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REVIEW

Initial anticoagulation in patients with pulmonary embolism: thrombolysis, unfractionated heparin, LMWH, fondaparinux, or DOACs?

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The initial treatment of haemodynamically stable patients with pulmonary embolism (PE) has dramatically changed since the introduction of low molecular weight heparins (LMWHs). With the recent discovery of the direct oral anticoagulant drugs (DOACs), initial treatment of PE will be simplified even further. In several large clinical trials it has been demonstrated that DOACs are not inferior to standard therapy for the initial treatment of PE, and because of their practicability they are becoming the agents of first choice. However, many relative contraindications to DOACs were exclusion criteria in the clinical trials. Therefore, LMWHs will continue to play an important role in initial PE treatment and in some cases there still is a role for unfractionated heparin (UFH). In this review we will give an overview of the biophysical, pharmacokinetic and pharmacodynamic properties of anticoagulants currently available for the initial management of PE. In addition, we will provide a comprehensive overview of the indications for the use of UFH, LMWHs and DOACs in the initial management of PE from a pharmacokinetic/-dynamic point of view.

Introduction

Untreated acute pulmonary embolism (PE) is associated with a mortality rate of up to 25% [1], and anticoagulation has been the backbone of PE treatment for decades. The goal of treatment is to reduce mortality by prevention of thrombus extension, embolization and/or formation of new thrombi. In the only randomized controlled clinical trial performed, anticoagulation decreased mortality in patients with pulmonary embolism [1], and subsequent uncontrolled trials have confirmed this finding [2–4]. Although both unfractionated **heparin** (UFH) and vitamin K antagonists (VKAs) have been used as anticoagulants for many decades, it was not until 1990 that it was demonstrated that early initial administration of heparin is essential for survival [5], and that a 5-day course of UFH is as effective as the formerly applied 10 days [6]. Because of pharmacokinetic and biological limitations of UFH, low-molecular-weight heparins (LMWHs) and the indirect factor Xa (FXa) inhibitor **fondaparinux** have been developed and have greatly simplified the initial management of PE [7]. With persisting limitations in terms of usability of LMWHs, fondaparinux and VKAs, direct oral anticoagulants (DOACs) have been developed recently [8]. This new class of oral anticoagulants simplifies initial treatment, prophylaxis and long-term management of PE even further as they are administered in fixed doses without any need for laboratory coagulation monitoring [8]. However, although the beneficial effects of

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LMWH and fondaparinux over UFH are clear, and there is increasing evidence that DOACs have, in most patients, a similar effect on the prevention of recurrent PE as LMWHs/fondaparinux, there are still indications for the primary use of UFH in the initial management of PE based on its pharmacokinetic and pharmacodynamic properties. In this review we will translate insights in the pharmacokinetic, pharmacodynamic and relevant off-target properties into a better understanding of the use of the old and new anticoagulants currently available for the initial management of PE.

Biophysical and pharmacokinetic properties

A schematic overview of the biophysical and pharmacokinetic properties of UFH, LMWHs, fondaparinux and DOACs is presented in Table 1.

UFH

In contrast to LMWHs, fondaparinux and DOACs, UFH does not have predictable pharmacokinetics. UFH is a glycosaminoglycan that consists of a heterogeneous mixture of polysaccharide chains with alternating residues of **D-glucosamin** and uronic acid, or glucoronic acid, or iduronic acid. The molecular weight ranges from about 3000 to 30 000 Da. UFH does not distribute into muscle or fat tissue, giving it a small volume of distribution (Vd) of 0.07 l kg^{-1} [9] with a relatively short half-life (about 0.5–1 h) [10]. The half life of UFH is not only very variable due to its earlier described heterogeneity [11], but also due to its two-phased and dose-dependent elimination (the half-life increases with increasing dose) [12]. The rapid, saturable elimination phase is thought to reflect UFH binding to vascular endothelial cells, macrophages and reticuloendothelial cells [13–17], where it is internalized, depolymerized and metabolized into smaller and less sulphated forms [17–19]. The slower phase corresponds to renal clearance. At low doses (less than 1000 IU), heparin is cleared mainly by the highly efficient saturable mechanism [18]. At higher doses, the cellular binding sites are saturated, and heparin is cleared predominantly by renal elimination [12, 18]. Another reason for the unpredictable pharmacokinetics of UFH is its binding to a number of endogenous plasma proteins including histidine-rich glycoprotein (HRGP), **platelet factor 4** (PF4), **vitronectin**, **fibronectin** and **von Willebrand factor** (vWF) [20]. Binding of UFH to plasma proteins reduces its anticoagulant activity because less UFH is available for interaction with antithrombin, and the unpredictable anticoagulant response reflects the wide variability in plasma

