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Old and new oral anticoagulants: food, herbal medicines and drug interactions

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Abstract

The most commonly prescribed oral anticoagulants worldwide are the vitamin K antagonists (VKAs) such as warfarin. Factors affecting the pharmacokinetics of VKAs are important because deviations from their narrow therapeutic window can result in bleedings due to over-anticoagulation or thrombosis because of under-anticoagulation. In addition to pharmacodynamic interactions (e.g., augmented bleeding risk for concomitant use of NSAIDs), interactions with drugs, foods, herbs, and over-the-counter medications may affect the risk/benefit ratio of VKAs. Direct oral anticoagulants (DOACs) including Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and thrombin inhibitor (dabigatran) are poised to replace warfarin. Phase-3 studies and real-world evaluations have established that the safety profile of DOACs is superior to those of VKAs. However, some pharmacokinetic and pharmacodynamic interactions are expected. Herein we present a critical review of VKAs and DOACs with focus on their potential for interactions with drugs, foods, herbs and over-the-counter medications.

Keywords: warfarin, direct anticoagulant drugs, loss of efficacy, toxicity, thrombotic/bleeding events, therapeutic context, patients characteristics, co-morbidities.

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1. Introduction

Until recently, the vitamin K antagonists (VKAs) were the only oral anticoagulant agents available, and warfarin remains the most commonly prescribed oral anticoagulant worldwide. Its indications include a wide range of clinical conditions from prevention of cardioembolic ischemic stroke to deep venous thrombosis and pulmonary embolism. Anticoagulants are used in patients with a history of atrial fibrillation or flutter, recent major surgery or immobility, heart valve replacement, ischemic stroke or other thrombotic event [1]. Warfarin has significant variability in dose-response across individuals and a narrow therapeutic window (the international normalized ratio [PT-INR] value must remain between 2.0 and 3.0 for most indications) [2]. Clinical outcomes are highly correlated with the amount of time patient's PT-INR values are maintained in range [3]. Patients with an average individual time in therapeutic range > 70% are considered to be at a low risk of a major hemorrhagic or thrombotic event [4]. Frequent monitoring of PT-INR lab values and dose adjustments, therefore, are necessary for safe and efficacious use of warfarin [5]. Likewise, patient instruction and identification of factors leading to over- or under-anticoagulation are critical [6; 7]. When combined with low-dose aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or clopidogrel, warfarin acts cumulatively, and risk of bleeding is significantly increased [8; 9]. VKAs are among the medications with the highest incidence of drug-related life-threatening events [1] and top the list of interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications [10; 11]. Interactions resulting in over- or under-anticoagulation drastically increase the risk of major hemorrhagic or thrombotic event.

Direct oral anticoagulants (DOACs), approved for the prevention and treatment of venous thromboembolism and of systemic and cerebral embolism in atrial fibrillation [12], are poised to replace warfarin for stroke prevention [13]. As their anticoagulant effect is more predictable and stable (i.e., less influenced by interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications), DOACs should prove safer and less problematic compared to the VKAs [14]. Clinical studies of venous and arterial thromboprophylaxis suggest that routine laboratory monitoring is not necessary with thrombin inhibitors or Factor Xa inhibitors. However,

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potential pharmacodynamic interactions and drug interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications must still be considered with the use of DOACs [15].

2. Vitamin K antagonists (VKAs)

The pharmacokinetic and pharmacodynamic effects on VKAs that result from interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications are summarized in Table 1, and detailed in the Online Appendix. A variety of drugs, herbal medicines, nutrients that may affect dietary intake of Vitamin K may interact with VKAs possibly changing their effect [16]. Mechanisms of such interactions are herein discussed.

2.1. Drug-drug interactions affecting pharmacokinetic of warfarin

Several prescriptions and over-the-counter medications, foods and herbal supplements alter the pharmacokinetics (absorption, distribution, metabolism and elimination) and pharmacodynamics (anticoagulant effect) of warfarin (Table 1) [17; 18].

The absorption of warfarin is reduced by concomitant use of cholestyramine and sucralfate [19]. As warfarin is highly bound to plasma proteins, other substances or medications that compete for protein-binding sites (e.g., ibuprofen, quinidine, fenofibrate, losartan, valsartan, amlodipine, felodipine, sulfinpyrazone, phenylbutazone and the principal metabolite of chloral hydrate. i.e. trichloracetic acid*)* displace warfarin, potentiating the anticoagulant action of VKAs [20]. This effect, often observed as marginally increased PT-INR, is typically transient and has a delayed onset ranging from 1 day to 3 weeks (in the case of phenprocoumon) after starting the concomitant drug regimen [21; 22].

The majority of drug interactions affecting warfarin involves inhibition of the expression and/or activity of CYP450 enzymes involved in warfarin metabolism (CYP2C9 for the *S*-enantiomer and

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CYPs 1A2, 2C19, 3A4 for *R*-enantiomer of warfarin). Interactions involving the *S*-enantiomer may be of greater impact because the activity (anticoagulant effect) of the *S*-enantiomer is 2 to 5-fold greater than that of the *R*-enantiomer [23]. The concomitant use of medications that induce CYP2C9 (e.g., rifampin and phenobarbital) results in increased clearance of warfarin and thus less anticoagulation [24].

Nearly 1 in 3 patients prescribed warfarin also prescribed a statin. Several statins are metabolized by CYP3A4 and CYP2C9 isoenzymes. Altered warfarin metabolism leading to increase PT-INR values has been reported with concomitant use of fluvastatin, lovastatin, simvastatin or atorvastatin [25; 26]. As the metabolism of pravastatin and rosuvastatin does not involve CYP450 enzymes, potential for drug-drug interactions with warfarin is limited [27; 28]. Other cardiovascular pharmacotherapies that interact with warfarin are listed in Table 2.

