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REVIEW

A Review of the Role of Non-Vitamin K Oral Anticoagulants in the Acute and Long-Term Treatment of Venous Thromboembolism

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ABSTRACT

Venous thromboembolism (VTE), which includes both deep vein thrombosis and pulmonary embolism (PE), is a very common disorder with high risk for recurrence and is associated with significant morbidity and mortality. The non-vitamin K oral anticoagulants (NOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, have been shown to be noninferior to conventional anticoagulant therapy for the prevention of recurrent VTE and are associated with more favorable bleeding risk. Evidence from the treatment of VTE with traditional therapy (low molecular weight heparin and vitamin K antagonists) implies that extended or indefinite treatment reduces risk of recurrence. Recently, mounting evidence suggests a role for the extended use of NOACs to reduce the risk of VTE recurrence. This review summarizes the existing evidence for the extended use of NOACs in the treatment of VTE from phase III extension studies with dabigatran, rivaroxaban, and apixaban. Additionally, it examines and discusses the major society guidelines and how these recommendations may change physician practices in the near future.

Keywords: Anticoagulation; NOAC; Venous thromboembolism

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BACKGROUND

Venous thromboembolism (VTE), which is comprised of deep venous thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease after myocardial infarction and stroke [1, 2]. VTE occurs for the first time in one to two adults in 1000 each year [3] with incidence rising to at least five in 1000 persons over the age of 70 years [4]. Nearly one-third of patients with VTE manifest with PE, whereas the remaining two-thirds present with DVT alone [5]. VTE is associated with significant morbidity and mortality. In the absence of treatment, the 30-day mortality rate for patients with first-time DVT is 3% and 31% for PE [6]. More generally, the 30-day mortality rates after VTE are 10.6% and 23% at 1 year, yet notably, these rates do not reflect the latest advances and treatment options available, principally, the NOACs discussed in this review [7]. Additionally, the management of VTE is associated with significant health care costs for not only the hospitalization and treatment of the initial VTE, but for associated recurrences

and readmissions [8]. This review aims to summarize the existing evidence for the use of NOACs in the acute and long-term treatment of VTE, examine major society guidelines, and discuss how these recommendations may change physician practices in the near future.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

VTE AS A CHRONIC DISEASE

The notable long-term complications of VTE include post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). Post-thrombotic syndrome presents with signs of chronic venous insufficiency such as pain, edema, and ultimately, ulcer formation caused in part by resultant venous hypertension. PTS is the most common long-term sequelae of lower extremity DVT, seen in 20–50% of patients in the year following the incident event, even with adequate treatment. The risk for the development of PTS is strongly associated with recurrent DVT [2, 9, 10]. Patients with chronic thromboembolic pulmonary hypertension present with progressive dyspnea, exercise intolerance, and even clinical signs of right heart failure such as peripheral edema and syncope. The incidence of CTEPH following PE is 0.56–3.8% [11, 12]. These chronic complications adversely affect quality of life and contribute to a significant financial burden on the healthcare system [13, 14].

Determining whether a venous thromboembolic event was unprovoked or provoked by some risk factor carries prognostic significance and influences treatment decisions. Recently, Kearon et al. [15] introduced a novel concept for further stratifying provoking risk factors by determining whether the risk factor is transient or persistent. A persistent risk factor, such as metastatic cancer, would be expected to have a much higher risk of recurrence than a transient risk factor, such as recent surgery, after the discontinuation of therapy. Although this nomenclature has not yet been adopted by the ACCP, its use may influence decisions regarding duration of anticoagulation.

Venous thromboembolic events are known to be associated with factors such as recent surgery, extended periods of immobility, pregnancy, puerperium, estrogen-based hormonal therapy, and active malignancy [16]. Nearly 50% of VTE patients, however, do not have any underlying risk factors and therefore experience unprovoked VTE [17]. In patients with unprovoked VTE, the risk of recurrence is 11% at 1 year and nearly 40% at 10 years [18]. Notably, the risk of recurrence of deep vein thrombosis and pulmonary embolism is similar. Furthermore, when DVT recurs, it usually does so as DVT and pulmonary embolism tends to recur as pulmonary embolism [19, 20]. After a first VTE episode, the rate of recurrence is highest in the first 6 months [19] and that risk is nearly double over the next 18 months [21].

