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Direct Oral Anticoagulants for Pulmonary Embolism

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Abstract

Venous thromboembolism (VTE) is the third most common cardiovascular disease. For most patients, the standard of treatment has long consisted on low-molecular-weight heparin followed by vitamin K antagonists, but a number of clinical trials and, subsequently, post-marketing studies have shown that direct oral anticoagulants (DOACs) with or without lead-in heparin therapy are effective alternatives with fewer adverse effects. This evidence has led to important changes in the guidelines on the treatment of VTE, including pulmonary embolism (PE), with the DOACs being now recommended as the first therapeutic choice. Additional research has contributed to identifying low-risk PE patients who can benefit from outpatient management or from early discharge from the emergency department with DOAC treatment. There is evidence to support the use of DOACs in intermediate-risk PE patients as well as in high-risk patients receiving thrombolytic treatment. The use of DOACs has also been proven to be safe and effective in special populations of PE patients, such as patients with renal impairment, liver impairment, and cancer.

Keywords

- pulmonary embolism
- treatment
- direct oral anticoagulants

Venous thromboembolism (VTE), a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease, affecting around 700,000 persons annually in North America.[1–3] For most patients, the standard of care has long consisted on low-molecular-weight heparin (LMWH) followed by vitamin K antagonists (VKAs),[4] but more recently several trials have shown that direct oral anticoagulants (DOACs) with or without lead-in heparin therapy are effective alternatives with fewer adverse effects.[5–8]

In this review, we want to summarize the current and most important literature regarding the use of DOACs in PE patients, a therapeutic strategy that has rapidly changed the acute phase treatment and secondary prevention of this disease.

We will initially focus on the studies that have placed the DOACs as the current treatment of choice of VTE, and we will then focus on the indications for these drugs in low- and high-risk patients and in the setting of special and complex situations such as cancer patients, patients with liver disease, and patients affected by renal insufficiency.

Evaluation of the Efficacy and Safety of DOACs in the Treatment of Pulmonary Embolism

The efficacy and safety of DOACs in the treatment of PE were mainly evaluated in five randomized controlled trials (RCTs), in which DOACs were compared to the standard treatment with LMWH followed by warfarin.

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HOKUSAI-VTE,[5] AMPLIFY,[6] RE-COVER,[7] and RE-COVER II[9] were designed as randomized, double-blind trials and included both patients with DVT and PE. EINSTEIN-PE[8] was a randomized, open-label trial including PE patients only.

In the RE-COVER and RE-COVER II studies, dabigatran was administered at a fixed dose of 150 mg twice daily after a lead-in treatment with parenteral unfractionated heparin, LMWH, or fondaparinux.[7,9] In particular, a median of 3 days of parenteral anticoagulation was administered before randomization, and a median of 6 days of parenteral anticoagulation was given after randomization. In the HOKUSAI-VTE study, edoxaban 60 mg daily was administered following at least 5 days of unfractionated heparin or LMWH. Edoxaban dose was reduced to 30 mg daily if creatinine clearance was between 30 and 50 mL/min, body weight was lower than 60 kg, or patients received a potent P-glycoprotein inhibitor.[5] A single therapeutic approach, without lead-in parenteral anticoagulants, was used in the EINSTEIN-PE study with rivaroxaban and in the AMPLIFY trial with apixaban.[6,8] Rivaroxaban was administered at a dose of 15 mg twice daily for 3 weeks followed by 20 mg once daily; apixaban at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily. The characteristics of the populations enrolled in these trials are summarized in ►Table 1. It should be noted that the population enrolled in these studies is generally a low-risk population. The mean age was around 55 years, and there was a low proportion of patients with renal failure or other comorbidities or with low body weight. These studies showed the noninferiority in efficacy of all DOACs compared to the standard of treatment with parenteral LMWH followed by warfarin (►Table 2). For rivaroxaban and apixaban, data supported the possibility to start treatment directly with a higher dose of these drugs, although about 90% of patients received parenteral anticoagulation for 1 or 2 days before randomization. In the EINSTEIN PE and AMPLIFY studies, the severity of PE was defined by its anatomical extent at computed tomography (CT) scan, with a quarter of patients having extensive PE (multiple lobes and >25% of the entire pulmonary vasculature) in the former study and more than one-third in the latter.[6,8] A subanalysis of the HOKUSAI study reported that parenteral heparin followed by edoxaban was more effective than parenteral heparin followed by warfarin in preventing recurrent VTE in patients with PE and right ventricular disfunction defined by elevated NT-proBNP or right ventricular dilation (right/left ventricle ratio ≥0.9).[10]

As concerns safety, major bleeding rates with dabigatran were similar to those on warfarin in both the RE-COVER and RE-COVER II studies, whereas the composite of major and clinically relevant nonmajor bleeding was significantly reduced with dabigatran, although the incidence of gastrointestinal bleeding was increased.[7,9] Of interest, the RE-COVER II study did not show any increased risk of bleeding in patients older than 75 years. Lead-in LMWH followed by edoxaban was also associated with a significant reduction in major or clinically relevant nonmajor bleeding, the primary safety outcome of the study, with no difference in major bleeding events.[5] In the EINSTEIN PE study, there were significantly fewer major bleeding events in the rivaroxaban

