clinical factors included in the tools.[14] Results from the proportional hazards models were summarized with the estimated hazard ratios and 95% confidence limits.[15] The 95% CIs were generated using Wald robust confidence limits. Model discrimination was assessed with the C-index which measures concordance of the predicted and observed results among patients.[16,17] The C-index analysis ranges in score from 0.5 to 1, with a score of 0.5 indicating a tool performs no better than chance at predicting an outcome, in this case a bleeding event, and a score of 1 indicating a tool perfectly

TABLE 1. Bleeding Risk Assessment Tools

Clinical Risk Factors	*OBRI*	*HAS-BLED*	*ATRIA*
Age	X	X	X (2 points)
History of Bleed	X	X	X
Abnormal Renal Function	X*	X	X (3 points)
Anemia	X*	X	X (3 points)
Hypertension		X	X
History of Stroke	X	X	
Abnormal Liver Function		X	
Labile INR		X	
Concomitant NSAIDs or Antiplatelets		X	
Alcohol Abuse		X	
Recent Myocardial Infarction	X*		
Diabetes Mellitus	X*		
Patient Population			
Restricted to AF Patients		X	X
Restricted to Patients Newly Initiated on Warfarin	X		
Restricted to Patients Taking Warfarin	X		X

All risk factors are worth 1 point for their respective tools unless otherwise noted
**The OBRI assigns 1 point for one, or a combination of more than one, of the following risk factors: abnormal renal function, anemia, recent myocardial infarction or diabetes mellitus*
AF: atrial fibrillation; INR: International Normalized Ratio; NSAID: non-steroidal anti-inflammatory drug