Table 1

Comparative pharmacokinetics

					FXa inhibitors		
	UFH	**LMWH**	**Fondaparinux**	**FII inhibitor Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Route of administration	iv	sc	sc	Oral	Oral	Oral	Oral
Molecular weight	3–30 kDa	5000 Da	1726 Da	627 Da	435 Da	459 Da	548 Da
Predictable pharmacokinetics	No	Yes	Yes	Yes	Yes	Yes	Yes
t_{max} (h)	Minutes	4–6	2–4	1–3	2–4	3–4	1–2
$t_{1/2}$ (h)	0.5–1.5	3–6	17–21	12–17	5–13	9–14	10–14
Bioavailability (%)	100	>90	100	3–10	>80	50	62
Volume of distribution (l kg^{-1})	0.07	0.04–0.06	0.1–0.2	0.8–1	0.71	0.3	0.77
Plasma protein binding (%)	>90	>90	>97	35	92–95	87	55
Renal elimination (%)	Only in high dose	>80	>80	80	33	27	50
CYP metabolism (%)	None	None	None	None	66	25	<4
P-gp	None	None	None	Yes	Yes	Yes	Yes
Risk of HIT	Yes	Low	None	None	None	None	None
Pregnancy	Not-contraindicated	Not-contraindicated	Unknown/ contraindicated	Unknown/ contraindicated	Unknown/ contraindicated	Unknown/ contraindicated	Unknown/ contraindicated
Reversal agent	Protamin	Protamin (partly)	Not available	Idarucizumab	Not available	Not available	Not available

FXa, factor Xa; HIT, heparin-induced thrombocytopenia; iv, intravenously; LMWH, low molecular weight heparin; NA, not applicable; p-gp, p-glycoprotein (for relevant drug interactions, see the interaction table in the online supplement); sc, subcutaneously; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; UFH, unfractionated heparin

concentrations of heparin-binding proteins. Some of these heparin-binding proteins are acute phase reactants, the concentration of which may increase in patients, whereas others like PF4 and vWF are released during the clotting process. Non-pharmacokinetic factors add to the unpredictable therapeutic effect of UFH: there is a high- and low-affinity moiety for binding to antithrombin (see also the 'mechanism of action' section below), and the high-affinity moiety has a longer half-life than its low-affinity counterpart [11]. Because of its heterogeneity (with varying high- and low-affinity moieties), half-lives will vary. Because of the unpredictable anticoagulant response, careful/close monitoring is essential when UFH is given in therapeutic doses.

LMWH

LMWHs are fragments of UFH produced by controlled enzymatic or chemical depolymerization processes that yield chains with a mean molecular weight of about 5000 Da [21]. The indirect factor Xa inhibitor fondaparinux is a synthetic analogue of the unique pentasaccharide that mediates the anticoagulant activity of both UFH and LMWHs [22]. Because LMWHs do not bind to endothelial cells, macrophages or reticuloendothelial cells, the plasma half-life is 2–4 times longer than that of UFH (3–6 *vs*. 0.5–1.5 h respectively) [21]. Fondaparinux has an even longer half-life of 17–21 h. In addition, because LMWHs and fondaparinux have much lower affinity for heparin-binding plasma proteins and are mainly removed by non-saturable renal filtration, their clearance is independent of dose and plasma concentration [22]. Moreover, in contrast to UFH and LMWHs, fondaparinux rarely causes heparin-induced thrombocytopenia (HIT), because fondaparinux does not bind PF4 (of which neo-epitopes are recognized by HIT-inducing antibodies) [23]. However, fondaparinux is unlicensed for treatment in HIT because on rare occasions fondaparinux can cause a disorder resembling HIT [24], for which the underlying mechanism remains to be elucidated.