Table 1 Characteristic of the study populations of DOAC trials

	HOKUSAI-VTE[5]		AMPLIFY[6]		RE-COVER[7]		RE-COVER II[9]		EINSTEIN-PE[8]	
	Edoxaban (*N* = 4,118)	Warfarin (*N* = 4,122)	Apixaban (*N* = 2,691)	Warfarin (*N* = 2,704)	Dabigatran (*N* = 1,273)	Warfarin (*N* = 1,266)	Dabigatran (*N* = 1,280)	Warfarin (*N* = 1,288)	Rivaroxaban (*N* = 2,419)	Warfarin (*N* = 2,413)
Mean age (y)	55.7 ± 16.3	55.9 ± 16.2	57.2 ± 16.0	56.7 ± 16.0	55.0 ± 15.8	54.4 ± 16.2	54.7 ± 16.2	55.1 ± 16.3	57.9 ± 7.3	57.5 ± 7.2
Male sex, *n* (%)	2,360 (57.3)	2,356 (57.2)	1,569 (58.3)	1,598 (59.1)	738 (58)	746 (58.9)	781 (61)	776 (60.2)	1,309 (54.1)	1,247 (51.7)
Cr. clearance, *n* (%)										
< 30 mL/min	NR	NR	14 (0.5)	15 (0.6)	NR	NR	NR	NR	4 (0.2)	2 (<0.1)
30–50 mL/min	268 (6.5)	273 (6.6)	161 (6.0)	148 (5.5)	NR	NR	NR	NR	207 (8.6)	191 (7.9)
50–80 mL/min	NR	NR	549 (20.4)	544 (20.1)	NR	NR	NR	NR	637 (26.3)	593 (24.6)
> 80 mL/min	NR	NR	1,721 (64.0)	1,757 (65.0)	NR	NR	NR	NR	1,555 (64.3)	1 + 617 (67.0)
PE patients, with or without DVT, *n* (%)	1,650 (40.1)	1,669 (40.5)	930 (34.5)	906 (33.0)	391 (30.7)	395 (31.2)	402 (31.4)	414 (32.1)	2,419 (100)	2,413 (100)
Cause of VTE, *n* (%)										
Unprovoked	2,713 (65.9)	2,697 (65.4)	2,416 (89.8)	2,429 (89.8)	NR	NR	NR	NR	1,566 (64.7)	1,551 (64.3)
Provoked	1,132 (27.5)	1,140 (27.7)	272 (10.1)	272 (10.1)	NR	NR	NR	NR	1,006 (42)	1,001 (41.4)
Active cancer	378 (9.2)	393 (9.5)	66 (2.5)	77 (2.8)	NR	NR	NR	NR	114 (4.7)	109 (4.5)

Abbreviations: Cr. clearance, creatinine clearance; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

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Table 2 Efficacy of DOACs in the different trials

	HOKUSAI-VTE[5]		AMPLIFY[6]		RE-COVER[7]		RE-COVER II[9]		EINSTEIN-PE[8]	
	Edoxaban ($N = 4,118$)	Warfarin ($N = 4,122$)	Apixaban ($N = 2,691$)	Warfarin ($N = 2,704$)	Dabigatran ($N = 1,274$)	Warfarin ($N = 1,265$)	Dabigatran ($N = 1,279$)	Warfarin ($N = 1,289$)	Rivaroxaban ($N = 2,419$)	Warfarin ($N = 2,413$)
Recurrent VTE, *n* (%)	130 (3.2)	146 (3.5)	59 (2.3)	71 (2.7)	64 (5)	59 (4.6)	64 (5.0)	58 (4.5)	50 (2.1)	44 (1.8)
Fatal PE, *n* (%)	4 (0.1)	3 (0.1)	1 (<0.1)	2 (0.1)	1 (0.1)	3 (0.2)	3 (0.2)	0 (0.0)	2 (<0.1)	1 (<0.1)
Death with PE not ruled out, *n* (%)	20 (0.5)	21 (0.5)	11 (0.4)	13 (0.5)	NR	NR	NR	NR	8 (0.3)	5 (0.2)
PE with or without DVT, *n* (%)	49 (1.2)	59 (1.2)	27 (1.0)	23 (0.9)	13 (1.0)	7 (0.6)	7 (0.5)	13 (1.0)	22 (0.9)	19 (0.7)
DVT alone, *n* (%)	57 (1.4)	63 (1.5)	20 (0.8)	33 (1.3)	16 (1.3)	18 (1.4)	25 (2.0)	17 (1.3)	18 (0.7)	17 (0.7)

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep venous thrombosis; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

group, whereas in the AMPLIFY study, apixaban was associated with a significant reduction of both major and clinically relevant nonmajor bleedings.[6,8] Data on safety are summarized in ►Table 3.

