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REVIEW

Phase III Trials of New Oral Anticoagulants in the Acute Treatment and Secondary Prevention of VTE: Comparison and Critique of Study Methodology and Results

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ABSTRACT

The traditional treatment of venous thromboembolism (VTE) has been use of heparin and vitamin K antagonists (VKA), and although shown to be effective, they have numerous limitations. New oral anticoagulants (NOACs) including direct thrombin (factor IIa) inhibitors (dabigatran) and selective factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) have emerged as promising alternatives with the potential to overcome the limitations of traditional treatments. Clinical trials have been performed with a view to making significant changes to the acute, long-term and extended treatment of VTE. Data are now available on the efficacy and safety, including bleeding rates, of the NOACs in comparison with VKA in the acute treatment and secondary prevention of VTE as well as in comparison with placebo extended VTE treatment. This review compares and contrasts the design and results of the Phase III trials of NOACs in VTE and discusses the implications of the NOACs in terms of treatment strategies in VTE patients.

Keywords: Clotting factor inhibitors; Low molecular weight heparin; New oral anticoagulants; Oral anticoagulant; Venous thromboembolism

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INTRODUCTION

Deep-vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), are a major healthcare concern resulting in considerable long-term morbidity and mortality. According to estimates, VTE affects more than one million

individuals each year across the EU and over 600,000 people each year in the USA [1, 2]. The number of annual VTE-related deaths is also considerable, approaching approximately 540,000 and 300,000 in the EU and USA, respectively [1, 2]. In addition, the burden of DVT frequently extends beyond the original event because patients with symptomatic VTE have a high risk of recurrence (including non-fatal and fatal PE) that persists for many years.

For half a century, the standard of care for most patients with VTE has been initial heparin, overlapped and followed up with a vitamin K antagonist (VKA) [3–5]. The effectiveness of this regimen has been well described in the short-term treatment of VTE, with the risks of recurrent disease reduced by around 82%. However, this regimen is complex to implement in clinical practice [6–9]. Although they are recommended in current guidelines for the treatment of VTE [5, 10], traditional VTE treatments have numerous limitations. For example, unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux require parenteral administration, while the oral VKAs have a slow onset of action, require regular international normalization ratio (INR) monitoring and have numerous drug and food interactions [3, 11, 12]. These limitations make the management of patients with VTE difficult, and they negatively affect patients' quality of life [13, 14]. Intensive research is continuing to focus on new oral anticoagulant (NOAC) agents, including three factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and one thrombin (factor IIa) inhibitor (dabigatran etexilate), all of which have the potential to overcome the limitations of traditional therapies [15]. VKAs act non-specifically at various steps in the coagulation cascade, while the NOACs act directly on factor Xa or thrombin and, unlike VKAs, they do not require routine INR monitoring and have minimal drug and food interactions [15].

Current VTE guidelines are generally vague on the length of therapy, particularly extended therapy beyond 3–6 months [5]. The prevention and treatment of VTE must be tailored to an individual patient's needs, which primarily depend on the risks of having a recurrent VTE event or a bleed. With traditional treatments, and also now with the emerging NOACs, these two important potential outcomes need to be carefully weighed against each other, and with on-going assessment of other risks and benefits when a decision is made on the duration of VTE treatment (Table 1) [5, 16–19]. Recent studies investigating the acute treatment, secondary prevention and extended treatment of VTE with NOACs, warfarin and aspirin have made many clinicians reconsider the risks and benefits of anticoagulant treatment. These investigations

Table 1 Risk factors for recurrence of VTE and bleeding

Risk factors for VTE recurrence [16–19]	Risk factors for bleeding [5]
Idiopathic presentation	Aged >75 years
Thrombophilia	Previous gastrointestinal bleeding
Presentation of primary DVT	Previous stroke (non-cardioembolic)
Increasing age	Chronic renal or hepatic disease
Proximal DVT	Concomitant antiplatelet therapy
Cancer	Poor anticoagulant control
Residual thrombus mass	Sub-optimal anticoagulation monitoring
Male gender	