HIV-positive patients often require anticoagulation therapy because they are at increased risk of venous thromboembolism or cardiovascular disease [29]. As several of the anti-retroviral agents (*e.g.,* nevirapine, efavirez, saquinavir and ritonavir) used to treat HIV interact with warfarin metabolism by inhibiting/inducing CYP enzymes (Table 3), clinicians treating HIV-positive patients should be informed about the increased likelihood of adverse reactions or decreased efficacy of warfarin therapy in this patient population [30; 31; 32; 33].

Some of the anti-fungal drugs (e.g., fluconazole, miconazole), and antibiotics (e.g., azithromycin, ciprofloxacin) inhibit specific CYP450 iso-enzymes (Table 3), altering warfarin pharmacokinetics and increase PT-INR values and risk of hemorrhage when combined with warfarin [22; 34]. In addition, they can also diminish gut absorption of Vitamin K by altering the gut flora. Although this is rarely of clinical significance (other than in malnourished patient populations), this altered ability to absorb vitamin K can result in lowered synthesis of vitamin K-dependent coagulation proteins and, ultimately, in an increased risk of hemorrhage [35].

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Several over-the-counter medications significantly alter warfarin metabolism. Increased PT-INR and pro-hemorrhagic effects (e.g. ecchymosis, subcutaneous hematomas, hematuria) have been reported after 2 weeks of concomitant use of over-the-counter anti-fungal "Miconazole (oral gel)", a strong CYP2C9 inhibitor, used for the treatment of oral Candidiasis [36]. Two case reports of decreased PT-INR values with concomitant use of over-the-counter menthol drops (antitussives) provide another example of potential interactions between warfarin and over-the-counter medications [37; 38].

Drug-drug interactions may also affect warfarin elimination. For example, the concomitant use of miconazole and phenylbutazone results in increased warfarin elimination and decrease efficacy of warfarin therapy, by inhibiting the elimination of the *S*-enantiomer [16].

2.2. Drug-drug interactions affecting pharmacodynamic of warfarin

Guidelines [1; 4] recommend avoiding routine concomitant use of warfarin and antiplatelet agents, with the exception of appropriate therapeutic regimens in certain well identified clinical conditions [19; 39]. Medications affecting platelet function have a synergistic pharmacodynamic interaction with warfarin; concomitant use, therefore, can result in significant increases in PT-INR and, in turn, in an increased risk of bleeding [40; 41; 42].

*A*cetaminophen, a widely used over-the-counter analgesic and antipyretic does not alter platelet function [43], but concomitant use of acetaminophen at doses ≥ 2g/d for several days increases the pharmacodynamic effect (increased PT-INR) of warfarin. Pharmacodynamic drug interactions with warfarin are often of more clinical relevance than those affecting only the pharmacokinetic of warfarin. Oral contraceptives increase the risk of thrombosis by 4-5 folds compared to placebo [44], and their use in patients prescribed warfarin must be carefully assessed as they decrease protein S and increase the synthesis of vitamin K dependent clotting factors [45].

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3. Foods and herbal medicines interactions with warfarin

3.1. Pharmacokinetic interactions of warfarin with food and herbal medicines

Nearly 15% of the US population uses complementary and alternative medicines (CAMs) in parallel with conventional treatments [46]. Detailed clinical information regarding various herbal supplements and medicines and their interactions with warfarin are summarized in Table 4. Unfortunately, most patients receiving warfarin have poor knowledge about the potential interactions of some CAMs and warfarin and seldom inform their clinicians about their concomitant use of CAMs [47].

One study of patients prescribed warfarin for chronic atrial fibrillation found that about 50% were also taking an herbal supplement or medication. Warfarin patients taking no herbal medications or only 1 herbal < 4 times per week were more likely to have PT-INR values within the optimal therapeutic range (2.0 to 3.0) compared to those taking >1 type of herbal ≥ 4 times per week (58.1% vs 51.1%, P = 0.046) [48]. Findings from several *in vitro* studies have shown that components of herbal supplements may inhibit CYP2C9. This is seldom of clinical significance because these CYP2C9 components rarely achieve appreciable intrahepatic concentrations [49]. In addition, no data have been reported to date suggesting that foods or nutrients (other than those containing Vitamin K) interact significantly with warfarin CYP2C9 metabolism [50; 51].
The most important advice for patients is to maintain their usual diet, since warfarin interactions with food have generally not clinical implications when patients follow a stable diet.[52] Old recommendations for diets low in vitamin K should be considered obsolete [52].

3.1.1. Grapefruit

Components of grapefruit and grapefruit juice, mainly the furanocoumarins, inhibit CYP3A4 activity [53; 54]. However, only a few cases of elevated PT-INR and/or minor hematomas have been

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reported [55]. Nonetheless, clinicians and patients should be aware of the potential interaction between warfarin and grapefruit [54].

3.1.2. Green tea

Although green tea has several reported health benefits [28], high doses markedly reduce PT-INR. A change in PT-INR value from 3.8 to 1.4 has been reported, suggesting the potential for a significant interaction between green tea and VKAs when green tea is consumed in high doses [48]. Moderate consumption of green tea, however, is not likely to affect anticoagulant therapy because green tea contains minimal amount of Vitamin K [56; 57] and the amounts of other compounds that alter CYP activity, such as catechin and flavonoids, are often insufficient to have an appreciable effect on PT-INR [58].

3.1.3. Chamomile (Matricaria chamomilla)

Chamomile, an herbal treatment for gastric discomfort, anxiety and catarrh [59], *in vitro* inhibits CYP1A2 and, to a lesser extent, 3A4 and 2C9 [60]. A case of serious bleeding was observed in a 70-year old female patient on warfarin therapy who consumed large quantities of chamomile [61].

3.1.4. Soybean or soy milk

Soybeans can be used to treat symptoms of menopause, osteoporosis and hyperlipidemia [62]. Although *in vitro* soybean extracts inhibit CYP3A4 and CYP2C9, they may also impair the anticoagulant activity of warfarin [63; 64] because they contain significant amounts of Vitamin K [65].