DOACs for PE Patients in the Guidelines

After these studies that consistently highlighted the noninferiority in efficacy of the DOACs in the treatment of PE as compared to the standard of treatment, with an improved safety profile, all major international guidelines updated their indication. The most recent editions of the European Society of Cardiology guidelines on acute PE (2019),[11] the American Society of Hematology guidelines (2020),[12] and the American College of Chest Physicians guidelines (2021)[13] suggest the use of a DOAC over the use of a VKA for patients with PE without hemodynamic decompensation. These guidelines do not suggest the use of a specific DOAC over another and suggest taking into consideration factors such as once versus twice daily dosing, requirement of lead-in parenteral anticoagulation, renal function, concomitant treatment, or cancer for the therapeutic decision. At present, DOACs are not recommended in patients with severe renal impairment, pregnancy, or lactation, and in patients with antiphospholipid antibody syndrome. Anticoagulation should be maintained for at least 3 months and then discontinued if the patient had a PE secondary to a major transient/reversible risk factor. Indefinite anticoagulant treatment is recommended for patients with recurrent VTE, PE with nonidentifiable risk factor, or PE with persistent risk factors. Finally, when extended oral anticoagulation is required after PE in patients without cancer, a reduced dose of apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) should be considered after 6 months of treatment. This recommendation derives from the favorable results of the AMPLIFY Extension and EINSTEIN Choice trials, which showed the efficacy and safety of these reduced doses as compared to placebo or aspirin (in the latter study) in a population that included about one-third of patients with isolated PE.[14,15]

Post-Marketing Studies

As mentioned earlier, the RCTs enrolled mainly a low-risk population characterized by younger patients, with fewer comorbidities and lower proportion of renal function impairment than in the so called real-world population. Thus, the results of RCTs may not be fully translatable to wider populations. For this reason, post-marketing studies were conducted to better understand the safety and effectiveness of DOACs in a more general, real-world population.[16–22] The GARFIELD-VTE study included patients with multiple comorbidities, severe renal impairment, cancer, and pregnancy-related VTE, many of whom were excluded from RCTs; however, the adjusted all-cause mortality in VTE patients receiving DOACs was approximately one-fourth lower than that of patients receiving VKAs.[16,17] Moreover, fatal bleed and VTE-related deaths were reduced in patients receiving DOACs, while the rates of recurrent VTE and bleeding were

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Table 3 Safety of DOACs in different trials

	HOKUSAI-VTE[5]		AMPLIFY[6]		RE-COVER[7]		RE-COVER II[9]		EINSTEIN-PE[8]	
	Edoxaban ($N = 4,118$)	Warfarin ($N = 4,122$)	Apixaban ($N = 2,691$)	Warfarin ($N = 2,704$)	Dabigatran ($N = 1,274$)	Warfarin ($N = 1,265$)	Dabigatran ($N = 1,279$)	Warfarin ($N = 1,289$)	Rivaroxaban ($N = 2,419$)	Warfarin ($N = 2,413$)
Major bleeding, *n* (%)	56 (1.4)	66 (1.6)	15 (0.6)	49 (1.8)	20 (1.6)	24 (1.9)	15 (1.2)	22 (1.7)	26 (1.1)	52 (2.2)
Fatal bleeding, *n* (%)	2 (<0.1)	10 (0.2)	1 (<0.1)	2 (0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (0.1)	2 (<0.1)	3 (0.1)
Nonfatal major bleeding in critical site, *n* (%)	13 (0.3)	25 (0.6)	4 (0.1)	14 (0.5)	1 (<0.1)	9 (0.7)	6 (0.4)	4 (0.3)	7 (0.3)	26 (1.1)
Nonmajor bleeding, *n* (%)	298 (7.2)	368 (8.9)	103 (3.8)	215 (8.0)	NR	NR	NR	NR	228 (9.5)	235 (9.8)
Major bleeding or clinically relevant nonmajor bleeding, *n* (%)	349 (8.5)	423 (10.3)	115 (4.3)	261 (9.7)	71 (5.6)	111 (8.8)	64 (5.0)	102 (7.9)	249 (10.3)	274 (11.4)

Abbreviations: DOAC, direct oral anticoagulant; NR, not reported.

similar. About 38% of patients had PE. The ETNA-VTE confirmed the efficacy of edoxaban, highlighting that the rate of VTE recurrence at 3 months in patients treated with a lead-in course of LMWH followed by edoxaban was as low as 0.34%.[18] Also, the risk of bleeding was lower in the edoxaban group with major bleeding at 3 months occurring in 0.97% of patients, a result that was consistent with that observed in the HOKUSAI-VTE trial. The composite outcome of major or clinically relevant nonmajor bleeding occurred in 2.58% of the population, which is lower than the rate reported in the HOKUSAI-VTE trial.[18]

The RE-COVERY study enrolled a higher proportion of older patients with renal impairment in comparison to the population enrolled in the RE-COVER studies.[19] In this observational study, the number of patients receiving DOACs and VKAs was almost the same between elderly and nonelderly patients, even if the use of DOACs decreased with worsening renal function. The study, however, confirmed the safety and effectiveness of the use of DOACs in this higher-risk population, with about 40% of patients with PE.[19] Finally, in the XALIA and XALIA-LEA studies, rivaroxaban, when compared to LMWH treatment followed by VKAs, has shown lower rates of major bleeding, recurrent VTE, and all-cause mortality, confirming the generalizability of the EINSTEIN-PE results for the wider VTE population treated in routine clinical practice.[20–22] It should be mentioned that an increase in the incidence of uterine bleeding in younger women (<55 years) was observed, attributable to an increased prolonged menstrual or abnormal vaginal bleeding with rivaroxaban.

