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Review Article

Drug-drug interactions with direct oral anticoagulants associated with adverse events in the real world: A systematic review☆

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ABSTRACT

Background: Direct oral anticoagulants (DOACs) have emerged as safe and effective alternatives to Vitamin-K antagonists for treatment and prevention of arterial and venous thrombosis. Due to their novelty, pharmacokinetic DOAC drug-drug interactions (DDIs) that result in clinical adverse events have not been well-documented.

Objective: This study aims to systematically review reported pharmacokinetic DDIs resulting in clinical adverse events through documented observational evidence to better inform clinicians in clinical practice.

Methods: A comprehensive literature review of EMBASE, MEDLINE, and Ovid HealthStar was conducted through March 10th, 2020. Two independent reviewers screened and extracted data from eligible articles according to pre-established inclusion and exclusion criteria. Articles reporting bleeding or thrombotic outcomes in non-controlled (observational) settings resulting from suggested pharmacokinetic DOAC DDIs were included.

Results: A total of 5567 citations were reviewed, of which 24 were included following data extraction. The majority were case reports (n = 21) documenting a single adverse event resulting from a suspected DOAC DDI, while the remaining papers were a case series (n = 1) and cohort studies (n = 2). The most commonly reported interacting drugs were amiodarone and ritonavir (bleeding), and phenobarbital, phenytoin, and carbamazepine (thrombosis). Bleeding events more often resulted from a combined mechanism (P-glycoprotein AND CYP3A4 inhibition), whereas thrombotic events resulted from either combined OR single P-glycoprotein/CYP3A4 induction.

Conclusion: Current literature evaluating the real-world risk of DOAC DDIs is limited to few case reports and retrospective observational analyses. Clinicians are encouraged to continue to report suspected drug interactions resulting in adverse events.

1. Introduction

Warfarin has historically been a cornerstone for treating or preventing thrombosis in various settings. Warfarin, due to its variable interpatient response, requires systematic monitoring of the international normalized ratio (INR) to ensure safety and efficacy. Warfarin is subject to numerous food and drug interactions, and there is reasonable quality evidence that some of these interactions are associated with bleeding and/or thrombotic complications [1,2]. However, the universal availability of international normalized ratio (INR) testing can mitigate the impact of these interactions by allowing real-time dose adjustment. In the last decade, direct oral anticoagulants (DOACs) have emerged as an effective and safe alternative to warfarin [3–5].

DOACs are administered in fixed doses and have fewer drug-drug interactions (DDIs) compared to warfarin but are still subject to DDI-induced alterations in plasma concentrations that may result in bleeding or thrombotic events. All DOACs (including dabigatran, rivaroxaban, apixaban, and edoxaban) are substrates of the efflux

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transporter permeability-glycoprotein (P-gp, also referred to as p-gp transportor, ABCB1, and p-gp multidrug transporter), which regulates the absorption of DOACs from the gastrointestinal lumen and is also involved in their hepatic and renal excretion. Additionally, rivaroxaban and apixaban have CYP450-mediated metabolism (rivaroxaban primarily by CYP3A4 with minor contribution by CYP2J2 and apixaban primarily by CYP3A4 with minor contributions by CYP2C19, CYP1A2, CYP2C8, and CYP2C9) [6,7]. Drugs that induce P-gp or CYP3A4 may reduce the plasma concentration of the DOAC; conversely, drugs that inhibit P-gp or CYP3A4 may increase the plasma concentration of the DOAC.

