Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions

Sara R. Vazquez

Pharmacy Services Department, University of Utah Health, Salt Lake City, UT

Oral anticoagulants are commonly prescribed but high risk to cause adverse events. Skilled drug interaction management is essential to ensure safe and effective use of these therapies. Clinically relevant interactions with warfarin include drugs that modify cytochrome 2C9, 3A4, or both. Drugs that modify *p*-glycoprotein may interact with all direct oral anticoagulants, and modifiers of cytochrome 3A4 may interact with rivaroxaban and apixaban. Antiplatelet agents, nonsteroidal anti-inflammatory drugs, and serotonergic agents, such as selective serotonin reuptake inhibitors, can increase risk of bleeding when combined with any oral anticoagulant, and concomitant use should be routinely assessed. New data on anticoagulant drug interactions are available almost daily, and therefore, it is vital that clinicians regularly search interaction databases and the literature for updated management strategies. Skilled drug interaction management will improve outcomes and prevent adverse events in patients taking oral anticoagulants.

Learning Objectives

- Identify clinically relevant drug-drug interactions for both warfarin and the direct oral anticoagulants
- Formulate a management strategy for an identified oral anticoagulant drug-drug interaction

Introduction/background

Oral anticoagulants are some of the most commonly prescribed drugs, particularly among the elderly,[1] and they are one of the highest-risk drug classes to cause adverse events.[2] In fact, anticoagulants are one of the three initial targets of the Centers for Disease Control and Prevention National Action Plan for Adverse Drug Event Prevention.[3] Recent trends show an increasing prescription rate of the direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban,[4] and many patients remain on warfarin for a variety of reasons.[5,6]

An essential component of high-quality anticoagulation therapy management and ensuring safe use of these high-risk drugs is drug-drug interaction management. All oral anticoagulants have interactions with other drugs that warrant vigilance and often, intervention. Although warfarin is notorious for its numerous drug interactions, no drug is considered contraindicated with warfarin as long as the drug interaction is considered before the initiation of the interacting drug. The ability to adjust the warfarin dose allows the clinician to account for the interaction via monitoring of the international normalized ratio (INR). DOACs, while having the advantage of fewer drug interactions, do not have a well-recognized laboratory monitoring or management strategy for how to deal with interactions when they do occur due to limited experience and little data about whether dose adjustment should be made without compromising safety and efficacy. Finally, pharmacodynamic interactions with antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and serotonergic agents should not be overlooked, and they may actually present a similar if not greater risk for adverse effects than pharmacokinetic interactions.

For both warfarin and the DOACs, the clinician must determine which of the potential interactions is truly clinically relevant and then develop a patient-specific management strategy. An important starting point for managing oral anticoagulant drug interactions and determining their clinical relevance is understanding the mechanisms of potential interactions and what other factors may contribute to patient risk for adverse events. The purpose of this review is to highlight the most clinically relevant drug interactions for both warfarin and DOACs and corresponding management strategies. It is beyond the scope of this review to provide a comprehensive analysis of all possible oral anticoagulant drug interactions.

Warfarin

Warfarin has >200 identified drug interactions, some with limited supporting evidence,[7,8] and therefore, the clinician must determine which interactions are clinically relevant and prudent to act on. Anecdotal experience can be helpful, but clinicians should exercise caution in extrapolating one patient experience to all patients. A patient's response to warfarin is highly individualized, and drug interactions are no exception.

Warfarin is exclusively hepatically metabolized, with *S*-warfarin (the more potent enantiomer) metabolized primarily via cytochrome (CYP) 2C9, with some contribution of CYP3A4. The less potent

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R-warfarin enantiomer is metabolized via CYP1A2 and CYP3A4, with a minor contribution of CYP2C19. The most clinically significant interactions are those involving inhibition or induction of the CYP pathways that metabolize both *S*-warfarin and *R*-warfarin.[7,8]

Inhibitors

The CYP450 inhibitor interactions that should capture the most attention in their magnitude and reliability are easily remembered using the "FAB-Four" mnemonic: fluconazole (and other oral -azoles), amiodarone, Bactrim (sulfamethoxazole-trimethoprim), and Flagyl (metronidazole).[9] The reason for highlighting these interacting drugs as most clinically significant involves their inhibition of *S*-warfarin, the more potent warfarin enantiomer. Fluconazole affects *S*-warfarin metabolism by inhibiting CYP2C9 and CYP3A4 as well as *R*-warfarin metabolism by CYP2C19,[10] and this manifests as elevated INR and has resulted in bleeding adverse events.[8,11-13] A common indication for fluconazole is one-dose administration for vaginal candidiasis, and at least one case report has cited increased INR after single-dose fluconazole administration in warfarin patients.[14] This inhibitory response is deemed to be slightly lower magnitude for voriconazole,[15,16] likely due to weaker inhibition of CYP2C9.

Amiodarone is also well known to interact with warfarin and cause prolongation of the prothrombin time due to its inhibition of the metabolism of both *S*-warfarin and *R*-warfarin.[17] There are numerous reports of decreased warfarin dose requirements and increased INR related to the warfarin-amiodarone interaction.[8,18-21] The data are mixed as to bleeding events related to this interaction,[19,22] although it is possible that vigilant warfarin management may prevent bleeding adverse events and alter the ability to accurately interpret this data. Compounding the difficulty in managing this interaction is amiodarone's long half-life and the presence or absence of a loading dose, which can make discerning the timing of interaction onset and offset difficult.