Management of Low-Risk Patients and Early Discharge with the DOACs

PE is a disease characterized by a wide spectrum of severity, ranging from low risk defined by an incidence of early adverse events, such as death or clinical deterioration, below 1% to high risk defined by an incidence of events higher than 15%.[23] Identifying patients with low-risk features could permit early discharge from the emergency department and outpatient treatment, minimizing the complications related to hospitalization, reducing the impact on health care costs and improving quality of life.[24–27] Different studies highlighted the low rate of complications when treating low-risk patients as outpatients,[28] but only a small number of eligible patients are currently treated as outpatients.[29,30] In a recent prospective cohort study, only 1.2% of PE patients were directly discharged from the emergency department, while 5.8% were discharged early from the hospital, within 48 hours.[31]

Correct identification of patients at low risk is crucial for optimal management and early home discharge. Current guidelines support the use of the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI), or the Hestia criteria, for this scope.[11] Moreover, patients should have no other reasons for hospitalization; they should have family or social support and easy access to medical care if needed. In a systematic review of studies conducted in the era of LMWH and VKAs, among patients treated at home (defined as less

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than 24 hours of hospitalization), the 3-month rate of VTE recurrence was 1.5%, the rate of major bleeding was 0.8%, and the rate of death was 1.6% at 3 months.[32]

Another meta-analysis, however, indicated that right ventricular (RV) disfunction on admission may increase the risk of early PE-related adverse events and death in patients classified as low risk solely with the use of clinical parameters and scores.[33] The study also highlighted how integrating clinical scores with the evaluation of RV disfunction (with laboratory biomarkers or imaging findings) increases the prognostic sensitivity.

The DOACs have indeed the potential to facilitate early discharge and outpatient management of carefully selected low-risk PE patients. The HOT-PE study investigated the efficacy and safety of early discharge (<48 hours) and ambulatory treatment with rivaroxaban.[34] Patients were eligible if they were defined as low risk using clinical scores and after the exclusion of RV dysfunction on admission (RV enlargement or dysfunction and free-floating thrombi in the right atrium or ventricle assessed by echocardiography or CT pulmonary angiography). In this study, the 3-month rate of symptomatic or fatal recurrent VTE was 0.6% and major bleeding occurred in 1.2% of the population. No PE-related deaths were observed.[34] On the basis on these results, it seems appropriate to rule out RV disfunction in patients who are considered for immediate or early (<48 hours) home discharge[11] (►Fig. 1).

