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Drug Interactions Affecting Oral Anticoagulant Use

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Abstract

Oral anticoagulants (OAC) are medications commonly used in patients with atrial fibrillation and other cardiovascular conditions. Both warfarin and direct oral anticoagulants (DOAC) are susceptible to drug-drug interactions (DDI). DDI are an important cause of adverse drug reactions and exact a large toll on the healthcare system. DDI for warfarin mainly involve moderate to strong inhibitors / inducers of cytochrome P450 (CYP) 2C9, which is responsible for the elimination of the more potent S-isomer of warfarin. However, inhibitor / inducers of CYP3A4 and CYP1A2 may also cause DDI with warfarin. Recognition of these precipitating agents along with increased frequency of monitoring when these agents are initiated or discontinued will minimize the impact of warfarin DDI. DOAC DDI are mainly affected by medications strongly affecting the permeability glycoprotein (P-gp), and to a lesser extent, strong CYP3A4 inhibitors / inducers. Dabigatran and edoxaban are affected by P-gp modulation. Strong inducers of CYP3A4 or P-gp should be avoided in all patients taking DOAC unless previously proven to be otherwise safe. Simultaneous strong CYP3A4 and P-gp inhibitors should be avoided in patients taking apixaban and rivaroxaban. Concomitant antiplatelet / anticoagulant use confers additive risk for bleeding, but their combination is unavoidable in many cases. Minimizing duration of concomitant anticoagulant/antiplatelet therapy as indicated by evidence-based clinical guidelines is the best way to reduce the risk of bleeding.

Keywords

drug interactions; anticoagulant drugs; direct oral anticoagulants; vitamin K antagonists; pharmacokinetics

Introduction

Oral anticoagulants (OACs) are now commonly prescribed for atrial fibrillation (AF) and other conditions associated with risk for thromboembolism.[1–4] These conditions occur more frequently in older patients who are also at higher risk for the bleeding complications of OACs.[5, 6] As of 2017, over 37 million people worldwide have AF with the highest risk among developed countries.[5] While vitamin K antagonists (VKA) have long been associated with a narrow therapeutic index, clinically relevant changes in the serum concentration of direct acting oral anticoagulants (DOACs) can also alter their efficacy and safety.[7] It is estimated that up to 80% of AF patients will receive a medication that interacts with their OAC over their lifetime.[8] Thus, it is important for clinicians to be aware of the common medications that interact with OACs.

In this state-of-the-art review, we summarize drug-drug interactions (DDI) and drug-food interactions affecting VKAs and DOACs and provide recommendations to minimize adverse interactions. Recommendations in this paper will generally apply to patients without significant genetic polymorphisms that precipitate increased or decreased drug clearance. The benefits of pharmacogenetic testing prior to initiation of both VKA and DOAC have been studied, however, there is currently not enough evidence to recommend routine pharmacogenetic testing in clinical practice.[9–12] Throughout the paper, we refer to specific drugs as strong, moderate or weak inhibitors of cytochrome P450 (CYP) enzymes, according to the following definitions: a strong inhibitor causes a > 5-fold increase in the plasma area under the plasma concentration versus time curve (AUC) or ≥80% decrease in clearance; a moderate inhibitor causes a > 2-fold increase in the AUC or ≥50% to <80% decrease in clearance; a weak inhibitor causes a > 1.25-fold increase in the AUC or ≥20% to <50% decrease in clearance.[13] A strong CYP inducer will decrease the AUC ≥80%; a moderate inducer will decrease the AUC by ≥50% to <80%; and a weak inducer will decrease AUC by ≥20% to <50%.

Vitamin K Antagonist: Warfarin

Pharmacodynamics and pharmacokinetics of warfarin

Warfarin, a vitamin K epoxide reductase inhibitor, exerts its anticoagulation effects by inhibiting synthesis of vitamin K, which is required to activate key components of the coagulation cascade (Figure 1).[14] Commercially available warfarin is a racemic mix of 2 active stereoisomers: the S-enantiomer, metabolized by the CYP2C9 enzyme, is approximately 5 times more potent than the R-enantiomer, which is primarily metabolized by CYP3A4, but with contributions from CYP1A1, CYP1A2, CYP2C8, CYP2C18, and CYP2C19. [13, 15, 16] Warfarin is almost completely eliminated via hepatic metabolism with an elimination half-life of 35 hours.[15] It is highly bound to plasma proteins with anticoagulant effects stabilizing approximately 3 days after warfarin plasma concentrations reach steady state.[15, 16]

Drug Interactions

There are over 500 distinct warfarin drug interactions reported in the literature.[17] For the majority of these interactions, there is a lack of consensus regarding their clinical significance.[17] Moreover, certain warfarin drug interactions may only be clinically relevant under certain circumstances, such as, in patients with certain genetic polymorphisms of CYP2C9 substrates.[18]

The order of initiation of a precipitant drug versus warfarin can also affect the impact of a warfarin-drug interaction. When warfarin is initiated in the setting of a CYP2C9 inhibitor, as is estimated to occur 20% of the time, a patient may not develop a supratherapeutic INR because monitoring is more frequent during the initiation phase of warfarin.[19, 20] However, if the same precipitant drug is initiated in the setting of chronic and stable warfarin therapy, then the patient may develop an elevated INR if the interaction goes unrecognized and more frequent INR monitoring is not performed. Figure 2 depicts a simple algorithm clinicians can use to screen and manage drug interactions with warfarin use. Given the plethora of

warfarin-drug interactions, it is helpful to categorize the interactions into certain high-risk drug classes.[14]

Antibiotics

All antibiotics can alter the gut microbiome, which is a rich source of vitamin K, and thereby potentiate anticoagulant effects of warfarin.[16, 21] Thus, it is important to monitor INRs closely whenever antibiotics are initiated in the setting of chronic warfarin use.[14] However, antibiotics known to inhibit the CYP2C9 isoenzyme (Table 1), such as sulfonamides, including sulfaphenazole and sulfamethoxazole (commonly administered in combination with trimethoprim as trimethoprim/sulfamethoxazole), and metronidazole, can further exacerbate this interaction.[22–24] The interaction between sulfamethoxazole and warfarin has not only been described in multiple case reports, but large national insurance database analyses have confirmed the risk of serious bleeding that nearly doubles compared to patients receiving warfarin alone.[25, 26] Pre-emptive warfarin dose reductions of 25% and 33% for sulfamethoxazole and metronidazole respectively, are recommended when co-administered with warfarin.[24, 27]

CYP1A2 (Table 2) and 3A4 inhibitors decrease clearance of the less potent R-isomer of warfarin. Ciprofloxacin, a strong CYP1A2 inhibitor, can increase serum R-warfarin concentrations.[28] Other fluoroquinolones in combination with warfarin can elevate the INR and increase the risk of adverse bleeding versus those taking warfarin alone, both in case reports as well as large national database registries.[25, 26, 29] Similarly, the macrolide antibiotics have also been widely reported to potentiate warfarin's effects.[25, 26]

Clarithromycin and erythromycin are strong and moderate inhibitors, respectively, of CYP3A4.[30] (Table 3) The intravenous formulation of azithromycin was cited by the United States (US) Food and Drug Administration (FDA) in 2009 as a drug that may significantly increase the risk of bleeding when co-administered with warfarin.[16] The antibiotic dose will also contribute to the severity of this interaction. In a prospective study of 120 patients who received a combination of amoxicillin/clavulanate, patients who received the higher maintenance dose (10–12 g/day) versus the usual dose (3.6 g/day) developed a higher proportion of INR values ≥ 4.[31]

Several antibiotics have also been identified as major CYP450 enzyme inducers. Nafcillin is a CYP3A4 and CYP2C9 inducer and significantly higher maintenance doses of warfarin were required after initiating long-term (> 6 weeks) nafcillin treatment.[13, 32, 33] Several case reports for other anti-staphylococcal penicillins, including flucloxacillin and cloxacillin, show a similar effect.[34, 35] Flucloxacillin has been shown to induce CYP3A4.[36] In two patients, the dose of warfarin needed to be doubled from 5 mg/day to 10 mg/day after initiation of cloxacillin to maintain a therapeutic INR.[35] Another antibiotic well-known to induce CYP450 enzymes is rifampin.[37]

These CYP450 inducing antibiotics are particularly important because they are indicated for conditions such as endocarditis or tuberculosis which require a protracted course of treatment. After increasing the warfarin dose to account for these interactions, it is important to remember to decrease the dose of warfarin once the course of treatment with these

antibiotics is completed. The full induction of involved CYP450 enzymes appears to take 2–4 weeks after nafcillin initiation, and the effects persist for up to 2–4 weeks after nafcillin discontinuation.[32, 33] It is therefore important to more frequently monitor the INR both during the initiation and discontinuation of these particular antibiotics.[14] A list of clinically significant antibiotic-warfarin interactions is provided in Table 4.

