

# Treatment of Venous Thromboembolism in Special Populations with Direct Oral Anticoagulants

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## Abstract

As a result of the successful completion of their respective phase III studies compared with vitamin K antagonists (VKAs), four direct oral anticoagulants (DOACs) have been approved for the treatment and secondary prevention of venous thromboembolism (VTE). These DOACs—apixaban, dabigatran, edoxaban, and rivaroxaban—have subsequently seen a steady uptake among clinicians since their approval. Despite the suitability of DOACs for a broad range of patients, they are not appropriate in certain situations, whereas in others they require additional considerations such as dose reductions. Subanalyses of phase III trials and studies on specific VTE patient populations have been conducted to evaluate the safety and efficacy of the DOACs in a broad range of settings, such as patients with renal impairment, patients with cancer, patients of childbearing potential, patients with multiple comorbidities and pediatric patients. Furthermore, many recent guidance documents from important hematological societies and other specialists have incorporated several of these developments. These documents also identify the patients for whom DOACs are not suitable and where traditional anticoagulation options such as heparins or VKAs should be considered instead. This review provides an overview of key VTE patient subgroups, the clinical evidence supporting the use of anticoagulation in these patients, and a discussion of the most appropriate approaches to their management, including considerations such as dosing, acute and extended treatment durations, and DOAC selection.

## Keywords

- ▶ comorbidities
- ▶ direct oral anticoagulants
- ▶ special populations
- ▶ venous thromboembolism

## Introduction

The treatment of venous thromboembolism (VTE)—comprising deep vein thrombosis (DVT) and pulmonary embolism (PE)—has evolved with the introduction of the direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, and rivaroxaban), whereas previously vitamin K antagonists (VKAs) were the only option for oral anticoagulation. VKAs are usually administered overlapping with and followed by parenteral anticoagulation until the desired therapeutic

levels are obtained (parenteral/VKA therapy).<sup>1</sup> Dabigatran and edoxaban are indicated to be used after  $\geq 5$  days of initial parenteral therapy for the acute venous thromboembolic event, whereas apixaban and rivaroxaban are eligible to be prescribed in the acute phase without prior parenteral use (→ Fig. 1).<sup>2–5</sup> Recent data from the GARFIELD-VTE registry demonstrated that nearly half of the patients with VTE enrolled between 2014 and 2017 were prescribed a DOAC, 26.8% received parenteral/VKA therapy, 17.6% a parenteral anticoagulant only, and 5.9% a VKA only.<sup>6</sup>

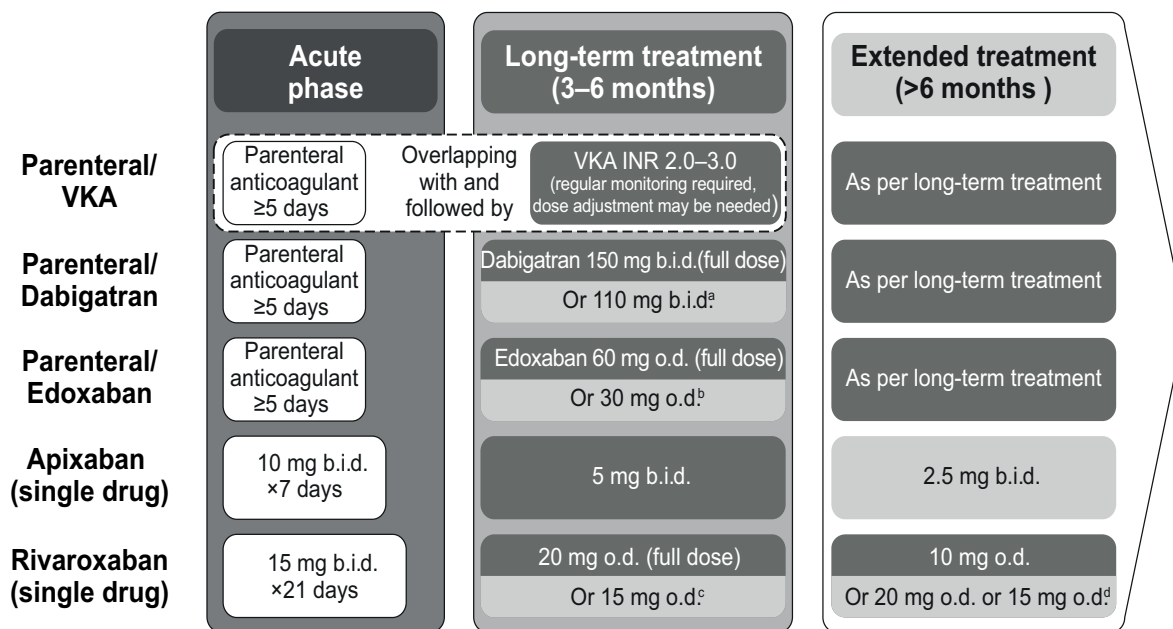
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**Fig. 1** Dosing schemas of oral anticoagulants approved for the treatment and/or secondary prevention of VTE.<sup>2–5,19</sup> Figure adapted from: Thrombosis Adviser. Dosing schemas of the NOACs for VTE treatment (online). 2020. Available at: [thrombosisadvisor.com/dosing-schemas-NOACs-VTE/](http://thrombosisadvisor.com/dosing-schemas-NOACs-VTE/). Accessed March 13, 2020. <sup>a</sup>Recommended for patients aged ≥80 years or those receiving concomitant verapamil. To be considered for patients aged 75 to 80 years old, with CrCl 30 to 50 mL/min, with gastritis, oesophagitis or gastroesophageal reflux, or at risk of bleeding (based on individual assessment of thromboembolic vs. bleeding risk); <sup>b</sup>in patients with CrCl 15 to 50 mL/min and/or weight ≤60 kg and/or concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole; <sup>c</sup>in patients with CrCl 15 to 49 mL/min if the patients' assessed risk of bleeding outweighs that of VTE; <sup>d</sup>when extended prevention of recurrent DVT and PE is indicated, the recommended dose is rivaroxaban 10 mg o.d. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with multiple comorbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10 mg o.d., a dose of rivaroxaban 20 mg o.d. should be considered (or 15 mg o.d. in patients with CrCl 15–49 mL/min). b.i.d., twice daily; CrCl, creatinine clearance; DVT, deep vein thrombosis; INR, international normalized ratio; NOAC, nonvitamin K oral anticoagulants; o.d., once daily; PE, pulmonary embolism; VTE, venous thromboembolism; VKA, vitamin K antagonist.