3.1.5. Mango

Mango contains high concentrations of retinol, a known inhibitor of CYP2C19 [66]. Increases in PT-INR resulting from consuming even small amounts of mango while receiving warfarin therapy can

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be clinically relevant, and patients and clinicians need be aware of this potential interaction [66; 67].

3.1.6. Ginseng

Ginseng does not affect the pharmacokinetics or pharmacodynamics of warfarin [68].

3.1.7. St. John's wort (*Hypericum perforatum*)

St. John's wort, often used to treat moderate depression, sleep disorders, anxiety and pain [69; 70], induces CYP1A2 [71], 2C9 [72; 73] and 3A4 [74], resulting in increased clearance and reduction of plasma concentrations of warfarin. Long-term consumption of St. John's wort increases the clearance of both the S (+29%, via CYP2C9) and the R (+23%, via CYP3A4/CYP1A2) enantiomers of warfarin, resulting in a clinically significant reduction of the pharmacological effect of warfarin [54; 68].

3.1.8. Ginkgo biloba

Consumption of Ginkgo can increase the risk of bleeding in surgical patients. Although one study was unable to detect a difference in warfarin anticoagulation due to concomitant use of Ginkgo, *in vitro* studies have shown that several flavonol aglycones (e.g., amentoflavone) found in Ginkgo are potent inhibitors of human CYP2C9 [75; 76].

3.1.9. Cranberry (Vaccinium myrtillus)

Case-reports document increased PT-INR and incidence of hemorrhage attributed to the co-administration of cranberry juice (often used in urinary infections) in patients on warfarin [77; 78; 79]. Cranberry juice contains marginal amounts of Vitamin K [80; 81] and flavonoids' oil. Although *in vitro* [82], animal [83] and small clinical studies [84; 85; 86] suggest that cranberry juice alters

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CYP2C9 and 3A4 activity, moderate daily consumption of cranberry juice (240-280 mL/d) has little impact on PT-INR.

3.2. Pharmacodynamic interactions of foods and herbal supplements and medicines with warfarin

Green, leafy vegetables and certain vegetable oils contain significant amounts Vitamin K, and their consumption in excess may result in decreased PT-INR. Conversely, decreased consumption or absorption (secondary to changes in gut flora secondary to antibiotic use) of Vitamin K and increased elimination (secondary to diarrhea) of Vitamin K may result in drastic increases in PT-INR and over anticoagulation [28]. Likewise, biliary obstruction and malabsorption have also been associated with decreased levels of Vitamin K and over-anticoagulation [22].

3.2.1. Ginkgo biloba

Ginkgolides, the major chemical components of Ginkgo biloba, have anti-inflammatory and anti-platelet properties [87]. In a patient with chronically stable PT-INR values on warfarin, intracranial hemorrhage was reported after 2 months of concomitant use of Ginkgo biloba [88]. However, findings from two separate clinical trials reported that standardized extract of Ginkgo (240 mg/d/1 week or 100 mg/d/4weeks) does not alter the pharmacodynamic of warfarin [89]. Nevertheless, routine monitoring of PT-INR is recommended for patients taking ginkgo in addition to warfarin [54].

3.2.2. Ginseng

Ginsenosides, the major active components of ginseng, inhibit CYP1A2 [87], platelet aggregation and thromboxane formation [90; 91]. The findings from three separate reports suggest that ginseng marginally increases the anticoagulant effect of warfarin [90; 92; 93].

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4. Interactions affecting pharmacokinetic or pharmacodynamics of phenprocoumon and acenocumarol

In patients on chronic phenprocoumon, the increased risk of bleeding of patients co-medicated with verapamil [59] and the increased risk of thrombosis of patients co-medicated with carbamazepine [94] suggest changes in phenprocoumon bioavailability as well as specific effects on CYP450 enzymes playing a major role in the metabolism of this VKA. Interactions between phenprocoumon and ambrisentan [95], esomeprazole [96] and metformin [97] were also reported. In addition, interactions with older macrolide antibiotics erythromycin and clarithromycin, which inhibit CYP3A4, can trigger life-threatening hemorrhage and contribute to the incidence of medical drug-related hospitalizations [98]. Likewise, inhibition of CYP3A4-catalyzed metabolism of phenprocoumon by clarithromycin may result in an increase of both bioavailability and risk of bleeding [99]. Avoidance of concomitant use of co-trimoxazole with phenprocoumon (or acenocoumarol) is a safer approach for the prevention of these potential interactions [100].

4.1. Phenprocoumon

A significantly elevated risk of major bleeding has been observed for drugs with known pharmacodynamic interactions with phenprocoumon [101]. For instance, an increased risk of bleeding was reported with the combined use of phenprocoumon and clopidogrel [101]. Antibiotics associated with an increased risk of hemorrhage in phenprocoumon users include quinolones with ORs ranging from 2.74 (95% CI: 1.80-4.18) for ciprofloxacin to 4.40 (95% CI: 2.45-7.89) for levofloxacin, to 2.99 (95% CI: 1.39-6.42) for amoxicillin plus clavulanic acid and to 3.57 (95% CI: 2.36-5.40) for cotrimoxazole [102; 103]. Among NSAIDs, ketoprofen and naproxen were associated with the highest risks [101]. Selective serotonin reuptake inhibitors (SSRIs), such as citalopram, which inhibits the transport of serotonin into the platelets, lead to impaired platelet function thus increasing the risk of bleeding [104; 105].