Antifungals

The triazole antifungals fluconazole and voriconazole inhibit CYP2C9 and can increase the risk of serious bleeding in patients taking warfarin.[38–40] Fluconazole is also a moderate inhibitor of CYP3A4, while voriconazole is also a moderate inhibitor of CYP2C19.[13] Analysis of a large national prescription database of treatment for oral candidiasis demonstrated that systemic fluconazole administration was associated with increased INR levels in warfarin users.[39] Additionally, voriconazole is a moderate inhibitor of CYP2C19 and a weak inhibitor of CYP2C9.[13] Ketoconazole is a strong inhibitor of CYP3A4 and a moderate inhibitor of CYP2C19, and itraconazole is a strong inhibitor of CYP3A4.[13] Due to these CYP450 interactions, triazole antifungals should be initiated carefully and increased monitoring of the INR is warranted [14]

Topical administration of antifungals has been associated with supratherapeutic INR and bleeding events.[39, 41, 42] A large national prescription database study of oral candidiasis therapy demonstrated that miconazole oral gel use was associated with increased INRs in warfarin users. However, the same study demonstrated that nystatin oral solution use did not appreciably affect the INR, making this a good alternative for oral candidiasis.[39] Vaginal administration of miconazole cream has also been reported to potentiate bleeding among warfarin users.[42] Griseofulvin decreases the anticoagulation effect of warfarin. Patients on chronic warfarin therapy starting griseofulvin generally will require higher than baseline doses of warfarin to maintain therapeutic INR.[43]

Antivirals

Antiretroviral agents are the most common antivirals that interact with warfarin; ritonavir is the most-commonly cited drug.[44, 45] Ritonavir, a protease inhibitor capable of strong CYP3A4 inhibition, is commonly used to “boost” the potency of other protease inhibitors that are metabolized by CYP3A4.[46] Paradoxically, however, antiretroviral regimens that involve ritonavir require higher doses of warfarin to maintain INR values in the therapeutic range. The mechanism is thought to be concomitant induction of CYP2C9 and CYP1A2, which will increase clearance of the S-isomer of warfarin.[44, 45, 47] Nevirapine has also been found to increase warfarin maintenance dose requirements.[45] On the contrary, efavirenz and saquinavir potentiated effects of warfarin.[45]

With the exception of antiretrovirals, other antivirals tend to have little interaction with warfarin. A 5-day course of prophylactic oseltamivir for influenza prophylaxis maximally elevated the INR at day 4 by a mean of 0.13, not considered clinically significant.[48]

Cardiovascular medications

Statins, specifically fluvastatin, lovastatin, rosuvastatin, and simvastatin may interact with warfarin.[49–54] An analysis of a large national database registry demonstrated that atorvastatin, rosuvastatin, and simvastatin all increased the mean INR by approximately 0.3, with a peak at around 4 weeks.[55] This degree of INR elevation was not thought to be clinically significant to warrant a preemptive dose reduction of warfarin. The authors of this study recommended close monitoring after initiation of these statins, as patients with certain CYP450 genotypes may be more vulnerable.[49, 55]

The mechanism of this interaction for atorvastatin, rosuvastatin, and simvastatin is likely a combination of displacement of warfarin from plasma protein binding in addition to inhibition of CYP3A4, which will increase the unbound plasma concentration of warfarin.[51, 54] Fluvastatin, on the other hand, inhibits CYP450 2C9, and likely potentiates warfarin to a greater extent given its effect on the more potent S-isomer of warfarin.[51, 52] Pitavastatin, at a dose of 4 mg, did not appear to increase INR levels among healthy controls taking warfarin.[53] An American Heart Association (AHA) Scientific Statement recommends close monitoring of the INR after the initiation of a statin or a change in statin dose and reports that pitavastatin and atorvastatin exert the lowest impact on the INR..[54]

Other anti-hyperlipidemic mediations may interact with warfarin. Cholestyramine and other bile acid sequestrants interfere with intestinal absorption of warfarin, and while spacing warfarin administration 2 hours before or 6 hours after bile acid sequestrant administration will mitigate this interaction, this inhibition is unavoidable as warfarin undergoes enterohepatic circulation.[14, 56, 57] Case reports describe clinically significant increases in INR for patients taking gemfibrozil.[58, 59] The mechanism is unclear but the authors recommend a preemptive 20% dose reduction in warfarin maintenance doses.[58] Case reports also suggest fenofibrate may potentiate warfarin's effects[60]. However, a large retrospective study of 321patients showed no effect on the INR nor warfarin maintenance dosages after initiating fenofibrate.[61] Also, fish oil (1–2 g/day) can increase INR and has antiplatelet effects.[62] Antiplatelet and antiarrhythmic medications will be discussed in a separate section.

Psychotropics

Many psychotropic drugs can interact with warfarin.[19, 63–75] Two older antiepileptic medications, carbamazepine and phenytoin, are known inducers of multiple CYP 450; carbamazepine decreased mean INR levels by 0.63 and, in a large retrospective cohort study, patients already taking warfarin required a 50% increase in warfarin maintenance dose after initiation of carbamazepine.[69, 70] Phenytoin exerts a biphasic interaction with warfarin.[14] Upon initiation, phenytoin will displace warfarin from protein binding sites, transiently potentiating bleeding effects.[72] However, phenytoin will ultimately induce CYP 450 enzymes so that higher doses of warfarin are required to maintain therapeutic INR.[72]

Selective serotonin reuptake inhibitors (SSRI) can affect warfarin dosing.[71] In a retrospective, single-center study, the concomitant use of SSRI with warfarin more than doubled the risk of bleeding compared to warfarin alone.[76] A large national insurance

database analysis also demonstrated increased risk of hospitalization for GI bleeding following SSRI initiation.[77] The mechanism of action of these interactions is believed to be mediated by inhibition of CYP450 enzymes.[71] Fluvoxamine and fluoxetine deserve special attention as they inhibit CYP2C9 and CYP 3A4.[68, 71, 74] In these cases, sertraline and citalopram/escitalopram are better alternatives if an SSRI is required.

Other miscellaneous psychotropics that potentiate warfarin via inhibition of CYP450 enzymes include quetiapine,[75] valproic acid,[67] entacapone,[64] and tramadol.[65, 73] In contrast, Small et al. published a case series on an interaction between warfarin and trazodone possibly related to the induction of CYP450 enzymes in which high doses of warfarin were required to maintain therapeutic INR after initiation of trazodone.[73]

Cancer Chemotherapy

Several chemotherapeutic agents interact with warfarin.[78–84] Two fluoropyrimidines in particular have been widely reported to interact with warfarin: fluorouracil and capecitabine.[78, 80] Fluorouracil increases INR and the risk of bleeding via many mechanisms, including inhibition of CYP2C9, direct injury to the gastrointestinal (GI) tract, or alteration of GI flora; experts recommend decreasing the dose of warfarin prophylactically by 20–70%.[78] Capecitabine increases INR in patients taking warfarin, and decreased warfarin requirements may continue for up to two weeks after discontinuing capecitabine.[80] Gemcitabine also interacts with warfarin, and even intra-bladder instillation of gemicitabine can cause an elevated INR in patients taking warfarin.[81, 82]

Paclitaxel can potentiate warfarin anticoagulation by displacing it from protein binding sites.[84] Enzalutamide, a strong inducer of CYP2C9, enhances clearance of warfarin and the INR should be monitored closely during its initiation and following discontinuation.[79] Two cases of warfarin potentiation with concomitant trastuzumab administration have been reported.[85]

Aprepitant, a weak inducer of CYP2C9, can reduce serum plasma concentrations of warfarin.[86] Increased warfarin requirements during co-administration of aprepitant have been reported.[83]

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID) potentiate the risk of bleeding with warfarin.[14, 19, 87, 88] This increased risk of bleeding is present for non-selective cyclooxygenase (COX) as well as COX-2 selective inhibitor NSAIDs.[14, 88] The nature of this interaction extends beyond purely a pharmacological interaction, but comprises a pharmacokinetic component as well, likely involving displacement of warfarin from plasma proteins.[89] Zapata et al demonstrated that a combination of NSAID and warfarin doubles the risk of bleeding versus warfarin alone.[88] The results of a retrospective, single center study demonstrated that the odds of bleeding with concomitant NSAID and warfarin administration are similar to concomitant administration of a CYP2C9 inhibitor and warfarin.[19] Therefore, the combination of any NSAID, with the exception of aspirin in certain circumstances, and warfarin should be discouraged.[14] However, if an NSAID must be co-administered, a large retrospective national insurance database analysis suggests that

using a proton pump inhibitor may reduce the risk of GI bleeding.[90] Interactions with aspirin and other antiplatelet agents are discussed below.