Although fewer in number than warfarin [1,2,8], the clinical importance of pharmacokinetic DOAC DDIs is increased as the lack of an "INR-equivalent" results in less testing and monitoring – thus such interactions are likely to remain unnoticed until a complication occurs since DOAC levels are not routinely monitored. Currently, pharmacokinetic studies, case reports, and guidance documents based on these reports in the literature propose several pharmacokinetic DDIs for DOACs demonstrated by significant alterations in plasma DOAC concentrations [9–18] but some occur in the absence of adverse clinical events [19–22]. While the ability of P-gp and/or CYP3A4 modifiers to alter DOAC drug levels is well-established, given the wider therapeutic index of the DOACs relative to a narrow therapeutic index drug like warfarin, it is unknown if these pharmacokinetic alterations are sufficient to contribute to clinical adverse events. Therefore, to aid clinicians in deciphering the clinical significance of DOAC DDIs, this study seeks to systematically evaluate the existing body of literature of pharmacokinetic DOAC DDIs that result in clinical adverse events (bleeding and thrombosis) in uncontrolled clinical settings. As the pharmacodynamic interactions between anticoagulants and antiplatelet medications, non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are known to enhance bleeding risk [23–29], this review focuses exclusively on pharmacokinetic drug interactions with DOACs.

2. Methods

This systematic review was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30]. A protocol was synthesized and registered under the International Prospective Register of Systematic Reviews (PROSPERO).

2.1. Search strategy and information sources

A comprehensive search of EMBASE, MEDLINE, and Ovid HealthStar was performed with the guidance of a Health Sciences research librarian at McMaster University through March 10th, 2020. Search terms used include drug interactions; non-vitamin K oral anticoagulants; novel oral anticoagulants, direct oral anticoagulants, NOAC, DOAC, dabigatran, rivaroxaban, apixaban, and edoxaban. The different search strings used for each database can be found in the online supplement.

2.2. Eligibility criteria

Studies to be included in the review had to report either a thrombotic or bleeding event due to potential pharmacokinetic drug-drug interaction between a DOAC an another drug in a non-controlled clinical setting. Studies that did not control for concurrent administration of SSRIs, NSAIDs, antiplatelets, thrombolytics, and other anticoagulants were excluded as these drugs can independently cause bleeding or as the result of pharmacodynamic interactions.

2.3. Selection of studies

After conducting the literature search, all citations were uploaded onto the Covidence systematic review software (Veritas Health Innovation Ltd) for independent screening. Screening was done across two stages. First, two investigators (A.L. and M.K.L.) screened using title and abstracts, the remainder of which was then screened through full-text analysis; all discrepancies were resolved through discussion and adjudication with a third investigator (S.R.V. or M.C.).

2.4. Data extraction and data synthesis

For each study that was included, investigators evaluated the study quality (if applicable) using the NewCastle-Ottawa Scale [31], and extracted data using pre-composed data extraction templates on Microsoft Excel. Extracted data included outcome observed (bleeding or thrombosis), DOAC involved, interacting drug, study population, coagulation or DOAC plasma concentration measurements (if available), and a drug-interaction probability score (DIPS) (if available). Using a 10-item questionnaire, the DIPS tool considers a variety of factors including alternative causes, and previous documentation of the DDI [32,33]. It is a widely used reference standard for determining the probability of drug interactions and has been shown through a 2015 systematic review to overcome limitations present in other assessment instruments [32,33]. Data synthesis involved utilizing tables and descriptive statistics to summarize data. The mechanism of the interaction was objectively identified using Lexi-Drugs Wolters Kluwer Clinical Drug Information database.

3. Results

3.1. Study selection

After our initial search among the databases, 6580 articles were identified from our search. Of these studies, a total of 1013 duplicates were removed with 5567 proceeding to title and abstract screening. Of these, 5453 articles were deemed ineligible, with 114 articles moved to full-text review. A total of 90 citations were excluded based on exclusion criteria, leaving 24 for data extraction (Fig. 1, online supplement). Of the 24 included publications, 21 were case reports, one was a case series, and the remaining two were large cohort studies.