Of note, obese patients clear LMWHs faster than non-obese patients due to hyperfiltration, and because LMWHs are hydrophilic, one might expect that the volume of distribution of LMWHs is not that much increased in obese patients. However, LMWHs are not dosed on lean or adjusted body weight but on total body weight. This is based on three small studies that demonstrated that the use of total body weight is as appropriate as adjusted body weight: both total body weight and adjusted body weight provided a moderate correlation with volume of distribution and clearance (a poor correlation was seen with lean body weight) [25], and mean anti-factor Xa activity was equal in obese and non-obese patients when dosed on total body weight [26, 27].

DOACs

DOACs are small synthetic molecules with a molecular weight ranging from 430 to 670 Da. They are either direct **thrombin** inhibitors or **factor Xa** (FXa) inhibitors. **Dabigatran etexilate** is the only approved oral direct thrombin inhibitor, and **rivaroxaban**, **apixaban** and **edoxaban** are oral FXa inhibitors. From a pharmacokinetic point of view, there are several differences in terms of bioavailability, plasma protein binding, metabolism with or without **cytochrome (CYP)450** and/or P-glycoprotein (P-gp) handling, and mechanisms of elimination (see Table 1 for details). Dabigatran etexilate has a very low bioavailability ranging from 3–10%, in which Pg-p handling plays an important role. Because of relatively large uptake variability, unpredictable interindividual differences in dabigatran plasma levels can occur, although it seems that this does not affect its clinical activity in the majority of patients [28, 29]. In a small subset of patients this variability in plasma levels can be clinically relevant which implies that monitoring might be useful nevertheless, especially in patients 'at risk'; for example, the elderly, patients with impaired renal function or obese patients [30–35]. Patients with (sub)total gastrectomy or gastric bypass surgery should rather avoid dabigatran or use it with caution. Because dabigatran is a P-gp substrate, there are several drug interactions (for an overview of drug interactions, see supplementary Table S1 in the online supplement). Dabigatran is the only DOAC not metabolized by the liver, and therefore does not have CYP450 drug–drug interactions. Rivaroxaban, apixaban and edoxaban are all, at least to some extent, CYP450 and P-gp substrates, potentially leading to drug interaction (for an overview of drug interactions, see supplementary Table S1 in the online supplement) [36]. In addition, high dosed rivaroxaban (15 or 20 mg daily) must be taken with food because of higher bioavailability (from 66% to more than 80%) [37]. The other DOACs do not have this requirement [38, 39]. In crushed form, apixaban and rivaroxaban have similar bioavailability and therefore can be administered via a nasogastric tube [40, 41]. Theoretically, DOACs could be used for treatment in HIT as they do not bind PF4, although this would be off-label use.

Mechanism of action

A schematic representation of mechanisms of action of anticoagulation therapies is depicted in Figure 1. In summary, activated factor X (aFX) activates thrombin (factor II) which activates conversion of fibrinogen to fibrin. Both unfractionated heparin, low-molecular-weight heparins and fondaparinux exert their anticoagulant activity by inhibiting thrombin-activated conversion of **fibrinogen** to fibrin [7, 42]: binding of a unique pentasaccharide to antithrombin causes a conformational change in **antithrombin** that accelerates its interaction with thrombin and FXa by about 1000 times. Binding of the pentasaccharide to antithrombin results directly in inhibition of FXa, whereas inhibition of thrombin also requires binding by at least 12 saccharide units. The pentasaccharide also blocks the activation of **factor IX** and neutralizes aFX by activating factor X inhibitor. Fondaparinux is a synthetic analogue of this unique polysaccharide, but for UFH and LMWHs this sequence is randomly distributed along the heparin chains. Approximately one third of the chains of unfractionated heparin, and about 15–25% of the chains of LMWHs, contain this pentasaccharide sequence. Unlike UFH, which has equivalent activity against factor Xa and

