# Pharmacists' Bleed Risk Tool and Treatment Preferences Prior to Initiating Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Cross-Sectional Survey

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## ABSTRACT

**Objective:** To determine pharmacists' preferences in bleed risk tool (BRT) usage and gastroprotection when bleed risk was lower than or equal to stroke risk in patients with nonvalvular atrial fibrillation and who were candidates for oral anticoagulation therapy (warfarin or direct oral anticoagulants [DOACs]).

**Methods:** A survey consisting of 4 domains (demographics, clinical experience, BRT usage, and treatment preferences based on cases where bleed risk was lower than or equal to stroke risk) was developed. The anonymous survey was disseminated via REDCap software to members of the American College of Clinical Pharmacy ambulatory care and cardiology Practice-based Research Networks. Descriptive statistics were calculated for all study variables and inferential statistics were employed as necessary.

**Results:** Of 165 BRT users, 97% preferred HAS-BLED. When bleed risk was lower than stroke risk, 151 respondents chose either DOACs (65%) or warfarin (35%); 15% added gastroprotection. When bleed risk was equal to stroke risk, 141 respondents chose DOACs (50%), warfarin (45%), or aspirin (5%); 40% added gastroprotection.

**Conclusion:** In addition to BRT usage, pharmacists were judicious in their recommendation to add gastroprotection and would consider doing so if there was a specific indication. As more than 80% of extracranial bleeds are gastrointestinal bleeds and most BRTs are nonspecific for predicting these bleeds, randomized, prospective studies stratified by HAS-BLED and stroke risk scores are needed to provide further guidance on the efficacy and safety of oral anticoagulation therapy with or without gastroprotection.

*Keywords:* NVAF; gastroprotection; proton pump inhibitors; warfarin; oral anticoagulants.

Management of patients with nonvalvular atrial fibrillation (NVAF) with oral anticoagulation therapy (OACT) requires constant attention to maintain a balance between preventing strokes and minimizing bleeds. Several validated bleed risk tools (BRTs) available for use in NVAF patients include HAS-BLED, HEMORR$_2$HAGES, ATRIA, and mOBRI.[1,2] A high bleed risk score is not a contraindication to OACT, but, prior to and throughout therapy, bleed risk should be assessed and modifiable risk factors addressed.[3] While intraluminal gastrointestinal (GI) bleeds are not considered a critical bleed site, they are a common complication of chronic OACT and can result in hemodynamic compromise and permanent discontinuation of therapy.[4,5] In 3233 patients with nonvariceal upper GI bleeds (2005-2016), the adjusted odds ratio of hospital admission, transfusion, and re-bleeding while on OACT (warfarin, heparin, or apixaban) was 3.48, 2.53, and 2.26, respectively.[6] Addition of acid-suppressive therapy with a proton pump inhibitor (PPI) or histamine-2 receptor antagonist (H$_2$RA) in NVAF patients at increased risk for upper GI bleeds and receiving OACT may result in fewer bleeds.[7,8]

Pharmacists play an integral part in managing patients on warfarin,[9-11] and data on their role in managing patients receiving direct oral anticoagulants (DOACs) are

increasing.[12-16] Inpatient pharmacists actively participate in multidisciplinary collaborative teams and use clinical decision-support systems or enhanced monitoring to ensure safe prescribing of high-risk medications.[12,15,16] Pharmacist-managed, outpatient-based anticoagulation services in patients on warfarin were associated with lower rates of bleeding and thromboembolic events and lower health care utilization versus routine care.[17] However, it is unclear how pharmacists manage patients who are candidates for OACT but who may be at increased risk for upper GI bleeds. Using a US-based survey, the investigators sought to determine pharmacists' preferences in BRT usage and gastroprotection when bleed risk was lower than or equal to stroke risk.

## Methods

This cross-sectional study was conducted after receiving approval by Nova Southeastern University's Institutional Review Board. The survey consisted of 16 items divided into 4 domains: demographics, clinical experience, use of BRTs, and treatment preferences based on cases where bleed risk was lower than or equal to stroke risk (**Figure 1**). Queries were multiple choice and allowed for free-text input when "Other" was selected. Licensed pharmacists ≥ 18 years of age who routinely provided care to patients with NVAF were eligible to participate in the study. Participants who reported using a BRT (users) completed all study domains, while participants who reported not using a BRT (nonusers) completed domains 1 through 3 only.