Factors such as residual vein thrombosis at ultrasound assessment, persistently elevated level of D-dimer, male sex, and the early development of post-thrombotic syndrome, have all been shown to increase the risk of VTE recurrence [9, 22, 23]. The DASH scoring system, a prediction tool based on a meta-analysis of 1818 patients with unprovoked VTE, was developed to estimate risk of recurrence. The scoring factors include abnormal D-dimer after anticoagulation therapy (2 points), age < 50 years (1 point), male sex (1 point), and in women, the use of hormonal therapy at the time of the VTE (-2 points). The recently validated scoring system was designed to highlight low-risk patients who could potentially avoid long-term anticoagulation after unprovoked VTE [24, 25].

DEFINING TREATMENT

The anticoagulant treatment of VTE is traditionally marked by three different phases. Initial anticoagulant therapy is the first phase and is administered in the days immediately following a diagnosis of VTE [26]. Recommended choices for initial anticoagulation include unfractionated heparin (UFH) or low molecular weight heparin (LMWH) with subsequent introduction of a vitamin K antagonist (VKA),

as well as two of the non-vitamin K oral anticoagulants (NOACs) rivaroxaban and apixaban [26]. Dabigatran and edoxaban have also been used for initial therapy, however, in the studies that evaluated these NOACs, patients received at least 5 days of parenteral anticoagulation with UFH or LMHW prior to initiating NOAC therapy [27, 28].

Chronic or long-term treatment spans from the end of the initial phase to the end of a designated end point, usually 3 months. The agent of choice can be the same as the initial agent, or can be transitioned to a new anticoagulant. Extended anticoagulation therapy refers to treatment beyond an established, defined endpoint, which is usually 3–6 months, often with an indefinite duration of therapy [26].

Historically, the initial treatment of VTE would consist of at least 5 days of parenteral anticoagulation (UFH or LMWH) along with a VKA until a therapeutic anticoagulation window was achieved. This treatment strategy is limited by its dependence on initial parenteral anticoagulation administration, delayed onset, and numerous medication and dietary interactions. Furthermore, warfarin requires frequent coagulation monitoring and dose adjustments to ensure the international normalized ratio (INR) is in therapeutic range [29].

The optimal duration of anticoagulant therapy after the first episode of unprovoked VTE remains unclear. In patients with identifiable, major, transient risk factors (i.e., recent surgery), anticoagulation therapy is usually discontinued after 3 months, whereas continued therapy without a scheduled stop date (extended anticoagulation) is recommended in patients with cancer-associated thrombosis [29].

GUIDELINES

The most recent guidelines on the management of VTE from the American College of Chest Physicians (ACCP) [26] were released in 2016 and they differ notably from the earlier recommendations released in 2012. The earlier guidelines [30] recommended the use of VKA over LMWH in patients without cancer and LMWH over VKA in patient with cancer. VKAs were recommended over NOACs (dabigatran or rivaroxaban at that time) in both groups of patients given the existing evidence at that time.

The 2016 ACCP guidelines [26] take into consideration the large body of evidence gathered in recent years supporting the use of NOACs in the treatment of acute VTE. Based on these guidelines, NOACs are recommended over VKAs for the first 3 months of anticoagulation therapy for patients with proximal DVT of the leg or PE in patients without cancer. For patients with cancer, LMWH is still the recommended anticoagulant.

The current guidelines recommend 3 months of anticoagulation therapy for patients with proximal DVT of the leg or PE in the setting of a surgical or nonsurgical transient risk factor. New to the most recent guidelines, however, is the recommendation that patients with a first VTE that is an unprovoked proximal DVT or PE with a low or moderate bleeding risk receive extended or indefinite anticoagulation as opposed to 3 months of therapy. The guidelines further advise that extended or long-term therapy beyond 3 months continue with the initial therapy of choice [26].

Guidelines from the European Society of Cardiology (ESC) [31] that were published in 2014 also included recommendations for the extended treatment of VTE. These guidelines identified patients with cancer and those who have experienced an unprovoked proximal DVT or PE who are at low risk of bleeding as candidates for indefinite treatment. The guidelines also comment on the use of NOACs with a recommendation (Class IIa, Level of Evidence B) to consider dabigatran, rivaroxaban, or apixaban over VKA in patients who require extended anticoagulation therapy.