The increasing use of DOAC therapy coincided with recent updates to guidelines in 2016 from the American College of Chest Physicians (ACCP)<sup>1</sup> for antithrombotic therapy for VTE and in 2019 from the European Society of Cardiology (ESC) for acute PE.<sup>7</sup> Mainly due to the positive safety profile of the DOACs, these guidelines recommend the use of DOACs over VKA therapy in patients without cancer.<sup>1,7</sup> These recommendations are based upon the respective phase III randomized controlled trials (RCTs) for acute VTE treatment, long-term VTE secondary prevention,<sup>8–13</sup> and extended VTE secondary prevention.<sup>12,14,15</sup> Furthermore, DOACs overcome some of the practical limitations associated with VKA therapy due to their more predictable pharmacological properties.<sup>16</sup> Nonetheless, DOACs are not suitable for all patients with VTE (e.g., patients with severe renal impairment were excluded from the phase III RCTs of DOACs for VTE), and for other patient groups, dose adjustment or caution may be necessary (e.g., in patients with mild or moderate renal impairment).<sup>2–5</sup> A growing pool of data from subanalyses of the phase III VTE treatment RCTs and new RCTs for cancer-associated thrombosis (CAT) provide an opportunity to further optimize the use of DOACs in special populations. Findings from these studies have been generally supported by evidence collected from clinical practice.

This review will discuss important questions regarding the use of DOACs in patients with VTE, including DOAC suitability, dose, and duration of treatment across important patient groups, including patients with renal impairment, cancer, or multiple comorbidities; pediatric patients; patients with high body mass index (BMI); and in circumstances of pregnancy and breastfeeding.

## Direct Oral Anticoagulants: An Overview

Before discussing the use of DOACs in individual special VTE patient populations, we first consider the properties of VKAs and DOACs that might underpin drug choice and dosing decisions. Dosing strategies are outlined in ► **Fig. 1**. Criteria for dose reductions and cautions and contraindications are outlined in ► **Table 1**.

Apixaban, dabigatran, edoxaban, and rivaroxaban are indicated for both the treatment and secondary prevention of VTE and will, therefore, be the focus of this review.<sup>2–5</sup> Betrixaban is an additional factor Xa inhibitor, currently only indicated for VTE prophylaxis in patients hospitalized for acute medical illness and will,<sup>17</sup> therefore, not be discussed further. Compared with the DOACs, the inhibitory effects of

**Table 1** Dose reduction criteria and cautions and contraindications for direct oral anticoagulants approved for the treatment and/or secondary prevention of venous thromboembolism<sup>2-5,19</sup>

DOAC	Dose reduction	Criteria for dose reduction	Cautions and contraindications
Dabigatran	150–110 mg b.i.d.	Recommended for: patients aged $\geq 80$ years or those receiving concomitant verapamil. To be considered for patients: aged 75–80 years old; with CrCl 30–50 mL/min; with gastritis, oesophagitis or gastroesophageal reflux; at risk of bleeding (based on individual assessment of thromboembolic versus bleeding risk).	Contraindicated in patients using other anti-coagulants or strong P-gp inhibitors, or with CrCl $< 30$ mL/min, active clinically relevant bleeding, conditions/lesions with high bleeding risk, certain hepatic diseases, prosthetic valves or who are pregnant or breastfeeding. Caution advised in patients at risk of bleeding or undergoing surgery. Not recommended in patients with hepatic impairment, active cancer or using P-gp inhibitors.
Edoxaban	60–30 mg o.d.	CrCl 15–50 mL/min and/or weight $\leq 60$ kg and/or concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole.	Contraindicated in patients using other anticoagulants, or with active clinically relevant bleeding, severe uncontrolled hypertension, conditions/lesions with high bleeding risk, certain hepatic diseases, or who are pregnant or breastfeeding. Not recommended for patients with ESRD or undergoing dialysis, severe hepatic impairment, active cancer, <sup>a</sup> hemodynamically unstable PE. Caution advised in elderly patients taking ASA, patients with moderate hepatic impairment.
Apixaban	None apply	N/A	Contraindicated with clinically significant bleeding, hepatic disease associated with coagulopathy or bleeding risk, conditions/lesions with high bleeding risk, or use of other anticoagulants. Caution advised in elderly patients taking ASA, those at risk of hemorrhage, with mild/moderate hepatic impairment, CrCl 15–29 mL/min, or taking medications that affect hemostasis. Not recommended in patients with prosthetic valves, hemodynamically unstable PE, active cancer, CrCl $< 15$ mL/min, severe hepatic impairment, using strong CYP3A4 or P-gp inhibitors or inducers, who are pregnant or breastfeeding, or for certain surgeries.
Rivaroxaban	None apply <sup>b</sup>	N/A	Contraindicated in patients using other anti-coagulants, or with active clinically significant bleeding, conditions/lesions with high bleeding risk, certain hepatic diseases, or who are pregnant or breastfeeding. Caution advised in patients with CrCl 15–29 mL/min or taking medicines affecting hemostasis. Not recommended in patients undergoing surgery, at risk of hemorrhage, or with CrCl $< 15$ mL/min, prosthetic valves, hemodynamically unstable PE, or who are treated with strong CYP3A4 or P-gp inhibitors. <sup>a</sup>

Abbreviations: ASA, acetylsalicylic acid; b.i.d., twice daily; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; DOAC, direct oral anticoagulant; ESRD, end-stage renal disease; N/A, not applicable; o.d., once daily; PE, pulmonary embolism; P-gp, P glycoprotein; VTE, venous thromboembolism.

<sup>a</sup>Edoxaban and rivaroxaban are now considered options for the treatment of cancer-associated thrombosis in recently published guidance (based on results from the Hokusai-VTE-Cancer and SELECT-D studies).<sup>7,37,38,48,49,52,53</sup>

<sup>b</sup>Dose reduction from 20 to 15 mg o.d. can be considered in patients with CrCl 15 to 49 mL/min if the patients' assessed risk of bleeding outweighs that of VTE.

VKAs are indirect and affect several coagulation factors.<sup>18</sup> DOACs are also absorbed more rapidly than VKAs, reaching peak plasma concentrations between 2 and 4 hours<sup>2-5</sup> compared with approximately 24 hours (and up to 96 hours) for VKAs.<sup>19</sup> These properties underlie the rationale for apixaban and rivaroxaban use for acute-phase VTE treatment. Furthermore, the DOACs have short half-lives of approximately 5 to 14 hours depending on the age and renal function of a

patient,<sup>2-5</sup> compared with a half-life of approximately 40 hours for VKAs.<sup>19</sup> A shorter half-life is advantageous in the event of overdose, bleeding or to ensure low preoperative DOAC levels in preparation for elective surgery,<sup>20,21</sup> but may be considered a risk in circumstances of a missed dose or poor adherence to therapy.<sup>22</sup> DOACs have demonstrated a greater consistency in dose-dependent plasma levels and have a lower potential for food–drug and drug–drug

interactions than VKAs; as a result, no regular blood tests for anticoagulation monitoring are required with DOAC use.<sup>16</sup> All DOACs have a degree of renal excretion as active metabolites, impacting on their use in patients with severe renal impairment<sup>2–5</sup>; conversely, VKAs are almost entirely metabolized before urinary excretion.<sup>19</sup> As well as differences in the pharmacokinetic profiles of DOACs and VKAs, the bleeding profiles also differ. An analysis of the phase III acute VTE trials showed that DOACs were associated with a >50% decrease in intracranial hemorrhage or fatal bleeding events compared with VKAs.<sup>23</sup> No differences in major gastrointestinal (GI) bleeding rates were reported in patients receiving DOACs compared with those treated with VKAs.<sup>23</sup>

