Drug–Drug Interactions between Direct Oral Anticoagulants and Hepatitis C Direct-Acting Antiviral Agents: Looking for Evidence Through a Systematic Review

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Abstract

Background Direct oral anticoagulants (DOACs), as substrates of cytochrome P450 (CYP) 3A4 and/or P-glycoprotein, are susceptible to drug–drug interactions (DDIs). Hepatitis C direct-acting antiviral agents (DAAs), via P-glycoprotein or CYP3A4 inhibition, may increase DOAC exposure with relevant bleeding risk. We performed a systematic review on DDIs between DOACs and DAAs.

Methods Two reviewers independently identified studies through electronic databases, until 7 July 2020, supplementing the search by reviewing conference abstracts and the ClinicalTrials.gov website.

Results Of 1386 identified references, four articles were finally included after applying the exclusion criteria. Three phase I clinical studies in healthy volunteers assessed interactions between dabigatran and glecaprevir/pibrentasvir, odalasvir/simeprevir, or sofosbuvir/velpatasvir/voxilaprevir, showing an increase in the dabigatran area under the concentration–time curve (AUC) by 138%, 103%, and 161%, respectively.

Conclusions DOACs and DAAs are under-investigated for DDI risk. Real-world studies are needed to assess the clinical relevance of the pharmacokinetic interactions with dabigatran and describe the actual spectrum of possible DDIs between DAAs and other DOACs.

Key Points

This is the first systematic review assessing evidence about direct oral anticoagulants/direct-acting antiviral agents (DOACs/DAAs) drug–drug interactions (DDIs).

DAAs increase dabigatran concentration, while no studies were available for other DOACs.

Real-world studies are needed to evaluate clinical relevance of this interaction and to describe the actual spectrum of possible DDIs between DAAs and other DOACs.

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1 Introduction

In recent years, the direct oral anticoagulants (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban have been progressively introduced worldwide. By virtue of their favorable pharmacological properties, including predictable pharmacokinetics [1], compared with vitamin K antagonists (VKAs), DOACs are recommended by major guidelines as first-choice anticoagulants for the treatment of venous thromboembolism (VTE) and stroke prevention in non-valvular atrial fibrillation (AF), as documented by current estimates on the incidence of new users [2–4].

Nevertheless, risk of bleeding remains a potentially serious complication and preventive strategies should be

targeted to real-world susceptible patients, largely under-represented in clinical trials, such as extreme weights, severe kidney insufficiency, and concomitant administration of potentially interacting medications.

Among the various unsettled issues, the impact of polypharmacy and drug–drug interactions (DDIs) is perceived as a key research priority [5], also to disentangle the contribution of pharmacodynamic and pharmacokinetic mechanisms. Although DOACs have fewer DDIs than VKAs, significant interactions can still occur; DOACs are substrates of cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp), making them susceptible to pharmacokinetic DDIs (see Table 1). In particular, coadministration of dabigatran and rifampicin, via P-gp induction, has been documented to lower dabigatran concentration by more than 60%; coadministration of rivaroxaban with ketoconazole or ritonavir has instead been shown to raise rivaroxaban concentrations by more than 150%, via CYP3A4 and P-gp/BCRP (ABCG2) inhibition [6, 7]. At present, there is no accepted threshold for a change in DOAC concentrations that defines clinical significance; however, the anticoagulant effect of DOACs is concentration-dependent, and significant changes in DOAC concentrations likely affects clinical outcomes [8].

While laboratory tests to assess the intensity of anticoagulation and the detection of DDIs are easily accessible for VKAs by monitoring the international normalized ratio, DOAC-specific tests and guidance for using them in special situations are now available with several limitations. In particular, there is actually no consensus on the therapeutic range of DOACs, even if information can be derived from phase II–III clinical trials regarding the 'on-therapy' range [9]. Based on data from pharmacokinetic studies, expert societies have proposed algorithms and thresholds for some clinical situations, which need to be validated in targeted prospective studies [9, 10].

In parallel with the increasing uptake of DOACs, several direct-acting antiviral agents (DAAs) for chronic hepatitis C virus (HCV) have been licensed in recent years; these agents have expanded the pharmacological armamentarium for treating HCV infection, with remarkable effectiveness and a good tolerability profile [11]. However, relevant treatment regimens contain at least two and up to five drugs, and carry potential metabolic- or transport-mediated DDIs via P-gp or CYP3A4 inhibition (see Table 1) [12, 13]. The potential for DDIs needs special consideration for HCV-infected individuals with concomitant comorbidities, such as AF or VTE, requiring anticoagulant treatment.