The sulfamethoxazole component of the combination drug sulfamethoxazole-trimethoprim also is known to inhibit the metabolism of *S*-warfarin and displace warfarin from protein binding sites, thus increasing the INR and risk for bleeding.[8,11,13,23,24]

Finally, metronidazole has been shown to increase the INR and cause bleeding adverse events when combined with warfarin due to its inhibition of *S*-warfarin metabolism.[8,25]

Inducers

Drugs that induce the enzyme activity of CYP2C9, CYP3A4, and to a lesser extent, CYP1A2 can actually reduce the effectiveness of warfarin and expose patients to risk of thrombosis. Well-known enzyme inducers, such as rifampin and carbamazepine, can cause significant decreases in the INR and increases in warfarin dose requirements.[8,26-30] In contrast with inhibitor interactions, the onset and offset of inducer interactions can be delayed due to the time required for the liver to synthesize additional enzyme,[26-29,31] but they are also dependent on the inducer drug's half-life.[32]

Management strategies

Understanding of the timing of onset and offset as well as the magnitude of effect of clinically significant interactions is key to warfarin drug interaction management. Reports show that concomitant warfarin-fluconazole and warfarin-amiodarone administration may require a 20% to 50% and a 20% to 40% warfarin dose reduction, respectively. The magnitude of both interactions seems to be dose dependent (the higher the fluconazole or amiodarone dose, the greater the magnitude of interaction).[18,19,21,33] The magnitude of the sulfamethoxazole-trimethoprim and metronidazole interactions seems to be similar, requiring a 25% to 40% warfarin dose reduction.[24]

As is typical for CYP inhibitor-type interactions, the onset can be relatively rapid, within 3 to 5 days.[24,32] For long-acting amiodarone, onset can be seen as early as the first week, especially if an amiodarone loading dose is used.[20] For azole antifungals, sulfamethoxazole-trimethoprim, and metronidazole, monitoring the INR on day 3, 4, or 5 of therapy is an appropriate timeframe to begin to see an INR rise, with subsequent warfarin dose adjustment and INR monitoring as necessary for the remaining duration of the interacting drug. Offset of enzyme inhibition is similar to onset, and patients can generally resume prior stable warfarin dose after offset of the interacting drug. For amiodarone, a common strategy is to monitor the INR 1 week after amiodarone initiation and then once weekly until the INR is stable. Given its long half-life, timing of offset can be difficult to discern, but a similar once-weekly strategy may be prudent.

Inducer interactions may need to be handled differently given the possibility of delayed onset and offset. The rifampin interaction can manifest as early as a few days after rifampin initiation given its relatively short half-life,[32] and reports have shown that it can take weeks to stabilize the INR given the magnitude of the interaction. Offset is similar, with concerns for significantly elevated INR after the interacting drug is discontinued.[26,27,30] Some patients have required over 50% warfarin dose increase after rifampin initiation and a similar subsequent decrease after rifampin discontinuation.[26,27,30,31] It is not unusual to see warfarin dose requirements of 20 to 25 mg/d when rifampin is coprescribed. A prudent management strategy with rifampin initiation should include frequent INR monitoring (eg, 2 times per week) with aggressive warfarin dose increases, with a similar strategy for frequent monitoring and dose decreases with rifampin discontinuation. Carbamazepine induction can take weeks to onset and offset due to its longer half-life. Patients have required as much as a 49% dose increase with concomitant carbamazepine.[28,29] Management of the carbamazepine-warfarin interaction should include weekly INR monitoring with aggressive warfarin dose increases after initiation and decreases after discontinuation.

Given the reputation of these drugs for causing significant changes in the INR, some clinicians may advocate for empiric warfarin dose adjustments[24,32,34-36] to avoid risk of supratherapeutic or subtherapeutic INR and potentially reduce the number of INR monitoring visits surrounding the drug interaction. Although these drug interactions are fairly common and this may be an effective strategy in some patients, not all patients will respond uniformly, and an empiric dose adjustment in a nonresponder could result in an out-of-range INR. Appropriate timing of INR monitoring and warfarin dose adjustment should be the cornerstone of warfarin drug interaction management (Table 1). Developing a guideline for drug interaction management that includes identifying warfarin drug interactions and provides recommendations for timing of INR monitoring and warfarin dose adjustments has been successful in improving time in therapeutic range.[37] It is important to remember that other factors should be considered in the setting of warfarin-antimicrobial interactions. For example, acute infection on its own can increase the INR in warfarin patients, independent of potential interacting antimicrobial drug therapy.[38] This could be a result of the body's stress response to acute infection or decreased dietary Vitamin K intake due to illness, malaise, or appetite alteration.

Table 1. Suggested management strategies for warfarin pharmacokinetic drug interactions: *S*-warfarin (CYP2C9/CYP3A4) and *R*-warfarin (CYP1A2/CYP3A4/CYP2C19)[7]

Inducers[26-32]	Inhibitors[18-21,24,32,33]
Monitor the INR within at least 5 d of inducer initiation and then at least once to twice weekly	Monitor the INR 3-5 d after inhibitor initiation (after 1 wk with amiodarone) and adjust warfarin dose accordingly
Consider aggressive warfarin dose increases until therapeutic INR is reached	Expect that patients may need a 20%-50% decrease in warfarin dose from baseline
Expect that patients may need at least a 50%-100% increase in warfarin dose from baseline	Consider other factors that may independently contribute to elevated INR, such as acute infection and dietary Vitamin K changes
Consider seeking an alternative noninteracting drug	Consider seeking an alternative noninteracting drug
Monitor the INR within at least 5 d of inducer discontinuation and then at least once to twice weekly	Allow 3-5 d for inhibitor offset (longer for amiodarone)
Expect to decrease warfarin dose to approximately preinducer levels	Expect to decrease warfarin dose to approximately preinhibitor levels

Finally, for patients with INR lability due to frequent initiation/discontinuation of an interacting drug, an alternative strategy may be to seek a different noninteracting drug to treat the condition if appropriate. A clinician could consider switching warfarin to a DOAC if the interacting drug does not also interact with the DOAC.