An invitation containing the survey link was sent to the American College of Clinical Pharmacy ambulatory care (n = 2237) and cardiology (n = 1318) pharmacists listed in the organization's Practice-based Research Networks. The survey was administered in the United States between April and June 2016 via Research Electronic Data Capture (REDCap) software, a secure Web application for building and managing online surveys designed to support data collection for research studies.[18]

Survey responses were downloaded, and data were analyzed using NCSS 2019 Statistical Software, LLC (Kaysville, UT). Descriptive statistics were calculated for all study variables. Demographic and clinical experience data for the group that used a BRT versus the group that did not were compared using Pearson's chi-square, ANOVA, or the Cochran-Armitage test for trends. Logistic regression with hierarchical forward selection with switching was used to identify predictors of drug selection and use of gastroprotection.

## Results

Of 230 respondents who completed the survey (response rate 6.5%), 165 (72%) used a BRT and 65 (28%) did not. No significant differences were found for age, gender, duration in clinical practice, the percentage of time spent in patient care, or practice specialty between users and nonusers (**Table**). The median age of users was 32 years; 68% were females; the median duration in clinical practice was 6 years; 75% of their time was spent in clinical practice; and clinical settings included ambulatory care, cardiology, and internal medicine. A significant difference was found for practice region between users versus nonusers ($P = 0.014$). Respondents who managed more than 200 NVAF patients per year used a BRT more often than those who managed fewer than 100 NVAF patients per year ($P = 0.001$).

Of those who used a BRT, 97% utilized the HAS-BLED tool (n = 160). The remainder used HEMORR$_2$HAGES (n = 3), ATRIA (n = 1), and mOBRI (n = 1). Reasons for choosing HAS-BLED included "familiarity/ease-of-use," "preference by institution/clinical team," and the fact that it was a "validated tool for NVAF."

When bleed risk was lower than stroke risk, 151 of 165 users (92%) chose a treatment option (**Figure 2**). Of those, 65% chose a DOAC and 35% chose warfarin. Fourteen respondents chose "other" and explained that they "would initiate OACT after weighing patient factors and preferences." When a DOAC was selected, 9% (n = 9) chose PPI co-therapy and 4% (n = 4) chose a H$_2$RA. When warfarin was selected, 13% (n = 7) chose PPI co-therapy and 4% (n = 2) chose a H$_2$RA. Respondents who chose gastroprotection did not provide reasons for doing so, but those who did not add it explained that they "would add gastroprotection only if patient is also on an NSAID or has a history of GI bleed" or cited "patient preference." Specific to warfarin, some respondents would not add gastroprotection, as anticoagulation with warfarin is "easily reversed."

When bleed risk was equal to stroke risk, 141 of 165 users (85%) chose a treatment option (**Figure 3**). Fifty

**Figure 1.** Survey tool. DOAC, direct-acting oral anticoagulant; NVAF, nonvalvular atrial fibrillation.

| **Demographics** | **"Cases"** |
|---|---|
| 1. Please provide your age in years (drop-down menu) | 9. If NVAF patient is a candidate for anticoagulation, and bleed risk score is *less than* stroke risk score, which of the following treatment options would you recommend? |
| 2. Please check your gender<br>    a. Male<br>    b. Female |     a. No treatment<br>    b. Warfarin<br>    c. DOAC<br>    d. Aspirin<br>    e. Aspirin + $P2Y_{12}$ inhibitor<br>    f. Other |
| 3. In which state do you currently practice? (drop-down menu) | |
| 4. Which of the following best describe your specialty?<br>    a. Cardiology Pharmacist<br>    b. Ambulatory Care Pharmacist<br>    c. Internal Medicine Pharmacist<br>    d. Other | 9a. With or without gastroprotection?<br><br>9b. If with gastroprotection, select<br>    a. Proton pump inhibitors<br>    b. Histamine-2 receptor antagonists<br>    c. Other |
| **Clinical Experience** | 10. If NVAF patient is a candidate for anticoagulation, and bleed risk score is *equal to* stroke risk score, which of the following treatment options would you recommend? |
| 5. How many years have you been in clinical practice? (drop-down menu) |     a. No treatment<br>    b. Warfarin<br>    c. DOAC<br>    d. Aspirin |
| 6. About what percent of your time is spent in clinical practice or direct patient care as opposed to non-direct patient care activities, including order verification?<br>    a. % of Time |     e. Aspirin + $P2Y_{12}$ inhibitor<br>    f. Other |
| **Bleed Risk Tool Usage** | 10a. With or without gastroprotection? |
| 7. Do you currently use a risk scoring tool to determine the risk of bleeding in NVAF patients?<br>    a. Yes<br>    b. No (did not view "cases") | 10b. If with gastroprotection, select<br>    a. Proton pump inhibitors<br>    b. Histamine-2 receptor antagonists<br>    c. Other |
| 8. Which scoring tool do you currently use to determine the risk of bleeding in NVAF patients?<br>    a. HAS-BLED<br>    b. $HEMORR_2HAGES$<br>    c. ATRIA<br>    d. Other | |