In comparing the DOACs among themselves, apixaban, dabigatran, and edoxaban can be taken with or without food, whereas the higher (15 mg once daily [o.d.] and 20 mg o.d.) doses of rivaroxaban should be taken with food. This is because food increases the bioavailability of rivaroxaban at higher doses and facilitates full resorption. In terms of drug interactions, all DOACs are substrates of ATP-binding cassette transporters such as P-glycoprotein, and rivaroxaban and apixaban are also metabolized by the cytochrome P450 3A4 pathway.<sup>2–5</sup> Renal excretion as active metabolites ranges from 27% for apixaban to 85% for dabigatran to approximately one-third for edoxaban and rivaroxaban. Although the DOACs all have similar pharmacokinetic properties, apixaban and dabigatran are dosed twice daily (b.i.d.) and edoxaban and rivaroxaban o.d. for long-term and extended secondary prevention of VTE.<sup>2–5,20</sup> As discussed previously, apixaban and rivaroxaban are approved for acute-phase VTE treatment without prior parenteral anticoagulation; to replace the use of a parenteral therapy an intensified b.i.d. dosing regimen applies.<sup>2,5</sup> The observational XALIA study demonstrated that in clinical practice the majority of patients with DVT without PE (89%) and with PE (74%) treated with rivaroxaban received no more than 48 hours of parenteral therapy before use.<sup>24</sup> Conversely, dabigatran and edoxaban should follow at least 5 days of initial parenteral therapy for acute VTE,<sup>3,4</sup> based on the design of their respective phase III RCTs (RE-COVER and Hokusai-VTE).<sup>10,11</sup> Reversal agents are now available for dabigatran (idarucizumab)<sup>25</sup> and the direct and indirect Factor Xa inhibitors (andexanet alfa; approved for use in the United States, granted a conditional marketing authorization in the EU as of 1 March 2019).<sup>26,27</sup>

## Direct Oral Anticoagulants in Special Patient Populations: Clinical Evidence and Practical Considerations

### Patients with Renal Impairment

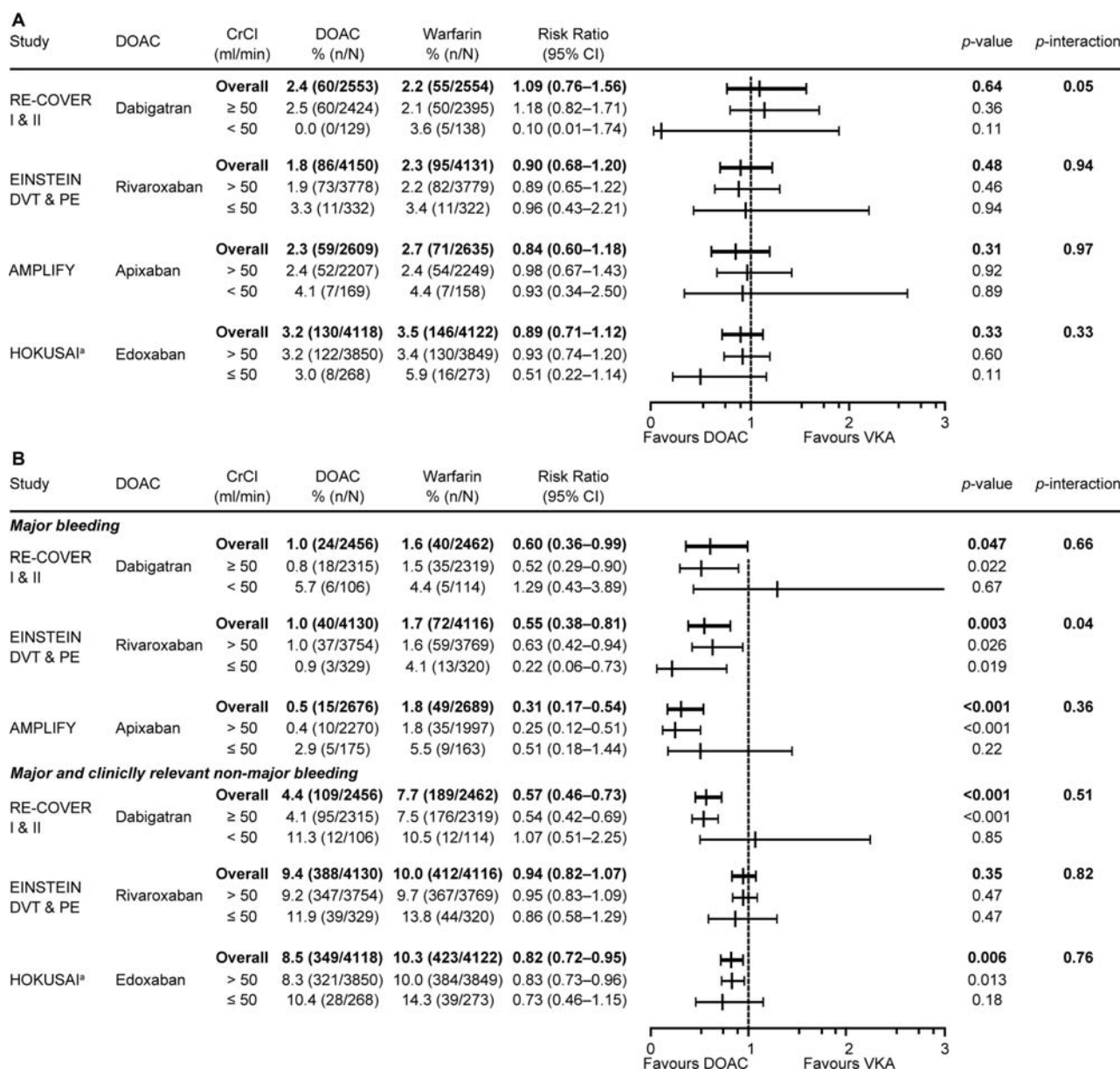
Renal impairment is a frequently encountered comorbidity in patients with VTE. For example, of 5,710 hospitalized patients with VTE in a study based in Germany, >40% had at least moderate renal impairment.<sup>28</sup> In the GARFIELD-VTE registry, which enrolled 10,685 patients with VTE from a diverse range of care settings, 4.6% of patients had severe (creatinine clearance [CrCl] < mL/min), and 15.7% had moderate (CrCl: 30–59 mL/min) renal impairment.<sup>6</sup> Both the risk