Acetaminophen

Acetaminophen co-administration increases INR in a dose dependent manner, with the risk of developing an INR > 6 increasing 10-fold once acetaminophen intake exceeds 9.1 gram per week.[91] In a prospective, placebo-controlled study of patients on stable warfarin therapy, concomitant acetaminophen administration at doses >2 g/day significantly increased INR by day 3 by an average by 0.7. As a result, the authors recommend close monitoring of INR during the initiation of acetaminophen.[92]

Miscellaneous agents

Alcohol ingestion inhibits hepatic enzymes, impairs warfarin clearance and can significantly increase INR levels. However, modest consumption of alcohol (~60gm or 2 ounces/day) has been shown to be safe in patients taking warfarin.[93] A meta-analysis of smoking and warfarin demonstrated that increased warfarin dosages were required among smokers, suggesting that warfarin clearance is enhanced in smokers.[94] In a small, prospective, cohort study, omeprazole was found to interact with warfarin via inhibition of CYP450 2C19.[95] Uno et al concluded this was not a clinically significant interaction unless patients were extensive CYP2C19 metabolizers.[95] Danazol potentiates warfarin by inhibiting its metabolism, and case reports of serious bleeding have been reported.[96]

Herbal supplements

Determining risks of interactions with herbal supplements is challenging due to lack of standardization and quality control.[14] Most reported data come from case reports or small case series.[97–101] However, St. John's wort, a popular herbal antidepressant, is well-documented to enhance clearance of warfarin via induction of CY2C9, 2C19, and 3A4.[66, 71, 102] In a small, prospective cohort study amongst healthy controls, St. John's Wort increased warfarin clearance and reduced the INR by 20%.[102] In this same study, ginseng did not affect warfarin clearance or INR.[102] Ginkgo and ginger do not appear to interact with warfarin at modest doses.[103] Green tea also does not affect INR at modest doses although a case of decreased INR following excessive consumption of green tea (up to 1 gallon / day) has been reported. [104, 105] While there are multiple reports of cranberry potentiating warfarin effects, sometimes fatally, in a small, randomized, placebo-controlled trial, modest cranberry consumption did not affect INR.[99, 106] There are several case reports of various fruits (including pomegranate, avocado, grapefruit, mango, and papaya) interacting with warfarin.[100] However, these reports are limited by the lack of standardization and quantification of fruit consumed. For now, it is recommended that in patients who prefer cranberry juice, no more than 24 ounces / day be consumed.[100] In patients who prefer grapefruit juice, no more than 200cc/day should be consumed.[107] Clinicians should also inquire about consumption of mangos, pomegranate, and avocados.[100]

Direct acting Oral Anticoagulants (DOACs)

Pharmacodynamics and pharmacokinetics

Apixaban, edoxaban, and rivaroxaban exert their anticoagulant activity by selectively inhibiting factor Xa and prothrombinase, thereby preventing the conversion of prothrombin into thrombin. Dabigatran is a direct thrombin inhibitor. These drugs reduce thrombus formation and thrombin-induced platelet aggregation. Apixaban and rivaroxaban undergo some metabolism via CYP3A4 and this can create clinically relevant drug interactions.[1–4] DOACs are also substrates for the permeability glycoprotein (P-gp), a drug effluxer in the cell membranes of many barriers, with the intestinal lining and renal tubules being the sites most clinically relevant for DOAC interactions. A strong P-gp inhibitor will increase the AUC of a substrate drug by more than 2-fold.[108] A P-gp inducer that will decrease the AUC of a substrate drug by more than 50% will be referred to as a strong inducer. Figure 3 provides a useful and convenient algorithm to quickly screen for clinically significant DOAC interactions, which are listed in detail on Table 5. In certain clinical scenarios, when an combination is unavoidable, plasma level assessment of the DOAC is an option, but this should only be done at specialized centers with expertise in this area.[109]

Apixaban is 25% hepatically metabolized and a substrate for P-gp.[2] The enzyme mainly responsible for this metabolism is CYP3A4 with CYP1A2, 2C8, 2C9, 2C19, and 2J2 playing minor roles.[2] Apixaban achieves peak plasma concentration between 1–3 hours after oral administration.[110, 111] With a half-life of ~12 hours, apixaban reaches steady state levels within 3 days; it is highly bound to plasma proteins.[2, 110]

Edoxaban is minimally metabolized by CYP3A4 oxidation. While it is a substrate of P-gp, it is not affected by other transport proteins.[3] After oral administration, edoxaban plasma concentrations peak at 1.3 hours.[112] The elimination half-life is 9–11 hours, so steady state anticoagulant effects are achieved within 3 days.[112, 113] Edoxaban is 55% plasma protein bound.[3]

Rivaroxaban is metabolized by the liver more than other DOACs; 51% of the drug is recovered in the urine and feces as inactive metabolites. CYP3A4, 3A5, and 2J2 are the primary sites for oxidative degradation. Like the other DOACs, it is also a substrate for P-gp.[4] With an elimination half-life of 5–9 hours in healthy adults, steady state concentrations are expected within 2–3 days.[114] Rivaroxaban levels peak just under 2 hours after oral administration.[114] Rivaroxaban is extensively bound to plasma proteins. Of note, rivaroxaban absorption is significantly increased when administered with fatty food, so the manufacturer recommends that doses of 15–20 mg be taken with food, and, preferably, the largest meal of the day, to increase bioavailability.[4]

Dabigatran etexilate is a pro-drug, undergoing rapid ester hydrolysis to its active moiety, dabigatran, with no significant CYP 450 metabolism.[1, 115] After oral administration, plasma concentrations peak within 1.5 hours.[116] The drug is then eliminated renally with a half-life of 12–14 hours.[116, 117] Dabigatran levels are very sensitive to P-gp interactions and renal function, and it is the only DOAC that is substantially removed by dialysis.[1, 118] Dabigatran is so sensitive to P-gp modulation that it is commonly used as a probe drug to help quantify

a precipitant drug's effect on the P-gp transporter.[108] A list of P-gp modulators can be found on Table 6.

All DOACs must be dose-adjusted in the setting of renal impairment due to reduced clearance, but, in the setting of mild hepatic impairment, drug clearance was not significantly affected.[118] In patients with moderate hepatic impairment (Child-Pugh B), dabigatran and apixaban exposure was not significantly increased while manufacturers for edoxaban and rivaroxaban specifically do not recommend use in this patient population.[1–4, 119, 120]

Apixaban drug interactions

Apixaban interacts with drugs that induce or inhibit CYP3A4 or P-gp.[2, 121–123] Pharmacokinetic analysis reports significant decreases in (AUC_{∞}) with rifampin, a combined P-gp and strong CYP3A4 inducer.[123] Reduced drug exposure could lead to an increased risk of thrombotic outcomes and lower efficacy. Conversely, combined P-gp and strong CYP3A4 inhibitors increase maximum concentration (C_{max}) and AUC_{∞}, increasing the risk of bleeding.[121, 122] However, this effect is less pronounced with P-gp inhibitors that only moderately inhibit CYP3A4.[121] This has led researchers to question the significance of P-gp transporter interactions and assert CYP3A4 interactions may play a greater role than P-gp interactions in affecting apixaban metabolism.[121, 124, 125]

Extensive pharmacokinetic studies detailing the effect of strong inhibitors and inducers on DOAC plasma concentrations outside of healthy controls are not available. One retrospective study examining the safety of clarithromycin (a strong CYP3A4 and P-gp inhibitor) versus azithromycin (a P-gp inhibitor) for patients taking DOACs, including apixaban, found that clarithromycin use was associated with a higher incidence of hospitalization for major bleeding.[126] A post-hoc analysis of the ARISTOTLE trial evaluated the effect of drug interactions on safety and efficacy.[127] Combined moderate CYP3A4 and P-gp inhibitors comprised most drug interactions with apixaban and no differences in outcome was found compared to those patients not taking potentially interacting medications.[127]

Experts recommend avoiding the combination of apixaban with a strong CYP3A4 and P-gp inhibitor. If the combination of apixaban and strong CYP3A4 inhibitors is unavoidable, reduce the dose of apixaban by 50% if on a regimen of 5–10 mg by mouth twice daily.[2] Concomitant use is not recommended for dosing regimens of 2.5 mg by mouth twice daily.[2] Empiric reduction of standard apixaban doses is not recommended when co-administrated with moderate CYP3A4 inhibitors. Strong inducers of CYP3A4 or P-gp should be avoided with apixaban use.[2, 128]

Dabigatran drug interactions

The majority of drug interactions involve P-gp inhibitors and inducers. Co-administration of rifampin, a P-gp inducer, for 6 days decreased total AUC of dabigatran by 66%. This effect was no longer present 7 days after daily rifampin administration.[1]. Therefore, strong inducers of P-gp should be avoided with dabigatran.[1, 128] The co-administration of P-gp inhibitors likewise increases dabigatran effects by enhancing absorption.[1, 129, 130] The

administration of ketoconazole more than doubles the plasma dabigatran concentrations, and dosing adjustments should be made if there is renal impairment. (Table 5) [1] Since dabigatran is ~80% eliminated renally, drug accumulation due to strong P-gp inhibition in the setting of renal impairment (CrCl < 50 mL/min) is significantly exacerbated, likely more than tripling the AUC, and should therefore be avoided. (Figure 3) [1, 116, 128, 131] However, administration of amiodarone, dronedarone, and verapamil only moderately increased dabigatran $AUC_{0-\infty}$ by 12%, 10%, 23% respectively in real-world, pharmacokinetic studies.[129, 130] Furthermore, this effect, potentiated by P-gp, can be mitigated when the drugs are administered 2 hours after dabigatran.[1, 130] A good example of this is seen with a loading dose of ticagrelor, which increases the peak concentration of dabigatran by 65% if given together; however, when the dose is staggered 2 hours apart, the peak concentration is only increased by 24%.[1]