percent chose DOACs, 45% chose warfarin, and 5% chose aspirin. Logistic regression analysis (outcome DOAC versus warfarin area-under-ROC curve, 0.67) showed that as the number of NVAF patients seen in 12 months increased, respondents were more likely to select a DOAC over warfarin (odds ratio, 1.7; 95% CI, 1.1-2.5). Therefore, for every 50-patient increase per year, the probability of recommending a DOAC increased 1.7-fold.

Of respondents who selected either a DOAC or warfarin, 38% (n = 50) also added gastroprotection (Figure 3). When a DOAC was selected, 34% (n = 24) favored PPI co-therapy and 7% (n = 5) chose a $H_2RA$. When warfarin was selected, 19% (n = 12) favored PPI co-therapy, while 13% (n = 8) chose a $H_2RA$. Rationale for choosing gastropro-

tection, regardless of OACT selection, included "stroke is more devastating, so if patient wants to continue treatment, but knew risks of bleeding were similar, would recommend gastroprotection to help minimize bleeding risk" and "patient-specific consideration." Rationales for not choosing gastroprotection included "would add gastroprotection only if patient is on dual antiplatelet therapy or has another indication"; "in most patients, stroke risk outweighs bleed risk so no need for gastroprotection unless there is a stated reason"; "would use apixaban as has lowest bleeding rate of all DOACs in clinical trials"; and "gastroprotection has not been shown to be beneficial in large scale trials."

Eight respondents chose aspirin because it was "easy and relatively low cost." Twenty-four respondents chose

Table. **Respondent Demographics**

| | Users (n = 165) | Nonusers (n = 65) | P Value |
|---|---|---|---|
| Age, median (IQR), y | 32 (28-38) | 33 (30-38.5) | 0.4[a] |
| Gender | | | |
| Female, no. (%) | 113 (68) | 41 (63) | 0.4[b] |
| Male, no. (%) | 52 (32) | 24 (37) | |
| Practice region, no. (%) | | | |
| Midwest | 66 (40) | 17 (26) | |
| Southeast | 49 (30) | 21 (32) | |
| Northeast | 20 (12) | 19 (29) | 0.014[b] |
| West | 21 (13) | 4 (6) | |
| Southwest | 9 (5) | 4 (6) | |
| Specialties, no. (%) | | | |
| Ambulatory Care | 63 (38) | 24 (37) | |
| Cardiology | 52 (31) | 12 (19) | 0.1[b] |
| Internal Medicine | 34 (21) | 19 (29) | |
| Other | 16 (10) | 10 (15) | |
| Duration in clinical practice, median (IQR), y | 6 (3-11) | 6 (3-15) | 0.4[a] |
| Percent time spent in direct patient care, median (IQR) | 75 (50-90) | 70 (50-82.5) | 0.3[a] |
| NVAF patients seen in a 12-month period, no. (%) | | | |
| Less than 100 | 48 (29) | 33 (51) | |
| 100-199 | 56 (34) | 18 (28) | 0.001[c] |
| 200 or more | 61 (37) | 14 (21) | |

IQR, interquartile range; NVAF, nonvalvular atrial fibrillation.

[a]ANOVA.
[b]Pearson's chi-square.
[c]Cochran-Armitage trend test.