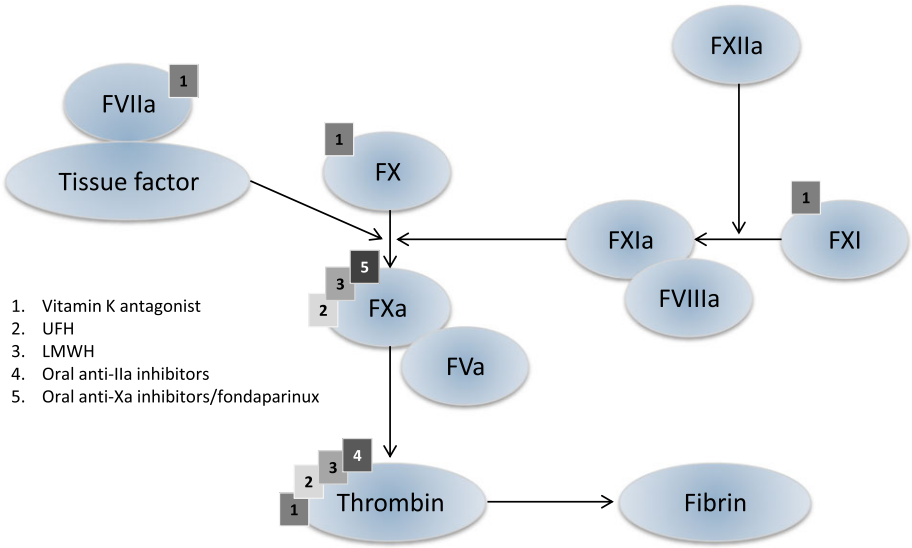

Figure 1

Schematic representation of the coagulation cascade and coagulation factors which are inhibited by different anticoagulation therapies UFH, unfractionated heparin; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulatory drugs

thrombin, LMWHs and fondaparinux have greater activity against factor Xa. This can be explained by the fact that long heparin chains can inhibit both **factor IIa** and Xa, while shorter chains only inhibit factor Xa [43–45]. The effects of UFH, when used in pulmonary embolism, may not be fully explained by its anticoagulant actions: there is some evidence that UFH decreases bronchospasm and vasospasm associated with pulmonary embolism [46, 47]. It is hypothesized that these effects result from the inhibition of serotonin release from platelets [47–49], which may be of additional value in patients with intermediate risk PE (see below). The DOACs are direct inhibitors of factor II or X (both serine proteases), thereby preventing thrombin-activated conversion of fibrinogen to fibrin [50]. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Apixaban, rivaroxaban and edoxaban are highly selective, direct and reversible factor Xa inhibitors. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. The factor Xa inhibitors do not inhibit thrombin (activated factor II), and no direct effects on platelets have been demonstrated.

Clinical implications of pharmacokinetic and -dynamic properties for treatment of acute PE

General

A schematic overview of the initial treatment of PE is depicted in Figure 2. In contrast to thrombolysis, there is no proof that UFH or LMWHs/fondaparinux or DOACs have a direct effect on preformed thrombi, but the discontinuation of the coagulation cascade will facilitate endogenous fibrinolysis and thereby the dissolution of the thrombus in the longer term [51]. For the initial management, anticoagulants are protective by preventing further thrombus formation and subsequent thrombin-mediated platelet aggregation. This interruption of fresh thrombus formation is crucial to short-term PE prevention because recently formed thrombi are mechanically much more unstable and thus prone to detachment and embolization. Whether vasodilating and antibronchospastic effects of heparins in particular convey additional acute benefit has never been studied specifically.

In haemodynamically unstable PE patients, thrombolysis is clearly indicated [52]. Thrombolysis is usually not accompanied by concomitant anticoagulant therapy, but initiated subsequently [53]. In haemodynamically stable intermediate risk PE patients, potential benefits of thrombolysis are offset by a significantly increased bleeding risk [54]. In such patients, and all others at lower risk, anticoagulant therapy (with UFH, LMWH/fondaparinux or DOACs) instead of thrombolysis is recommended for the initial treatment of PE [42].

LMWHs and fondaparinux have been directly compared to UFH in a large number of trials. A recent Cochrane systematic review concluded that LMWHs/fondaparinux are preferred over (intravenous (iv) or subcutaneous (sc)) UFH for initial anticoagulation in patients with PE, as they result in fewer recurrent thromboembolic events, less major bleeding and lower mortality compared to UFH [55]. In addition to these improved clinical outcomes, other advantages of LMWH or fondaparinux over UFH include more predictable pharmacokinetics with less inter-individual variability in anticoagulant response to fixed doses, a longer plasma half-life making once or twice daily administration possible, and a decreased likelihood of heparin-induced thrombocytopenia [7]. The preference for LMWH or subcutaneous fondaparinux

