PRACTICE TOOL

PEER-REVIEWED

Drug interactions involving warfarin: Practice tool and practical management tips

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Introduction

Warfarin has been the mainstay of oral anticoagulant therapy for the past 60 years and it is most commonly used to treat or prevent thrombosis or thromboembolism in patients with venous thromboembolism, atrial fibrillation and prosthetic heart valves.[1] However, this drug is efficacious only when the dosage is maintained within a narrow therapeutic index, measured by the international normalized ratio (INR). Multiple challenges exist in appropriately achieving and maintaining therapy within this narrow index. Recent data have identified genetic variants that may reduce a person's requirement for warfarin.[2,3] Furthermore, once a suitable dosage of warfarin has been established, control of therapy can be affected by changes in intake of vitamin K, development of acute medical conditions (e.g., fever, diarrhea), changes in certain chronic medical conditions (e.g., heart failure) and interactions with prescription, nonprescription and herbal products.[1]

The numerous drug interactions involving warfarin are well known among health care providers. Although community pharmacies have software systems that will alert users to a potential interaction, these systems are limited in their capacity to assist the clinician in managing the interaction. Similarly, many published reports provide lists of drugs that are likely to interact with warfarin, along with their directional impact on the INR, but only rarely do they offer suggestions for managing the interaction.[1,4] Data on the timing of the onset (and offset, namely the removal of the interacting drug with washout phase) of an interaction with warfarin, in addition to the mechanism, are needed to assist the front-line clinician in effectively managing common drug interactions. As such, we sought to compile a practical, user-friendly practice tool that clinicians could use to proactively manage the care of individual patients during concomitant therapy with warfarin and drugs known to interact with warfarin.

Development of the practice tool

The practice tool for drug interactions involving warfarin presented here was originally developed by a single practitioner (T.J.B.) working in an anticoagulation management service, who began charting common interactions between warfarin and other prescription drugs and the management strategies used to address them. A pharmacy resident (E.Y.) further developed this chart by conducting a formal search of the literature to compile a list of established interactions between warfarin and other drugs. Despite this literature review, it must be emphasized that the information in the practice tool reflects years of experience in the tracking and proactive day-to-day management of common interactions by the 2 largest anticoagulation clinics in Alberta, namely the Anticoagulation Management Service at the University of Alberta Hospital and the Calgary Zone Anticoagulation Management Service. Interactions specific to HIV-related medications were reviewed and refined by a pharmacist practising within this area (M.F.). The practice tool does not include all documented interactions with warfarin, but instead focuses on those for which clinical management strategies have been employed by the 2 anticoagulation management services. For interactions that are not proactively managed within these services yet are likely to be observed, evidence-based (as opposed to experience-based) information is presented.

To ensure practical applicability, the practice

tool contains information on aspects deemed pertinent in assessing and managing interactions for individual patients, including the effect on INR (in terms of both directional trend and severity), mechanism of the interaction, time of onset, offset and suggested management strategies employed by the anticoagulation management services. We included only drugs with established interactions, (i.e., we excluded theoretical interactions) and we did not include interactions with chemotherapeutic agents. Furthermore, we excluded herbal preparations and supplements, because of their heterogeneous nature. It should be acknowledged that some disease states, such as those producing alterations in thyroid function, will alter the metabolism of clotting factors, which can, in turn, affect warfarin requirements. A detailed review of these drug–disease interactions is beyond the scope of this article.

The practice tool was reviewed by the clinical pharmacist leaders and interested staff of 2 anticoagulation management services in Alberta. Because the 2 clinical pharmacist leaders spearheaded the development of intellectual content for provincial educational programs focusing on anticoagulation management, a portion of the tool was integrated into those programs. Specifically, a portion of an earlier version of the tool was included in a paper-based overview entitled "Anticoagulation: On the Road to Practice Change" and another version was included as a handout for individuals attending a 2-day workshop administered through the Office of Continuing Pharmacy Education, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, in the fall of 2009.[5] Since then, the practice tool has been updated as described above.

Mechanisms of drug interactions

Warfarin is well absorbed, is highly bound to the plasma proteins (99%) and is metabolized via the cytochrome P450 system.[1] It is an indirect anticoagulant, exerting its effect by preventing the internal recycling of oxidized vitamin K to reduced vitamin K. Reduced vitamin K is necessary to enable carboxylation of the terminal g-glutamic acid residue of the vitamin K–dependent clotting factors (factors II, VII, IX and X). The metabolism of warfarin allows for both pharmacokinetic and pharmacodynamic mechanisms for drug interactions.