ROLE OF NOACS IN THE TREATMENT OF ACUTE VTE

The four NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) were compared with conventional therapy (parenteral anticoagulation followed by VKA) for the treatment of

acute VTE in six clinical trials. These four drugs are synthetic, selective, and reversible inhibitors of either factor Xa (rivaroxaban, apixaban, and edoxaban) or thrombin (dabigatran). The NOACs, administered orally in fixed doses, produce predictable anticoagulant responses that do not require routine monitoring.

The study populations were similar across the trials evaluating all four drugs. All trials were designed to demonstrate noninferiority of the NOAC compared to conventional treatment with LMWH followed by VKA. In all six trials, the primary efficacy outcome was recurrent VTE or VTE-related mortality. The primary safety outcome was major bleeding defined by the International society of Thrombosis and Haemostasis criteria in the apixaban and dabigatran trials, but a composite of major or clinically relevant non-major (CRNM) bleeding in the rivaroxaban and edoxaban trials. The rivaroxaban trials had separate DVT and PE studies, both powered for each population, whereas the other NOAC studies grouped all VTE patients together with varying numbers of patients with each condition. All the trials except for the rivaroxaban ones were double-blinded. Additionally, patients with severe renal dysfunction were excluded from all the studies. Of note, in the dabigatran and edoxaban trials, patients in both the NOAC and conventional therapy arm received 5 days of parenteral anticoagulation. This differs from the rivaroxaban and apixaban trials, where patients were started immediately on either agent. All four NOACs were found to be non-inferior to conventional treatment with regards to the primary efficacy outcomes in the referenced phase III clinical trials. In terms of safety, apixaban was associated with significantly fewer major bleeding events [0.6 vs. 1.8%; HR 0.31; 95% CI (0.17–0.55); $P < 0.001$] and edoxaban was associated with significantly fewer major or CRNM bleeding events [8.5 vs. 10.3%; HR 0.81; 95% CI (0.71–0.94); $P = 0.004$ for superiority]. Table 1 highlights the primary efficacy and safety outcomes from these phase III clinical trials.

A fifth NOAC, betrixaban, an oral, direct factor Xa inhibitor has not yet been studied in acute VTE or in prevention of VTE recurrence, but has gained approval from the United States Food and Drug Administration for VTE prophylaxis in acutely ill medical patients. The APEX trial [32] compared the use of extended-duration betrixaban (for 35–42 days) to a standard subcutaneous enoxaparin regimen (for 10 ± 4 days) in 7513 patients hospitalized for acute medical illnesses. The study population was stratified into different cohorts based on D-dimer level and age, but in the overall study population, betrixaban was associated with significantly fewer asymptomatic proximal DVT and symptomatic VTE [165 vs. 223; RR 0.76; 95% CI (0.63–0.92); $P = 0.006$] with no difference in major bleeding [25 vs. 21; RR 1.19; 95% CI (0.67–2.12); $P = 0.55$].

Edoxaban became the first NOAC evaluated for use in cancer-associated VTE in the Hokusai VTE Cancer study [33]. This open-label, noninferiority study compared 6–12 months of edoxaban to subcutaneous dalteparin (a LMWH) in patients with active cancer who were found to have acute symptomatic or incidental VTE. Although the rate of recurrent VTE was nonsignificantly reduced with edoxaban compared to LMWH [41 vs. 59; HR 0.71; 95% CI (0.48–1.06); $P = 0.09$], significantly more major bleeding events were associated with edoxaban [36 vs. 21; HR 1.77; 95% CI (1.03–3.04); $P = 0.04$]. Although none of the NOACs are yet indicated or approved for use in cancer-associated VTE, these results are promising for this population of patients (Table 2).

