# Rivaroxaban Scores High Marks for Acute DVT

## *'Results from EINSTEIN-DVT could transform the way physicians treat deep vein thrombosis.'*

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STOCKHOLM — Fixed-dose rivaroxaban is at least as effective as current standard treatment for acute deep vein thrombosis—and far simpler to use, based on the large phase III EINSTEIN-DVT trial presented in a hotline session at the congress.

"Results from EINSTEIN-DVT could transform the way physicians treat deep vein thrombosis," Dr. Harry R. Büller predicted in presenting the data.

Congress program chair Dr. Fausto J. Pinto of Lisbon University agreed. Indeed, in a wrap-up session at the close of the conference he singled out EINSTEIN-DVT as one of the meeting's several top highlights, citing the trial's likely practice-changing impact for the treatment of a problem that affects 2-3/1,000 adults per year in the Western world.

EINSTEIN-DVT was an open-label study involving 3,449 patients at 253 centers in 32 countries. All had acute symptomatic DVT but no pulmonary embolism.

Participants were randomized to oral rivaroxaban, an investigational direct inhibitor of factor Xa, at 15 mg twice daily for 3 weeks, followed by 20 mg once daily, or to current standard therapy consisting of subcutaneous enoxaparin, typically for about 7 days, followed by warfarin or another vitamin K antagonist at a target international normalized ratio (INR) of 2-3. Treatment duration could be 3, 6, or 12 months at the physician's discretion.

EINSTEIN-DVT was designed to show whether rivaroxaban is noninferior to standard therapy, which is known to be highly effective, reducing the recurrent venous thromboembolism rate by about 90% compared with no treatment. But standard therapy is also quite cumbersome because of warfarin's well-known shortcomings, explained Dr. Büller, chairman of vascular medicine at the Academic Medical Center, Amsterdam.

Recurrent venous thromboembolism, the primary study end point, occurred in 2.1% of the rivaroxaban group, compared with 3.0% of those on standard therapy.

The resultant 32% relative risk reduction was so robust that it not only established rivaroxaban's noninferiority, it came within a hair's breadth of demonstrating statistically significant superiority for the single-drug regimen, he continued.

The primary safety end point in the EINSTEIN-DVT trial was the combined rate of major bleeding or clinically relevant nonmajor bleeding.

This adverse outcome occurred in 8.1% of both groups.

For the prespecified secondary combined end point of recurrent venous thromboembolism or major bleeding, the rates were 2.9% in the rivaroxaban arm compared with 4.2% with standard therapy, for a highly significant 33% reduction in risk.

The rivaroxaban regimen was equally safe and effective regardless of patient age, sex, body mass index, creatinine clearance, or the presence of cancer. Monthly monitoring of liver function tests showed no evidence of hepatotoxicity with the drug. In the standard therapy arm, once patients were off low-molecular-weight heparin and on warfarin they were within the target INR 58% of the time.

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DR. BÜLLER

American physicians often initially hospitalize patients with DVT for 5-7 days or more of therapy with unfractionated heparin. Asked to comment on this strategy, Dr. Büller was blunt: "It's time to change."

"I visit the United States often, and I am absolutely surprised that so many physicians there hospitalize their DVT patients for unfractionated heparin. In many other parts of the world, 80%-90% of these patients are treated out of hospital with low-molecular-weight heparin followed by a vitamin K antagonist," he said.

Discussant Dr. Harald Darius, noting that the oral direct thrombin inhibitor dabigatran is widely expected to be the first of the new antithrombins to receive marketing approval for the treatment of acute DVT, observed that rivaroxaban's performance in EINSTEIN-appeared to be roughly comparable to that of dabigatran in the RE-COVER trial (N. Engl. J. Med. 2009;361:2342-52). Rivaroxaban had a 2.1% incidence of recurrent venous thromboembolism, while dabigatran at 150 mg twice daily for 6 months had a 2.4% rate.

However, the use of dabigatran was preceded by at least 5 days of subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin, he noted.

Dr. Darius declared, "I'm quite positive that we're facing a new era of antithrombotic therapy in patients with DVT, but with some questions still to be resolved."