Induction or inhibition of cytochrome P450 isozymes

Warfarin has 2 active isomers.[1] The *S*-isomer is approximately 2 to 4 times more potent than the *R*-isomer and is metabolized primarily by the cytochrome P450 2C9 isozyme (CYP2C9). The *R*-isomer is metabolized by cytochrome P450 1A2 and 3A4 isozymes. Drugs that induce or inhibit these enzyme systems have the ability to alter warfarin metabolism and to decrease or increase the INR, respectively. Most notable are interacting substances that affect CYP2C9, given the increased potency of the *S*-isomer. Interactions involving these isoenzymes tend to be delayed, for a variety of reasons. First, the complete effect of the interaction will not be observed until the interacting agent has reached a steady state (about 5 half-lives).[6] Second, given the indirect effect of warfarin, time must be allowed for the newly established "warfarin concentration" to affect the vitamin K–dependent clotting factors being newly synthesized by the liver. Concomitantly, clotting factors present in the circulation before initiation of the interacting agent must be depleted. An effect on the INR is typically observed within 3 to 5 days for interacting substances with short half-lives. The effect on the INR of drugs with longer half-lives will be even further delayed. Generally, onset and offset occur over similar intervals. Relative to inhibitory interactions, the onset of induction interactions takes longer because of the time required for up-regulation (i.e., the process of induction) and synthesis of new proteins and enzymes. The full impact of steady-state interactions may not be apparent for 2 to 3 weeks, depending on the inducer involved. Likewise, when the inducer is discontinued, a wash-out period of several weeks may be required before normalization of the hepatic enzymes. These factors must all be considered when dosing and monitoring warfarin.[6]

Displacement of binding with plasma proteins

As noted above, warfarin is highly bound to proteins (primarily albumin) in the plasma and has the potential for interactions with other highly protein-bound substances. The effect is usually transient and the clinical significance may be questionable.[7] This type of interaction is probably more significant in the presence of an enzyme inhibitor, because the body is unable to compensate by increasing the metabolism of the higher free fraction of the displaced drug.

Alterations in vitamin K status

Dramatic alterations in vitamin K status can affect the INR. For example, increases in the consumption of vitamin K through the diet or supplements will decrease the INR, whereas reductions in vitamin K, through decreased consumption or increased elimination (e.g., diarrhea or medi-

cations altering gastrointestinal flora), tend to increase the INR. Patients should be encouraged to have a consistent overall consumption of vitamin K to avoid this type of variation.

Broad-spectrum antibiotics are postulated to potentiate warfarin by altering the normal intestinal flora, thereby reducing the body's ability to synthesize vitamin K. However, this factor is unlikely to be clinically significant for most patients, except those who are malnourished or have other issues with malabsorption.[7,8]

Contribution of hemorrhagic or thrombotic risk

Any medication that impairs the platelets' ability to function (e.g., acetylsalicylic acid, clopidogrel, nonsteroidal anti-inflammatory drugs) and is given concomitantly with warfarin may increase the risk of bleeding without affecting the INR. Conversely, certain medications (such as estrogens) increase the risk of thrombosis and their use in patients who are taking warfarin must be carefully assessed.[9]

Clinical use of the practice tool

This practice tool is designed to be used for patients already taking warfarin who are beginning therapy with a potentially interacting drug. To apply the practice tool to an individual patient, the clinician will need some basic information about the patient. First, assess the individual's risk of clotting (according to the indication for warfarin) in relation to his or her risk of bleeding. On the basis of this assessment, conceptually define whether you would rather have the patient's next INR value above or below the target INR range. Second, assess the patient's current anticoagulation status. Whether the patient is at the higher or lower end of the therapeutic INR range may influence your decision about altering the warfarin dosage. Because many patients take different amounts of warfarin on different days of the week, changes in the warfarin regimen are typically determined in terms of a percentage change in the weekly dose. Third, review the practice tool to determine the onset of the interaction and the expected degree of alteration in the INR (if reported), consider the need to alter the present dose of warfarin and estimate the appropriate time for follow-up INR testing. Finally, take into account the offset of the interaction, giving consideration to clinical experience, published reports, the half-life of the interacting drug (and hence its clearance from the body) and the mechanism of the interaction (recognizing that induction or inhibition of hepatic CYP450 isozymes may add to the complexity of the interaction and result in further delays in the offset). Once these factors have been accounted for, it should be possible to estimate the timing of resumption of the baseline (maintenance) warfarin dose.

We hope that this practice tool will assist clinicians in providing proactive patient care in managing interactions between warfarin and other drugs. ■

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PRACTICE TOOL **Warfarin drug interactions***

Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{½}$)†	Suggested management
Acarbose[10]	↑ INR Moderate	Unknown: effect may be due to increase in warfarin absorption or to drug-associated diarrhea	2–3 days	NR ($t_{½}$ = 2 hours)	Monitor INR closely when starting or stopping acarbose
Acetaminophen[10,11] (doses >2 g/d)	↑ INR Moderate	Decrease in warfarin metabolism and/or decrease in production of clotting factors	2–5 days	NR ($t_{½}$ = 2–4 hours)	Monitor INR when starting or stopping higher doses of acetaminophen; minimize use of drug (e.g., <2 g/d for short courses [<1 week])
Allopurinol[10]	↑ INR Moderate	Unknown	3–5 days	NR ($t_{½}$ = 1–2 hours; for active metabolite, oxypurinol, $t_{½}$ = 15–25 hours)	Reports of interaction are inconsistent; monitor INR when starting or stopping allopurinol Reassess in 1 week
Amiodarone[10,12]	↑ INR Moderate to severe	Inhibition of warfarin metabolism; amiodarone may also increase or reduce INR by inducing hyper- or hypothyroidism, respectively	3–7 days	~ 90 days; may be longer if amiodarone therapy is prolonged ($t_{½}$ = 26–107 days)	Monitor INR closely (i.e., weekly) when starting or stopping amiodarone; if loading doses of amiodarone are used, interaction will occur sooner; AMS considers empiric 10%–25% warfarin dose reduction 1 week after starting amiodarone, in anticipation of eventual dose reductions of up to 60%
Amprenavir‡[10,13,14]	↑ INR Moderate	May inhibit warfarin metabolism (through CYP3A4 inhibition)	Delayed	Delayed ($t_{½}$ = 7–10 hours)	Monitor INR more frequently when starting or stopping amprenavir; addition of ritonavir booster (CYP2C9, CYP1A2 inducer) may result in net decrease in INR; see entry for ritonavir for additional information
ASA[10,15]	No effect at doses < 6 g/d, ↑ risk of bleeding Major	Irreversible inhibition of platelet function	1–3 days	5–7 days (inhibitory effects of ASA on platelets last for lifetime of each platelet)	Use lowest effective dose of ASA; use enteric-coated formulation; monitor for bleeding
Atazanavir‡[10,14,16,17]	↑ INR Moderate	May inhibit warfarin metabolism (through CYP3A4 inhibition)	Delayed	Delayed ($t_{½}$ = ~7 hours)	Monitor INR more frequently when starting or stopping atazanavir; addition of ritonavir booster (CYP2C9, CYP1A2 inducer) may result in net decrease in INR; see entry for ritonavir for additional information
Azathioprine and mercaptopurine[10,18]	↓ INR Moderate	Possible increase in warfarin metabolism	1–3 days	NR ($t_{½}$ = 5 hours)	Monitor INR when azathioprine therapy is started or discontinued or dosage is adjusted; significantly more (2- to 3-fold) warfarin may be required when given concurrently with azathioprine
Azithromycin[10,19]	↑ INR Moderate	Possible decrease in warfarin metabolism; interaction is often compounded by other factors that may increase INR (e.g., fever, decreased appetite)	3–7 days	NR ($t_{½}$ = 68 hours)	Inconsistent effect; monitor INR closely when starting or stopping azithromycin; AMS will not empirically decrease warfarin unless patient has other factors affecting INR (e.g., fever, decreased appetite)

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Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{½}$)†	Suggested management
Bismuth subsalicylate[10]	↑ risk of bleeding Moderate	Possible displacement of protein binding	1–3 days	NR ($t_{½}$ = 2–5 hours)	Avoid this drug, if possible, especially at high doses; monitor INR and monitor for bleeding
Bosentan[10]	↓ INR Moderate	May induce warfarin metabolism (through CYP3A4 and/or CYP2C9)	5–10 days	NR ($t_{½}$ = 5–8 hours)	Monitor INR when starting or stopping bosentan; AMS considers empiric 15%–20% warfarin dose increase, with further increases according to weekly INR; may need increase in warfarin dose of as much as 50%
Carbamazepine (CBZ)[10,20]	↓ INR Moderate to severe	Increase in warfarin metabolism (through CYP2C9 induction)	10–35 days	Delayed (14–40 days) ($t_{½}$ = 12–17 hours)	Monitor INR closely when starting, stopping, or adjusting CBZ; increase in warfarin dose of 50%–100% may be required when initiating CBZ; decrease warfarin dose by ~50% when stopping CBZ
Celecoxib[10]	↑ INR Major (especially in elderly patients)	Celecoxib is metabolized by CYP2C9 but does not inhibit or induce this isozyme	2–5 days	NR ($t_{½}$ = 11 h)	Monitor INR closely when starting or stopping celecoxib; monitor for bleeding; AMS considers empiric 0%–15% warfarin dose reduction
Cholestyramine[10]	↓ INR Moderate	Decrease in absorption of warfarin	1–3 days	NR	Monitor INR more frequently when starting or stopping cholestyramine; avoid administering cholestyramine within 2 hours of warfarin
Cimetidine[10]	↑ INR Moderate	Decrease in warfarin metabolism	3–5 days	~1 week ($t_{½}$ = 2 hours)	Monitor INR closely when starting or stopping cimetidine until INR is stable; consider changing to another H2RA or PPI instead of using cimetidine
Ciprofloxacin[10,21,22]	↑ INR Moderate	Unknown; may be due to CYP1A2 inhibition; interaction more prevalent among elderly patients taking multiple medications	2–5 days	2–4 days ($t_{½}$ = 3–6 hours)	Monitor INR more frequently when starting or stopping ciprofloxacin; most patients will have increase in INR, but some will experience no effect; AMS considers empiric 10%–15% warfarin dose reduction
Clarithromycin[10,23]	↑ INR Moderate	Inhibition of warfarin metabolism (through CYP3A4 inhibition)	3–7 days	NR ($t_{½}$ = 5–7 hours)	Monitor INR more frequently when starting or stopping clarithromycin; AMS considers empiric 15%–25% warfarin dose reduction
Clopidogrel[10]	No effect on INR, ↑ risk of bleeding Severe	Antiplatelet effects of clopidogrel combined with anticoagulant effect of warfarin impair clotting	~2 hours for antiplatelet impact	3–7 days (platelet aggregation is irreversibly inhibited by metabolite of clopidogrel for lifetime of the platelet)	Monitor for bleeding
Cloxacillin[10]	↑ INR Moderate	Unknown	Delayed	NR ($t_{½}$ = 0.5–1 hour)	Monitor INR frequently when starting or stopping cloxacillin; AMS will not empirically decrease warfarin unless patient has other factors affected INR (e.g., decreased appetite, fever)