Recent studies have suggested an increased risk of VTE among HCV-infected patients, coupled with an increased incidence of AF [14, 15], thus resulting in a likely rise in the number of DOAC prescriptions in the near future in patients with HCV infection. In addition, the use of DOACs in patients with liver disease is expected to increase in the next years as a result of the link between metabolic as well as viral liver disease and cardiovascular complications, and due to the concomitant increasing prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH) [16]. In particular, on the one hand, HCV infection is often associated with both hepatic steatosis and with a specific HCV-associated dysmetabolic syndrome [17], while on the other hand, NASH currently represents the leading cause of chronic liver disease and is independently associated with an increased risk of cardiovascular diseases, namely cardiac rhythm disorders (mainly AF) and VTE [18–21]. Therefore, an increasing number of patients affected by chronic liver disease will be candidates for anticoagulant treatment with DOACs [16].

In patients with cirrhosis, the use of DOACs is controversial and challenging for a number of reasons, including (1) cirrhosis was an exclusion criteria of pivotal trials; (2) patients with cirrhosis are at risk of both bleeding and thrombotic complications; and (3) DOACs, especially rivaroxaban, have been associated with increased reporting of serious and early-onset liver injury [22, 23]. For these reasons, current guidelines and drug regulatory agencies (US FDA and European Medicines Agency) contraindicated all DOACs in patients with cirrhosis Child–Turcotte–Pugh (CTP) class C, while variously allowing their use in patients with cirrhosis CTP class B and A [3, 24]. Emerging real-world data suggest that DOACs can effectively and safely be used in CTP A patients, and cautiously in CTP B cirrhotic patients, compared with VKAs [16], thus supporting the importance of an accurate evaluation of possible DDIs in HCV co-infected cirrhotic patients.

Because of these pharmacokinetic bases, the combination of DOACs and DAAs is not recommended, or is to be used with caution, as per major guidelines and online tools, albeit with little information on clinical relevance and relative proper management [11, 12].

We aimed to systematically assess the evidence regarding DDIs between DOACs and DAAs, and to provide adjunctive information on their clinical relevance, including management in clinical practice.

2 Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. The protocol was designed a priori but was not submitted to public repositories.

Table 1 Predicted pharmacokinetic drug interactions between the main hepatitis C direct-acting antiviral agents and direct oral anticoagulants

		DDIs with DOACs (PK prediction)			
		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
P-gp substrate		Yes	Yes	No (minimal)	Yes
CYP3A4 substrate		No	Yes (moderate, 18%)	Yes (moderate, 25%)	No (minimal, 4%)
BCRP substrate		No	Yes	Yes	No
OATP1B1 substrate		No	No	No	Yes
Hepatitis C direct-acting antiviral agents	PK pathway causing DDIs				
Sofosbuvir		No interaction expected	No interaction expected	No interaction expected	No interaction expected
Sofosbuvir/ledipasvir	Mild to moderate P-gp inhibition (by ledipasvir) Weak inhibition of OATPB1 (by ledipasvir)	Potential interaction	Potential interaction	Potential interaction	Potential interaction
Sofosbuvir/velpatasvir	Mild P-gp inhibition (by velpatasvir) Inhibition of BCRP (by velpatasvir)	Potential interaction	Potential interaction	Potential interaction	Potential interaction
Ombitasvir/paritaprevir/ ritonavir + dasabuvir	P-gp inhibition Inhibition of CYP3A4 (by paritaprevir and ritonavir) Inhibition of BCRP (by ritonavir and dasabuvir) Inhibition of OATP1B1 (by paritaprevir)	Potential interaction	Avoid coadministration (not recommended)	Avoid coadministration (not recommended)	Potential interaction
Grazoprevir/elbasvir	Weak inhibition of CYP3A4 (by grazoprevir) Mild P-gp inhibition (by elbasvir) Inhibition of BCRP (by elbasvir/grazoprevir)	Potential interaction	Potential interaction	Potential interaction	Potential interaction
Sofosbuvir/velpatasvir/ voxilaprevir	Mild P-gp inhibition (by velpatasvir and voxilaprevir) Inhibition of BCRP (by velpatasvir and voxilaprevir) Inhibition of OATP1B1 (by velpatasvir and voxilaprevir)	Avoid coadministration (not recommended)	Potential interaction	Potential interaction	Avoid coadministration (not recommended)
Glecaprevir/pibrentasvir	Weak inhibition of CYP3A4 Strong inhibition of P-gp Inhibition of BCRP	Avoid coadministration (not recommended)	Potential interaction	Potential interaction	Potential interaction
Simeprevir	Mild–moderate P-gp inhibition Inhibition of CYP3A4 Inhibition of OATPB1	Potential interaction	Potential interaction	Potential interaction	Potential interaction