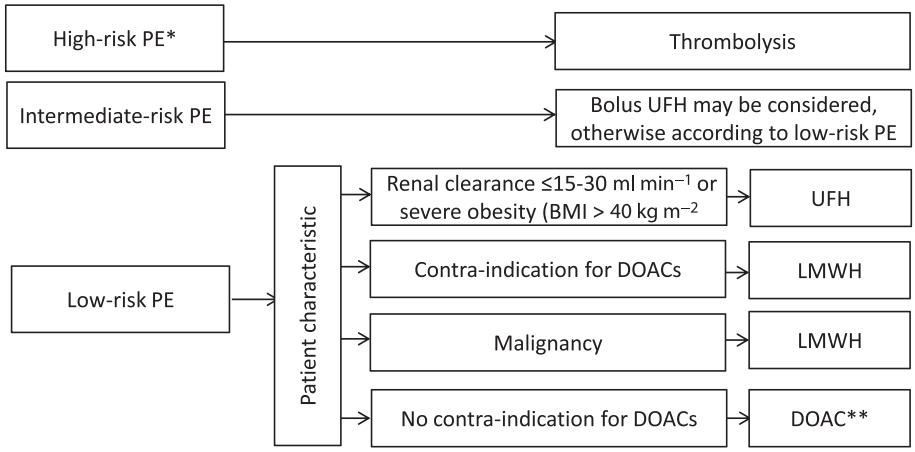

Figure 2

Initial pulmonary embolism treatment flowchart PE, pulmonary embolism; UFH, unfractionated heparin; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulatory drugs; * haemodynamically unstable PE and/or respiratory depression; ** whether or not preceded by a short course of LMWH/fondaparinux administration. For an overview of contraindications see the online supplement

should be guided by clinician familiarity, costs and availability because benefits and potential harms are similar [42]. A fairly recent meta-analysis showed that once daily LMWH is as effective and as safe as a twice daily regimen (2.2 *vs*. 2.9% major bleeds respectively in 1508 pooled patients), although PE patients were underrepresented [56].

Dabigatran, rivaroxaban, apixaban and edoxaban have been compared with conventional anticoagulant therapy for the treatment of acute symptomatic VTE, and compared with placebo and with VKAs for extended treatment [57, 58]. In these large RCTs it was demonstrated that the DOACs are not inferior to initial LMWH therapy followed by VKA treatment in the prevention of recurrent VTE [57]. Moreover, it was demonstrated that the DOACS have a lower all-cause mortality driven primarily by a decrease in fatal intracranial bleeding risks [57, 59]. Therefore, and because they are administered orally and do not need monitoring routinely, DOACs have become the agents of first choice in the treatment of acute and extended treatment of PE for most patients (fitting the clinical trial population profiles) [60]. However, only rivaroxaban and apixaban are approved for the first days of treatment of PE, as dabigatran and edoxaban both require the initial treatment of LMWHs for several days. Of note, this approach is not based on the pharmacokinetic properties of the different DOACs (as they all have a similarly short t_{max}, which is in the same range as LMWHs; see Table 1), but is guided by the different study designs in which non-inferiority has been demonstrated. In addition, despite decreased all-cause mortality, concerns have been raised about increased gastro-intestinal bleeding risk for rivaroxaban, and high-dose dabigatran and edoxaban, especially in the elderly [61, 62]. The reason for this difference remains to be elucidated. For dabigatran it is suggested that the low bioavailability may cause bleeding via a luminal effect. The difference between apixaban and rivaroxaban may be explained by once *vs*. twice daily dosing respectively, leading to higher peak levels of rivaroxaban. However, it should be taken into account that there are no randomized clinical trials (RCTs) comparing one DOAC confirming the superiority of apixaban in this respect. Accordingly, it has been described that rivaroxaban may predispose to heavy menstrual bleeding (20–25%), which should be taken into account in premenopausal female patients [63, 64].

Another concern in clinical practice which may guide DOAC choice, is the availability of a reversal agent. For dabigatran, a recent study showed that **idarucizumab** (a humanized dabigatran-specific (Fab) antibody fragment) is able to normalize coagulation tests within 10–30 min after administration without increased risk of thrombosis [65], and it has been approved for treatment of life-threatening bleeding in dabigatran-treated patients. **Andexanet alfa** (a recombinant modified human factor Xa decoy protein) was developed as a reversal agent for the FXa inhibitors. Recently it was demonstrated that andexanet alfa decreases factor Xa activity effectively in FXa inhibitor-treated patients with life-threatening bleeding, which resulted in good clinical haemostasis in 79% of patients [66]. However, an increased risk of thrombosis was observed in patients treated with andexanet because of life-threatening bleeding [66], and andexanet alfa is not yet registered for treatment of bleeding complications. Finally, Ciraparantag/PER977 is a small cationic molecule which has the potential to serve as an universal antidote because it binds direct Xa inhibitors, direct thrombin inhibitors, and unfractionated and LMWH through non-covalent hydrogen bonds and charge–charge interactions.

