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REVIEW

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The impact of advanced age on anticoagulant therapy for acute venous thromboembolism

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ABSTRACT

Introduction: Management of venous thromboembolic events (VTE) has been completely changed after the introduction of direct oral anticoagulants (DOAC). VTE is common in the geriatric population, but the management of DOACs remains complex because of the lack of specific data in this poly-medicated fragile population.

An exhaustive search of anticoagulants in the indication of VTE was performed on PubMed, including data from clinical trials, observational studies, real-world data, drug-drug interaction studies, as well as various guidelines from scientific societies.

Areas covered: The present review aims to summarize our current knowledge on the era of DOACs in the management of VTE in the elderly. This involves learning the pharmacokinetics/pharmacodynamics of drugs specific to geriatrics, the problem of drug-drug interactions, and the main randomized clinical trials validating the use of DOACs.

Expert opinion: DOACs have become an essential part of the management of VTE in the elderly, both for their efficacy and safety. However, we are faced with a list of unmet needs, such as the relevance of DOACs in the very elderly, cancer patients, and those with renal impairment. Clinicians and pharmacists must remain cautious about comedications, as well as about the patient's comorbidities.

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Elderly; venous thromboembolism; direct oral anticoagulant; pharmacokinetic; pharmacodynamic; drug-drug interactions; geriatric issues

1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is very common in the elderly population. This population has a significantly increased risk of VTE, with an increase in incidence with age [1,2]. The annual incidences is ranging from 0.75 to 2.69 per 1000 individuals in the world population and increase to between 2 and 7 per 1000 among those aged over 70 years of age [3]. Notably, increased age seems to be associated with a particularly increase in the risk of pulmonary embolism (PE) rather than deep venous thrombosis (DVT), PE being associated with the higher mortality [2].

VTE is associated with an increased risk of mortality, as well as thrombo-embolic complications such as post-thrombotic syndrome, organ failure (heart failure, chronic thromboembolic pulmonary hypertension) [4]. Older adults, due to their comorbidities, requiring multidisciplinary management, may encounter difficulties in diagnosing but also in treating VTE. Age over 75 years is an independent risk factor for major bleeding [5–8]. It is thus a major issue in the management of these patients, both in the prevention of thromboembolic risk and in the curative treatment of these events.

Anticoagulation is the cornerstone therapy for VTE. Direct oral anticoagulants (DOACs), including apixaban, rivaroxaban, dabigatran and edoxaban, have replaced vitamin K antagonists (VKAs) in recent years particularly because of their ease of use (no biological monitoring, no need for bridging with heparins/VKA relay, and reduction of major bleeding). The management of VTE (both primary and secondary prevention), and of anticoagulants has many particularities and may differs according to patient characteristics. The last few years have been rich in new recommendations by scientific societies regarding the management of VTE [9–12]. But, elderly patients, patients with frequent comorbidities (such as renal failure), patients with co-medications (such as P-gp inhibitors), and subjects with any condition that (in the judgment of the investigator) would place the subject at increased risk of harm if he or she participated in the study, were often excluded from trials. However, the questions surrounding the management of VTE are sometimes unclear and unanswered, in the elderly, especially on the safety of DOACs, given that the average age of patients in the four large Phase 3 trials is less than 60 years, yet the majority of VTEs occur in the elderly.

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Article highlights

- Aging has a major impact on drug pharmacokinetics affecting the pharmacodynamic properties of direct oral anticoagulants.
- Direct oral anticoagulants' (DOAC) efficacy and safety (in the treatment of VTE), may be strongly influenced in case of drug-drug interactions (DDI).
- Many specific data are missing to optimize the management of VTE in the elderly (pharmacokinetic data, renal insufficiency, data in the very elderly or in elderly patients with cancer).

This box summarizes key points contained in the article.

Faced with these elements, an exhaustive search of anticoagulants in the indication of VTE was performed on PudMed, during the last decade, including data from clinical trials, observational studies, real-world data, drug-drug interaction studies, as well as various guidelines from scientific societies.

Thus, in this review, we will see the different elements concerning the advanced age on the anticoagulation therapies for acute venous thromboembolism, the issue of drug-drug interactions, as well as unmet needs.

2. Influence of age on drug pharmacology, and hemostasis

Medicine for the elderly is specific. Aging is characterized by a decrease in the functional reserves of multiple organs that are likely to influence the pharmacokinetics and pharmacodynamics of drugs [13]. Thus, a 'standard' treatment can lead to fatal complications, notably due to comorbidities and interactions with long-term treatments for other pathologies. We can take as an example the vitamin K antagonists, which must be initiated at a lower dose in geriatrics because of a greater pharmacological response (and therefore an increased risk of bleeding), hence the need to develop specific algorithms for initiating certain drugs in geriatrics [14,15]. In addition, certain clinical situations called geriatric syndromes (falls, undernutrition, cognitive disorders, etc …) are common in the elderly. They have a multi-factorial origin, combining chronic diseases and acute events which can make it difficult to manage anticoagulants as a treatment for VTE [16]. This can lead to hemorrhagic events (major hemorrhages on falls, pharmacokinetic changes on undernutrition, or when taking too much medication in patients with cognitive disorders), or recurrences of VTE (forgetting to take medication in patients with cognitive disorders).

