



Updates in Hospital Medicine

Updates in Hospital Medicine: Anticoagulation

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UPDATE I

Apixaban has a lower bleeding risk than rivaroxaban for acute venous thromboembolism

Hospitalists frequently treat acute venous thromboembolism (VTE), both as admitting diagnoses as well as secondary diagnoses for patients admitted for other reasons. Immediate anticoagulation is indicated for the treatment of VTE to prevent progression and secondary complications. Direct oral anticoagulants (DOACs) are currently recommended as first-line therapy for VTE over Vitamin K antagonists due to a safer profile, equal efficacy, and increased convenience.^{1,2}

Current VTE guidelines do not recommend the use of one DOAC over another despite a signal that apixaban may have a lower gastrointestinal bleeding risk.¹⁻³ The recent Comparison of Bleeding Risk between Rivaroxaban and Apixaban (COBRRA) trial by Castellucci et al. is the first trial to directly compare the bleeding risk of DOACs when used for treatment of acute VTE.³ The COBRRA trial was an international, prospective, randomized, open-label, blinded endpoint study conducted in Canada, Australia, and Ireland. Adult patients with symptomatic VTE were randomly assigned to receive either three months of apixaban (10mg twice daily for 7 days followed by 5mg twice daily) or rivaroxaban (15mg twice daily for 21 days followed by 20mg daily).

The primary outcome of the study was a composite of “clinically relevant bleeding”, including major bleeding (defined by the International Society of Thrombosis and Hemostasis as one of the following: bleeding into a critical area, a 2 g/deciliter drop in hemoglobin, requirement of 2 units of blood transfusion, or death) or clinically rel-

evant non-major bleeding (defined as one of the following: required medical intervention, led to hospitalization or increased level of care, or prompted in-person evaluation by health care professional). Secondary outcomes included recurrent symptomatic VTE within 3 months of anticoagulation initiation.

After randomization, 1345 patients received apixaban and 1355 patients received rivaroxaban. The mean age was 58 years, 44% were female, and 10% self-reported non-White race. The composite outcome of clinically relevant bleeding was significantly lower in the apixaban group (3.3%) than in the rivaroxaban group (7.1%) (relative risk, 0.46; 95% CI, 0.33 to 0.65; $P < 0.001$). Furthermore, both major and nonmajor bleeding outcomes were lower in the apixaban group than in the rivaroxaban group (0.4% vs. 2.4% for major bleeding and 2.9% vs. 4.9% for nonmajor bleeding, respectively). The higher bleeding rate in the rivaroxaban group was most pronounced during the first 3 weeks after initiation, which may be explained by its 21-day loading period. Importantly, the efficacy of the DOACs was equivalent, with symptomatic recurrent VTE occurring in 1.1% of patients in the apixaban group and 1.0% in the rivaroxaban group during the 3-month study period.

Limitations of this study include a lower medication adherence rate in the apixaban group (66%) than in the rivaroxaban group (75%). Although the recurrence rate of VTE was similar in both groups, the study was not powered to detect statistically significant differences in recurrent VTE rates. Of note, patients with cancer-associated VTE, concomitant severe liver dysfunction, and body weight greater than 120 kg were not included, prompting the need for further studies to include these populations.

Take-away: Apixaban presents a significantly lower risk of clinically relevant bleeding than rivaroxaban in patients receiving treatment for acute symptomatic VTE, particularly during rivaroxaban's loading dose period, and thus should be used by hospitalists as first-line therapy for most patients.

UPDATE 2

Patients on direct oral anticoagulants for atrial fibrillation need to be highly adherent to avoid stroke

Patients hospitalized with cardioembolic stroke due to atrial fibrillation (AF), despite being prescribed oral anticoagulation (OAC), present a unique challenge to hospitalists and neurologists (see 'Update 3' below).⁴ It is well-known that AC adherence is difficult and that non-adherence is associated with worse outcomes.⁵ However, it is less clear exactly how adherent patients need to be in the real world to achieve their desired health outcomes, which in AF includes stroke avoidance.

In research, this metric is often referred to as an "adherence threshold," typically expressed as a proportion of days covered (PDC).⁶ Every individual medication, along with the desired clinical outcome, has a different PDC, expressed as 0-100% or 0.0-1.0 (ratio). The adherence threshold of 0.8 is commonly used for OAC and AF; i.e., a patient needs to take OAC $\geq 80\%$ of the time to avoid stroke.⁷ However, this has not been rigorously validated, and preliminary evidence suggests it should be set even higher.⁸

The focus of this review, Safari et al. aimed to identify optimal adherence thresholds for OAC in patients with AF, according to pharmacologic agent.⁹ Province-wide (British Columbia, Canada) outpatient, inpatient, and pharmacy records from 1996-2019 were used to identify an incident cohort of adults with non-valvular AF who were new OAC users. These 44,000 patients were followed until the study period ended, or until they had a study outcome of interest: primary outcomes included stroke or systemic embolism (SSE) or composite SSE, TIA, or death. Patient covariates included age, sex, SSE risk score, bleeding risk score, co-morbidities, socioeconomic status, and polypharmacy, among others. PDCs were calculated for the 90 days prior to the occurrence of an outcome based upon fill history, and in the case of vitamin K antagonist (VKA) was further adjusted by a validated model.

