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MINI REVIEW

# Drug–Drug Interactions Between DAAs and Anticoagulants or Antiplatelets: A Position Paper of the Italian Anticoagulation Clinics

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## ABSTRACT

The natural history of chronic hepatitis C virus (HCV) infection has changed after the introduction of direct-acting antiviral agents (DAAs). Screening programs have been ongoing to reach the World Health Organisation's goal of HCV elimination by 2030, and most infected people are eligible for treatment. Given the increased cardiovascular risk in people with HCV infection and the metabolic pathways of DAAs, it is not uncommon to face the issue of drug–drug interactions (DDIs) with antiplatelet or anticoagulant drugs. In the absence of clinical trials, we offer suggestions to deal with DDIs in case of treatment of patients with DAAs who are also receiving antiplatelet or anticoagulant drugs, based on the best available evidence from pharmacodynamics and pharmacokinetics studies in conjunction with clinical experience in the field of haemostasis and thrombosis.

## 1 | Introduction

Chronic hepatitis C virus (HCV) infection is one of the most important causes of chronic liver disease, with 71 million chronically infected individuals in the world. Genotypes 1 and 3 are the most common causes of infection [1]. In Europe, Italy bears a considerable burden, exhibiting an estimated HCV prevalence of 0.66% [2, 3].

Over the past decade, a revolutionary class of drugs, the direct-acting antiviral agents (DAAs), has emerged for the treatment of HCV infection. DAAs demonstrate superior efficacy compared to interferon and/or ribavirin resulting in higher sustained virologic response (SVR) rates and associated good tolerability. The introduction of DAAs has radically changed the natural history of HCV infection and a gradual decrease in prevalence is expected in the upcoming years, due to depletion of the virus reservoir [2].

**Abbreviations:** AF, atrial fibrillation; ASA, acetylsalicylic acid; BCRP, Breast Cancer Resistance Protein; COX-1, cyclooxygenase-1; CRNMB, clinically relevant non major bleeding; CYP450, cytochrome P450 enzyme; DAA, direct-acting antiviral agent; DDI, drug-to-drug interaction; DOAC, Direct oral anticoagulant; dTTs, diluted thrombin times; EQA, external quality control; FCSA, Italian Federation of Anticoagulation Clinics; HCV, hepatitis C virus; ICSH, International Council for Standardisation in Haematology; INR, international normalised ratio; LMWH, low-molecular-weight heparins; MACE, major adverse cardiovascular events; MB, major bleeding; NSAID, Non-Steroidal Anti-Inflammatory Drug; OATP, Organic Anion-Transporter Polyprotein; P-gp, transporter Permeability Glycoprotein; SVR, sustained virologic response; UFH, unfractionated heparin; VKA, Vitamin K Antagonist; VTE, venous thromboembolism.

**Summary**

- Screening programs for HCV infection are ongoing, most people are eligible for treatment.
- HCV infection increases cardiovascular risk.
- Drug–drug interactions between antiplatelet or anticoagulant drugs and direct-acting antiviral agents are common.
- We offer practical tips to deal with these drug–drug interactions.

It is recognised that HCV infection is associated with an overall increased morbidity and mortality, not just related to liver disease. It has been shown that HCV infection is an independent predictor factor for major adverse cardiovascular events (MACE), especially for venous thromboembolism (VTE), cardiovascular diseases, and atrial fibrillation (AF) [4, 5]. Moreover, HCV-infected individuals with AF exhibit both higher CHA2DS2VASc and HAS-BLED scores [6].

In alignment with the World Health Organisation's ambitious goal of HCV elimination by 2030, extensive screening programs are ongoing. These efforts have led to the identification of a relevant number of asymptomatic subjects infected with HCV, the majority of them are candidates for DAA therapy. There is no age limit for access to treatment of HCV infection with DAAs and there are very few contraindications to treat, such as short life expectancy or concomitant drug-to-drug interactions (DDIs) with life-saving drugs. DAA regimens, often comprising at least two drugs over 8–12 weeks, pose a risk for DDIs, particularly when administered alongside other medications [1].

Given the increased cardiovascular risk associated with HCV infection, it is commonplace for patients to be concurrently treated with oral anticoagulant or antiplatelets drugs. This concomitant medication use introduces a complex array of challenges, including DDIs, navigating contraindications in patients with advanced liver cirrhosis or chronic renal failure, and addressing the multifaceted nature of bleeding risk.