DOACs

Each of the DOACs is a substrate for *p*-glycoprotein (*p*-gp), an efflux transporter located in the gut mucosa, and therefore, all DOACs are susceptible to drugs that induce or inhibit *p*-gp. Additionally, rivaroxaban and apixaban undergo minor metabolism by CYP enzymes in the liver.[39] Alterations in other modes of elimination (eg, renal) should be considered as possibly additive to the effects of the absorption and metabolic changes caused by drug-drug interactions. These relevant mechanisms are summarized in Table 2. Assessing the clinical relevance of DOAC drug interactions is challenging given that the available data are frequently limited to pharmacokinetic studies in small numbers of healthy volunteers or subanalyses of clinical trial patients. Real-world experience is limited to published case reports of interactions and adverse events, which are subject to publication bias.

Inhibitors

p-gp and CYP3A4 inhibitor interactions can be difficult to assess. Product labeling for rivaroxaban and apixaban states that only drugs that inhibit *p*-gp and strongly inhibit CYP3A4 are relevant due to the relatively minor metabolic contribution of CYP3A4 (Table 3).[40-45] For dabigatran, edoxaban, and betrixaban, labeling is drug specific as to how to handle some *p*-gp inhibitor interactions (Tables 3 and 4).[46-52] What can be difficult to discern in the real world is the magnitude of CYP3A4 inhibition of one or more potential interacting drugs as well as the additive impact of other relevant factors to increase DOAC drug levels and thus, increase bleeding risk. For example, older age, low body weight, and renal or hepatic impairment have all been shown to increase DOAC exposure independent of drug interactions, and they can be additive in the presence of drug interactions.[53-55]

Inducers

All DOACs are subject to drug interactions with inducers of *p*-gp, and rivaroxaban and apixaban are subject to interactions with inducers of CYP3A4.[39] Published case reports of these interactions include subtherapeutic dabigatran levels without thrombosis due to intervention in patients on concomitant carbamazepine[56] and thrombotic adverse events as a consequence of inducer interactions.[57-65] Based on pharmacokinetic data showing significant decreases in DOAC drug concentrations and increased risk of treatment failure and thrombotic adverse effects, guidance statements[66-68]and the manufacturers of each of the DOACs have recommended against concomitant use of *p*-gp and CYP3A4 inducers.[40-50] Emerging data may allow for more nuanced inducer interaction dosing decisions. One case report cites normal apixaban concentrations in a patient taking relatively low-dose carbamazepine, supporting a dose-dependent inducer effect.[69] A pharmacokinetic study using dabigatran as a *p*-gp probe drug showed ability to predict the magnitude of *p*-gp induction relative to CYP3A induction: specifically, rifampin showed one level lower *p*-gp induction than its CYP3A induction.[70] The clinical relevance of these findings requires further investigation.

Management strategies

Product labeling does provide some specific guidance for management of inhibitor interactions. The recommendations among the US, Canadian, and European labeling differ in some aspects, despite all regulatory agencies relying on the same data to derive their recommendations (Tables 3 and 4). For clarithromycin, a *p*-gp inhibitor and strong CYP3A4 inhibitor, updated labeling reflects recent studies that suggest that a clinically relevant interaction is absent with dabigatran, rivaroxaban, and apixaban,[40,42-47,71] despite a previous recommendation to avoid this combination. An edoxaban dose reduction is recommended with concomitant clarithromycin use according to the US product labeling[49] but not in Canada or Europe.[50,51] The potential interactions with DOACs that cause the most angst involve drugs that are *p*-gp and weak or moderate CYP3A4 inhibitors, because the magnitude of interaction is often unclear. The

Table 2. Pharmacokinetic characteristics of the DOACs

Characteristic	Dabigatran, %	Rivaroxaban, %	Apixaban, %	Edoxaban, %	Betrixaban, %
Hepatic metabolism[39,52]	None	18 (CYP3A4/CYP3A5)	25 (CYP3A4/CYP3A5)	<4	<1
p-gp substrate[39,52]	Yes	Yes	Yes	Yes	Yes
Oral bioavailability[39,52]	6-7	66	50	62	34
Renal elimination[39,52]	80	36	27	50	5-7

Table 3. Product labeling drug interaction recommendations for direct factor Xa inhibitors[40-45,49-52]

Regulatory agency	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Pharmacokinetic inducer interactions				
United States	Avoid *p*-gp and strong CYP3A4 inducers	Avoid *p*-gp and strong CYP3A4 inducers	Avoid rifampin	Not addressed
Canada	Generally avoid *p*-gp and strong CYP3A4 inducers	Generally avoid *p*-gp and strong CYP3A4 inducers	Generally avoid *p*-gp inducers	Not approved for use
Europe	Avoid CYP3A4 inducers unless the patient is closely observed for signs and symptoms of thrombosis	Use *p*-gp/CYP3A4 inducers with caution in AF and VTE orthopedic surgery prophylaxis indications Do not use *p*-gp/CYP3A4 inducers in acute VTE treatment indication	Use *p*-gp inducers with caution	Not approved for use
Pharmacokinetic inhibitor interactions				
United States	Avoid use of combined *p*-gp/strong CYP3A4 inhibitors Do not use rivaroxaban in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined *p*-gp and moderate CYP3A4 inhibitors unless the potential benefit justifies the potential risk	If taking apixaban 5 or 10 mg twice daily, reduce apixaban dose by 50% when used with *p*-gp and strong CYP3A4 inhibitors; avoid use of combined *p*-gp/strong CYP3A4 inhibitors if taking apixaban 2.5 mg twice daily	AF: no dose adjustment for concomitant *p*-gp inhibitors VTE: reduce edoxaban dose to 30 mg once daily with verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole	Reduce initial and maintenance betrixaban dose by 50% when used with *p*-gp inhibitors
Canada	Systemic ketoconazole and ritonavir are contraindicated with rivaroxaban	Combined *p*-gp/strong CYP3A4 inhibitors systemic are contraindicated	Reduce edoxaban dose to 30 mg once daily with cyclosporine, dronedarone, erythromycin, ketoconazole, or quinidine	Not approved for use
Europe	Azole antifungals and HIV protease inhibitors are not recommended with rivaroxaban Avoid use of dronedarone with rivaroxaban	*p*-gp/strong CYP3A4 inhibitors are not recommended	Reduce edoxaban dose to 30 mg daily with cyclosporine, dronedarone, erythromycin, or ketoconazole	Not approved for use

AF, atrial fibrillation; CrCl, creatinine clearance; VTE, venous thromboembolism.