Optimal adherence thresholds were defined by the authors as the PDC cut-offs at which the outcome risk diverged the most starkly above and below them. The authors used categorical modeling to determine these optimal thresholds for both direct OAC (DOAC) and VKA dosing.

Results revealed that the optimal adherence thresholds for both DOACs (0.9 across all outcomes) and VKAs (0.9 or 0.95 depending on outcome) were higher than previously reported in the literature. Interestingly, the optimal adherence threshold for DOACs had more clinical importance than for VKAs. As an example, for DOACs, adherence above the 0.9 threshold yields a hazard ratio of 0.48 for ischemic stroke compared with adherence below the threshold. Alternatively, for VKAs, the same comparison yielded a hazard ratio of 0.91, which was not statistically significant.

These results strongly suggest that OAC adherence thresholds should be recalibrated to ≥ 0.9 (i.e., 90% of doses). The clinical significance of adherence is particularly important for DOACs as compared to VKAs. For example, missing greater than one dose of rivaroxaban in a 10-day stretch would put your patient at significantly higher risk of ischemic stroke. The clinical insignificance of the optimal adherence threshold for VKAs may be related in part to their more complex pharmacodynamics and longer duration of effect.

Limitations associated with this retrospective administrative data set include the fact that hazard ratios for outcomes are associations rather than causations. Additionally, using the OAC fill history as a metric for adherence is imperfect because picking up a medication does not necessarily mean it was consumed.

Take-away: Hospitalists should invest time counseling their patients with atrial fibrillation on OACs regarding the importance of adherence. Missing more than one of ten doses increases a patient's risk of stroke, most dramatically for patients on DOACs.

UPDATE 3

No evidence to support changing oral anticoagulant therapy after a breakthrough stroke

Prophylaxis against acute ischemic events in patients with atrial fibrillation (AF) remains one of the main pillars of management, specifically with oral anticoagulation (OAC). Direct oral anticoagulants (DOACs; apixaban, rivaroxaban, edoxaban, dabigatran) have become the first-line therapy for stroke prevention in patients with AF, demonstrating equivalent efficacy and reduced risk of major bleeding compared with traditional vitamin K antagonists (VKAs).¹⁰ Despite the improved outcomes, recurrent ischemic events may occur, which leaves the clinician with the dilemma of selecting an optimal anticoagulation strategy when the initial strategy may have failed.

In the event of a secondary ischemic event, traditional causes of recurrent events should be investigated. These include patient adherence to the anticoagulant (see 'Update 2' above), drug-drug interactions, appropriate dosing of the medication, and other contributing risk factors for ischemic stroke.^{9,11} When all these potential reasons

are ruled out, clinicians are left with the clinical question of continuing OAC, changing to an alternative OAC agent, or intensifying treatment.

There is a paucity of high-quality data supporting any of the previously mentioned treatment strategies; however, the standard of care for many providers has been to switch to an alternative OAC, often with a different mechanism of action (e.g., a factor Xa inhibitor to a direct thrombin inhibitor or a VKA). The focus of this review, the ASPERA study by D'Anna et al., aimed to investigate whether continuation of current DOAC was noninferior to switching OAC agents, with both a retrospective arm (ASPERA-R)⁴ and a prospective 5-year outcome arm (ASPERA-P, currently ongoing). The ASPERA-R study included consecutive adult patients with AF and ischemic stroke while on DOAC therapy from 35 stroke centers from 9 European and North African countries over the time span of 2020 to 2025.⁴ Investigators utilized an emulated trial design to apply randomized clinical trial criteria to this retrospective cohort study. Patients were grouped according to one of two treatment strategies following a breakthrough ischemic stroke: switching to an alternative OAC (including DOAC or VKA) or continuing current DOAC therapy. The primary outcome was “net clinical benefit” at 90 days (composite outcome of recurrent ischemic stroke and moderate to severe bleeding that aims to give a sense of the effectiveness and safety of the OAC).

This investigation included 1,006 participants, of which 46% (n=463) continued the same DOAC and 54% (n=543) changed OAC therapy. Median age was 80 years, with 50% of participants being women. The primary outcome of net clinical benefit was observed in 4.9% of the patients who switched therapy and 5.1% of the patients who remained on the same treatment following their breakthrough event, demonstrating noninferiority between the two treatment strategies. Specifically, recurrent

ischemic stroke at 90 days occurred in 8% of patients switching therapy compared to 7.4% of patients continuing therapy. Safety outcomes were infrequent and similar between the two groups: symptomatic ICH (0.9% in the switching group vs. 1.2% in the continuation group) and moderate-to-severe extracranial bleeding (2.2% in the switching group vs. 2.7% in the continuation group).

The results of this study suggest that changing OAC following a breakthrough stroke is likely not necessary in most circumstances. The largest limitation of this study is its retrospective design; however, in the absence of a randomized clinical trial, a well-designed retrospective analysis such as the ASPERA-R study provides evidence challenging the long-standing strategy of changing OAC agents. Patient demographics, preferences, and concomitant medications may help aid in decision-making around changing or continuing OAC therapy following a breakthrough stroke.

Take-away: At present, there is no evidence to support changing to an alternative OAC strategy following a breakthrough ischemic stroke for most patients. Instead, hospitalists should focus on adherence, dosing, drug-drug interactions, and modifiable risk factors.

Disclosures/Conflict of Interest

The authors declare they have no conflicts of interest.

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