Specifically, the coadministration of oral anticoagulant or antiplatelets drugs and DAAs is a topic of concern with major guidelines and pharmacokinetic data and online tools cautioning against or advising careful use of such combinations, despite the paucity of concrete clinical data to delineate the full scope of these interactions' implications [7]. Indeed, there is no post-marketing real-world data about the clinical impact of coadministration of DAAs with oral anticoagulant or antiplatelets drugs, but it is well-known that there is high heterogeneity in the management of oral anticoagulant drugs during the period of HCV infection treatment. Table 1 presents a comprehensive overview of the pharmacokinetic pathways implicated in the main DDIs between DAAs and oral anticoagulant or antiplatelet drugs. The primary mechanisms through which these interactions occur involve the cytochrome P450 enzyme (CYP450) and the transporter Permeability Glicoprotein (P-gp), an efflux pump. Additionally, significant interactions are mediated through the Organic Anion-Transporter Polyprotein (OATP), an influx transporter, and the efflux transporter Breast Cancer Resistance Protein (BCRP), both of which play crucial roles in modulating intestinal absorption of various drugs [8].

Oral anticoagulants and antiplatelet drugs acting as substrates for these enzymes and transporters introduce a layer of complexity in predicting the extent and the clinical significance of interactions with DAAs. This complexity is further amplified by treatment regimens that encompass multiple drugs, each with its distinct pharmacokinetic profile.

To mitigate the risk and clinical impact of these DDIs, several strategies are recommended. Clinical and laboratory monitoring, particularly for elderly patients receiving polypharmacy, is essential for early detection and management of potential adverse interactions. Distancing the administration of drugs with potential interactions can also serve as a practical approach to

**TABLE 1** | Pharmacokinetic pathways involved in the main DDIs between DAAs and anticoagulant/antiplatelet medications. Adapted from EASL 2020 [1], https://www.hep-druginteractions.org (University of Liverpool) [9] and Bellesini et al. (2020) [7].

| DAA | Genotype | Duration of treatment | PK pathways involved in DDIs |
|---|---|---|---|
| Sofosbuvir/velpatasvir (Epclusa) | 1a, 1b, 2, 3, 4, 5, 6 | 12 weeks | Mild P-gp inhibition (by velpatasvir)<br>Inhibition of BCRP (by velpatasvir) |
| Glecaprevir/ pibrentasvir (Maviret) | 1a, 1b, 2, 3, 4, 5, 6 | 8–12 weeks | Weak inhibition of CYP3A4<br>Strong inhibition of P-gp<br>Inhibition of BCRP |
| Grazoprevir/elbasvir (Zepatier) | 1b | 12 weeks | Weak inhibition of CYP3A4 (by grazoprevir)<br>Mild P-gp inhibition (by elbasvir)<br>Inhibition of BCRP (by elbasvir/grazoprevir) |
| Sofosbuvir/velpatasvir/ voxilaprevir (Vosevi) | 1a, 1b, 2, 3, 4, 5, 6 | 8–12 weeks | Mild P-gp inhibition (by velpatasvir and voxilaprevir)<br>Inhibition of BCRP (by velpatasvir and voxilaprevir)<br>Inhibition of OATP1B1 (by velpatasvir and voxilaprevir) |

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; DAA, Direct Antiviral Agent; DDI, Drug–Drug Interaction; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein; PK, pharmacokinetic.

reducing the likelihood of significant DDIs [10]. Moreover, it is imperative to emphasise to patients the critical importance of adhering to DAA regimens as prescribed. Achieving a SVR is critically dependent on the correct medication intake. Healthcare providers should also be prepared to address and manage any complications that may arise from DDIs, ensuring patients are fully informed of the potential risks and are closely monitored throughout their treatment course.

## 2 | Italian Federation of Anticoagulation Clinics (FCSA)'s Suggestions

Given the daily clinical need of commencing DAAs in patients on anticoagulant or antiplatelet drugs and the scant evidence, each clinical decision should be shared between the hepatologist and the expert of thrombosis and haemostasis or cardiologist. The Italian Federation of Anticoagulation Clinics (FCSA) formulated the following suggestions. These are designed to mitigate potential clinically relevant interactions between DAAs and anticoagulant and antiplatelet drugs, thereby minimising the risk of adverse bleeding and/or thrombotic events triggered by unwarranted modifications in antithrombotic therapy.

FCSA's suggestion
First, the patient's bleeding risk (such as thrombocytopenia severity, presence of oesophageal varices, and concomitant antiplatelet therapy) and his/her thrombotic risk profile have to be evaluated.