Edoxaban drug interactions

As edoxaban is minimally metabolized by CYP3A4, drug interactions with this CYP enzyme are less relevant than those of P-gp inhibitors.[122, 132, 133] One study evaluated the pharmacokinetic effect of strong CYP3A4 and/or P-gp inhibitor coadministration on edoxaban plasma concentrations in healthy volunteers.[122] CYP3A4 inhibition alone did not significantly affect edoxaban exposure and serum concentration; however, P-gp inhibition with or without CYP3A4 inhibition increased edoxaban C_{max} and $AUC_{0-\infty}$ by greater than 2.3-fold and 1.7-fold, respectively.[132, 133] P-gp inhibition occurs primarily through intestinal P-gp efflux transporters based on bioavailability data which demonstrated significantly greater increases in edoxaban $AUC_{0-\infty}$ with oral compared to intravenous administration.[134] While data from clinical trials do not support dose reduction of edoxaban in the setting of a strong P-gp inhibitor, some experts recommend switching edoxaban to warfarin instead, especially in the setting of renal impairment (CrCl < 50mL/min).[3, 128, 135–137] Strong CYP3A4 and P-gp inducers should be avoided with edoxaban.[3, 128]

Rivaroxaban drug interactions

Rivaroxaban has a similar drug interaction profile as apixaban because it is metabolized by enzymes CYP3A4 and 2J2 and is also a substrate of P-gp.[2, 138] Pharmacokinetic studies show that rivaroxaban C_{max} and AUC_{∞} are significantly increased and total body clearance is decreased when given with combined strong CYP3A4, CYP2J2, and P-gp inhibitors such as ketoconazole, ritonavir, and cobicistat.[122, 138] When rivaroxaban is given to patients taking a strong CYP3A4 and P-gp inducer, C_{max} and AUC_{∞} are decreased.[4]

Rivaroxaban drug-drug interactions can be clinically relevant. Multiple studies have evaluated the clinical effect of combined strong CYP3A4 and P-gp inhibitor use on patients taking rivaroxaban and found increased risk of major and minor bleeding.[126, 139] Patients taking rivaroxaban, in combination with strong CYP3A4 and P-gp inducers, have reduced effectiveness as evidenced by recurrent thromboembolism.[140, 141] Therefore, concomitant use of strong CYP3A4 and P-gp inhibitors or inducers with rivaroxaban should be avoided.[128] Moderate CYP3A4 and P-gp inhibitors increase rivaroxaban plasma concentrations, though this does not correlate to an increased risk of bleeding in patients with normal kidney function.[138, 142–144]. In a pharmacokinetic study evaluating the effect of renal dysfunction on the concentration of rivaroxaban in subjects taking erythromycin,

a moderate CYP3A4 and P-gp inhibitor, AUC_{∞} was significantly increased by 76% and 99% in mild and moderate renal impairment, respectively.[4] C_{max} was also increased in both groups.[4] P-gp is primarily responsible for active renal secretion of rivaroxaban which could explain why these inhibitors have a greater effect in patients with renal dysfunction.[122, 124, 138] However, a post hoc analysis of the ROCKET-AF trial demonstrated that there was not a clinically significant difference in terms of efficacy and safety outcomes between those taking a moderate inhibitor of CYP3A4 randomized to receive rivaroxaban vs. warfarin.[145] Therefore, as long as renal function is preserved, moderate CYP3A4 and P-gp inhibitors are safe to use with rivaroxaban.[146]

Oral anticoagulants and anti-arrhythmic drugs

Quinidine is a moderate inhibitor of P-gp and modestly increases the plasma concentration of edoxaban and dabigatran.[3, 108, 136] In patients who are at high risk for edoxaban or dabigatran accumulation, such as those with impaired renal function or taking another P-gp inhibitor, consider using warfarin instead.[128] Quinidine is also a weak inhibitor of CYP3A4 and INR should be monitored more frequently when quinidine is initiated in the setting of chronic warfarin use.[14, 147]

Dronedarone is a strong inhibitor of P-gp and simultaneous oral administration with dabigatran can double plasma concentrations.[1] This increase in plasma concentration can be tempered by administering dronedarone 2 hours after DOAC administration, but this combination should generally be avoided with all DOACs. [128, 147] While a study reported no clinically significant elevation in INR in patients taking warfarin who were initiated on dronedarone, a moderate CYP3A4 inhibitor, cases of dronedarone-associated increases in INR have been reported.[148, 149]

Amiodarone is a less potent inhibitor of P-gp, can be co-administered with DOACs as long as other risk factors for DOAC accumulation, such as impaired renal function or administration of another P-gp inhibitor, are not present.[128] Amiodarone is a moderate inhibitor of CYP2C9 which increases warfarin levels in proportion to the dose of amiodarone administered.[150, 151] In a national database analysis of 754 patients, the mean INR increased from 2.6 to 3.1 following initiation of amiodarone therapy, necessitating an average 25% decrease in warfarin dose.[152]

Verapamil is a potent inhibitor of P-gp.[108] Like dronedarone, simultaneous administration with dabigatran significantly increased dabigatran plasma concentrations and can be avoided by spacing verapamil 2 hours after dabigatran is given.[1] However, verapamil should be avoided if risk factors for DOAC accumulation are present.[128] In contrast, diltiazem did not significantly increase plasma concentrations of apixaban, and may be a more suitable combination in some circumstances.[2] Diltiazem, also a moderate CYP3A4 inhibitor, also does not appear to impair warfarin clearance to an appreciable extent.[153]

Oral anticoagulants with antiplatelet therapy

Perhaps one of the most important and common anticoagulant drug-drug interactions cardiologists encounter is concomitant antiplatelet therapy. As both of these classes of

drugs increase the risk of bleeding, it is not surprising that adverse bleeding is compounded when taken together.[154] However, there are many scenarios when these classes of drugs have to be taken together, such as AF patients undergoing angioplasty or in the immediate post-procedural setting after valve implantation.[155, 156] In these situations, clinicians must be familiar with the indications for concomitant anticoagulant/antiplatelet administration and minimize the amount of overlap between these drug classes per current guidelines and recommendations to optimize risk/benefit ratio of this combination therapy.[155, 156]

Anticoagulants and antiplatelet drugs are commonly given together in the immediate postoperative setting after valve implantation. Patients with a transcatheter aortic valve replacement should receive anticoagulation during the first 3 months after valve implantation, whereas those with other bioprosthetic valves should receive anticoagulation for the first 6 months and warfarin should be used during this period, targeting an INR of 2.5.[156] The addition of aspirin to warfarin during this period was shown to decrease the incidence of thrombotic events (1.0% vs 0.6%) at the expense of increased bleeding (1.4% vs 2.8%) at 3 months in a registry cohort of 25,656 patients undergoing bioprosthetic aortic valve implantation.[157] Therefore, it is reasonable to add aspirin to warfarin in patients at high risk for thrombotic complications during the initial 3 months after valve implantation along with a PPI, but the dose of aspirin should not exceed 100 mg.[90, 156] For patients with AF or another long-term indication for anticoagulation, anticoagulation can be continued alone, either with warfarin or a DOAC, as there is no evidence to support continued antiplatelet use beyond the initial 3–6 months unless a patient is at an exceptionally high risk for stroke or has another indication for antiplatelet use.[156, 158] This is in contrast to patients with mechanical valves, who require lifelong aspirin, 75–100mg/day, in addition to anticoagulation with warfarin only and not a DOAC.[156] The addition of clopidogrel after TAVR to aspirin and warfarin can be considered in certain high-risk patients, but the risk of bleeding needs to be carefully weighed against the potential benefits, and should not exceed 6 months.[156]