EXTENDED TREATMENT OF VTE

Evidence for VKA

Much of the evidence and rationale for the long-term treatment of VTE stems from earlier experience with VKA. The incidence of recurrent VTE was evaluated following long-term versus extended duration therapy of idiopathic DVT by the Warfarin Optimal Duration Italian Trial Investigators [34]. In this trial, following isolated DVT, patients were randomized to extended warfarin treatment for 12 months versus standard 3 months. Nearly two-thirds of the recurrences of thromboembolic events occurred in the first year after discontinuation

Table 1 Efficacy and safety of NOACs for the acute treatment of VTE: results from clinical trials

Trial	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER [27]	RE-COVER II [43]	EINSTEIN-DVT [40]	EINSTEIN-PE [44]	AMPLIFY [45]	Hokusai-VTE [28]
Year	2009	2014	2010	2012	2013	2013
Design	Double-blind	Double-blind	Open-label	Open-label	Double-blind	Double-blind
# of patients	2539	2589	3449	4832	5395	8292
LMHW/heparin bridge	Yes	Yes	No	No	No	Yes
Treatment protocol	Dabigatran 150 mg BID	Dabigatran 150 mg BID	Rivaroxaban 15 mg BID for 3 weeks; then 20 mg daily	Rivaroxaban 15 mg BID for 3 weeks; then 20 mg daily	Apixaban 10 mg BID for 7 days; then 5 mg BID	Edoxaban 60 mg daily; or 30 mg daily for patients w/CrCl 30–50 ml/min, weight $\leq$ 60 kg, or receiving P-glycoprotein inhibitors
Duration of therapy (months)	6	6	3, 6, or 12	3, 6, or 12	6	$\leq$ 12
Primary efficacy outcome	Recurrent VTE and related death	Recurrent VTE and related death	Recurrent VTE	Recurrent VTE	Recurrent VTE and related death	Recurrent VTE and related death
Event rate of primary efficacy outcome: NOAC vs. VKA	2.4% vs. 2.1%	2.3% vs. 2.2%	2.1% vs. 3.0%	2.1% vs. 1.8%	2.3% vs. 2.7%	3.2% vs. 3.5%
Hazard ratio (HR), 95% confidence interval (CI)	1.10 (0.65–1.84) $P < 0.001$	1.08 (0.64–1.80) $P < 0.001$	0.68 (0.44–1.04) $P < 0.001$	1.12 (0.75–1.68) $P = 0.003$	0.84 (0.60–1.18) $P < 0.001$	0.89 (0.70–1.13) $P < 0.001$
Primary safety outcome	Major bleed	Major bleed	Major or CRNM bleed	Major or CRNM bleed	Major bleed	Major or CRNM bleed

Table 1 continued

Trial	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER [27]	RE-COVER II [43]	EINSTEIN-DVT [40]	EINSTEIN-PE [44]	AMPLIFY [45]	Hokusai-VTE [28]
Event rate of primary safety outcome: NOAC vs. VKA	1.6% vs. 1.9%	1.2% vs. 1.7%	8.1% vs. 8.1%	10.3% vs. 11.4%	0.6% vs. 1.8%	8.5% vs. 10.3%
HR, 95% CI	0.82 (0.45–1.48)	0.69 (0.36–1.32)	0.97 (0.76–1.22) $P = 0.77$	0.90 (0.76–1.07) $P = 0.23$	0.31 (0.17–0.55) $P < 0.001$	0.81 (0.71–0.94) $P = 0.004$

BID twice daily dosing, *CrCl* creatinine clearance, *CRNM* clinically relevant nonmajor, *DVT* deep vein thrombosis, *LMWH* low molecular weight heparin, *NOAC* non vitamin K oral anticoagulant, *PE* pulmonary embolism, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

of anticoagulation in both treatment groups and at 3 years of follow-up, there was no significant difference in incidence of recurrence between the two treatment groups; thereby suggesting that extended anticoagulation treatment only delayed recurrence rather than reducing the risk of recurrence. Additionally, the rates of major bleeding were 3.0 vs. 1.5% in the extended treatment group compared to the placebo group.

The PADIS-PE study [35] similarly investigated the role of extended VKA use but in patients with PE as opposed to DVT. After 6 months of warfarin therapy, patients with PE were randomized to 18 months (12 additional months) extended therapy versus placebo. Once again, extended warfarin therapy significantly reduced the outcome of recurrent VTE (rate 3.3%) during the 18-month study period, but the benefit was not maintained after discontinuation, as evidenced by a recurrence rate of 13.5% in the placebo group [hazard ratio (HR), 0.22; 95% confidence interval (CI), 0.09–0.55; $P = 0.001$]. Rates of recurrent VTE did not differ at the end of the 42-month trial.

