

Selected Warfarin Drug-Drug Interactions and Monitoring Guidelines*

Drug/Drug Class	INR Effect [†]	Potential Clinical Impact	Mechanism	Suggested Monitoring [‡]
Co-trimoxazole (Bactrim [®] , Septra [®]) ^{1,2}	↑↑	Increased bleeding; increased gastrointestinal (GI) bleed/hospitalization risk ³	Strong cytochrome P450 enzyme inhibition of more active S-isomer of warfarin ^{1,4}	Avoid concomitant use ⁴ unless benefit outweighs risk; monitor INR closely; dosage reduction of warfarin often required.
Metronidazole (Flagyl [®]) ^{1,5}	↑↑	Increased hemorrhage risk, possibly greater in elderly ^{6,7}	Strong cytochrome P450 enzyme inhibition of more active S-isomer of warfarin ⁴	Avoid concomitant use ⁴ unless benefit outweighs risk; monitor INR closely; dosage reduction of warfarin often required.
Quinolones ^{1,2,8-12}				
– Ciprofloxacin (Cipro [®])	↑↑	Increased bleeding	Cytochrome P450 enzyme inhibition of warfarin by ciprofloxacin ¹	Use alternative antibiotic when possible; monitor INR closely. ⁴
– Levofloxacin (Levaquin [®])	↑			
– Moxifloxacin (Avelox [®])	↑			
Macrolides ^{1,13}				
– Erythromycin	↑↑	Increased bleeding	Cytochrome P450 enzyme inhibition of warfarin by erythromycin and clarithromycin ⁴	Avoid concomitant use with erythromycin when possible; monitor INR closely. ⁴
– Azithromycin (Zithromax [®])	↑			
– Clarithromycin (Biaxin [®])	↑			
Antifungals ^{1,3,5}				
– Fluconazole (Diflucan [®])	↑↑	Increased bleeding; increased GI bleed/hospitalization risk ³	Cytochrome P450 enzyme inhibition of warfarin ¹	Avoid concomitant use when possible ⁴ ; monitor INR closely; dosage reduction of warfarin may be required.
– Itraconazole (Sporanox [®])	↑			
– Miconazole vaginal (Micatin [®] Monistat [®])	↑↑			
– Voriconazole (Vfend [®])	↑			
Non-steroidal anti-inflammatory drugs (NSAIDs) ^{1,14,15}				
– Ibuprofen (Advil [®] , Motrin [®])	↔, ↑	Increased bleeding, elderly at increased risk ^{14,15} , many case reports of possible interactions in elderly ^{16,17,18} ; PT/INR may be unchanged despite increased bleeding risk ⁴	NSAID anti-platelet action and direct injury to gastrointestinal mucosa when combined with warfarin yields enhanced pharmacodynamic effects that increase bleeding risk ^{4,14,15} Celecoxib may displace warfarin from protein binding sites or inhibit its metabolism ^{4,16,17}	Avoid concomitant use, especially in patients at increased risk for NSAID gastropathy (age >75, history of peptic ulcer disease); consider therapy modification ⁴ ; because INR may not change, patient should be monitored for evidence of bleeding; acetaminophen preferred analgesic ⁴ (acetaminophen, especially at doses above 2 grams, may increase bleeding risk especially if INR increases ^{19,20,21}). Monitor celecoxib therapy ¹¹ closely; consider alternatives.
– Naproxen (Aleve [®] , Naprosyn [®] , Naprelan [®])				
– Diclofenac (Voltaren [®] , Arthrotec [®])				
– Celecoxib (Celebrex [®])	↔, ↑			

Key: ↑↑ – potentially large effect on INR; ↑ – potentially moderate effect on INR; ↔ – potentially minor effect on INR.

*Not meant as an exhaustive list. Many antibiotics alter the intestinal flora resulting in a reduced synthesis of Vitamin K, which may enhance warfarin's effects. Antibiotics, such as those listed above that interfere with warfarin via pharmacokinetic pathways, have increased potential for clinically significant effects on INR and bleeding. Please consult additional references for information on these and other drug-drug interactions with warfarin.

[†]International normalized ratio (INR) effect represents the expected effect on INR based on available literature. The actual effect on INR can vary widely among patients and can be affected by other factors such as dose, length of therapy of object/precipitant drug, concomitant drugs and foods, pharmacogenetics, disease states, advanced age, etc.

[‡]**Weigh risk vs. benefit for all drug pairs. The use of drugs that interact with warfarin should be avoided.** When potentially interacting drugs must be used together, monitor INR closely. Follow-up monitoring requirements will vary widely depending on the drug pairs involved. INR and bleeding should be monitored at regular intervals whenever drug therapy is started, stopped, or changed.