It is clear that there are differences in the pharmacokinetics and pharmacodynamics of drugs in the geriatric population compared to younger subjects. Aging is accompanied by important physiological functional changes influencing the ADMET (Absorption, Distribution, Metabolism, Elimination, Toxicity) system of drugs [17–20]. These changes can lead to significant iatrogenic risks, including major hemorrhages when taking anticoagulant treatments.

To prevent these various potentially avoidable risks, specific pharmacokinetic studies of anticoagulants in the geriatric population are needed. Unfortunately, these studies are very rarely performed, with the absence of specific data in this population. Frequently, geriatric patients are excluded from clinical trials, due to their functional dependencies resulting from their comorbidities (organ failure, neurocognitive disorders, neoplasic pathology, etc.) [21,22]. As a result, dosage adjustments of therapeutics are made on the basis of extrapolations of data obtained in young populations, or by means of modeling incorporating modified geriatric physiological parameters.

The main pharmacokinetic changes encountered in geriatrics are grouped in Table 1. Principally we can note, there is a formal change in the distribution of total body water. In fact, the composition of the body is modified with an increase in fat mass and a decrease in total body water. This decrease can lead to an increase or decrease in the plasma level of drugs. In addition, due to undernutrition or chronic inflammatory pathologies frequently found in the elderly, albumin is lowered, increasing the unbound fraction of the drug in the blood and therefore its activity [23,24]. Hepatic metabolism is strongly affected by the decrease in hepatic mass and blood flow, hindering the correct elimination of the drug. Regarding excretion, it is noted that renal mass and renal blood levels decrease with age [25,26]. Thus, glomerular filtration and tubular secretion are altered, which can lead to an accumulation of the drug.

The higher thrombotic risk in old age is partly explained by a change in hemostasis. Numerous changes are observed in the vasculature (rigidity of vessel wall), alteration of platelet function, coagulation and fibrinolytic factors [27]. Among other things, it has been noted that in parallel with aging, the plasma concentrations of certain coagulation factors (fibrinogen, factor V, factor VII, factor VIII, factor IX, high molecular weight kininogen and prekallikrein) increase. The fibrinolytic system is also affected with strong evidence that plasminogen activator inhibitor (PAI)-1 (the major inhibitor of fibrinolysis), increases with aging [28].

Table 1. Pharmacokinetics and drug metabolism in the elderly by Klotz U. et al [20].

Absorption	Reduced gastric emptying
	Increased gastric pH
	Decreased absorption surface
	Decreased gastrointestinal motility
	Decreased blood flow
Distribution	Decrease in body mass
	Decrease in total body water
	Increase in fat mass
	Decreased blood flow
	Decreased serum albumin
	Increased α1 acid glycoprotein
Metabolism	Decrease in hepatic mass
	Reduced hepatic blood flow
	Decreased hepatic metabolic clearance
Elimination	Decrease in biliary secretion
	Decrease in renal mass
	Reduced renal blood flow
	Decrease in glomerular filtration
	Decrease in tubular secretion

These pharmacokinetic and hemostasis changes will impact the properties of direct oral anticoagulants.

3. Pharmacological data

3.1. Pharmacokinetic properties of DOACs

The different pharmacokinetic properties of DOACs are described in Table 2. There are currently four approved DOACs for the treatment of VTE. Dabigatran specifically inhibits factor IIa, while apixaban, edoxaban and rivaroxaban specifically inhibit factor Xa.

Concerning the absorption, – xabans (apixaban [29], edoxaban [30], and rivaroxaban [31]) are administered directly in the active form, unlike dabigatran [32], which is a pro-drug (dabigatran etexilate) that is rapidly hydrolyzed in plasma and liver by Carboxiesterase-1. Their bioavailability are variable, ranging from 6.5% for dabigatran [33] to 80–100% for rivaroxaban [34], 50% for apixaban [35,36], and about 60% for edoxaban [37,38]. DOACs are rapidly absorbed, and peak concentrations are obtained 1 to 4 hours after taking the tablet.

Then, the -xabans are highly bound to plasma proteins, and are therefore not dialyzable, unlike dabigatran (35% plasma protein binding), which is dialyzable.

Rivaroxaban undergoes degradation by CYP3A4/3A5 (major), CYP2J2 (minor). Apixaban is also a CYP3A4 substrate. Edoxaban is only very slightly metabolized by CYP3A4.