## 3 | Oral Anticoagulant Drugs

### 3.1 | Vitamin K Antagonists

The inhibition of vitamin K dependent hepatic synthesis of coagulation factors (namely factor II, VII, IX, X) is the mechanism of action for Vitamin K Antagonists (VKAs). A narrow therapeutic index, multiple drug interactions, and interindividual variability in dose–response relationship characterise the pharmacology of VKA [10–12]. Changes in concomitant medications can reduce or increase levels of anticoagulation beyond the target range, placing patients at risk for thromboembolism or haemorrhage [12]. When adding other medications, the physician must assess interactions to predict potential dose adjustment [11]. CYP2C9 isoenzyme metabolises the S-enantiomer of warfarin (the more potent one). Warfarin is also a CYP1A2 substrate.

The use of DAAs together with VKA is not predicted to cause significant DDIs, nevertheless a close monitoring of international normalised ratio (INR) is recommended [6]. Indeed, the co-administration of VKA and glecaprevir/pibrentasvir may increase VKA exposure due to mild CYP1A2 inhibition, and lower exposure of warfarin has been observed when co-administered with DAAs, particularly with ombitasvir, paritaprevir-ritonavir, and dasabuvir (although these drugs are no longer used for HCV eradication) [11]. Moreover, changes in liver function during treatment with DAAs could result in different synthesis of coagulation factors [12]. In most cases decreases in INR were reported during concomitant treatment [11, 13].

FCSA's suggestion
In case of VKA treatment, we suggest:

- Increasing the frequency of INR monitoring during concomitant treatment (e.g. weekly in the first period of coadministration) and make adjustments when necessary, considering the risk of changing INR.
- Frequent monitoring of INR in the post-DAA-treatment period, particularly if any dose adjustment has occurred, paying greater attention in case of cardiac mechanical valves.

### 3.2 | Direct Oral Anticoagulants

In the last decade, the use of DOACs has become increasingly widespread, and they are the first choice for primary prevention of stroke and systemic embolism in patients with non-valvular AF, and for treatment and secondary prevention of VTE. The mechanism of action of these anticoagulants is direct inhibition of factor Xa (apixaban, edoxaban, rivaroxaban) or of thrombin (dabigatran). Their pharmacokinetics can be affected by DDIs modifying their plasma concentration and thus their anticoagulant activity, making them potentially less effective or less safe.

DOAC activity is concentration-dependent, but there is lack of consensus regarding the therapeutic range of plasma concentration and whether the measurement of DOAC levels may improve treatment efficacy. Thresholds of DOAC plasma concentrations are yet to be validated in prospective studies and they are based on extrapolation from pharmacokinetic studies. Nonetheless, assessment of DOAC plasma exposure is advisable in specific situations: suspected drug accumulation in acute renal/liver failure or overdose, before urgent surgery or prior to thrombolytic therapy for acute ischemic stroke, in extremes of body weight or gastrointestinal malabsorption and in patients with polypharmacy with expected DDIs. The diluted thrombin times (dTTs) can determine dabigatran level with a good accuracy and dedicated anti-Xa chromogenic assays using specific apixaban, edoxaban or rivaroxaban calibrators are able to measure a wide range of plasma concentrations. These assays are available in most hospitals and measuring DOAC levels could be easily implemented: it has no technical difficulty and its cost is affordable [14]. Laboratories are encouraged to participate in international external quality control (EQA) and an institutional protocol is advised. Currently, results of DOAC plasma measurement can be compared with expected peak and trough levels. The results have to be discussed with a laboratory medicine specialist and/or an expert in haemostasis and thrombosis, to be interpreted correctly [15–17]. Plasma DOAC concentrations should be measured at trough, just before the next pill intake, after five or more intakes to ensure the DOAC has reached its steady state [15]. Table 2 shows expected levels of DOAC trough concentrations correlated with DOAC doses (from International Council for Standardisation in Haematology—ICSH—recommendations for laboratory measurement of DOAC, 2018) [16].