DVT deep-vein thrombosis, *VTE* venous thromboembolism

may result in an adjustment of the balancing of bleeding risk and VTE recurrence, and therefore of the recommendations for the duration of therapy. This is because the NOACs dabigatran, rivaroxaban, apixaban and edoxaban have demonstrated non-inferior efficacy compared with the standard of care either versus LMWH and VKA (rivaroxaban and apixaban) or VKA (dabigatran and edoxaban). Rivaroxaban, apixaban and dabigatran were superior in terms of efficacy to placebo in extended therapy [20–27]. With regard to bleeding rates during acute treatment of patients with VTE, the results varied by the outcome measured, however, both standard measurements, described below, showed a trend to reduction for all four NOACs. Patients who received apixaban had significantly fewer major bleeds than those with VKA and in patients with PE, rivaroxaban was associated with a significantly lower rate of major bleeding than VKA [18, 21]. Edoxaban, apixaban and dabigatran were associated with significantly fewer of the combined major or clinically relevant non-major bleeding events than VKA, while rivaroxaban showed no difference versus VKA [17–19, 21–23]. During studies of extended treatment of VTE, only dabigatran was compared with VKA treatment and was associated with significantly less major or clinically relevant non-major bleeding [20].

As there is a very limited amount of long-term clinical evidence with the NOACs versus VKA treatment and limited post-marketing surveillance with the NOACs, the safety of these agents for long-term treatment in clinical practice is currently unclear.

Clinical studies with the NOACs were performed with a view to making significant changes to the acute and extended treatment of VTE. It is important to understand and compare the methodology utilized in each of the studies, to assess their limitations and put results with the NOACs into perspective. This review will compare and contrast the design and results of the Phase III trials of NOACs in VTE and discuss the implications of the NOACs in terms of treatment strategies in VTE patients.

Table 2 Frequent limitations in clinical studies

Limitations in clinical trials
Too small
Too restricted in age (lack of young or elderly)
Too well, little comorbidity, milder disease, safer and more compliant patients
Too short and follow-up limited
Too little information on drug interactions

Studies were identified from a search of the PubMed database (US National Library of Medicine, Bethesda, USA) for each of the NOACs, apixaban, dabigatran, edoxaban and rivaroxaban with venous thromboembolism, and Phase III clinical studies were identified (Tables 1, 2).

The analyses in this article are based on previously conducted studies, and no new studies of human or animal subjects performed by any of the authors are presented.

DESIGN AND LIMITATIONS OF NOAC STUDIES IN VTE

A number of limitations have been observed in the phase III clinical trials (Table 2). The studies with dabigatran, rivaroxaban, apixaban and edoxaban vary in terms of their individual designs and patient characteristics (Tables 3, 4). All of the studies comparing a NOAC with either LMWH and VKA, or VKA were non-inferiority studies. In addition, all of the VTE studies had exclusion criteria for patients with severe renal impairment because they are all at

Table 3 Comparison of design of VTE studies that compared NOACs with either LMWH and VKAs or VKAs