All DOACs are P-gp and BCRP substrates [39]. In addition, they are metabolized by cytochrome P450, particularly CYP3A4, inducing potential risk of drug-drug interactions (DDI). DDI (described in part 4 of this review) accounted for a great part of DOACs variability.

The elimination half-life of DOACs is globally superposable at around 10–13 hours. All DOACs are eliminated in part by the renal pathway. Dabigatran is eliminated 80% by the renal pathway, unchanged, while the -xabans show a slightly variable renal elimination depending on the molecule, around 30%. A significant portion (approximately 50%) of edoxaban is eliminated unchanged in the bile.

Advanced age will potentially impact all of the above parameters. This is due to decreases in renal and hepatic clearance, increasing the half-life of drugs. Advanced age will also increase the risk of co-morbidities, which will also expose the patient to a modification of the pharmacokinetic properties of the drug, and therefore, to a modification of the benefit/risk ratio (increased risk of bleeding in relation to renal insufficiency, cancer, or co-prescriptions, etc.)

Table 2. Pharmacokinetic profile of DOACs.

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Facteur IIa	Factor Xa	Factor Xa
Bioavailability (%)	50	6,5	62	80–100
Plasma protein binding (%)	87	35	55 (in vitro)	92–95
Prodrug	No	Yes	No	No
Tmax (h)	3–4	0,5–2	1–2	2–4
Half-life (h)	12	13,4	5–11	7–11
Renal elimination (%)	≈25	≈80	≈35	≈35
Hepatic elimination (%)	≈75	≈20	≈65	≈34
Metabolism Pathway	CYP3A4/ 3A5		Hydroxylation	CYP3A4/ 3A5 CYP2J2

3.2. Safety and efficacy

Validation studies of DOACs for the acute treatment of VTE are described in Table 3 with results on the efficacy and safety criteria expressed as relative risk. In summary, the results of a meta-analysis show us that in all phase III trials, the efficacy of NOACs in preventing VTE recurrence was maintained in the elderly subgroup [40]. The safety of DOACs in elderly patients was consistent with the results of the overall study.

All studies have been conducted to show non-inferiority in terms of efficacy. For all these studies, the primary efficacy endpoint was symptomatic recurrence of a thromboembolic event, or death related to a thromboembolic event during the treatment period. The safety endpoint exposed in Table 3 was the occurrence of clinically relevant bleeding (HOKUSAI-VTE) or a major bleeding (AMPLIFY, EINSTEIN pooled, RE-COVER pooled) event as defined by the International Society on Thrombosis and Hemostasis, i.e. overt bleeding associated with a decrease in hemoglobin of 2 g per deciliter or more, or requiring the transfusion of 2 or more units of blood, or occurring in a critical site, or contributing to death [35].

3.2.1. Apixaban

Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy (AMPLIFY), is a randomized, double-blind, non-inferiority trial [41]. This trial is studying apixaban 10 mg twice daily for 7 days, then 5 mg twice daily for 6 months versus conventional therapy (LMWH, followed by warfarin). These dose choices are based on the BOTTICELLI study comparing different doses of apixaban [42]. AMPLIFY demonstrates that a fixed-dose regimen of apixaban alone was non-inferior to conventional therapy in the treatment of acute VTE and was associated with a significant reduction in major bleeding events. These results were consistent with the subgroup analysis of the elderly (749 of the 5395 patients), with a significant reduction in major bleeding events (RR 0.23 [0.08;0.65]). These results are confirmed with other studies, including a small Japanese cohort (AMPLIFY-J) of 80 patients, with 23 patients aged 75 years or older, with similar efficacy and safety profiles [43].

3.2.2. Dabigatran

Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism (RE-COVER) trial includes the 2 major clinical trials (RE-COVER 1 and RE-COVER 2) [44,45]. People 75 years of age or older represented about 12% of the study

Table 3. DOACS, Study design, and Subgroup analyses in Elderly.

		Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Study		AMPLIFY [41]	RECOVER [44,45] (pooled analyses)	HOKUSAI-VTE [47]	EINSTEIN [49] (pooled analyses)
Experimental design		Double-blind	Double-blind	Double-blind	Open-label
Number of patients	Total	5395	5107	8292	8282
	Age≥75	749 (13.9%)	603 (11.8%)	1104 (13.3%)	1283 (15.5%)
Dosing		10 mg bid 7 days, then 5 mg bid 6 months	LMWH for 5 to 11 days, then dabigatran 150 mg bid 6 months	Parenteral anticoagulation then 60 mg od (30 mg od if weight<60 kg, or concomitant use of a strong P-gp inhibitor, or CrCl of 30 to 50 mL/min) 3 to 12 months	15 mg bid 21 days, then 20 mg od 3, 6 or 12 months
Mean age	Drug Test	57.2 ± 16.0	54.8 ± 16.0	55.7 ± 16.3	57.0 ± 17.0
	Control	56.7 ± 16.0	54.7 ± 16.2	55.9 ± 16.2	57.0 ± 16.8
Non-inferiority margin		1.8	2.75	1.5	1.75
Efficacy	Overall	0.84 [0.60;1.18]	1.09 [0.76;1.56]	0.89 [0.71;1.12]	0.90 [0.68;1.20]
RR(95%CI)	Age≥75	0.50 [0.21;1.20]	0.65 [0.17;2.45]	0.50 [0.27;0.94]	0.62 [0.33;1.17]
Safety	Overall	0.31 [0.17;0.54]	0.60 [0.36;0.99]	0.82 [0.72;0.95]	0.55 [0.38;0.81]
RR(95%CI)	Age≥75	0.23 [0.08;0.65]	0.91 [0.37;2.19]	0.83 [0.62;1.12]	0.27 [0.13;0.59]