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Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{½}$)†	Suggested management
Colchicine[10]	↑ INR Moderate	Possibly due to diarrhea associated with colchicine	1–3 days	1–3 days ($t_{½}$ = 26.6–31.2 hours)	If patient is experiencing significant diarrhea with colchicine (>3–4 loose stools per day), check INR; decrease in warfarin dose may be needed during concurrent therapy with colchicine
Danazol[10,24]	↑ INR Moderate	Decrease in warfarin metabolism; may relate to direct inhibition of fibrinolytic systems	3–7 days	Delayed ($t_{½}$ = 24 h)	Monitor INR when starting or stopping danazol; warfarin dose reductions of ~50% may be necessary
Darunavir‡[10,17,25,26]	↓ INR Moderate	Induction of warfarin metabolism observed with use of ritonavir (through CYP2C9, CYP1A2 induction); AUC for *S*-warfarin decreased by 21% when given with darunavir / ritonavir combination. Induction of warfarin metabolism likely due to ritonavir (through CYP2C9, CYP1A2 induction)	1 week	Delayed ($t_{½}$ = ~15 hours)	Monitor INR more frequently when starting or stopping darunavir; warfarin dose increase of up to 20% may be required; inductive effect on warfarin may be due to coadministration of ritonavir
Delavirdine[10,14,27]	↑ INR Moderate	Possible inhibition of warfarin metabolism (through CYP3A4 inhibition)	Delayed	Several days ($t_{½}$ = ~ 6 hours)	Monitor INR more frequently when starting or stopping delavirdine; decrease in warfarin dosage may be required
Diclofenac[10]	No effect on INR, ↑ risk of bleeding Moderate	Inhibition of platelets and gastroprotective prostaglandins	2–5 days	3–7 days ($t_{½}$ = 2 hours)	Minimal interaction if diclofenac administered topically; minimize oral use; watch for bleeding, especially gastrointestinal bleeding
Disopyramide[10]	↑ INR Moderate	Unknown	2–5 days	2–5 days ($t_{½}$ = 4–10 hours)	Monitor INR when starting or stopping disopyramide
Doxycycline[10,28]	↑ INR Moderate	Unknown; possible inhibition of CYP3A4-mediated warfarin metabolism and/or protein-binding displacement	2–5 days	NR ($t_{½}$ = 15–24 hours)	Monitor INR when starting or stopping doxycycline; AMS will not empirically decrease warfarin unless patient has other factors affecting INR (e.g., decreased appetite, fever)
Dronedarone[29]	↔ or ↑ INR Mild	Dronedarone 600 mg bid increased *S*-warfarin 1.2-fold via moderate inhibition of CYP3A4, INR increased 1.07-fold	3-5 days	NR ($t_{½}$ = 25–30 hours; completely eliminated after 2 weeks)	No evidence of safety concerns with coadministration in clinical trials
Efavirenz[10,14,30]	↑ or ↓ INR Moderate to severe	Inhibition or induction of warfarin metabolism (efavirenz induces CYP3A4 and may inhibit CYP2C9)	2–3 weeks	Several weeks ($t_{½}$ = 40–55 hours)	Consider empiric reduction of warfarin dose; monitor INR more frequently when starting or stopping efavirenz; one patient required 4-fold reduction in warfarin dose[30]
Erythromycin[10]	↑ INR Moderate	Decrease in warfarin metabolism (through CYP3A4 inhibition)	3–5 days	3–5 days ($t_{½}$ = ~1.5 hours)	Monitor INR when starting or stopping erythromycin; AMS considers empiric 10%–15% warfarin dose reduction