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4.2. Acenocumarol

CYP2C9 polymorphisms have an impact on drug-drug interactions during acenocoumarol treatment [106]. Case-reports and case-series document interactions between acenocoumarol and levofloxacin [107], topical terbinafine [108], amorolfine [109] or ciclopirox [110]. Increased PT-INR after acenocoumarol co-administration with gefitinib [111] or with capecitabine [112] have also been reported. Phenytoin and acenocoumarol share the same metabolizing pathway by hepatic CYP2C9. The co-administration of therapeutic doses markedly decreases the metabolism of both drugs, leading to acute phenytoin toxicity and increased PT-INR, especially in individuals homozygous for CYP2C9*3 [113].

Special emphasis has been devoted to oral anticoagulation in HIV patients. Interaction between antiretroviral drugs (efavirenz and atazanavir/ritonavir) with acenocoumarol has been documented together with the possibility of a safe concurrent use (i.e. the lack of interaction) of acenocoumarol with raltegravir [114]. Pulmonary arterial hypertension is an uncommon although life-threatening complication of HIV infection, which is treated with bosentan and oral anticoagulants. However, because of its ability to induce the acenocoumarol metabolism and, in turn, to increase PT-INR values, bosentan co-administration with acenocoumarol (and other VKAs) requires a closer PT-INR monitoring not only during the first weeks of treatment, but also during longer periods [115]. Sitaxentan is a conventional therapy for pulmonary hypertension with/without HIV positivity. Sitaxentan inhibits the metabolism of acenocoumarol, resulting in a need for adjustment of acenocoumarol dose when the two drugs are co-administered. In a subset of patients enrolled in the STRIDE-3 study, a PT-INR ≥ 5 in at least one determination was observed in 13 patients on long-term co-treatment with acenocoumarol, although no a clinically significant bleeding event was recorded [116].

A potentiation of acenocoumarol-induced anticoagulation by co-medication with omeprazole or esomeprazole and inhibition of CYP2C19 were also reported [117]. The risk for over-anticoagulation was most pronounced for esomeprazole (HR 1.99, 95% CI 1.55-2.55) and

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lansoprazole (HR 1.49, 95% CI 1.05-2.10), whereas a non-significant risk increase for the other proton-pump inhibitors (PPIs) was observed [117]. In the same report, no modification of these findings was reported because of different CYP2C19*2 genotypes. Laryngeal hematoma in relation to interaction between acenocoumarol and topical econazole lotion has also been reported because of drug-drug interaction affecting acenocoumarol elimination [118]. Finally, in addition to red Ginseng (used for tiredness and dizziness), reduction of anticoagulant therapy efficacy (low PT-INR) with need to increase the dosage of acenocoumarol was reported for a series of herbal medicines used for weight loss [119].

A 15% decrease in acenocoumarol clearance ($P < 0.05$) when 1 g of amoxicillin + 250 mg of clavulanic acid were co-administered has been reported in healthy volunteers [120]. In contrast, co-administration of sulfamethoxazole-trimethoprim with acenocoumarol increased by 3-fold the risk of over-anticoagulation. Clopidogrel and acetylsalicylate are also relevant to increase the risk of bleeding [121], while oral contraceptives and hormone replacement therapy tend to offsetting the effect of acenocoumarol [121].

5. Direct Oral Anticoagulant Drugs (DOACs)

Comparative pharmacokinetics and pharmacodynamics of DOACs vs warfarin are summarized in Online Table S1 and detailed in the Online Appendix of this report.

5.1. Dabigatran

5.1.1. Drug-drug interactions affecting the pharmacokinetic of dabigatran

Pharmacokinetic interactions of DOACs with drugs are reported in Table 5; relevant pharmacological interactions with dabigatran and their clinical relevance are summarized in Table 6 and those with Factor Xa inhibitors in Table 7.

Dabigatran etexilate, being not metabolized by cytochrome P450, has low potential for clinically relevant interactions with drugs metabolized by cytochrome P450 [122]. By contrast, this drug is a

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substrate for P-glycoprotein 1 (P-gp) [123] and its co-administration with strong P-gp inhibitors (e.g. ketoconazole and verapamil) or P-gp inducers (e.g. rifampicin, St. John's wort, carbamazepine and phenytoin) should be avoided [124]. No dose adjustment is needed with the concomitant use of P-gp inhibitor amiodarone, whereas the usual dose 150 mg BID should be reduced to 110 mg BID in patients receiving verapamil [125]. Dronedarone should not be co-administered with dabigatran because it increases the levels of the later drug up to 2-fold [126]. Overall, dabigatran etexilate should be given at least 2 h prior to co-administering any P-gp inhibitor [127].

Atorvastatin (CYP3A4 substrate), diclofenac (CYP2C9 substrate) or digoxin (P-gp inhibitor) have limited impact on dabigatran efficacy, safety and tolerability [128]. Dabigatran absorption is reduced by co-administration of anti-acids such as PPIs [129], even if this effect is seldom of clinical relevance. Dabigatran bioavailability increases after co-administration of ketoconazole [130] or quinidine [131] and decreases after co-administration of rifampicin [132]. Hence, these co-administrations should be avoided.

5.1.2. Drug-drug interactions affecting the pharmacodynamic of dabigatran

The co-administration of dabigatran with other anticoagulant/antiplatelet drugs should be avoided and/or limited in time, unless specifically defined. Co-administration with clopidogrel increases the AUC and the C_{max} of dabigatran of 30 and 40%, respectively [28]. In addition, co-administration of dabigatran with aspirin (or diclofenac) requires caution, because of the high risk of bleeding [19].

5.2. Rivaroxaban

5.2.1. Drug-drug interactions affecting the pharmacokinetic of rivaroxaban

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin leads to ≈50% decrease in mean AUC of Rivaroxaban [125]. Thus, decreases in rivaroxaban plasma

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concentrations are expected in patients concomitantly treated with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's wort). Hence, caution is mandatory for such co-administrations.