	EINSTEIN-DVT [21]	**EINSTEIN-PE** [22]	**RE-COVER I** [23]	**RE-COVER II** [27]	**RE-MEDY** [24]	**AMPLIFY** [25]	**Hokusai-VTE** [26]
Identifier	NCT00440193	NCT00439777	NCT00291330	NCT00680186	NCT00329238	NCT00643201	NCT00986154
Release	2010	2012	2009	2013	2013	2013	2013
Indications	Acute proximal DVT	Acute symptomatic PE	Acute symptomatic proximal DVT or PE	Acute symptomatic proximal DVT or PE	Extended treatment in VTE	Acute VTE	Acute symptomatic proximal DVT or PE
NOAC	Rivaroxaban	Rivaroxaban	Dabigatran	Dabigatran	Dabigatran	Apixaban	Edoxaban
Dosing regimen	Rivaroxaban 15 mg BID (3 weeks), then 20 mg QD	Rivaroxaban 15 mg BID (3 weeks), then 20 mg QD	Heparin/ Dabigatran 150 mg BID	Heparin/ Dabigatran 150 mg BID	Dabigatran 150 mg BID	Apixaban 10 mg BID (7 days), then 5 mg BID	Enoxaparin or UFH/ Edoxaban 60 mg QD (or 30 mg QD adjustment)
Comparator	LMWH/VKA	LMWH/VKA	Heparin/VKA	Heparin/VKA	VKA	LMWH/VKA	Enoxaparin or UFH/VKA
Design	Randomized, open-label, non-inferiority	Randomized, open-label, non-inferiority	Randomized, double-blind, non-inferiority	Randomized, double-blind, non-inferiority	Randomized, double-blind, non-inferiority	Randomized, double-blind, non-inferiority	Randomized, double-blind, non-inferiority
Duration (months)	3, 6 or 12	3, 6 or 12	6	6	(3 to 12) + 6 to 36	6	3–12
Heparin lead in	No	No	Yes	Yes	No	No	Yes
Dose adjustment	No	No	No	No	No	No	Yes
Randomized patients	3,449	4,833	2,564	2,568	2,866	5,400	8,292

Table 3 continued

	EINSTEIN-DVT [21]	EINSTEIN-PE [22]	RE-COVER I [23]	RE-COVER II [27]	RE-MEDY [24]	AMPLIFY [25]	Hokusai-VTE [26]
Mean age (years)	56.1	57.7	54.7	Not indicated	54.5	57.0	55.8
Inclusion criteria	Aged ≥18 years, confirmed acute symptomatic DVT without PE	Aged ≥18 years, confirmed acute symptomatic PE with or without DVT	Aged ≥18 years, confirmed acute symptomatic DVT or PE	Aged ≥18 years, confirmed acute symptomatic DVT or PE	Aged ≥18 years, confirmed acute symptomatic DVT or PE, previously treated with VKA for 3 to 12 months or dabigatran for 6 months	Aged ≥18 years, confirmed acute symptomatic DVT or PE	Aged ≥18 years, confirmed acute symptomatic DVT and/or PE
Exclusion criteria							
Estimated CrCl	<30 ml/min excluded	<30 ml/min excluded	<30 ml/min excluded	<30 ml/min excluded	≤30 ml/min excluded	Impaired kidney function excluded	<30 ml/min excluded
Liver disease	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Active cancer	Life expectancy <3 months excluded	Life expectancy <3 months excluded	Life expectancy <6 months excluded	Life expectancy <6 months excluded	Life expectancy <6 months excluded	Patients with short life expectancy excluded	Excluded if LMWH anticipated (life expectancy <3 months)
Chronic NSAID use	Discouraged	Discouraged	Not indicated	Not indicated	Not indicated	Not indicated	Excluded
Aspirin/ clopidogrel	Aspirin 100 mg/ clopidogrel 75 mg allowed	Aspirin 100 mg/ clopidogrel 75 mg allowed	Aspirin ≤100 mg allowed	Aspirin ≤100 mg allowed	Not indicated	Not indicated	Aspirin ≤100 mg allowed

Table 3 continued

	EINSTEIN-DVT [21]	EINSTEIN-PE [22]	RE-COVER I [23]	RE-COVER II [27]	RE-MEDY [24]	AMPLIFY [25]	Hokusai-VTE [26]
Coagulation disorder	Not indicated	Not indicated	Not indicated	Not indicated	Excluded	Not indicated	Excluded