A 1999 study published in the NEJM by Kearon et al. [36] compared warfarin to placebo in patients who had already completed 3 months of therapy for a first episode of idiopathic VTE. Although the study was designed for subjects to receive an additional 24 months of anticoagulation, pre-specified interim analysis led to the early termination of the study after patients had been followed for an average of 10 months. Significantly more recurrent VTE were observed in the placebo group [27.4 vs. 1.3%/patient-year; HR 0.05; 95% CI (0.01–0.37); $P < 0.001$]. This was followed by a 2003 study [37] that compared low-intensity warfarin therapy (INR goal 1.5–1.9) to conventional intensity (INR goal 2.0–3.0) in the long-term prevention of recurrent VTE in patients who had completed 3 months of conventional warfarin therapy. Low-intensity warfarin therapy was associated with more episodes of recurrent VTE compared to conventional dosing [16 vs. 6; HR 2.8; 95% CI (1.1–7.0); $P = 0.03$]. Furthermore, the low-intensity group experienced more bleeding episodes than the conventional intensity [39 vs. 31 events; HR 1.3; 95% CI (0.8–2.1); $P = 0.26$].

EVIDENCE FOR NOACS

There is a growing body of literature regarding the extended use of NOACs in the treatment of VTE. Currently, dabigatran, apixaban, and

Table 2 Efficacy and safety of NOACs for the extended treatment of VTE: results from clinical trials

Trial	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-MEDY [38]	RE-SONATE [38]	EINSTEIN-EXT [40]	EINSTEIN-CHOICE [41]	AMPLIFY-EXT [42]	Hokusai-VTE [28]
Year	2013	2013	2010	2017	2013	2013
Design	Double-bind	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
# of patients	2856	1343	1196	3396	2486	8292
Comparison arm	Warfarin	Placebo	Placebo	ASA 100 mg daily	Placebo	Warfarin
Treatment protocol	Dabigatran 150 mg BID	Dabigatran 150 mg BID	Rivaroxaban 20 mg daily	Rivaroxaban 20 mg or 10 mg daily vs. ASA 100 mg daily	Apixaban 5 mg BID or apixaban 2.5 mg BID	Edoxaban 60 mg daily; or 30 mg daily for patients w/CrCl 30–50 ml/min, weight $\leq$ 60 kg, or receiving P-glycoprotein inhibitors
Duration of therapy (months)	6–36 months; after completing initial 3 months	6 months; after completing initial 3 months	6–12 months; after completing initial 6–12 months	Up to 12 months; after completing initial 6–12 months	12 months; after completing initial 6–12 months	3–12 months
Primary efficacy outcome	Recurrent or fatal VTE	Recurrent or fatal VTE or unexplained death	Recurrent VTE	Recurrent fatal and nonfatal VTE and unexplained death	Recurrent VTE or death from any cause	Recurrent VTE or death from any cause
Event rate of efficacy outcome: NOAC vs. comparison	Dabigatran 150 mg BID: 1.8% Warfarin: 1.3%	Dabigatran 150 mg BID: 0.4% Placebo: 5.6%	Rivaroxaban 20 mg: 1.3% Placebo: 7.1%	Rivaroxaban 20 mg: 1.5% Rivaroxaban 10 mg: 1.2% ASA 100 mg: 4.4%	Apixaban 5 mg: 4.2% 2.5 mg: 3.8% Placebo: 11.6%	Edoxaban: 3.2% Warfarin: 3.5%

