

Overview of Warfarin Drug Interactions

Warfarin (Coumadin®, Jantoven®) is the most widely prescribed oral anticoagulant and has established efficacy for prevention and treatment of thromboembolic disorders. Warfarin exerts its effect by decreasing the amount of vitamin K available for the production of clotting factors II, VII, IX, and X. The primary source of vitamin K comes from production by enteric bacteria and to a lesser extent from dietary sources.

Even though warfarin is frequently prescribed by most physicians, management of this medication can be problematic from several perspectives. Warfarin has a narrow therapeutic window that must be maintained in order to provide maximum efficacy while minimizing over anticoagulation and increased bleeding risks. Also, literally hundreds of other medications can increase or decrease warfarin's activity. Optimal management of warfarin anticoagulation can also be complicated by changes in dietary factors that may have an impact on total body stores of vitamin K. Two-thirds of all drug-drug interactions identified through analysis of Medicare Part D claims data involve warfarin. This article will review the mechanisms of these interactions with warfarin and review specific drug combinations and their impact on warfarin activity.

Factors Influencing Warfarin Activity

Changes in Warfarin Metabolism: Warfarin is a mixture of R- and S-stereoisomers. Most of the anticoagulant effect is attributed to the S-warfarin isomer. Cytochrome P450-2C9 (CYP2C9) is the principal enzyme responsible for S-warfarin metabolism. Therefore, any factors that modify the expression of this hepatic enzyme system can potentially alter warfarin activity.

It is well known that patients exhibit genetic polymorphisms in the expression of the CYP2C9 enzyme.¹ Up to 21% of the population has an under-expression of this enzyme by 30-80%. This genetic trait results in the patient being ultra sensitive to warfarin's effect. Other patients have an over-expression of the vitamin K oxide reductase (VKOR) enzyme likely to be the cause of warfarin resistance in some individuals. Recently a laboratory test has

been developed to determine a patient's genetic expression of these enzyme systems, however application to routine management of warfarin is yet to be determined.

Medications also have the potential to alter the metabolism of warfarin. Drugs that *inhibit* the CYP2C9 enzyme (e.g. co-trimoxazole (Bactrim®), metronidazole, antifungals, amiodarone, some SSRIs) will *potentiate the effect of warfarin* and necessitate a *lower* dose. Fortunately only a few drugs, most notably rifampin, carbamazepine, phenobarbital, have the potential to *induce enzyme activity* thus having the opposite effect of *decreasing warfarin activity* requiring *larger* than expected doses.

Reduced synthesis of vitamin K by intestinal micro-flora:

Warfarin activity is dependent on body stores of vitamin K. Intestinal bacteria are the primary source of vitamin K₂, with dietary sources contributing a variable source. Many antibiotics, particularly those with broad spectrums and/or anaerobic activity can disrupt normal GI flora and reduce the primary source of endogenous vitamin K. This change in vitamin K production and the subsequent increase in INR values should be expected but is often unpredictable. It is also important to remember that many of

the antibiotics that can disrupt intestinal micro-flora can also directly decrease warfarin metabolism by inhibition enzymatic process described above (co-trimoxazole, metronidazole, macrolides and fluoroquinolones).³

Injury to gastrointestinal mucosa: Nonsteroidal antiinflammatory agents cause dose and duration dependent gastrointestinal injury in a significant population of patients. Multiple population based analyses have shown a significant increase in the risk of GI bleed, up to a four-fold increase,⁴ with both nonselective NSAID and COX-2 inhibitors in patients also taking warfarin.^{4,7,8} In each of these studies no significant difference in the risk of bleeding was observed between the use of a nonselective NSAID or a COX-2 inhibitor when used in combination with warfarin.

Interference with platelet function: Platelet aggregation is the critical first step in hemostasis.



Concomitant use of antiplatelet therapy (aspirin, clopidogrel) increases the risk of major hemorrhage in patients taking warfarin, and they do so without increasing INR lab values. Delaney and colleagues reported an increased risk ratio of 2.23 in GI bleeds over the agents used alone.⁴

There is also evidence that SSRIs can inhibit platelet aggregation by depleting platelet serotonin levels, therefore having an additive impact on increasing risk of bleeding associated with these drug interactions.⁵ It could be expected that there could be an additive effect when used with other antiplatelet agents.

Interruption of the vitamin K cycle:

Acetaminophen has historically been the analgesic of choice over NSAIDs and aspirin for patients taking warfarin. Acetaminophen has been shown to increase INRs in patients stabilized on warfarin.⁶ Parra and colleagues determined this interaction to be clinically significant in patients taking multiple doses per day on successive days. There are several theories on the nature of this interaction, one of the most plausible being that a metabolite of acetaminophen inhibits enzymes systems responsible for producing active forms of vitamin K.⁶

Alterations in clotting factor production: Varying levels of thyroid hormone levels can have a significant impact on the body's metabolism of clotting factors. Hypothyroid patients will metabolize the vitamin K dependent clotting factors at a slower rate, resulting in the need for larger doses of warfarin. Addition or increased doses of a thyroid replacement and return to a euthyroid state will result in more rapid metabolism of these clotting factors. Therefore, if a patient has been stabilized on warfarin, adding or increasing the dose of a thyroid replacement agent may result in a need to decrease the warfarin dose.

Conclusion:

Patients taking warfarin are susceptible to literally hundreds of drug interactions. Fortunately for clinicians the most common interactions generally fall into familiar therapeutic categories of medications. It was possible to describe only a few of the most frequently occurring and most predictable interactions in this article. Most clinicians would agree that it is a challenge to anticipate the impact of any medication added to a patient stabilized on warfarin. Until the time when safer, more predictable and less complicated forms of anticoagulation are available it will be up to physicians, nurses and pharmacists to identify and monitor patients to minimize the risk for bleeding complications associated with the use of warfarin.

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American Geriatric Society Discourages NSAID and COX-2 Agents in Older Adults

During their Annual Scientific Meeting in May, the American Geriatric Society (AGS) released new guidelines addressing the pharmacologic management of persistent pain in older adults. The expert panel focused on senior's 75-years and older, as this group tends to be more frail and suffers from multiple chronic illnesses – all causes of persistent pain.

A major change stemming from the new guidelines is the near elimination of utilizing non-steroidal anti-inflammatory agents (NSAIDs). Original guidelines recommended seniors use over-the-counter or prescription NSAIDs or COX-2 inhibitors before using opioid drugs. The updated guidelines point to newer information suggesting that this is a risky strategy in older persons. The Panel states that the risks of NSAIDs in older patients, which increase cardiovascular risk and gastrointestinal toxicity, usually outweigh the benefits. Based on newer clinical trials as well as clinical observation, the panel recommends that NSAIDs and COX-2 inhibitors **be considered rarely and with extreme caution and only in highly selected individuals**. The guidelines recommend that all patients with moderate-severe pain or diminished quality of life due to pain should be considered for opioid therapy, which may be safer for many patients than with long term use of NSAIDs.

The guidelines will be published in the August issue of the *Journal of the American Geriatrics Society*.



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