BID twice daily, *CrCl* creatinine clearance, *DVT* deep-vein thrombosis, *LMWH* low molecular weight heparin, *NOAC* new oral anticoagulant, *NSAID* non-steroidal anti-inflammatory drug, *PE* pulmonary embolism, *QD* once daily, *UFH* unfractionated heparin, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

least partially excreted via the kidneys. Major differences in design were seen in the use of initial heparin therapy, open-label or double-blind treatment, once-daily or twice-daily dosing, dose adjustment during the study, treatment duration and follow-up duration (Tables 3, 4). The EINSTEIN-PE (NCT00440193) and EINSTEIN-DVT (NCT00439777) studies that compared rivaroxaban with heparin and VKA were open-label, which contrast with the double-blind studies that compared dabigatran, apixaban and edoxaban with VKA [20–26, 28]. Another substantial difference is the use of a heparin lead in, which is the recommended standard of care [5]. The RE-COVER I (NCT00291330) and RE-COVER II (NCT00680186) studies with dabigatran and the Hokusai-VTE (NCT00986154) study with edoxaban used a heparin lead in, but heparin was not used in the VTE studies with rivaroxaban and apixaban [20–23, 26–28]. Regarding dosing, a long-term once-daily dosing regimen was used in the rivaroxaban studies and a once-daily regimen was used throughout the edoxaban studies, while a twice-daily regimen was used in the dabigatran and apixaban studies. Dose adjustment at randomisation or maintenance-dose adjustment during the course of the study did not occur during the EINSTEIN, AMPLIFY (NCT00643201), RE-COVER, RE-MEDY (NCT00329238) or RE-SONATE (NCT00558259) studies [20–25, 27]. However, dose adjustment at randomisation and also at any point during the study was performed in the Hokusai-VTE study with edoxaban. In addition, Hokusai-VTE was the only study to assess all patients at the same time point (12 months), regardless of treatment duration (3–12 months) [26]. A large degree of variation is seen in the size of the acute VTE studies. The largest was Hokusai-VTE in 8,292 patients [28].

Table 4 Comparison of design of placebo-controlled VTE extension studies with NOACs

	EINSTEIN-Extension [21]	**AMPLIFY-Extension [20]**	**RE-SONATE [24]**
Identifier	NCT00439725	NCT00633893	NCT00558259
Release	2010	2012	2013
Indications	Extended treatment in proximal DVT or PE	Extended treatment in acute proximal DVT or PE	Extended treatment in proximal DVT or PE
NOAC	Rivaroxaban	Apixaban	Dabigatran
Dosing regimen	Rivaroxaban 15 mg BID (3 weeks), then 20 mg QD	Apixaban 5 mg BID or Apixaban 2.5 mg BID	Dabigatran 150 mg BID
Comparator	Placebo	Placebo	Placebo
Design	Randomized, double-blind, superiority	Randomized, double-blind, superiority	Randomized, double-blind, non-inferiority
Duration (months)	[6 to 12] + 6 or 12	[6 to 12] + 12	[6 to 18] + 6 to 18
Heparin lead in	No	No	No
Dose adjustment	No	No	No
Randomized patients	1,197	2,486	1,353
Mean age (years)	58.3	56.7	55.8
Inclusion criteria	Aged 18 and above, confirmed acute symptomatic PE or DVT, previously treated with rivaroxaban or VKA for 6 or 12 months and clinical equipoise for continued anticoagulation	Aged 18 and above, confirmed acute symptomatic DVT or PE, previously treated with apixaban or VKA for 6 to 12 months and clinical equipoise for continued anticoagulation	Aged 18 and above, confirmed acute symptomatic DVT or PE, previously treated with VKA for 6–18 months or dabigatran for 6 months
Exclusion criteria			
Estimated CrCl	<30 ml/min excluded	<25 ml/min excluded	≤30 ml/min excluded
Liver disease	Excluded	Excluded	Excluded
Active cancer	Life expectancy <3 months excluded	Excluded if on indefinite anticoagulation	Excluded
Chronic NSAID use	Discouraged	Permitted with caution	Not indicated

Table 4 continued

	EINSTEIN-Extension [21]	AMPLIFY-Extension [20]	RE-SONATE [24]
Aspirin/ clopidogrel	Aspirin 100 mg/clopidogrel 75 mg allowed	Low-dose single agent allowed	Not indicated
Coagulation disorder	Not indicated	Excluded	Excluded

BID twice daily, *CrCl* creatinine clearance, *DVT* deep-vein thrombosis, *NOAC* new oral anticoagulant, *NSAID* non-steroidal anti-inflammatory drug, *PE* pulmonary embolism, *QD* once daily, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

The two RE-COVER studies with dabigatran were the smallest acute VTE trials, with approximately 2,570 patients each [23, 27].

