

# Dabigatran, Rivaroxaban Vie as Warfarin Alternatives

*Both drugs eliminate the need for regular dose monitoring and adjustment required with warfarin.*

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FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

CHICAGO – Rivaroxaban, the first in class, oral factor Xa inhibitor, showed noninferiority to warfarin for preventing stroke and other embolic events in a pivotal trial with more than 14,000 atrial fibrillation patients.

But with the report of these results coming less than 2 weeks after the release of dabigatran, the rival, new anticoagulant that came onto the U.S. market on Nov. 3, the question by many people who heard the results was not just how rivaroxaban compared with warfarin but how to weigh its clinical role versus dabigatran.

Cardiologists had no firm answer, and expect none until rivaroxaban and dabigatran go head to head in a trial. But talk at the meeting about both drugs made it clear that warfarin's time as the go-to anticoagulant for atrial fibrillation patients had passed. Both of the new drugs eliminate the regular dose monitoring and adjustment required for patients on warfarin.

## Comparing the Competitors

How rivaroxaban compares with dabigatran "is the inevitable question," said Dr. Kenneth W. Mahaffey, a cardiologist at Duke University in Durham, N.C., who reported the results from Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF).

He noted the pitfalls in comparing the outcomes of ROCKET AF with results from the pivotal trial for dabigatran, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (N. Engl. J. Med. 2009;361:1139-51). ROCKET AF enrolled substantially sicker patients, with an average CHADS score of 3.5 compared with an average 2.1 score in RE-LY, and ROCKET AF was run in a double-blind, double-dummy fashion while in RE-LY patients and physicians knew who received dabigatran or warfarin.

Dr. Mahaffey's coinvestigator in ROCKET AF, Dr. Robert M. Califf,

agreed. The researchers who ran ROCKET AF "have been discussing [the comparison of rivaroxaban and dabigatran] incessantly, but there is no scientifically valid way to compare the two, so we'll be left with our feelings."

Dr. Califf cited his 84-year-old mother, on warfarin and in remission from multiple myeloma, who has been unhappy with her monitoring regimen. "I can assure you that she will go on one of these two new drugs just because of convenience, but she can afford it," said Dr. Califf, professor of cardiology at Duke. "Cost will ultimately have to be a factor that we need to be sensitive about."

## What Role Will Price Play?

Price will likely be a major factor in deciding the role for both alternatives to warfarin, and the cost calculation is not simple.

No price yet exists for rivaroxaban, an agent not yet approved for sale in any country. But on Nov. 3, Boehringer-Ingelheim, the company that markets dabigatran (Pradaxa) announced that the direct thrombin inhibitor was available for U.S. sale at a wholesale price of \$6.75/day for either two 150-mg pills or two 75-mg pills, the two dosages approved for U.S. use by the Food and Drug Administration. A recent, informal survey of several large, U.S. retail pharmacies found the 150-mg dose often selling for just under \$8 per day. That compares with a drug cost for generic warfarin of usually less than \$1 a day. But the price of warfarin therapy also includes the substantial cost for laboratory monitoring of patients on warfarin and the cost of the complications patients have when they are either over- or under-anticoagulated with warfarin.

An analysis that was published online Nov. 1 presented a cost-effectiveness analysis of dabigatran compared with warfarin (Ann. Intern. Med. 2010, Nov. 1 [epub ahead of print 0003-4819-154-1-201101040-00289v2]). According to the analysis, at a daily cost of \$8, treatment of patients with atrial fibrillation with dabigatran had an incremental cost-effectiveness ratio of about \$12,500 per quality adjusted life-year compared with warfarin, said Dr. James V. Freeman, a cardiologist at Stanford (Calif.) University and lead author of the cost-effectiveness analysis. Although this figure is still subject to adjustment based on newly updated clinical-event data in RE-LY, an incremental cost-effectiveness ratio of "roughly \$10,000-\$20,000 is likely in the ballpark" based on current dabigatran pricing, Dr. Freeman said in an interview.

"This is in a range generally considered very cost effective. By comparison, implantable cardioverter defibrillators have been estimated to have an incremental cost-effectiveness ratio of \$34,000-\$70,000 per quality adjusted life-year, compared with control therapy," he said.

Even if calculations show that dabigatran is cost effective, a monthly prescription could still deliver a patient an unexpectedly high drug bill. "We've been very careful, in this early phase, that patients don't get whacked with a \$200 bill they can't pay," said Dr. Peter R. Kowey, a cardiologist and professor of medicine at Thomas Jefferson University in Philadelphia. "We call each insurance company to make sure the patient will have some kind of compensation. That's our biggest concern with dabigatran."

