

New hope on finding better blood thinners

October 26 2009, By Marie McCullough

Warfarin, one of the most inconvenient, dangerous and disliked drugs in the world, has remained vitally important for more than 50 years.

That tells you how much difficulty scientists have had coming up with safer, easier pills to do what warfarin does -- fight life-threatening [blood clots](#).

Now, at long last, better oral [blood thinners](#) are on the horizon. In July, the [Food and Drug Administration](#) approved Effient to prevent clots in patients undergoing angioplasty to unblock a coronary artery. The maker of Brilinta plans to seek [FDA approval](#) for use in such patients by year's end.

Next in the race for the FDA's imprimatur may be Xarelto and Rendix; both were recently approved in Europe for clot prevention in orthopedic-surgery patients.

At least five other clot-fighters are in late stages of development -- all eager to tap the estimated \$20 billion global market for such drugs.

The hope is that, with more choices and less hassle, doctors can tailor therapy to patients' needs. Surgery, heart disease, faulty [heart valves](#), cancer treatment -- any of these can make short-term or long-term clot-fighting crucial.

So can the abnormal heartbeat called atrial fibrillation, which puts an estimated 2.2 million Americans at elevated risk of stroke. In a study

published in August, Rendix became the first drug to show benefits over warfarin in a-fib patients.

And unlike warfarin, Rendix does not need constant monitoring and dosage adjustment. "The characteristics of (Rendix) are so much more user-friendly than warfarin," said cardiologist Michael D. Ezekowitz, vice president of clinical research at Main Line Health System and a leader of international Rendix studies.

Still, the new blood thinners have minuses as well as pluses, and they won't come cheap. Physicians may also be reluctant to change long-established practices involving warfarin, which began its long history as a rat poison.

Geno J. Merli, who has tested many of the new entrants as director of Jefferson University Hospital's Vascular Disease Center, called them promising but said their value in real-life clinical practice remained to be seen.

"We're all looking for a replacement for warfarin," Merli said. "But these new drugs are not the panacea."

Until now, the only oral blood thinners besides warfarin have been Plavix (clopidogrel), the world's second best-selling drug, and aspirin, the over-the-counter pain reliever.

Tinkering with the clotting system is dicey because it maintains an exquisitely complex balance. It keeps the circulating blood fluid, yet instantly congeals a bit of blood at just the right spot to plug an injured vessel.

Injury or irritation signals disk-shaped blood cells called platelets to morph into star shapes and interlock at the site of damage. Then a

cascade of clotting factors, culminating with the enzyme thrombin, overlays a sticky mesh that catches passing red blood cells and knits the whole plug together.

Platelets dominate the clotting process in the arteries, while the thrombin pathway dominates in the veins. This also complicates the therapeutic challenge because, depending where the drug disrupts this system, it may help one patient but not another.

Plavix, for example, inhibits platelet action, so it is good at retarding clots in arteries. These clots often form on top of fatty plaque, the hallmark of heart disease, and block the artery. That can trigger painful angina or a full-blown heart attack.

But Plavix, made by Sanofi-Aventis, is not as good as warfarin against clots in veins deep in the legs or pelvis -- the kind that typically develop after surgery. These tiny clumps can travel to the lungs or the brain, with devastating consequences.

Brilinta, made by AstraZeneca, also inhibits platelets, but faster and stronger than Plavix. In a study published last month, Brilinta was slightly better than Plavix at preventing heart attack, stroke and cardiovascular death in patients hospitalized with chest pain.

Even so, the FDA is sure to scrutinize a risk inherent in blood thinners: bleeding. Both Brilinta and Plavix caused life-threatening or disabling bleeding in about 11 percent of patients; Brilinta had higher rates of less serious bleeding than Plavix.

Daniel Hoffman, president of Pharmaceutical Business Research Associates, a consulting firm, said, "The FDA has pretty much signaled to (drugmakers) that where there are available therapies, unless you can show a substantial clinical benefit that advances the standard of care, the

FDA is going to have a very low risk tolerance."

Bleeding risk may chill interest in Effient (prasugrel), a platelet inhibitor made by Eli Lilly and Daiichi Sankyo. Although Effient was more effective than Plavix at preventing heart attacks and strokes in [angioplasty](#) patients, it increased fatal bleeding.

The FDA required Effient's label to carry a "black box" warning of the bleeding risks.

Another issue is the as-yet-undetermined prices of the new platelet inhibitors. Plavix, now about \$500 a year, will have a generic -- thus, cheaper -- version in 2012.

The question, Hoffman said, is whether the new drugs "offer a sufficiently higher benefit-to-risk ratio over generic Plavix to justify the cost."

Unlike Plavix, warfarin, also called Coumadin, works by inhibiting the metabolism of Vitamin K, used by the liver to make clotting factors. (Trivia: Warfarin was discovered in moldy clover in the 1920s after grazing cows died of internal bleeding.)

Although warfarin costs only about \$160 a year, it is not cheap therapy. Patients require frequent blood tests to check clotting time and dosage, because warfarin's potency can be affected by certain drugs, dietary supplements, genetic variations and Vitamin K-laden vegetables.

Problems with warfarin are the most common reason for emergency-room visits by older adults, according to the Centers for Disease Control and Prevention.

Lisa Eizen, 62, of Philadelphia, who went on warfarin in July to dissolve

a postsurgical deep vein clot, had to cut way back on the salads and veggies that help her stay healthy and slim.

"I'm glad I don't have to be on it forever," she said last month as her clotting time was checked at Jefferson.

Atrial-fibrillation patients, in contrast, need anticoagulation indefinitely to prevent strokes. Warfarin's protection was better than Plavix plus aspirin in a study.

Stroke is a risk because during an a-fib episode, the heart twitches, or fibrillates, allowing blood to pool for a moment in a heart chamber. Over time, a clot can grow, break free, and travel to the brain, where it may block a blood vessel and trigger an "ischemic" stroke. Researchers estimate that a-fib causes 20 percent of all strokes.

Of course, a warfarin overdose can trigger a different stroke -- a brain hemorrhage.

And even monitoring does not guarantee safety. In 2002, St. Agnes Medical Center in South Philadelphia was embroiled in a costly scandal after it revealed that laboratory miscalculations led to warfarin overdoses in hundreds of patients, including three who bled to death.

Given the bother and dangers of warfarin, only half of a-fib patients take it, even though it reduces stroke risk from 3 percent to 1 percent a year, said Ezekowitz at Main Line Health.

That's one reason he is excited that Rendix may be an alternative. The pill, made by Boehringer Ingelheim, inhibits thrombin and does not require monitoring.

It was as effective as warfarin at preventing strokes, while reducing the

incidence of brain hemorrhage, in the study of 18,100 a-fib patients.

And Rendix showed no liver toxicity, a side effect that sunk another new thrombin inhibitor, AstraZeneca's Exanta.

"What was remarkable about this trial was that there was no price to pay for the added efficacy," Ezekowitz said. Then again, Rendix patients had a tiny increase in heart attacks that researchers can't yet explain. Jefferson's Merli believes Rendix may be eclipsed by Xarelto and similar drugs that inhibit a clotting factor earlier in the chemical cascade.

In any case, Rendix already has a fan in Ruth Pulwer, 84, of Ardmore, Pa. She participated in the Rendix trial for atrial-fibrillation patients.

"It had no ill effects for me at all and it was easy to use," she said. "It's going to be a big boon to people who really suffer" with warfarin.

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Citation: New hope on finding better blood thinners (2009, October 26) retrieved 20 April 2024 from <https://medicalxpress.com/news/2009-10-blood-thinners.html>

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