Based on https://www.hep-druginteractions.org (University of Liverpool) [12] and Talavera Pons et al. [13]

CYP cytochrome P450, *P-gp* P-glycoprotein, *BCRP* breast cancer resistance protein, *PK* pharmacokinetic, *DOACs* direct oral anticoagulants, *DDIs* drug–drug interactions, *OATP* organic anion-transporting polypeptide

We searched studies that assessed DDIs between DOACs and DAAs, using the MEDLINE (1966 to 7 July 2020) and EMBASE (1980 to 7 July 2020) electronic databases. The search strategy was developed without any language restriction using https://www.embase.com: 'antiinfective agent' AND 'hepatitis c' AND 'anticoagulant agent'.

We supplemented our search by handsearching unpublished literature, including the ClinicalTrials.gov website

Table 2 Characteristics of the included studies and *outcome measures*

	Kosloski et al. [28]	Boyle et al. [29]	Ouwerkerk-Mahadevan et al. [30]	Garrison et al. [31]
Journal, year	Journal of Pharmacology and Experimental Therapeutics, 2019	Journal of Hepatology, 2019	Clinical Pharmacology and Therapeutics (CPT), 2018	Journal of Hepatology, 2017
Data presentation	Full text	Congress poster (EASL)	Congress poster (ASCPT)	Congress poster (EASL)
Study type	Phase I	Retrospective observational	Phase I	Phase I
Population	Healthy volunteers (11)	UK DOAC + DAA patients (54) over 1 year DOACs: 37 rivaroxaban, 14 apixaban, 2 dabigatran, 1 edoxaban	Healthy volunteers (15)	Healthy volunteers
Intervention	Dabigatran + glecaprevir/pibrentasvir	None. Review of management strategies for DDIs between DOACs and DAAs (various types of combination)	Dabigatran + odalasvir/simeprevir Sequential administration	Dabigatran + sofosbuvir/velpatasvir/voxilaprevir
Comparator	No comparator	No comparator	No comparator	No comparator
Outcome measures	Dabigatran C_{max} and AUC_∞ were 105% and 138% higher, respectively, during coadministration with glecaprevir/pibrentasvir compared with dabigatran alone	Management strategies: 24 (44.4%) clinical monitoring, 13 (24.1%) anti-Xa activity blood monitoring, 9 (16.7%) switch to LMWH, 7 (13%) switch DAAs, 1 (1.9%) wait until DOACs completed for finite courses No serious bleeding reported	Dabigatran C_{max}, AUC_{last} and AUC_∞ increased by 48%,76%, and 68%, respectively, upon coadministration with odalasvir (day 17), and by 70%, 114%, and 103%, respectively, upon coadministration with odalasvir/simeprevir (day 26), versus dabigatran alone (day 1) No deaths or serious adverse events were reported	Total dabigatran AUC was $\uparrow$161% following administration of sofosbuvir/velpatasvir/voxilaprevir with dabigatran

ASCPT American Society for Clinical Pharmacology and Therapeutics, *AUC* area under the concentration–time curve, AUC_∞ AUC from time zero to infinity, AUC_{last} AUC from time zero to time of the last quantifiable concentration, C_{max} maximum plasma concentration, *DAAs* direct-acting antivirals, *DDIs* drug–drug interactions, *DOACs* direct oral anticoagulants, *EASL* European Association for the Study of the Liver, *LMWH* low-molecular-weight heparin, $\uparrow$ indicates increased

Overall, the paucity of data urgently calls for dedicated real-world studies to verify the actual clinical relevance of the pharmacokinetic interactions with dabigatran, and investigate the real risk in users of anti-factor Xa drugs, both in terms of bleeding risk and occurrence of liver injury. In fact, both rivaroxaban and apixaban are P-gp and BCRP substrates, whereas the active substrate of edoxaban is also a substrate of OATP1B1, thus making clinically important drug interactions highly likely.