participants. On subgroup analyses, with age analyzed as a continuous variable, it appears that the efficacy of dabigatran compared with warfarin was slightly lower in younger patients compared with the elderly [46]. Regarding the safety criterion of clinically relevant bleeding, RE-COVER showed that the risk reduction with dabigatran was influenced by age, with a higher risk reduction with dabigatran compared to warfarin in the youngest patients. There is a change in this effect from 85 years of age onwards with a trend of higher risk reduction for warfarin compared to dabigatran [45]. It is noted that prior to initiation of dabigatran therapy, it is necessary to use parenteral therapy for 5 to 11 days.

3.2.3. Edoxaban

Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism (HOKUSAI-VTE) [47]. It is one of the DOACs adapting its dosage according to certain characteristics (i.e. 30 mg if the patient's weight is less than 60 kg, or if his CrCl is between 30 and 50 mL/min, or if the patient is using a strong P-gp inhibitor concomitantly). The choice of doses is based on studies of edoxaban in atrial fibrillation. Edoxaban was not inferior to warfarin on the primary efficacy end point (RR 0.89 [0.71;1.12]). In the subgroup analysis of the elderly, the results were even more pronounced, with an RR of 0.50 (95% CI [0.27;0.94]). A second analysis of HOKUSAI-VTE, shows that recurrent VTE increases with advanced age, multiple comorbidities, and polypharmacy in patients treated with warfarin in contrast to those treated with edoxaban [48]. As with dabigatran, parenteral therapy is required before initiating edoxaban therapy.

3.2.4. Rivaroxaban

The randomized, open-label, non-inferiority trial oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism, pooled analyses [49], combines the trial studying rivaroxaban for the management of pulmonary embolism (EINSTEIN-PE) [50], and the trial for the management of deep vein thrombosis (EINSTEIN-DVT) [51]. The choice of doses of 15 mg twice a day for 21 days, then 20 mg once follows 2 large phase 2 studies [52,53]. Rivaroxaban was noninferior to warfarin (RR 0.90 [0.68;1.20]), with similar results in those aged 75 years or older (RR 0.62 [0.33;1.17]). Major bleeding was significantly reduced in the rivaroxaban group (RR 0.55 [0.38;0.81]), with even greater results in those aged 75 years or older (0.27 [0.13;0.59]). A subgroup analysis included frail patients (i.e. those 75 years of age or older, and/or with moderate or severe renal failure, and/or low body weight). It was shown that the rate of recurrent VTE was higher in frail patients compared with non-frail patients. There was no statistically significant difference in treatment efficacy between the rivaroxaban group versus standard therapy in either frail or non-frail patients. Contrary to major bleeding, where there was a statistically significant difference in favor of rivaroxaban (1.3%) versus standard therapy (4.5%) in frail patients (HR 0.27 [0.13;0.54]), whereas this difference was not found in non-frail patients.

3.3. Living database and observational studies

Patients included in randomized clinical trials validating different DOACs in the management of VTE are relatively young (<60 years). Real-life data specific to geriatric patients are still needed to provide objective data on the true efficacy and safety of direct oral anticoagulants in the elderly. In recent years, some observational studies have been performed mainly on the 2 most prescribed DOACs, ie, apixaban and rivaroxaban.

Apixaban was studied in a real-world observational study using a living database from the United States Medicare population of patients over 65 years of age [54]. 22,726 patients belonged to the post-matched cohort, with 13,286 patients who were 75 years of age or older. Warfarin was associated with a higher risk of major bleeding (HR 1.31 (1.10–1.57) compared with apixaban. The risks of recurrent VTE (HR 0.96

(0.70–1.33)) and all-cause hospitalization (HR (0.99–1.12)) were similar in patients on warfarin and apixaban.