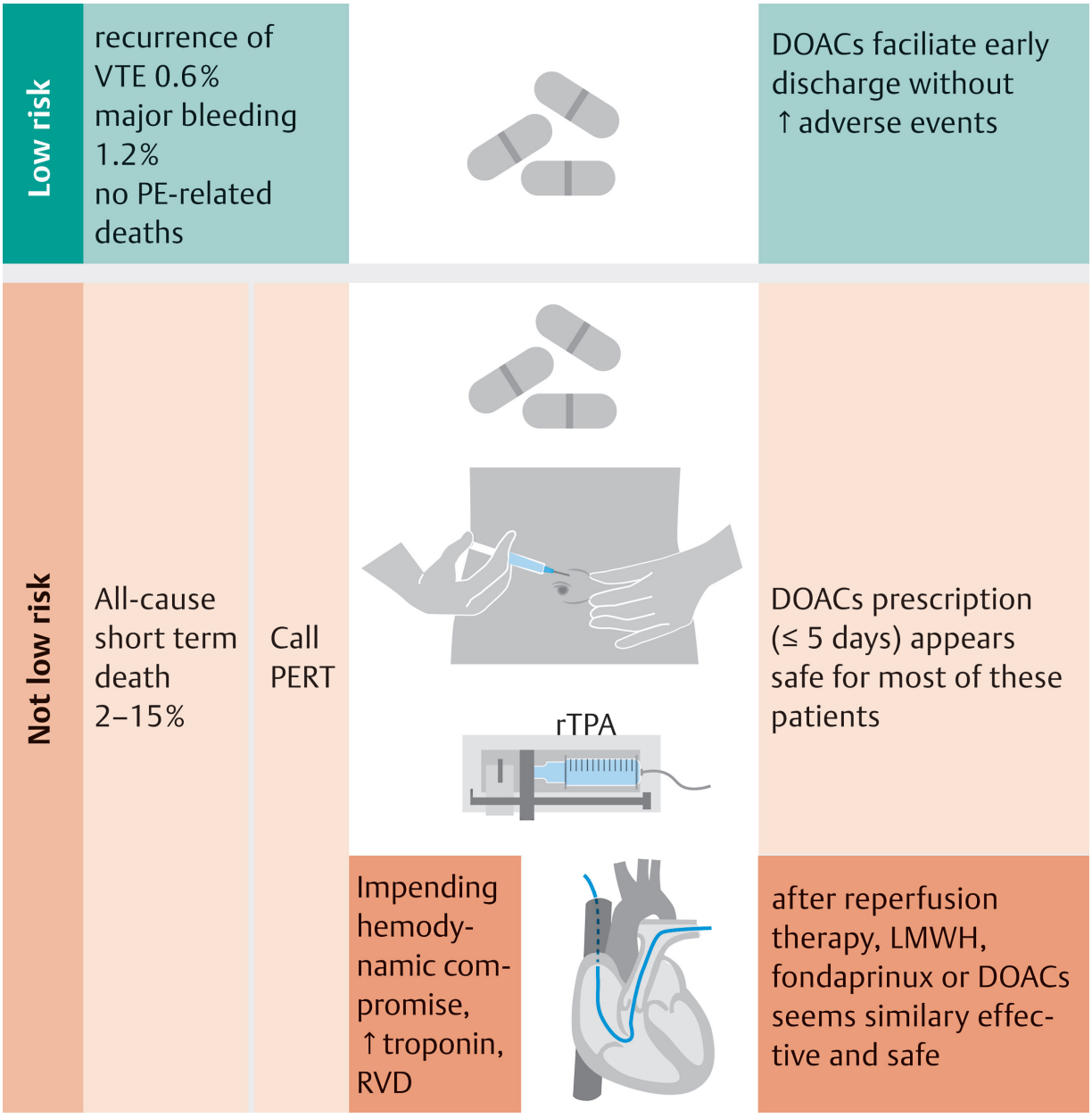

Fig. 1 Therapy of pulmonary embolism (PE) in normotensive patients. DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PERT, PE response team; rtPA, recombinant tissue plasminogen activator; RVD, right ventricular dysfunction; VTE, venous thromboembolism

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DOACs in the Treatment of PE Patients at Intermediate to High Risk of Mortality

Recent registries have shown that about 60 to 70% of patients with acute PE qualify for intermediate risk of early death (in-hospital or after 30 days), defined as a hemodynamic stability associated an RV dysfunction and/or troponin alteration according to the guidelines of the European Society of Cardiology or the American Heart Association.[11,31,35] The expected mortality in these normotensive patients with clinical risk factors for death (PESI III–V or sPESI $\geq$ 1) and/or evidence of RV overload by imaging or by increased troponin varies between 2 and 15% in the short term. Among patients included in this wide risk category, there is a subgroup with a considerable risk of requiring rescue reperfusion or cardiopulmonary resuscitation for clinical deterioration. According to the European Society of Cardiology, the combination of PESI III to V or sPESI $\geq$ 1, RV dysfunction at imaging and increased troponin identify a subgroup of about 25% of all PE patients having a short-term mortality as high as 10 to 15%.[31–36] In addition to the uncertainties on the criteria for identification of the intermediate- to high-risk patients, the optimal regimen of anticoagulation for these patients in the initial phase is also unknown.[31,37,38] The European Society of Cardiology guidelines still recommend the use of unfractionated heparin for intermediate- to high-risk patients in the early phase of anticoagulation[11]; LMWH could be an alternative to avoid the need for monitoring and to promptly guarantee therapeutic anticoagulation.[39] As parenteral anticoagulation was used in all currently available studies assessing the efficacy and safety of thrombolytic treatment in patients with acute PE, initial heparin course can safely allow upgrading to systemic or percutaneous reperfusion in the event of clinical deterioration.

Two regimens of DOACs have been developed for the treatment of acute PE. Dabigatran and edoxaban have been validated for introduction after heparin lead-in, to take advantage of a consolidated regimen of parenteral anticoagulation in the very initial phase.[40,41] Rivaroxaban and apixaban have been developed to be used according to the single drug approach, that is, completely oral and composed of an initial high-dose regimen followed by a maintenance dose, without heparin lead-in.

Phase III trials with DOACs for the treatment of VTE did not require any specific risk stratification in patients entering the studies for index PE.[5–8,42,43] The radiological extension of emboli was reported in all the studies, the proportion of patients with extensive PE varying from 24 to 47%.[44] In a post hoc analysis including 3,319 patients with PE from the Hokusai-VTE, NT-proBNP was increased in 30 and 32% of patients randomized to edoxaban and warfarin, respectively. Among patients with increased NT-proBNP, recurrent VTE occurred in 3 and 6% of patients in the edoxaban and warfarin groups, respectively (hazard ratio [HR]: 0.50; 95% confidence interval [CI]: 0.26–0.94). The right-to-left ventricular diameter ratio was 0.9 or higher in 44 and 45% of evaluable patients in the edoxaban and warfarin groups, respectively. Recurrent VTE occurred in 3 and 5% of the patients in the edoxaban and warfarin groups, respectively (HR: 0.57; 95% CI: 0.27–1.17). Overall, this subanalysis suggests that among hemodynamically stable patients with acute PE, the efficacy of edoxaban after heparin lead-in is confirmed in those with increased NT-BNP or increased right-to-left ventricular diameter ratio.

More recently, the PEITHO2 trial assessed the role of early switch from parenteral anticoagulation to dabigatran (within 72 hours from diagnosis) in patients with acute PE at intermediate to high risk.[45] PE-related death, hemodynamic decompensation, or hemodynamic collapse occurred in less than 1% of 283 patients.[45] In 653 PE patients at intermediate- to high risk of death, 302 received a DOAC during hospitalization and were categorized as early (within 72 hours after the admission) and delayed switchers (after 72 hours).[46] The composite of all-cause death or hemodynamic decompensation at 30 days occurred in 4.8% (95% CI: 1.6–10.9); hemodynamic decompensation occurred in 2.9% (95% CI: 0.6–8.3). The relative risk of all-cause death or hemodynamic decompensation at 30 days was reduced in the early switchers (odds ratio [OR]: 0.38; 95% CI: 0.11–1.38). Taken together, these studies show that early DOAC prescription appears safe for most patients at intermediate to high risk, but in a minority of cases, adverse outcomes might occur. Thus, further efforts are needed to identify these patients (►Fig. 1).