The new oral hepatitis C drugs are examples where interpretation of a potential interaction may be particularly complex due to multiple drugs with different pharmacokinetic profiles concomitantly administered [32]. For instance, ledipasvir and sofosbuvir are P-gp substrates in vitro (and ledipasvir is also a P-gp inhibitor), whereas paritaprevir, ritonavir and dasabuvir all inhibit P-gp in vitro. Our data (even a twofold increased AUC of dabigatran) strongly suggest the clinical importance of this pharmacokinetic interaction. Apart from additional stringent clinical monitoring of susceptible patients (e.g. elderly with organ impairment receiving polypharmacy), outdistanced administration of the object and precipitant drug could be a viable option to minimize the likelihood of a pharmacokinetic interaction between dabigatran and DAAs, as previously demonstrated with verapamil (a P-gp and CYP3A4 inhibitor); administration of dabigatran etexilate (the prodrug) 2 h before verapamil did not significantly increase exposure to dabigatran etexilate (< 20% increase in AUC) [33].

Notably, there are key differences in the pharmacokinetic profiles among DOACs; apart from P-gp interactions (with dabigatran, as a prodrug, more likely to be affected), the extent of hepatic metabolism varies substantially, with rivaroxaban and apixaban undergoing non-negligible (65–75%) liver pathways, mediated for 25% by CYP3A4/5 and CYP2J2 [34]. Therefore, real-world studies are essential to verify the actual bleeding risk in users of DOACs and DAAs, especially considering that different DAAs possess additional properties on CYP3A4 (inhibitors or substrates), and the potential mismatch between pharmacokinetic data and observed associations in population-based studies [32, 35]. For dabigatran (in patients aged > 85 years), recent cohort studies on rivaroxaban and edoxaban found increased bleeding occurrence in patients exposed to P-gp inhibitors and moderate CYP3A4 inhibitors, as also expected from clinical trials, where frequencies of bleeding events and mortality, but not stroke and systemic embolism, were increased with the increasing number of concomitant drugs [36–38].

Moreover, as shown in our review, DDIs between dabigatran and the DAAs tested resulted in a change of dabigatran concentration > 25%; this cut-off was used in a previous review assessing DDIs of DOACs as a clinically significant change for maximum concentration (C_{max}) and AUC, in line with FDA guidance [39]. The actual relationship between these pharmacokinetic bases and clinical outcomes is still debated.

We noted partial disagreement between international guidelines; the EASL guidelines contraindicated some combinations of DAAs/DOACs, whereas there is no specific mention in the 2018 European Heart Rhythm Association (EHRA) guidelines, and only coadministration of an HIV protease inhibitor (e.g. ritonavir) with DOACs is not recommended [3, 11]. Our findings may support an evidence-based update of future guidelines, in particular regarding coadministration of dabigatran with glecaprevir/pibrentasvir, odalasvir/simeprevir, or sofosbuvir/velpatasvir/voxilaprevir. However, with regard to DDIs between DOACs and antiretroviral HIV treatment (sharing similar predicted pharmacokinetic DDIs with DAAs), in a recent small series of 14 HIV-infected patients concurrently treated with a variety of an antiretroviral and dabigatran for AF, dabigatran levels remained within the population expected range [40]. This further highlights the need for real-world targeted studies to assess the clinical relevance of the pharmacokinetic interaction that emerged in our review between dabigatran and HCV DAAs.

The strengths of our study include its systematic approach, including the implementation of our search with gray literature, through handsearching of conference abstracts. However, limitations of this systematic review should be acknowledged, which are mainly related to study design and full-text availability.

Apart from the very limited number of available studies, most studies were pharmacokinetic phase I trials, conducted in a small number of healthy volunteers. However, we believe this limitation should further raise awareness of clinicians on the risk of bleeding in subjects with chronic HCV and concomitant diseases, such as AF or VTE, taking several medications.

Due to the study design, a comparator was not tested. Therefore, no conclusions can be drawn as to whether the use of other anticoagulant treatments (such as heparin or VKAs), instead of DOACs, would bring benefit in this context. Although no major complications or major bleeding were reported in the studies included, also considering the small number of subjects enrolled, no firm conclusions can be made on the clinical relevance of these results due to the lack of consensus on clinically relevant changes in DOAC concentrations correlating with actual clinical outcomes.

Lastly, little information was available in the literature on how to manage potential DDIs between DOACs and DAAs in clinical practice; the only study available was a small observational study showing heterogeneity in the approaches used by clinicians to handle DDIs between DOACs and DAAs [41]. Therefore, our results further highlight the

lack of data available and the urgent conduction of targeted studies.

5 Conclusions

The paucity of data documented by this systematic review underline the need to assess the actual clinical impact of anticipated pharmacokinetic interactions between DOACs and DAAs through real-world studies, thus supporting clinicians in safe prescribing.

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