of VTE and bleeding while receiving an anticoagulant increases with declining renal function.<sup>29,30</sup> In the control (parenteral/VKA therapy) arm of a pooled analysis of data from the EINSTEIN DVT and EINSTEIN PE studies, the risk of recurrent VTE was 1.9% in patients with normal renal function (CrCl  $\geq$  80 mL/min) versus 3.2% in patients with moderate renal impairment (CrCl: 30–49 mL/min).<sup>31</sup> On the other hand, impaired renal function is also a risk factor for major bleeding, as demonstrated in the RIETE registry. The RIETE registry is an ongoing prospective registry of >10,000 patients with objectively confirmed symptomatic acute VTE. In an analysis of results up to March 2005 (at which point the registry included >10,000 patients), impaired renal function was associated with an increased risk of major bleeding (5.4% with a CrCl <30 mL/min vs. 1.0% with a CrCl >60 mL/min; odds ratio [OR]: 5.6, 95% confidence interval [CI]: 3.7–8.4;  $p < 0.001$ ) and fatal bleeding (1.2% with a CrCl <30 mL/min vs. 0.2% with a CrCl >60 mL/min; OR: 6.5, 95% CI: 2.7–16.0;  $p < 0.001$ ) compared with normal renal function. The registry also described an increased risk of fatal PE (6.6% with a CrCl <30 mL/min vs. 1.0% with a CrCl >60 mL/min; OR: 7.2, 95% CI: 4.9–11.0;  $p < 0.001$ ).<sup>32</sup>

The safety and effectiveness of DOACs in patients with renal impairment ranging from moderate to mild (but not severe) has been evaluated through RCTs, and data collected from clinical practice. The DOAC phase III VTE treatment trials included more than 7,000 patients with impaired renal function (~5–8% had moderate [CrCl: 30–49 mL/min] and approximately 20 to 25% mild [CrCl: 50–79 mL/min] renal impairment). Severe renal impairment (CrCl <30 mL/min [except in the AMPLIFY trial of apixaban, which used a threshold of CrCl <25 mL/min]) was an exclusion criterion across these studies.<sup>8,11,31,33</sup> As a result, patients with severe renal impairment made up <1% of the DOAC study populations,<sup>8,11,31</sup> and in a pooled analysis of dabigatran in the RE-COVER and RE-COVER II studies, such patients were excluded entirely.<sup>33</sup>

Subgroup analyses of outcomes according to renal function suggest that DOACs are effective and at least as safe as enoxaparin/VKA therapy for the treatment of VTE in patients with mild-to-moderate renal impairment. In a meta-analysis of these data, the risk of recurrent VTE or VTE-related death with DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) therapy was similar to enoxaparin/VKA therapy in patients with a CrCl  $\geq$  50 mL/min and a CrCl of 30 to 49 mL/min, whereas the risk of major bleeding was lower with DOAC therapy versus enoxaparin/VKA in both subgroups.<sup>23</sup> In another meta-analysis, the observed reduction in the risk of bleeding with DOAC versus enoxaparin/VKA therapy in patients with a CrCl  $\leq$  50 mL/min reached significance with rivaroxaban, and was observed as a nonsignificant trend with apixaban. The risk appeared more equal between treatment arms with dabigatran (–Fig. 2).<sup>34</sup>

Because drug exposure can increase with declining renal function in accordance with the proportion of the agent that is excreted renally,<sup>35</sup> careful consideration of anticoagulant choice is important. Furthermore, because renal function can decline over time—particularly in elderly patients and those taking multiple medications—regular assessment of renal



**Fig. 2** Rates of (A) recurrent VTE and (B) major bleeding and major plus clinically relevant nonmajor bleeding<sup>a</sup> with DOAC versus warfarin therapy in the phase III DOAC for VTE treatment trials.<sup>34,a</sup> Data for major bleeding in the Hokusai-VTE trial and major plus clinically relevant nonmajor bleeding in the AMPLIFY trial were not reported in the original studies. Figure adapted from Geldhof et al.<sup>34</sup> CI, confidence interval; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism.

function during the use of anticoagulation therapy is necessary.<sup>36</sup> Of all the DOACs, dabigatran has the highest degree of renal elimination as an active metabolite and apixaban the lowest. However, the use of DOACs is only contraindicated in cases of severe renal impairment (CrCl <15 mL/min or CrCl <30 mL/min for dabigatran); for less severe cases, cautions and dose reductions sometimes apply (► **Table 1**).<sup>2–5,19</sup> With regard to VKAs, some evidence suggests that they are associated with accelerated progression in chronic kidney disease, possibly because of renal vascular calcification.<sup>37</sup>

### Patients with Cancer

Cancer and its treatments are associated with a hypercoagulable state and are well-known risk factors for VTE (com-

monly referred to as cancer associated thrombosis [CAT]). Extended periods of anticoagulation therapy of at least 6 months are recommended for patients with CAT.<sup>7,38,39</sup> Until recently, low molecular weight heparin (LMWH) was the preferred therapy based on superior efficacy and/or safety compared with VKAs in the oncology setting.<sup>40–43</sup> Advantages of LMWH therapy for CAT include reliability in patients who have difficulty with oral therapy (e.g., those suffering from nausea/vomiting),<sup>1</sup> and there has been some experience gained in managing LMWH dosing in circumstances of thrombocytopenia (a complication often secondary to chemotherapy).<sup>1,44</sup> However, long-term persistence with LMWH may be challenging for some patients because of the burden and discomfort of daily subcutaneous injections;

furthermore, LMWHs are costly, with reimbursement an issue in some countries.<sup>45</sup> Indeed, low persistence with LMWH therapy and frequent use of oral alternatives (namely VKAs and rivaroxaban) have been observed in clinical practice.<sup>46–48</sup> This warranted the evaluation of DOACs versus LMWH for the treatment of CAT.