Note: This document is intended for educational purposes only to identify some of the more common drug-drug interactions with warfarin. It is not intended to override a clinician's judgment in individual patient management. Prescribing decisions are complex and must be based on an individual's full clinical picture.

References

1. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crouther M, et al. Systematic overview of warfarin and its drug and food interactions. *Archives of Internal Medicine*. 2005 May 23;165(10):1095-1106.
2. Glasheen JJ, Fugit RV, Prochazka AV. The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. *Journal of General Internal Medicine*. 2005 Jul;20(7):653-656.
3. Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. *Clinical Pharmacology and Therapeutics*. 2008 Nov;84(5):581-588.
4. Lexi-Comp, Inc. [Internet]. Hudson (OH): Lexi-Comp, Inc.; 2009 [cited 2009 Apr 2]. *Lexi-Interact™*. Available from: <http://webstore.lexi.com/Store/Individual-Databases/Lexi-Interact>.
5. Thi L, Shaw D, Bird J. Warfarin potentiation: a review of the “FAB-4” significant drug interactions. *Consultant Pharmacist*. 2009 Mar;24(3):227-230.
6. Zhang K, Young C, Berger J. Administrative claims analysis of the relationship between warfarin use and risk of hemorrhage including drug-drug and drug-disease interactions. *Journal of Managed Care Pharmacy*. 2006 Oct;12(8):640-648.
7. Howard-Thompson A, Hurdle AC, Arnold LB, Finch CK, Sands C, Self TH. Intracerebral hemorrhage secondary to a warfarin-metronidazole interaction. *American Journal of Geriatric Pharmacotherapy*. 2008 Mar;6(1):33-36.
8. Mathews S, Cole J, Ryono RA. Anticoagulation-related outcomes in patients receiving warfarin after starting levofloxacin or gatifloxacin. *Pharmacotherapy*. 2006 Oct;26(10):1446-1452.
9. Israel DS, Stotka J, Rock W, Sintek CD, Kamada AK, Klein C, et al. Effect of ciprofloxacin on the pharmacokinetics and pharmacodynamics of warfarin. *Clinical Infectious Disease*. 1996;22(2):251-256.
10. Ravnan SL, Locke C. Levofloxacin and warfarin interaction. *Pharmacotherapy*. 2001 Jul;21(7):884-885.
11. Arnold LM, Nissen LR, Ng TM. Moxifloxacin and warfarin: additional evidence for a clinically relevant interaction. *Pharmacotherapy*. 2005 Jun;25(6):904-907.
12. Elbe DH, Chang SW. Moxifloxacin-warfarin interaction: a series of five case reports. *Annals of Pharmacotherapy*. 2005 Feb;39(2):361-364.
13. Beckey NP, Parra D, Colon A. Retrospective evaluation of a potential interaction between azithromycin and warfarin in patients stabilized on warfarin. *Pharmacotherapy*. 2000 Sep;20(9):1055-1059.
14. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Archives of Internal Medicine*. 1993 Jul 26;153(14):1665-1670.
15. Knijff-Dutmer EA, Schut GA, van de Laar MA. Concomitant coumarin-NSAID therapy and risk for bleeding. *The Annals of Pharmacotherapy*. 2003 Jan;37(1):12-16.
16. Stading JA, Skrabal MZ, Faulkner MA. Seven cases of interaction between warfarin and cyclooxygenase-2 inhibitors. *American Journal of Health-System Pharmacy*. 2001 Nov 1;58(21):2076-2080.
17. Mersfelder TL, Stewart LR. Warfarin and celecoxib interaction. *The Annals of Pharmacotherapy*. 2000 Mar;34(3):325-327.
18. Haase KK, Rojas-Fernandez CH, Lane L, Frank DA. Potential interaction between celecoxib and warfarin. *The Annals of Pharmacotherapy*. 2000 May;34(5):666-667.
19. Mahe I, Bertrand N, Drouet L, Simoneau G, Mazoyer E, Bal Dit Sollier C, Caulin C, Bergmann JF. Paracetamol: a haemorrhagic risk factor in patients on warfarin. *British Journal of Clinical Pharmacology*. 2005 Mar;59(3):371-374.
20. Parra D, Beckey NP, Stevens GR. The effect of acetaminophen on the international normalized ratio in patients stabilized on warfarin therapy. *Pharmacotherapy*. 2007;27(5):675-683.
21. Mahe I, Bertrand N, Drouet L, Bal Dit Sollier C, Simoneau G, Mazoyer E, et al. Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled randomized study. *Haematologica*. 2006 Dec;91(12):1621-1627.



557 Cranbury Road, Suite 21 ♦ East Brunswick, NJ 08816-5419
Phone: 732-238-5570 ♦ Fax: 732-238-7766 ♦ Website: www.hqsi.org