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JOURNAL CLUB

ISSN #1555-0117 (online)

BRINGING CLINICIANS TOGETHER TO DISCUSS CURRENT DRUG THERAPY

August 2022 • Vol. 19, No. 8

Checklist

BEFORE THE MEETING

- ☐ Print your copy of *Pharmacist's Letter Journal Club* LEADER NOTES, which will be emailed to you from *Pharmacist's Letter*
- ☐ Provide the LEADER NOTES to the *Pharmacist's Letter Journal Club* discussion leader
- ☐ Instruct your *Pharmacist's Letter Journal Club* participants to go to PharmacistsLetter.com to print their PARTICIPANT NOTES. Instruct them to look for "Journal Club" under the "Browse" heading. Be sure to tell them which month of *Pharmacist's Letter Journal Club* you intend to use
- ☐ Provide instructions to your PARTICIPANTS and LEADERS about how to obtain PDFs of original articles from your local medical library (Adhere to institution's copyright policy)

DURING THE MEETING

- ☐ Pass out any needed *Pharmacist's Letter Journal Club* PARTICIPANT NOTES
- ☐ Use your *Pharmacist's Letter Journal Club* LEADER NOTES to facilitate the discussion

AFTER THE MEETING

Go to PharmacistsLetter.com to learn about other topics in this month's issue, including charts, algorithms, toolboxes, etc, and listen to panelists and experts discuss our recommendations in *Emerging Recommendations Panel*

Pharmacist's Letter Journal Club. We do the digging, you do the discussing.

LEADER NOTES

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The following succinct analysis appeared in *Pharmacist's Letter*. Based on vol. 38. No. 8

ANTICOAGULANTS

Direct oral anticoagulant (DOAC) dosing errors continue to crop up...but you can help prevent them.

For example, evidence suggests DOACs (Eliquis, etc) are UNDERdosed almost 25% of the time for atrial fib...which is linked with increased mortality. And we know OVERdosing can lead to bleeding.

Help ensure appropriate DOAC dosing. Resist the urge to rely on memory...due to the laundry list of uses, doses, and durations.

Watch for key factors...and reevaluate the dose periodically.

Obesity. Advise usual dosing up to 120 kg or a BMI of 40.

If a DOAC is preferred for patients with a higher weight, suggest Eliquis (apixaban) or Xarelto (rivaroxaban) at usual doses...based on limited data. Otherwise, recommend warfarin.

Kidney impairment. For atrial fib, usually expect a lower dose.

For instance, think of "ABC" with Eliquis. Advise reducing the dose for patients with 2 of these 3 features...Age over 80, Body weight under 60 kg, or serum Creatinine over 1.5 mg/dL.

Recommend reducing Xarelto for CrCl under 50 mL/min.

On the other hand, don't extend atrial fib dosing "rules" to venous thromboembolism (VTE) treatment...this may undertreat acute clots.

In this case, only Savaysa (edoxaban) needs a lower dose... there's no evidence for reducing other DOACs. But avoid Pradaxa (dabigatran) for CrCl below 30 mL/min...or Xarelto below 15 mL/min.

For patients on dialysis, consider cautious use of Eliquis at the usual dose if a DOAC is preferred for atrial fib or VTE.

If you don't have access to kidney function, look for clues... such as meds being used at a lower dose or meds for kidney disease.

Interactions. Eliquis and Xarelto are metabolized by CYP3A4... and absorption of all 4 DOACs is affected by P-glycoprotein (P-gp).

For example, recommend reducing Eliquis 5 or 10 mg by half when it's used with a strong CYP3A4 and P-gp inhibitor (itraconazole, Paxlovid, etc). Avoid Xarelto in this case.

If you spot a nonstandard dose, but it isn't changed...due to patient frailty, bleeding history, etc...document your discussion.

Get our resource, Appropriate Use of Oral Anticoagulants, for help choosing a med...including in special populations (cancer, etc).

(For more on this topic, see Clinical Resource #380802 at PharmacistsLetter.com.)

Camm AJ, Cools F, Virdone S, et al. Mortality in Patients With Atrial Fibrillation Receiving Nonrecommended Doses of Direct Oral Anticoagulants. J Am Coll Cardiol. 2020 Sep 22;76(12):1425-1436.