Numerous observational studies have been performed for rivaroxaban, including the XALIA study (n = 5142) in the treatment of deep vein thrombosis [55]. Data from subgroups of the patient study showed no significant differences in the rates of major bleeding or recurrent venous thromboembolism between treatments as a function of age. However, these subgroup analyses used a low age (60 years) for comparison. The observational REMOTEV study included 177 patients aged 75 years or older, with similar results to the phase 3 trials (EINSTEIN-DVT, and PE) [56]. A living database using Danish national registries, encompassing 12,318 patients (including 3154 patients aged 75 years or older), and subgroup analyses suggest that rivaroxaban appears to be safe in elderly patients with multiple comorbidities, with no affect on the safety or efficacy of rivaroxaban in the elderly [57].

Apixaban and rivaroxaban were studied using RIETE data to compare the rates of recurrence of VTE or major bleeding (composite outcome) during anticoagulation according to the use of rivaroxaban or apixaban in frail patients with VTE, for initial and long-term treatment [58]. It showed a similar risk of recurrence of VTE or major bleeding with no differences between drugs in the rate of the composite outcome (RR 1.08 (0.35–3.30) or all-cause death (RR: 0.99 (0.32–3.08)).

4. Drug-drug interactions and aging

4.1. Drug-drug interactions: non specific issues in geriatrics

Drug-related problems are very common in the elderly. They include iatrogenic adverse drug reactions, drug abuse or non-compliance, and drug-drug interactions. These events can compromise the patient's quality of life, but above all play a role in the risk of death (therapeutic inefficiency, or serious adverse events such as major bleeding in the case of anticoagulants).

These drug-related problems are more frequent in the geriatric population, due to the fact that patients are polymorbid and therefore prone to taking numerous medications. On average, daily consumption is 3.6 medications per person aged 65 and over. It increases from 3.3 different drugs per day for those aged 65–74, to 4.0 for those aged 75–84, and 4.6 for those aged 85 and over [59]. The risk of inappropriate prescribing is increased in geriatrics, despite the fact that polymedication is indicated and beneficial for many elderly people with comorbidities. Several studies show that inappropriate prescriptions in the elderly are significantly associated with repeat hospitalizations and mortality [60,61].

Many factors can influence the pharmacokinetics of drugs in elderly patients such inter/intra-individual variability in pharmacokinetic steps, drug-drug interactions related to multiple co-medications. Cognitive disorders with medication compliance remain a major problem.

These events are responsible for more than 10% of hospitalizations in elderly subjects, and nearly 20% in octogenarians [59].

Therefore, it is essential to construct helpful drug-drug interaction studies in order to optimize the treatment of elderly patients. Various tools need to be put in place, taking the example of the 'Drug-drug interaction predictor' developed by the Faculty of Pharmacy of Lyon (France) which provides clinically useful, reliable, up-to-date and evidence-based information [62].

4.2. Drug-drug interactions: specific issues with DOACs in geriatrics

Direct oral anticoagulants are all P-glycoprotein substrates, and apixaban and rivaroxaban are substrates of cytochromes P450 (particularly CYP3A).

4.2.1 Aging and efflux transporters

Efflux transporters (such as P-gp and BCRP) are strongly associated with the ADMET properties of drugs and contribute to decrease toxicity by removing compounds from cells, thus preventing intracellular accumulation. They are thus highly expressed in the organs and tissues involved in these pharmacokinetic processes [63]. P-Glycoprotein, is the most studied efflux transporter at present, and is the first to be identified as limiting the oral bioavailability of drugs.

The expression of these efflux proteins (especially P-gp) has a major role on drug-drug interactions A few studies have looked at the association between aging and the expression of membrane efflux transporters. The animal model points to a decrease in the expression of efflux proteins with aging [64]. This decrease remains to be proven in humans. Nevertheless, we observe a decrease in the expression of efflux transporters as a function of the aging of the blood-meningeal barrier in humans [65,66]. This decrease could be partly responsible for the development of neurodegenerative diseases by facilitating the accumulation of toxic substances in the brain [67,68]. At the hepatic and renal level, Prasad et al. did not show a correlation between P-gp expression and age, but the studies included very few people at the extreme ages [69,70]. The impact of aging on efflux proteins may play a critical role on the efficacy and safety of DOACs and should be investigated, as all DOACs are P-gp substrates [39,71,72].

4.2.2 Aging and Cytochromes P450

The majority of drugs must be biotransformed into metabolites by several cytochromes P450 (in the liver and in the small bowel), before their final elimination. Although total liver weight and hepatic clearance decrease, enzyme functionality does not appear to be altered with aging. Enzyme activity is unaffected by in vitro data in the liver microsomal protein content [73]. This has also been shown in humans in liver biopsy samples, or cryopreserved human microsomes where CYP450 did not decrease with age in the range of 10 to 85 years [74–76].

Table 4. Main drug-drug interactions with DOACs.