3.2. Case reports and case series

Of the case reports, just over half ($n = 11$) reported DDIs resulting in thrombotic outcomes while the other half reported bleeding outcomes. The most frequently reported DDI for bleeding events in the case reports involved the combinations of amiodarone and dabigatran (via inhibition of P-gp) and ritonavir and rivaroxaban (via inhibition of both P-gp and CYP3A4). The most frequently reported DDI for thrombosis involved the antiepileptic drugs phenobarbital, phenytoin, and carbamazepine (via induction of P-gp and/or CYP3A4). Five case reports included a statement involving a DIPS (Drug Interaction Probability Scale) score (Table 1, online supplement).

In cases that also reported laboratory values (13 of 21 reports), seven cases reported only coagulation laboratory tests, three reported only DOAC plasma concentrations, and three reported a combination of coagulation and DOAC-specific laboratory tests. In the bleeding cases reporting coagulation laboratory results, five reported the prothrombin time (PT), four reported the aPTT, and two reported the INR; all results were above the reference range. For the thrombotic cases, one case reported an elevated PT but all other coagulation labs were within normal limits. Six of the 20 case reports reported DOAC-specific drug levels. All three bleeding cases reported above on-therapy range DOAC levels. One thrombotic case reported an on-therapy trough for apixaban in the presence of phenobarbital, yet a random plasma apixaban level

quadrupled with the removal of phenobarbital.

We found one case series by Bortz et al., which evaluated a series of patients treated with rivaroxaban and carbamazepine. Four of seven patients in this study developed some form of recurrent or extension of a thrombus during concurrent treatment (Table 2, online supplement) [34].

3.3. Cohort studies

Both cohort studies scored a perfect on the NewCastle-Ottawa Scale for Nonrandomized Studies and assessed bleeding outcomes.

Chang et al. identified 91,330 Taiwanese atrial fibrillation patients taking DOACs during a 5-year period and analyzed them for bleeding events (defined as a hospitalization or an emergency department visit with a primary diagnosis of intracranial hemorrhage or gastrointestinal, urogenital, or other bleeding event) during DOAC therapy with and without the presence of CYP3A3 and P-gp modifying drugs [35]. Results demonstrated that after inverse probability of treatment weighting using the propensity score including adjustment for several confounders, the use of dabigatran or rivaroxaban with amiodarone, fluconazole, or phenytoin was associated with a higher rate of major bleeding; apixaban combined with fluconazole or cyclosporine was associated with a higher rate of bleeding [35]. (Table 3, online supplement) Pham et al., also evaluated bleeding outcomes [36]. Using the IBM Watson MarketScan Databases, this study identified 9886 patients that were prescribed a DOAC with concomitant verapamil, diltiazem, amlodipine, or metoprolol from January 2019 to July 2019. Bleeding rates were compared between patients that were prescribed known CYP3A4 and P-gp transporter inhibitors (verapamil or diltiazem) with a DOAC to patients prescribed with non-interacting drugs (amlodipine or metoprolol) with a DOAC. Dabigatran had statistically significant increases in bleeding risk when paired with diltiazem than with amlodipine and when paired with verapamil than with metoprolol. The rest of the comparisons did not reach statistical significance (Table 4, online supplement). Among both case reports and the cohort study, 11 unique drugs were implicated as a contributor to bleeding events. The most commonly identified mechanism of interaction was a drug that was a *combined* inhibitor of CYP3A4 and P-gp. For the case reports of thrombotic adverse events, eight unique drugs were implicated, with only three having a combined CYP3A4/P-gp induction mechanism. Three reports of DDIs causing bleeding events had an unclear mechanism (topical miconazole, loperamide, and phenytoin) (Table 1).

Table 1
Proposed mechanisms of drug interactions reported.