Chief among these questions in his view is the optimal treatment duration using rivaroxaban and the other new agents. Neither EINSTEIN-DVT nor RE-COVER was designed to provide an answer.

"If you look at the guidelines, the treatment duration is extended with every new edition," noted Dr. Darius of Vivantes Hospital, Berlin.

Rivaroxaban is also under development for other potential indications, including stroke prevention in patients with atrial fibrillation, secondary prevention of acute coronary syndrome, treatment of acute pulmonary embolism, and prevention of venous thromboembolism in high-risk hospitalized, medically ill patients.

Dr. Büller disclosed having received research grants and serving as a consultant to Bayer Schering Pharma, which sponsored the EINSTEIN-DVT trial. Dr. Darius declared no financial conflicts. ■

# Apixaban Reduced Risk

**Apixaban** *from page 1*

systemic embolic events, MI, or vascular death occurred at an annual rate of 6.2% on aspirin and 4.1% on apixaban, for a highly significant 33% relative risk reduction.

Cardiovascular hospitalizations (another secondary end point) occurred at an annual rate of 14.9% in the aspirin arm, compared with 11.8% with apixaban, for a 21% relative risk reduction, reported Dr. Connolly of McMaster University in Hamilton, Ont.

The annual rate of major bleeding was 1.2% with aspirin and 1.4% with apixaban, a nonsignificant difference.

However, minor bleeds not involving physician intervention or discontinuation of therapy were more frequent in the apixaban arm, by a margin of 5.2% per year, compared with 4.1% per year.

Dr. Connolly estimated that treating 1,000 AF patients for 1 year with apixaban instead of aspirin would prevent 18 strokes, most of which would be large and disabling. It would also prevent 10 deaths and 31 cardiovascular hospitalizations.

These benefits would come at a cost of two major hemorrhages.

The much-anticipated Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial comparing the investigational factor Xa inhibitor head to head against warfarin is due to report next year.

Discussant Dr. Harald Arnesen of Ullevål University Hospital, Oslo, called AVERROES "a landmark trial." The study shows that apixaban is quite capable of filling the major unmet need for more effective alternatives to aspirin for stroke prevention in patients with AF who ought to be on warfarin but can't take it.

It has been estimated that up to 50% of AF patients who should be on warfarin are not on the drug, most often because of difficulty in controlling their INR, bleeding problems, [or] drug-drug interactions, or because they find it too much of a hassle.

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DR. CONNOLLY

Comparing the AVERROES results to those for the investigational direct thrombin inhibitor dabigatran in the 18,000-patient RELY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study (N. Engl. J. Med. 2009;361:1139-51), for which Dr. Connolly was also principal investigator, Dr. Arnesen said it appears the two drugs achieve similar reductions in stroke, but that dabigatran has a higher major bleeding rate: 2.7% per year when given at 110 mg twice daily and 3.1% per year at 150 mg twice daily, compared with 1.4% for apixaban in AVERROES.

But such cross-trial comparisons aren't really scientifically valid, and not too much should be made of them, Dr. Arnesen was quick to add.

He predicted that when apixaban reaches the market, the AF management guidelines will have to be revised because of AVERROES. "The use of aspirin will probably be drastically reduced," the cardiologist added.

Session co-chair Dr. Ralph Brindis went even further in an interview: "I think when these anti-Xa drugs become commercially available, warfarin is going to basically just go away. Formularies will be very hard pressed not to include them. Patients and doctors will insist on it. The patients have been begging for a replacement for warfarin," said Dr. Brindis, the current president of the American College of Cardiology and senior advisor for cardiovascular disease for Northern California Kaiser Permanente, Oakland.

As for AVERROES, he considers the study of value mainly as proof of safety.

"I would have been shocked if it didn't show efficacy. We already know that an antithrombin is going to be more effective than aspirin; there's nothing new there," the cardiologist said.

AVERROES was sponsored by Bristol-Myers Squibb and Pfizer. Dr. Connolly disclosed receiving research grants and lecture and consulting fees from the two companies. Dr. Arnesen and Dr. Brindis reported no financial conflicts. ■