For patients with AF or an indication for anticoagulation, acute coronary syndrome (ACS) is the most common scenario when dual antiplatelet therapy must be initiated on top of anticoagulation. Prospective randomized studies have demonstrated that “triple therapy”, or aspirin + a P_2Y_{12} inhibitor + an OAC, is no better than a P_2Y_{12} inhibitor + anticoagulant at preventing thrombotic events and triple therapy caused more bleeding events.[159] The initial antiplatelet of choice in patients receiving anticoagulation during ACS is clopidogrel due to higher risk of bleeding associated with ticagrelor versus clopidogrel.[155] However, in patients who are at an exceptional high-risk for stent thrombosis, the risks of bleeding may not outweigh the benefits of ticagrelor use, and ticagrelor may be a better P_2Y_{12} inhibitor to use in these circumstances.[155] Currently, triple therapy should only be reserved to patients at the highest risk for thrombotic complications, and triple therapy should ideally not exceed 30 days.[155, 160] The dose of aspirin should not exceed 100 mg in these cases.[155] Apixaban was superior to warfarin in reducing bleeding events in the setting of ACS with no difference in thrombotic events, and guidelines currently recommend a DOAC over warfarin.[155, 160] In an effort reduce GI bleeding, a proton pump inhibitor should be initiated prophylactically in patients on simultaneous antiplatelet and anticoagulant therapy.[90, 155]

In patients with new onset AF with an indication for anticoagulation who are already on aspirin for ACS, aspirin should be discontinued after anticoagulation is initiated. However, for patients with stable coronary artery disease, antiplatelet medications should be stopped no later than 12 months after the last percutaneous coronary intervention. Within 6 months of drug eluting stent placement, the recommended antiplatelet medication is clopidogrel, and between 6–12 months, either aspirin or clopidogrel can be given concomitantly with anticoagulation.[155] As with ACS, DOAC are also preferred over warfarin in patients with stable coronary artery disease when an indication for anticoagulation is present.[155]

It is essential that cardiologists be aware of indications for concomitant anticoagulants / antiplatelet administration and adhere to current recommendations whenever possible to reduce the risk of adverse bleeding. Though these 2 classes of drugs should predominantly be prescribed together for the minimal amount of time recommended by guidelines, clinicians must also carefully assess risk and benefit for each patient and individualize therapy in cases when patients have an extraordinary history of bleeding or thrombosis.

Discussion/Recommendation

Warfarin has many drug interactions, but most of these can be addressed with a basic understanding of warfarin pharmacokinetics and frequent drug monitoring. On the other hand, DOACs have a very wide therapeutic window, and there are only a handful of medications that cannot be administered concomitantly with DOACs. These medications include strong inducers of CYP3A4, strong inducers of P-gp, and strong inhibitors of either or both CYP3A4 and P-gp, depending on the DOAC. These DDI interactions are particularly important in certain clinical settings, such as renal impairment or the presence of additional pharmacokinetic inhibitors.

Conclusions

Drug-drug-associated adverse effects from OACs represent a major problem for electrophysiologists. AF patients, in particular, have a high incidence of polypharmacy.[161] Unsurprisingly, polypharmacy is a risk factor for DDI related adverse drug reaction.[162] Strong inhibitors and inducers of CYP2C9 and CYP3A4 tend to be problematic for VKA while P-gp and CYP450 3A4 modulators affect DOAC. Dietary interactions, although substantially less important with DOAC use, is another source of interactions for VKA. As renal function is a major determinant of DOAC clearance, impaired renal function can exacerbate DOAC DDI to a greater extent than it can VKA DDI. Increasing providers' awareness about drug-drug interactions coupled with strengthening pharmacists' oversight will reduce drug interaction related adverse drug events.

Nonstandard Abbreviations and Acronyms:

AF	atrial fibrillation
AP	anti-platelet
AUC	area under the curve

C_{max}	peak plasma concentrations
COX	cyclooxygenase
CRCL	creatinine clearance
CYP	cytochrome P-450
DDI	drug-drug interactions
DOAC	direct oral anticoagulant
FDA	Food and Drug Administration
GI	gastrointestinal
INR	international normalized ratio
NSAID	non-steroidal anti-inflammatory drug
OAC	oral anticoagulants
P-gp	permeability glycoprotein
PM	poor metabolizers
SSRI	selective serotonin reuptake inhibitor
TdP	torsade de pointes
VKA	vitamin K antagonists

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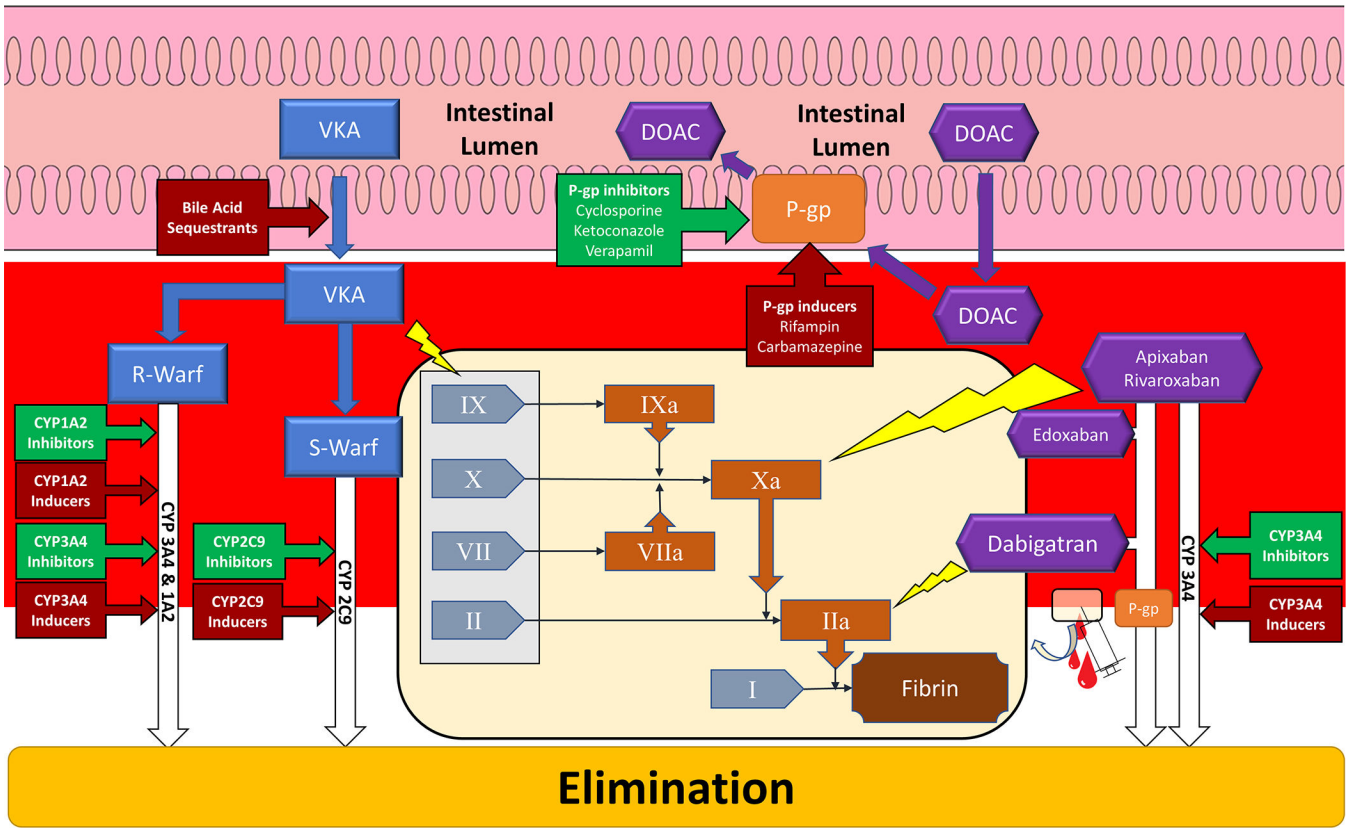

Figure 1:

Schematic of major vitamin K antagonist and direct oral anticoagulant sites of drug interactions. Tan panel depicts simplified coagulation cascade and yellow lightning bolts indicate sites of inhibition by anticoagulants (blue rectangles – vitamin K antagonist; purple hexagons – direct oral anticoagulant). Gray rectangle encompass coagulation factors affected by vitamin K antagonism. Red arrowed boxes indicate interactions that inhibit anticoagulation. Green arrowed boxes indicate interactions that potentiate anticoagulation. CYP – Cytochrome P-450; DOAC – Direct oral anticoagulant; R-Warf – R-warfarin; S-Warf – S-warfarin; P-gp – P-glycoprotein; VKA – Vitamin K Antagonist; I – Fibrinogen; II – Prothrombin; IIa – Thrombin; VII – Factor 7; VIIa – Activated Factor 7; X – Factor 10; Xa – Activated Factor 10; IX – Factor 9; IXa – Activated Factor 9