US, Canadian, and European product labels are all consistent in recommending that no dose adjustment is required with the DOACs and amiodarone, and this is supported by pharmacokinetic studies as well as subanalyses of clinical trial populations.[72-75] Dronedarone has either dose reduction recommendations or is contraindicated with dabigatran, and it has edoxaban dose reduction recommendations in Canada and Europe. Finally, verapamil presents an interesting dilemma, because a clinical trial subanalysis reported no difference in safety or efficacy in patients taking verapamil[76]; however, labeling recommendations vary from dose separation to dose reduction to no dose modification at all.[46-48] What makes these moderate inhibitor interactions more confusing in addition to the varied labeling recommendations is how the magnitude of the interaction is affected by other factors. For example, pharmacokinetic modeling data show a significant increase in rivaroxaban exposure when given with verapamil and particularly, as renal function declines,[77,78] but product labeling is either vague or varies.[40-42] Until data become available to the contrary, it seems prudent to abide by the product labeling if specific recommendations exist. Use clinical judgment if a moderate interaction becomes additive with other factors, such as additional moderate interacting drugs, advanced age, low body weight, renal impairment, or concomitant antiplatelet medications. Carefully weigh the risks of bleeding due to the additive risk factors vs the risks of thrombosis as a result of perhaps inappropriately reducing the DOAC dose, and discuss with the patient the balance of risk and his or her values and preferences. It is prudent to avoid empiric dose adjustments, because the interaction may not manifest the same way in all patients.[69,79]

If concern exists about a DOAC drug combination, consider the following.

- Can the interacting drug be changed to a noninteracting alternative?
- Is the patient willing and able to switch to warfarin?
- Is separating dabigatran and *p*-gp inhibitor drug by 2 hours feasible? This may be a strategy to circumvent the *p*-gp interaction.[47,80,81] This is based on the premise that dabigatran etexilate (the prodrug of dabigatran) is a *p*-gp substrate but not dabigatran itself. By separating dabigatran etexilate administration from the *p*-gp inhibitor administration, it allows time for dabigatran etexilate absorption at expected levels as opposed to increased levels of absorption in the presence of a *p*-gp inhibitor. This strategy will likely not be effective for any of the other DOACs, because they are not prodrugs.

Laboratory monitoring for the purpose of drug interaction assessment and potential dose adjustment has several limitations. The laboratory assay is not widely available, and even if it were, there is no evidence-based approach to guide monitoring, including appropriate timing of

Table 4. Product labeling drug interaction recommendations for dabigatran[46-48]

Drug	United States	Canada	Europe
Pharmacokinetic inducer interactions			
p-gp inducer	Should generally be avoided	Not recommended; caution is advised if used	Avoid
Pharmacokinetic inhibitor interactions			
Amiodarone	Reduce dabigatran dose to 150 mg daily for VTE orthopedic surgery prophylaxis indication	No dose adjustment required	Reduce dabigatran dose to 150 mg daily for VTE orthopedic surgery prophylaxis indication
Clarithromycin	No dose adjustment required	No dose adjustment required	Clinically relevant interaction cannot be excluded; close monitoring should be exercised
Dronedarone	AF indication: reduce dabigatran dose to 75 mg twice daily if CrCl 30-50 mL/min	Avoid use	Contraindicated
Keoconazole	AF indication: reduce dabigatran dose to 75 mg twice daily if CrCl 30-50 mL/min	Contraindicated	Contraindicated
Quinidine	No dose adjustment required	Reduce dabigatran dose to 150 mg daily for VTE orthopedic surgery prophylaxis indication	No dose adjustment required
Verapamil	No dose adjustment required	For AF and VTE treatment indications, give dabigatran at least 2 h before verapamil; caution should be exercised; close clinical surveillance is required Reduce dabigatran dose to 150 mg daily for VTE orthopedic surgery prophylaxis indication	Reduce dabigatran dose to 110 mg twice daily
Renal function	Avoid use of *p*-gp inhibitors if CrCl 15-30 mL/min VTE treatment and prophylaxis: avoid use of *p*-gp inhibitors if CrCl $<$ 50 mL/min	None	None

AF, atrial fibrillation; CrCl, creatinine clearance; VTE, venous thromboembolism.

when to draw the laboratory, an established therapeutic range for all DOAC indications, or dose adjustment protocols.

For the DOAC inducer interactions, the labeling recommendations are generally consistent to avoid the combination given the data showing reduced DOAC plasma concentrations and the risk of loss of efficacy.[40-51]

Pharmacodynamic interactions

In discussing oral anticoagulant drug interactions, much of the focus is on pharmacokinetic interactions involving transporters and metabolizing enzymes. Although these are important, perhaps the single most impactful intervention that clinicians can make when it comes to preventing harm from anticoagulant drug interactions could be consideration of the additive bleeding effect of antiplatelet therapy (APT). The presence of this drug interaction is quite prevalent, with a meta-analysis of the four warfarin/DOAC atrial fibrillation (AF) trials citing that 33.4% of $>$42 000 studied patients were on an antiplatelet drug in addition to the anticoagulant.[82] This is consistent with findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation registry, with 35% of patients on anticoagulant-aspirin therapy.[83] It is well established that the combination of warfarin and either single or dual APT significantly increases the risk of major bleeding by 2- to 4-fold, respectively.[84] What distinguishes the warfarin-APT interaction from others is that the INR frequently remains unaffected in the presence of APT, and therefore, no warfarin dose adjustment or increased laboratory monitoring can circumvent the interaction. Although fewer data are available for the DOACs, it seems that the increased risk of bleeding with concomitant APT persists compared with in patients with no APT, although it is still difficult to quantify how this compares with warfarin APT-related bleeding. In the AF clinical trials meta-analysis, patients on a DOAC plus APT had a 33% higher rate of bleeding compared with those on DOAC alone without deriving additional thromboembolic event prevention.[82] In two recent clinical trials comparing DOAC plus P2Y12 therapy with warfarin-based triple therapy (warfarin plus aspirin plus P2Y12 inhibitor) in patients with AF undergoing percutaneous coronary intervention with coronary stenting, the risk of major or clinically relevant nonmajor bleeding was significantly lower in the DOAC-based dual-therapy group than the warfarin-based triple-therapy group.[85,86] Aspirin use was found to be an independent predictor of intracranial hemorrhage in AF patients taking either warfarin or apixaban, and mortality after intracranial hemorrhage approaches 50%, regardless of anticoagulant used.[87]