LEADER NOTES

Discussion Questions

OVERVIEW OF CURRENT THERAPY

1. **What are factors that affect direct oral anticoagulant (DOAC) dosing for atrial fibrillation?**

   - Renal excretion is important for each of the 4 DOACs (apixaban, dabigatran, edoxaban, rivaroxaban). Therefore, US labeling generally recommends use of a reduced dose in the case of kidney impairment.
   - The patient's weight is also a factor to consider when dosing DOACs for atrial fibrillation, especially apixaban.
   - DOACs are also subject to CYP3A4 and P-glycoprotein (P-gp) interactions, with DOAC labeling recommending dose reduction when used with certain strong inhibitors.
   - Prior evidence suggests DOAC underdosing is associated with cardiovascular hospitalization and that DOAC overdosing is associated with increased all-cause mortality when compared to labeled doses.
   - The current study provides more data related to the impact of nonrecommended DOAC doses on patient outcomes, as well as factors that may lead to use of low or high DOAC doses.

2. **What type of study was this? How were the patients selected for inclusion?**

   - This was a prospective cohort study aiming to assess prescribing patterns for DOAC dosing, the impact of nonrecommended dosing on the rate of events, and predictors of underdosing.
   - This study utilized the Global Anticoagulant Registry in the FIELD-AF (GARFIELD-AF) database. This registry includes patients age 18 and over with atrial fibrillation diagnosed within the prior 6 weeks, who have at least 1 risk factor for stroke. Patients with valvular disease were not eligible for inclusion.
   - The GARFIELD-AF registry prospectively enrolled 5 cohorts of approximately 10,000 patients each between March 2010 and August 2016 from 35 countries in Africa, Asia, Australia, Europe, North America, and South America. In total, this registry includes data from 52,080 patients.
   - The registry contains data on patient demographics, medical history, care setting, type of atrial fibrillation, and antithrombotic treatment (warfarin, DOACs, and antiplatelets). Stroke and bleeding risk of patients was stratified based on CHAD2DS2-VASc and HAS-BLED scores.

3. **How were the study groups defined?**

   - This study included data from the final 3 cohorts of GARFIELD-AF because the first 2 cohorts did not collect individual drug names.

LEADER NOTES

- Three patient groups were compared (nonrecommended low dosing, recommended dosing, nonrecommended high dosing). Patients from the registry were divided into these groups based on prescription labeling approved by the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).
- While each DOAC's labeled dosing is based on CrCl, or serum creatinine in the case of apixaban, these parameters were not available in the GARFIELD-AF registry. Investigators instead assessed kidney function based on the eGFR ranges within each stage of chronic kidney disease as defined by the National Kidney Foundation.
- Dosing also took into account body weight, age, and bleeding risk if labeled dosing included those factors.

4. How were the outcomes evaluated?

- The main goals of the study were to analyze dosing patterns, outcomes in patients on nonrecommended doses versus recommended doses, and predictors of underdosing.
- Results were given as medians for continuous variables and percentages for categorical variables.
- Statistical analysis was complex. GARFIELD-AF scores for mortality, stroke/SE, and bleeding were calculated. Multivariate imputation by chained equations was performed with 5 datasets. This was done to account for missing data.
- Logistic regression was performed to define predictors of nonrecommended dosing, and to provide odds ratios (OR) and 95% confidence intervals (CI). A 30-fold cross-validation was performed. Cross-validation is a method to estimate accuracy of the model.
- A Poisson model was used to estimate event rates (all-cause mortality, stroke or systemic embolism [SE], major bleeding) per 100 person-years. The time at risk was calculated from the time of enrollment up to the occurrence of the first event or 2 years. Only the first occurrence of each event was included in the analysis.
- Cox proportional hazards models were used to analyze if off-label high or low DOAC doses were associated with events compared to patients receiving recommended doses. These results were given as hazard ratios (HR) and 95% CIs.
- Models were adjusted for relevant patient characteristics.

5. What were the outcomes of this study?

- Of the 34,926 patients in GARFIELD-AF cohorts 3 to 5, 23,503 patients were not treated with an anticoagulant or DOAC, 11 were on more than 1 DOAC, and 986 had no data available related to starting date, CKD stage, or dose.
- The final cohort included 10,426 patients. Of these, 4,491 received rivaroxaban, 3,290 received apixaban, 2,359 received dabigatran, and 286 received edoxaban.
- Most patients (72.9%) received recommended dosing, with 23.2% of patients being underdosed and 3.8% of patients being overdosed.
- Patients were approximately 74 years old. Compared to patients who received recommended doses, patients in the nonrecommended dose groups were older; more likely to be women; more likely to be nonsmokers and nonusers of alcohol; and had higher CHAD2DS2-VASc and GARFIELD-AF scores for death, stroke/SE, and bleeding.