FIGURE 1. C-Index for Major Bleeds With 95% Confidence Intervals

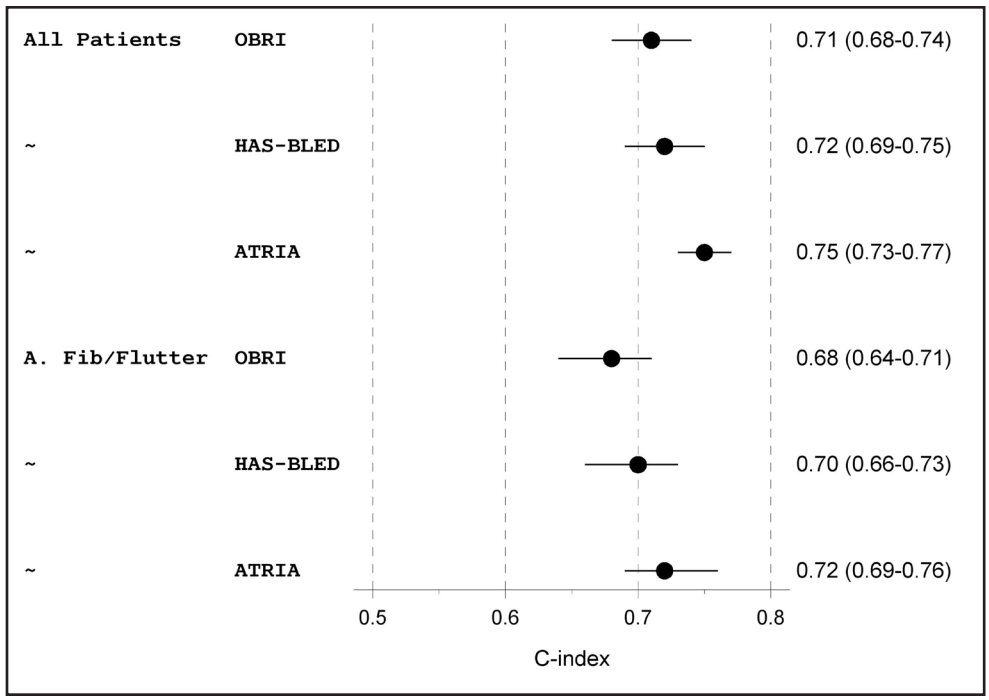

TABLE 2. Frequency of Clinical Risk Factors with Hazard Ratios*

Clinical Risk Factor	Without Bleed (n=16,841)	Major Bleed (n=526)	Hazard Ratio	95% Confidence Interval	CRNM or Major Bleed (n=851)	Hazard Ratio	95% Confidence Interval
OBRI							
Age ≥ 65 years	72.3	84.2	2.54	1.97-3.26	82.6	2.05	1.7-2.46
Prior stroke	6.6	11.2	1.73	1.31-2.28	11.2	1.69	1.36-2.1
Prior GI bleed	28	35.8	1.52	1.27-1.82	40.2	1.71	1.49-1.97
Recent MI	0.6	0.9	1.15	0.43-3.07	0.6	0.9	0.38-2.17
HCT < 30%	2.4	4.3	2.8	1.98-3.95	4.0	2.42	1.81-3.24
Scr > 1.5 mg/dl	7.3	16.0	3.0	2.41-3.73	12.7	2.45	2.04-2.94
Diabetes mellitus	29.1	39.7	1.68	1.41-2.0	38.9	1.57	1.37-1.81
HAS-BLED							
Age ≥ 65 years	72.3	84.2	2.54	1.97-3.26	82.6	2.05	1.7-2.46
Prior stroke	6.6	11.2	1.73	1.31-2.28	11.2	1.69	1.36-2.1
Uncontrolled hypertension	3.4	4.6	1.75	1.21-2.53	4.4	1.5	1.1-2.04
Scr > 2.3 mg/dl	1.3	5.4	4.44	3.13-6.31	3.6	3.42	2.5-4.69
Dialysis	1.2	3.8	4.05	2.75-5.98	3.0	3.17	2.25-4.48
Abnormal liver function	3.1	3.8	1.18	0.75-1.86	4.2	1.27	0.9-1.8
Anemia	31.9	53.8	2.52	2.12-3.0	50.0	2.26	1.98-2.59
Any prior bleed	54.7	65.3	1.44	1.21-1.72	69.4	1.62	1.4-1.87
Labile INR	34.4	43.9	1.31	1.1-1.56	45.0	1.32	1.15-1.51
Concomitant NSAIDs or anticoagulants	44.5	51.1	1.46	1.23-1.73	50.3	1.38	1.2-1.58
ATRIA							
Anemia	16.6	34.1	3.0	2.52-3.58	34.1	2.6	2.26-2.99
eGFR < 30 ml/min	3.2	8.1	3.27	2.47-4.33	8.1	2.9	2.29-3.67
Dialysis	1.2	3.8	4.05	2.75-5.98	3.8	3.17	2.25-4.48
Age ≥ 75 years	47	61	2.06	1.72-2.47	61	1.92	1.67-2.21
Any prior bleed	54.7	65.3	1.44	1.21-1.72	69.4	1.62	1.4-1.87
Hypertension diagnosis	76.4	87.5	1.93	1.51-2.47	87.4	1.81	1.5-2.19

**Values are percent patient-years*
Abbreviations: eGFR: estimated glomerular filtration rate; HCT: hematocrit; GI Bleed: gastrointestinal bleed; INR: International Normalized Ratio; NSAIDs: non-steroidal anti-inflammatory drugs; Recent MI: myocardial infarction within previous 3 months; Scr: serum creatinine; Uncontrolled hypertension: most recent systolic blood pressure > 160 mm/Hg; Abnormal Liver Function: chronic hepatic disease or most recent bilirubin 2 times the upper limit of normal, or most recent AST/ALT/alkaline phosphatase > 3 times the upper limit of normal; HAS-BLED anemia: any previous diagnosis of anemia (identified via ICD-9 codes between 280.0 and 285.9); Labile INR: INR values over previous 6 months were in the range of 2-3 less than 60% of the time; ATRIA anemia: most recent hemoglobin < 13 g/dl for men or < 12 g/dl for women

predicts an outcome.