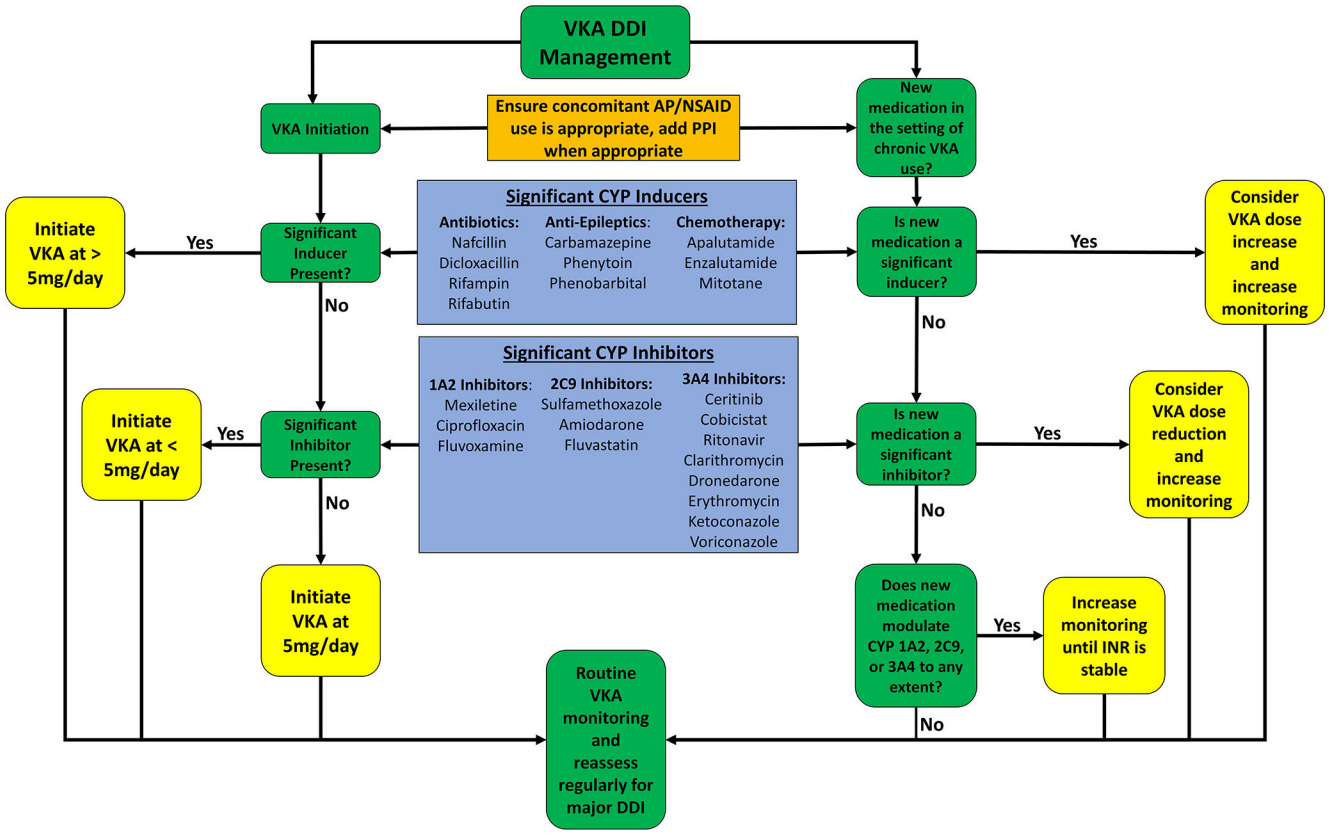

Figure 2:

Algorithm to manage warfarin drug-drug interactions during warfarin initiation as well as adding a potentially interacting drug on chronic warfarin therapy. AP – Anti-platelet; CYP – cytochrome P450; DDI – drug-drug interaction; INR – International normalized ratio; NSAID – Non-steroidal anti-inflammatory drugs; VKA - warfarin

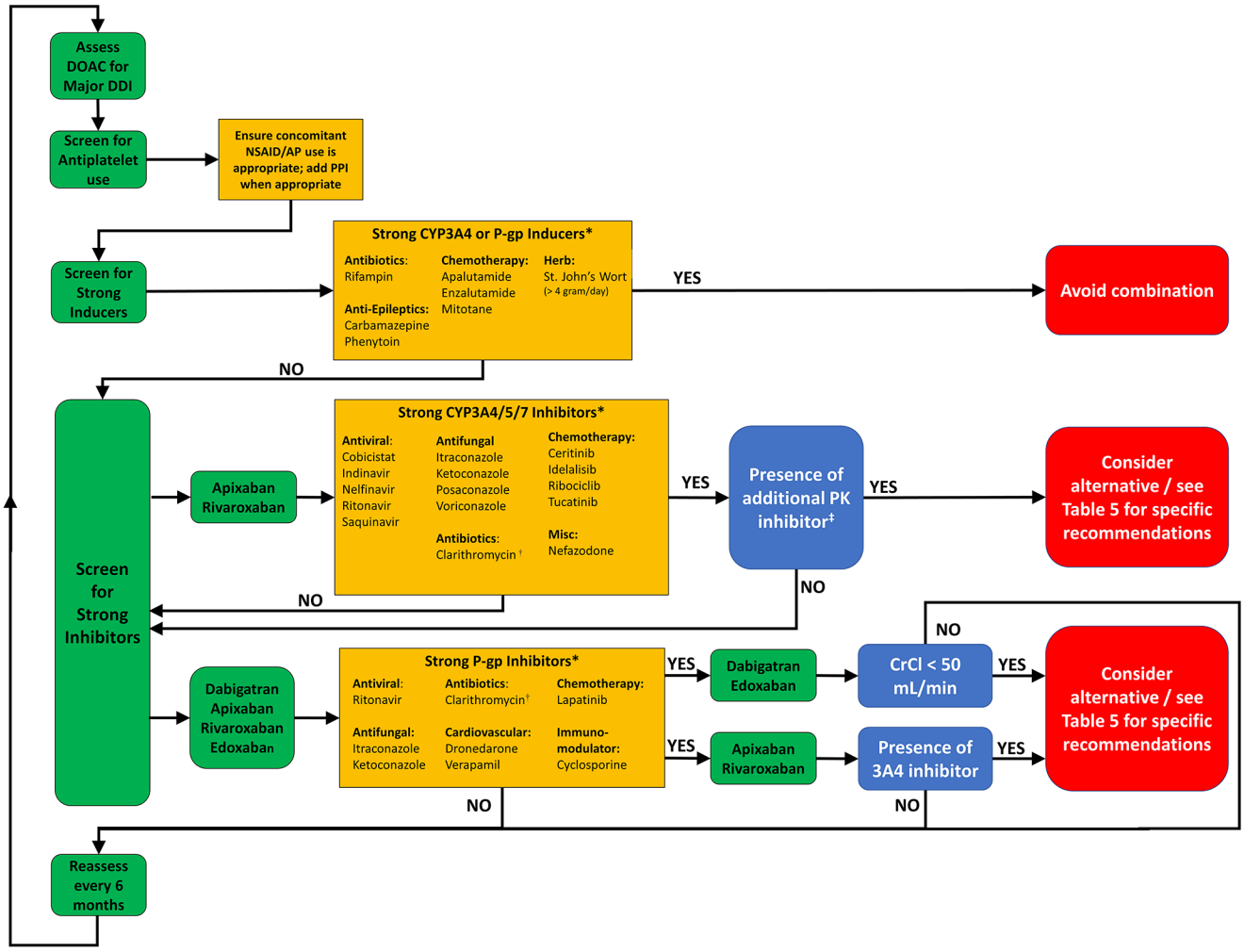

Figure 3:

Algorithm to screen for significant direct oral anticoagulant drug-drug interactions. AP – Anti-platelet; DDI – drug-drug interaction; DOAC – direct oral anticoagulant drug-drug; CYP – Cytochrome P450; NSAID – Non-steroidal anti-inflammatory drugs; P-gp – P-glycoprotein; PK – Pharmacokinetic *List is not exhaustive †Although clarithromycin is both a strong CYP3A4 and P-gp inhibitor, pharmacokinetic analyses show that it is safe to use with apixaban and rivaroxaban ‡Refers to additive P-gp inhibition from the same interacting agent, or another agent that the patient is taking with either CYP3A4 or P-gp inhibition

Table 1:

CYP450 2C9 Modulators – adopted from[13, 18, 56, 163]

CYP450 2C9 Modulator			
Inhibitor		**Inducer**	
Strong Inhibitor	Sulfaphenazole	Strong Inducer	
Moderate Inhibitor	Amiodarone	Moderate Inducer	Enzalutamide
	Fluconazole		Rifampin
	Metronidazole		
	Miconazole		
Weak Inhibitor	Capecitabine	Weak Inducer	Apalutamide
	Certinib		Aprepitant
	Disulfirim		Carbamazepine
	Efavirenz		Ritonavir
	Fluvastatin		
	Fluvoxamine		
	Isoniazid		
	Quercetin		
	Sulfamethoxazole		
	Voriconazole		
In-vitro or undetermined	Alcohol	In-vitro or undetermined	Aminoglutethimide
	Azapropazone		Bosentan
	Berberine		Carbamazepine
	Co-trimoxazole		Dabrafenib
	Delavirdine		Fosphenytoin
	Doxifluridine		Griseofulvin
	Etravirine		Letermovir
	Fenofibrate		Nafcillin
	Fluorouracil		Nelfinavir
	Gemfibrozil		Phenobarbital
	Leflunomide		Phenytoin
	Mifepristone		Primidone
	Rucaparib		Rifapentine
	Sulfamethizole		Secobarbital
	Sulfinpyrazone		St. John’s wort
	Tamoxifen		
	Valproic Acid		
	Zafirlukast		