By affecting its intestinal excretion, P-gp increases rivaroxaban plasma concentrations [133]. Active substances, however, which strongly inhibit only one of the elimination pathways, e.g. CYP3A4 or P-gp, increase rivaroxaban concentrations only at a limited extent. For instance, co-administration of the strong CYP3A4 inhibitor and moderate P-gp inhibitor clarithromycin (or erythromycin) leads to small and clinically irrelevant increases in mean rivaroxaban AUC and C_{max} [133]. In contrast, co-administration of rivaroxaban with the strong CYP3A4 and P-gp inhibitors ketoconazole or ritonavir leads to a 2.6- and 2.5-fold increase in mean rivaroxaban AUC and a 1.7- and 1.6-fold increase in mean rivaroxaban C_{max}, respectively, which translates into a higher than normal risk of bleeding [134; 135]. Thus, concomitant treatment with strong inhibitors of both CYP3A4 and P-gp is contraindicated.

5.2.2. Drug-drug interactions affecting the pharmacodynamic of rivaroxaban

No significant pharmacodynamic effects were reported when aspirin [136] or clopidogrel [137] were co-administered with rivaroxaban. In a study, however, clopidogrel does significantly prolong (≈3-fold) the mean bleeding time of subjects treated with Rivaroxaban [138]. Similarly, co-administration of 15 mg rivaroxaban with 500 mg naproxen for two consecutive days was associated with a non-clinically significant prolongation of the bleeding time [139]. Finally, because of its additive effect, co-administration of rivaroxaban with other anti-coagulant drugs (e.g. the anti Xa enoxaparin) is discouraged [28; 140].

5.3. Apixaban

5.3.1. Drug-drug interactions affecting the pharmacokinetic of apixaban

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The concomitant use of apixaban with strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital, rifampicin, or St. John's wort) may lead to reduced apixaban plasma concentrations; hence caution is mandatory when apixaban is co-administered with strong CYP3A4 and P-gp inducers [141].

Apixaban is not recommended also in patients receiving concomitant treatment with strong CYP3A4 or P-gp inhibitors, such as Ketoconazole and ritonavir, which may increase dramatically its plasma concentrations [142; 143; 144]. Diltiazem and other moderate CYP3A4 inhibitors as well as weak P-gp inhibitors lead to small increases in mean apixaban AUC and C_{max} and, in turn, to little effects on apixaban pharmacokinetics. Naproxen an inhibitor of P-gp but not of CYP3A4, leads to a 1.5- and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively [145]. No dose adjustment is needed when apixaban is co-administered with weak inhibitors of CYP3A4 and/or P-gp.

5.3.2. Drug-drug interactions affecting the pharmacodynamic of apixaban

In healthy volunteers or in patients with atrial fibrillation [146], but not in those with acute coronary syndromes [147], apixaban can be safely combined with aspirin or clopidogrel. In contrast, co-administration of naproxen and apixaban leads to an increased bioavailability of this DOAC [148]. As for rivaroxaban, also the co-administration of apixaban with low-molecular weight heparins is discouraged.

5.4. Edoxaban

5.4.1. Drug-drug interactions affecting the pharmacokinetic of edoxaban

Concomitant treatment with edoxaban is contraindicated in subjects receiving ritonavir, cyclosporine, erythromycin, azithromycin, clarithromycin, ketoconazole, itraconazole because

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these drugs increase its steady-state plasma concentrations [149]. Edoxaban metabolism is also largely affected by P-gp inhibitors or inducers. Edoxaban dose should be halved when co-administered with P-gp inhibitors that increase edoxaban exposure ≥1.5-fold (dronedarone: 84.5%; quinidine: 76.7%; verapamil: 52.7%) [150; 151], whereas no dose adjustment is needed when edoxaban is co-administered with amiodarone that increases edoxaban exposure by only 40% [152].

5.4.2. Drug-drug interactions affecting the pharmacodynamic of edoxaban

In line with other DOACs, also edoxaban has major pharmacodynamic interactions with antibiotics (clarithromycin, erythromycin, rifampicin), anticoagulants (enoxaparin, warfarin), NSAIDs (ketoprofen, naproxen) and platelet inhibitors (naproxen, clopidogrel, aspirin) [153; 154; 155]. Pharmacodynamic interactions of edoxaban with low-dose (100 mg) or high-dose (325 mg) of aspirin, or naproxen (500 mg) administered to healthy subjects, seems not to be clinically relevant [155]. In fact, although concomitant administration of edoxaban with high-dose aspirin, low-dose aspirin, or naproxen increases template bleeding times (BT) of approximately 2-fold, the effects of edoxaban on PT-INR, anti-FXa, and intrinsic FXa activity were not influenced by either aspirin or naproxen. Moreover, inhibition of platelet aggregation by high-dose aspirin, low-dose aspirin, or naproxen is not affected by edoxaban [155].

6. Foods and herbal medicines interactions with pharmacokinetic or pharmacodynamics of DOACs

No direct evidence is available regarding the inherent risk of co-administration of food or herbal medicines with DOACs. St. John's wort, a potent inducer of P-gp and CYP3A4, is expected to lower plasma concentrations of dabigatran (substrate of P-gp) and of rivaroxaban or apixaban (substrates of P-gp and CYP3A4). Such co-administration should be made with caution with

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dabigatran and avoided with rivaroxaban or Apixaban [124]. Although, in theory, food or herbal inhibitors/inducers of CYP3A4 might interfere with the pharmacokinetics of DOACs, no direct evidence of such interactions exists. Some food and herbal medicines modulate P-gp *in vitro* (Table 8) [156] but no information is available whether these substances interact with DOACs. Finally, to the best of our knowledge, no information is available concerning pharmacodynamic interactions of DOACs with foods or herbal medicines.

7. Food, herbal medicines and drug interactions with oral anticoagulants: clinical relevance and conclusions

7.1. Warfarin

Due to its complex multi-step metabolism, the large majority of warfarin interactions are mediated by CYP2C9, 1A2, 2C19 and 3A4 isoenzymes. Inhibitors and inducers of these enzymes do affect the pharmacological activity of warfarin and, in turn PT-INR values. In most cases adverse drug reactions due to these interactions lead to bleeding events that may be severe, life-threatening and even fatal.