Real-world data on contemporary management of VTE show that about half of PE patients receive parenteral anticoagulation followed by oral anticoagulation.[10]

Timing of Initiation of DOACs after Thrombolysis

Thrombolytic treatment in intermediate- to high-risk patients with acute PE reduces the risk of death or clinical deterioration at 7 days, but this benefit is counterbalanced by a 10-fold increased risk of intracranial hemorrhage (ICH) and 3-fold risk of major bleeding.[47,48] A new trial is currently evaluating the efficacy and safety of reduced-dose thrombolysis for intermediate- to high-risk patients (NCT04430569).[49] Pulmonary reperfusion techniques could be an alternative to systemic thrombolysis; however, the role of these techniques must still be proven (NCT04790370).[50–56]

Patients who had received thrombolysis were excluded from phase III clinical trials.[5–8] Current guidelines suggest driving the timing of switching to oral anticoagulation on clinical judgment.[11]

Few data exist on the efficacy and safety of switching to DOACs after systemic thrombolysis. A cohort study assessed a 24-hour course of unfractionated heparin followed by rivaroxaban after thrombolysis in 96 high- or intermediate-risk PE patients. No death, major bleeding, or recurrent VTE was observed during the hospitalization.[57]

In a recent retrospective study in 102 patients treated with thrombolysis (both systemic and catheter directed), no differences were observed in the 30-day mortality between patients treated with DOACs (early <48 hours or delayed >48 hours) or LMWH after unfractionated heparin, with a reduction in hospitalization in the DOAC group.[58]

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In a retrospective study, normotensive PE patients treated with catheter-directed thrombolysis were switched to oral anticoagulation early after the procedure; the oral agent was warfarin in 36 patients and DOACs in 26 patients.[59] There was no difference in the time to initiation of oral anticoagulant in the warfarin versus DOAC groups (2.9 vs. 2.3 days; $p = 0.16$). In these studies, early switch to DOACs provided shorter hospitalization than VKAs.

In summary, few and uncontrolled data are available on the use of LMWH, fondaparinux, and DOACs after thrombolysis; all these approaches seem to have similar efficacy and safety.[59,60]

When managing patients in these gray areas, the multidisciplinary PE response team (PERT) team may assume an important role in merging expertise and tailoring the best care for the patients.

DOACs for Specific Patient Groups

Validated regimens of DOACs to be used for the treatment of VTE are reported in ►Table 4.

Renal Impairment

About 10% of patients with a diagnosis of VTE have a concomitant severe reduction of renal function (creatinine clearance below 30 mL/min).[61] Severe renal failure is associated with increased mortality in a wide range of clinical settings. Irrespective of the formula used for their identification, patients with severe renal impairment have a higher risk of major bleeding under anticoagulant therapy in comparison to patients with normal renal function (OR: 2.26; 95% CI: 2.01–2.53).[62]

Of 10,684 patients with an objective diagnosis of VTE (excluding superficial vein thrombosis) included in the Garfield Registry, 1,245 (11.7%) patients had moderate (creatinine clearance between 30 and 49 mL/min) renal failure and 273 (2.6%) had severe renal failure (creatinine clearance lower than 29 mL/min).[62] In patients with renal insufficiency, the unadjusted rates of recurrent VTE and major bleeding were comparable between treatment groups, while the rate of all-cause mortality was lower in those receiving DOACs than in those receiving VKAs (4.70 vs. 9.97 per 100 person-years).

In the Hokusai-VTE study, 541 of 8,240 patients had moderate renal failure (creatinine clearance: 30–50 mL/min). In these patients, edoxaban confirmed noninferiority and no increase in bleeding complications in comparison to warfarin. Among the 363 Hokusai-VTE patients fulfilling the criteria for dose reduction with edoxaban due to moderate renal failure (i.e., patients with creatinine clearance of 30–50 mL/min), the recurrence rate was 3.3 versus 6.7% and incidence of clinically relevant nonmajor bleeding was 9.2 versus 14.0% in patients randomized to edoxaban (reduced dose) and warfarin, respectively.[63] In a meta-analysis of nine trials, no significant difference was observed between DOACs (dabigatran, rivaroxaban, apixaban) and warfarin in the risk of recurrent VTE and bleeding events in patients with moderate chronic kidney disease.[64]

Table 4 Validated regimens of DOACs to be used for the treatment of VTE

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Validated regimens/dose Initial dose Maintenance dose	10 mg twice a day for 5–7 d then, 5 mg twice a day	(Heparin lead-in) 60 mg/d, or 30 mg/d if creatinine clearance 15–50 mL/min or body weight ≤60 kg Use of P-gp inhibitors	15 mg twice a day for 21 d 20 mg	(Heparin lead-in) 150 mg twice a day
Liver impairment (Child–Pugh A)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
Liver impairment (Child–Pugh B)	Use with caution	Use with caution	Contraindicated	Use with caution
Liver impairment (Child–Pugh C)	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Renal impairment up to 30 mL/min	No data on reduced dose	Reduced dose if creatinine clearance 15–50 mL/min	No data on reduced dose	No data on reduced dose
Cancer	Same regimen as noncancer patients Caution in gastrointestinal or genitourinary cancer			No ad hoc clinical trial

Abbreviations: DOAC, direct oral anticoagulant; P-gp, P-glycoprotein; VTE, venous thromboembolism.