Table 2 continued

Trial	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-MEDY [38]	RE-SONATE [38]	EINSTEIN-EXT [40]	EINSTEIN-CHOICE [41]	AMPLIFY-EXT [42]	Hokusai-VTE [28]
Hazard ratio (HR), 95% confidence interval (CI)	1.44 (0.78–2.64) $P = 0.01$	0.08 (0.02–0.25) $P < 0.001$	0.18 (0.09–0.39) $P < 0.001$	20 mg vs. ASA: 0.34 (0.20–0.59) $P < 0.001$ 10 mg vs. ASA: 0.26 (0.14–0.47) $P < 0.001$ 20 mg vs. 10 mg 1.34 (0.65–2.75) $P = 0.42$	2.5 mg vs. placebo: 0.33 (0.22–0.48) 5 mg vs. placebo: 0.36 (0.25–0.53)	0.89 (0.70–1.13) $P < 0.001$
Primary safety outcome	Major bleed	Major bleed	Major or CRNM bleed	Major bleed	Major bleed	Major or CRNM bleed
Event rate of primary safety outcome: NOAC vs. comparison	Dabigatran 150 mg BID: 0.9% Warfarin: 1.8%	Dabigatran 150 mg BID: 0.3% Placebo: 0%	Rivaroxaban 20 mg: 6% Placebo: 1.2%	Rivaroxaban 20 mg: 0.5% Rivaroxaban 10 mg: 0.4% ASA 100 mg: 0.3%	Apixaban 5 mg: 0.1% 2.5 mg: 0.2% Placebo: 0.5%	Edoxaban: 8.5% Warfarin: 10.3%
HR, 95% CI, *P* value	0.52 (0.27–1.02) $P = 0.06$	Not estimable, $P = 1.0$	5.19 (2.3–11.7) $P < 0.001$	20 mg vs. ASA: 2.01 (0.50–8.04) $P = 0.32$ 10 mg vs. ASA: 1.64 (0.39–6.84) $P = 0.50$ 20 mg vs. 10 mg:1.23 (0.37–4.03) $P = 0.74$	2.5 mg vs. placebo 0.49 (0.09–2.64) 5 mg vs. placebo 0.25 (0.03–2.24) 2.5 mg vs. 5 mg 1.93 (0.18–21.25)	0.81 (0.71–0.94) $P = 0.004$

ASA aspirin, *BID* twice daily dosing, *CRNM* clinically relevant non-major, *NOAC* non vitamin K oral anticoagulant, *VTE* venous thromboembolism

rivaroxaban have been studied in this setting (RE-MEDY/RE-SONATE, EINSTEIN, AMPLIFY-EXT). These studies examined the continued and extended treatment of patients who had already been started on anticoagulation treatment for VTE.

The extended treatment with dabigatran was studied in the RE-SONATE and RE-MEDY trials. In the RE-SONATE [38] placebo control study, investigators compared 12 months of extended use of dabigatran (150 mg twice daily) to placebo following initial treatment. The rates of recurrent VTE or death (primary endpoint) were significantly lower in the treatment group [0.4 vs. 5.6%; HR 0.08; 95% CI (0.02–0.25); $P < 0.001$]. There were significantly higher rates of major or CRNM bleeding in the dabigatran group compared to warfarin [5.3 vs. 1.8%; HR 2.92; 95% CI (1.52–5.60); $P = 0.001$].

The RE-MEDY [38] trial is the only trial to date that has compared the extended use of a NOAC directly to warfarin for recurrent VTE prevention. This active control study randomized patients to either dabigatran (150 mg twice daily) or warfarin for 6–36 months, following at least 3 months of initial anticoagulation therapy. Recurrent or fatal VTE occurred in 1.8 and 1.3% of patients on dabigatran and warfarin, respectively [HR 1.44; 95% CI (0.78–2.64); $P = 0.01$ for noninferiority]. Although the number of major bleeding events between the two groups did not significantly differ, the number of major or CRNM bleeding events did, with significantly fewer in the dabigatran group [5.6 vs. 10.2%, HR 0.58; 95% CI (0.41–0.71); $P < 0.001$]. As seen in prior studies comparing dabigatran to warfarin, the number of ACS events was higher in the dabigatran group (0.9 vs. 0.2%, $P = 0.02$) [39].

The extended use of rivaroxaban was first evaluated in EINSTEIN-EXT [40], a study conducted in parallel to the original EINSTEIN-DVT study, which found rivaroxaban to be non-inferior to LMWH/VKA for the treatment of acute, symptomatic DVT. The extended study was a double-blind, randomized, event-driven superiority study that compared rivaroxaban (20 mg once daily) to placebo for an additional 6–-12 months in patients who had already completed 6–12 months of treatment for VTE and in whom there was equipoise with regards to continuing anticoagulation. Rivaroxaban was associated with significantly fewer recurrent VTE than placebo [1.3 vs. 7.1%, HR 0.18; 95% CI (0.09–0.39); $P < 0.001$]. Additionally, there was a significant increase in the rate of major (0.7 vs. 0%) and major or CRNM bleeding complications in the treatment group vs. placebo [6.0 vs. 1.2%; HR 5.19; 95% CI (2.3–11.7); $P < 0.001$].