**TABLE 2** | Expected trough DOAC concentrations in patients treated for stroke prevention in NVAF or PE/VTE. Adapted from ICSH Recommendations for Laboratory Measurement of Direct Oral Anticoagulants (2018) [16].

| | Dabigatran | | Rivaroxaban | | Apixaban | | Edoxaban | |
|---|---|---|---|---|---|---|---|---|
| Indication | Stroke prevention in NVAF | Treatment VTE | Stroke prevention in NVAF | Treatment VTE | Stroke prevention in NVAF | Treatment VTE | Stroke prevention in NVAF | Treatment VTE |
| Dose | 150 mg bid | 150 mg bid | 20 mg qd | 20 mg qd | 5 mg bid | 5 mg bid | 60 mg qd | 60 mg qd |
| Trough concentration ng/mL | 91[a] (61–143) | 60[a] (39–95) | 44[b] (12–137) | 26[b] (6–87) | 103[c] (41–230) | 63[c] (22–177) | 36[d] (19–62) | 19[d] (10–39) |

Abbreviations: IQR, Interquartile range; NVAF, Non Valvular Atrial Fibrillation; PE, Pulmonary Embolism; VTE, Venous Thromboembolism; bid twice daily; qd, once daily.
[a]Mean (25th–75th percentile).
[b]Mean (5th–95th percentile).
[c]Median (5th–95th percentile).
[d]Median (IQR).

Interactions involving CYP450, P-gp, OATP and BCRP are the major causes of DDI between DAAs and DOACs. Inhibition of transport proteins (P-gp, OATP and BCRP) results in direct competition between drugs with increased DOAC's serum concentration caused by reduced renal secretion and gut ri-secretion associated to lower hepatic uptake [18]. Inhibition of CYP450 can contribute to the increase of serum concentration as well, particularly for rivaroxaban and apixaban. Conversely, induction of transport proteins and enzymes induces a reduction of serum concentration of DOAC [19].

DOACs are substrates and not themselves considerable inhibitors or inducers of these metabolic pathways, therefore they should not affect DAA's metabolism. There are no post-marketing prospective studies about the clinical impact of pharmacokinetic interaction between DAAs and DOACs. Often, DDIs are predicted based on pharmacokinetic parameters [7].

For *dabigatran* only there are dedicated phase I studies on healthy volunteers. Dabigatran is a P-gp substrate and its concentration increases 161% when co-administered with sofosbuvir/velpatasvir/voxilaprevir and by 138% with glecaprevir/pibrentasvir via P-gp inhibition [20–22].

*Edoxaban* is a substrate of OATP1B1 and P-gp. Edoxaban and sofosbuvir/velpatasvir/voxilaprevir interaction is expected to significantly increase edoxaban concentration via inhibition of both OATP1B1 and P-gp [9, 21, 23, 24]. The active metabolite of edoxaban is a substrate of OATP1B1 [25], and its concentration may increase due to inhibition of OATP1B1 by velpatasvir and voxilaprevir. Inhibition of P-gp by velpatasvir and voxilaprevir may further increase edoxaban concentration. Coadministration with sofosbuvir/velpatasvir/voxilaprevir has not been studied in vivo. Still, it would not be recommended and the European SPC for Vosevi suggests to consider use of apixaban or rivaroxaban in place of edoxaban [9, 23, 24].

The use of *apixaban* (substrate of P-gp and CYP3A4) is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as HIV protease inhibitors (e.g. ritonavir). For example, coadministration of apixaban and ombitasvir/paritaprevir/ritonavir ± dasabuvir, a drug that is no longer recommended for HCV eradication, increased apixaban exposure by twofold or greater in the presence of severe renal impairment [26].

*Rivaroxaban*, a P-gp, CYP3A4 and BCRP substrate, is not recommended in patients receiving concomitant strong inhibitors of both CYP3A4 and P-gp.

Similarly to apixaban, coadministration of rivaroxaban with ritonavir leads to a significant increase in mean rivaroxaban concentration, with significant increases in pharmacodynamic effects with potential increased bleeding risk [27].

Although DAA-DOAC combinations have multiple DDIs (see Table 3), shifting to VKA or low-molecular-weight heparins (LMWH) is not indicated a priori, especially for the short period of co-administration of the therapies. This applies to both strong interactions and potential interactions (red and orange in Table 4).

The shift to VKA for 8–12 weeks may generate discomfort for the patient who has to perform close venous samples, particularly at the beginning of the treatment. Also, it may generate difficulty for the physician to find the dosage to ensure a correct INR range, and in some cases it may take some weeks to reach the target. Moreover it has to be pondered the potential underdosing or overdosing of the VKA with the consequent thrombotic or haemorrhagic risk. It is also described an increased thrombotic risk associated with the transition from one anticoagulant therapy to another.

On the other hand, the use of LMWH may create some difficulty for the patient who undergoes one or two subcutaneous injections daily for 2–3 months instead of taking oral therapy. In addition, the long term use of LMWH in stroke prevention in non-valvular AF is not supported by RCTs [28].

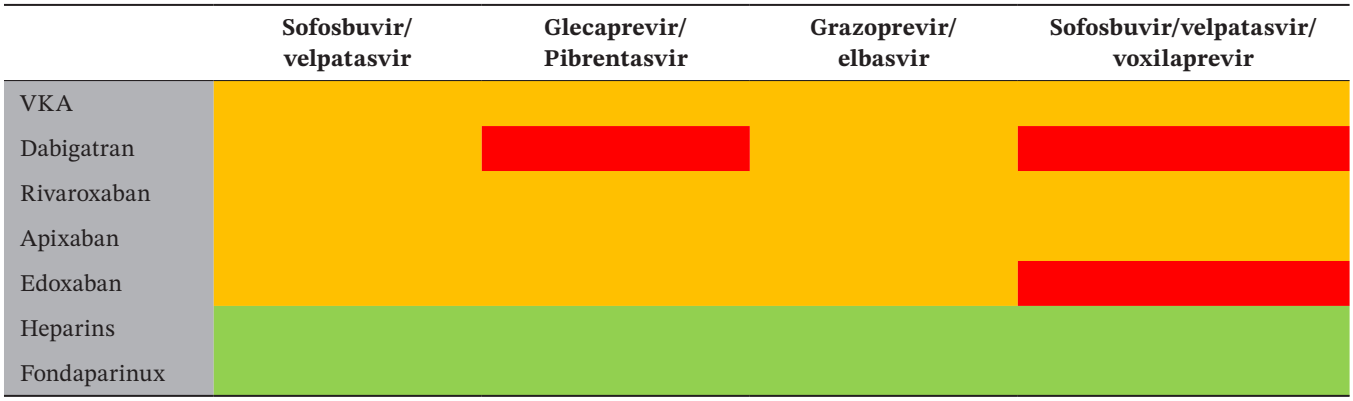
In conclusion, our suggestions are:

**TABLE 3** | Expected interactions between anticoagulant drugs and DAAs. Adapted from EASL 2020 [1], https://www.hep-druginteractions.org (University of Liverpool) [9], Bellesini et al. (2020) [7] and Ferri et al. (2022) [21].

| | | Sofosbuvir/velpatasvir | Glecaprevir/pibrentasvir | Grazoprevir/elbasvir | Sofosbuvir/velpatasvir/voxilaprevir |
|---|---|---|---|---|---|
| VKA | CYP2C9 (and CYP1A2) substrate | No inhibition of CYP2C9, possible INR change due to changes in liver function[a] | Possible increased VKA exposure due to mild CYP1A2 inhibition[a] | No inhibition of CYP2C9, possible INR change due to changes in liver function[a] | No inhibition of CYP2C9, possible INR change due to changes in liver function[a] |
| Dabigatran | P-gp substrate | Possible increased dabigatran exposure due to P-gp inhibition by velpatasvir[a] | Increased dabigatran exposure due to strong P-gp inhibition | Possible increased dabigatran exposure due to P-gp inhibition by elbasvir[a] | Increased dabigatran exposure due to P-gp inhibition by velpatasvir and voxilaprevir |
| Rivaroxaban | P-gp substrate CYP3A4 substrate BCRP substrate | Possible increased rivaroxaban exposure due to P-gp and BCRP inhibition by velpatasvir[a] | Possible increased rivaroxaban exposure due to P-gp inhibition, weak CYP3A4 inhibition and BCRP inhibition[a] | Possible increased rivaroxaban exposure due to mild P-gp inhibition, weak CYP3A4 inhibition and BCRP inhibition[a] | Possible increased rivaroxaban exposure due to P-gp and BCRP inhibition[a] |
| Apixaban | P-gp substrate CYP3A4 substrate BCRP substrate | Possible increased apixaban exposure due to P-gp and BCRP inhibition by velpatasvir[a] | Possible increased apixaban exposure due to strong P-gp inhibition and BCRP inhibition[a] | Possible increased apixaban exposure due to weak inhibition of CYP3A4, mild inhibition of P-gp, and inhibition of BCRP[a] | Possible increased apixaban exposure due to P-gp and BCRP inhibition[a] |
| Edoxaban | P-gp substrate OATP1B1 substrate | Possible increased edoxaban exposure due to P-gp and OATP1B1 inhibition by velpatasvir[a] | Possible increased edoxaban exposure due to strong P-gp and OATP1B1 inhibition[a] | Possible increased edoxaban exposure due to P-gp inhibition by elbasvir[a] | Increased edoxaban exposure due to P-gp and OATP1B1 inhibition by velpatasvir and voxilaprevir[a] |
| Heparins | Not substrate of CYP450 or P-gp | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] |
| Fondaparinux | Not substrate of CYP450 or P-gp | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] |

Abbreviations: BCRP, breast cancer resistance protein; CYP450, cytochrome P450; DOAC, direct oral anticoagulant; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein; VKA, vitamin K antagonist.
[a]Co-administration has not been studied.

**TABLE 4** | Schematic representation of FCSA suggestions for anticoagulant drugs. Adapted from EASL 2020 [1], https://www.hep-druginteractions.org (University of Liverpool) [9], Bellesini et al. (2020) [7] and Ferri et al. (2022) [21].




*Note:* GREEN: No expected clinically significant interaction. ORANGE: No switching a priori to another anticoagulant. In case of VKA: increase frequency of INR monitoring during and after treatment with DAA. In case of DOAC: (dabigatran, rivaroxaban, apixaban and edoxaban) monitor plasma dosage at the beginning of treatment and after 1–2 weeks. If out-of-range plasma dosage switch to VKA or LMWH consulting a cardiologist/expert in haemostasis and thrombosis. RED: Do not co-administer. Switch to another DOAC without strong (red) DDI and monitor plasma dosage, or consider VKA or LMWH.
Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

- In case of expected strong DOAC-DAA interaction (red interactions in Table 4), the DOAC should not be administered becuse of the risk of increased exposure and potential bleeding risk. It may be reasonable to switch to a DAA with comparable effectiveness but without strong interaction with DOAC, or switch to a DOAC that does not have strong DDI with the chosen DAA, monitoring plasma concentration of the anticoagulant. This may improve the patient's compliance to treatment: he or she will have to undergo only two venous draws over the entire treatment period with DAA, keeping his or her perceived quality of life unaffected.
- In case of potential DDI between DOAC and DAA (orange in Table 4), plasma level is advisable to check for safe co-administration of the drugs.

DOAC plasma dosage has to be checked at the beginning and after 1–2 weeks of coadministration of DOAC–DAA. Plasma concentrations should be measured at trough, just before the next pill intake. In case of out-of-range DOAC plasma levels (see Table 2), switching to VKA or LMWH is recommended. The choice between VKA and LMWH should be made according to the indication of anticoagulant treatment and the patient's preference, consulting an expert of thrombosis and haemostasis or cardiologist.

A recent retrospective study of 204 patients examined major bleeding (MB) and clinically relevant non major bleeding (CRNMB) rates during coadministration of DAAs and DOACs, both in non-cirrhotic and in cirrhotic patients. Sofosvubir/velpatasvir and rivaroxaban were the most prescribed DAAs and DOACs. There were 3 MB (occurred in patients > 65 years old and/or with concomitant antiplatelet drugs) and no CRNMB, with no difference in bleeding rates among patients with or without cirrhosis. The authors concluded that the DAA–DOAC combination is sufficiently safe [29]. Another observational study of 54 patients on concurrent DAA and DOAC reported no major bleeding events during the period of treatment [30]. It is relevant to remind that rivaroxaban should also not be used in patients with Child B liver cirrhosis due to a > twofold increase in drug exposure in these patients [31], while dabigatran, apixaban and edoxaban may be used with caution in this setting [32, 33].

FCSA's suggestion
In case of DOAC treatment:

- Unsafe combinations based on phase I studies or predicted pharmacokinetic interactions (indicated as red in Table 4), i.e.

  1. Dabigatran and glecaprevir/pibrentasvir via strong inhibition of P-gp [22]
  2. Dabigatran and sofosbuvir/velpatasvir/voxilaprevir via mild P-gp inhibition [20]
  3. Edoxaban and sofosbuvir/velpatasvir/voxilaprevir via inhibition of OATP1B1 by velpatasvir and voxilaprevir and via P-gp inhibition [21, 9–24]

The choice of DAA is leading, but another combination of DAA-DOAC with comparable effectiveness should be considered, if available.
When another DAA-DOAC combination is not possible, we suggest:

- To shift to another DOAC without unsafe combination, and Plasma levels of DOAC before initiation of DAA and after 1–2 weeks of treatment should be determined. In case of out-of-range DOAC plasma levels [15] switching to VKA or LMWH is recommended (choice based on the indication of treatment and the patient's preference).
- Combinations classified as requiring caution (indicated as orange in Table 4):

Switching to LMWH or to a VKA is not advisable ex ante.

We suggest considering measurement of DOAC plasma levels before initiation of DAA and after 1–2 weeks of treatment. In case of out-of-range DOAC plasma levels [15], switching to VKA or LMWH is recommended (choice based on the indication of treatment and the patient's preference).