"other" and explained that the choice of OACT depended on patient preference after they had discussed stroke and bleed risk with the patient and/or determined the etiology driving bleed risk.

## Discussion

This is the first national survey exploring US pharmacists' preferences in BRT usage and treatment based on bleed risk. Pharmacists preferred the HAS-BLED tool and considered patient-specific factors and evidence-based data when weighing the risk-benefit of OACT with or without gastroprotective therapy.

Similar to our findings, where three-quarters of pharmacists used a BRT, a recent Medscape/American College of Cardiology (ACC) survey reported that 74% of cardiologists used a BRT (eg, HAS-BLED) always/most of the time or sometimes to assess a patient's overall risk of bleeding prior to initiating DOAC therapy; 27% never or rarely used a bleed risk score before prescribing DOACs.[19] Although reasons for BRT preference were not provided, they may be similar to those reported by our respondents (ie, familiarity/ease-of-use). In both surveys, rationales for not using a BRT were not obtained, but possible reasons include lack of confidence with bleed risk calculators,[20] inconsistent implementation of comprehensive assessments (stroke risk, bleed risk, and medication-related issues prior to decision-making),[21] and nonspecific guideline recommendations.[22]

More recently, a network meta-analysis found that HAS-BLED and HEMORR$_2$HAGES had modest but balanced sensitivity (defined as the ratio between the number of major bleeding events in high-risk stratification and the total

**Figure 2.** Pharmacists' treatment preferences if bleed risk is less than stroke risk (n = 151). Data of 14 pharmacists are not included in figure, as they chose "other" treatment.

DOAC, direct-acting oral anticoagulant (apixaban [n = 66]; rivaroxaban [n = 25]; other [n = 7]); PPI, proton pump inhibitor; $H_2RA$, histamine-2 receptor antagonist.

number of bleeding events) and specificity (defined as the ratio between the number of nonmajor bleeding events in the low-risk population and total nonbleeding events) for predicting major bleeding events.[2,3] Several respondents did comment that, although HAS-BLED was imprecise and only studied with warfarin, it was necessary to identify bleed risk in a patient starting a high-risk medication, and that the ACC anticoagulation application uses HAS-BLED with $CHA_2DS_2VASc$ along with clinical trial data to estimate stroke risk and bleed risk, with projected risk reduction (strokes) and risk increases (bleeds) expected with each treatment (www.acc.org/tools-and-practice-support/mobile-resources/features/anticoag-evaluator). The 2019 AHA/ACC/HRS atrial fibrillation guideline recommends that HAS-BLED scores be used to assess bleed risk in patients for whom anticoagulation is being considered, and that the need for and choice of OACT should be periodically reevaluated to reassess stroke and bleed risks.[23]

Although more than 80% of extracranial bleeds are GI bleeds,[24] most BRTs are nonspecific for predicting GI bleeds. Indeed, one respondent used a spreadsheet with several BRTs to maximize treatment guidance for patients with multiple risk factors for strokes and bleeds. A comprehensive approach to determining factors that increase bleed risk should be adopted. These factors include age (HAS-BLED, $HEMORR_2HAGES$, mOBRI, ATRIA); anemia (mOBRI, $HEMORR_2HAGES$, ATRIA); hepatic/renal disease (HAS-BLED, $HEMORR_2HAGES$, ATRIA, mOBRI); concomitant medications/alcohol use, including NSAIDs, corticosteroids, and antiplatelet therapy (HAS-BLED, $HEMORR_2HAGES$); bleed history/rebleeding risk

(HEMORR$_2$HAGES, HAS-BLED, ATRIA); and GI bleeds (mOBRI).[1,2] Additional risk factors for GI bleeds include being a tobacco smoker and/or being infected with *Helicobacter pylori*. A prospective cohort study that analyzed data from questionnaires completed by 99,359 individuals from the Copenhagen General Population Study reported that the multivariable adjusted hazard ratio for current smokers versus never smokers was 2.20 (95% CI, 1.84-2.62) for GI bleeds.[25] Presence of *H pylori* should be investigated, with a subsequent eradication regimen implemented, as patients with warfarin-associated upper GI bleeds who were *H pylori*-positive had lower HAS-BLED scores versus those who were negative.[26]

When bleed risk was lower than stroke risk (eg, HAS-BLED < 3, $CHA_2DS_2VASc \geq 1$), respondents appropriately initiated therapy with an OAC (predominantly apixaban); a small proportion also added gastroprotection. If the patient did not have any other GI bleed risk factors (eg, a previous GI bleed or on chronic antiplatelet or NSAID therapy), the choice of OACT depended on the attributes of each OAC and patient preference.[27] Selection of warfarin was appropriate if cost, formulary restrictions, and availability of an inexpensive reversal agent were important concerns to patients and/or their health care providers. Rivaroxaban was selected because of its once-daily dosing and low risk for GI bleeding.