Patient Characteristics

The design of the VTE studies, characteristics of patients randomized and the variation in study design impose a number of limitations in relation to the generalizability of the results obtained to a clinical practice setting.

Mortality is an important indicator of level of illness in any group of patients enrolled into a clinical study. The rates reported in the acute VTE studies are, therefore, of great interest to fully understand the relevance of the studies in clinical practice. The studies that had around 6 months of follow-up including the EINSTEIN studies reported mortality rates slightly above 2% and the AMPLIFY and RE-COVER studies reported rates slightly below 2% [21–23, 25, 27]. The study that followed all patients for 12 months, Hokusai-VTE, reported approximately 3.2% total mortality [26]. However, the different lengths of follow-up and the different analyses of the study populations, with and without patients off treatment, do not allow direct between-study comparisons of mortality rates.

In addition to mortality, the range of anatomical extent of PE at baseline also provides an important insight into the relevance of the studies in clinical practice. Both the EINSTEIN-PE and Hokusai-VTE studies used the same criteria to define anatomical extent of PE, with extensive PE defined as involvement of multiple lobes with 25% or more of the entire vasculature. In EINSTEIN-PE, extensive PE was present in approximately 24% of patients and in Hokusai-VTE it was present in approximately 45.8% of patients. The AMPLIFY study used different criteria to define extensive PE, which were at least two lobes with at least 50% of vasculature for each lobe, and approximately 37.2% of patients had extensive PE according to these criteria in AMPLIFY [22, 25, 26]. Despite the varying criteria utilized, the highest reported proportion of patients with extensive PE was in the Hokusai-VTE study [18, 21, 22].

Patient age is a key factor and it has previously been found that the half-life and exposure of the NOACs dabigatran, rivaroxaban and apixaban are higher in the elderly [29]. Also, elderly patients are more likely to suffer greater bleeding complications both with and without anticoagulation [30]. Although no upper-age limits were set with regard to randomisation of patients, elderly and younger patients were under-represented and mean ages ranged from 54 to 58 years (Table 3). The placebo group of the EINSTEIN-Extension

(NCT00439725) trial had the highest mean age in any of the trials at 58.4 years [21]. With regard to race and ethnicity, patients were predominantly Caucasian in most of the studies even though the trials were multinational. For example, 94.8% of patients in the RE-COVER study were Caucasian [23]. Although the larger Hokusai-VTE study had a predominantly Caucasian study population (approximately 70%), the study also had a varied ethnic composition with 21% Asian and around 3.5% Black or African–American patients, and hence was the largest and most internationally representative VTE study [26].