There is no convincing evidence to indicate that any food or nutrient (other than Vitamin K) interacts significantly with warfarin through modulation of CYP2C9 activity [50; 51].

Herbal medicines that inhibits CYP2C9 *in vitro* would not be clinically important unless the inhibitor reaches the liver in sufficient concentrations to inhibit the enzyme in vivo. The discrepancy between *in vitro* [75] and *in vivo* [76] effects of the potent inhibitors of human CYP2C9 flavonol aglycones clearly elucidates this concept.

Drug interactions involving CYP2C9, CY1A2 and CY3A4 isozymes are usually delayed. The effect of the interaction will not be observed until the interacting agent has reached a steady state (about

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5 half-lives of the interacting agent) [157]. Additionally, given the indirect mechanism of the effect of warfarin, clotting factors present in the circulation should be depleted prior to detecting the effect of the interacting agent. This will take several days. Together, the onset and the offset of the interaction (i.e. the effect on the PT-INR) is observed within 3 to 5 days for interacting substances with short half-lives and at longer time intervals for drugs with longer half-lives. All in all, depending on the interacting agent employed, the full impact of steady-state interactions may not be apparent for-2 to 3 weeks. Likewise, a-wash-out period of several weeks may be needed before normalization of the hepatic enzymes, when the inducer is discontinued.

Genetic polymorphisms of the CYP2C9 and of the Vitamin K epoxide reductase complex subunit 1 (VKORC1, see Online Appendix) enzymes have a strong impact on drug interactions and, in turn, the responsiveness of warfarin [158]. Individuals with polymorphisms that reduce the expression of functional CYP2C9 will appear to be “warfarin sensitive,” in that usual warfarin doses cause excessive anticoagulation [159]. The 2C9*3 variant (Ile359Leu) shows an 80% loss of enzymatic activity *in vitro*, whereas the CYP2C9*2 variant (Arg144Cys) reduces the activity by ≈30%. Under these conditions, decreased clearance and increased in vivo anticoagulant effect have been shown [160]. The inter-individual variation due to the CYP2C9 genotype appears to be comparable to that related to a major non-genetic factor e.g. patient age [161].

Age, body weight, body surface area, sex, antibiotics that alter the intestinal environment, disease conditions and dietary intake of Vitamin K affect the responsiveness to warfarin as much as genetic polymorphisms [162; 163]. In patients with significant medical illness requiring multiple medications and having a poor nutritional status, the ability to isolate the impact of a particular medication on the patient’s coagulation status is difficult. Broad-spectrum antibiotics are postulated to potentiate warfarin by altering the normal intestinal flora, thereby reducing the body’s ability to synthesize Vitamin K. However, this factor is unlikely to be clinically significant for most patients, except those who are malnourished or have malabsorption [164]. In addition to albumin, warfarin is highly bound

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to a variety of plasma proteins and has the potential for interacting with other highly protein-bound substances. However, the effect of such interactions is usually transient and its clinical significance questionable [22].

Pharmacodynamic drug interactions with warfarin are more clinically relevant than those with foods and drugs. Any medication that impairs the ability of platelets to function (e.g., acetylsalicylic acid, clopidogrel, NSAIDs) and is given concomitantly with warfarin may increase the risk of bleeding without affecting the PT-INR. Aspirin and NSAIDs behave like this [41]. Conversely, medications such as estrogens increase the risk of thrombosis and their use in patients who are taking warfarin should be carefully assessed [44].

7.2. DOACs

Large-scale phase 3 studies [14], and real-world evaluations have definitely established that the use of DOACs is well tolerated (as compared to warfarin), and that adverse reactions (including intra-cerebral bleeding) are quantitatively and qualitatively less relevant than those with warfarin from a clinical standpoint [165; 166]. Thus, the use of DOACs is likely to grow as more data become available regarding their long-term use and their use in specific patients' populations.

Pharmacokinetics of Factor Xa inhibitors may be affected by the co-administration of inducers/inhibitors of CYP3A4 and/or P-gp [133; 167; 168]. In particular, potent inhibitors of CYP3A4 and of P-gp (e.g. ketoconazole - antifungal drug - or protease inhibitors of HIV) should be avoided [169]. Caution is also suggested for the co-administration of potent inducers of CYP3A4 and of P-gp (e.g. carbamazepine, phenytoin) [170].

Being able to affect circulating levels of the anticoagulant drug, strong inhibitors/inducers of P-gp should not be co-administered with dabigatran, a specific substrate for P-gp.

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Little information is so far available as to the interaction of DOACs with food, most herbal medicines or over-the-counter medications. Since some herbal drugs and over-the-counter medications modulate P-gp activity (Table 8), their ability to affect the anticoagulant potential of DOACs should be thoroughly analyzed. However, while ad hoc phase IV studies are needed in this area, a limited clinical impact of such herbal drugs and over-the-counter medications to affect DOACs effects is predicted [165; 166].

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Practice Points

- Multiple pharmacokinetic and pharmacodynamic interactions with food, herbs, over-the-counter and other drugs can influence efficacy and safety of both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs).
- Bleeding disorders associated to VKAs-interactions have been often described as severe, life-threatening and even fatal, whereas those associated to DOACs-interactions appear to be less relevant.
- VKAs interactions have been widely investigated; those involving DOACs were much less studied.

Research Agenda

The safety profile of DOACs with a specific focus on their interactions with foods, herbs and/or over-the-counter medications needs further assessments.

Conflict of interest

None.

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Table 1.