The recently published ARISTOPHANES study provides evidence that apixaban is an appropriate choice in patients with a HAS-BLED score < 3. In this retrospective observational study, more than 70% of patients received standard doses of DOACs (apixaban 5 mg, dabigatran 150 mg, or
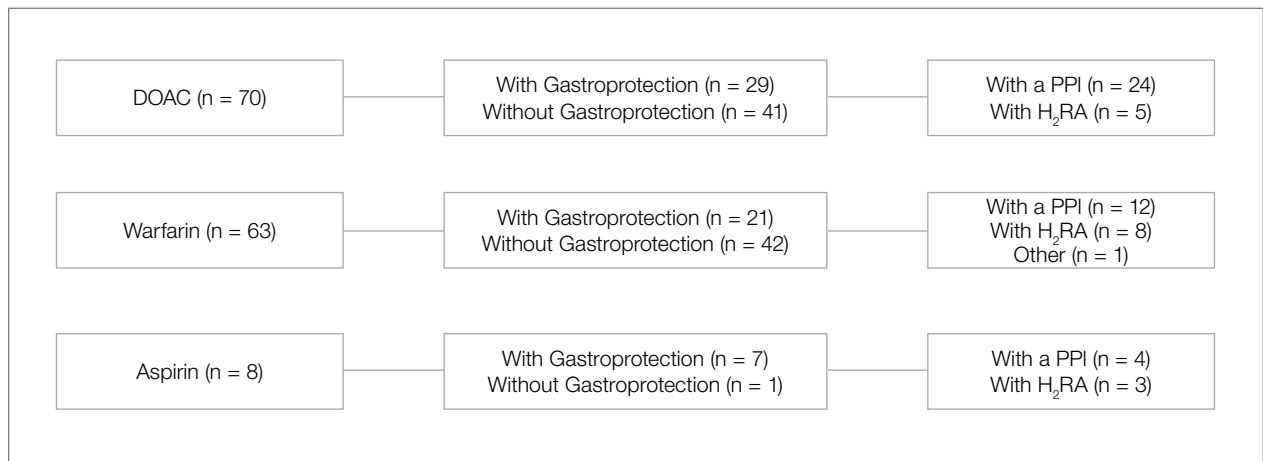
**Figure 3.** Pharmacists' treatment preferences if bleed risk is equal to stroke risk (n = 141).

Data of 24 pharmacists are not included in figure, as they chose "other" treatment. DOAC, direct-acting oral anticoagulant (apixaban [n = 56]; rivaroxaban [n = 11]; other [n = 3]); PPI, proton pump inhibitor; $H_2RA$, histamine-2 receptor antagonist.

rivaroxaban 20 mg) and about 20% had a bleeding history, about 30% were on PPIs, less than 25% were on NSAIDs, and about 40% had a HAS-BLED score < 3. The study found that apixaban was more effective (reduced rates of ischemic or hemorrhagic strokes/systemic embolism) and safer (reduced rates of major GI bleed or intracranial bleed) than warfarin.[28] Dabigatran and rivaroxaban were also more effective than warfarin for stroke prevention and had a lower risk for major intracranial bleed risk; while the risk of major GI bleed was similar between dabigatran and warfarin, major GI bleed risk was higher for rivaroxaban. When compared with each other, the 3 DOACs were effective at stroke prevention, with apixaban more effective than dabigatran and rivaroxaban; similar efficacy was noted for dabigatran versus rivaroxaban. Apixaban was associated with fewer GI bleeds versus dabigatran and rivaroxaban, but with similar intracranial bleed risks; dabigatran was associated with fewer GI bleeds but similar intracranial bleed risks versus rivaroxaban.[28] Efficacy and safety findings from a subgroup analysis based on HAS-BLED scores < 3 and ≥ 3 were generally consistent with the main results.

