

Corey Lyon, DO; Alex Reed, PsyD, MPH; Shailendra Prasad, MBBS, MPH

University of Colorado Family Medicine Residency Program, Denver (Drs. Lyon and Reed); University of Minnesota North Memorial Family Medicine Residency, Minneapolis (Dr. Prasad)

DEPUTY EDITOR

James J. Stevermer, MD, MSPH

Department of Family and Community Medicine, University of Missouri-Columbia.

## Direct oral anticoagulants or warfarin for A fib?

A recent study evaluated the effectiveness of 3 direct oral anticoagulants and warfarin in patients with atrial fibrillation. So which agents came out on top?

### PRACTICE CHANGER

Use direct oral anticoagulants instead of warfarin in patients with atrial fibrillation because they are just as effective at preventing ischemic stroke and systemic emboli as warfarin, and because apixaban and dabigatran have lower bleeding rates.

### STRENGTH OF RECOMMENDATION

**B:** Based on a single, prospective, cohort study.

Larsen TB, Skjøth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2016;353:i3189.<sup>1</sup>

### ILLUSTRATIVE CASE

A 66-year-old man with a history of hypertension and diabetes mellitus type 2 is hospitalized for palpitations and dizziness, and is given a diagnosis of atrial fibrillation (AF). His heart rate is successfully controlled with a beta-blocker. His CHA<sub>2</sub>DS<sub>2</sub>-VASc score is 3, meaning he is a candidate for anticoagulation. Which agent should you start?

**T**hromboembolism in patients with AF results in stroke and death and can be decreased with appropriate use of antithrombotic therapy. Evidence-based guidelines recommend patients with AF at intermediate or high risk of stroke (CHA<sub>2</sub>DS<sub>2</sub> score  $\geq 2$  or prior history of cardioembolic stroke or transient ischemic attack) receive

antithrombotic therapy with oral anticoagulation, rather than receive no therapy or therapy with antiplatelets.<sup>2,3</sup>

The American College of Chest Physicians also recommends the use of the direct oral anticoagulant (DOAC) dabigatran over warfarin for those patients with nonvalvular AF with an estimated glomerular filtration rate (eGFR)  $\geq 15$  mL/min/1.73 m<sup>2</sup>.<sup>3</sup>

A meta-analysis of large randomized controlled trials (RCTs) of individual DOACs (dabigatran [a direct thrombin inhibitor], rivaroxaban, apixaban, and edoxaban [factor Xa inhibitors]) revealed similar or lower rates of ischemic stroke and major bleeding (except gastrointestinal bleeds; relative risk=1.25; 95% CI, 1.01 to 1.55) when compared with warfarin (at an international normalized ratio [INR] goal of 2-3).<sup>4</sup> In addition, 3 separate meta-analyses that pooled results from large RCTs involving dabigatran, apixaban, and rivaroxaban also concluded that these medications result in a significant reduction in embolic stroke and reduced the risk of major bleeds and hemorrhagic stroke when compared with warfarin.<sup>5-7</sup>

However, we know less about the comparative effectiveness and safety of the DOACs when they are used in clinical practice, and it is not clear which, if any of these agents, are superior to others. Moreover, only about half of the patients in the United States with AF who are eligible to take DOACs are currently managed with them.<sup>8</sup>

## STUDY SUMMARY

### One DOAC is better than warfarin at one thing; 2 others are better at another

This large cohort study examined the effectiveness of 3 DOACs compared with warfarin in 61,678 patients with AF by combining data from 3 Danish national databases. The patients had newly diagnosed AF (without valvular disease or venous thromboembolism) and were prescribed standard doses of DOACs (dabigatran 150 bid [N=12,701], rivaroxaban 20 mg/d [N=7192], apixaban 5 mg bid [N=6349]) or dose-adjusted warfarin to an INR goal of 2 to 3 (N=35,436). Patients were followed for an average of 1.9 years.

#### ■ Ischemic stroke, systemic emboli.

In the first year of observation, there were 1702 ischemic strokes or systemic emboli. The incidence of ischemic stroke or systemic embolism was either the same or better for each of the 3 DOAC treatments than for warfarin (DOACs, 2.9-3.9 events per 100 person-years; warfarin, 3.3 events per 100 person-years; no *P* value provided). Ischemic stroke or systemic emboli events occurred less frequently in the rivaroxaban group compared with warfarin at one year (hazard ratio [HR]=0.83; 95% confidence interval [CI], 0.69-0.99) and after 2.5 years (HR=0.80; 95% CI, 0.69-0.94). The rates of ischemic stroke and systemic emboli for both apixaban and dabigatran were not significantly different than that for warfarin at one year and 2.5 years.

■ **Bleeding events** (defined as intracranial, major gastrointestinal, and traumatic intracranial) were lower in the apixaban group (HR=0.63; 95% CI, 0.53-0.76) and dabigatran group (HR=0.61; 95% CI, 0.51-0.74) than in the warfarin group at one year. Significant reductions remained after 2.5 years. There was no difference in bleeding events between rivaroxaban and warfarin.

■ **Risk of death.** Compared with warfarin, the risk of death after one year of treatment was lower in the apixaban (HR=0.65; 95% CI, 0.56-0.75) and dabigatran (HR=0.63; 95% CI, 0.48-0.82) groups, and there was no significant difference in the rivaroxaban group (HR=0.92; 95% CI, 0.82-1.03).

## WHAT'S NEW

### No agent "has it all," but DOACs have advantages

This comparative effectiveness and safety analysis reveals that all of the DOACs are at least as effective as warfarin in preventing ischemic stroke and systemic emboli, and that rivaroxaban may be more effective, and that apixaban and dabigatran have a lower risk of bleeding than warfarin.

## CAVEATS

### This non-randomized cohort trial lacked INR data

This study was a non-randomized cohort trial. And, while propensity weighting helps, the researchers were unable to completely control for underlying risk factors or unknown confounders.

INR data for patients on warfarin was not provided, so it is not clear how often patients were out of therapeutic range, which could affect the stroke and bleeding results in the warfarin group. This, however, is seen with routine use of warfarin. We feel that this study reflects the challenge of maintaining patients in warfarin's narrow therapeutic range.

## CHALLENGES TO IMPLEMENTATION

### It comes down to cost

Cost could be a barrier, as health insurance coverage for DOACs varies. Patients with high-deductible health insurance plans, or who find themselves in the Medicare "donut hole," may be at a particular disadvantage. **JFP**

#### ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

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#### References

1. Larsen TB, Skjøth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2016;353:i3189.
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary. *J Am Coll Cardiol*. 2014;64:2246-2280.



Rivaroxaban may be more effective than warfarin at preventing ischemic stroke and systemic emboli, and apixaban and dabigatran have a lower risk of bleeding.

CONTINUED

3. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e531S-e575S.
4. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-962.
5. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation*. 2012;126:2381-2391.
6. Adam SS, McDuffie JR, Ortel TL, et al. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism. *Ann Intern Med*. 2012;157:796-807.
7. Ntaios G, Papavasileiou V, Diener H, et al. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. *Stroke*. 2012;43:3298-3304.
8. Barnes GD, Lucas E, Alexander GC, et al. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128:1300-1305.

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