Results

The study cohort consisted of 17,692 patients which comprised 24,402 patient-years of observed follow-up time. The mean age at first study observation was 69 years (range 18-105), and 51% were male. The patient cohort was largely white and non-Hispanic (98%). There were 7,232 patients (29.6%) who had a diagnosis of atrial fibrillation or atrial flutter, which comprised 14,303 patient-years (58.6%).

Out of 851 validated bleeding events, 526 events met the definition of a major bleed, and 325 events met the definition of CRNM bleed. This resulted in an annual event rate of 2.2% major bleeds

per year and 3.5% CRNM or major bleeds per year. There were 474 (56%) gastrointestinal hemorrhages, 136 (16%) intracranial hemorrhages, and 241 (28%) hemorrhages that were not gastrointestinal or intracranial.

The frequency rates of the clinical risk factors included in the HAS-BLED, ATRIA, and OBRI tools that were observed in the Anticoagulation Service population with and without a bleed are compared in Table 2. With the exception of abnormal liver function (HAS-BLED) and recent myocardial infection (OBRI), all clinical factors have strong positive associations with bleeding risk.

The amount of observed time and frequency of events for each bleeding risk score are summarized in Tables 3, 4 and 5. Events per 100 patient-years are equivalent to an annualized event rate. For each risk assessment tool, the event rate increased with increasing risk score with an annualized event rate for major bleeds ranging from 0.71% to 6.4% for OBRI, 0.35% to 13.5% for HAS-BLED, and 0.49% to 9.41% for ATRIA.

The C-index scores generated by HAS-BLED, ATRIA, and OBRI are illustrated in Figure 1 (major bleeds) and Figure 2 (CRNM or major bleeds). All three tools showed similar levels of predictive discrimination with respect to major bleeds with C-indices ranging from 0.71 to 0.75 for all patients and 0.68 to 0.72 for patients with atrial fibrillation or atrial flutter. All three tools predicted bleeds better than chance, and none of the tools outperformed their counterparts to a statistically significant extent.

Discussion

Important differences exist between various bleeding risk assessment tools, specifically regarding which clinical factors are included, how these clinical factors are defined, and how these clinical factors are weighted with respect to bleeding risk. The HAS-BLED tool includes the most clinical factors of the three tools, while the ATRIA tool is the only tool with a sophisticated weighting system based on the effect size of various risk factors. These differences in risk assessment criteria can drastically alter a clinician's perception of bleeding risk depending on the risk assessment

TABLE 3. Event Rates for OBRI Scores

OBRI	Events/PY	Events/100PY	Events/PY	Events/100PY
	Major Bleed		CRNM or Major Bleed	
0	25/3514	0.71	48/3514	1.36
1	135/9029	1.5	217/9029	2.4
2	210/8443	2.49	351/8443	4.16
3	138/3148	4.37	208/3148	6.6
4	17/268	6.4	27/268	10.2

PY: Patient-Year

TABLE 4. Event Rates for HAS-BLED Scores

HAS-BLED	Events/PY	Events/100PY	Events/PY	Events/100PY
	Major Bleed		CRNM or Major Bleed	
0	3/854	0.35	5/854	0.59
1	25/3616	0.69	53/3616	1.47
2	106/7816	1.36	187//7816	2.39
3	189/7748	2.44	304/7748	3.92
4	154/3638	4.23	229/3638	6.3
5	40/669	5.98	63/669	9.42
6	8/59	13.5	9/59	15.2
7	0/24	0	0/24	0
8	0	0	0	0