When bleed risk was equal to stroke risk, the difficulty was determining how OACT in a patient at high stroke risk ($CHA_2DS_2VASc$ score ≥ 2) and high bleed risk (HAS-BLED score ≥ 3) should be managed. Eight respondents chose aspirin and added gastroprotection with either a PPI or $H_2RA$; however, currently, aspirin is not recommended as the sole

antithrombotic for patients with NVAF.[23] With the OACT, an interesting finding was that as the number of patients seen in 12 months increased, pharmacists were almost twice as likely to select a DOAC over warfarin. Moreover, pharmacists were judicious in their recommendation to add gastroprotection, and would consider doing so if there was a specific indication. At the time of our survey, several studies described DOAC-associated GI bleeds,[29-31] but data on the effectiveness of acid-suppressive therapy, specifically with PPIs, in the prevention of upper GI bleeds were sparse.[4,7,32] Respondents most likely were familiar with GI bleed risk factors and prevention strategies from various guidelines published between 2009 and 2010, which did not include DOACs.[33-35]

Another important finding was pharmacists' uncertainty as to the effectiveness of PPIs in preventing GI bleeds in combination with DOACs. The data are conflicting. A meta-analysis of older studies (2007-2015) showed that PPIs (but not $H_2RAs$) reduced the risk of upper GI bleeds in patients on warfarin but not for dabigatran.[36] A retrospective cohort study of Medicare beneficiaries on OACTs (2011-2015) showed the adjusted incidence of hospitalization for upper GI bleeds in patients on PPI co-therapy was significantly lower compared with patients not on PPI co-therapy (76 versus 115 per 10,000 person-years, respectively).[8] Apixaban without PPI co-therapy was associated with the lowest risk of upper

GI bleed hospitalizations (73/10,000 person-years), and PPI co-therapy further reduced this risk (49/10,000 person-years). Warfarin without PPI co-therapy was associated with the next lowest risk (113/10,000 person-years), followed by dabigatran (120/10,000 person-years) and rivaroxaban (144/10,000 person-years). PPI co-therapy significantly reduced the risk of upper GI bleed hospitalizations with all OACTs, but the incidence of upper GI bleed hospitalizations with rivaroxaban was significantly greater than with the other OACTs.[8] Therefore, if there are concerns about the safety of PPIs,[37-39] or the patient is unable to tolerate a PPI, then apixaban may be the most appropriate DOAC for a patient with high bleed risk. Notably, a 2020 review of data from the PINNACLE registry (average age, 75-77 years; 31% on PPIs) found that the relative GI bleed safety advantage of apixaban and dabigatran versus warfarin was attenuated in patients ≥ 75 years.[40] Last, since the risk for lower GI bleeds is not reduced by PPIs,[41] consideration of their use should be accompanied by an assessment to detect bleeds (eg, low hemoglobin/hematocrit, presence of bright red blood, hematochezia/melena, fecal occult testing), with prompt management as necessary.[5]

### *Limitations*

Limitations of our survey included an overall low response rate, which can generate a biased sample if respondents are systematically different from nonrespondents. In addition, to maintain simplicity and reduce respondents' time commitment, our survey did not include actual $CHA_2DS_2VASc$ stroke risk scores, HAS-BLED bleed risk scores, or specific GI bleed risk factors when querying pharmacists about treatment options based on bleed risk. The addition of these variables would have improved the robustness of the data.

### Conclusion

In addition to applying BRTs in the management of NVAF patients, pharmacists considered patient-specific variables, prescriber preferences, and evidence-based guidance when recommending OACT with or without gastroprotection. To avoid suboptimal patient management, busy pharmacists should be granted time to attend continuing education programs describing optimal OACT selection and formulation of individualized, evidence-based plans to address modifiable risk factors for bleeding, including the appropriate use of gastroprotection. Randomized, prospective, long-term studies stratified by HAS-BLED and $CHA_2DS_2VASc$ scores are needed to further clarify efficacy, safety, and cost-effectiveness of OACT, with and without PPIs, in patients who may be at risk for upper GI bleeds.

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