Table 5. Suggested management strategies for oral anticoagulant pharmacodynamic drug interactions

APT[84]	Use combination anticoagulant-APT for shortest duration possible; if continuing combination therapy, regularly reassess appropriateness of both anticoagulant and antiplatelet
NSAIDs[90,91]	Routinely assess and document both prescription and nonprescription NSAID use; educate patients about the risks of bleeding, and if no other alternative exists, use NSAIDs for the shortest duration possible; if long-term combined anticoagulant-NSAID use is required, consider a COX-2–specific agent or adding a gastroprotective agent
Serotonin-modifying agents[92]	Magnitude of bleeding risk remains unclear; weigh risk and benefit of anticoagulant-serotonergic use, especially when other risk factors for bleeding are present (e.g., advanced age, renal impairment, other interacting drugs, history of bleeding)

There are certain specific scenarios that warrant the addition of APT to oral anticoagulant therapy, such as in the first year after coronary stent placement in a patient with another indication for anticoagulation and in patients with prosthetic heart valves.[88,89] However, clinicians should regularly assess the continued need for both the APT and the anticoagulant as well as other bleeding risk factors and discontinue one of the therapies as soon as clinically feasible. This will likely require communication and consultation among different provider specialties as well as the patient in a shared decision-making process. The routine implementation of this simple approach will help to achieve safer anticoagulation therapy.

It is well established that the combination of anticoagulants and NSAIDs increases the risk of bleeding, particularly upper gastrointestinal bleeding.[90,91] Selective cyclooxygenase-2 (COX-2) enzyme inhibitors cause less bleeding than nonspecific COX-1 inhibitors; nevertheless, the risk of bleeding is still elevated above that of NSAID nonusers. Proton pump inhibitors may reduce the risk of gastrointestinal bleeding in patients on either type of NSAID.[91] It is vital to educate patients taking anticoagulants about the potential bleeding risk and routinely evaluate NSAID use in this patient population, because many NSAIDs are available without prescription, and their use may otherwise go unreported. If an NSAID is absolutely necessary for pain control and no acceptable alternatives are available, consider if a COX-2 selective agent would be appropriate, and/or consider addition of a gastroprotective agent, such as a proton pump inhibitor.

Finally, serotonergic agents, such as selective serotonin reuptake inhibitors (SSRIs), may increase the risk of bleeding when combined with oral anticoagulants, particularly gastrointestinal bleeding and intracranial hemorrhage. In response to vascular injury, platelets release serotonin, which stimulates platelet aggregation. When drugs, like the SSRIs, exert their inhibitory effect, platelets release less serotonin, potentially impairing platelet aggregation and increasing risk for bleeding. Specific to gastrointestinal bleeding, SSRIs may also increase gastric acidity.[92] Studies evaluating bleeding outcomes in patients taking anticoagulants and SSRIs are, however, inconclusive. Data are limited mostly to retrospective case-control or cohort studies, with some reporting increased major bleeding in patients on anticoagulants and SSRIs and others reporting no difference.[93-97] Until additional data are available to guide clinical decision making, clinicians should consider bleeding risk factors that could be additive in patients taking oral anticoagulants and serotonin-modifying agents.

With the increased risk of gastrointestinal bleeding with dabigatran and rivaroxaban compared with warfarin,[40-42,46-48] evaluating appropriateness of APT, NSAIDs, and serotonergics becomes an increasingly important discussion point in patients taking these particular agents. Table 5 has a summary of recommendations for management of anticoagulant pharmacodynamic interactions.

Drug interaction resources

Judicious oral anticoagulant drug interaction management includes regular consultation of drug interaction references. These should be used and interpreted within their limits. For example, subscription-based tertiary electronic drug interaction databases accessible to medical providers, such as Micromedex and Lexicomp Online, are user friendly and usually updated relatively frequently; however, they may lack necessary detail that a nuanced clinical decision requires. For a more in-depth description of an interaction, searching the primary literature for case series or reports may be helpful but limited in scope and generalizability. For information on how drugs are classified as *p*-gp or CYP modifiers, the US Food and Drug Administration defines this in their Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.[98] An inclusive list of potentially interacting drugs has intentionally not been included in this review. Many such lists exist, but they may contradict each other, may omit relevant interactions, may contain inaccuracies, or are inadequately referenced. In light of these limitations, a suggested approach is to consult multiple resources in search of agreement among resources and appropriate detail needed for clinical decision making. Finally, because the drug interaction field is dynamic, particularly for the DOACs, it is essential to repeat interaction database and literature searches, because new evidence is added to the body of literature almost daily.

Conclusion

Oral anticoagulant drug interaction management is complex. It requires knowledge of which interactions are clinically relevant and metabolic and elimination pathways of substrate and modifier drugs as well as mechanisms of interaction to ensure continued safety and efficacy in the presence of interacting drugs. Engaging in a shared decision-making process with the patient and other specialty providers may be required in the more complex scenarios. Vigilant monitoring by knowledgeable clinicians in addition to emerging data on drug interactions can help health care systems move toward achieving the shared goal of preventing adverse events in patients taking oral anticoagulants.

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Correspondence

Sara R. Vazquez, Pharmacy Services Department, University of Utah Health, 50 N Medical Dr, Rm 1R211, Salt Lake City, UT 84132; e-mail: sara.vazquez@hsc.utah.edu.

