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FEATURE ARTICLE

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Bleeding Risk of Direct Oral Anticoagulants Compared With Warfarin in Patients With Nonvalvular Atrial Fibrillation

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ABSTRACT: Differences in the major bleeding risks between the direct oral anticoagulants (DOACs) and warfarin in patients with nonvalvular atrial fibrillation (NVAF) have been reported in the literature. This article summarizes and highlights these findings. Dabigatran may have an increased risk of gastrointestinal (GI) tract bleeding but a lower risk of intracranial hemorrhage (ICH), with equal rates of all-cause mortality compared with warfarin. Rivaroxaban may have an increased risk of GI bleed and ICH, with evidence of an increased risk of major bleeding and all-cause mortality compared with the other DOACs and warfarin. Apixaban has consistently shown to have an equal or lower risk of major bleeding compared with rivaroxaban and warfarin.

KEYWORDS: Major bleeding, anticoagulation, apixaban, rivaroxaban, dabigatran, warfarin, intracranial hemorrhage, nonvalvular atrial fibrillation, gastrointestinal bleed

Atrial fibrillation is becoming more prevalent in the United States, with a lifetime incidence of approximately 1 in 4 after the age of 40.[1] The morbidity of stroke is one of the leading strains on the US health care system, and approximately 15% to 20% of stroke events are directly linked to atrial fibrillation.[2] To combat the increased risk of stroke, the approach to antithrombotic therapy in patients with atrial fibrillation (AF) has been evolving in the last decade since the advent of novel anticoagulants. An increasing number of patients with AF are being treated with the direct oral anticoagulants (DOACs) rather than with older vitamin K antagonists (VKAs) such as warfarin. Determining which antithrombotic therapy is the most effective and safest for each patient is essential for clinicians, since significant risks are associated with the different drugs.

According to large, multicenter, pharmaceutical industry–funded trials such as RE-LY,[3] ROCKET AF,[4] and ARISTOTLE,[5] dabigatran, rivaroxaban, and apixaban have all shown either noninferiority or superiority to VKAs in cerebrovascular accident (CVA) prevention in patients with nonvalvular atrial fibrillation (NVAF). As a result, several guidelines have been developed supporting the use of DOAC therapy without clearly discerning the individual risks of the 3 DOACs in relation to one other. These large trials focused only on patients with NVAF, essentially excluding patients with valvular disorders who already would be at high risk for stroke, systemic embolism, or major bleeding as a result of anticoagulation.[6,7] Major bleeding—as identified in literature as fatal bleeding, major organ bleeding, or bleeding resulting in a drop in hemoglobin of more than 2 g/dL or requiring blood transfusion—is the most concerning adverse effect in this medication category.[7] Accordingly, the aim of this review is to discuss the specific risks of major bleeding with use of DOAC therapy in patients being treated for NVAF.

PRESCRIBING PRACTICES

A 2014 study looked at changing prescribing practices in the United States by analyzing insurance data for patients being treated for NVAF.[8] DOACs accounted for 62% of all new prescriptions of anticoagulants for the treatment of NVAF. However, patients with higher $CHADS_2$ (for predicting the risk of stroke in patients with AF) and HAS-BLED (for assessing the 1-year risk of major bleeding in patients taking anticoagulants with AF) scores, who were female, and with lower household income had a lower rate of being prescribed DOACs.[8] Despite the increasing prevalence of DOAC use, patients with a $CHADS_2$ score of 2 or higher were predominantly prescribed warfarin.[8] The lower than expected prescription rate in this 2014 study could be explained by the uncertainty and novelty of the DOAC medications at the time of the trial. The lack of availability (whether in the market or in hospital settings) of reversal agents for novel anticoagulants is a likely reason for the inverse relationship between DOAC prescriptions and higher $CHADS_2$ and HAS-BLED scores in the United States.[8]

A 2017 prospective cohort study in Australia looked at whether oral anticoagulation rates had changed since the DOACs had become available.[9] The researchers found that in patients with

