

# Drug Interactions With Warfarin Often Serious

*Warfarin tops the list of medications that can cause fatal drug interactions.*

BY MIRIAM E. TUCKER  
Senior Writer

PHILADELPHIA — Drug interactions involving warfarin are among the most dangerous that occur commonly in clinical practice, Dr. Douglas S. Paauw said at the annual meeting of the American College of Physicians.

As many as one-third of all hospitalizations in the United States are associated with drug interactions or side effects, and warfarin is one of the main culprits. "If you look statistically at what are the drug interactions that kill people, warfarin interactions are at the top of the list," noted Dr. Paauw, professor of medicine at the University of Washington, Seattle.

With binders such as cholestyramine, for example, the interference actually happens twice. Cholestyramine directly binds the anticoagulant and decreases its absorption when the two drugs are taken together. In addition, the enterohepatic cir-

ulation of warfarin—in which it is excreted in the bile and then reabsorbed—results in a "second pass" anticoagulant effect and a second interaction with the binder, which can lead to a further decrease in warfarin effectiveness. This secondary effect can't be prevented by separating the doses.

If possible, try to avoid using binders in patients taking warfarin, Dr. Paauw advised. If both must be taken, be sure to separate them so that the warfarin is taken at night and the binder taken in the morning and perhaps in the afternoon. Very close monitoring of the international normalized ratio (INR) is essential when initiating the binder. "But if you can get away from [using the two concurrently], that's a safer way to go," he said.

Interactions between antibiotics and warfarin are also quite common, with trimethoprim-sulfamethoxazole (TMP-SMX) having the greatest potential to cause a severe interaction. Other an-

tibiotics that can lead to overanticoagulation when taken with warfarin include erythromycin, amiodarone, ketoconazole/fluconazole (in high doses), itraconazole, and metronidazole. None, however, is as powerful as the interaction with TMP-SMX, because it has a shorter half-life than other antimicrobials and therefore the effect can occur within 2-3 days. With the others, there is usually enough time for the increase in INR to be picked up and treated before it gets out of hand, Dr. Paauw noted.

Other antibiotics that may increase the INR in some, but not all, anticoagulated patients include quinolones, omeprazole, clarithromycin, and azithromycin. These drugs are more likely to cause problems in elderly patients and in those who are taking many concurrent medications.

In a retrospective study involving 104 patients on stable warfarin therapy, INR increased by 0.51 with azithromycin, 0.85 with levofloxacin, and 1.76 with TMP-SMX, compared with an insignificant drop of 0.15 with terazocin, which was used as the control. The incidence of over-

anticoagulation was 5% with terazocin, 31% with azithromycin, 33% with levofloxacin, and 69% with TMP-SMX (J. Gen. Intern. Med. 2005;20:653-6).

Over-the-counter medications might also interact with warfarin. Acetaminophen, which is often recommended for pain relief to patients taking warfarin specifically because it doesn't increase the risk of gastrointestinal bleeding, can actually increase bleeding by interacting with the anticoagulant. In one study, acetaminophen doses of greater than 9,100 mg/week led to a 10-fold risk of having an INR greater than 6 (JAMA 1998;279:657-62). That amount of acetaminophen is the equivalent of just 2-3 extra-strength Tylenol tablets a day, Dr. Paauw pointed out.

In a randomized, double-blind crossover trial of patients on daily warfarin, adding 4 g/day of acetaminophen (the upper limit recommended on the bottle) resulted in an INR 1.75 times greater than that which occurred with placebo.

Still, acetaminophen is much safer for anticoagulated patients than are nonsteroidal drugs and

shouldn't cause a problem in a patient who takes only a couple of tablets every few weeks for occasional pain. For patients with chronic pain who need daily analgesia, INR should be measured within 4-5 days after starting the analgesic, he advised.

Alternative treatments also can cause problems with warfarin. Garlic, ginger, ginkgo biloba, feverfew (used for migraines), and the herb dong quai (for menstrual cramps) can all increase the anticoagulant effect, while ginseng can decrease it. Ginkgo, used to treat a variety of vascular problems, has its own anticoagulant effect, and there have been case reports of spontaneous subdural hematomas in patients taking it. No data are available to quantify the risk, but "it makes sense not to take it when you're anticoagulated," Dr. Paauw said.

St. John's wort, a metabolically active supplement used to treat depression, can both increase and decrease warfarin's anticoagulant effect and therefore should be avoided in patients on warfarin, he recommended.

Dr. Paauw is on the speakers' bureau for Pfizer Inc. ■

## Radiofrequency Ablation Simplifies Cox Maze for Atrial Fib

BY MITCHEL L. ZOLER  
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PHILADELPHIA — A modified version of the Cox maze procedure has simplified and shortened the surgical treatment of atrial fibrillation.

This new version of the Cox maze treatment substitutes bipolar, radiofrequency ablation for most of the atrial lesions that were previously placed with a cut-and-sew technique.

"In our experience, use of radiofrequency-ablation technology significantly simplifies the surgical treatment of atrial fibrillation and broadens the application of this curative procedure," Dr. Shelly C. Lall said at the annual meeting of the American Association for Thoracic Surgery.

