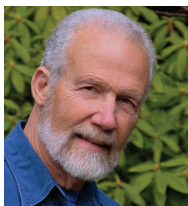


# Warfarin Prescribed Despite Potentially Serious Interactions with Other Medications

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Warfarin has been used for over half a century, and its interactions with other drugs have been exhaustively investigated. It has numerous interactive properties due to its metabolism by cytochrome P450 isozymes, primarily CYP2C9. In addition, the associated bleeding risk may be increased by drugs that inhibit platelet function (through a variety of mechanisms) or otherwise impair hemostasis. Drugs that cause gastrointestinal (GI) bleeding are also problematic.

Recent evidence from Sweden, and earlier data from the United States and Canada, suggest that despite the wealth of information on warfarin drug interactions, patients on warfarin may still be exposed to potentially serious drug interactions.

## The Evidence

Researchers in Sweden hypothesized that in patients receiving warfarin, clinicians would avoid using certain other drugs with which warfarin has potentially serious interactions.<sup>1</sup> The researchers looked at the odds of patients on warfarin receiving concurrent therapy with a drug with a potentially serious interaction versus a comparator drug with a much lower interaction risk. For example, they looked at the odds of a warfarin-treated patient receiving sulfamethoxazole (which can have a serious interaction with warfarin) versus ciprofloxacin (which has a much lower risk of interaction with warfarin). These data were then compared with sulfamethoxazole and ciprofloxacin use in patients not receiving warfarin.

The study results suggested that in

patients on warfarin, Swedish clinicians regularly prescribed sulfamethoxazole despite the fact that (1) the interaction is well documented and clearly can increase the risk of hemorrhage and (2) the warfarin-sulfamethoxazole interaction appears on the prescribing support software that 80% of Swedish physicians use. Data from the United States and Canada suggest that the combination of warfarin and sulfamethoxazole continues to be prescribed and dispensed in these countries as well.<sup>2,3</sup>

The use of sulfamethoxazole (usually combined with trimethoprim in the form of cotrimoxazole) has been known for decades to impair the CYP2C9 metabolism of warfarin and to substantially increase the warfarin plasma concentration and the anticoagulant effect. Moreover, in a case-control epidemiologic study of 134,637 warfarin-treated patients older than 65 years, those who were hospitalized for upper GI tract hemorrhage were almost 4 times more likely than the controls to be recent recipients of cotrimoxazole.<sup>3</sup> Because this study looked only at hospitalizations for GI hemorrhage, it is likely that many other patients bled, but that it was handled on an outpatient basis. There is little doubt, therefore, that the use of sulfamethoxazole with warfarin increases the risk of serious bleeding, but decision support software seems to have little effect on discouraging the concurrent use of these drugs.

On the bright side, the Swedish study found that clinicians did markedly reduce prescribing of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients on warfarin compared with those not on warfarin.<sup>1</sup> Presumably, the prescribers were aware that the ability of NSAIDs to both inhibit platelet function and increase the risk of GI hemorrhage created a serious risk in

patients on warfarin. Thus, in warfarin-treated patients, they either avoided prescribing NSAIDs or heeded the warning about the interaction on decision support software.

Thus, it seems likely that the NSAID-warfarin interaction is known to most prescribers, regardless of whether they are warned about it by decision support software; however, the sulfamethoxazole-warfarin interaction is not common knowledge among prescribers. If this hypothesis is true,

one solution might be to increase prescriber knowledge regarding potentially serious drug interactions. This might serve the dual purpose of reducing the number of serious drug interactions prescribed and increasing the likelihood that prescribers will heed warnings about such interactions from decision support software.

## Summary

Studies suggest that in patients receiving warfarin, prescribers tend to

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avoid giving NSAIDs but usually do not avoid giving sulfamethoxazole. Because both interactions are included on virtually all drug interaction decision support systems, it appears that prescriber knowledge about the NSAID-warfarin interaction and lack of knowledge about the sulfamethoxazole-warfarin interaction may be the reason for the difference. Perhaps every prescriber and pharmacist should have personal knowledge about a core group of potentially serious drug interactions. Such knowledge could substantially enhance the usefulness of drug interaction decision-support systems. ■

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