Currently, plans for Phase III trials with edoxaban have been announced. Hence, with no currently available FXa inhibitor antidote and potential severe bleeding complications in FXa inhibitor-treated patients, antifibrinolytic agents (e.g. tranexaminic acid) should be administered, and in the case of life-threatening bleeding, four-factor prothrombin complex concentrates (PCCs) should be administered. Importantly, evidence from randomized trials is lacking regarding these strategies. Treatment with PCCs is based on the ability

of PCCs to attenuate bleeding or correct anticoagulation tests in preclinical models [67, 68], and as it carries a substantial prothrombotic risk, it should only be used in patients with life-threatening bleeding. In addition, unabsorbed drug should be removed from the gastrointestinal tract by administration of oral-activated charcoal if the last dose was recent enough that unabsorbed drug is likely to be present (apixaban within 6 h, dabigatran within 2 h, edoxaban within 2 h, rivaroxaban within 8 h). Of note, active dabigatran is the only DOAC that can be removed from the circulation by haemofiltration as the FXa inhibitors are highly protein bound.

Hence, the choice between the different DOACs should be guided by patient characteristics, pharmacokinetic/pharmacodynamic properties, and possible side effects (Figure 3). The first-day treatment (whether or not preceded by a short course of LMWH/fondaparinux administration) should be adapted accordingly. Importantly, many relative contraindications to DOACs were exclusion criteria in the clinical trials (see the online supplement for an overview of contraindications). Therefore, LMWHs will continue to play an important role in initial PE treatment and in some cases there remains a role for UFH.

Indications for unfractionated heparin therapy

Despite the clear benefits of LMWHs/fondaparinux over UFH, and of DOACs over LMWHs/fondaparinux, UFH is not totally obsolete in the acute treatment of PE. The first two indications for iv UFH treatment are a creatinineclearance