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Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{1/2}$)†	Suggested management
Ethinyl estradiol[10]	↑ or ↓ INR ↑ or ↓ anticoagulation Moderate	Unknown; case reports of substantial increase in INR after administration of emergency contraceptive pill; long-term estrogen therapy thought to be thrombogenic	2–7 days	Delayed ($t_{1/2}$ = 13–27 hours)	Avoid concurrent use if possible; monitor INR closely; monitor clinically for signs of bruising or bleeding
Etravirine[14,17,31]	↑ INR Moderate	Inhibition of warfarin metabolism (through CYP2C9 inhibition)	1–2 weeks	1–2 weeks ($t_{1/2}$ = 41 hours)	Consider empiric reduction of warfarin dose; monitor INR more frequently when starting or stopping etravirine
Fenofibrate[10,32]	↑ INR Major	Unknown	5–10 days	Delayed ($t_{1/2}$ = 20–22 hours)	Monitor INR closely (i.e., weekly) when starting or stopping fenofibrate; AMS considers initial empiric 10%–15% warfarin dose reduction, in anticipation of eventual reduction of up to 40%
Fluconazole[8,10,33]	↑ INR Moderate	Inhibition of warfarin metabolism (via CYP2C9- and CYP3A4)	2–3 days	7–10 days ($t_{1/2}$ = ~30 hours; prolonged in elderly patients)	Monitor INR closely when starting or stopping fluconazole; effects more pronounced in patients with reduced renal function due to reduced clearance of fluconazole; AMS considers empiric 25%–30% warfarin dose reduction, with eventual reductions approaching 80%
Fluvastatin[10,34]	↑ INR Moderate	Inhibition of warfarin metabolism (via CYP2C9)	1–3 weeks	Delayed ($t_{1/2}$ = 2.5 h)	Monitor INR when starting or stopping fluvastatin; consider alternate statin (interactions involving pravastatin and atorvastatin have not been reported)
Fosamprenavir‡[10,13,14,17]	↑ INR Moderate	Possible inhibition of warfarin metabolism (through CYP3A4 inhibition)	Delayed	Several days to weeks ($t_{1/2}$ = ~ 7.7 hours)	Monitor INR more frequently when starting or stopping fosamprenavir; addition of ritonavir booster (CYP2C9, CYP1A2 inducer) may result in net reduction in INR; see entry for ritonavir for additional information
Gemfibrozil[10,35,36]	↑ INR Moderate	Inhibition of warfarin metabolism (via CYP2C9); displacement of warfarin from plasma-protein binding sites	5–7 days	Delayed ($t_{1/2}$ = 1.3 h)	Monitor INR when starting or stopping gemfibrozil; consider empiric 10%–30% warfarin dose reduction, with ongoing monitoring (based on published case reports)[35]
Glyburide[10]	↑ INR Moderate	Unknown	Delayed	Delayed ($t_{1/2}$ = 5–10 hours)	Monitor INR closely when starting or stopping glyburide
Ibuprofen[10]	No effect, ↑ risk of bleeding Moderate	Inhibition of functioning of platelets and gastroprotective prostaglandins	~2–5 days	3–7 days ($t_{1/2}$ =1.8–2.4 hours)	Monitor for bleeding (especially gastrointestinal); minimize or avoid concurrent use of ibuprofen; take with food

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Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{1/2}$)†	Suggested management
Indinavir‡[10,14,17,37]	↑ or ↓ INR Moderate	Inhibition of warfarin metabolism (through CYP3A4 inhibition)	Several weeks	1 week ($t_{1/2}$ =1.4–2.2 hours)	Monitor INR more frequently when starting or stopping indinavir; paradoxical case report described unboosted indinavir leading to decrease in INR, which required 50% increase in warfarin dose[37]; addition of ritonavir booster (CYP2C9, CYP1A2 inducer) may result in net reduction in INR; see entry for ritonavir for additional information
Indomethacin[10]	Potential ↑ INR, ↑ risk of bleeding Moderate	Inhibition of platelet aggregation and gastroprotective prostaglandins	2–5 days	3–7 days ($t_{1/2}$ = 4.5 hours)	Monitor INR with concomitant use; monitor for bleeding (especially gastrointestinal); minimize use; take with food
Isoniazid[10,21]	↑ INR Moderate	Inhibition of warfarin metabolism (via CYP2C9)	3–5 days	Delayed ($t_{1/2}$ = ~1–4 hours)	Monitor INR when starting or stopping isoniazid; consider empiric 10%–15% warfarin dose reduction initially, then further reductions based on close monitoring of INR (at least weekly)
Isotretinoin[10,38]	↓ INR Moderate	Possible CYP-enzyme induction	Unclear	Unclear ($t_{1/2}$ = 10–20 hours)	Monitor INR when starting or stopping isotretinoin; case reports indicate that increase in warfarin dose of 33%–50% may be required[38]
Itraconazole and ketoconazole[10]	↑ INR Moderate	Inhibition of warfarin metabolism (via CYP2C9 and CYP3A4)	2–5 days	3–14 days (itraconazole $t_{1/2}$ = 64 ± 32 hours; ketoconazole $t_{1/2}$ = 2–12 hours)	Monitor INR closely when starting or stopping itraconazole or ketoconazole; AMS considers empiric 25%–30% warfarin dose reductions
Lactulose[10]	↑ INR Moderate	Decreased intestinal absorption of vitamin K	1–3 days	Delayed	Monitor INR closely when starting or stopping lactulose
Lansoprazole[10]	↑ INR Moderate	Unknown	2–7 days	NR ($t_{1/2}$ = 0.9–1.5 hours)	Monitor INR when starting or stopping lansoprazole; consider re-assessing INR in 1 week
Leflunomide[10,39]	↑ INR Major	Inhibition of warfarin metabolism (via CYP2C9)	2–10 days	Delayed ($t_{1/2}$ = ~2 weeks)	Monitor INR closely when starting or stopping leflunomide
Levofloxacin[10,21,40,41]	↑ INR Moderate	Unknown; possible CYP1A2 inhibition; clinically significant interaction more common among elderly patients	3–5 days	5–10 days	Monitor INR closely when starting or stopping levofloxacin; INR will be affected by severity of illness; AMS considers empiric 0%–15% warfarin dose reduction
Levothyroxine[10]	↑ INR Moderate	Patients with hypothyroidism have higher requirements for warfarin because of decreased catabolism of clotting factors; correcting hypothyroidism therefore decreases warfarin requirements	1–2 weeks	1–2 weeks ($t_{1/2}$ = 6–7 days)	Monitor INR closely (every 1–2 weeks) when starting or adjusting levothyroxine; adjust warfarin gradually according to INR results