LEADER NOTES

- Underdosage occurred in approximately 16% to 29% of patients on apixaban, dabigatran, and rivaroxaban. But the rate was much higher with edoxaban (approximately 56%). However, the number of patients on edoxaban was very small.
- Overdosage was rare, ranging from 1.3% with dabigatran to 6.5% with rivaroxaban. Of these patients, almost 68% had moderate to severe CKD, which is a much higher rate than in patients who received the recommended dose or who were underdosed.
- The rate of all-cause death was higher in patients treated with either off-label low or high doses compared with patients treated with standard doses. Unadjusted HRs were significant for both high or low dosing. However, the adjusted HR was only significant for low dosing (adjusted HR low dosing 1.25, 95% CI 1.04 to 1.50; adjusted HR high dosing 1.19, 95% CI 0.83 to 1.71).
- While the reasons for all-cause death were provided, there didn't appear to be clear trends pointing toward specific causes of the increase in patients treated with low doses.
- However, the rate of stroke/SE was not significantly higher with either low or high doses compared with standard doses using either unadjusted or adjusted analysis (adjusted HR low dosing 0.92, 95% CI 0.62 to 1.37; adjusted HR high dosing 1.51, 95% CI 0.79 to 2.91).
- The risk of major bleeding was lower with low doses compared to standard doses with adjusted analysis (adjusted HR 0.50, 95% CI 0.28 to 0.88), but was not significantly different when high doses were compared to standard doses.
- Analysis to determine predictors of nonstandard dosing was only performed in patients who received low doses due to the small number of patients who were given high doses. The strongest predictors of underdosing were female sex, age, non-Caucasian ethnicity, weight up to 80 kg, acute coronary syndrome, vascular disease, prior stroke, diabetes, moderate to severe chronic kidney disease, and antiplatelet therapy.

6. What were the strengths and weaknesses of this study?

- This was a well-done, large, prospective cohort study suggesting that while almost 75% of patients receive recommended DOAC dosing, underdosing is associated with increased risk of all-cause mortality. In addition, multiple predictors of underdosing were found including female sex, non-Caucasian ethnicity, and concomitant antiplatelet therapy.
- The results of this study are similar to prior studies such as the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT AF-II). This study also found that the majority of patients with atrial fib receive labeled dosing (87%). Underdosing was more common than overdosing and was associated with cardiovascular hospitalization. This study also found similar predictors of lower dosing.
- The cohort design is a good approach when the aim is to study whether a rare outcome (e.g., stroke, death) is associated with a particular exposure. Although cohort studies are observational and can only test whether associations exist, in this case, a randomized study would not be practical. That's because a huge number of study participants would be required to have enough statistical power to limit type II error (false negative results, not finding a significant difference when one may exist). Also, intentionally randomizing patients to an under- or overdosed DOAC would be unethical.

LEADER NOTES

- However, although the study was large, very few patients received overdoses. Therefore, the results of analyses in patients who received high DOAC doses may still be subject to type II error.
- While cohort studies are observational, the prospective design of this study limits some disadvantages. For example, in contrast to retrospective cohort studies, data collected about outcomes in a prospective study doesn't rely on extraction from medical records, which can be coded inaccurately leading to misclassification bias.
- In addition, prospective studies are able to determine which data elements are needed for the study rather than being limited to data that's already been collected. Despite this, serum creatinine and calculated CrCl were not collected in the GARFIELD-AF registry, which limited investigators to assessment of kidney function based on eGFR ranges within each stage of chronic kidney disease as defined by the National Kidney Foundation. It is difficult to determine the impact of this limitation on study results.
- Prospective cohort studies often require a long period of follow-up, which can make them expensive to conduct. This can also lead to loss of follow-up and missing data. Investigators performed multiple imputation to account for missing data.
- Cohort studies are also subject to confounders. These are variables associated with the exposure and outcome being investigated but not part of the "causal pathway" between the exposure and outcome. That's why investigators provided HRs that were adjusted for multiple confounding factors including age, sex, ethnicity, type of atrial fibrillation, and history of bleeding.
- Other study limitations include the inability to determine whether patients actually took the DOAC as prescribed or assess for drug interactions. In addition, analysis of outcomes related to under- or overdosing with individual DOACs was not performed.
- This study report appears to include most elements recommended by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), guidelines for reporting observational studies. STROBE consists of a 22-item checklist that helps ensure quality reporting and assessment of study methods, results, sources of bias, and other limitations.
- This study was funded by an unrestricted grant from Bayer AG to the Thrombosis Research Institute, which sponsors the GARFIELD-AF registry. Therefore, bias due to influence of study sponsors isn't likely.

7. Were the results expressed in terms we care about and can use?

- Yes. The outcomes were clinically important and what patients and caregivers are concerned about (e.g., the impact of nonrecommended dosing on stroke or death).

HOW SHOULD THE NEW GUIDELINES CHANGE CURRENT THERAPY?