AF, rates of oral anticoagulation initiation increased with DOAC availability, suggesting that prior to DOAC availability many patients had been suboptimally treated. This study also found that patients with a higher CHA_2DS_2VASc (the revised version of $CHADS_2$) score and equal bleed risk were being started on DOACs over VKAs, suggesting that over time, more experience with these drugs has led to increased prescribing of them.[9] A different 2017 study in Denmark identified approximately 52,000 patients with NVAF and found that patients with a history of prior cardioembolic stroke were 35% more likely to be started on DOACs rather than VKAs.[10]

Cost and prescription coverage are major factors that often influence prescribing patterns and the decision to choose name-brand drugs such as DOACs versus VKAs. Thirty-day out-of-pocket expenses for DOACs can range from $300 to $400 compared with closer to $5 for warfarin.[11] A large benefit of DOACs in terms of cost is that they do not need drug monitoring with laboratory testing, in contrast with warfarin, where the international normalized ratio (INR) is monitored weekly to monthly in most patients. A 2013 pharmaceutical review evaluated the lifetime cost and quality-adjusted life-years between DOACs and warfarin.[12] After analyzing major bleeding events, hospitalizations, adverse effects, drug costs, and drug monitoring, the study concluded that DOACs were cost-effective when compared with warfarin, and that apixaban provided the highest estimated quality-adjusted life-years.[12]

DABIGATRAN

Dabigatran is the only direct thrombin inhibitor among the DOACs. Dabigatran gained Food and Drug Administration approval in 2010 after the large, multicenter, pharmaceutical industry–funded RE-LY[3] and RE-COVER[13] trials showed comparable results with warfarin in the treatment of NVAF and venous thromboembolism (VTE). The benefits of prescribing dabigatran are that INR does not need to be monitored, dosage does not need to be adjusted, and a reversal agent, idarucizumab, is on the market. The drug is primarily renally excreted and as a result should be used with caution in patients with decreased renal function.[14]

The RE-LY trial compared dabigatran at 2 different doses, 110 mg twice a day or 150 mg twice a day.[3] The study yielded significant results in that 110 mg of dabigatran had equal cardioembolic stroke occurrence rates and lower overall major bleeding compared with warfarin. Higher-dose dabigatran (150 mg) had lower rates of cardioembolic stroke and similar rates of major bleeding compared with warfarin.[3] Dabigatran 150 mg twice daily had an overall lower mortality rate compared with warfarin and dabigatran 110 mg twice daily, which is why it is currently the approved dosage in the United States.[3] Despite the decrease in mortality, dabigatran 150 mg twice daily had a higher rate of gastrointestinal (GI) bleeding compared with warfarin.[3,15] A similar conclusion of higher rates of GI bleed with dabigatran use compared with warfarin use was found in a meta-analysis looking at DOAC bleeding risk in the elderly.[16]

In another meta-analysis, 5 phase-3 clinical trials of dabigatran and warfarin were compared, including the RE-LY trial and 4 other large trials looking at dabigatran use in VTE treatment.[15] From the analysis of the 5 trials enrolling more than 27,000 patients, the researchers found no statistical difference in major bleed rates between dabigatran and warfarin groups, but they did find that patients who were treated with dabigatran required more blood transfusions overall. Inversely, they concluded from data analysis that of the patients who had major bleeding episodes, 30-day mortality and intensive care unit stays were lower with dabigatran.[15] An important note is that these trials were conducted before idarucizumab, a reversal agent for dabigatran, had been approved for the market.

A large 2016 trial used 2 nationwide reporting registries in Norway to analyze 32,000 patients taking oral anticoagulation between January 2013 and June 2015.[17] Dabigatran had lower rates of major bleeding than warfarin and rivaroxaban and equal rates to apixaban. Furthermore, the researchers compared specific forms of major bleeding and found dabigatran to have a lower risk of intracranial hemorrhage (ICH) but a higher risk of GI bleed compared with apixaban or warfarin.[17]

A recently published meta-analysis used 23 randomized controlled trials (RCTs) involving approximately 95,000 patients to compare the efficacy, safety, and cost-effectiveness of DOACs.[18] Dabigatran dosed at 150 mg twice daily was found to have equal rates of major bleeding compared with warfarin and rivaroxaban but higher rates compared with apixaban. Looking into this difference, the researchers further found that the risk of GI bleed was also significantly higher with dabigatran compared with other DOACs and warfarin. Although this was a large study pooling data from several clinical trials, the data were from indirect comparisons between the DOACs rather than from head-to-head trials.[18] Therefore, although dabigatran was comparable in effectiveness in preventing thrombotic events in patients with NVAF, this study showed significant differences when comparing safety.