Table 2:

CYP1A2 modulators – adopted from [13, 56, 163]

CYP450 1A2 Modulator			
Inhibitor		**Inducer**	
Strong Inhibitor	Ciprofloxacin	Strong Inducer	
	Fluvoxamine		
		Moderate Inducer	Phenytoin
Moderate Inhibitor			Rifampin
			Ritonavir
Weak Inhibitor	Citalopram		Teriflunomide
	Efavirenz		Tobacco
	Quercetin		
	Ribociclib	Weak Inducer	
	Simeprevir		
		Undetermined	Broccoli
Undetermined	Amiodarone		Brussels sprouts
			Carbamazepine
			Insulin
			Methylcholanthrene
			Modafinil
			Nafcillin
			Omeprazole
			Rucaparib

Table 3:

CYP3A4 – Modulators – adopted from[13, 56, 163–165]

CYP450 3A4 Modulator			
Inhibitor		**Inducer**	
Strong Inhibitor	Boceprevir	Strong Inducer	Apalutamide
	Ceritinib		Carbamazepine
	Clarithromycin* although a strong inhibitor of both 3A4 and P-gp, pharmacokinetic data suggests concomitant use with a DOAC is safe (labels)		Enzalutamide
	Cobicistat		Mitotane
	Grapefruit Juice		Phenytoin
	Idelalisib		Rifampin
	Indinavir		St. John's wort
	Itraconazole		
	Ketoconazole	Moderate Inducer	Bosentan
	Nefazodone		Efavirenz
	Nelfinavir		Etravirine
	Posaconazole		Phenobarbital
	Ribociclib		Primidone
	Ritonavir		
	Saquinavir	Weak Inducer	Armodafinil
	Telaprevir		Modafinil
	Tucatinib		Rufinamide
	Voriconzole		
		Undetermined	Aminoglutethimide
			Bexarotene
Moderate Inhibitor	Aprepitant		Brigatinib
	Ciprofloxacin		Dabrafenib
	Conivaptan		Dexamethasone
	Crizotinib		Dicloxacillin
	Cyclosporine		Eslicarbazepine
	Diltiazem		Fosphenytoin
	Dronedarone		Griseofulvin
	Erythromycin		Lesinurad
	Fluconazole		Lumacaftor
	Fluvoxamine		Nafcillin
	Grapefruit		Nevirapine
	Imatinib		Rifabutin
	Netupitant and Palonostrone (Akynzeo®)		Rifapentine
	Verapamil		Sarilumab
			Telotristat

CYP450 3A4 Modulator			
Inhibitor		**Inducer**	
Weak Inhibitor	Amiodarone		Tocilizumab
	Atomoxetine		Troglitazone
	Chlorzoxazone		Vemurafenib
	Cilostazol		Vinblastine
	Clotrimazole		
	Entrectinib		
	Esomeprazole		
	Fosaprepitant		
	Istradefylline		
	Ivcaftor		
	Lomitapide		
	Omeprazole		
	Quercetin		
	Ranitidine		
	Ranolazine		
	Simeprevir		
	Ticagrelor		
Undetermined	Amprenavir		
	Atazanavir		
	Berberine		
	Chloramphenicol		
	Dalfoprestin		
	Danazol		
	Darunavir		
	Dasatinib		
	Delavirdine		
	Dexmedetomidine		
	Ethinyl Estradiol		
	Fosaprenavir		
	Isavuconazonium		
	Isoniazid		
	Lapatinib		
	Larotrectinib		
	Letermovir		
	Miconazole		
	Mifepristone		
	Netupitant		
	Palbociclib		

CYP450 3A4 Modulator			
Inhibitor		Inducer	
	Quinupristin (Synercid)		
	Simeprevir		
	Stiripentol		
	Tamoxifen		
	Voxilaprevir		

Table 4:

Important warfarin-drug interactions and management recommendations

	Precipitant Drug	Nature of Interaction	Recommendations
Antibiotics	All antibiotics	Alteration in gut flora production of vitamin K[21]	Closer monitoring of INR levels
	Sulfonamides	CYP450 2C9 inhibition[24]	Reduce dose of warfarin by 25%[24]
	Metronidazole	CYP450 2C9 inhibition[27]	Reduce dose of warfarin by 33%[27]
	Ciprofloxacin	CYP450 1A2 inhibition[28]	Closer monitoring of INR levels
	Clarithromycin	CYP450 3A4 inhibition[30]	Closer monitoring of INR levels
	Erythromycin	CYP450 3A4 inhibition[30]	Closer monitoring of INR levels
	Azithromycin	CYP450 3A4 inhibition[16]	Closer monitoring of INR levels
	Nafcillin	CYP450 3A4 induction[32, 33]	Closer monitoring of INR levels; full induction of CYP450 enzymes occurs in 2–4 weeks after initiation and persists up to 2–4 weeks after discontinuation of nafcillin
	Flucloxacillin	CYP450 3A4 induction[34]	Closer monitoring of INR levels
	Cloxacillin	CYP450 3A4 induction[35]	Closer monitoring of INR levels
	Rifampin	CYP450 3A4 induction[166]	Closer monitoring of INR levels
Antifungals	Fluconazole	CYP450 2C9 inhibition [38]	Use alternative if possible, otherwise closer monitoring is warranted
	Voriconazole	CYP450 2C9 inhibition [40]	Use alternative if possible, otherwise closer monitoring is warranted
	Miconazole	CYP450 2C9 inhibition [38]	Consider alternative such as nystatin, otherwise closer monitoring is warranted
Antiretrovirals	Ritonavir	CYP450 3A4[46]	Closer monitoring of INR levels
Antiarrhythmic drugs	Amiodarone	CYP450 2C9 and 3A4 inhibition[150]	Decrease dose of warfarin by 25%[152]
	Dronedarone	CYP450 3A4 inhibition[148]	Closer monitoring of INR levels
Anti-lipidemic agents	Atorvastatin	CYP450 3A4 inhibition [51]	Closer monitoring of INR levels
	Rosuvastatin	CYP450 3A4 inhibition[51]	Closer monitoring of INR levels
	Simvastatin	CYP450 3A4 inhibition [51]	Closer monitoring of INR levels
	Fluvastatin	CYP450 2C9 inhibition [51]	Decrease dose of warfarin by 25%
	Gemfibrozil	CYP450 2C9 inhibition[56]	Decrease dose of warfarin by 20% [58]
Antiepileptic drugs	Carbamazepine	CYP450 enzyme induction [69]	Increase dose of warfarin by 50% with close follow-up[69]
	Phenytoin	Biphasic interaction with initial displacement from protein binding and then enzyme induction[72]	Closer monitoring of INR levels
Antidepressants	Fluvoxamine	CYP450 2C9 and 3A4 inhibition ([68, 71]	Consider alternatives such as sertraline, citalopram, or escitalopram; otherwise closer monitoring of INR levels is warranted[71]
	Fluoxetine	CYP450 2C9 and 3A4 inhibition [71, 74]	Consider alternatives such as sertraline, citalopram, or escitalopram; otherwise closer monitoring of INR levels is warranted[71]

	Precipitant Drug	Nature of Interaction	Recommendations
Anti-platelet agents	Aspirin Clopidogrel Prasugrel Ticagrelor	Potentiation of bleeding	Minimize overlap to shortest duration indicated and consider starting a proton pump inhibitor [155]
Chemotherapy	Fluorouracil	Multiple mechanisms [78]	Decrease dose of warfarin by 20% [78]
	Capecitabine	Possible enzyme induction	Closer monitoring of INR levels
	Paclitaxel	Displacement from protein binding or CYP450 3A4 inhibition [84]	Closer monitoring of INR levels
	Enzalutamide	CYP450 enzyme induction[79]	Closer monitoring of INR levels
	Apreptiant	CYP450 enzyme induction [86]	Closer monitoring of INR levels
Non-steroidal anti-inflammatory drugs	Both selective and non-selective cyclooxygenase inhibitors	Cyclooxygenase inhibition[88]	Avoid unless benefits clearly outweigh risk [14]
Miscellaneous agents	Ethanol	CYP450 2C9 inhibition [56]	Avoid excessive alcoholic consumption (< 60 gm/ day) [93]
	Acetaminophen	CYP450 enzyme inhibition[92]	When doses of acetaminophen exceed 2g/day, closer monitoring of INR levels is warranted
	Danazol	Inhibition of metabolism [96]	Closer monitoring of INR levels
Herbal Agents	St. John's Wort	CYP450 enzyme induction [66, 71, 102]	Closer monitoring of INR levels
	Grapefruit Juice	CYP450 3A4 enzyme inhibition [100]	Consume no more than 200 mL per day[107]
	Cranberry Juice	CYP450 enzyme inhibition [100]	Consume no more than 24 ounces per day[100]