## 4 | Parenteral Anticoagulant Drugs

### 4.1 | Heparins and Fondaparinux

Unfractionated heparin (UFH) and LMWH catalyse the inactivation of thrombin by antithrombin and of factor-Xa. They are not absorbed by oral administration and are typically administered subcutaneously or intravenously. There are no expected interactions with CYP450 or P-gp pathways [34].

Fondaparinux specifically inhibits factor Xa. It is administered subcutaneously. No in vitro interaction with CYP450 or P-gp systems was found [35].

> FCSA's suggestion
> In case of heparin treatments, there is no contraindication to co-administrate DAA and heparins or fondaparinux.

Table 3 shows the main predicted metabolic interactions between anticoagulant drugs and DAAs and Table 4 resumes our suggestions based on indications of major guidelines and online tools (EASL recommendations 2020, EHRA Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation, Liverpool HEP interactions) [1, 9, 19], which do not recommend, or suggest to use with caution, combinations with DAA.

## 5 | Antiplatelets Drugs

### 5.1 | Acetylsalicylic Acid

> FCSA's suggestion
> In case of treatment with aspirin, there is no contraindication to co-administrate DAAs.

Aspirin is an acetylated derivative of salicylic acid and belongs to the Non-Steroidal Anti-Inflammatory Drug (NSAIDs) class, exhibiting antiplatelet activity through irreversible acetylation and inhibition of the cyclooxygenase-1 (COX-1) enzyme. This action impedes the biosynthesis of thromboxane A2, a potent vasoconstrictor and platelet aggregant, thereby manifesting antithrombotic properties at low dose (75–100 mg/day). Biotransformation of ASA into salicylate occurs via esterase's in the gastrointestinal tract and liver, with negligible metabolic interactions with DAAs.

### 5.2 | P2Y12 Receptor Inhibitors

#### 5.2.1 | Clopidogrel

Clopidogrel is an oral thienopyridine agent. It is a prodrug and is converted to its active metabolite principally via CYP3A4 and CYP2C19. Clopidogrel acts as a potent inhibitor of CYP2C8.

Notably, co-administration with ritonavir, a potent inhibitor of CYP3A4, can decrease clopidogrel plasma concentration. Additionally, pharmacokinetic studies have demonstrated significant elevations in dasabuvir plasma concentrations when co-administrated with ritonavir and clopidogrel indicative of CYP2C8-mediated interaction dynamics [36].

Co-administration of clopidogrel with DAAs recommended by the most recent guidelines (and listed above) has not been studied but a clinically significant interaction is unlikely: glecaprevir/pibrentasvir and grazoprevir are only weak inhibitors of CYP3A4 and should not affect the exposure of clopidogrel in a clinically relevant extent.

#### 5.2.2 | Prasugrel

Another prodrug within the thienopyridine family, prasugrel undergoes rapid hydrolysis in the intestine to a thiolactone, which is subsequently converted to the active metabolite by CYP isoforms of CYP3A4, 2B6, 2C9 and 2C19. Nevertheless, prasugrel is less susceptible to DDIs with potent CYP3A4 inhibitors, ritonavir and cobicistat [37]. Thus, clinically significant interaction with weak inhibitors such as glecaprevir/pibrentasvir and grazoprevir is unlikely.

#### 5.2.3 | Ticlopidine

As an early member of the thienopyridine class, ticlopidine undergoes metabolic activation predominantly through CYP3A4, 2B6, and 2C19 isoforms to generate its antithrombotic active metabolite. These enzymes are not affected by sofosbuvir, velpatasvir and voxilaprevir, while glecaprevir/pibrentasvir and grazoprevir are only weak inhibitors of CYP3A4 and should not change plasma concentration of ticlopidine. Its pharmacokinetic profile suggests potential for DDIs with drugs with substantial CYP3A4 inhibitory activity.

It is critical to note that ticlopidine is generally not recommended for new patient prescriptions due to its association with severe adverse effects. These include haematological reactions such as neutropenia and thrombotic thrombocytopenic purpura.

#### 5.2.4 | Ticagrelor

Unlike thienopyridines, ticagrelor is a direct-acting, reversible P2Y12 receptor antagonist that does not require metabolic activation. It has a narrow therapeutic index. As a substrate of CYP3A4 and P-gp ticagrelor's pharmacokinetics can be significantly affected by CYP3A4 inhibitors, such as ritonavir and ketoconazole, leading to increased systemic exposure and heightened bleeding risk due to elevated plasma concentrations of ticagrelor and its active metabolite [38]. Its concentration may increase because of inhibition of P-gp by velpatasvir, voxilaprevir, glecaprevir, pibrentasvir and elbasvir and of weak inhibition of CYP3A4 by glecaprevir/pibrentasvir and grazoprevir. There are no studies available about co-administration of these drugs and the clinical relevance of these DDIs is unknown, but caution is required especially in patients with high haemorrhagic risk.