P-gp/CYP3A inhibitors	P-gp/CYP3A inducers
Amiodarone	Carbamazepine
Clarithromycin	Phenytoin
Diltiazem	Phenobarbital
Dronedarone	Rifampicin
Erithromycin	
Fluconazole	
HIV protease inhibitors (e.g. Ritonavir)	
Ketoconazole	
Posaconazole	
Quinidine	
Verapamil	
Voriconazole	

4.2.3 P-gp and CYP3A4-mediated drug-drug interactions

This double inhibition, both by P-gp inhibition and by CYP3A4, may be the cause of major bleeding events, associated with the failure of different therapies [77]. As a result, they may be responsible for serious drug-drug interaction events in the presence of potent inhibitors or inducers of P-gp and CYP3A.

Thus, a P-gp and CYP3A4 inhibitor will lead to an increase in DOAC concentration with a potential risk of bleeding, while a P-gp and CYP3A4 inducer will lead to a decrease in DOAC concentration and thus a potential thrombotic risk.

However, to be clinically relevant, these DDI have to involve strong modulators. Among the CYP3A4 inhibitors, we can find diltiazem, ketoconazole, ritonavir, as well as frequently prescribed antibiotics such as clarithromycin or erithromycin [78,79]. The best known enzyme inducers are rifampicin and carbamazepine [80,81]. Therefore, precautions must be taken to avoid the association of these drugs with DOACs.

Fortunately, very few compounds strongly affect both systems and these drugs should be checked before prescribing a DOAC. Most of them could be replaced by alternative molecules. A reduced dose has been evaluated and proposed for some DOACs in the presence of potent P-gp inhibitors, notably for edoxaban [47]. But several questions remain unanswered, including the impact of several moderate modulators on DOACs (are they equivalent to one strong P-gp/CYP3A4 inhibitor?); But also, the lack of solid evaluation of the pharmacokinetic variability of DOACs in oncologic patients with VTE, as revealed by the team of Bellesoeur et al. [82].

Table 4 summarizes the major CYP3A4, P-gp-mediated drug-drug interactions with DOACs.

5. Conclusion

The management of thromboembolic events in the elderly has been revolutionized by the introduction of direct oral anticoagulants. They offer major advantages over vitamin K antagonists. The elderly is under-represented in clinical trials, if not totally excluded. Although the few current studies seem to be reassuring about the use of DOACs in the elderly, both in terms of safety and efficacy, data are still lacking.

The clinician, along with the pharmacist, will need to be cautious, both about the risk of drug-drug interactions (particularly those mediated by P-glycoprotein), and about the pharmacokinetic properties of DOACs that may be affected by aging.

It is important to remain vigilant about the correct indications for DOACs in geriatrics, and to ensure their proper use. The current challenge is to develop future research studies to make their use in the elderly safer and more secure.

6. Expert opinion

Direct oral anticoagulants have become an essential part of the management of thromboembolic events in the elderly in recent years. As an expert opinion, we highlight the unmet needs that must be developed in the coming years.

6.1. Unmet needs

6.1.1 Missing pharmacokinetic data

In clinical practice, thromboembolic events frequently occur in patients over 75 years of age. But the majority of randomized clinical trials evaluating DOACs have included patients with VTE whose mean age was less than 60 years. In addition, pharmacokinetic data for DOACs are mainly available from trials involving atrial fibrillation.

Due to the diverse metabolism/elimination of DOACs (renal, hepatic, P-gp substrate), associated with age-related variations in drug pharmacokinetics, and frequent use of interacting drugs, there is major inter-individual variability in the pharmacokinetic response of DOACs (such as bleeding risk). However, recommendations are based on the general pharmacokinetics of the various DOACs determined in a general population and may not apply to an elderly person with comorbidities. A few available small studies (including less than 50 subjects) show higher plasma concentrations in elderly subjects for apixaban and rivaroxaban [83,84]. These pharmacokinetic differences raise questions about the discontinuation of anticoagulation and the procedures to follow during scheduled or semi-emergent surgery, to avoid bleeding complications [85]. Comparative studies of kinetic profiles, as proposed by Goto et al. should be performed [86]. It is essential to provide population-based approaches via modeling tools (population model), to compare plasma concentrations of apixaban, dabigatran, edoxaban and rivaroxaban [87–89]. This would allow one DOAC to be preferred over another in the elderly based on patient characteristics.

Several observational studies show that direct oral anticoagulants were not necessarily prescribed at the indicated dose, including the use of lower doses [90]. This is most apparent in the elderly population. As a result, some patients do not benefit fully from their anticoagulant therapy for the management of their VTE.

However, several recent studies suggest that most elderly patients with lower than recommended DOAC doses have concentrations within the expected range [91,92]. This would indicate the value of using low doses of DOACs for long-term therapy in the elderly VTE patients. There is a need for thorough and appropriate studies of the optimal target range of

DOACs, in order to optimize the risks of bleeding and thrombosis in these frails patients [93]. The RENOVE (REduced Dose Versus Full-dose of Direct Oral Anticoagulant After uNprOvoked Venous thromboembolism) trial (NCT03285438) will provide better data in these patients, as it compares usual vs low-doses of DOACs in extended anticoagulant therapy.