Effect of commonly employed drugs on PT-INR [18; 28]**.**

	Drugs that increase PT-INR	Drugs that lower PT-INR
Drugs active on the Central Nervous System		
	Citalopram*	Barbiturates*
	Disulfiram	Carbamazepine*
	Entacapone*	Chlordiazepoxide
	Phenytoin	Propofol
	Fluoxetine	Ethanol
	Propoxyphene	
	Fluvoxamine	
Anti-inflammatory drugs		
	Acetaminophen	Azathioprine
	Allopurinol	Mesalazine
	Celecoxib	Sulfasalazine
	Dextropropoxyphene	
	Indomethacin	
	Interferon	
	Methyl-prednisolone	
	Phenylbutazone	
	Piroxicam*	
	Sulindac	
	Sulfinpyrazone	
	Tramadol	
Other		
	Cimetidine*	Chelating agents

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Omeprazole	Cyclosporine
Orlistat	Etretinate
CMF	Anti-flu vaccine
Danazol	Menthol (anti-cough)
5-FUrouracile	Mercaptopurine
Ifosphamide	Methimazole
Levamisole	Multivitamin supplies
Levonorgestrel	Raloxifene
Tamoxifen	
Zileuton*	

***** Clinically relevant interactions with warfarin.

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Table 2.

Cardiovascular drugs interfering with the metabolism/clearance of warfarin [28].

Drug [Reference(s)]	Mechanism(s)
Drugs that increase PT-INR	
Acetyl-salicylic acid	pharmacodynamics
Amiodarone* [24]	moderate inhibitor of CYP3A4, CYP1A2, CYP2C9
Dronedarone* [168; 171]	moderate inhibitor of CYP3A4, inhibitor of P-gp
Atorvastatin [172]	inhibitor of CYP3A4
Quinidine [173]	inhibitor of CYP3A4
Clofibrate* [174]	inhibitor of CYP3A4
Diltiazem* [28]	inhibitor of CYP3A4
Disopyramide [175]	inhibitor of CYP3A4
Fenofibrate* [172]	inhibitor of CYP3A4
Glucagon [176]	Inhibitor of CYP3A4
Lovastatin [172]	inhibitor of CYP3A4
Propafenone* [177]	inhibitor of CYP3A4
Propranolol* [178]	Inhibitor of CYP1A2
Rosuvastatin [179]	inhibitor of CYP3A4
Simvastatin [25]	inhibitor of CYP3A4

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Drugs that lower PT-INR	
Cholestyramine [28]	interference with warfarin absorption
Telmisartan [180]	inhibitor of CYP3A4

***** Clinically relevant interactions with warfarin.

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Table 3.

Anti-infective drugs interfering with the metabolism/clearance of warfarin [28; 181]**.**

Drug [Reference(s)]	**Mechanism(s)**
Amoxicillin, clavulanic acid [102; 103]	reduced intrinsic vitamin K biosynthesis.
Azithromycin [182]	moderate inhibitor of CYP3A4, P-gp
Chloramphenicol [183]	inhibitor of CYP450
Ciprofloxacin [184]	strong inhibitor of CYP1A2
Clarithromycin [28]	moderate inhibitor of CYP3A4, P-gp
Sulfamethoxazole [185]	inhibitor of CYP3A4
Doxycycline [186]	inhibitor of CYP3A4
Efavirez [32]	moderate inhibitor of CYP2C19 and of CYP3A4
Erithromycin [187]	moderate inhibitor of CYP3A4, P-gp
Fluconazole [188]	moderate inhibitor of CYP3A4, CYP1A2, CYP2C9
Isoniazid [24]	inhibitor of CYP2C9
Itraconazole [28]	strong inhibitor of CYP3A4 e P-gp
Ketoconazole [28]	strong inhibitor of CYP3A4 e P-gp
Levofloxacin [189]	inhibitor of CYP1A2
Metronidazole [190]	inhibitor of CYP1A2, CYP2C9
Miconazole gel [191]	inhibitor of CYP1A2, CYP2C9
Miconazole vaginal suppositories [192]	inhibitor of CYP1A2, CYP2C9
Nalidixic acid [24]	inhibitor of CYP1A2
Norfloxacin [185]	inhibitor of CYP3A4
Ritonavir [193]	strong inhibitor of CYP3A4, P-gp

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Saquinavir [194]	inhibitor of CYP3A4
Tetracycline [24]	inhibitor of CYP3A4
Voriconazole [195]	strong inhibitor of CYP3A4, CYP1A2, CYP2C9, P-gp
Griseofulvin [196]	inducer of warfarin-metabolizing enzymes
Ritonavir [193]	strong inducer of CYP2C19
Nafcillin [197]	strong inducer of CYP3A4
Nevirapine [33; 193]	strong inducer of CYP3A4
Rifampicin [24]	inducer of CYP3A4,CYP2C9

In bold, clinically relevant warfarin-drug interactions.

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Table 4.

Pharmacokinetic interaction of Natural Substances/ Foods with Warfarin [20].

Natural substance	Presence of Inhibitor(s) of
Citrus bergamia	CYP2C9
Carum Ajowan	CYP3A4
Citrus aurantium (Orange)	CYP3A4
Uncaria (Una de gato)	CYP3A4
Vaccinium Myrtillus	CYP2C9
Devil's clam	CYP2C9
Dehydroepiandrosterone	CYP3A4
Echinacea (purpurea and/or angustifolia)	CYP3A4
Eucalyptus globulus	CYP1A2, 2C9, 2C19, 3A4
Tanacetum parthenium	CYP1A2, 2C9, 2C19, 3A4
Fo-ti-root	CYP1A2, 2C9, 2C19, 3A4
Garlic	CYP2C9, 2C19, 3A4
Hydrastis canadensis	CYP3A4
Grape juice	CYP1A2, 3A4
Ipriflavone	CYP1A2, 2C9
Kava (*Piper methysticum)*	CYP1A2, 2C9, 2C19, 3A4
Licorice	CYP3A4
Lime	CYP3A4
Wolfberries	CYP2C9
Silybum marianum	CYP2C9, 3A4
Peppermint	CYP1A2, 2C9, 2C19, 3A4
Trifolium pratense	CYP1A2, 2C9, 2C19, 3A4
Resveratrol	CYP1A2, 3A4
Sulforaphane	CYP1A2

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Valeriana officinalis	CYP3A4
Prunus avium (wild cherry)	CYP3A4

Natural substance	**Presence of Inducer(s) of**
3,3′-Diindolylmethane	CYP1A2
Ginseng	CYP1A2, 2C9, 2C19, 3A4
Guggul	CYP3A4
Grapes (Vitis vinifera)	CYP1A2
Indole-3-carbinol	CYP1A2
Limonene	CYP2C9
Hypericum perforatum	CYP1A2, 2C9, 3A4

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Table 5.