RIVAROXABAN

Rivaroxaban is a direct factor Xa inhibitor that was approved for the United States market in 2011. ROCKET AF, a large, double-blind, multicenter trial, compared once-daily rivaroxaban with warfarin in the treatment of NVAF.[4] The trial showed rivaroxaban to be noninferior to warfarin in the prevention of stroke, but it also showed clinically significant differences in bleeding outcomes. Rivaroxaban showed a higher incidence of decreases in hemoglobin by 2 g/dL and required more transfusion events overall, but it had fewer clinically significant fatal bleeding events and bleeding at critical anatomical sites than did warfarin.[4] Overall, the study results showed that rivaroxaban caused more major bleeding events but did not decrease mortality.

A 2018 post hoc analysis used data from the ROCKET AF trial to look for differences in outcomes in patients with NVAF and carotid artery disease (CD).[19] The authors noted that patients with CD had a higher overall $CHADS_2$ score, had more frequent stroke events, and had a higher rate of major bleeding events compared with patients without CD. However, within this cohort, patients being treated with warfarin instead of rivaroxaban had no statistically significant differences in all endpoints, including major bleeding.[19]

A 2016 retrospective cohort study compared major bleeding rates associated with DOACs and found rivaroxaban and warfarin to have higher risks of major bleeding compared with apixaban.[20] Similar data were seen in a 2017 meta-analysis, showing that daily rivaroxaban 20 mg and warfarin presented an equal risk of major and clinically relevant bleeding.[18] Subgroup analysis of the data showed a lower risk for ICH with rivaroxaban but a significantly higher risk of GI bleeding.[18] This finding of increased GI bleeding risk was not isolated to this study alone. A large 2016 study in Norway using unique patient data showed that rivaroxaban had a higher risk of GI bleeding compared with warfarin.[17]

Two large European and Taiwanese retrospective registry cohort studies compared major bleeding rates between the DOACs and showed similar rates of major bleeding between warfarin and rivaroxaban but significantly lower rates in dabigatran and apixaban.[21,22] A large 2018 European prospective open-cohort study showed an overall increase in all-cause mortality in patients taking rivaroxaban compared with warfarin.[23]

In several of these studies, ICH risk among rivaroxaban was significantly lower compared with warfarin and was equal to that of the other DOACs.[17,19,21] It appears that rivaroxaban may have an equal rate of major bleeding compared with warfarin. However, in comparison with the other DOACs, rivaroxaban may predispose to higher risks of GI bleeding while having an overall comparable risk of ICH.

APIXABAN

Apixaban, also a direct factor Xa inhibitor, was approved in the United States in 2012 after the ARISTOTLE trial.[5] ARISTOTLE looked at more than 18,000 patients and compared the efficacy of reduction in CVA rates and safety of apixaban to warfarin. Major bleeding was the primary safety outcome, and the investigators observed a significant decrease in major bleeding events in the apixaban arm of the study, with a hazard ratio of 0.69 (CI, 0.60-0.80; $P<0.001$).[5]

A 2017 meta-analysis found that of the 3 DOACs, apixaban had a lower rate of overall major bleeding compared with warfarin, whereas the other 2 were comparable. Exploring further, the authors also noted that GI bleed and ICH rates were lower with apixaban compared with warfarin.[18] When comparing apixaban to the other DOACs, 2 large retrospective cohort studies in the United States found apixaban to have a significantly lower risk of major bleeding

compared with warfarin and rivaroxaban.[2,24] In certain patients in whom VKAs were not suitable, a double-blind RCT showed favorability of apixaban in reduction of cardioembolic stroke and nonsignificant differences in major bleeding risk between apixaban and aspirin therapy.[25]

A more-focused meta-analysis used data from 5 RCTs that compared apixaban's adverse events and found an overall reduced risk of major and clinically relevant nonmajor bleeding with apixaban compared with VKAs (relative risk, 0.60).[26] However, it is important to note that differences in major bleeding alone were not statistically significant, and that the predominant patient data from this study came from the ARISTOTLE trial.[26]