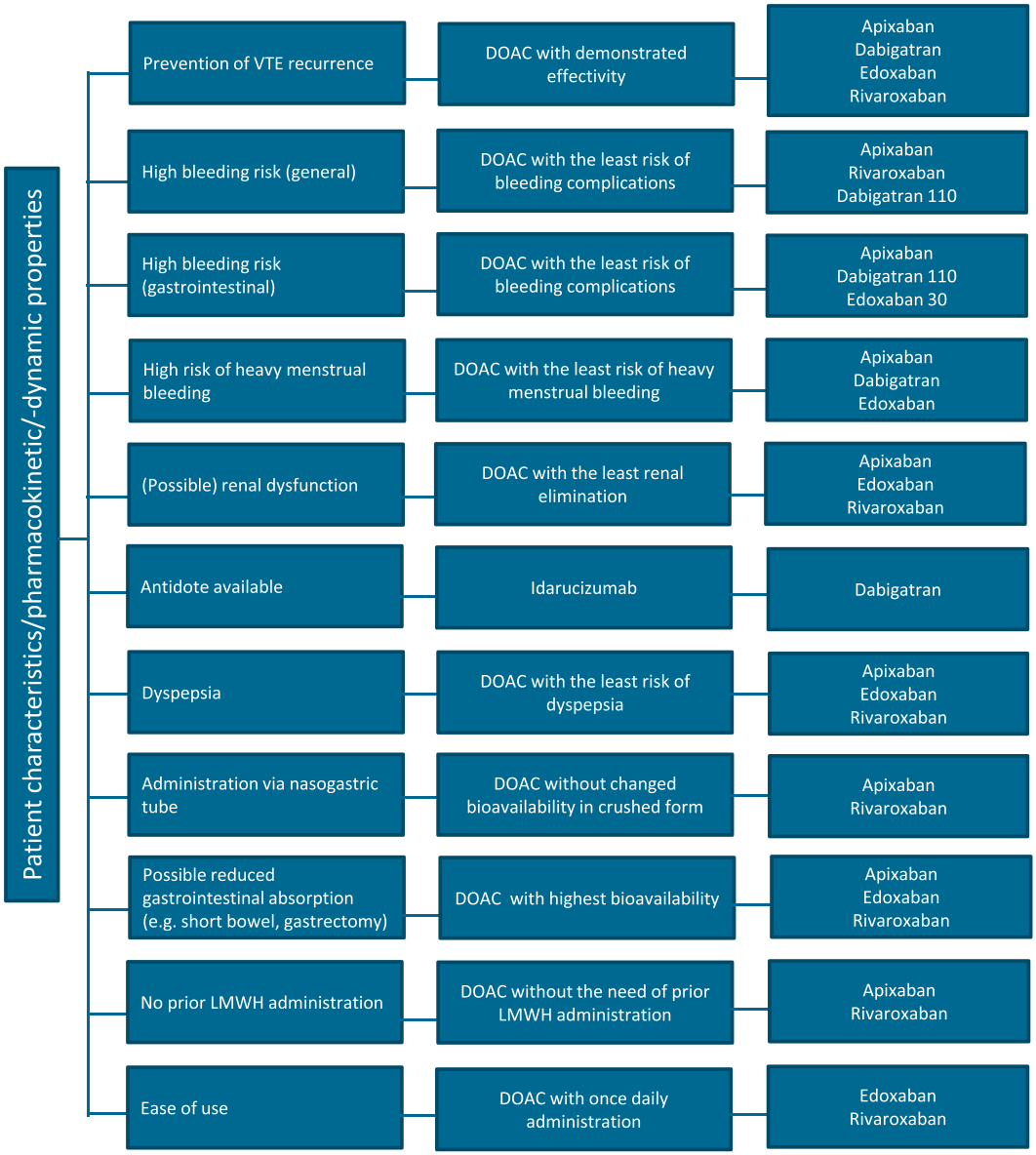

Figure 3

DOAC flowchart based on pharmacokinetic and pharmacodynamic properties and patient preferences

of ≤30 ml min^{-1} [42], and severe obesity (BMI > 40 kg m^{-2}) [69]. The rationale is two-fold. First, the efficacy of LMWHs, fondaparinux and DOACs in patients with acute PE and severe renal failure and/or severe obesity has not been well studied because most RCTs excluded such patients or failed to specify whether these patients were recruited [69, 70]. Second, severe renal insufficiency and/or severe obesity alter the pharmacokinetics of the anticoagulants, requiring that activity be monitored. It is more convenient to monitor UFH than LMWH/fondaparinux/DOACs because activated partial thromboplastin time (aPTT) testing is generally more readily available and less expensive than anti-Xa or anti-IIa assays (dTT). Nevertheless, anti-factor Xa assays are increasingly used to dose LMWH in patients with renal failure or severe obesity in clinical practice, although data regarding the correlation between anti-factor Xa activity and the reduction of thromboembolic events or bleeding complications are limited. Of note, in patients with severe renal failure treated with enoxaparin, it was demonstrated that anti-factor Xa levels poorly correlate with the occurrence of haemorrhage [71]. Additional studies are clearly needed for specific dose guidance of anti-factor Xa. Until then, in our opinion, anti-factor Xa dose guidance should be cautiously applied. A third indication for IV UFH is the consideration of thrombolysis: because of the short half-life of UFH, the patient is subjected to concomitant anticoagulant and thrombolytic activity for the shortest duration, during which the anticoagulant effect can be effectively interrupted with protamine.

Intermediate risk pulmonary embolism

Special concern applies to patients with intermediate risk PE [72]. These patients are defined by acute right ventricular dysfunction and myocardial injury without overt haemodynamic compromise and are at a much higher risk for adverse outcome than patients with low risk PE [54, 73]. In recent years several clinical trials aimed to reduce mortality in these patients by the use of thrombolysis [54, 74]. However, the clear benefit of thrombolysis in terms of reduced PE-related mortality were counterbalanced by the higher incidence of severe bleeding complications [54]. Therefore, thrombolysis for these patients was ultimately not included in the clinical guidelines. Nevertheless, strategies to reduce mortality and morbidity in these patients are much needed. An initial bolus of UFH before the start of LMWHs/fondaparinux/DOACs could be considered for several reasons: firstly, intermediate risk PE patients are more likely to become haemodynamically unstable requiring secondary thrombolysis, which is contra-indicated for use of anticoagulants with longer half-lives. Secondly, with a t_{max} ranging from 4–6 h for LMWHs, 2–3 h for fondaparinux, and 1–4 h for DOACs (Table 1), it seems rational from a pharmacokinetic point of view to start with an initial bolus of UFH in these patients in order to overcome the delay in onset of full anticoagulation. Unfortunately, the potential benefit of this approach has never been systematically studied. Finally, the earlier described preclinical evidence that UFH inhibits serotonin release from platelets associated with a decrease in vasospasm (and bronchospasm) may be of additional value in these patients (although large clinical trials investigating this approach are lacking). In all intermediate risk PE patients, despite the choice of initial therapy, careful initial monitoring is recommended for the first 24 h [72, 74].