PY: Patient-Year

FIGURE 2. C-Index for CRNM or Major Bleeds With 95% Confidence Intervals

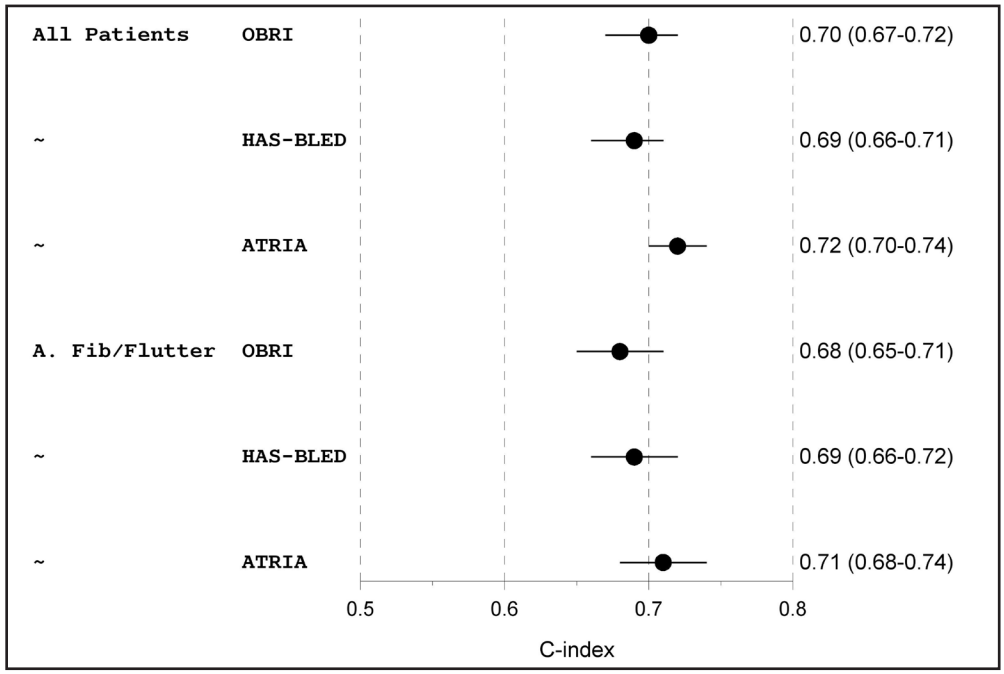

TABLE 5. Event Rates for ATRIA Scores

ATRIA	Events/PY	Events/100PY	Events/PY	Events/100PY
	Major Bleed		CRNM or Major Bleed	
0	9/1855	0.49	17/1855	0.92
1	35/4563	0.77	65/4563	1.42
2	50/4246	1.18	106/4246	2.49
3	46/3245	1.41	73/3245	2.24
4	121/5759	2.1	202/5759	3.51
5	42/1098	3.79	64/1098	5.86
6	43/1074	3.99	66/1074	6.13
7	119/1952	6.11	181/1952	9.27
8	24/171	13.8	28/171	16.2
9	7/122	6.12	11/122	8.74
10	30/317	9.41	38/317	12

PY: Patient-Year

tool they utilize. For example, a patient diagnosed with hypertension that has an estimated glomerular filtration rate < 30 ml/min and a hemoglobin value < 10 could conceivably have an ATRIA score of 7, yet have HAS-BLED and OBRI scores of 1. This suggests clinicians may make more accurate judgements by calculating the risk scores of multiple tools before making clinical decisions rather than relying on any single tool.

Despite the possibility of widely varying scores based on which tool is used, these three risk assessment tools performed similarly in the present analysis of 17,692 patients on warfarin. All three tools performed better than chance, but were only moderately effective at predicting bleeds. A tool that combines the weighting system of ATRIA and includes additional important risk factors from the OBRI and HAS-BLED tools could potentially outperform any currently available tool.

There are both strengths and limitations to our analysis. A key limitation, due to the retrospective nature of our study, was reliance on the accuracy of data previously entered into our electronic health record including ICD-9 codes, patient medication lists, and laboratory values. In addition, we were unable to extract information regarding patient's alcohol use from our electronic health record, which may have impacted the overall performance of the HAS-BLED scoring tool. The major strengths of our analysis included a large sample size, 3.5 year follow-up time, and updated bleeding risk scores throughout the study period. In addition, unbiased patient selection with respect to inclusion of multiple indications for warfarin use provides a more comprehensive view of risk assessment for patients at risk for thromboembolic events.

