COMMENTARY

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Drug-Drug Interactions with Direct Oral Anticoagulants: Practical Recommendations for Clinicians

INTRODUCTION

Current guidelines from the European Society of Cardiology and American Heart Association widely recommend direct oral anticoagulants (DOACs) instead of vitamin K antagonists (VKAs) in the vast majority of patients with nonvalvular atrial fibrillation.[1,2] In theory, DOACs do not require routine monitoring because of their stable pharmacological profiles compared with VKAs.[3] However, when they are used in real-world conditions and outside the stringent framework of clinical trials, substantial interindividual variations in dose-concentration response are observed, leading to consider dose adjustment outside the standard risk groups.[4] Of note, drug-drug interactions are barely mentioned in the dose adjustment guidelines and product information can be contradictory.[5,6] This represents a significant issue for clinicians because it is well-established that patients with atrial fibrillation receive numerous medications and that polymedication increases the bleeding risk.[7] A growing number of case reports have also highlighted a direct role of drug-drug interactions in bleeding or thrombotic events involving DOACs.[8,9] Several large registry-based retrospective studies have also suggested an increased risk of bleeding when DOACs are coadministered with P-glycoprotein (Pgp) or cytochrome P450 (CYP) 3A4/5 inhibitors.[10-12] A multidisciplinary team (composed of clinical pharmacologists, pharmacists, internal medicine physicians, and hemostasis physicians) proposes practical recommendations for pharmacokinetic drug-drug interactions based on the best available clinical and pharmacological evidence that can be implemented easily at the patient's bedside (Table 1). Each time a problematic scenario is met we suggest: 1) stopping or finding an alternative to the perpetrator (eg, the drug responsible for the drug-drug interaction), and 2) consider the use of VKAs if the first step cannot be achieved. We admit that VKAs have potential drug-drug interactions too but offer the possibility of monitoring with the international normalized ratio, which alleviates this issue.[14]

Strong Pgp or CYP 3A4/5 Inhibitors

There is currently sufficient evidence showing an association between exposure to DOACs and major bleeding.[15] Dabigatran median trough concentration in patients with major bleeding was 55% higher than in those without major bleeding (116 vs 75.3 ng/mL).[16] A doubling of apixaban area under the curve (AUC) resulted in a near doubling of the risk of major bleeding (2% to 4% a year).[17] According to in vivo studies in healthy volunteers, the strong CYP3A4/5 and Pgp/CYP3A4/5 inhibitors are the most likely to increase the DOACs AUC by a factor of 2 and put the patient at high risk for bleeding.[18,19] Consequently, in presence of strong CYP3A4/5 inhibitors, edoxaban, dabigatran, or VKAs should be specifically preferred to apixaban and rivaroxaban, which are more significantly eliminated by CYP3A4/5. Because all DOACs are substrates for Pgp, strong Pgp/CYP 3A4/5 inhibitors should be considered at risk for all DOACS. The reader will easily find the potency of the most prescribed inhibitory and inducing drugs on the US Food and Drug Administration website.[13] We also provide a nonexhaustive list of moderate to strong inhibitors and inducers in Tables 2 and 3.

Moderate to Weak Pgp and CYP 3A4/5 Inhibitors

In the presence of moderate to weak inhibitors of Pgp or CYP 3A4/5, or if in vivo human data show an increase in DOACs AUC of less than 2-fold in the presence of a given inhibitor, the use of DOACs appears safe in absence of other risk factors.

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Table 1 Practical Recommendations for Drug-Drug Interactions Management with DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Strong Pgp inhibitor only		Association not recommended (unless proven otherwise*) *-> consider VKA as a first-line treatment or if possible change the perpetrator to a noninteracting molecule*		
Strong CYP3A/5 inhibitor only or combined Pgp/CYP3A4/5 inhibitor	OK	Association not recommended (unless proven otherwise*) *-> consider VKA as a first-line treatment or if possible change the perpetrator to a noninteracting molecule*		OK
Moderate to Weak Pgp inhibitor only		Use with caution *Weigh risk-to-benefit ratio or consider VKA as a first-line treatment if ≥2 risk factors† or if CL<30 mL/min*		
Moderate to Weak CYP3A4/5 inhibitor only	OK	Use with caution *Weigh risk-to-benefit or consider VKA as a first-line treatment if ≥2 risk factors† or if CL<30 mL/min*		OK
CYP3A4/5 or combined Pgp/CYP3A4/5 inducer		Association not recommended (unless proven otherwise[1]) *-> consider VKA as a first-line treatment or if possible change the perpetrator to a noninteracting molecule*		

CL = clearance; DOACs = direct oral anticoagulants; VKA = vitamin K antagonists.