The phase III Hokusai-VTE-Cancer study<sup>49,50</sup> of edoxaban versus dalteparin and the randomized SELECT-D pilot study<sup>51</sup> of rivaroxaban versus dalteparin were the first cancer-population-specific randomized trials for DOACs in patients with CAT, and the first to compare DOACs with LMWH in this setting. The study designs and results are summarized in ► **Table 2**. As per the CLOT study design,<sup>41</sup> the dalteparin dose was reduced after 4 weeks from 200 to 150 IU/kg/day in both studies. Therefore, full-dose anticoagulation with edoxaban or rivaroxaban was compared with reduced-dose dalteparin.<sup>49,51</sup> In Hokusai-VTE-Cancer, edoxaban was noninferior to dalteparin for the composite outcome of recurrent VTE and major bleeding (12.8 vs. 13.5%; hazard ratio [HR]: 0.97, 95% CI: 0.70–1.36;  $p = 0.006$ ). Whereas the risk of recurrent VTE was significantly lower with edoxaban versus dalteparin, the risk of major bleeding was significantly higher (► **Table 2**). In line with previous observational data,<sup>46–48</sup> patients randomized to the edoxaban arm continued therapy for significantly longer than patients randomized to LMWH (211 vs. 184 days;  $p = 0.01$ ); 14.9% of patients who discontinued dalteparin did so because of the inconvenience of dosing (compared with 4.0% of patients who received edoxaban). A sensitivity analysis demonstrated that the longer duration of edoxaban versus dalteparin therapy did not heavily influence efficacy outcomes.<sup>49</sup> In the SELECT-D pilot study, rivaroxaban was associated with a lower rate of recurrent VTE at 6 months but a higher rate of major bleeding and clinically relevant nonmajor bleeding (CRNM; ► **Table 2**). However, the study was not powered to test efficacy and safety hypotheses.<sup>51</sup> One potential reason for the higher rates of major bleeding observed with DOACs compared with dalteparin, in both Hokusai-VTE-Cancer and SELECT-D, is the reduction in dalteparin dose after 4 weeks. In both studies, the majority of major bleeding events were GI bleeding, which were largely responsible for the higher rates of bleeding associated with DOAC versus dalteparin therapy (► **Table 2**). Furthermore, GI bleeding events were most frequent in patients with GI tract tumors.<sup>49,51</sup> In SELECT-D, only 19 patients with cancer of the esophagus or gastroesophageal tract were enrolled, with these cancer types excluded from enrolment part way through the study following an interim safety analysis, in which a nonsignificant increase in major bleeding with rivaroxaban versus dalteparin was demonstrated.<sup>51</sup> Results from the ADAM-VTE trial, an investigator-led, randomized, open-label study of apixaban versus dalteparin for the treatment of CAT ( $n = 300$ ) demonstrated a very low incidence of major bleeding in both treatment groups (0 in the apixaban arm vs. 1.4% in the dalteparin arm; HR not estimable;  $p = 0.14$ ) and comparable incidences of major and CRNM bleeding events in both groups (6.2% in the apixaban arm vs. 6.3% in the dalteparin arm; HR: 0.93, 95% CI: 0.43–2.02;  $p = 0.88$ ). Of note, this study included fewer patients with upper GI malignancies than the Hokusai-VTE-Cancer and

SELECT-D trials. VTE recurrence was, as observed in the Hokusai-VTE-Cancer and SELECT-D trials, lower in the DOAC arm (apixaban) compared with the dalteparin arm (0.7 vs. 6.3%, respectively; HR: 0.099, 95% CI: 0.013–0.780;  $p = 0.03$ ). All-cause mortality was also low in both treatment arms (16% with apixaban vs. 11% with dalteparin; HR: 0.40, 95% CI: 0.82–2.43;  $p = 0.31$ ); the reasons for these low event rates are unclear and cannot be explained by patient characteristics.<sup>52</sup>

Considering the latest data, the 2019 update of guidelines from the American Society of Clinical Oncology (ASCO) recommend that a parenteral anticoagulant (LMWH, unfractionated heparin or fondaparinux) or rivaroxaban is used for the initial treatment of CAT and that LMWH, edoxaban or rivaroxaban is used for long-term therapy. The guidelines also advise caution with DOACs in settings with a high risk of mucosal bleeding, including in patients with GI and genitourinary malignancies and note the potential for drug–drug interactions should be checked before use.<sup>38</sup> The 2019 update to the ESC guidelines on the management of acute PE recommend that LMWHs are considered for the first 6 months over VKAs, and that edoxaban and rivaroxaban can be considered as alternatives to LMWH in patients without GI cancer.<sup>7</sup> Recently published guidance also suggests edoxaban and rivaroxaban (International Society on Thrombosis and Haemostasis [ISTH]; International Initiative on Thrombosis and Cancer [ITAC]),<sup>39,53</sup> or edoxaban preferred over rivaroxaban (National Comprehensive Cancer Network)<sup>54</sup> over LMWH for selected patients, with some but not all patients with cancer suitable for DOAC therapy.<sup>39,53,54</sup> These guideline and guidance documents also note that patient preferences should be considered when deciding upon the anticoagulant and duration of therapy, and that final treatment recommendations should be made after shared decision-making with patients.<sup>7,38,39,53,54</sup> In the noninterventional, single-arm COSIMO study, patients with active cancer and CAT who switched from  $\geq 4$  weeks of traditional anticoagulants (predominately LMWH) to rivaroxaban reported an increase in treatment satisfaction, noting in particular a significant decrease in burdens associated with anticoagulation between baseline (the point of change) and week 4, which persisted at months 3 and 6.<sup>55</sup> A discrete choice experiment conducted during the study demonstrated that, outside of effectiveness and safety, route of administration was the strongest attribute for driving treatment decision-making, with patients demonstrating a strong preference for oral over injectable anticoagulants.<sup>56</sup>

Although the evidence base to date generally supports the use of DOACs for the treatment of CAT, increased granularity of data is required, that is, according to cancer type/stage and systemic oncological therapy is needed. Additional data on the use of DOACs for the treatment of CAT will come from the ongoing phase III RCT CARAVAGGIO<sup>57</sup> for apixaban versus dalteparin and subanalyses of the preexisting data, as well as additional studies for rivaroxaban in CAT (the phase III CASTA-DIVA<sup>58</sup> and CONKO-011<sup>59</sup> studies).

DOACs are also under investigation for the primary prevention of CAT in ambulatory cancer patients receiving systemic cancer therapies and results from the AVERT study for apixaban, and the CASSINI study for rivaroxaban (both placebo-controlled

**Table 2** Direct oral anticoagulants for the treatment of cancer-associated thrombosis: study designs and results from the Hokusai-VTE-Cancer, SELECT-D, and ADAM VTE trials

	Hokusai-VTE-Cancer <sup>49,92</sup> (edoxaban vs. dalteparin)		SELECT-D <sup>50</sup> (rivaroxaban vs. dalteparin)		ADAM VTE <sup>51</sup> (apixaban vs. dalteparin)	
	Edoxaban	Dalteparin	Rivaroxaban	Dalteparin	Apixaban	Dalteparin
Number of patients	522	524	203	203	145	142
Median duration of assigned therapy	6.9 months	6.0 months	5.9 months	5.8 months	5.8 months	5.7 months
Study duration	12 months		6 months		6 months	
Dose	60 mg o.d. and following LMWH for $\geq 5$ days	200 IU/kg o.d. for 1 month and then 150 IU/kg o.d.	15 mg b.i.d. for 21 days and then 20 mg o.d.	200 IU/kg o.d. for 1 month and then 150 IU/kg o.d.	10 mg b.i.d. for 7 days and then 5 mg b.i.d.	200 IU/kg o.d. for 1 month and then 150 IU/kg
Recurrent VTE or major bleeding <sup>a</sup>	12.8% HR: 0.97, 95% CI: 0.70–1.36; $p = 0.006$ for noninferiority <sup>c</sup>	13.5%	N/A	N/A	N/A	N/A
Recurrent VTE	7.9% (6 months: 6.5%) HR: 0.71, 95% CI: 0.48–1.06; $p = 0.09^c$	11.3% (6 months: 8.8%)	6-month cumulative rate: 4%	6-month cumulative rate: 11%	0.7%	6.3%
Major bleeding	6.9% (6 months: 5.6%) HR: 1.77, 95% CI: 1.03–3.04; $p = 0.04^c$	4.0% (6 months: 3.2%)	6-month cumulative rate: 6%	6-month cumulative rate: 4%	0	1.4%
Major bleeding severity category 3 or 4 <sup>b</sup>	2.3%	2.5%	NR	NR	NR	NR
Fatal bleeding	0	0.4%	0.5%	0.5%	0	0
ICH	0.4%	0.8%	0	0	NR	NR
GI bleeding	3.8%	1.1%	3.9%	2.0%	NR	NR
Clinically relevant nonmajor bleeding	14.6%	11.1%	6-month cumulative rate: 13%	6-month cumulative rate: 4%	6.2%	4.2%
Mortality	HR: 1.38, 95% CI: 0.98–1.94 39.5% (6 months: 26.8%) HR: 1.12, 95% CI: 0.92–1.37 <sup>c</sup>	36.6% (6 months: 24.2%)	HR: 3.76, 95% CI: 1.63–8.69 23.6%	27.6%	NR	15.9%
						10.6%
						NR