	Mechanism of interaction[a] [37]
Interacting drug (bleeding outcomes)	
Ritonavir [38,39]	Strong CYP3A4 inhibitor/P-gp inhibitor
Amiodarone [35,40–42]	Weak CYP3A4 inhibitor/P-gp inhibitor
Clarithromycin [43]	Strong CYP3A4/P-gp inhibitor
Miconazole (topical) [44]	Mechanism unclear
Loperamide [45]	Mechanism unclear
Quinidine [46]	Moderate P-gp inhibitor
Fluconazole [35]	Moderate CYP3A4 inhibitor
Cyclosporine [35]	Weak CYP3A4/P-gp inhibitor
Phenytoin [35,42,47]	Mechanism unclear
Diltiazem [36,48]	Moderate CYP3A4/P-gp inhibitor
Verpamil [36]	Moderate CYP3A4/P-gp inhibitor
Interacting drug (thrombotic outcomes)	
Rifampicin [49]	Strong CYP3A4 inducer/P-gp inducer
Nevirapine [50]	Weak CYP3A4 inducer
Tocilizumab [51]	Indirect P-gp inducer
Phenytoin [42,47]	Strong CYP3A4 inducer/P-gp inducer
Phenobarbital [42,52]	Strong CYP3A4 inducer
Carbamazepine [34,42,53]	Strong CYP3A4 inducer/P-gp inducer
Oxcarbazepine [53]	Weak CYP3A4 inducer
Efavirenz [54]	Moderate CYP4A3 inducer

CYP3A4 = Cytochrome P450 3A4; P-gp = permeability-glycoprotein.
[a] Lexi-Drugs Wolters Kluwer Clinical Drug Information database was used as a neutral source for reporting drug interaction mechanism.

4. Discussion

This systematic review resulted in 20 case reports, one case series, and two observational cohort studies documenting clinical adverse events resulting from proposed DOAC DDIs. Although a vast number of interactions have been proposed to cause an increased risk of DOAC-related bleeding or a reduced antithrombotic efficacy leading to thrombosis [18], this review found that after a decade of use, the overall number of published DOAC DDIs contributing to adverse events is relatively low, since only 23 reports of such interactions have been reported in the literature. This does not necessarily imply the absence of interactions, but it may speak to several important points regarding the identification and application of drug interaction data. First, it is possible that DOAC adverse events occurred without a drug interaction being identified as the cause. Second, the significant time and effort required to craft and submit a drug interaction report for publication may be beyond the scope of many already overworked and under-resourced clinicians. Third, the precautions clinicians may have employed in avoiding concomitant drugs proposed to interact with DOACs based on published pharmacokinetic studies and manufacturer labeling may have effectively limited the number of reported interaction-related adverse events. Current labeling for each of the DOACs recommends against use of strong P-gp/CYP3A4 inducers and some strong inhibitors [55–58].

Most pharmacokinetic case reports of DDIs resulting in bleeding outcomes are consistent with the suggested mechanism of P-gp and/or CYP3A4 inhibition, with two exceptions. Case reports of bleeding resulting from miconazole-rivaroxaban and loperamide-dabigatran DDIs demonstrate no clear mechanism involving P-gp or CYP3A4. The case report authors cite miconazole as both an inhibitor of P-gp and a strong inhibitor of CYP3A4, however, the reference cited in the case report for this only studied fluconazole and ketoconazole as significantly increasing rivaroxaban drug exposure. Upon literature search no other references could be found to indicate that miconazole has similar inhibitory properties to its azole antifungal relatives. In the miconazole case the patient was taking a higher-than-recommended dose for atrial fibrillation in a setting of moderate renal impairment (estimated creatinine clearance 44 mL/min) which could have contributed to the bleeding rather than the proposed DDI [44]. In the loperamide case the patient experienced hematuria in the setting of a urinary tract infection [45] which could cause hematuria independent of a DDI. Additionally, loperamide is a *substrate* of P-gp but not an inhibitor, as the authors proposed [37]. The reference cited by the case report authors corroborate loperamide's P-gp substrate properties but not as an inhibitor. Literature search did not reveal anything to indicate P-gp inhibition by loperamide. Similarly, most culprit drugs resulting in thrombotic outcomes are classified as CYP3A4/P-gp inducers, which is consistent with the proposed mechanism of decreasing DOAC bioavailability and reducing anticoagulant effects. The case report by King et al. involved a single patient on phenobarbital who experienced cardioembolic stroke while on an appropriate dose of dabigatran and then subsequently experienced a new stroke while on an appropriate dose of apixaban. Phenobarbital is a well-established inducer of CYP3A4 [59,60], which would provide a rational explanation for the apixaban interaction, but controversy exists about its role as a P-gp inducer, relevant to the dabigatran interaction. Literature reports of P-gp induction are limited to human in vitro data [61]. Further study is required to establish phenobarbital's role as a human P-gp inducer in vivo. The case report of a mesenteric artery thrombosis due to tocilizumab-dabigatran interaction was postulated to be due to the inhibition of P-gp by interleukin-6. With tocilizumab's mechanistic inhibition of interleukin-6, this would result in reduced level of dabigatran. The P-gp inhibitory properties of