8. Do the guidelines change your practice? How?

- Yes and no.
- Continue to evaluate key factors that impact DOAC dosing, including patient weight, kidney function, and drug interactions.
- Resist the urge to rely on memory to dose DOACs due to their various uses, doses, and durations. Check labeling and use your judgment.

LEADER NOTES

- For patients with kidney impairment, expect to generally use a lower DOAC dose. Keep in mind that apixaban's dose is based on age, body weight, and serum creatinine.

APPLY THE NEW FINDINGS TO THE FOLLOWING CASE

JE is a 73-year-old female with past medical history of hypertension and hyperlipidemia who comes to see you in clinic following recent hospital discharge during which she was diagnosed with paroxysmal atrial fibrillation. Her CHAD2DS2-VASc score was at least 3. She was prescribed the DOAC apixaban 5 mg bid at discharge; however, reports she never started the medication due to uncertainty about potential risks and side effects.

A review of JE's medications shows she is currently on lisinopril 20 mg, amlodipine 10 mg, metoprolol XL 25 mg and simvastatin 20 mg daily. Her vital signs for today's visit are: BP 135/65 mmHg, HR 95, height 5'5", weight 69 kg. Review of her inpatient labs revealed no kidney or liver impairment.

9. How do you counsel JE regarding her available options for anticoagulation and the associated risks?

- Due to the increased risk for thromboembolic disease associated with atrial fibrillation and JE's CHAD2DS2-VASc score, anticoagulation is recommended for stroke prevention.
- Available anticoagulation options for JE include DOACs: apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), rivaroxaban (Xarelto), and warfarin.
- DOACs are typically chosen for their ease of use as they do not require INR monitoring needed with warfarin; however, they are typically also more expensive.
- Furthermore, apixaban was found to prevent more stroke, death, and major bleeds when compared to warfarin.

You discuss the risks and benefits of apixaban and JE agrees to start the medication. Because DOAC dosing is so nuanced, you double-check the dose JE was prescribed.

10. What should you consider to ensure JE is receiving the correct DOAC dose?

- Remember that the dosing of DOACs is based on indication for use, age, weight, kidney function, and use of interacting medications.
- Recent literature suggests that DOACs are often underdosed, which is associated with an increased risk of all-cause mortality.
- To guide DOAC dosing, check renal function at baseline. And reassess dosing periodically since factors that impact dosing may change.
- Give the usual DOAC dose up to 120 kg or a BMI of 40. If a DOAC is preferred for patients with a higher weight, consider apixaban or rivaroxaban based on limited available data. Otherwise, use warfarin.
- You also review JE's other medications for potential drug interactions with the DOAC.

LEADER NOTES

You determine that JE was prescribed the appropriate dose of apixaban. You discuss with JE that while DOACs have fewer interactions than some other anticoagulants such as warfarin, it is important that she is aware DOACs can still have important interactions.

11. What should you keep in mind about possible DOAC interactions?

- While there are no specific interactions with the medications JE is currently taking, interactions should always be considered when new medications are started in patients taking a DOAC.
- Some DOACs may require dose adjustment or even avoidance in patients taking medications that inhibit or induce CYP3A4 or P-glycoprotein.
- Educate about increased bleeding risk if also taking OTCs with antiplatelet effects such as NSAIDs. Generally recommend avoiding NSAIDs in patients on a DOAC and caution against aspirin use unless it is indicated for another condition.

You continue to care for JE regularly in your practice over the next few years and she does well on the prescribed DOAC. About a decade later, she presents to you, now 83-years-old. Her most recent blood work shows worsening kidney function with serum creatinine of 1.7 mg/dL. You also notice that JE has lost weight as she has gotten older. Her vital signs at today's visit show a weight of 59 kg.

12. What modifications to JE's DOAC should you make at this time?

- Now that JE is over age of 80, and weighs under 60 kg, you recommend that she reduce the dose of apixaban to 2.5 mg bid.

You adjust JE's apixaban dose as appropriate for her age, weight, and kidney function, and ensure JE understands the reason for the dose adjustment.

LEADER NOTES

NOTES

LEADER NOTES

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LEADER NOTES

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For instance, think of "ABC" with Eliquis. Advise reducing the dose for patients with 2 of these 3 features...Age over 80, Body weight under 60 kg, or serum Creatinine over 1.5 mg/dL.

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DISCUSSION QUESTIONS

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2. **What type of study was this? How were the patients selected for inclusion?**

3. **How were the study groups defined?**

4. **How were the outcomes evaluated?**

5. **What were the outcomes of this study?**

See LEADER NOTES for answers to discussion questions.

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