Abbreviations: b.i.d., twice daily; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; LMWH, low molecular weight heparin; N/A, not applicable; NR, not reported; o.d., once daily; VTE, venous thromboembolism.

<sup>a</sup>Primary efficacy outcome.

<sup>b</sup>Category 3 included bleeding events that were considered to be a clinical emergency, such as bleeding with hemodynamic instability or intracranial bleeding with neurologic symptoms; and category 4 included bleeding events that led to death before or almost immediately after the patient entered the hospital.

<sup>c</sup>Statistical comparison for the incidence at 12 months.

randomized trials) are now published.<sup>60,61</sup> In the AVERT study, apixaban significantly reduced the risk of VTE (HR: 0.41, 95% CI: 0.26–0.65) and increased the risk of major bleeding compared with placebo (HR: 2.00, 95% CI: 1.01–3.95) in ambulatory patients with cancer with an intermediate-to-high risk of VTE (Khorana's score  $\geq 2$ ) who were initiating chemotherapy.<sup>61</sup> The CASSINI study, in which ambulatory patients with cancer and an intermediate-to-high risk of VTE (Khorana's score  $\geq 2$ ) received rivaroxaban, showed similar results, with the risk of the composite of VTE and VTE-related death (HR: 0.66, 95% CI: 0.40–1.09) and of major bleeding (HR: 1.96, 95% CI: 0.59–6.49) versus those receiving placebo, with both differences not reaching statistical significance.<sup>60</sup> Thromboprophylaxis is not routinely recommended in ambulatory patients with cancer.<sup>38,39,54</sup> However, for patients receiving systemic cancer therapy who are at an intermediate to high risk of VTE (i.e., a Khorana's risk score  $\geq 2$ ), and in the absence of significant risk factors for bleeding, the 2019 updates to the ASCO guidelines and ITAC guidance for cancer-associated VTE endorse the use of apixaban or rivaroxaban for thromboprophylaxis. The ASCO guidelines also endorse the use of LMWH in this setting, whereas ITAC guidance only recommends it in patients with locally advanced or metastatic pancreatic cancer.<sup>38,39</sup>

### The Multimorbid Patient

Patients with VTE often have a range of factors (e.g., old age and extremes in body weight) and comorbidities (e.g., cancer and renal disease) associated with an increased risk of VTE recurrence and/or bleeding with anticoagulation therapy. For example, in the PREFER in VTE registry (which enrolled patients with VTE between 2013 and 2015), the mean age was 60.8 years, the average BMI 27.9 kg/m<sup>2</sup>, 6.2% of patients had renal disease, and 53.3% active cancer.<sup>62</sup> Atrial fibrillation (AF) and cardiovascular (CV) disease (such as coronary artery disease and peripheral artery disease and CV risk factors such as hypertension) are also highly prevalent in patients with VTE. For example, of patients enrolled in the PREFER in VTE registry, 3.5% had a history of AF and 45% had CV disease (excluding hypertension), whereas hypertension alone was present in 42.3% of patients.<sup>62</sup> Studies have demonstrated a link between these thromboembolic diseases, reflecting shared underlying risk factors.<sup>63,64</sup> The presence of multiple indications for antithrombotic use complicates disease management because of differences in recommended drug choice and dosing regimens. Decisions in this regard may need to be based on clinical judgement and the expertise of a multidisciplinary team.

The relative efficacy and safety of DOAC versus VKA therapy across relevant high-risk subgroups has been demonstrated in the phase III DOAC VTE treatment studies; a pooled analysis of such data are shown in ►Table 3.<sup>23</sup> The EINSTEIN DVT and EINSTEIN PE studies for rivaroxaban and Hokusai-VTE for edoxaban considered multimorbid patients in subgroup analyses.<sup>65,66</sup> In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE, “fragile” patients were a group defined by the presence of  $\geq 1$  of the following criteria: age  $>75$  years, CrCl  $<50$  mL/min or low body weight  $\leq 50$  kg. As expected, rates of recurrent VTE and bleeding were higher in the “fragile” ( $n = 1,573$ )

versus “nonfragile” ( $n = 6,709$ ) populations. Whereas rates of recurrent VTE with rivaroxaban versus enoxaparin/VKA treatment in the “fragile” subgroup were similar, there was a statistically significant difference in rates of major bleeding favoring rivaroxaban over enoxaparin/VKA use (1.3 vs. 4.5%; HR: 0.27, 95% CI: 0.13–0.54). Overall, the composite outcome of symptomatic recurrent VTE and major bleeding was significantly lower with rivaroxaban versus enoxaparin/VKA in the “fragile” patient subgroup (4.6 vs. 8.4%; HR: 0.51, 95% CI: 0.34–0.77).<sup>65</sup> In a subanalysis of the Hokusai-VTE data, the impact of age, number of comorbidities and concomitant medications on efficacy, and safety outcomes was evaluated. In the warfarin group, but not in the edoxaban group, the risk of recurrent VTE increased with advancing age, increasing number of comorbidities and increasing number of drugs used. Indeed, edoxaban was more effective than warfarin in patients  $\geq 80$  years old with more than two comorbidities or receiving more than five concomitant medications (HR: 0.63, 95% CI: 0.41–0.96). In the same subgroup, the relative safety of edoxaban versus warfarin (in terms of major bleeding and CRNM bleeding) was well maintained despite the elevated risk of bleeding in both treatment arms. Overall, the net clinical benefit favored edoxaban use across the separate components of this subgroup.<sup>66</sup>

### Other Patient Groups

#### Pediatric Patients

Although the incidence of VTE in children is approximately 100 times lower than the incidence in adult patients, there is an increasing need for improved options for anticoagulation in the pediatric population. For example, anticoagulation might be needed in pediatric cases of VTE caused by surgery or illness such as cancer, in cases of severe thrombophilia or in female pediatric patients with newly prescribed oral contraception. However, based on challenges associated with enrolment and retention of younger patients in clinical trials and the collection of blood samples for monitoring purposes, there is a paucity of data supporting the use of anticoagulants in this patient population. Current guidelines are mainly based on extrapolation from trials in adults. Currently, none of the DOACs are approved for use in pediatric patients; however, challenges associated with intravenous/subcutaneous delivery of anticoagulants in this population warranted further study of oral options.<sup>67–69</sup>

Phase I/II trials for dabigatran<sup>70–72</sup> and rivaroxaban<sup>73</sup> established suitable age-/body weight-adjusted dosing regimens for these agents for pediatric use, and both DOACs were well tolerated in these studies. Dabigatran and rivaroxaban are now in phase IIb/III testing in open-label trials for the treatment of VTE in pediatric patients.