Table 5:

Important DOAC-drug interactions and management recommendations

DOAC	Precipitant Drug	Nature of Interaction	Recommendations	Clinical Significance
All DOACs	Apalutamide	Strong CYP3A4 induction[164]	Avoid Combination[1–4]	Major
	Carbamazepine	Strong CYP3A4 induction[1–4]	Avoid Combination[1–4]	Major
	Enzalutamide	Strong CYP3A4 induction[79]	Avoid Combination[1–4]	Major
	Phenytoin	Strong CYP3A4 induction[1–4]	Avoid Combination[1–4]	Major
	Rifampin	Strong CYP3A4 induction[123]	Avoid Combination[1–4]	Major
	Ritonavir	Strong P-gp inhibition and Strong CYP3A4 inhibition[163]	Avoid Combination[1–4]	Major
	St John's Wort	Strong CYP3A4 induction[1–4]	Limit St. John's Wort to less than 4g/day[167]	Minor
	Grapefruit Juice	Strong CYP3A4 inhibition	Minimize grapefruit juice intake[107] to < 200cc	Minor
Apixaban	Dronedarone	Strong P-gp inhibition and moderate CYP3A4 inhibition[2]	Monitor for bleeding	Minor
	Cyclosporine	Strong P-gp inhibition and CYP3A4 inhibition[2]	Combination is ok, monitor for bleeding[168]	Minor
	Itraconazole	Strong P-gp inhibition and moderate CYP3A4 inhibition[2]	Consider alternative, decrease dose by 50% if unavoidable[2]	Major
	Ketoconazole	Strong P-gp inhibition and moderate CYP3A4 inhibition[2]	Consider alternative, decrease dose by 50% if unavoidable[2]	Major
	Nefazodone	Strong CYP3A4 inhibition[13]	Ok if no other PK inhibitor is present, otherwise requires 50% apixaban dose reduction.[2]	Minor
	Posaconazole	Strong CYP3A4 inhibition[163]	Ok if no other PK inhibitor is present, otherwise requires 50% apixaban dose reduction [2]	Minor
	Protease inhibitors : Cobicistat Indinavir Nelfinavir Saquinavir	Strong CYP3A4 inhibition[163]	Ok if no other PK inhibitor is present, otherwise requires 50% apixaban dose reduction [2]	Minor
	Tyrosine kinase inhibitors	Strong CYP3A4 inhibition	Ok if no other PK inhibitor is present, otherwise requires 50% apixaban dose reduction.[2]	Minor
	Verapamil	Strong P-gp inhibition and moderate CYP3A4 inhibition	Ok if no other PK inhibitor	Minor
	Voriconazole	Strong CYP3A4 inhibition[2, 13]	Ok if no other PK inhibitor is present, otherwise requires 50% apixaban dose reduction.[2]	Minor
Dabigatran	Amiodarone	P-gp inhibition[129]	Administer amiodarone 2 hours after dabigatran[1]	Minor
	Cyclosporine	Strong P-gp inhibition[108]	Avoid use[169]	Major
	Dronedarone	P-gp inhibition[129]	Administer dronedarone 2 hours after dabigatran if CrCl is ≥ 50 mL/min[1], decrease dose to 75mg	Major

DOAC	Precipitant Drug	Nature of Interaction	Recommendations	Clinical Significance
			PO BID in patients with CrCl < 50mL/min if unavoidable[1], avoid if < 30 mL/min	
	Ketoconazole	Strong P-gp inhibition[108]	Consider alternative, decrease dose to 75mg PO BID in patients with CrCl < 50mL/min if unavoidable[1], avoid if < 30 mL/min	Major
	Lapatanib	Strong P-gp inhibition[108]	Not studied, avoid combination[1]	Major
	Ticagrelor	P-gp inhibition[1]	Administer ticagrelor 2 hours after dabigatran[1]	Minor
	Verapamil	P-gp inhibition[129]	Administer dabigatran 2 hours before verapamil.[170]	Minor
Edoxaban	Cyclosporine	Strong P-gp inhibition[108]	Ok unless another P-gp inhibitor is present. Reduce dose of edoxaban by 50% if anticoagulation is for venous thromboembolism or CrCl is < 50 mL/min [3, 135]	Major
	Dronedarone	Strong P-gp inhibition[108]	Administer dronedarone 2 hours after edoxaban. Reduce dose of edoxaban by 50% if anticoagulation is for venous thromboembolism or CrCl is < 50 mL/min [3, 135]	Major
	Itraconazole	Strong P-gp inhibition[108]	Ok unless another P-gp inhibitor is present. Reduce dose of edoxaban by 50% if anticoagulation is for venous thromboembolism or CrCl is < 50 mL/min [3, 135]	Major
	Ketoconazole	Strong P-gp inhibition[108]	Ok unless another P-gp inhibitor is present. Reduce dose of edoxaban by 50% if anticoagulation is for venous thromboembolism or CrCl is < 50 mL/min [3, 135]	Major
	Lapatinib	Strong P-gp inhibition[108]	Ok unless another P-gp inhibitor is present. Reduce dose of edoxaban by 50% if anticoagulation is for venous thromboembolism or CrCl is < 50 mL/min[3, 135]	Major
	Quinidine	Strong P-gp inhibition[108]	Reduce dose of edoxaban by 50% if anticoagulation is for venous thromboembolism or CrCl is < 50 mL/min[3, 134, 135]	Major
	Verapamil	Strong P-gp inhibition[108]	Reduce dose of edoxaban by 50% if anticoagulation is for venous thromboembolism or CrCl is < 50 mL/min [3, 132, 135]	Minor
Rivaroxaban	Amiodarone	Weak CYP3A4 and P-gp inhibition (PI)	Monitor for bleeding	Minor
	Cyclosporine	Strong P-gp inhibition and CYP3A4 inhibition[4]	Ok unless CrCl is < 50 mL/min[4, 171]	Minor
	Dronedarone	Strong P-gp inhibition and moderate CYP3A4 inhibition[4]	Ok unless CrCl is < 80 mL/min, otherwise consider alternative	Major
	Itraconazole	Strong P-gp inhibition and moderate CYP3A4 inhibition[4]	Avoid combination[4]	Major
	Ketoconazole	Strong P-gp inhibition and moderate CYP3A4 inhibition[4]	Avoid combination[4]	Major
	Lapatanib	Strong P-gp inhibition[108]	Not studied, avoid combination[4]	Major
	Nefazodone	Strong CYP3A4 inhibition[13]	Ok if no other PK inhibitor is present, otherwise avoid combination.[4]	Minor
	Posaconazole	Strong CYP3A4 inhibition[163]	Ok if no other PK inhibitor is present, otherwise avoid combination.[4]	Minor

DOAC	Precipitant Drug	Nature of Interaction	Recommendations	Clinical Significance
	Protease inhibitors : Cobicistat Indinavir Nelfinavir Saquinavir	Strong CYP3A4 inhibition[163]	Ok if no other PK inhibitor is present, otherwise avoid combination[4]	Major
	Tyrosine kinase inhibitors	Strong CYP3A4 inhibition[4]	Ok if no other PK inhibitor is present, otherwise consider alternative[4]	Major
	Verapamil	Strong P-gp inhibition and moderate CYP3A4 inhibition[4]	Ok unless CrCl is < 80mL/min, otherwise use diltiazem[4]	Minor
	Voriconazole	Strong CYP3A4 inhibition[13]	Ok if no other PK inhibitor is present, otherwise avoid combination.[4]	Minor

Table 6:

P-glycoprotein (P-gp) - Modulators – adopted from[56, 108, 128, 163]

P-gp modulators (Lund, Terrier, FDA website)			
Inhibitor		**Inducer**	
Strong Inhibitor	Cyclosporine	Strong Inducer	Carbamazepine
	Dronedarone		Rifampin
	Ketoconazole		St. John's Wort[167]*
	Itraconazole		
	Lapatinib		
	Ritonavir		
	Verapamil		
Weak Inhibitor	Amiodarone	Weak Inducer	Phenytoin
	Carvedilol		
	Clarithromycin		
	Diltiazem		
	Eliglustat		
	Fluvoxamine		
	Maraviroc		
	Mirabegron		
	Paroxetine		
	Propafenone		
	Quinidine		
	Ranolazine		
	Simeprevir		
	Saquinavir		
	Ticagrelor		
	Tipranavir		
Uncertain Inhibitor	Carbozantinib		
	Enzlutamide		
	Erythromycin		
	Ibrutinib		
	Imatinib		
	Irbesartan		
	Ivermectin		
	Ledipasvir		
	Lomitapide		
	Loperamide		
	Meflokine		

P-gp modulators (Lund, Terrier, FDA website)			
Inhibitor		Inducer	
	Ponatinib		
	Regorafenib		
	Simvastatin		
	Tacrolimus		