*If in vivo human studies show evidence of a ≤2 times increase in area under the curve (AUC) exposure for inhibitors or ≥20% decrease in exposure for inducers.

†Risk factors: renal failure (CL <50 mL/min according to Cockroft-Gault equation), weight <60 kg, advanced age (>80 years), additional Pgp or CYP3A4/5 inhibitor.

Classification of inhibitors/inducers according to the Food & Drug Administration.[13]

Table 2 Examples of Pgp, CYP3A4/5, and Combined Pgp/CYP3A4/5 Inhibitors (Nonexhaustive List)[13]

	Strong	Moderate to weak
Pgp or combined CYP3A4/5/Pgp inhibitors	ketoconazole, itraconazole, ritonavir, clarithromycin, erythromycin, dronedarone, cobicistat, posaconazole, voriconazole	amiodarone, diltiazem, quinidine, verapamil, cyclosporine, ticagrelor
CYP3A4/5 inhibitors	boceprevir, grapefruit juice	fluconazole

The accumulated evidence shows that the presence of several risk factors (such as drug-drug interactions and renal failure) add up to significantly increase exposure to DOAC and, thus, the risk of bleeding.[20-22] In the presence of a moderate to weak Pgp or CYP 3A4/5 inhibitor, we therefore recommend weighing the risks and benefits of using a DOAC compared with a VKA or stopping the perpetrator in the presence of 2 or more of the following additional risk factors: renal failure (clearance <50 mL/min according to Cockroft-Gault equation), weight <60 kg, advanced age (>80 years), or an additional concomitant Pgp inhibitor (or CYP3A4/5 inhibitor for apixaban and rivaroxaban). Indeed, all of these factors have been shown to increase the AUC of DOACs.[23,24] For patients with severe renal impairment (CL<30 mL/min), we suggest avoiding DOAC in the presence of a Pgp or CYP 3A4/5 inhibitor. Mild to moderate hepatic impairment (Child-Pugh A or B) does not appear to be a risk factor, except for rivaroxaban.[25]

Table 3 Examples of Moderate to Strong Pgp/CYP3A4/5 Inducers (Nonexhaustive List)[13]

apalutamide
bosentan
carbamazepine
dexamethasone
enzalutamide
efavirenz
mitotane
phenobarbital
phenytoin
primidone
rifampin (rifampicin)
St. John's wort

Pgp or CYP3A4/5 Inducers

Although the association between DOAC exposure and ischemic events seems less obvious according to the few data available,[15] the use of Pgp/CYP3A4/5 inducers with DOACs should be avoided because their efficacy in ischemic events may be affected. In addition, case reports in patients treated with inducers such as rifampicin or phenobarbital have shown the occurrence of ischemic events.[26,27] Because the therapeutic range is not known for DOACs, it seems reasonable to avoid moderate to strong Pgp/CYP3A4/5 inducers concomitantly with DOACs.

CONCLUSION

DOACs have the potential for drug interactions. We propose recommendations that pragmatically aim to clearly define the situations that require the clinician's attention. These guidelines provide the clinician the opportunity to discuss with the patient the benefits and risks of using a DOAC or VKA in situations where drug interactions are an issue. We also recommend discussing the appropriateness of stopping the inhibitor/inducer in specific settings.

DOACs remain an important advance in the management of patients requiring anticoagulation because of the overall decrease in major bleeding compared with VKAs and the absence of monitoring. However, prospective studies on the subject or studies that better define the therapeutic range of DOACs should address this issue in future.

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