Cancer-related pulmonary embolism

LMWH therapy is indicated in patients with cancer-related PE, not only for the initial treatment but also for the long-term treatment. It was demonstrated in large RCTs that LMWH therapy in patients with cancer-related PE has a beneficial effect on PE-related morbidity and mortality compared to VKA therapy [75–78], possibly because of a lower time in therapeutic range due to illness and co-medication. It is also suggested that heparin/LMWH itself has anti-neoplastic effects which have already been extensively reviewed elsewhere [79]. Heparin-induced inhibition of angiogenesis has, for example, been an area of intense research [80–83]. LMWHs were shown to inhibit proliferation of endothelial cells induced by **VEGF** [84–86]. Furthermore, the ability of LMWHs to inhibit metastasis in animal models is substantially documented [80]. Antimetastatic properties of LMWHs are likely due to interference with endothelial cell adhesion. The ability of heparins to interfere with selectin binding appears to be a major pathway for their anti-metastatic properties [87–90]. The possible mechanism may also involve interaction with **VLA-4**/**VCAM-1** [91]. The importance of selectins is emphasized by findings that the anti-metastatic effect of heparins cannot be demonstrated in animals deficient in P- or L-selectin [90, 92]. Based on these preclinical data, several studies with LMWHs in cancer patients were conducted. However, because conflicting clinical data have been presented, there is at present no approved use for LMWHs in cancer patients without a need for VTE prophylaxis or treatment [93–95].

Clinical trials investigating the effects of DOACs were not aimed at oncologic patients, although these patients were not excluded in the majority of studies. A trend towards reduced recurrent VTE and bleeding in favour of DOACs was observed compared to VKA therapy, although this was only in a limited number of patients [96]. DOAC *vs*. LMWH therapy for the treatment of cancer-related PE is currently being investigated (e.g. SELECT-D trial, CARAVAGGIO trial, CONCO-11 trial, CASTA-DIVA trial, CANVAS trial). Until these results are known, LMWH therapy remains the therapy of choice in these patients.

Further considerations

In addition to the improved usability and, consequently, improved quality of life, cost-effectiveness of the DOACs will determine whether these agents will remain the therapy of choice. However, in order to estimate the costs properly, not only the direct costs of the different anticoagulants should be taken into account, but also the costs of recurrent VTE including hospitalization monitoring anticoagulatory activity, the costs of bleeding complications and the cost of bleeding management should be weighted (including specific DOAC antidotes which became available very recently for dabigatran [65], or will be available in the near future for the oral Xa inhibitors [66]). Of note, the medical costs attributable to VTE in the pre-DOAC era in the United States were

estimated to be between $7 billion and $10 billion annually [97]. Other uncertainties, which will be solved in time, arise from the lack of specific tests with validated cutoff values to monitor anticoagulatory effects of DOACs, and from the absence of long-term clinical data and long-term side-effects.

Conclusion

Because DOACs are equally effective as other anticoagulatory regimens, have lower bleeding risks, do not need monitoring routinely, and are administered orally, they have recently become the agents of choice in the acute and chronic treatment of PE. In patients with a contraindication to DOACs, LMWH/fondaparinux is generally preferred over UFH therapy because of a better and more predictable therapeutic effect. Nevertheless, based on pharmacokinetic, pharmacodynamic and relevant off-target properties, there are still several indications for UFH therapy in the initial management of PE, for example in intermediate risk PE patients. There is a pathophysiological rationale for an initial bolus of UFH in LMWH- or DOAC-treated patients with intermediate risk PE, but the possible benefit of this approach remains to be investigated.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [98], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [99, 100].

Competing Interests

There are no competing interests to declare.

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Supporting Information

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Table S1 Overview of DOAC–drug interactions