Pharmacokinetic interactions of DOACs with drugs.*

		Direction of the change in plasma concentrations in response to coadministration of drugs reported in the first column:			
Drug	**Inhibitor of:**	**Dabigatran** [28]	**Rivaroxaban** [28; 136]	**Apixaban** [28; 136]	**Edoxaban** [149]
Cyclosporine	P-gp				
Digoxin	P-gp	↑			
Amiodarone	P-gp	↑			↑
Dronedarone	P-gp	↑			↑
Verapamil	P-gp	↑			↑
Quinidine	P-gp	↑			↑
Ritonavir	P-gp and CYP3A4	↑	↑	↑	↑
Ketoconazole	P-gp and CYP3A4	↑	↑		↑
Itraconazole	P-gp and CYP3A4	↑	↑		↑
Voriconazole	P-gp and CYP3A4		↑	↑	
Posaconazole	P-gp and CYP3A4		↑	↑	
Azithromycin	P-gp and CYP450				↑
Erythromycin	P-gp and CYP450	↑			↑
Clarithromycin	P-gp and CYP450	↑			↑
Drug	**Inducer of:**				

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Rifampicin	P-gp and CYP3A4	↓	↓	↓
Phenytoin	P-gp and CYP3A4	↓	↓	↓
Carbamazepine	P-gp and CYP3A4	↓	↓	↓
Fenobarbital	P-gp and CYP3A4		↓	↓

↑=increase in concentration; ↓=reduction in concentration.

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Table 6.
Clinical use of Dabigatran: relevant pharmacological interactions.

Drugs to be avoided	Drugs to be used with caution	Drugs of free use	Drugs that enhance the effect	Drugs that impair the effect
Carbamazepine[δ]	Quinidine[†]	Amiodarone[†]	Amiodarone	Proton pump
Cyclosporine[†]	Quinine	Atorvastatin	Dronedarone[†]	inhibitors
Dronedarone[†]	Verapamil[†]	(CYP3A4)	Ketoconazole[*]	
Ketoconazole[†]		Clarithromycin[*†]	Quinidine	
Phenytoin[δ]		Diclofenac	Quinine	
Rifampicin[δ]		(CYP2C9)	Verapamil	
St. John's wort[δ]		Digoxin (P-gp)		
Verapamil[†]				

*inhibitors of Cytochrome P450 iso-enzyme (CYP3A4);

°inducers of Cytochrome P450 iso-enzyme (CYP3A4);

[†]inhibitors of P-glycoprotein (P-gp);

[δ]inducers of P-glycoprotein (P-gp).

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Table 7.
Clinical use of Rivaroxaban, Apixaban and Edoxaban: relevant pharmacological interactions.

Drugs to be avoided	Drugs to be used with caution	Drugs of free use	Drugs that enhance the effect	Drugs that impair the effect
Amiodarone[†]	Carbamazepine[°]	Atorvastatin	Azithromycin	Carbamazepine
Chloramphenicol[*]	Hypericum	Clarithromycin	Clarithromycin	Hypericum
Clarithromycin[*†]	perforatum [δ°]	Digoxin	Cyclosporine	Perforatum
Cyclosporine[†]	Phenytoin[δ°]	Erythromycin	Diltiazem	Phenobarbital
Dronedarone[†]	Rifampicin[δ]	Fluconazole	Dronedarone[†]	Phenytoin
Itraconazole*		Midazolam	Erythromycin	Rifampicin
Ketoconazole*			Itraconazole	
Quinidine[†]			Ketoconazole	*Co-administration of apixaban with rifampicin causes a significant decrease in mean AUC and Cmax of apixaban*
Quinine			Naproxen	
Ritonavir[*]			Quinidine	
Verapamil[†]			Ritonavir	
			Systemic Antifungals	
Concomitant treatment with edoxaban is also contraindicated in subjects receiving erythromycin and azithromycin			Verapamil	
			The dose of edoxaban should be halved when the drug is co-administration with dronedarone, quinidine, or verapamil. No dose adjustment is required for amiodarone.	

*inhibitors of Cytochrome P450 iso-enzyme (CYP3A4);
°inducers of Cytochrome P450 iso-enzyme (CYP3A4);
[†]inhibitors of P-glycoprotein (P-gp);
[δ]inducers of P-glycoprotein (P-gp).

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Table 8.

Foods and herbal drugs that modulate P-gp activity [156]**.**

	Inhibitors [Reference(s)]	**Inducers [Reference(s)]**
Humans	Ginkgo biloba [198]	St. John's wort [199]
	Berberine [199]	
Animal models	Black pepper [200]	Quercetin [199]
	Grape juice [201]	Scutellaria [199]
	Apigenin [202]	Soy milk and miso [203]
	Rutin [202]	Sucralose [204]
	Capsaicin [205]	Licorice root [199]
In Vitro	Lemonin [206]	Genipin [207]
	Soybean extract [208]	Mango [209]
	Notoginsenoside R1 [210]	
	Curcumin [211]	
	Green tea [212]	
	Fisetin [213]	
	Honokiol [213]	

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