More recently, rivaroxaban was compared to aspirin for the extended treatment of VTE in EINSTEIN-CHOICE [41]. This randomized, double-blind, phase 3 study assigned patients with VTE who had already completed 6–12 months of therapy, and in whom there was equipoise with regards to continuing anticoagulation, to receive one of two different doses of rivaroxaban (20 or 10 mg once daily) or aspirin (100 mg once daily) for up to 1 year. Patients with clear indication for therapeutic dose anticoagulation were excluded from this study. Furthermore, of the patients randomized to rivaroxaban 20 and 10 mg and aspirin groups, 39.8, 42.6, and 41.4%, respectively, had histories of unprovoked VTE while the rest were provoked. Recurrent VTE occurred with significantly less frequency in both rivaroxaban groups than the aspirin group [20 mg: 1.5 vs. 4.4%, HR 0.34, 95% CI (0.20–0.59); 10 mg: 1.2 vs. 4.4% HR 0.26, 95% CI (0.14–0.47), $P < 0.001$ for both). There was no significant difference in rates of major bleeding in the two rivaroxaban groups vs. aspirin [20 mg: 0.5 vs. 0.3%; HR 2.01; 95% CI (0.50–8.04); $P = 0.32$; 10 mg: 0.4 vs. 0.3%; HR 1.64; 95% CI (0.39–6.84); $P = 0.50$]. This study introduced the concept of a low-dose of rivaroxaban (10 mg once daily), to be used after completing long-term therapy, that was more effective than aspirin in the prevention of recurrent VTE with a similar bleeding risk profile.

Apixaban is the third NOAC that has been studied for the extended treatment of VTE. AMPLIFY-EXT [42] was a randomized, double-blind study that compared two doses of apixaban (5 and 2.5 mg twice daily) to placebo for 12 months of extended therapy in patients who had already completed 6–12 months of apixaban for treatment of VTE. Over 90% of patients

enrolled in this trial had a history of unprovoked VTE. Both doses of apixaban were associated with significantly reduced recurrent VTE or death from any cause compared to placebo [5 mg: 4.2 vs. 11.6%; relative risk (RR) 0.36; 95% CI (0.25–0.53); $P < 0.001$; 2.5 mg: 3.8 vs. 11.6%, RR 0.33; 95% CI (0.22–0.48); $P < 0.001$]. Episodes of major bleeding did not differ significantly between groups but the 5-mg dose of the study drug did have significantly more episodes of CRNM bleeding than placebo [4.2 vs. 2.3%; RR 1.82; 95% CI (1.05–3.18)] whereas the 2.5-mg dose did not [3.0 vs. 2.3%; RR 1.29, 95% CI (0.72–2.33)].

Edoxaban has not yet been studied in a dedicated extension study. In the original randomized, double-blind, noninferiority study, Hokusai-VTE [28], patients with acute VTE were randomly assigned to receive edoxaban or warfarin for 3–12 months. Interestingly, efficacy was evaluated at 12 months of follow-up, regardless of the duration of treatment. Notably, 87% of patients (7227) continued treatment beyond 3 months and 40% of patients (3320) continued treatment for a full 12 months. Edoxaban was noninferior to warfarin in the primary efficacy outcome, first recurrent VTE or VTE-related death [130 vs. 146; HR 0.89; 95% CI (0.70–1.13); $P < 0.001$ for noninferiority]. Edoxaban was associated with significantly fewer episodes of major or CRNM bleeding [349 vs. 423; HR 0.81; 95% CI (0.71–0.94); $P = 0.004$ for superiority].

DISCUSSION

The 2016 recommendations from the American College of Chest Physicians will foreseeably change the way in which VTE is currently managed. The recent update recommends NOACs over VKA for the first 3 months of treatment in patients with DVT of the leg or PE without cancer [26]. Additionally, for extended or long-term therapy beyond 3 months, it is recommended to continue with the initial therapy of choice. Lastly, extended therapy (with no scheduled stop date) is recommended in patients with a first or second unprovoked proximal DVT of the leg or PE and a low or moderate bleeding risk. These new recommendations thereby created a significant population of candidates for indefinite anticoagulation.