The phase IIb/III DIVERSITY study evaluated the efficacy and safety of dabigatran following initial LMWH or UFH therapy in pediatric patients who are expected to require anticoagulation for  $\geq 3$  months. Initial dosing was determined using an algorithm and dabigatran administered b.i.d. as capsules, pellets or in liquid form according to the patient's age.<sup>74</sup> An interim analysis in approximately 220 patients demonstrated similar



**Table 3** Recurrent venous thromboembolism and major bleeding with direct oral anticoagulants versus vitamin K antagonist use across important patient subgroups in the phase III direct oral anticoagulants for venous thromboembolism treatment trials<sup>23</sup>

	Pooled DOAC n/N (%)	Pooled VKA n/N (%)	RR (95% CI)	p-Value
<b>First recurrent VTE or VTE-related deaths</b>				
Index event				
PE ± DVT	136/5,764 (2.4)	153/5,775 (2.6)	0.89 (0.71–1.12)	0.32
DVT only	199/7,655 (2.6)	213/7,654 (2.8)	0.93 (0.77–1.13)	0.49
Body weight (kg)				
<100	57/2,146 (2.7)	62/2,157 (2.9)	0.90 (0.77–1.06)	0.22
≥100	278/11,354 (2.4)	305/11,262 (2.7)	0.92 (0.64–1.32)	0.65
CrCl (mL/min)				
30–49	26/898 (2.9)	39/891 (4.4)	0.70 (0.43–1.15)	0.16
≥50	307/12,248 (2.5)	316/12,282 (2.6)	0.97 (0.83–1.14)	0.74
Age (y)				
<75	296/11,572 (2.6)	299/11,635 (2.6)	0.99 (0.85–1.17)	0.95
≥75	39/1,858 (2.1)	68/1,807 (3.8)	0.56 (0.38–0.82)	0.003
Cancer				
No	308/12,625 (2.4)	321/12,666 (2.5)	0.96 (0.82–1.12)	0.63
Yes	27/805 (3.4)	46/776 (5.9)	0.57 (0.36–0.91)	0.02
Major bleeding				
CrCl (mL/min)				
30–49	16/878 (1.8)	33/870 (3.8)	0.51 (0.26–0.99)	0.05
≥50	132/12,329 (1.1)	200/12,358 (1.6)	0.60 (0.40–0.90)	0.01
Age (y)				
<75	109/11,633 (0.9)	165/11,681 (1.4)	0.62 (0.45–0.84)	0.002
≥75	37/1,844 (2.0)	73/1,800 (4.1)	0.49 (0.25–0.96)	0.04
Cancer				
No	120/12,624 (1.0)	204/12,705 (1.6)	0.59 (0.41–0.83)	0.003
Yes	23/806 (2.9)	29/776 (3.7)	0.77 (0.44–1.33)	0.35

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.

efficacy and safety of dabigatran and standard of care, and confirmed the pharmacokinetic/pharmacodynamic profile of weight-adjusted dabigatran in children.<sup>75</sup> In addition, an interim analysis of a single-arm, prospective cohort, phase III study demonstrated a favorable safety profile of dabigatran used for up to 12 months in approximately 200 children aged 0 to <18 years who required anticoagulation for the secondary prevention of VTE and with a persistent risk factor for VTE.<sup>76,77</sup>

The phase III EINSTEIN Junior trial evaluated rivaroxaban (20 mg o.d. equivalent adjusted according to body weight following at least 5 days of initial heparin therapy) versus standard of care anticoagulation therapy for the treatment of acute VTE in approximately 500 children and neonates.<sup>78</sup> The risks of recurrent VTE (occurring in 4/335 [1.2%] of patients receiving rivaroxaban and in 5/165 [3.0%] receiving standard of care) and major bleeding events (occurring in 0/329 [0.0%] of patients receiving rivaroxaban and 2/162 [1.2%] receiving standard of care) were low and similar in patients receiving

rivaroxaban versus those receiving standard of care, and the results of the study were similar to those previously reported for adults.<sup>79</sup> Clinical data on the use of apixaban and edoxaban in pediatric patients are yet to be published, but studies are ongoing.<sup>80–82</sup>

#### Female Patients: Pregnancy, Fertility, and Breastfeeding

Patients who were pregnant or breastfeeding were excluded from the DOAC VTE treatment trials,<sup>8,9,11–13</sup> as well as trials for other thromboembolic indications. Based on this, and preclinical data, pregnancy and breastfeeding are contraindications for edoxaban and rivaroxaban use<sup>4,5</sup>; apixaban and dabigatran are also not recommended in these circumstances.<sup>2,3</sup> Reproductive toxicity has been demonstrated in animal studies evaluating dabigatran, edoxaban, and rivaroxaban; all three DOACs affected fetal development and dabigatran had negative impacts on female fertility.<sup>3–5</sup> For apixaban, animal studies did not indicate direct or indirect harmful effects on

pregnancy or fertility, but there is a lack of clinical data for human use.<sup>2</sup> It is unknown whether DOACs or their metabolites are excreted in human milk, but excretion has been demonstrated in animal studies for all four DOACs. Therefore, a risk to infants cannot be excluded.<sup>2-5</sup> Currently, LMWH is the preferred option in this clinical setting. Guidance on the management of DOACs during pregnancy has been issued by the Scientific and Standardization Committee (SSC) of the ISTH and ASH.<sup>83,84</sup> The SSC of the ISTH advises that all women of childbearing potential should receive documented counselling before initiation of DOACs, and there should be an emphasis on avoiding pregnancy while on a DOAC via implementing adequate and appropriate contraceptive methods. In those patients wishing to become pregnant, the guidance advises to switch from a DOAC to another anticoagulant prior to conception. The advised anticoagulant choices in this situation are VKAs (switching to LMWH as soon as possible when pregnant and before 6 weeks of gestation), or LMWH, taking into account that LMWH may necessitate a prolonged period of subcutaneous injections until pregnancy occurs.<sup>83</sup> Use of LMWH during pregnancy (in preference to UFH) is also recommended by the ASH guidelines, while DOACs are not considered in this setting due to concerns over these agents crossing the placenta and a lack of clear evidence on reproductive toxicity.<sup>84</sup> In cases of unintentional conception while receiving DOAC therapy, the SSC of the ISTH recommend that the DOAC is discontinued immediately and the patient is initiated on LMWH. However, inadvertent DOAC exposure after conception should not be considered in itself as medical grounds for abortion although early obstetric review and fetal monitoring are advised. The guidance provides details of an ongoing registry set up by the ISTH where physicians can submit data regarding cases of DOAC exposure during pregnancy.<sup>83</sup> In breastfeeding women, both sets of guidelines advise against the use of DOACs due to a lack of evidence of their safety in this setting.<sup>83,84</sup> The ASH guidelines suggest use of LMWH, warfarin, acenocoumarol, fondaparinux, UFH, or danaparoid during breastfeeding. Further clinical advice is provided around specific clinical scenarios and for subpopulations of female patients, for example, those with hereditary thrombophilia or who are undergoing androgen replacement therapy.<sup>84</sup>