From these observations, specific data on DOACs in the geriatric population are needed. A French multicenter cohort of 1500 patients studying pharmacoepidemiology treatment of symptomatic pulmonary embolism in hospitalized patients aged 75 years or more (PEAGE study) (NCT02360943), will provide essential and needed pharmacokinetic data on anticoagulants in a geriatric population. The results are expected in 2022.

6.1.2 Questions about thrombolysis?

It has been known for several years that increasing age is a major risk factor for bleeding complications after thrombolysis for pulmonary embolism [94]. The inclusion of elderly patients in studies studying thrombolytic therapy is associated with an increase in bleeding events [95]. Indeed, a meta-analysis shows that the association between thrombolytic therapy and the risk of major bleeding was lower in studies using an older age limit (OR 1.13 [0.47;2.71]) compared with studies including older patients (OR 3.71 [2.32;5.92]) [96].

The 2016 CHEST guidelines suggest thrombolytic therapy for pulmonary embolism with hypotension (eg, systolic blood pressure <90 mm Hg) in patients who do not have a high bleeding risk (grade 2B) [11]. Several criteria remain major contraindications to thrombolytic therapy, such as a history of intracranial hemorrhage. Age greater than 75 years is considered a relative contraindication to thrombolytic therapy, as is low body weight (less than 60 kg), which is frequently present in geriatrics.

In normotensive patients with pulmonary embolism, thrombolysis is not recommended regardless of age. This non-recommendation is even truer in patients over 75 years of age, with the results of the PEITHO (Pulmonary Embolism Thrombolysis) trial [97]. There were 4.3% deaths or hemodynamic decompensation in patients assigned to tenecteplase and 6.7% in those assigned to placebo (OR 0.63 [0.24;1.66] in intermediate-risk pulmonary embolism patients over 75 years of age, associated with 11.1% major extracranial bleeding, versus 0.6% in the placebo group (OR 20.38 [2.69;154.53]).

The clinician can use clinical scores to prevent the risk of bleeding events, such as the BACS (Bleeding, Age > 75 years, active Cancer, and Syncope) score, predicting the risk of major bleeding in the population of patients with pulmonary embolism receiving systemic thrombolysis [98].

Based on the lack of specific data and strict recommendations by learned societies, it is essential to continue studies on thrombolysis for elderly patients and consider studying a reduction in thrombolytic doses in the elderly.

6.1.3 The issue of renal failure

Nearly 1 in 3–4 patients with acute pulmonary embolism have associated acute kidney injury (OR 4.8 [4.44–5.28] if age>65 years), which results in a worse prognosis [99]. This may complicate existing chronic renal failure. The association between age and impaired renal function has been known for years. Moreover, chronic kidney disease is known to be a risk factor for both thrombosis and hemorrhage [100]. Impaired renal function alters, among other things, plasma protein binding and volume of distribution, resulting in less stable anticoagulation of warfarin [101]. This raises the question of DOACs, but patients with severe renal function were excluded from the Phase 3 clinical trials. Consequently, there is a lack of major data on the efficacy and safety of DOACs in elderly patients with severe renal failure (with a glomerular filtration rate below 30 ml/min/1.73 m^2).

The summaries of product characteristics suggest that in patients with mild to moderate renal impairment with VTE, no dose adjustment is necessary, and for patients with severe renal impairment it is indicated that apixaban should be used with caution [29]. Dabigatran is contraindicated in people with a glomerular filtration rate <30 mL/min [32]. It was noted that bleeding was less frequent with dabigatran than with warfarin in the RE-COVER pooled analysis according to age and renal function. There was no increase in recurrent VTE or bleeding in patients 75 years or older compared with those younger than 75 years when they had equivalent CrCl [46]. For edoxaban, the 30 mg dose is recommended when there is moderate or severe renal insufficiency [30]. This was shown in the HOKUSAI trial, where halving the daily dose of edoxaban to 30 mg maintained efficacy with significantly less bleeding than that seen in the warfarin group [47]. Finally, for rivaroxaban, in patients with moderate or severe renal impairment with VTE, a reduction in dosage after 3 weeks of proper anticoagulation from 20 mg once daily to 15 mg once daily should be considered only when the patient's risk of bleeding is estimated to be greater than the risk of recurrent DVT and PE [31]. This is based on the finding that the number of major bleeding events was significantly higher with decreasing renal function in the EINSTEIN trial [49].

