Which New Oral Anticoagulant for Stroke Prevention in AF?

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AALBORG, DENMARK, HAMILTON, ON, and BOSTON, MA — An indirect comparison analysis of the four non–vitamin-K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation has shed light on differences in their safety and efficacy profiles. In the absence of any direct, head-to-head trial, this analysis of four large published phase 3 trials that compared the individual NOACs with warfarin can help guide clinical practice, researchers say, with the caveat that it was an indirect comparison.

"Clinicians now have a choice and can fit the drug to the patient, and vice versa," coauthor Dr Torben Bjerregaard Larsen (Aalborg University, Denmark) told heartwire in an email.

As covered by heartwire, RE-LY, ROCKET-AF, and ARISTOTLE looked at three approved NOACs—dabigatran (Pradaxa, Boehringer Ingelheim), rivaroxaban (Xarelto, Bayer), and apixaban (Eliquis, Pfizer/Bristol-Myers Squibb), respectively—and more recently, ENGAGE-AF looked at edoxaban (Lixiana, Daiichi-Sankyo), which is under regulatory review in the US and Europe.

The indirect comparison analysis showed that high-dose edoxaban (60 mg, reduced to 30 mg depending on patient characteristics) had similar safety and efficacy as dabigatran 110 mg twice daily. Dabigatran 150 mg twice daily was associated with lower stroke/systemic embolism. High-dose edoxaban had similar efficacy in stroke prevention as rivaroxaban or apixaban, with less bleeding than rivaroxaban and more bleeding than apixaban.

Low-dose edoxaban (30 mg, reduced to 15 mg depending on patient characteristics) was less effective than the other drugs but was linked with less major bleeding.

"Indirect comparisons allows an 'informed choice'—[for example,] whether the prescriber is aiming for higher efficacy in reducing ischemic stroke (eg, dabigatran 150 mg twice daily) or greater safety with the lowest major bleeding profile, especially in the elderly or those at high bleeding risk (eg, dabigatran 110 mg twice daily, apixaban, or edoxaban)," Larsen and colleagues write.

However, "these results are hypothesis generating and should be confirmed in a head-to-head randomized trial," they caution.

The study is published in the May 2014 issue of Thrombosis and Haemostasis.
Risk vs Benefit for Individual Patient

In a related study published in the same journal[2], Dr Noel C Chan (Population Health Research Institute, Hamilton, ON) and colleagues looked at these same four studies and came to similar conclusions.

"The use of either apixaban or low-dose edoxaban is appealing in patients at high risk of bleeding, as they show the best bleeding profile and are not associated with a higher rate of GI bleeding compared with warfarin," they write.

"Low-dose edoxaban showed higher rates of ischemic stroke than warfarin, whereas apixaban showed a trend to lower rates of ischemic stroke.

"Rivaroxaban and higher-dose edoxaban have the advantage of once-daily dosing but appear to be associated with a higher rate of GI bleeding than warfarin."

Dabigatran 150 mg twice daily was the only regimen that showed significant superiority over warfarin in preventing nonhemorrhagic stroke. This high-dose dabigatran regimen, however, has the disadvantage of being associated with an increased risk of MI and GI bleeding and therefore should be used with caution and perhaps avoided in patients at high risk for GI bleeding and/or acute coronary syndrome, the authors say.

Of note, an FDA analysis of these two concerns, released earlier this week, found no signal of increased MI risk with dabigatran, but a significantly increased risk of GI bleeding.

"In the absence of head-to-head comparisons, the choice among NOACs for AF is likely to be influenced by considerations of efficacy for ischemic stroke prevention, major bleeding risk (especially intracranial hemorrhage and GI bleeding), MI risk, mortality benefit, and the convenience of once-daily dosing," they conclude.

"Lots to Learn"

"The clinician must tailor drug initiation decisions to each patient," Dr Christina L Cove (Boston University School of Medicine, MA), coauthor of a third related study[3], which identified knowledge gaps and suggested future research directions, explained to heartwire in an email. "Drug trials usually exclude sicker populations, [who might] benefit from novel anticoagulants. Specific attention should be paid to patients with renal dysfunction, especially those who may qualify for dose reductions up front. . . . In addition, octogenarians are largely excluded from drug trials, yet these are a group of patients at increased risk for renal dysfunction, intracranial hemorrhage, and gastrointestinal bleeding," she noted.

Differences in study population and design need to be considered when comparing these four trials, she noted. "For example, baseline CHADS2 scores in the ROCKET-AF and ARISTOTLE trials vary substantially (3.5 vs 2.1, respectively). In addition, time in
therapeutic range [TTR] in the warfarin comparator arms of each trial also varied significantly, which makes direct comparisons of efficacy difficult."

To be able to better compare the efficacy and safety data between the NOACs, baseline stroke and bleeding risk would need to be similar. Studies are also needed evaluating long-term safety and efficacy of NOACs in elderly populations and those with chronic kidney disease, she added.

The authors call for "data from real life, including major bleeding (intracranial and gastrointestinal) and the important issue of adherence, renal function, and drug interaction. I agree on these considerations," Larsen noted. "We still have a lot to learn about NOACs in daily clinical practice."

References