Renal function is also a key factor in treatment with a NOAC and patients with renal impairment were under-represented in clinical trials. The AMPLIFY and AMPLIFY-Extension (NCT00633893) trials excluded patients with a creatinine clearance of <25 ml/min [20]. In AMPLIFY, the apixaban arm had 64% of patients with a creatinine clearance >80 ml/min and approximately 6% of patients had a creatinine clearance <50 ml/min [25]. A similar proportion was observed in the AMPLIFY-Extension study, approximately 71% of patients in the apixaban arm had a creatinine clearance >80 ml/min and only 5–6% of patients had a creatinine clearance <50 ml/min [20]. The Hokusai-VTE trial also included few patients with renal impairment, less than 7% of patients had a creatinine clearance of ≥30 ml to <50 ml/min. Although patients with a creatinine clearance <30 ml/min were excluded from the EINSTEIN trials, some patients with a lower creatinine clearance were enrolled [21, 22]. Subsequent pharmacodynamic modeling resulted in rivaroxaban being utilized at an estimated glomerular filtration rate as low as 15 ml/min. Although no weight restrictions existed in the trials, it is also clear that participants with a body mass index (BMI) ≥35 kg/m^2 were not frequently randomized. The mean BMI of the dabigatran group in the RE-COVER trial was 28.9 [standard deviation (SD) ± 5.7] kg/m^2 [23]. In Hokusai-VTE, approximately 13% of patients had a body weight ≤60 kg and 15% weighed >100 kg [22]. The mean weight of the apixaban 2.5 mg group in the AMPLIFY-Extension trial was 85.7 (SD ± 19.8) kg. In the AMPLIFY study, approximately 72% of the apixaban group weighed 60–100 kg and 19% weighed ≥100 kg [25]. In the EINSTEIN studies, approximately 14% of patients had a body weight >100 kg [17, 18]. A BMI ≥30 kg/m^2 was found in around 30% of patients in the EINSTEIN, AMPLIFY and RE-COVER studies, and in AMPLIFY and RE-COVER around 12% had a BMI ≥35 kg/m^2 [21–23, 25]. The proportion of obese patients is broadly consistent with levels found in population studies.

Overall, the limited inclusion of elderly patients, patients with renal impairment, very obese patients and patients from non-white ethnic groups may reduce the generalizability of the results of VTE studies in clinical practice.

The VTE study publications also provide limited information on drug interactions, which may have been very useful information for clinical practice. The AMPLIFY and EINSTEIN trials excluded patients taking strong cytochrome P-450 inhibitors/inducers, which means that they should not be recommended for patients who require these agents [21, 22, 25, 26]. In addition, although concomitant low-dose aspirin use was permitted in all of the studies, only the Hokusai-VTE study investigators reported any analysis of the effect of aspirin on efficacy and bleeding rates. These subgroup analyses did not find any effect of concomitant aspirin on the efficacy and safety of edoxaban [26].

Heparin Lead In

There are other facets of trial design that are important to consider when translating trial evidence into clinical practice. The duration and use of a parenteral heparin lead in prior to commencing NOAC therapy varied across the trials. In the RE-COVER trial the median length of parenteral anticoagulation post-randomisation was 6 days and in Hokusai-VTE the median length was 7 days, therefore, there is currently no evidence to support the immediate use of initial dabigatran or edoxaban monotherapy in VTE treatment [23, 26]. The EINSTEIN-PE and EINSTEIN-DVT trials excluded patients who had received more than 48 h of parenteral anticoagulation and the AMPLIFY study also excluded patients who received more than 1 day of LMWH therapy, or more than 36 h of continuous intravenous heparin [21, 22, 25]. However, it is known that the rate of VTE recurrence is highest during initial parenteral therapy and during the transition to VKA in this treatment strategy [31]. This raises the possibility that recurrence rates could be higher than those observed in the trials. Only few patients in the clinical trials used rivaroxaban and apixaban as a monotherapy because approximately 80–90% received a pre-randomisation dose of parenteral heparin. However, a subgroup analysis of EINSTEIN did not confirm differences between patients who only received rivaroxaban and those who had initial parenteral therapy [21]. The optimal strategy for using or not using a heparin lead in has not been determined in a randomized trial and, therefore, this is an open issue. In clinical practice some physicians may prefer to use NOAC monotherapy for VTE treatment in lower risk patients suitable for outpatient therapy, while others may prefer a heparin lead in, especially for sicker patients requiring inpatient therapy.