The current risk assessment tools for bleeding events were created to serve as a rapid way of manually calculating bleeding risk for individual patients. However, with the increasing prevalence of integrated electronic health records and informatics teams, a more sophisticated bleeding risk assessment tool could be electronically calculated and displayed to the clinician. This would facilitate the creation, and pragmatic use, of a more complex bleeding risk assessment tool that could potentially outperform the tools currently available to clinicians. Additionally, the rapid calculation of risk assessment tools via the electronic health record could enable clinicians to view the risk scores of multiple tools efficiently, thus allowing the clinician to quickly identify patients that appear to be low risk according to one tool, while appearing to be high risk according to another tool.

David Baszynski conducted this project during his PGY1 pharmacy residency at Marshfield Clinic. He currently works at Texas Children's Hospital. Kori Krueger is the Medical Director of the Institute for Quality, Innovation, and Patient Safety (IQIPS). Brandon Parkhurst is a family medicine physician at Marshfield Clinic in Marshfield, WI. Richard Berg is a Biostatistician at Marshfield Clinic Research Institute, Biomedical Informatics Research Center in Marshfield, WI. Sara Griesbach is a Clinical Pharmacist at Marshfield Clinic, Clinical Pharmacy Services in Marshfield, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

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Box 1: Definitions of Bleeding Risk Assessment Categories

- OBRI criteria (each worth 1 point towards total score)
  - Age ≥ 65 years old
  - History of stroke
    - ICD 9 codes (rule of 2): '434.01', '434.11', '434.91', '433.01', '433.11', '433.21', '433.31', '433.91'
  - History of GI bleed
    - Any GI bleed ICD-9 (rule of 2); between 530 – 578.9 that includes hemorrhage (exclude negation)' and 578.0' 578.1 and '578.9' (GI bleeding)
  - Recent MI, Hct<30%, CR>1.5, or diabetes mellitus. (1 or a combination of more than 1 counts as 1 point towards total score)
    - MI within last 3 months ICD-9 Codes: (any MI within 3 months)
    - Hct<30% (most recent lab value <30%)
    - Cr>1.5 mg/dl – (most recent lab value >1.5 based on smoothing estimate)
    - Diabetes mellitus – ICD-9 codes: (a diagnosis of DM)
- HAS-BLED criteria (each worth 1 point towards total score)
  - Hypertension (systolic BP >160 mm Hg)
  - For determining hypertension, readings collected under acute distress (i.e. hospitalization, urgent care visit) will be excluded. If 2 of last 6 BP readings are >160, they will be considered to have uncontrolled hypertension. Abnormal renal function (Scr >2.3 mg/dL, chronic dialysis, renal transplantation)
    - Ever been on dialysis (cpt codes between '90935' and '90999')
    - Abnormal creatinine result (creatinine result > 2.3) [most recent value >2.3 based on smoothing estimate)
    - Renal transplant (any of these cpt codes: '50300', '50320', '50323', '50325', '50327', '50328', '50329', '50340', '50360', '50365', '50370', '50380', '50547')
  - Abnormal liver function (chronic hepatic disease, bilirubin >2 x ULN, AST/ALT/alkaline phosphatase >3 x ULN)
    - If any one of the following 5 criteria are met:
      - History of chronic hepatic disease diagnosis (rule of 2) -Identified using ICD 9 codes '571' through '571.99'
      - Abnormal bilirubin – if the bilirubin was > 2.8 for most recent lab
      - Abnormal AST – if the AST was > 3 times the upper limit of normal (>138 for males and > 123 for females) for most recent lab
      - Abnormal ALT – if the ALT was > 3 times the upper limit of normal (>183 for males and > 135 for females) for most recent lab
      - Abnormal Alkaline phosphatase – if the Alkaline phosphatase was > 3 times the upper limit of normal (>375) for most recent lab
  - Stroke (previous history)
    - Identified using the following ICD 9 codes (rule of 2): '434.01', '434.11', '434.91', '433.01', '433.11', '433.21', '433.31', '433.91'
  - Bleeding history or predisposition (anemia)
    - If any one of following 3 criteria are met: