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► To cite this version:

Victor Margelidon-Cozzolino, Xavier Delavenne, Judith Catella-Chatron, Elodie de Magalhaes, Souad Bezzeghoud, et al.. Indications and potential pitfalls of anticoagulants in pulmonary hypertension: Would DOACs become a better option than VKAs?. *Blood Reviews*, 2019, 37, pp.100579 - 10.1016/j.blre.2019.05.003 . hal-03487652

HAL Id: hal-03487652

<https://hal.science/hal-03487652>

Submitted on 20 Dec 2021

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Indications and potential pitfalls of anticoagulants in pulmonary hypertension: would DOACs become a better option than VKAs ?

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Abstract

Pulmonary hypertension (PH) comprises a cluster of severe conditions characterized by elevated mean pulmonary arterial pressure. While targeted therapies have been approved over the last twenty years for pulmonary arterial hypertension (PAH) and chronic-thromboembolic PH (CTEPH), the possible role of anticoagulant therapy as a supportive treatment of PH is still debated. In PAH, anticoagulant use remains frequent, although evidence appear to be poor (recommendation class IIb-C in international guidelines). In CTEPH treatment, anticoagulants are highly recommended, because it often involves thrombosis (recommendation class I-C in international guidelines). Historically, PH patients have been treated with vitamin K antagonists (VKA), which are the only available oral anticoagulants. In this context, risk/benefit ratio of VKA is affected by the risk of major bleeding events. This drawback could be mitigated with direct oral anticoagulants (DOACs): in addition to being less constraining for patients, DOACs have shown a lower risk of major bleeding events in their already approved indications (venous thromboembolism, atrial fibrillation). However, DOACs have never been specifically assessed in PAH and CTEPH patients. Bioaccumulation risk should be considered if DOACs are prescribed in PAH and CTEPH patients, especially the risk of drug-drug interaction mediated by P-glycoprotein and cytochrome 3A4 with targeted therapies.

Keywords: pulmonary hypertension; anticoagulants; direct oral anticoagulants; drug-drug interactions.

Abbreviations list

AF: Atrial Fibrillation

DOACs: Direct Oral Anticoagulants

CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension

INR: International Normalized Ratio

ISTH: International Society of Thrombosis and Haemostasis

P450 CYP3A4: Hepatic cytochrome 3A4

PAH: Pulmonary Arterial Hypertension

P-gp: P-glycoprotein

PH: Pulmonary Hypertension

TTR: Time in Therapeutic Range

VKA: Vitamin K Antagonists

VTE: Venous ThromboEmbolism

1. **Introduction**

Pulmonary hypertension (PH) is a severe condition which can lead to right heart failure and death. It is defined by elevated pulmonary arterial pressure (mean arterial pulmonary pressure ≥ 25 mmHg) measured during right heart catheterization [1]. It encompasses different diseases classified into five groups, each one characterized by common pathological, pathophysiological and clinical features (Table 1) [2]. Pre-capillary PH includes all causes of PH except those associated with left heart diseases (group 2). The estimated global prevalence of PH is about 0.3% [3,4]. Pulmonary arterial hypertension (PAH) (group 1) is considered as a rare disease, with an approximate prevalence of 15/100000 [5].

Pre-capillary PH pathophysiology mechanisms include pulmonary endothelial dysfunction, pulmonary artery smooth muscle cell proliferation, both resulting in remodeling of pulmonary arteries, vasoreactivity regulation abnormalities, and thrombotic phenomena in pulmonary arterial vessels, subsequent to inappropriate activation of coagulation [6].

In the past decade, patients from two specific groups (PAH and chronic thromboembolic pulmonary hypertension) have benefited from significant advances. Targeted therapies have been developed for patients with PAH [7]. These treatments target the three main pathways involved in the development of PH: endothelin, NO and prostacyclin [7]. These therapies have been specifically evaluated in dedicated high quality trials, and have demonstrated an improvement in short-term exercise capacity (6 minutes walking test) for all of them, and a decrease in the risk of clinical worsening for some combination therapies [8]. Among these drugs, one (riociguat) has also been approved for patients with chronic thromboembolic pulmonary hypertension (CTEPH) [9], a specific cause of PH, which can be treated by surgery (endarterectomy) [1]. Besides targeted therapies, patients with PAH or CTEPH receive supportive therapy [1], including diuretics and oral anticoagulants (mainly warfarin). Warfarin is currently being replaced by direct oral anticoagulants (DOACs) in atrial

fibrillation (AF) and venous thromboembolism (VTE), mostly because of their simplicity of use and because of their better safety profile [10]. This safer profile is based on lower risk of major (including fatal) bleeding [11], but their benefit/risk ratio may be altered by drug-drug interactions and PH comorbidities [12].

Some patients with PAH and CTEPH may now receive DOACs, whether for an approved associated indication (AF, VTE) or for PH (in an off-label way for PAH) [13]. A recent study has even shown that more than half of patients with CTEPH now receive DOACs in Germany [14]. However, the safety profile of DOACs in PH patients is currently unclear. In this comprehensive review, we discuss the role of anticoagulant therapy in patients with PAH and CTEPH, and the potential pitfalls of DOAC prescription in these frail patients.

2 Anticoagulant therapy in patients with PAH and CTEPH

2.1 Early rationale for anticoagulant therapy in PAH and CTEPH

Before the era of PH targeted therapy, vitamin-K antagonists (VKA) (mainly warfarin) were widely prescribed as a supportive treatment in patients with PAH, in combination with diuretics and oxygen [15]. This prescription was supported by both pathological data obtained in the 1980's, describing thrombotic lesions in the pulmonary arteries [16], and by biological studies [6,17]. Particularly, resistance to fibrinolysis has been found both in CTEPH and PAH patients [6].

Higher survival in PAH patients receiving VKA was first reported by Fuster et al. in a retrospective cohort study, and further by a prospective clinical trial which assessed the effect of calcium-channel blockers [18]. However, this trial was not designed to assess the effects of warfarin treatment on survival (clinicians were free to prescribe warfarin or not).

2.2 Evolution of anticoagulant prescription in PAH

As a consequence of these early findings, anticoagulant prescription remained widespread in PAH patients, as long as specific treatments had not yet appeared: data obtained from clinical registries in the middle of the 2000's indicates that the vast majority of PAH patients were receiving warfarin (90% of the patients included in the French registry [19]).

With the rise of properly evaluated targeted therapies, the frequency of anticoagulant treatment has simultaneously declined from 90% to 60% in the PAH patients from the COMPERA and REVEAL registries [20,21], and to 50% in recent trials [22]. Currently, anticoagulant therapy remains widely used in PAH, although its efficacy has not been clearly demonstrated, as highlighted by its low grade of recommendation based on poor level of evidence (IIb-C in the European recommendations, which state that oral anticoagulants “may be considered” in the treatment of idiopathic and heritable PAH and PAH due to anorexigens, but are not formally recommended) [1].

In contrast, life-long anticoagulant therapy is recommended (recommendation grade I-C, meaning that oral anticoagulation is formally recommended, though the level of evidence is weak in the literature) in patients with CTEPH [1]. This discrepancy is obviously due to the fact that anticoagulant therapy is mandatory for patients with CTEPH, because of their history of VTE. Indeed, in CTEPH, anticoagulant therapy is given because it is thought to prevent the recurrence of venous thromboembolism, whereas its impact on CTEPH progression itself is unknown [23].

2.3 Contrasting evidence for anticoagulation benefit in PAH

However, the risk/benefit ratio of anticoagulant therapy primarily depends on the indication. Outside the field of PH, anticoagulant treatments are associated with a marked

reduction of mortality when compared to placebo in approved indications such as AF [24] and VTE [25]. This important issue is a major confounding factor [26] affecting the most recent research evaluating the efficacy of anticoagulant therapy in PH patients [21,27].

In the absence of randomized controlled trials, the impact of anticoagulant therapy on the prognosis of PAH patients has been recently assessed with data collected from clinical registries [21,27]. The COMPERA registry assessed the survival of European patients with newly diagnosed PH, in relation to the use of anticoagulation [21]. Among 1,283 PAH patients, 738 (58%) received anticoagulation (VKA for 93% of them). The use of anticoagulant therapy was associated with a better three-year survival in patients with PAH, except in those with PAH associated to scleroderma. Of note, the results were confirmed in patients with idiopathic PAH, in a match-pair analysis built with a propensity score. The role of important confounding factors in these last results remains unclear, like the presence of comorbidities that could have directly influenced the anticoagulation prescription, and an “immortal time” bias (patients were classified in the anticoagulation group whatever the time of initiation and/or the duration of anticoagulant treatment).

On the other hand, the REVEAL registry did not find any survival benefit of anticoagulant therapy in their dataset of US patients [27]. The study design differs from the COMPERA study. Incident and prevalent PAH patients were included if they were not under anticoagulant therapy at enrollment in the REVEAL registry. Patients who received anticoagulant during follow-up (n=187) were compared with matched-pairs. Of note, long-term adherence to anticoagulant treatment was poor in this study, as about two thirds of idiopathic PAH patients who had received warfarine were no more treated with anticoagulant at the last assessment visit. This could account for the negative results for the three-year survival between the groups. A higher mortality seemed to be associated with anticoagulation in scleroderma-associated PAH, but this was not confirmed after adjustment on PH severity.

Hence, there is contrasting evidence about the potential benefit of anticoagulant therapy in patients with PAH, particularly in those with no-scleroderma PAH. Unfortunately, the information regarding the presence or absence of another indication (besides PAH) of anticoagulant therapy was unavailable in these two retrospective studies. Recently, Gabriel et al. found that one in two patients receiving anticoagulant therapy had an approved indication (ie AF or VTE merely), in a retrospective multicenter study of 366 PH patients [13]. A randomized controlled trial is needed to assess the impact of anticoagulant therapy on the prognosis of patients with PAH, but without any other indication of anticoagulant therapy.

2.4 Bleeding risk associated with anticoagulation in PH

While expecting the results of a trial evaluating the anticoagulant strategies in patients with PH, one has to remember that the major drawback of anticoagulant therapy is bleeding. Paradoxically, there is even less information on anticoagulant safety in patients with PH. In a retrospective monocentric study of 218 patients under VKA, Henkens et al. evaluated the rate of major bleeding (according to the ISTH definition) in patients with distinct sub-groups of PH [28]. They found that major bleeding risk differs according to the sub-group of PH, with a bleeding rate increasing from 2.4; 5.4 and 19 per 100 patient-years in patients with CTEPH, idiopathic PAH and PAH related to scleroderma, respectively. Hence, bleeding risk related to anticoagulation seem to be lower in CTEPH patients. Most of these major bleedings were gastro-intestinal bleedings. Of note, these results may be hampered by a center bias (for example: the INR target were higher than usual), and by its retrospective design. The relative young age of the patients included in this study, compared to the higher age of patients in main registries and cohorts, may also account for an important confusion bias, as bleeding risk increases with age [29]. Roldan et al confirmed these results in a bicentric retrospective cohort of PAH patients: the global incidence rate for major bleeding was 4.7 per 100 patients-

years (5.0 per 100 patients-years for idiopathic PAH patients). The excess of major bleeding events in patients with PAH associated with connective tissue diseases was not confirmed (incidence rate = 6.3 per 100 patients-years). The major bleeding hazard ratio was 2.7 ($p=0.036$) for anticoagulated PAH patients versus PAH control patients. Interestingly, HAS-BLED equal or superior to 3, history of prior bleeding, poor anticoagulation control, number of concomitant medications were associated with an increased risk of major bleeding [30]. Like Henkens' study, Roldan's work may be biased by retrospective design. One prospective multicenter cohort is on-going (NCT02800941) [31].

Moreover, the risk/benefit ratio of VKA highly depends on the quality of anticoagulation, which is usually assessed by the time in the therapeutic range (TTR). In a retrospective bicentric analysis, Roldan et al. found that anticoagulation control was poor in a cohort of 121 patients with PAH [30]. The mean TTR was 57%. Receiving a combination therapy for PAH was associated with a poorer control in the anticoagulant therapy (effect on TTR: -11.6 (-20.1 to -3.0), $p=0.009$).

Added to the control of anticoagulant therapy, the therapeutic target of anticoagulation itself may influence the risk/benefit ratio and the impact of anticoagulation on the prognosis of PH patients. In Henkens et al.'s study, the subgroup of patients with PAH related to scleroderma was that with both the highest number of reported bleeding events and the highest number of patients with unusually high INR targets (3.0 to 4.0 versus 2.5 to 3.5 for the majority of the patients) [28]. A trend towards more major bleedings in anticoagulated PAH patients with a targeted INR higher than 2.5 was reported by Roldan et al.

2.5 Which therapeutic range for VKA in PH?

The therapeutic target for VKA therapy in CTEPH (INR between 2 and 3) has been extrapolated from VTE studies. The INR range to reach is still unclear in PAH. The latest

European guidelines do not mention a specific target, while 2009 American guidelines recommend an INR target between 1.5 and 2 [32]. The expected benefit of low-intensity VKA is to decrease the risk of bleeding without losing too much anticoagulant effect. Data supporting this hypothesis is scarce. Jansa and colleagues assessed low-intensity warfarin anticoagulation in idiopathic PAH patients, correlating INR with biological thrombin generation parameters: INR between 1.5 and 2.5 was enough to obtain effective anticoagulation [33]. No correlation with clinical event (including bleeding) was provided. Of note, previous studies failed to demonstrate a better safety profile of low-intensity VKA in the long-term prevention of recurrent venous thromboembolism [34]. This may be explained by the variability of VKA effect.

3 Pharmacological pitfalls of DOACs use in patients treated for PH

3.1 Advantages of DOAC use for anticoagulation in PH patients

The recent development of direct oral anticoagulants (DOACs) could represent an interesting alternative to VKA in the field of anticoagulation in PH. DOACs are oral anticoagulants which specifically target whether activated-factor II (“-gatrans”) or activated-factor X (“-xabans”) [11]. They are currently substituted to VKA in their approved indications (AF, VTE)[10]. This trend may be related to their simplicity of use and a lower bleeding risk than VKA, particularly in patients with a low TTR [35]. Indeed, major randomized controlled studies which have assessed clinical efficacy of DOACs against VKA found no higher numbers of, or significantly lower numbers of major bleedings (especially intracranial bleedings) associated with DOAC prescription in VTE treatment and systemic embolism prevention in AF [36–39]. Additionally, the more stable and predictable pharmacokinetics and anticoagulant effect of DOACs allow prescription of regular doses and make biological monitoring (such as INR with VKA) unnecessary [11]. Pre-clinical data suggest that

Rivaroxaban may protect from the development of PH in animal models [40]. As a consequence, the use of DOACs would be less constraining than VKA which are currently prescribed in PH patients, may allow to decrease the frequency of hemorrhagic complications associated with anticoagulant therapy, and may have a specific role in the natural history of PH by decreasing the in-situ thrombosis process.

3.2 DOAC safety in PH

However, DOAC safety in PH patients is unclear. DOACs have not been evaluated in the context of PH and the favorable risk/benefit ratio found in AF and VTE patients may be compromised by several pitfalls [29].

First, DOACs are available at several dosages, each of them having been evaluated for the distinct risk periods in VTE [12]: a higher dose for the initial therapy (for rivaroxaban and apixaban), a regular dose for the maintenance therapy, and a reduced dosage for the extension therapy (for rivaroxaban and apixaban). The efficacy of reduced dose to protect patients at high risk for recurrent VTE is currently under investigation (NCT03285438) [41]. It is unclear whether reduced dosage is efficient in patients with PH.

Interestingly, DOACs pharmacology is characterized by a bioaccumulation risk, risk associated to conditions which have been excluded from most of AF and VTE trials. This bioaccumulation may lead to overdose and subsequently to increased bleeding risk [12,42]. Bleeding risk is an important issue, as the management strategies of DOAC-associated bleedings are still not fully consensual [43]. Main bioaccumulation risk factors are low weight (inferior to 60 kg), kidney or liver impairment, and drug-drug interactions.

3.3 Bioaccumulation risk and comorbidities

Renal failure is a frequent comorbidity in severe PH (about one in four patients [13]) as it is a consequence of PH-associated right ventricular failure and low cardiac output, resulting

in low renal perfusion. In such patients, renal failure can be a limiting factor to DOAC prescription (contraindication if creatinine clearance $<30 \text{ mL}\cdot\text{min}^{-1}$). Renal elimination importance in total drug elimination is highly prominent for dabigatran, whereas less important for anti-Xa DOACs [12]. Promising data have been published about apixaban used for atrial fibrillation, in patients with end-stage renal disease[44].

Liver impairment can commonly be associated with PH as a complication of right heart failure. Moderate (Child-Pugh Score B) liver impairment can increase rivaroxaban exposure while severe liver impairment is a formal contraindication [11]. Of note, severe chronic liver impairment is rare in patients with PH, and it is mainly concentrated in patients with porto-pulmonary hypertension, a setting in which anticoagulation is not recommended because of high bleeding risk [1].

Beside the presence of chronic renal and/or hepatic impairment in patients with stable PAH or CTEPH, patients may experiment acute worsening of PH, leading to a worsening of renal and/or hepatic impairments [45]. No clinical trial has evaluated such situation for PAH or CTEPH patients. We suggest to extrapolate from recent experience in the ICU setting [46], and then to withhold temporarily DOACs in patients with acute heart failure.

3.4 Drug-drug interactions

Among bioaccumulation risk factors, only drug-drug interactions appear to be a controllable risk factor. DOACs susceptibility to drug-drug interactions is mainly represented by pharmacokinetic drug-drug interactions (Table 2). These interactions are strongly linked to two molecular phenomena involved in DOAC pharmacokinetics: drug transport and drug hepatic metabolism [11,12].

All DOACs are substrates of ATP-binding cassette drug transporters (ABC drug transporter family) and more specifically of P-glycoprotein (also known as P-gp or ABCB1).

Apixaban and rivaroxaban are also substrates of ABC drug transporter Breast Cancer Resistance Protein (BCRP or ABCG2). As efflux transporters, P-gp and BCRP are involved in protecting the human body from xenobiotics (such as drugs): they are notably expressed in the membrane of small intestine, kidney and liver epithelial cells, where they limit drug absorption by the digestive tract and enhance drug elimination into bile and urine. As a consequence, efflux transporters can alter drug bioavailability and are major determinants of pharmacokinetic variability and drug-drug interaction.

P-gp plays a central role in DOAC pharmacokinetics. P-gp is particularly expressed at the apical side of enterocytes [47–49]. DOAC intestinal absorption is affected by P-gp efflux, since a part of intracellular DOAC amount which has passed through intestinal barrier is transported back out of enterocytes and is not eventually absorbed (Figure 1). DOAC efflux and resulting total absorbed fraction of DOAC can be modified by drug-drug interaction. P-gp inhibitor drugs can decrease DOAC efflux (Figure 1). Subsequently, if a P-gp inhibitor drug is administered simultaneously with DOACs, this drug-drug interaction can lead to increased DOAC absorbed fraction and increased bioavailability [42]. The same type of mechanism can be applied to DOAC renal elimination, since P-gp is also expressed in kidneys.

Additionally, Anti-Xa DOACs are liver P450 CYP3A4 cytochrome substrates. This common hepatic metabolism enzyme can be targeted by CYP3A4 inhibitor (which are often the same as P-gp inhibitor drugs) or inducer drugs. CYP3A4 inhibition leads to reduced DOAC metabolism and increased bioavailability [11,12]. Increased bioavailability (by P-gp and/or CYP 3A4 inhibitions) may subsequently increase bleeding risk.

3.5 Drug-drug interaction risk with targeted therapies in PH patients

Drug-drug interactions rise as an important issue for PH patients who may be candidates for DOAC administration (12%) [13]. Besides anticoagulant therapy, targeted PH therapies are noticeable providers of drug-drug interaction. Drug-drug interactions have been reported

between targeted therapies themselves (Bosentan and Sildenafil, for example), but also with commonly prescribed drugs, including VKA [50–54].

There is no specific available data about direct risks of drug-drug interaction between DOACs and PH targeted therapies, but some indirect data seems to indicate that it may be an important issue. Type 5 phosphodiesterase inhibitors (PDE5i) (sildenafil, tadalafil and vardenafil) are PH targeted therapies which have been shown to be *in vitro* P-gp inhibitors [55,56]. Interestingly, recent studies clearly demonstrated inhibition of P-gp-mediated DOAC efflux by PDE5i in an *in vitro* model of drug-drug interaction assessment [57]. Other targeted therapies, such as prostanoid receptor agonist selexipag, guanylate cyclase stimulator riociguat, and endothelin receptor antagonist ambrisentan are known as P-gp substrates, which means they could act as competitive P-gp inhibitors towards DOACs [58–61].

As for metabolism inhibition, PDE5i are CYP3A4 inhibitors as well, while riociguat, selexipag, endothelin receptor antagonist macitentan are CYP3A4 substrates and could similarly be competitive CYP3A4 inhibitors towards DOACs [62,63]. Endothelin receptor antagonist bosentan is a well-known CYP3A4 inducer [64].

Calcium channel blockers, which are given as a treatment of specific forms of vasoreactive PAH, are also P-gp and CYP3A4 substrates and are known P-gp and CYP3A4 inhibitors. This seems to be quite relevant, as it has been shown that calcium channel blockers could increase DOAC disposition and bleeding risk in patients treated with DOACs [65–68]. A dose reduction is mandatory for some DOACs in patients receiving concomitant calcium channel blockers.

To date, drug-drug interaction risk between DOACs and targeted therapy has not been properly investigated, but these data from literature suggest at least they could exist. PH patients frequently receive several simultaneous targeted therapies [8] and this could increase drug-drug interaction sources. These interactions could deeply affect the risk/benefit ratio of

DOACs in PH patients by modifying DOAC disposition. However, a recent clinical pharmacokinetic study found no relevant drug-drug interaction between rivaroxaban and macitentan, suggesting that some DOAC/PAH treatment combinations are probably safe [69].

3.6 A potential control of bioaccumulation risk

In order to control the potential increased risk of bleeding linked to bioaccumulation, investigators used an *a priori* reduced dosage of the last evaluated DOAC (edoxaban) in patients enrolled in the ENGAGE (for AF) and HOKUSAI (for VTE) trials with bioaccumulation factors [70,71]. Interestingly, this reduced dosage in the population at risk of bioaccumulation was associated with better safety, without any loss of efficacy, when compared to VKA. Consequently, it appears that a reduced dosage may be needed in patients with bioaccumulation factors, in order to maintain a similar risk/benefit ratio in patients without any of these risk factors. It was recently found that about half of the PH patients has at least one major risk factors for DOAC bioaccumulation among renal failure, low weight and known drug-drug interactions [13].

4 Future considerations

Anticoagulation in PH patients remains a challenging issue. While anticoagulation benefit in these patients is still questioned, DOACs could bring a new perspective in the field of anticoagulation in PH. DOACs may be easier to use than VKA, and may potentially involve a lower bleeding risk, because of the low TTR obtained in patients treated with VKA. This must be balanced against a specific potential drug-drug interaction risk with PH targeted therapies, which could lead to an increased bleeding risk and compromise DOACs safety in this context. P-gp and P450 CYP3A4 inhibition seems to be likely mechanisms involved in these interactions. More specific data is needed on this topic to investigate DOACs and PH

targeted therapies drug-drug interaction relevance, both with *in vitro* models of drug transport and metabolism, and clinical pharmacokinetic studies. These investigations could allow to choose the DOACs/targeted therapies associations with the least interaction risk and to anticipate dose adaptation. Future investigations are also needed in order to build dedicated randomized controlled trials assessing DOACs in the field of PAH and CTEPH, as currently assessed in an Australian study comparing a reduced dosage of apixaban versus placebo in scleroderma-associated PAH [72].

5 Practice Points

- In PAH, anticoagulant therapy can be prescribed as a supportive treatment (iPAH) or for co-existing frequent comorbidities (AF, VTE)
- In CTEPH, anticoagulant therapy is mandatory and is a cornerstone of the treatment.
- The major drawback of anticoagulation in this context is bleeding risk.
- VKAs are the only oral anticoagulants which have been studied in the context of PH.
- DOACs have not been investigated in the specific context of PH, but can already be prescribed in patients with PH and other indications (VTE, AF). They are easier to use, but specific attention should be paid to bioaccumulation risk factors, which are frequent in PH patients (renal or liver failure, drug-drug interactions).

6 Research Agenda

- Determining bleeding risk according to anticoagulant treatment class in prospective trials
- Conducting RCTs comparing effects of anticoagulants versus placebo on survival and hemodynamics, and of VKAs versus DOACs

- Obtaining more information on drug-drug interaction risk between DOACs and PH treatments
- Building dose adaptation models for DOACs for patients with bioaccumulation risk.

Acknowledgements

Financial support: This work was supported by La Fondation du Souffle (FdS); and Le Fonds de Recherche en Santé Respiratoire (FRSR).

The authors warmly thank Mr Anthony Saber (Newmed agency) for English revision.

Conflict of interest statements

V. Margelidon–Cozzolino reports grants from Actelion, outside the submitted work.

X. Delavenne reports no relevant conflict of interest.

J. Catella-Chatron reports invitations to symposia and congress by BMS, Pfizer, Actelion, Léo-Pharma, outside the submitted work.

E. De Magalhaes reports invitations to symposia and congress by Léo Pharma, Actélion, Bayer, BMS Pfizer, Boehringer Ingelheim, outside the submitted work.

S. Bezzeghoud reports no relevant conflict of interest

M. Humbert reports personal fees from Actelion, grants and personal fees from Bayer, grants and personal fees from GSK, personal fees from Merck, personal fees from United Therapeutics, outside the submitted work.

D. Montani reports grants and personal fees from Actelion, grants and personal fees from Bayer, personal fees from GSK, personal fees from MSD, personal fees from Pfizer, outside the submitted work.

L. Bertoletti reports grants and personal fees from Actelion, grants and personal fees from Bayer, grant and personal fees from MSD, grant and personal fees from Pfizer, outside the submitted work.

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Tables

Table 1: Classification of pulmonary hypertension sub-groups according to etiology.

Pulmonary hypertension classification	
Group 1: Pulmonary Arterial Hypertension	Idiopathic, Heritable (BMPR2, ALK1, endoglin mutations), Drug- or toxic-induced, Connective tissue diseases, HIV, Portal Hypertension, Congenital Heart Disease
Group 2: Left Heart Diseases	Systolic dysfunction, Diastolic dysfunction, Valvular disease
Group 3	Hypoxemia and/or Chronic Lung Diseases
Group 4	Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
Group 5	Unclear mechanisms, Multifactorial mechanisms.

Table 2: DOAC bioaccumulation factors: mechanisms, triggers.

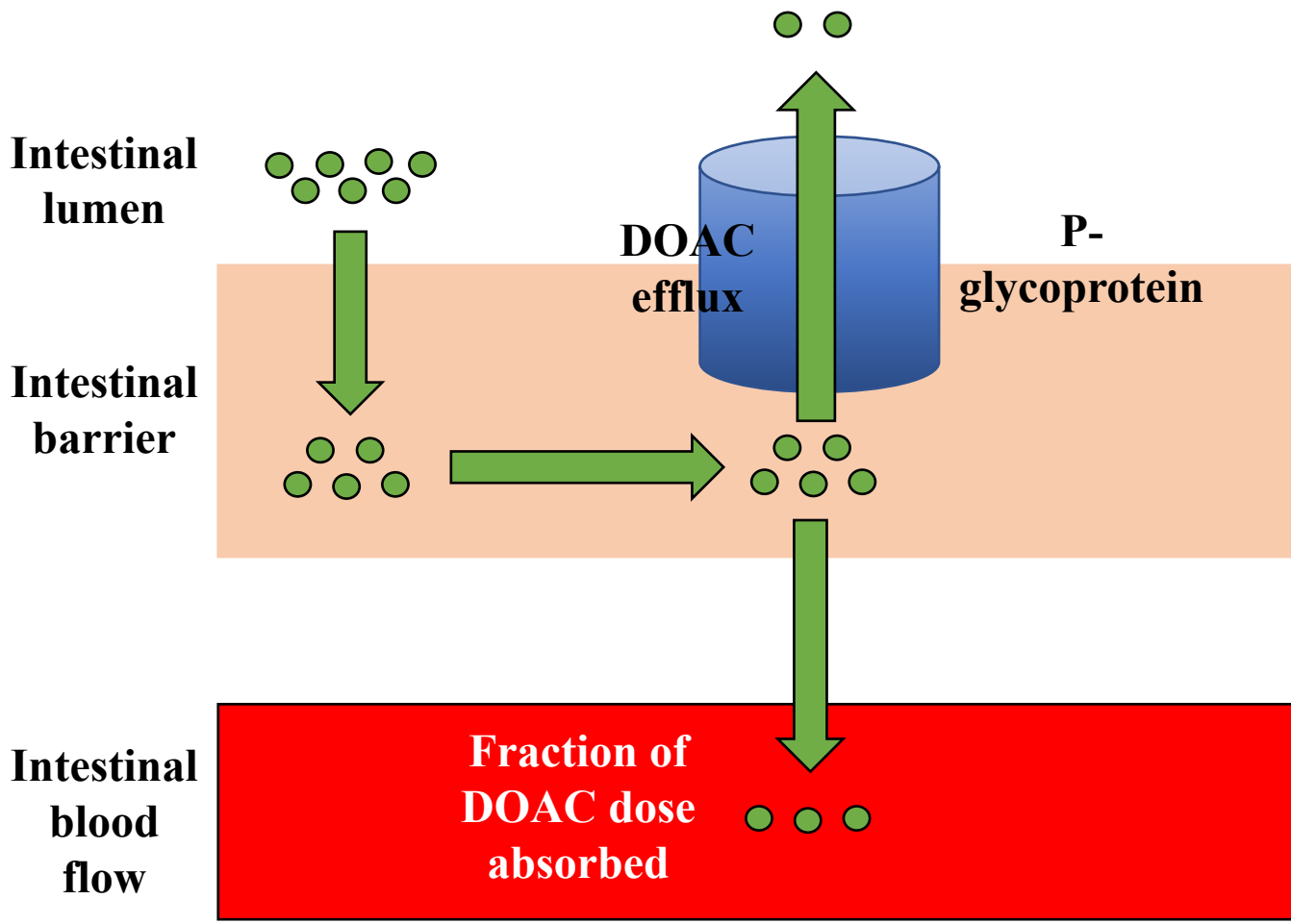
Molecule	Risk	Mechanism	Trigger
<u>Anti-Xa:</u> Rivaroxaban Apixaban Edoxaban	bioaccumulation	P-gp inhibition	Tacrolimus, amiodarone, pantoprazole.
		CYP3A4 inhibition (except for dabigatran)	grapefruit juice, erythromycin, diltiazem, cimetidine, ciprofloxacin, fluvoxamine
<u>Anti-IIa:</u> Dabigatran		Combined CYP3A4 AND P-gp inhibition (except for dabigatran)	Cyclosporine, verapamil, azole antifungals (ketoconazole, itraconazole...), protease inhibitors (ritonavir), clarithromycin
		Liver failure	Decompensated PH, chronic right heart failure, drug-induced hepatitis (endothelin receptor antagonists)
		Renal failure	Right heart failure, low cardiac output, nephrotoxic immunosuppressive therapy (tacrolimus, cyclosporine), diuretics (furosemide).
		Weight <60 kg	
	underdose	CYP3A4 induction (except for dabigatran)	Bosentan, Rifampicine, carbamazepine, St John's wort, pantoprazole.

Drugs in bold letters are frequently prescribed in patients with PH¹⁴.

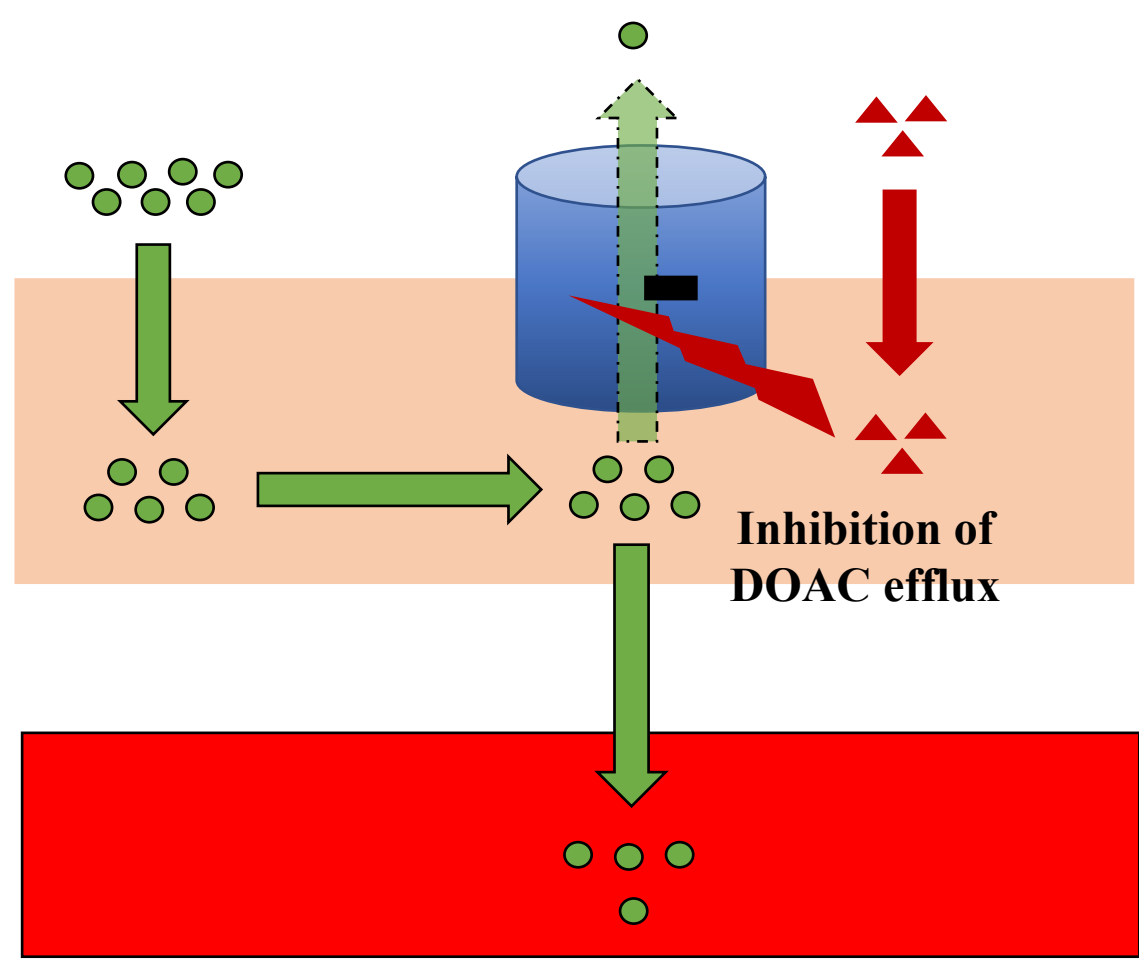
Figure legends

Figure 1



The role of P-glycoprotein in drug-drug interactions involving DOAC intestinal absorption. *On the left, the baseline process of DOAC intestinal absorption is represented. On the right, changes in DOAC absorption when coadministered with type 5 phosphodiesterase inhibitors (PDE5i). DOACs are figured with green circles, PDE5i with red triangles.*



DOAC intestinal absorption without P-glycoprotein inhibitor



DOAC intestinal absorption with P-glycoprotein inhibitor

	DOAC
	PDE5i