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Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{½}$)†	Suggested management
Lopinavir/ritonavir (Kaletra)‡[10,14,30,37,42,43]	↓ INR Moderate	Increase in warfarin metabolism (through CYP2C9, CYP1A2 induction)	Several days to weeks	Several days to weeks ($t_{½}$ = 5–6 hours)	Monitor INR more frequently when starting or stopping lopinavir–ritonavir; at steady-state, induction interaction more likely to prevail, resulting in reduced INR, requiring up to a 2-fold warfarin dose increase; see also entry for ritonavir
Mesalamine[10,44]	↓ INR Mild to moderate	Unknown	Delayed	NR ($t_{½}$ = 0.6–1.4 hours)	Monitor INR when starting or stopping mesalamine; one patient experienced dramatic decline in INR and deep vein thrombosis, but INR became therapeutic once mesalamine was stopped[44]
Methimazole[10]	↓ INR Moderate	Increased catabolism of clotting factors with introduction of methimazole and return of euthyroidism increases warfarin requirements	3–10 days	1–2 weeks ($t_{½}$ = 2–3 hours)	Monitor INR closely when starting, stopping, or adjusting methimazole
Methyl salicylate (topical)[10,45]	↑ INR, ↑ risk of bleeding Moderate	Inhibition of warfarin metabolism and platelet aggregation	Delayed	NR	Monitor INR closely; consider alternative therapy (topical capsaicin is preferred alternative)
Metronidazole[10]	↑ INR Major	Decrease in warfarin metabolism (through CYP2C9 inhibition)	3–5 days	~ 2 days ($t_{½}$ = 8 hours)	Monitor INR closely when starting or stopping metronidazole; AMS considers empiric 25% –40% warfarin dose reduction
Miconazole (oral, topical, or vaginal formulation)[10,46,47]	↑ INR Moderate	Inhibition of warfarin metabolism (via CYP2C9 and CYP3A4)	2–5 days	2–5 days ($t_{½}$ = 24 hours)	Monitor INR closely when starting or stopping topical, vaginal, or oral miconazole; consider alternative therapy (e.g., clotrimazole, which has no interaction with warfarin); AMS considers empiric 25%–30% warfarin dose reduction
Moxifloxacin[10,21,48]	↑ INR Major	Unknown; possible inhibition of CYP1A2; clinically significant interaction more common among elderly patients	2–5 days	2–3 days ($t_{½}$ = ~12.7 hours)	Monitor INR closely when starting or stopping moxifloxacin; INR will be affected by severity of illness; AMS considers 0%–25% warfarin dose reduction
Naproxen[10]	No effect on INR, ↑ risk of bleeding Major	Inhibition of platelet aggregation and production of gastroprotective prostaglandins	2–5 days	3–7 days ($t_{½}$ = 12–15 hours)	Monitor closely for bleeding (especially gastrointestinal); avoid or minimize concurrent use; take with food
Nelfinavir[10,14,43,49]	↑ or ↓ INR Moderate	Possible reduction or increase in warfarin metabolism possible (through CYP3A4 inhibition, CYP2C9 induction)	Several days	Several days ($t_{½}$ = 3.5–5 hours)	Monitor INR frequently when starting or stopping nelfinavir
Nevirapine[10,14,17,43,50,51]	↓ INR Moderate to severe	Increase in warfarin metabolism (through CYP3A4 induction)	Several days to weeks	Several days to weeks ($t_{½}$ = 45 hours)	Monitor INR more frequently when starting or stopping nevirapine; 2- to 4-fold increase in warfarin dose may be required (based on case reports)[43,50,51]

