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## Race On to Prevent Clots

*Studies Show Promise for Four Companies' Drugs in Potential \$20 Billion Market*

By **RON WINSLOW**

STOCKHOLM—Promising results for two experimental drugs provided fuel for a race to develop medicines to replace blood thinner warfarin for the prevention of blood clots—a global market that could eventually exceed \$20 billion a year in sales.

The findings are the latest in a string of large-scale, late-stage studies of anticoagulants that have raised hopes at several companies in an industry that is struggling to find effective new drugs to replace an aging product and restore the sector's flagging fortunes.

### Beat the Clot

Companies developing new drugs to replace the blood thinner warfarin and their progress toward approval to prevent strokes in patients with atrial fibrillation, or irregular heartbeat

COMPANY	DRUG	STATUS FOR ATRIAL FIBRILLATION
Boehringer Ingelheim	Dabigatran	Awaiting regulatory approval in Europe, U.S. and elsewhere
Bayer / Johnson & Johnson	Rivaroxaban	Results of major trial expected in November
Pfizer / Bristol-Myers Squibb	Apixaban	Results of major trial expected in 2011
Daiichi Sankyo	Edoxaban	Major trial recently launched
Merck / Portola	Betrixaban	Major trial to begin in 2011

Source: the companies

The studies, presented Tuesday at the European Society of Cardiology Congress here, add to evidence the end is near for the use of warfarin, a 60-year-old anticoagulant that is effective in preventing blood clots but notoriously difficult to use. The drug requires frequent blood tests to monitor its effect because it has a narrow margin between preventing clotting and possibly causing bleeding. It also interacts with food and drugs. As a result, only about half of patients who need the drug are on it.

"We are getting pretty close to the Holy Grail of finding a replacement for warfarin," said Ralph Brindis, president of the American College of Cardiology and who wasn't involved in the studies or the experimental drugs' development.

One of the drugs being developed could reach U.S. patients as soon as the fourth quarter, while another is poised for a possible regulatory decision next year.

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Editors' Deep Dive: Competing to Replace

In one of the new studies, rivaroxaban, co-developed by **Johnson & Johnson** and **Bayer AG**, was at least as effective as a regimen

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including warfarin in treating patients with a life-threatening clotting condition called deep-vein thrombosis.

The other drug, apixaban, from [Bristol-Myers Squibb Co.](#) and [Pfizer Inc.](#), was substantially more effective than aspirin in preventing strokes among patients with a common heart-rhythm disorder called atrial fibrillation. Such patients weren't good candidates for warfarin. Results of a major study of apixaban against warfarin are expected next year.

In both cases, researchers said the benefits were achieved without an increased risk of major bleeding, an important hurdle in developing medicines to prevent blood clots.

At least five drugs involving eight companies are in development to replace warfarin. The other competitors include [Daiichi Sankyo's](#) edoxaban; [Boehringer Ingelheim GmbH's](#) dabigatran; and betrixaban, being co-developed by [Merck & Co.](#) and closely held [Portola Inc.](#)

Dabigatran and rivaroxaban are already on the market in some countries outside the U.S. to prevent clots in patients undergoing hip- and knee-replacement surgery. The drugs are also being tested to treat deep-vein thrombosis.

But the big attraction for drug companies is atrial fibrillation, which afflicts more than three million people in the U.S. and an estimated total of eight million world-wide. The condition is a leading cause of stroke and prevention requires lifetime use of anticoagulant medicines.

Morgan Stanley analysts predict that if the drugs are approved for all conditions, the global market for the new anticoagulants could eventually exceed \$20 billion in annual sales. That would be comparable with the market for cholesterol-lowering statins, which surpassed \$20 billion at their height in the early 2000s before some blockbuster brands lost patent protection.

But many questions remain about the risks and benefits of individual drugs and how their cost, safety and effectiveness will affect their use among doctors and reimbursement by insurers. Warfarin, which is marketed as Coumadin by Bristol-Myers, is available in inexpensive generic versions.

In the rivaroxaban study, called Einstein-DVT, the J&J/Bayer drug was tested in 3,400 patients against a standard two-drug regimen of the anticoagulant enoxaparin, followed by warfarin or a similar drug for three to 12 months to prevent the recurrence of clots in patients with deep-vein thrombosis.

The condition, in which clots typically form in veins in the leg, affects about two million Americans each year. If clots break off they can be carried to the lung to cause a life-threatening pulmonary embolism. In current practice in the U.S. many patients are hospitalized for as long as five days and given the intravenous blood-thinner drug heparin to treat the clot before switching to warfarin, a pill.

Harry R. Büller, of Amsterdam's Academic Medical Center and principal investigator of the study, said 2.1% of rivaroxaban patients suffered a serious recurrent event, compared with 3% on the standard treatment. The incidence of bleeding that was life threatening, required a transfusion or was otherwise medically important, was 8.1% in both patient groups.

Dr. Büller said the findings suggest rivaroxaban provides a "simple, single-drug" strategy to treat deep-vein thrombosis. Other researchers not involved with the study said it could significantly reduce hospital stays for patients diagnosed with the condition.

Doctors say it is risky to use the study to reach conclusions about how rivaroxaban might perform in patients with atrial fibrillation. Results of a major study looking at that question are expected in November.

The apixaban study, called Averroes, involved 5,600 patients with atrial fibrillation and an increased risk of

stroke. Stuart Connolly, of the Population Health Research Institute, in Hamilton, Ontario, and lead investigator, said the drug reduced risk of stroke by 54% compared with aspirin. Major bleeding occurred at an annual rate of 1.4%, compared with 1.2% for aspirin, which isn't considered statistically significant.

The substantial benefit against aspirin didn't surprise other doctors. "I would have been shocked if the trial didn't show efficacy," said Dr. Brindis of the American College of Cardiology, who is also a cardiologist at Kaiser Permanente, a health plan based in Oakland, Calif. "It is encouraging that the drug was safe."

Pfizer and Bristol-Myers said results of an 18,000-patient head-to-head study of the drug against warfarin in atrial fibrillation are expected next year.

Boehringer Ingelheim's dabigatran, shown to be effective in atrial fibrillation in a big study presented a year ago, could get U.S. approval by year's end. J&J said it expects to complete U.S. regulatory filings on rivaroxaban by year-end, which could lead to a U.S. regulatory decision for at least one condition next year. Daiichi Sankyo recently launched a similar study of edoxaban. Merck and Portola plan to start a major trial of betrixaban in atrial fibrillation next year.

Despite intense interest in the new drugs, those that succeed will still enter a cost-conscious marketplace. In the Netherlands, for instance, patients are demanding dabigatran, said Martin Jan Schalij a cardiologist at Leiden University. But the government hasn't yet approved it for reimbursement. "Warfarin costs only a few cents a day. If you change to the new drugs, it will be very expensive," he said.

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