References

1. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the united states, 2005 vs 2011. *JAMA Intern Med*. 2016;176(4):473-482.
2. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA*. 2016;316(20):2115-2125.
3. Office of Disease Prevention and Health Promotion. National Action Plan for Adverse Drug Event Prevention. Vol. 2018. Washington, DC: US Department of Health and Human Services, Office of Disease Prevention and Health Promotion; 2014.
4. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *Am J Health Syst Pharm*. 2017;74(16):1237-1244.
5. Ikeda T, Yasaka M, Kida M, Imura M. A survey of reasons for continuing warfarin therapy in the era of direct oral anticoagulants in Japanese patients with atrial fibrillation: the SELECT study. *Patient Prefer Adherence*. 2018;12:135-143.
6. Bajorek B, Saxton B, Anderson E, Chow CK. Patients' preferences for new versus old anticoagulants: a mixed-method vignette-based study. *Eur J Cardiovasc Nurs*. 2018;17(5):429-438.
7. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl): e44S-e88S.
8. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. *J Thromb Thrombolysis*. 2011;31(3):326-343.
9. Thi L, Shaw D, Bird J. Warfarin potentiation: a review of the "FAB-4" significant drug interactions. *Consult Pharm*. 2009;24(3):227-230.
10. Black DJ, Kunze KL, Wienkers LC, et al. Warfarin-fluconazole. II. A metabolically based drug interaction: in vivo studies. *Drug Metab Dispos*. 1996;24(4):422-428.
11. Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin Pharmacol Ther*. 2008;84(5):581-588.
12. Crussell-Porter LL, Rindone JP, Ford MA, Jaskar DW. Low-dose fluconazole therapy potentiates the hypoprothrombinemic response of warfarin sodium. *Arch Intern Med*. 1993;153(1):102-104.
13. Lane MA, Zeringue A, McDonald JR. Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. *Am J Med*. 2014;127(7):657-663.e2.
14. Turrentine MA. Single-dose fluconazole for vulvovaginal candidiasis: impact on prothrombin time in women taking warfarin. *Obstet Gynecol*. 2006;107(2 part 1):310-313.
15. Purkins L, Wood N, Kleinermans D, Nichols D. Voriconazole potentiates warfarin-induced prothrombin time prolongation. *Br J Clin Pharmacol*. 2003;56(suppl 1):24-29.
16. Yamamoto H, Habu Y, Yano I, et al. Comparison of the effects of azole antifungal agents on the anticoagulant activity of warfarin. *Biol Pharm Bull*. 2014;37(12):1990-1993.
17. Heimark LD, Wienkers L, Kunze K, et al. The mechanism of the interaction between amiodarone and warfarin in humans. *Clin Pharmacol Ther*. 1992;51(4):398-407.
18. Holm J, Lindh JD, Andersson ML, Mannheimer B. The effect of amiodarone on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population. *J Thromb Haemost*. 2017;15(3):446-453.
19. Santos PC, Soares RA, Strunz CM, et al. Simultaneous use of amiodarone influences warfarin maintenance dose but is not associated with adverse events. *J Manag Care Spec Pharm*. 2014;20(4):376-381.
20. Edwin SB, Jennings DL, Kalus JS. An evaluation of the early pharmacodynamic response after simultaneous initiation of warfarin and amiodarone. *J Clin Pharmacol*. 2010;50(6):693-698.
21. Sanoski CA, Bauman JL. Clinical observations with the amiodarone/warfarin interaction: dosing relationships with long-term therapy. *Chest*. 2002;121(1):19-23.
22. Lam J, Gomes T, Juurlink DN, et al. Hospitalization for hemorrhage among warfarin recipients prescribed amiodarone. *Am J Cardiol*. 2013; 112(3):420-423.
23. Fischer HD, Juurlink DN, Mamdani MM, Kopp A, Laupacis A. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. *Arch Intern Med*. 2010;170(7):617-621.
24. Hale SF, Lesar TS. Interaction of vitamin K antagonists and trimethoprim-sulfamethoxazole: ignore at your patient's risk. *Drug Metabol Drug Interact*. 2014;29(1):53-60.
25. Howard-Thompson A, Hurdle AC, Arnold LB, Finch CK, Sands C, Self TH. Intracerebral hemorrhage secondary to a warfarin-metronidazole interaction. *Am J Geriatr Pharmacother*. 2008;6(1):33-36.
26. Martins MA, Reis AM, Sales MF, et al. Rifampicin-warfarin interaction leading to macroscopic hematuria: a case report and review of the literature. *BMC Pharmacol Toxicol*. 2013;14(1):27.
27. Krajewski KC. Inability to achieve a therapeutic INR value while on concurrent warfarin and rifampin. *J Clin Pharmacol*. 2010;50(6):710-713.
28. Mannheimer B, Andersson ML, Järnbert-Pettersson H, Lindh JD. The effect of carbamazepine on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population. *J Thromb Haemost*. 2016;14(4):765-771.
29. Parrish RH, Pazdur DE, O'donnell PJ. Effect of carbamazepine initiation and discontinuation on antithrombotic control in a patient receiving warfarin: case report and review of the literature. *Pharmacotherapy*. 2006;26(11):1650-1653.
30. Lee CR, Thrasher KA. Difficulties in anticoagulation management during coadministration of warfarin and rifampin. *Pharmacotherapy*. 2001;21(10): 1240-1246.
31. Shibata S, Takahashi H, Baba A, et al. Delayed de-induction of CYP2C9 compared to CYP3A after discontinuation of rifampicin: report of two cases. *Int J Clin Pharmacol Ther*. 2017;55(5):449-452.
32. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy*. 1998;18(1):84-112.
33. Kunze KL, Trager WF. Warfarin-fluconazole. III. A rational approach to management of a metabolically based drug interaction. *Drug Metab Dispos*. 1996;24(4):429-435.
34. Powers A, Loesch EB, Weiland A, Fioravanti N, Lucius D. Preemptive warfarin dose reduction after initiation of sulfamethoxazole-trimethoprim or metronidazole. *J Thromb Thrombolysis*. 2017;44(1):88-93.
35. Ahmed A, Stephens JC, Kaus CA, Fay WP. Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim-sulfamethoxazole or levofloxacin. *J Thromb Thrombolysis*. 2008;26(1):44-48.
36. Holt RK, Anderson EA, Cantrell MA, Shaw RF, Egge JA. Preemptive dose reduction of warfarin in patients initiating metronidazole. *Drug Metabol Drug Interact*. 2010;25(1-4):35-39.
37. Ha NB, Yang K, Hanigan S, et al. Impact of a guideline for the management of antimicrobial/warfarin interactions in the inpatient setting and across transition of care. *Ann Pharmacother*. 2016;50(9):734-740.
38. Clark NP, Delate T, Riggs CS, et al; Warfarin-Associated Research Projects and Other Endeavors Consortium. Warfarin interactions with antibiotics in the ambulatory care setting. *JAMA Intern Med*. 2014; 174(3):409-416.
39. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17(10):1467-1507.