Women aged <60 years who received rivaroxaban in the EINSTEIN DVT and EINSTEIN PE studies had a higher risk of uterine bleeding than those who received enoxaparin/VKA therapy (29.8 vs. 15.5%/year in patients with hormonal therapy and 30.7 vs. 13.4%/year in patients without hormonal therapy; adjusted HR: 2.13, 95% CI: 1.57–2.89).<sup>85</sup> In a *post hoc* analysis of the Hokusai-VTE trial, edoxaban was associated with a higher rate of abnormal vaginal bleeding compared with warfarin in women aged <50 years (15 vs. 9%/year; HR: 1.7, 95% CI: 1.1–2.5).<sup>86</sup> Furthermore, an analysis of data collected from female patients in the AMPLIFY trial indicated that the relative occurrence of vaginal bleeding events was higher in the apixaban group compared with the enoxaparin/warfarin group; CRNM vaginal bleeding occurred in 2.5 and 2.1% of women, respectively (OR: 1.2, 95% CI: 0.67–2.0).<sup>87</sup>

## Selecting Patients Suitable for Extended Venous Thromboembolism Treatment

The risk of recurrent VTE has been shown to persist for at least 10 years despite the use of acute-phase anticoagulation<sup>88</sup>; the optimum treatment goal is to prescribe anticoagulation therapy for as long as necessary and for as short as possible to manage the respective risks of VTE recurrence and bleeding. The 2016 update of the ACCP guidelines recommends 3 months' anticoagulation for VTE provoked by surgery, and extended therapy (>3 months) in patients with CAT or with unprovoked proximal DVT or PE dependent on the bleeding risk.<sup>1</sup> Apixaban, dabigatran, and rivaroxaban are all approved for extended secondary prevention of a recurrent VTE based on the placebo-controlled AMPLIFY-EXT,<sup>14</sup> RE-SONATE,<sup>15</sup> and EINSTEIN EXT<sup>12</sup> trials, respectively; the VKA versus dabigatran extended-use trial, RE-MEDY<sup>15</sup>; and the acetylsalicylic acid (ASA) versus two doses of rivaroxaban for extended-use trial, EINSTEIN CHOICE.<sup>89</sup> Efficacy and safety outcomes were largely consistent across patient subgroups in these trials.

—Fig. 1 provides an overview of approved DOAC dosing regimens for extended therapy, and it should be noted that a dose reduction for extended therapy applies for apixaban and rivaroxaban use.<sup>2,5</sup> In AMPLIFY-EXT, two doses of apixaban (5 and 2.5 mg b.i.d.) were compared with placebo, the apixaban 5 mg b.i.d. dose known to be effective for the prevention of stroke and systemic embolism in patients with AF, and the apixaban 2.5 mg b.i.d. dose being the lowest evaluated in phase II trials and effective for the prevention of VTE after major orthopaedic surgery. Compared with placebo, both doses were associated with a reduced risk of VTE, and bleeding risk was low and similar to that seen with placebo.<sup>14</sup> For rivaroxaban, EINSTEIN CHOICE looked to provide a lower dose option for extended rivaroxaban use in patients at clinical equipoise for extended prevention of VTE recurrence this being (rivaroxaban 10 mg o.d. vs. the earlier approved rivaroxaban 20 mg o.d. dose), and ASA was the comparator. Both doses were superior to ASA for the extended prevention of recurrent VTE, with a similar risk of major bleeding (<1%) and CRNM bleeding.<sup>89</sup> This was consistent with previous studies that demonstrated that although ASA might reduce the risk of VTE recurrence compared with placebo (as demonstrated in the WARFASA trial, but not the ASPIRE trial),<sup>90,91</sup> rivaroxaban was associated with a greater relative risk reduction versus placebo. EINSTEIN CHOICE provides a head-to-head validation of superior rivaroxaban efficacy and similar bleeding risk compared with ASA.<sup>89</sup> Of relevance to special populations, the risk of recurrent VTE was consistently lower with both doses of rivaroxaban therapy versus ASA across subgroups including age group, body weight and those with normal renal function or mild renal impairment. Of note, the possibility to reduce the rivaroxaban 20 to 15 mg o.d. dose for patients with CrCl between 15 and 49 mL/min still applied.<sup>5</sup> The risk of major bleeding and CRNM bleeding was favorable toward rivaroxaban use in patients aged >75 years, with a history of VTE and classed as fragile.<sup>89</sup>

A new data analysis of EINSTEIN EXT and EINSTEIN CHOICE supported the use of extended therapy in patients

with unprovoked VTE (as already established), and suggested that patients with minor transient (e.g., immobilization) or minor persistent risk factors (e.g., BMI >30 kg/m<sup>2</sup>, CrCl <50 mL/min, congestive heart failure) might also benefit from extended therapy.<sup>92</sup>

## Conclusion

The approval of DOACs following their respective VTE phase III treatment studies has provided physicians with effective and safe oral anticoagulation options with fewer burdens than traditional therapies such as VKAs and parenteral agents, which is reflected in their widespread uptake into clinical practice. Furthermore, subanalyses of the phase III studies in patients with comorbidities such as renal impairment, and specific studies in key patient groups such as those with cancer, have further supported the use of the DOACs in a broad range of patients with VTE. Despite this, and the incorporation of these findings into guidelines as they evolve, many important clinical questions exist regarding the use of DOACs in this setting. This review has discussed many of these queries, including DOAC suitability, dose and duration of treatment across important patient groups, as well as identifying gaps in current knowledge. Ongoing research has also been highlighted, and these efforts will contribute greatly to illuminating our understanding of VTE management and continuing to refine the management of all patients with VTE.

### Conflict of Interest

C.E.K. reports personal fees from Bayer Health Care, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Pfizer Pharma during the conduct of the study; personal fees from Amgen and Sanofi-Aventis outside the submitted work. S.M. reports grants and personal fees from Aspen, Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, GSK, Portola, Sanquin, and Sanofi during the conduct of the study.

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