PRACTICE TOOL **Warfarin drug interactions***

Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{½}$)†	Suggested management
Omeprazole[10]	↑ INR Mild to moderate	Decrease in warfarin metabolism through stereoselective inhibition of the hepatic metabolism of the less potent (*R*)-warfarin enantiomer	3–5 days	NR ($t_{½}$ = 0.5–1 hour)	Interaction of doubtful clinical significance; minimal effect on INR; no empiric warfarin dose adjustment required
Orlistat[10]	↑ INR Moderate	Decreased absorption of fat-soluble vitamins, including vitamin K	Unknown	NR	Monitor INR closely with concomitant use; avoid concomitant use if possible
Phenobarbital[10,36]	↓ INR Moderate	Induction of hepatic metabolism of warfarin	Delayed	NR ($t_{½}$ = 1.5–4.9 days)	Monitor INR closely, especially when starting or stopping phenobarbital; according to published reports, 30%–60% warfarin dose increases may be required after barbiturate initiation[11,36]
Phenytoin[10,36,52]	Initially, transient ↑ in risk of bleeding; with long-term use, ↓ INR Moderate	Initially, displacement of warfarin from protein-binding sites; with long-term use, induction of hepatic metabolism of warfarin	Initial: 1–3 days Subsequent: 2–4 weeks	10–14 days ($t_{½}$ = 22 hours)	Monitor INR closely when starting or stopping phenytoin; AMS recommends no empiric dose adjustment when phenytoin is initiated, but monitoring of INR at least weekly; some patients may require up to 50% warfarin dose increase several weeks after phenytoin is initiated; warfarin also affects phenytoin concentration
Prednisone[10]	↑ or ↓ INR Mild	Unknown	Delayed	NR ($t_{½}$ = 2.6–3 hours)	Monitor INR when starting or stopping prednisone; AMS recommends no empiric dose adjustment when initiating prednisone; warfarin dose adjustment may be required for patients receiving large bolus or pulse doses of steroids; monitor for bleeding
Propafenone[10,53]	↑ INR Moderate	Decrease in warfarin metabolism; 39% increase in plasma concentration of warfarin reported[53]	2–5 days	~2 days ($t_{½}$ = 2–10 h)	Monitor INR when starting or stopping propafenone; AMS empirically reduces warfarin dose by 15%–30% and monitors closely, with further reductions as required
Propoxyphene[10]	↑ INR Moderate	Unknown (may be due to propoxyphene alone or to acetaminophen component when used in combination)	Delayed	NR ($t_{½}$ = 2.6–3 hours)	Monitor INR when starting or stopping propoxyphene (based on published case reports only)[11]
Propylthiouracil[10]	↓ INR Moderate	Increased catabolism of clotting factors with introduction of propylthiouracil and return of euthyroidism increases requirement for warfarin	Within 2 weeks	1–2 weeks ($t_{½}$ = 1.5–5 hours)	Monitor INR closely when starting, stopping, or adjusting dose of propylthiouracil
Quetiapine[10,54]	↑ INR Moderate	Competitive inhibition of CYP3A4 and CYP2C9	7–14 days	NR ($t_{½}$ = ~6 h)	Monitor INR when starting or stopping quetiapine (based on single case report only)[54]
Raloxifene[10]	↓ INR Moderate (based on single-dose studies only; no data on long-term use)	Unknown	Rapid	NR ($t_{½}$ = 27 hours)	Monitor INR closely when starting or stopping raloxifene

PRACTICE TOOL **Warfarin drug interactions***

Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{1/2}$)†	Suggested management
Ranitidine[10]	↑ INR Moderate	Inhibition of hepatic metabolism of warfarin	1–2 weeks	3–7 days ($t_{1/2}$ = 1.9–3 hours)	Monitor INR when starting or stopping ranitidine; consider using famotidine or nizatidine instead of ranitidine
Ribavirin[55]	↓ INR Moderate	Unknown	2–4 weeks	2–4 weeks ($t_{1/2}$ = 298 hours)	Monitor INR frequently when initiating or discontinuing ribavirin in patients taking warfarin until INR stabilizes (~4 weeks)
Rifampin[10,56]	↓ INR Moderate to severe	Induction of hepatic metabolism of warfarin	1–3 weeks	1–5 weeks ($t_{1/2}$ = 1.5–5 hours)	Monitor INR carefully (at least weekly) when starting or stopping rifampin; AMS considers empiric 25%–50% warfarin dose increase initially, with further increases based on frequent monitoring of INR (at least weekly); patients may require 2–3 times their regular weekly warfarin dose when rifampin is added
Ritonavir‡[10,14,17,37,49,57,58]	↑ or ↓ INR Moderate	Induction of warfarin metabolism (through CYP2C9, CYP1A2 induction)	Several days to weeks	1 week ($t_{1/2}$ = 3–5 hours)	Monitor INR more frequently when starting or stopping ritonavir; up to 2-fold increase in warfarin dose[37,57] and 3-fold increase in acenocoumarol dose[58] documented in case reports; another case report documented the opposite effect (increased INR requiring vitamin K and decrease in warfarin dose);[49] see also entry for lopinavir–ritonavir
Ropinirole[10]	↑ INR Severe	Competitive inhibition of CYP1A2-mediated warfarin metabolism and/or displacement of warfarin from binding sites	5–10 days	NR ($t_{1/2}$ = 6 hours)	Monitor INR closely when starting or stopping ropinirole (based on single published case report)[10]
Rosuvastatin[10,59]	↑ INR Moderate	Unknown	3–7 days	3–7 days ($t_{1/2}$ = 19 hours)	Monitor INR when starting or stopping rosuvastatin; consider alternative statin (no reports of interaction with warfarin for atorvastatin or pravastatin); AMS empirically reduces warfarin dose by 10%–25% and reassesses INR within 1 week
Saquinavir‡[10,14,60]	↑ INR Moderate	Decrease in warfarin metabolism (through CYP3A4 inhibition)	Up to 4–8 weeks	3–7 days ($t_{1/2}$ = 13 hours)	Consider empiric decrease in warfarin dose with use of unboosted saquinavir; monitor INR more frequently when starting or stopping saquinavir; one patient required a 20% decrease in warfarin dose with unboosted saquinavir;[60] addition of ritonavir booster (CYP2C9, CYP1A2 inducer) may result in net decrease in INR; see entry for ritonavir for additional information
Simvastatin[10,34,61]	↑ INR Mild to moderate	Competition for CYP3A4-mediated metabolism	3–7 days	3–7 days ($t_{1/2}$ = 3 hours)	Monitor INR when starting or stopping simvastatin; interaction may range from negligible to clinically significant; consider using alternative statin (atorvastatin or pravastatin)