interleukin-6 have only been demonstrated via animal models, so further research in humans is warranted to inform clinical decisions on this potential interaction.

Only five of the 20 cases reported DOAC-specific drug levels in the setting of adverse events, which reflects the limited availability of these laboratory tests. Of note, DOAC plasma concentrations were above the published on-therapy reference ranges in all bleeding cases, as were the more widely available coagulation laboratory tests. Recently, one Italian center noted a six-fold increase in the trough DOAC concentration of patients hospitalized for COVID-19 pneumonia who were also receiving antiviral therapy with ritonavir [62]. No bleeding complications were reported in these patients; however, over half had the DOAC discontinued as a result of the concerning elevation in trough concentration. In our study, a DOAC-ritonavir DDI was responsible for two reported bleeding events, and given this risk, DOAC-specific labeling recommendations include avoiding this drug combination or employing a DOAC dose reduction [55,56,58]. Ritonavir is likely a contributor to the elevated DOAC concentrations in these COVID-19 patients, but the scenario is likely multifactorial. In addition to antiviral therapy with ritonavir, some patients in the Italian study were also receiving darunavir (a strong CYP3A4 inhibitor) and/or azithromycin (a p-gp inhibitor) which could represent an additive DDI effect on DOAC concentrations. Additionally, renal impairment is a common sequela of COVID-19 infection and could impair DOAC clearance [63].

In our study, all but one coagulation test was within normal limits for patients with thrombotic events. This reinforces the concept that standard coagulation tests may be helpful to qualitatively assess excess DOAC effect in the absence of DOAC-specific assays [64] but may have limited utility in suspected DOAC failures or thrombotic events.

The included cohort studies also warrants discussion. The Chang et al. study's findings with amiodarone are consistent with the case reports in this analysis and with other literature finding no difference in adverse outcomes with the combination of apixaban and amiodarone [64]. However, a systematic review showed no difference in clinical outcomes in patients taking any DOAC and amiodarone [66]. The finding that phenytoin contributed to increased bleeding risk is paradoxical given the proposed mechanism of interaction is phenytoin's strong induction of P-gp and CYP3A4. The expected effect would be reduced levels of DOAC and increased thrombotic risk. It is possible that other concomitant interacting medications may have outweighed potential effect of the phenytoin DDI, or other factors not accounted for, including the DOAC dose, hepatic or renal impairment, and frailty may have contributed to bleeding outcomes [67]. The Chang et al., study also concluded DOAC administration with concomitant verapamil and diltiazem led to no increase in bleeding risk. However, the Chang et al., study has seen several response letters regarding limitations of their study [68–70]. To further investigate the bleeding risk of DOACs and antihypertensive drugs, the Pham et al., study analyzed the rate of bleeding between DOACs and concomitant verapamil and diltiazem against DOACs with non-CYP3A4 and P-gp modifiers. Pham et al., found an increase bleeding risk for dabigatran, contrary to the Chang et al., study; however, this may be due to Pham et al., using an active comparator group instead of a non-user group.