In most other respects, dabigatran is a winner so far, Dr. Kowey said. The RE-LY results showed the 150-mg b.i.d. dosage had superior efficacy compared with warfarin, while in ROCKET AF, rivaroxaban proved noninferior but failed to show significant superiority in an intention-to-treat analysis (rivaroxaban showed significant superiority to warfarin in the on-treatment analysis).

"That's where I get stuck, on the superiority thing," Dr. Kowey said in an interview. "One drug proved itself better than warfarin in a gigantic trial, the other didn't." Based on what he called the "pristine" RE-LY results, "if you need to pick one of these anticoagulants for your patient it would have to be dabigatran," he said.

## Switch With Caution

Despite dabigatran's advantages, he warned physicians against precipitously switching patients who are well controlled on warfarin to dabigatran.

"You can't pull the rug out" from patients. "I hope physicians won't make that mistake." He noted that some patients maintain a "rock stable" anticoagulated state on warfarin, the drug itself is inexpensive, and some patients enjoy the social contact they have by regularly returning to their anticoagulation clinic.

On the other hand, patients should know that dabigatran is an option, with its superior stroke prevention and reduced cerebral hemorrhage rate compared with warfarin, he said.

Other experts weren't as sure about dabigatran's edge over rivaroxaban, citing rivaroxaban's performance in ROCKET AF in patients with a high comorbidity profile based on their average CHADS score of 3.5. Rivaroxaban's performance in very sick patients in ROCKET AF was "very impressive," commented Dr. Christine M. Albert, a cardiologist and director of the Center for Arrhythmia Prevention at Brigham and Women's Hospital in Boston. "We may put a patient on rivaroxaban rather than dabigatran because RE-LY was not done in such a sick population. We'll probably individualize [use of each drug] based on which patients were studied in each trial," Dr. Albert said in an interview.

Others cited additional considerations needed when prescribing dabigatran,

and eventually rivaroxaban. "Dabigatran is 80% renally cleared. That will pose problems for some patients, and there is some gastrointestinal bleeding and some dyspepsia with dabigatran," said Dr. Elaine M. Hylek, a cardiologist and warfarin specialist at Boston University. I can't say that warfarin will disappear. There will be some compelling reasons why warfarin will remain."

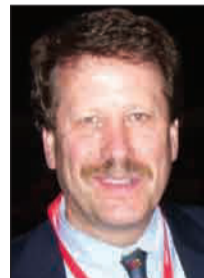
A limitation for rivaroxaban is that it is hepatically metabolized, which may pose difficulties or at least require dose adjustment for patients with liver disease who are prescribed rivaroxaban, noted Dr. Gordon F. Tomaselli, professor of medicine and chief of cardiology at Johns Hopkins University in Baltimore. But availability of dabigatran, and the

DR. CALIFF

promise from the ROCKET HF results that rivaroxaban will soon join it on the market, spells the end of warfarin treatment for the vast majority of atrial fibrillation patients, Dr. Tomaselli predicted.

"Over the course of the next year, a lot of my patients will change from warfarin to one of these two [new] drugs," he said in an interview. "What I hear from patients now who are on warfarin is, 'When can I start with the new drug so that I can stop the rat poison?'" ■

**Disclosures:** ROCKET AF was sponsored by Bayer, the company developing rivaroxaban (Xarelto). RE-LY was sponsored by Boehringer-Ingelheim, the company marketing dabigatran (Pradaxa). Dr. Mahaffey has received consulting fees and research grants from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, Novartis, and Sanofi Aventis. He has also received research grants from Portola, Regado, and The Medicines Company. Dr. Califf has been a consultant to AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Heart.org, and Kowa research. He received research grants from Amlin and Johnson & Johnson-Scios. Dr. Kowey has been a consultant to Astellas, AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Blue Ash, Gilead, GlaxoSmithKline, HUYA, Johnson & Johnson, Medtronic, Novartis, Otsuka, Pfizer, Procter & Gamble, Sanofi Aventis, Sequel, Solvay, and St. Jude. He has been a speaker for Sanofi Aventis, he owns stock in Cardionet, and he has received honoraria from GlaxoSmithKline. Dr. Albert has been a consultant to Novartis, worked on a study sponsored by GlaxoSmithKline, and received research support from St. Jude. Dr. Hylek has served on advisory boards for Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Genentech, Medtronic, Merck, Pfizer, and Sanofi-Aventis. She has received research grants from Bristol-Myers Squibb and Ortho-McNeil. Dr. Tomaselli had no disclosures.



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