She and her associates at Barnes-Jewish Hospital in St. Louis named this modified procedure the "Cox maze IV." Since its introduction about 5 years ago, they have used the new procedure on 88 patients, and now use it exclusively when patients undergo surgical treatment for atrial fibrillation. Until this change, the previous procedure—known as the Cox maze III—was their standard technique for surgically treating atrial fibrillation, said Dr. Lall, a cardiac surgeon at Barnes-Jewish Hospital and at Washington University, St. Louis.

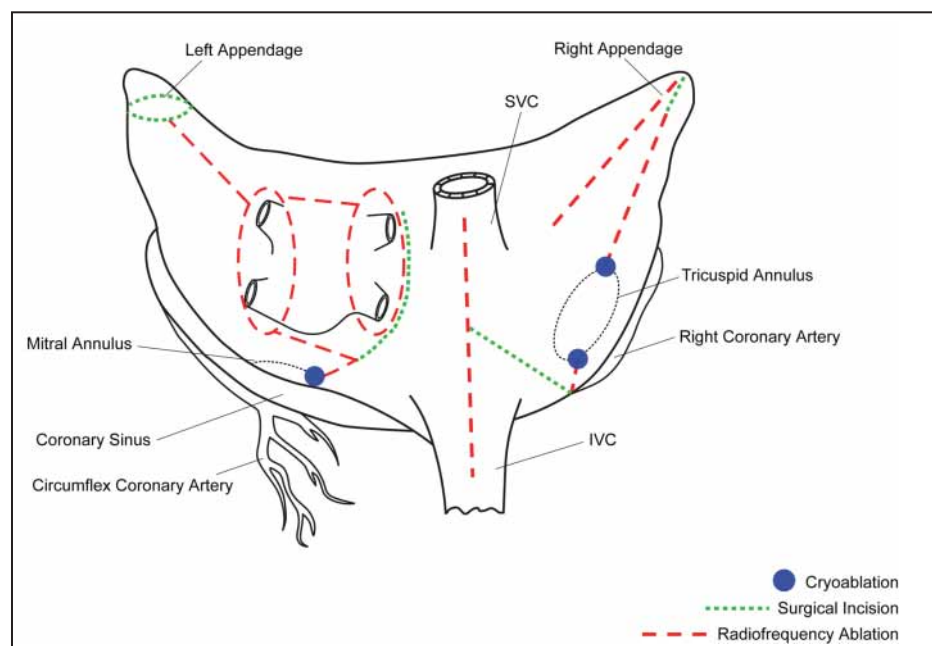
The results "suggest that the new method could supersede the traditional operation as the standard," commented discussant Dr. W. Randolph Chitwood Jr., chairman of the department of surgery at East Carolina University, Greenville, N.C.

The Cox maze IV procedure was developed by a group headed by Dr. Ralph J. Damiano Jr., chief of cardiac surgery at Barnes-Jewish Hospital and the John M. Shoenberg Professor of Surgery at Washington University.

The lesion set used in the Cox maze IV procedure includes all of the lesions of Cox maze III. The only difference is that most—but not all—of the surgical incisions of the Cox maze III procedure are replaced by lesions produced using bipolar, radiofrequency ablation. (See diagram.) The Barnes-Jewish Hospital group has used two different radiofrequency-ablation devices when performing Cox maze IV procedures. Some patients were treated with a device made by AtriCure Inc., and the rest were treated with a device made by Medtronic Inc. Dr. Damiano is a consultant to both companies.

To assess the effect of the Cox maze IV procedure on atrial fibrillation management, Dr. Lall and her associates compared the outcomes of patients who were treated with Cox maze IV with those treated with Cox maze III. Since April 1992, 154 patients were treated at Barnes-Jewish Hospital with the Cox maze III procedure.

The researchers used a propensity analysis to identify matched patients from the two treatment series. The analysis identified 58 patients who were treated with Cox maze III and 58 very similar patients who were treated with Cox maze IV. Although seven clinical and demographic variables were used in the matching



The new Cox maze approach substitutes bipolar, radiofrequency ablation for most of the atrial lesions that were previously placed with a cut-and-sew technique (SVC: superior vena cava; IVC: inferior vena cava).

process, the most important variables for matching were age and New York Heart Association Classification for heart failure before surgery. Late follow-up data were available for 112 of these 116 patients, with an average follow-up of 4.3 years in the Cox maze III group and an average of 1.2 years in the Cox maze IV group.

The two techniques were equally effective. At 1 year following surgery, 96% of patients treated with Cox maze III were free of atrial fibrillation, compared with 93% of patients treated with Cox maze IV, a dif-

ference that was not statistically significant.

The Cox maze IV procedure had the advantage of speed, requiring an average cross clamp time of 76 minutes, compared with an average cross clamp time of 121 minutes among the patients treated with Cox maze III, a statistically significant difference. All other measured aspects of the patients' surgery and outcome were similar in the two groups, Dr. Lall said. These included ICU and hospital stay, 30-day mortality, permanent pacemaker placement, and early atrial tachyarrhythmias. ■