PRACTICE TOOL **Warfarin drug interactions***

Drug	Direction and severity of effect on INR	Mechanism	Anticipated onset	Anticipated offset ($t_{½}$)†	Suggested management
Sulfamethoxazole[10,62,63] (with or without trimethoprim)	↑ INR Severe	Inhibition of warfarin metabolism and displacement of warfarin from protein-binding sites	2–5 days	2–14 days ($t_{½}$ = 10 hours)	Monitor INR closely when starting or stopping sulfamethoxazole-containing drug regimens; AMS considers empiric 25%–40% warfarin dose reduction
Sulfasalazine[64]	↓ INR Moderate	Unknown	Unknown	NR ($t_{½}$ = ~7.6 hours)	Monitor INR frequently when starting or stopping sulfasalazine; one patient required 250% increase in weekly warfarin dose when sulfasalazine was started[64]
Sulfinpyrazone[10]	↑ INR Moderate	Inhibition of warfarin metabolism (primarily *S*-isomer)	Delayed	1–2 weeks ($t_{½}$ = 4–4.3 hours)	Monitor INR when starting or stopping sulfinpyrazone; average daily warfarin dose decreased by ~50% in small case series[11]
Terbinafine[10]	Both ↑ and ↓ INR have been reported Moderate	Unknown	Unknown	NR ($t_{½}$ = 36 hours)	Monitor INR when starting or stopping terbinafine
Tetracycline[10]	↑ INR Moderate	Reduced plasma prothrombin activity	2–5 days	NR ($t_{½}$ ~8–10 hours)	Monitor INR
Ticlopidine[10]	↑ INR, ↑ risk of bleeding Moderate	Inhibition of metabolism of *R*-warfarin (minimal increase in INR); decreased platelet aggregation	1–5 days	3–7 days for platelet function to return to baseline	Monitor INR when starting or stopping ticlopidine; monitor for increased bleeding (patient may be at risk even if INR does not increase)
Tipranavir‡[10,14,17,50,65]	↔ or ↓ INR Mild	Possible increase in warfarin metabolism (through CYP3A4 induction); however manufacturer predicts ↔ on *S*-warfarin concentration	Delayed	Several days to weeks ($t_{½}$ = 5.5–6 hours)	Monitor INR more frequently when starting or stopping tipranavir; addition of ritonavir booster (CYP2C9, CYP1A2 inducer) may result in net decrease in INR; use caution when combining with warfarin, as tipranavir has been associated with increased risk of intracranial hemorrhage; see entry for ritonavir for additional information
Tramadol[10,66]	↑ INR Moderate	Unknown (possible inhibition of CYP3A4-mediated warfarin metabolism)	3–7 days	3–7 days ($t_{½}$ = 5.6–6.7 hours)	Monitor INR when starting or stopping tramadol; dose reductions of 25%–30% may be required; AMS considers empiric 0%–20% warfarin dose reduction
Voriconazole[10]	↑ INR Major	Inhibition of CYP2C9-mediated metabolism of *S*-warfarin	3–7 days	NR ($t_{½}$ = 6 hours)	Monitor INR carefully when starting or stopping voriconazole; AMS considers empiric 25%–30% warfarin dose reduction

AMS = Anticoagulant Management Service; ASA = acetylsalicylic acid; AUC = area under the curve; CYP = cytochrome P450; H2RA = histamine$_2$ receptor antagonist; INR = international normalized ratio; NR = not reported; PPI = proton pump inhibitor; $t½$ = half-life.

*AMS management is done in reviewing the patient's current anticoagulation status in light of their overall bleed versus clot risk. Each patient must be assessed individually. Management options, when suggested, reflect practices / options within 2 large anticoagulation clinics in Alberta. Information in this tool should be used with clinical judgment. This tool does not contain all drug products that may interact with warfarin and should not be used as a substitute for comprehensive references.

†Elimination half-life assumes oral dosing in an adult with normal renal and hepatic function.

‡With the exception of nelfinavir, protease inhibitor therapy includes low-dose ritonavir, which serves as a therapeutic booster to increase concentrations of other protease inhibitors. Interpretation of interaction data should also take into account the impact of ritonavir on warfarin metabolism (anticipate an inductive effect at steady-state, which would result in subtherapeutic INR and a need to increase the dose of warfarin). For more information, refer to sections on lopinavir–ritonavir and ritonavir.

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