Use of Blinding

Another major difference in trial design is the use of open- or double-blinded methodology. Double-blinded trials are traditionally viewed as the ‘gold standard’ in design. Blinding protects against detection and reporting bias arising from patients and investigators knowing which treatment is being received. However, blinding results in the loss of information that may reflect true differences in a randomized trial with respect to the quality of life experienced with different regimens. The EINSTEIN-DVT and EINSTEIN-PE trials were open-label and, therefore, a direct comparison of the effects of rivaroxaban and VKA on quality of life could be performed. A higher rate of recurrent VTE episodes was suspected in the rivaroxaban arm than in the VKA arm in the EINSTEIN-DVT trial, indicating a possible diagnostic-suspicion bias against rivaroxaban. However, the blinded central adjudicating committee did not confirm higher VTE recurrences in the rivaroxaban arm [21]. Double-blinded trials are complex in the context of anticoagulant therapy. The AMPLIFY, Hokusai-VTE and RE-COVER trials used double-dummy methodology to maintain blinding and minimize bias. In these studies, the arm receiving active NOAC also received placebo warfarin together with ‘sham INR’ monitoring. In addition to making patient recruitment harder, patient selection bias may occur in double-dummy trials as investigators may doubt the ability of elderly or frail patients to follow complex instructions [32]. In general, double-dummy trials also tend to have higher discontinuation rates, as is seen in the RE-COVER trial (15.2% discontinuation) compared with the open-label EINSTEIN-PE (11.5% discontinuation) and EINSTEIN-DVT (12.8% discontinuation) trials. However, the double-dummy Hokusai-VTE study had a

discontinuation rate of 4.2%, which was the lowest in any of the VTE studies. This may be explained by the extremely low proportion of patients who withdrew consent (<0.9%) or who were lost to follow-up (<0.2%) in Hokusai-VTE [26]. Double-dummy design may also bias towards a higher time in therapeutic (TTR) range, in relation to INR control, by selecting more compliant patients [32]. The mean TTR observed in clinical studies using a VKA to treat VTE has been estimated at 60% [33]. Although the methods of assessing TTR vary from trial to trial, the RE-MEDY trial with dabigatran had the highest mean TTR of 65% [24]. A selection-to-continue bias present in the extended treatment RE-MEDY trial may have also contributed to the higher TTR achieved. The EINSTEIN-DVT open-label trial with rivaroxaban had a lower TTR of 57% than the EINSTEIN-PE which had a TTR of 63%, indicating more stringent control in PE patients compared with DVT patients. Clinical trial results for TTR are higher than normally seen in clinical practice. The mean TTR varies in reported series, however, a very large study in the United States demonstrated that in a real-world population, less than 50% of warfarin patients achieved INR values within the therapeutic range [34]. Furthermore, adherence is often poor, missed and extra doses are not uncommon and subsequently INR is frequently out of range [35]. It is important to consider that missing doses of NOACs would also result in patients' anticoagulation becoming sub-therapeutic. NOACs have a shorter half-life than warfarin, and therefore a missed dose may pose a greater short-term risk of VTE recurrence [36].

Statistical Analyses and Sample Size

All of the trials comparing a NOAC with VKAs were designed to assess for non-inferiority and utilized intention-to-treat analyses, but it is recommended to also perform a per-protocol analysis because this strengthens an equivalence finding if both analyses are in agreement [37]. The evidence for non-inferiority of NOACs may depend on the quality of VKA treatment reflected by TTR. In addition, premature discontinuation, small sample size, lack of blinding and effects of concomitant medication all may increase the chance of finding non-inferiority when a true difference exists [38]. The incentive to reduce the impact of these factors is greater when a trial aims to demonstrate superiority. The importance of sample size was observed in the non-inferiority RE-COVER trial, which may have initially been too small as a low rate of recurrent VTE was observed [23]. The replica RE-COVER II study was then conducted to confirm the findings of RE-COVER [27]. The VTE trial with the largest study population was Hokusai-VTE in 8,292 patients, which was more than double the size of RE-COVER [22].