40. Janssen Pharmaceuticals, Inc. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2017.
41. Health Canada. Xarelto [product monograph]. Mississauga, ON, Canada: Bayer Inc.; 2018.
42. European Medicines Agency. Xarelto [summary of product characteristics]. Leverkusen, Germany: Bayer AG; 2017.
43. Bristol-Myers Squibb Company and Pfizer Inc. Eliquis [package insert]. Princeton, NJ: Bristol-Myers Squibb Company and Pfizer Inc.; 2018.
44. Health Canada. Eliquis [product monograph]. Kirkland, QC, Canada: Pfizer Canada Inc. and Bristol-Myers Squibb Canada; 2018.
45. European Medicines Agency. Eliquis [summary of product characteristics]. Uxbridge, Middlesex, United Kingdom: Bristol-Myers Squibb/Pfizer EEIG; 2017.
46. Boehringer Ingelheim Pharmaceuticals, Inc. Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2018.
47. Health Canada. Pradaxa [product monograph]. Burlington, ON, Canada: Boehringer Ingelheim Canada Ltd.; 2016.
48. European Medicines Agency. Pradaxa [summary of product characteristics]. Ingelheim am Rhein, Germany: Boehringer Ingelheim International GmbH; 2017.
49. Daiichi Sankyo, Inc. Savaysa [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2017.
50. Health Canada. Lixiana [product monograph]. Laval, QC, Canada: Servier Canada Inc.; 2017.
51. European Medicines Agency. Lixiana [summary of product characteristics]. Munich, Germany: Daiichi Sankyo Europe GmbH; 2017.
52. Portola Pharmaceuticals, Inc. Bevyxxa [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc.; 2017.
53. Kaserer A, Schedler A, Jetter A, et al. Risk factors for higher-than-expected residual rivaroxaban plasma concentrations in real-life patients. *Thromb Haemost*. 2018;118(5):808-817.
54. Cheong EJY, Goh JJN, Hong Y, Kojodjojo P, Chan ECY. Rivaroxaban with and without amiodarone in renal impairment. *J Am Coll Cardiol*. 2018;71(12):1395-1397.
55. Gong IY, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. *Can J Cardiol*. 2013;29(7 suppl):S24-S33.
56. Laureano M, Crowther M, Eikelboom J, Boonyawat K. Measurement of dabigatran drug levels to manage patients taking interacting drugs: a case report. *Am J Med*. 2016;129(10):e247-e248.
57. Bates D, Dalton B, Gilmour J, Kapler J. Venous thromboembolism due to suspected interaction between rivaroxaban and nevirapine. *Can J Hosp Pharm*. 2013;66(2):125-129.
58. Altena R, van Roon E, Folkeringa R, de Wit H, Hoogendoorn M. Clinical challenges related to novel oral anticoagulants: drug-drug interactions and monitoring. *Haematologica*. 2014;99(2):e26-e27.
59. Risselada AJ, Visser MJ, van Roon E. Pulmonary embolism due to interaction between rivaroxaban and carbamazepine [in Dutch]. *Ned Tijdschr Geneeskd*. 2013;157(52):A6568.
60. Serra W, Li Calzi M, Coruzzi P. Left atrial appendage thrombosis during therapy with rivaroxaban in elective cardioversion for permanent atrial fibrillation. *Clin Pract*. 2015;5(3):788.
61. Wiggins BS, Northup A, Johnson D, Senfield J. Reduced anticoagulant effect of dabigatran in a patient receiving concomitant phenytoin. *Pharmacotherapy*. 2016;36(2):e5-e7.
62. Hager N, Bolt J, Albers L, Wojcik W, Duffy P, Semchuk W. Development of left atrial thrombus after coadministration of dabigatran etexilate and phenytoin. *Can J Cardiol*. 2017;33(4):554.e13-554.e14.
63. Stöllberger C, Finsterer J. Recurrent venous thrombosis under rivaroxaban and carbamazepine for symptomatic epilepsy. *Neurol Neurochir Pol*. 2017;51(2):194-196.
64. Burden T, Thompson C, Bonanos E, Medford AR. Lesson of the month 2: pulmonary embolism in a patient on rivaroxaban and concurrent carbamazepine. *Clin Med (Lond)*. 2018;18(1):103-105.
65. King PK, Stump TA, Walkama AM, Ash BM, Bowling SM. Management of phenobarbital and apixaban interaction in recurrent cardioembolic stroke. *Ann Pharmacother*. 2018;52(6):605-606.
66. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016;41(1):206-232.
67. Thrombosis Canada. NOACs/DOACs: Comparison and Frequently-Asked Questions. Vol. 2018. Whitby, ON, Canada: Thrombosis Canada; 2017.
68. Steffel J, Verhamme P, Potpara TS, et al; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace*. 2018;20(8):1231-1242.
69. Evanger N, Szkotak A, Stang L, Bungard TJ. Apixaban concentration with and without coadministration of carbamazepine: a case with no apparent interaction. *Can J Hosp Pharm*. 2017;70(6):463-467.
70. Lutz JD, Kirby BJ, Wang L, et al. Cytochrome P450 3A induction predicts p-glycoprotein induction. Part 1: establishing induction relationships using ascending dose rifampin. *Clin Pharmacol Ther*. 2018.
71. Xu R, Ge W, Jiang Q. Application of physiologically based pharmacokinetic modeling to the prediction of drug-drug and drug-disease interactions for rivaroxaban. *Eur J Clin Pharmacol*. 2018;74(6):755-765.
72. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *J Thromb Haemost*. 2011;9(11):2168-2175.
73. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al; ROCKET AF Steering Committee and Investigators. Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: results from the ROCKET AF trial. *Heart Rhythm*. 2014;11(6):925-932.
74. Flaker G, Lopes RD, Hylek E, et al; ARISTOTLE Committees and Investigators. Amiodarone, anticoagulation, and clinical events in patients with atrial fibrillation: insights from the ARISTOTLE trial. *J Am Coll Cardiol*. 2014;64(15):1541-1550.
75. Steffel J, Giugliano RP, Braunwald E, et al. Edoxaban vs. warfarin in patients with atrial fibrillation on amiodarone: a subgroup analysis of the ENGAGE AF-TIMI 48 trial. *Eur Heart J*. 2015;36(33):2239-2245.
76. Washam JB, Hellkamp AS, Lokhnygina Y, et al; ROCKET AF Steering Committee and Investigators. Efficacy and safety of rivaroxaban versus warfarin in patients taking nondihydropyridine calcium channel blockers for atrial fibrillation (from the ROCKET AF Trial). *Am J Cardiol*. 2017;120(4):588-594.
77. Ismail M, Lee VH, Chow CR, Rubino CM. Minimal physiologically based pharmacokinetic and drug-drug-disease interaction model of rivaroxaban and verapamil in healthy and renally impaired subjects. *J Clin Pharmacol*. 2018;58(4):541-548.
78. Greenblatt DJ, Patel M, Harmatz JS, Nicholson WT, Rubino CM, Chow CR. Impaired rivaroxaban clearance in mild renal insufficiency with verapamil coadministration: potential implications for bleeding risk and dose selection. *J Clin Pharmacol*. 2018;58(4):533-540.
79. Mochalina N, Juhlin T, Platonov PG, Svensson PJ, Wieloch M. Concomitant use of dronedarone with dabigatran in patients with atrial fibrillation in clinical practice. *Thromb Res*. 2015;135(6):1070-1074.
80. Lock J, Patel RK, Brookes C, Patel JP. Clinical experience of prescribing dabigatran etexilate with dronedarone: the role of therapeutic drug monitoring. *Ther Drug Monit*. 2016;38(6):813-814.
81. Härtter S, Sennewald R, Nehmiz G, Reilly P. Oral bioavailability of dabigatran etexilate (Pradaxa(®)) after co-medication with verapamil in healthy subjects. *Br J Clin Pharmacol*. 2013;75(4):1053-1062.
82. Kumar S, Danik SB, Altman RK, et al. Non-vitamin K antagonist oral anticoagulants and antiplatelet therapy for stroke prevention in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. *Cardiol Rev*. 2016;24(5):218-223.
83. Steinberg BA, Kim S, Piccini JP, et al; ORBIT-AF Investigators and Patients. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. *Circulation*. 2013;128(7):721-728.

84. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med*. 2010;170(16):1433-1441.
85. Cannon CP, Bhatt DL, Oldgren J, et al; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(16):1513-1524.
86. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375(25): 2423-2434.
87. Lopes RD, Guimarães PO, Kolls BJ, et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. *Blood*. 2017;129(22):2980-2987.
88. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published comment in *J Am Coll Cardiol*. 2016;8(10):E1226-E1229]. *J Am Coll Cardiol*. 2016;68(10):1082-1115.
89. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):e1159-e1195.
90. Tielleman T, Bujanda D, Cryer B. Epidemiology and risk factors for upper gastrointestinal bleeding. *Gastrointest Endosc Clin N Am*. 2015; 25(3):415-428.
91. Bakhriansyah M, Souverein PC, de Boer A, Klungel OH. Gastrointestinal toxicity among patients taking selective COX-2 inhibitors or conventional NSAIDs, alone or combined with proton pump inhibitors: a case-control study. *Pharmacoepidemiol Drug Saf*. 2017;26(10): 1141-1148.
92. Andrade C, Sharma E. Serotonin reuptake inhibitors and risk of abnormal bleeding. *Psychiatr Clin North Am*. 2016;39(3):413-426.
93. Scheitz JF, Turc G, Kujala L, et al; TRISP Collaboration. Intracerebral hemorrhage and outcome after thrombolysis in stroke patients using selective serotonin-reuptake inhibitors. *Stroke*. 2017;48(12): 3239-3244.
94. Renoux C, Vahey S, Dell'Aniello S, Boivin JF. Association of selective serotonin reuptake inhibitors with the risk for spontaneous intracranial hemorrhage. *JAMA Neurol*. 2017;74(2):173-180.
95. Samuel NG, Seifert CF. Risk of bleeding in patients on full-dose enoxaparin with venous thromboembolism and selective serotonin reuptake inhibitors. *Ann Pharmacother*. 2017;51(3):226-231.
96. Quinn GR, Singer DE, Chang Y, et al. Effect of selective serotonin reuptake inhibitors on bleeding risk in patients with atrial fibrillation taking warfarin. *Am J Cardiol*. 2014;114(4):583-586.
97. Cochran KA, Cavallari LH, Shapiro NL, Bishop JR. Bleeding incidence with concomitant use of antidepressants and warfarin. *Ther Drug Monit*. 2011;33(4):433-438.
98. US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Vol. 2018. Silver Springs, MD: US Food and Drug Administration; 2017.