The summaries of product characteristics of DOACs use the Cockcroft and Gault formula method of estimating renal function. However, there is evidence that this formula may overestimate renal function [102]. It should be noted that the risk of bleeding differs depending on the formula used to estimate renal function. An analysis of patients in the RIETE registry revealed discordant results in 40.7% with the use of the Cockcroft and Gault formula and/or the chronic kidney disease epidemiology collaboration (CKD-EPI), in patients with severe renal failure [103]. It seems necessary to study which renal function formula to use, especially in geriatrics, to optimize the benefit/risk ratio of anticoagulants in severe renal failure patients with high bleeding risk.

In a combined phase 3 clinical trial, DOACs significantly reduced major bleeding in patients with creatinine clearance between 30 and 49 mL/min (RR 0.51 [0.26;0.99]) and in patients over 75 years of age (RR 0.49 [0.25;0.96]) [104]. Although the data seem reassuring, data are still missing and are needed. Studies are being set up, notably the VERDICT study (Venous Thromboembolism in Renally Impaired Patients

and Direct Oral Anticoagulants) (NCT02664155). The purpose is to evaluate the reduced doses of apixaban, and rivaroxaban compared with heparins/VKA regimen in VTE patients with moderate or severe renal impairment in terms of net clinical benefit (recurrent VTE and major bleeding) at 3 months. The results are expected in 2022.

6.1.4 Very elderly population

Clinical trials incorporating data from the very elderly are rare or non-existent for some therapies [105]. The average age of clinical trials that have validated DOACs is less than 60 years. The balance between the efficacy and safety of anticoagulant therapy in very elderly patients receiving anticoagulant therapy for venous thromboembolism remains highly uncertain.

Data from the very elderly come primarily from observational studies. Among them, we can mention one recent study with data from the RIETE registry [106]. Among centenarians, as of January 2016, 0.08% of patients (n = 47) were 100 years or older. The majority of patients were initially treated with low-molecular-weight heparin (LMWH) (95%), then 30% switched to vitamin K antagonists, and 29 (62%) remained on long-term LMWH therapy. On these data, one observation stands out: there were no patients receiving DOACs.

Poli et al. in 2019, conducted a prospective cohort study of VTE patients aged 85 years or older enrolled in the Survey on anticoagulaTed pAtients RegisTer (START2-Register) on treatment with VKAs or DOACs [107]. 272 patients were enrolled in the cohort, with 58.7% on VKAs and 41.3% on DOACs. It is shown that the mortality rate was lower with DOACs (HR 0.30 [0.1;0.9]), but the bleeding rate was higher (crude HR 4.7 [1.5;15.01]). Nevertheless, the complication rates in this study were very low, with 2 major bleeding events in the VKAs group (0.6%), versus 3 (2.6%) in the DOACS group. The recurrence rate of VTE was similar in both groups.

Cohorts of very elderly patients, as well as clinical trials, should be initiated to explore the potential role of DOACs in this population.

6.1.5 Elderly with cancer and VTE

Cancer and venous thromboembolic (VTE) diseases are strongly associated. VTE is the second most common cause of death in cancer patients [108]. The treatment of VTE in cancer patients is a challenge, justifying the development of specific trials to propose dedicated scientific recommendations. Low molecular weight heparins (LMWH) have been the standard treatment for cancer-related thrombosis for several years. Some studies have recently examined direct oral anticoagulants (DOACs) in the management of VTE in cancer [109–112]. A meta-analysis of these four randomized clinical trials showed that DOACs reduced the risk of recurrent VTE without significantly increasing the likelihood of bleeding, at six months, compared to the reference treatment [113]. These different studies have led to new international guidelines, suggesting the use of some DOACs for the treatment of cancer-associated VTE in specific patients [9,114,115]. Cancer patients have a high risk of bleeding under anticoagulant therapy, it is therefore recommended to use DOACs with caution in gastrointestinal and genitourinary cancers, as well as when there is a risk of drug interactions [82,116].

These new recommendations should be taken with caution for elderly subjects, due to a median age of 64 years (±11 years) for the HOKUSAI VTE cancer trial, and ADAM VTE trial [110,111]. Moreover, in the subgroup analysis of CARAVAGGIO, it was shown that in patients under 65 years of age, apixaban was more effective than dalteparin in preventing recurrence of venous thromboembolic disease, but that this effectiveness decreased with age [112]. Specific geriatric data are lacking to consider the use of DOACs in elderly oncology patients.

6.2 Conclusion

Now that direct oral anticoagulants have taken a significant place in the management of thromboembolic events in the elderly, it is still time to answer various questions.

Thus, the next few years will be crucial in research projects specific to thromboembolic disease in the elderly. The benefit/risk ratio will have to be clarified in certain special populations (oncology patients, severe renal failure, etc.).

Over the next 5 years, the results of studies such as VERDICT or PEAGE will provide many answers, revealing precise pharmacokinetic data that could lead us to a personalized medicine approach. This field of personalized medicine is essential to develop, taking into account the precise profiles of each patient, and the various changes that can be encountered in our elderly patients.

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