**TABLE 5** | Schematic representation of FCSA suggestions for antiplatelets drugs. Adapted from EASL 2020 [1], https://www.hep-druginteractions.org (University of Liverpool) [9] and Canonico et al. (2022) [6].

| | Sofosbuvir/ velpatasvir | Glecaprevir/ Pibrentasvir | Grazoprevir/ elbasvir | Sofosbuvir/velpatasvir/ voxilaprevir |
|---|---|---|---|---|
| Aspirin | | | | |
| Clopidogrel | | | | |
| Prasugrel | | | | |
| Ticlopidine | | | | |
| Ticagrelor | | | | |

*Note:* GREEN: No expected clinically significant interaction. ORANGE: No switching a priori to another antiplatelet drug. Consider transition to clopidogrel if elevated haemorrhagic risk (consulting a cardiologist).

**TABLE 6** | Expected interactions between antiplatelet drugs and DAAs. Adapted from EASL 2020 [1], https://www.hep-druginteractions.org (University of Liverpool) [9] and Canonico et al. (2022) [6].

| | | Sofosbuvir/ velpatasvir | Glecaprevir/ pibrentasvir | Grazoprevir/elbasvir | Sofosbuvir/ velpatasvir/ voxilaprevir |
|---|---|---|---|---|---|
| Aspirin | Not substrate of CYP450 or P-gp | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] |
| Clopidogrel | CYP3A4 and CYP2C19 substrate. CYP2C8 inhibition | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] |
| Prasugrel | CYP3A4 and CYP2B6 substrate | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] |
| Ticlopidine | CYP3A4 substrate | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] | No expected interactions[a] |
| Ticagrelor | P-gp and CYP3A4 substrate | Probable increased ticagrelor concentration by mild P-gp inhibition by velpatasvir[a] | Probable increased ticagrelor concentration by weak CYP3A4 inhibition and P-gp inhibition[a] | Probable increased ticagrelor concentration by weak CYP3A4 inhibition by grazoprevir and mild P-gp inhibition by elbasvir: unknown clinical significance[a] | Probable increased ticagrelor concentration due to P-gp inhibition by velpatasvir and voxilaprevir[a] |

Abbreviations: BCRP, breast cancer resistance protein; CYP450, cytochrome P450; OATP organic anion-transporting polypeptide; P-gp, P-glycoprotein.
[a]Co-administration has not been studied.

### 5.3 | Others

Very few data are available on other antiplatelets drugs.

FCSA's suggestion
In case of treatment with P2Y12 receptor inhibitors:

- Combinations classified as requiring caution (indicated as orange in Table 5):

Pre-emptive switching from ticagrelor therapy to another antiplatelet drug is not recommended. It is advised to assess the patient's haemorrhagic risk profile. In instances of elevated haemorrhagic risk (e.g. concurrent anticoagulant therapy, moderate to severe thrombocytopenia or dual antiplatelet therapy), a transition to clopidogrel therapy may be considered, in accordance with the cardiologist.

Table 6 shows the main metabolic interactions between antiplatelets drugs and DAAs and Table 5 summarises indications of major guidelines and online tools (EASL recommendations 2020, Liverpool HEP interactions) [1, 6, 9], along with our suggestions.

#### Author Contributions

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#### Conflicts of Interest

Elisabetta Tombolini, Gian Marco Podda and Daniela Poli have no competing interests to declare that are relevant to the content of this article. Alessandro Squizzato had honoraria for lectures and/or participation on advisory board from Daiichi-Sankyo, Bayer, Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi, Techdow,

Werfen, Alexion, Roche and Viatris. Alessio Aghemo had payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, MSD, Gilead, Ipsen and participation on a Data Safety Monitoring Board or Advisory Board from Abbvie, Gilead, Ipsen. Nicola Ferri had payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer and consulting fees from Daiichi-Sankyo. Simone Segato had payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events and support for attending meetings from Gilead. Marco Paolo Donadini had grants or contracts from Italian Ministry of Health (outside the submitted work; payment made to institution) and participation on a Data Safety Monitoring Board or Advisory Board from PlasFree (outside the submitted work).

## Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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