Overall, an interesting mechanistic finding in this study is that more DDI-related bleeding adverse events were likely resulting from a *combination* CYP3A4/P-gp inhibition mechanism, whereas thrombotic adverse events could have been either from a *single* CYP3A4 inducer or a combined CYP3A4/P-gp inducer. Further study could focus on the difference in clinical relevance of combined versus single CYP3A4/P-gp modifier interactions.

Only five of the 20 case reports cited in this analysis used the DIPS, a validated scoring tool to evaluate the likelihood of a drug-drug interaction being present. It allows the clinician to objectively assess different parameters of the interaction such as drug properties, timing, laboratory evaluations, and reasonable alternative causes for the event [32,33]. Many clinicians may be unaware of this tool, but applying it in the setting of a proposed drug interaction can aid in clinical decision-making.

It is important to note that this analysis focused on literature reporting clinical adverse events resulting from DDIs. Equally relevant to clinical decision-making in the realm of drug interactions are negative studies, that is, those reporting the *absence* of a DDI. There are a few examples of this in the DOAC DDI literature. A sub-analysis of the rivaroxaban atrial fibrillation clinical trial and a retrospective case-cohort study showed no significant difference in bleeding outcomes in patients taking a combination of rivaroxaban and nondihydropyridine calcium channel blockers diltiazem or verapamil [71,72]. The Chang et al. cohort study included in this analysis found no increased risk of bleeding with nondihydropyridine calcium channel blockers [35]; similarly no case reports of adverse events related to these drugs were identified in this analysis. A sub-analysis of the apixaban atrial fibrillation clinical trial found no significant differences in bleeding outcomes in patients taking apixaban and amiodarone [65], and as mentioned above, a systematic review showed no difference in clinical outcomes in patients taking any DOAC and amiodarone [62]. The Chang et al. study showed an increase in bleeding related to combinations of dabigatran-amiodarone and rivaroxaban-amiodarone, but not apixaban-amiodarone [35]. As previously noted, amiodarone-dabigatran-related bleeding was cited in two case reports [40,41]. Interestingly, the manufacturer prescribing information for both rivaroxaban and apixaban have been recently updated to allow the use of clarithromycin with these DOACs, despite its being a strong inhibitor of both P-gp and CYP3A4 [55,56]. Pharmacokinetic data indicate that changes in DOAC exposure due to clarithromycin are not likely to be clinically relevant [73,74]. This is consistent with the findings of the Chang et al. study [35].

As most of the body of literature in this area consists of case reports, reporting bias potentially limits the scope and findings of our review. Specifically, underreporting of clinical events has almost certainly occurred, making it difficult or impossible to identify all clinically relevant interactions resulting in adverse events. Finally, other reports may have been published and not fallen into the search criteria for this systematic review. The safety and efficacy profile of a drug is often well tested and documented in clinical trials prior to reaching the market, however, its profile will continue to evolve and build after reaching the market [75]. The topic of drug-drug interactions may be best addressed by a collaboration between already established governmental databases such as the United States Food and Drug Administration Adverse Event Reporting System, the pharmaceutical industry, and academia. One collaborative product could be the creation of a mandatory de-identified prospective registry. This could eliminate reporting bias by identifying clinically relevant DDIs associated with adverse events in addition to the *absence* of clinically relevant DDIs. Efforts to make DOAC-specific laboratory monitoring tests more widely available would allow for more quantitative data in the setting of DDIs. Publicizing existing internal data and/or funding of prospective studies to investigate how DOAC-specific laboratory tests correlate to clinical adverse events would provide useful clinical guidance. As such collaboration between these agencies and academia is called upon and can promote efficient and expansive research toward drug-drug interactions [76,77].

The strengths of this study lie in the reporting of DDIs that resulted in adverse events. Many prior DDI studies have been conducted in highly controlled environments with healthy subjects, or drew conclusions from in vitro data [23–27]. Although our study had to utilize lower quality of evidence case reports and observational data, it offers insight toward the DDIs that would most likely be encountered in a real-world clinical scenario. Furthermore, we choose to look at studies comparing specific DOACs with specific CYP3A4/P-gp modifiers. Studies where DOACs and modifiers are grouped together and assessed for risks may overestimate the risk for bleeding or thrombotic outcomes.

Table 2
Practical recommendations for direct oral anticoagulant pharmacokinetic drug-drug interaction management.

- Assess the relative contributions of drug absorption, metabolic and elimination pathways and the clinical significance of each. Recognize drug-drug interactions may involve multiple pathways and multiple individual patient characteristics and consider the net effect on the patient.
- When assessing drug-drug interaction literature, prioritize reports of **human *in vivo*** data in actual **patients**, particularly those reporting on **adverse clinical outcomes** as a result of a proposed drug-drug interaction.
- Utilize labeled recommendations for avoiding drug combinations that have been demonstrated to cause bleeding or thrombotic events and utilize recommended dose reductions according to product labeling.
- Apply the Drug Interaction Probability Scale (DIPS) to retrospectively assess the likelihood of a drug-drug interaction.
- Report drug-drug interactions that result in adverse events as per institutional protocol and to the Food and Drug Administration Adverse Event Reporting System (FAERS) as appropriate, and write up a report of the proposed DDI and adverse event for publication and contribution to the literature as a case report.

5. Conclusion and relevance

Current literature evaluating the real-world risk of DOAC DDIs is limited to case reports and retrospective observational analyses. The most commonly reported interacting drugs to cause bleeding events were amiodarone and ritonavir via inhibition of P-gp and CYP3A4; culprit drugs for thrombotic events were phenytoin and carbamazepine (via combined strong induction of P-gp and CYP3A4), and phenobarbital (via strong induction of CYP3A4). Clinicians are encouraged to recognize multiple pathways of interaction and other clinical factors, assess the DDI literature appropriately, and identify and report potential interactions they encounter and to determine the likelihood of the validity of the interaction using validated tools such as the DIPS score (Table 2).

Further study in this area is warranted given the widespread use of DOACs and potentially interacting medications, and the clinical impact of any resultant complication which can include life-threatening thrombosis or bleeding. Our results suggest that the development of reliable databases or registries with mandatory reporting of adverse events will be required to develop more reliable information on clinically important interactions. Current methodologies are insufficiently large, and depend on voluntary reporting, resulting in very poor quality data in this clinically important area.

Author contributions

Conception and design: AL, MC, SRV.
Data collection: AL, MKL, SRV, MC.
Analysis and interpretation: AL, MKL, SRV, MC.
Writing the article: AL, MKL, SRV, MC.
Critical revision of the article: AL, MKL, SRV, MC.
Final approval of the article: AL, MKL, SRV, MC.
Obtained funding: Not applicable.
Overall responsibility: AL, MKL, SRV, MC.

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Declaration of competing interest

No funding was provided for conduction of this study.
AL has no conflicts to disclose.
ML has no conflicts to disclose.
SRV serves as an editorial consultant for UpToDate®, which is a product of Wolters-Kluwer who also produces Lexi-Comp® drug interaction database. She is also a member of the board of directors for the Anticoagulation Forum.

MC discloses Data Safety Monitoring board work for Bayer, Advisory Board work for Servier Canada, Asahi Kasei, and Precision Biologicals and preparation of educational materials and/or presentations for Pfizer, CSL Behring and Diagnostica Stago. Doctor Crowther holds individual stocks in Alnylam. Doctor Crowther has ongoing relationships with a number of for profit, and not for profit agencies and has worked on medicolegal cases involving anticoagulant therapy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.08.016.

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