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The risk of major bleeding increased when the degree of kidney impairment increased. There was no significant difference between apixaban and warfarin for VTE outcomes in dialysis patients.

In an observational, cohort study in patients with acute VTE and severe renal failure, 626 DOAC patients were matched to 1,071 warfarin patients.[65] There was no statistically significant difference in recurrent VTE, clinically relevant bleeding, ischemic stroke, and all-cause mortality between the two treatment groups.

Among 29,790 VTE patients with chronic kidney disease selected from five U.S. claims databases, apixaban was initiated in 10,669 (35.8%) patients and warfarin in 19,121 (64.2%) patients.[66] After inverse-probability treatment weighting balance, the apixaban group had a significantly lower risk of recurrent VTE (6.2 vs. 7.6%; HR: 0.78; 95% CI: 0.66–0.92), major bleeding (8.2 vs. 10.5%; HR: 0.76; 95% CI: 0.65–0.88), and clinically relevant nonmajor bleeding (HR: 0.86; 95% CI: 0.80–0.93) than the warfarin group. When stratified by the stage of chronic kidney disease (stage I/II: 8.2%; stage III: 49.4%; stage IV: 12.8%; stage V/end-stage renal disease [ESRD]: 12.0%; stage unspecified: 17.6%), patients with end stage chronic kidney disease had the highest event rates (recurrent VTE: 7.7 vs. 11.6%; major bleeding: 16.9 vs. 18.0%); however, stages of chronic kidney disease did not have any significant impact on treatment effects for recurrent VTE and major bleeding.

In a retrospective cohort study in 12,206 individuals receiving dialysis in the United States who received a new prescription for apixaban or warfarin following a VTE diagnosis, apixaban was associated with lower risks of both recurrent VTE (HR: 0.58; 95% CI: 0.43–0.77) and major bleeding (HR: 0.78; 95% CI: 0.62–0.98) over 6 months, compared with warfarin.[67] However, there was no difference between apixaban and warfarin in terms of risk of all-cause death (HR: 1.04; 95% CI: 0.94–1.16).

Overall, the above-reported data suggest that the efficacy to safety profile of DOACs, and in particular that of apixaban, could apply to the peculiar setting of patients with severe renal failure. RCTs are awaited mainly to assess the optimal regimen of DOACs in this clinical setting.

Liver Impairment

Patients with cirrhosis are at an increased risk of thromboembolic and bleeding events.[68–70] The international normalized ratio (INR) increases over 2.0 together with thrombocytopenia were previously thought to protect against VTE; however, recent data disproved this theory. In randomized trials, VKAs reduced the risk of thromboembolism in patients with AF or VTE and impaired liver function.[71] Among DOACs, apixaban and rivaroxaban have significant proportions of hepatic clearance (73 and 65%, respectively) mostly through CYP3A4-type cytochrome P450-dependent elimination, while edoxaban (50%) and dabigatran (20%) have lower proportions.[72] Liver diseases leading to impaired hepatic function can all influence pharmacokinetic properties of DOACs to variable degrees. Several DOACs have a high plasma protein binding capacity, which can translate into elevated free drug fraction levels when liver albumin production is reduced. In the presence of liver diseases, the excretion of all DOACs in the bile is reduced. Finally, when liver disease is accompanied by hepatorenal syndrome, renal clearance of DOACs may be compromised. Overall, significant liver disease can hugely affect hepatic clearance and drug metabolism, and impaired function of liver enzymes and transporters may affect drug response and facilitate drug-induced liver injury.

Patients with advanced and active liver disease including cirrhosis or those with persistent increase of liver enzymes or bilirubin were excluded from phase III trials with DOACs for the treatment of VTE. As of today, DOAC use is allowed without restrictions in patients with Child–Pugh A, with caution in patients with Child–Pugh B, and avoided or contraindicated in patients with Child–Pugh C.

Currently, there is paucity of data on the efficacy and safety of DOACs in patients with advanced liver diseases. In a retrospective study including patients with Child–Pugh B and C cirrhosis receiving therapeutic anticoagulation, bleeding occurred in 36% of patients in the DOAC group and in 22% of patients in the traditional group.[73] In the DOAC population, 31 and 70% of patients with Child–Pugh B or C cirrhosis experienced a bleeding event. Thromboembolic events were reported in 4% of the DOAC group and none in the traditional anticoagulation group.

Cancer-Associated VTE

Several randomized studies have been conducted with the aim to assess the efficacy and safety of DOACs in comparison to dalteparin for the treatment of cancer-associated VTE[74] (►Table 5). These trials differ for experimental agents, primary study outcome, treatment duration, and, finally, sample size. Overall, anti-Xa oral anticoagulants were at least noninferior to dalteparin with potential for 10% risk reduction in recurrent VTE. The safety profile differed across DOACs; an excess of gastrointestinal bleeding was observed in the edoxaban and rivaroxaban arms. Based on these results, current guidelines recommend caution when prescribing anti-Xa agents to patients with nonresected mucosal cancers.[75,76] Although these studies allowed us to clarify a number of issues beyond the general efficacy and safety of anti-Xa agents in the general population of patients with cancer, additional data are required to clarify the role of DOACs in the treatment of VTE in patients with brain cancers, hematological malignancies, and thrombocytopenia, and when used in association with specific anticancer agents.

