

## Rivaroxaban vs. Warfarin for Treatment of DVT and PE

COREY LYON, DO; SETH MATHERN, MD; and JESSICA DEVITT, MD, *University of Colorado Family Medicine Residency, Denver, Colorado*

KRISTEN DeSANTO, MSLS, MS, RD, AHIP, *University of Colorado Health Sciences Library, Denver, Colorado*

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### Clinical Question

Is rivaroxaban (Xarelto) as effective as vitamin K antagonists for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)?

### Evidence-Based Answer

Rivaroxaban, along with the other factor Xa inhibitors, is as effective as or better in the short term (three months) than warfarin (Coumadin) for preventing recurrent DVT, nonfatal PE, and fatal PE, with no differences in mortality or bleeding events. (Strength of Recommendation: A, based on consistent, high-quality meta-analyses of moderate- to high-quality randomized controlled trials [RCTs] with patient-oriented outcomes.)

### Evidence Summary

A 2015 Cochrane meta-analysis of 11 RCTs (N = 27,945) compared direct thrombin inhibitors, factor Xa inhibitors (rivaroxaban, apixaban [Eliquis], and edoxaban [Savaysa]), and standard anticoagulants (unfractionated heparin, low-molecular-weight heparin, and vitamin K antagonists such as warfarin) in the treatment of venous thromboembolism (VTE) and PE.<sup>1</sup> Eight of the RCTs (N = 16,356) compared factor Xa inhibitors with standard anticoagulants; four (N = 9,428) compared rivaroxaban with standard anticoagulants (international normalized ratio goal of 2 to 3). Primary outcomes included recurrent VTE, recurrent DVT, and fatal and nonfatal PE. After three months, there was a significant trend in favor of factor Xa inhibitors compared with warfarin for the prevention of recurrent VTE (five trials, three with rivaroxaban; N = 5,001; odds ratio [OR] = 0.69; 95% confidence interval [CI], 0.48 to 0.99)

and recurrent DVT (four trials, two with rivaroxaban; N = 4,917; OR = 0.51; 95% CI, 0.31 to 0.84). When treatment was extended beyond three months, there were no significant differences in rates of recurrent VTE (three trials, one with rivaroxaban; N = 11,355; OR = 0.97; 95% CI, 0.78 to 1.22) or recurrent DVT (three trials, one with rivaroxaban; N = 11,355; OR = 0.87; 95% CI, 0.63 to 1.20) compared with warfarin. Overall, there was a significant decrease in rates of recurrent VTE with factor Xa inhibitors compared with standard anticoagulants at three months (eight trials; N = 16,356; OR = 0.69; 95% CI, 0.48 to 0.99), but not when treatment was extended beyond three months (OR = 0.97; 95% CI, 0.78 to 1.22). Rates of fatal and nonfatal PE were similar between factor Xa inhibitors and warfarin; no studies comparing rivaroxaban with warfarin for the primary outcome of PE prevention lasted more than three months.

Another 2015 Cochrane meta-analysis of five RCTs (N = 7,897) examined the effectiveness of direct thrombin inhibitors and factor Xa inhibitors vs. standard anticoagulants (unfractionated heparin, low-molecular-weight heparin, and warfarin) for the long-term treatment of PE.<sup>2</sup> Three of the RCTs tested oral factor Xa inhibitors such as rivaroxaban for the prevention of recurrent PE. Primary outcomes included recurrent PE, recurrent VTE, or clinically overt DVT. Secondary outcomes included all-cause mortality and adverse effects, such as major bleeding. There were no significant differences between oral factor Xa inhibitors (including rivaroxaban) and warfarin for recurrent PE (two trials, one with rivaroxaban; N = 4,509; OR = 1.08; 95% CI, 0.46 to 2.56). Overall, there was too much

heterogeneity to form a pooled analysis of the effectiveness of factor Xa inhibitors for the prevention of recurrent PE.

A systematic review of 11 RCTs (N = 11,104) assessed the relative effectiveness and safety of direct thrombin inhibitors, factor Xa inhibitors, aspirin, and warfarin for extended treatment (more than three months) and prevention of VTE in adults who had received prior treatment for VTE.<sup>3</sup> Four of these trials compared direct thrombin inhibitors and factor Xa inhibitors vs. placebo or warfarin (international normalized ratio goal of 2 to 3). Primary outcomes included VTE and VTE-related death, major or clinically relevant nonmajor bleeding events, and all-cause mortality. Additional outcomes included nonfatal PE, DVT, and VTE-related death (i.e., any VTE-related event that resulted in death, or where VTE could not be ruled out as a cause of death). Based on pooled data, the authors compared rivaroxaban with dabigatran (Pradaxa), apixaban, and warfarin (international normalized ratio goal of 2 to 3). When rivaroxaban was compared with warfarin, there were no significant differences in rates of VTE and VTE-related mortality (relative risk [RR] = 2.34; 95% credible interval [CrI], 0.79 to 6.76), nonfatal PE (RR = 2.30; 95% CrI, 0.20 to 29.87), all-cause mortality (RR = 2.25; 95% CrI, 0.06 to 39.25), or bleeding events (RR = 0.99; 95% CrI, 0.37 to 2.74). This study was funded by the pharmaceutical industry.

A consensus guideline published in 2016 recommends using dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonists for the first three months of therapy in patients with DVT or PE and no cancer.<sup>4</sup> However, this guideline does not contain more recent evidence, including the meta-analyses discussed previously.

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Address correspondence to Corey Lyon, DO, at [corey.lyon@ucdenver.edu](mailto:corey.lyon@ucdenver.edu). Reprints are not available from the authors.

Author disclosure: No relevant financial affiliations.

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