Providers considering whether extended anticoagulation is indicated for their patient should therefore take four variables into consideration: the locations of the VTE, whether the patient has active cancer, whether the VTE was provoked or unprovoked, and the patient's bleeding risk. The ACCP recommends extended use anticoagulation in the treatment of a first time, unprovoked, proximal DVT or PE in a patient with a low or moderate bleeding risk or a patient with a second time, unprovoked DVT or PE in a patient with a low or moderate bleeding risk [26].

Currently, there are no head-to-head comparisons of NOACs in the extended treatment of VTE. Furthermore, trying to draw comparisons based on the individual studies mentioned above is limited by differences in study designs, inclusion and exclusion criteria, patient demographics, and characteristics. That is why the guidelines do not recommend a specific NOAC, but instead advise that drug-specific adverse events, individual cost and coverage, dosing frequency, and patient preference be taken into consideration when choosing a NOAC. Of the existing NOACs, only rivaroxaban and apixaban have been examined at doses lower than established regimens, although edoxaban was studied at reduced doses for patients with CrCl 30–50 ml/min, weight ≤ 60 kg, or those receiving P-glycoprotein inhibitors.

The emergence of reduced-dose regimens with the EINSTEIN-CHOICE and AMPLIFY-EXT studies are likely to further change the future management of extended therapy for secondary VTE prevention. The authors of AMPLIFY-EXT make a strong argument for extended therapy with apixaban with a number needed to treat to prevent one episode of recurrent VTE (fatal or nonfatal) of 14, and a number needed to harm (major or CRNM bleeding) of 200 [42]. The EINSTEIN-CHOICE study noted a reduction in the relative risk of recurrent VTE by nearly 70% with both the 20- and 10-mg doses of rivaroxaban. The benefits observed in the study came with rates of major and CRNM bleeding that were similar to aspirin, at both doses of

rivaroxaban. The authors do caution, however, that the EINSTEIN-CHOICE study was not powered to demonstrate the noninferiority of the 10-mg dose of rivaroxaban to the established treatment dose of 20 mg.

The results of AMPLIFY-EXT are limited by the patient characteristics of the study, principally the fact that only 15% of the patients studied were greater than 75 years of age and over 90% of patients had a creatinine clearance (CrCL) greater than 50 ml/min. The patient population of EINSTEIN-CHOICE is similar with a CrCL greater than 50 ml/min in over 95% of patients and an average age of 58 years [41]. Additionally, only 2–3% of patients had a known cancer and 6–7% a known thrombophilia, thereby limiting the extrapolation of the data to these unique populations. Special patient populations, such as patients with cancer, the elderly, and those at the lowest and highest weight indices were only lightly represented in the extension studies. Furthermore, those with severe renal dysfunction were excluded. Therefore, the data drawn from the extension studies largely applies to a middle-aged adult population, and must be carefully considered when applied to a more complex patient.

Based on the results of the EINSTEIN-CHOICE study, the FDA recently approved the use of the reduced dose (10 mg) of rivaroxaban for risk reduction of recurrent VTE after completing 6 months of initial anticoagulant therapy with conventional dosing.

In patients at high risk for recurrence with low to moderate bleeding risk, the use of low-dose regimens offers a proven option for risk reduction with a favorable bleeding risk. The lack of anticoagulation monitoring, coupled with simple dosing regimens with oral route of administration, suggests that NOACs will continue to be more widely used as a first-line agent in patients with VTE.

CONCLUSIONS

The general conclusion that can be drawn from these studies is that certain patient populations largely benefit from extended anticoagulation therapy for the prevention of recurrent VTE. The extension studies described above highlight the efficacy and confirm the safety of the protracted use of apixaban, dabigatran, rivaroxaban, and edoxaban for the secondary prevention of recurrent VTE. Recent guidelines also recommend the extended use of these NOACs in this setting. The introduction of a thromboprophylactic dose of anticoagulation, with comparable efficacy and tolerable bleeding risk profiles, may further contribute to future changes in the secondary prevention of recurrent VTE. We expect these recent studies, combined with the changes in guideline recommendations, to translate to a larger population of patients on extended duration therapy with a NOAC for the prevention of recurrent VTE. Further research is needed in broader patient populations to complement the existing literature to determine the effectiveness and safety of extended NOAC use, in varying doses, in patients with VTE.

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