Anticoagulant agents with direct anti-XI effect are currently under clinical development for the treatment of VTE in patients with active cancer.

Frail Patients

Frailty is a complex geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems.[77] Limited data are currently available on the efficacy and safety of DOACs based on geriatric definition of frailty. Rather data are available on the efficacy and safety of DOACs versus standard of care for the treatment of acute VTE in fragile patients identified as presence/absence of one or

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Table 5 DOAC trials on cancer-associated VTE patients

Study	Hokusai-VTE Cancer (2018)	SELECT-D (2018)	ADAM VTE (2019)	Caravaggio (2020)	CASTA-DIVA (2022)	Canvas (2021)
Experimental agent	Edoxaban	Rivaroxaban	Apixaban	Apixaban	Rivaroxaban	Anti-Xa
Control	Dalteparin	Dalteparin	Dalteparin	Dalteparin	Dalteparin	LMWH
Design	Randomized, open-label, noninferiority, PROBE	Randomized, open-label, pilot, PROBE	Randomized, open-label, superiority, PROBE	Randomized, open-label, noninferiority, PROBE	Randomized, open-label, noninferiority	Unblinded hybrid comparative effectiveness noninferiority trial[a]
Duration of treatment (mo)	6–12	6	6	6	3	6
Primary outcome	Composite of recurrent VTE and major bleeding	Recurrent VTE including unusual sites thrombosis	Major bleeding	Efficacy: recurrent VTE Safety: major bleeding	Recurrent VTE, including unusual worsening obstruction	Recurrent VTE
No. of patients	1,050	408	300	1,158	158	775

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.
[a]With randomized and preference cohorts.

more predefined criteria (age >75 years, calculated creatinine clearance <50 mL/min, or body weight ≤50 kg).[78] Rates of recurrent VTE were higher in fragile patients than in nonfragile patients. No difference in VTE recurrence was observed between rivaroxaban and standard therapy in fragile and nonfragile patients, but a significantly lower incidence of major bleeding was observed with rivaroxaban compared with standard therapy in fragile patients (1.3 vs. 4.5%; HR: 0.27; 95% CI: 0.13–0.54). These results were confirmed in retrospective administrative data[79] using the Johns Hopkins Claims-Based Frailty Indicator score for the identification of frail patients. In an analysis of the RIETE registry, 42% of 15,079 patients belonged to the frail group: 37% were aged ≥75 years, 20% had creatinine clearance levels ≤50 mL/min, and 3.6% weighed ≤50 kg.[80] The study showed that in real life the attending clinician tailors anticoagulant therapy on the risk of bleeding and recurrence of fragile patients.

Elderly

Current evidence mostly concerns elderly populations (65–79 years), while very elderly populations (≥80 years) have been underrepresented in randomized clinical trials. In these patients, different mechanisms are involved in platelet disorders (age-related amyloid angiopathy, vascular wall abnormalities, and impaired renal function) and increase risk of bleeding[81]

In a meta-analysis, DOACs reduced VTE recurrence compared with warfarin in patients older than 75 years.[82] In the RIETE cohort, VTE patients aged older than 90 years were less often treated with DOACs in comparison to younger patients. In patients aged older than 90 years, the rate of major bleeding was approximately 4.5-fold higher than that of VTE recurrence.[83]

Extreme Body Weight

In a post hoc analysis of the COMMAND VTE registry, the adjusted risk of major bleeding and all-cause death was higher in patients with body weight lower than 60 kg (HR: 1.57; 95%CI: 1.16–2.12 and HR: 1.50; 95%CI: 1.24–1.81) than in patients weighting more than 60 kg.[84]

In a post hoc analysis of AMPLIFY on patients with body mass index (BMI) > 40 kg/m^2 or body weight overpassing 120 kg,[85] the use of apixaban was not associated with an increased risk of recurrent VTE or VTE-related death. In a recent meta-analysis including patients with high body weight or morbid obesity, DOACs significantly decreased the risk of VTE recurrence (OR: 0.72; 95% CI: 0.57–0.91) and bleeding (OR: 0.74; 95% CI: 0.58–0.95; $I^2 = 0\%$; $p < 0.05$) compared to the standard of care.[86]

The ISTH SCC for the control of anticoagulation reports that DOAC use is appropriate for patients with weight greater than 120 kg or BMI greater than 40 kg/m^2, without regular laboratory monitoring.[87] However, it should be mentioned that in the treatment of VTE only edoxaban allows the use of a validated dose reduction based on body weight.

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Concomitant Thrombocytopenia

The management of anticoagulation in patients with thrombocytopenia (defined as a platelet count of $<100 \times 10^9$/L) is still an issue, mostly because the majority of these patients have a cancer-associated thrombosis. To reduce recurrence in the acute phase of VTE (within the first 30 days), a therapeutic dose of anticoagulation is recommended.[88] Currently no evidence is available for DOACs in patients with a severe thrombocytopenia (platelet counts of $<50 \times 10^9$/L).

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Walter Ageno received fees for lecture from Astra Zeneca, BMS Pfizer, Leo Pharma and Viatris and participated in Advisory Board for Astra Zeneca, Bayer, Leo Pharma, Norgine, Sanofi and Viatris.
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