A 2018 retrospective observational cohort study conducted in the United States compared major bleeding outcomes in patients on warfarin versus apixaban 5 mg or 2.5 mg twice daily in patients with NVAF.[27] When matching patients for similar comorbidities and CHA_2DS_2-VASc and HAS-BLED scores, both the 5-mg and 2.5-mg apixaban groups had lower risks of major bleeding within 1 year of initiating treatment compared with warfarin.[27]

A separate 2018 retrospective cohort study in Taiwan showed similar findings of all 3 DOACs having lower overall major bleeding risks compared with warfarin.[22] However, the investigators found standard doses of apixaban 5 mg twice daily to have significantly lower major bleeding compared with dabigatran 150 mg twice daily and rivaroxaban 20 mg daily.[22] A large 2018 European prospective cohort trial showed apixaban to have a decreased risk of major bleeding and ICH compared with warfarin and rivaroxaban, although apixaban and warfarin had comparable rates of all-cause mortality.[23]

The largest study to date comparing the safety profiles of the DOACs was the 2018 ARISTOPHANES study, which was a retrospective observational study involving more than 280,000 patients in the United States.[28] In the study, comparisons were made between DOACs and warfarin and between the DOACs themselves in patients with NVAF. The study showed apixaban and dabigatran to have lower rates of major bleeding compared with warfarin, with the inverse being true for rivaroxaban. All 3 DOACs had lower rates of ICH and hemorrhagic stroke, but rivaroxaban was shown to have higher rates of GI bleeding compared with warfarin. Comparisons between the DOACs showed apixaban to have a lower rate of major bleeding compared with dabigatran and rivaroxaban, while dabigatran had a statistically significant lower rate of major bleeding compared with rivaroxaban. In terms of mortality, all DOACs had lower rates compared with warfarin; however, the mortality rate of apixaban was significantly lower than that of dabigatran and rivaroxaban when compared directly.[28]

DISCUSSION

The current AF guidelines from the American Heart Association (AHA) were published in 2014, and although they make no significant recommendations among the 3 DOACs, they do recommend starting a DOAC for patients who are unable to maintain a therapeutic INR.[29] The American College of Chest Physicians (ACCP) published its guidelines in 2018 and recommended the use of DOACs over warfarin in patients with NVAF—a change from the 2012 ACCP recommendations, which equated DOACs with warfarin.[30] The Canadian Cardiovascular Society (CCS) made recommendations in 2016, stating that in patients with a $CHADS_2$ score greater than 1, DOACs are recommended over warfarin unless contraindicated.[31]

Each of the DOACs are all at least noninferior in terms of cardioembolic stroke incidence reduction. For dabigatran, there appear to be inconsistent data in terms of major bleeding rates in the studies discussed. What seems to be common from the literature reviewed is that in patients taking dabigatran 150 mg twice daily, there is likely an increased risk of GI bleed but a decreased risk of ICH compared with warfarin.[14,15,18] Similar evidence was found for rivaroxaban, studies of which showed parallel data with higher rates of GI bleed but lower rates of ICH compared with warfarin.[17,18,20,28] Other studies have shown comparable major bleeding rates compared with warfarin but overall higher rates compared with dabigatran and apixaban.[20-22,28] For apixaban, several studies showed an overall equal to lower rate of major bleeding, including GI bleed and ICH compared with warfarin and rivaroxaban.[2,18,22,24,26-28] For all three DOACs, there is evidence showing overall decreased risk of ICH compared with warfarin, which likely contributes to the overall decreased risk of mortality when using these agents.[28]

CONCLUSION

The aim of this article is not to make recommendations on specific DOACs over others but to highlight the common findings from the larger studies pertaining to antithrombotic therapy for NVAF. Among the 3 DOACs, apixaban has consistently shown a comparable to lower rate of major bleed risk compared with the other DOACs and with warfarin.

The major drawback to this area of research is the lack of head-to-head controlled trials comparing the DOACs directly. Most of the data used in drawing comparisons between the drugs are from post hoc analyses of individual DOACs compared with warfarin trials or from retrospective cohorts and meta-analyses. The caveat to much of the US trial data is that the studies controlled for patients with renal disease and higher CHA_2DS_2VASc and HAS-BLED scores, which overall may misrepresent these drugs as options for the patient population.

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