Treatment Duration

The duration of VTE treatment is a key issue for every patient to balance the risk of recurrence and bleeding effectively. It is important to optimize treatment duration dependent on patients' characteristics. Although the risk of VTE recurrence is highest within the initial 6 months, it does not return to normal after this period and it is also of note that the optimal duration of VTE treatment still remains unclear in clinical guidelines [31]. Most of the acute VTE trials with the NOACs did not have long follow-up periods, and important information about the recurrence rates of VTE upon cessation of NOAC treatment compared with VKA was not obtained. A more complete picture of the effect of length of treatment could have been

determined if all patients in the NOAC trials were followed for the same length of time and all events were collected over that time period. The only exception was Hokusai-VTE, which had a flexible treatment duration of 3–12 months and all patients were analyzed at 12 months [26]. In the double-blind, double-dummy Hokusai-VTE trial, 40% of patients completed 12 months of treatment, approximately 62% had >6 months of therapy and 26% had 3 to ≤6 months of therapy [26]. This suggests that in a patient population comprised of large numbers of patients with extensive PE (46%) and extensive DVT (42%), the extent of disease does not determine length of therapy. The investigators' previous double-dummy clinical trial experience and the flexible treatment duration in Hokusai-VTE may have been two of the reasons that very low levels of patient discontinuation and withdrawal of consent were observed, as compared with the other VTE studies. Insights into the appropriate duration of treatment for provoked, unprovoked, limited and extensive PE and DVT could be made from further analyses of the Hokusai-VTE study, including recurrence rates after cessation of treatment. In addition, the extension trials with dabigatran, rivaroxaban and apixaban add to the growing evidence in support of continued anticoagulation in certain clinical settings.

CLINICAL RESULTS FROM NOAC STUDIES IN VTE

Acute Treatment and Secondary Prevention Studies

Promising results have been obtained with the NOAC agents dabigatran, rivaroxaban, apixaban and edoxaban in acute VTE treatment and secondary prevention studies (Table 5). The RE-COVER trial compared heparin/dabigatran 150 mg twice daily with heparin/warfarin in the prevention of recurrent or fatal VTE and found that heparin/dabigatran was non-inferior to heparin/warfarin ($p < 0.001$ for non-inferiority) [23]. Dabigatran was also associated with significantly fewer major or clinically relevant non-major bleeding, as well as any bleeding events (Table 5) [23]. The replica RE-COVER II trial confirmed that the efficacy of heparin/dabigatran in acute VTE was non-inferior to heparin/warfarin and dabigatran also had a lower risk of bleeding [27]. Similar results have been observed with rivaroxaban, which was compared with standard enoxaparin/VKA therapy in acute symptomatic proximal DVT in EINSTEIN-DVT and in acute symptomatic PE with or without symptomatic DVT in EINSTEIN-PE [21, 22]. Both studies found rivaroxaban was non-inferior compared with enoxaparin/VKA in the prevention of symptomatic, recurrent VTE. In both studies, rivaroxaban was associated with comparable levels of major or clinically relevant non-major bleeding and in EINSTEIN-PE the rivaroxaban group had significantly fewer major bleeding events than standard therapy [21, 22]. The AMPLIFY study demonstrated that apixaban was non-inferior to conventional therapy with enoxaparin followed by warfarin, in the prevention of recurrent VTE or related death. Apixaban treatment was also associated with a significantly lower risk of major or clinically relevant non-major bleeding than conventional therapy [25]. The Hokusai-VTE study demonstrated that edoxaban was non-inferior to warfarin in the prevention of recurrent symptomatic VTE and edoxaban was also associated with significantly fewer major or clinically relevant non-major bleeding events

Table 5 Comparison of results of VTE studies that compared NOACs with either LMWH and VKAs or VKAs

	EINSTEIN-DVT [21]	EINSTEIN-PE [22]	RE-COVER I [23]	RE-COVER II [27]	RE-MEDY [24]	AMPLIFY [25]	Hokusai-VTE [26]
Study population (%)							
Unprovoked	62.0	64.5	Not indicated	Not indicated	Not indicated	89.8	65.7
Proximal DVT	98.7	0	68.9	Not indicated	65.1	99.9	Not indicated
PE	0.7	100.0	31.0	Not indicated	34.8	34.0	40.0
Previous VTE	19.3	19.5	25.6	Not indicated	0.9	16.2	18.5
Active Cancer	6.0	4.6	4.8	Not indicated	4.1	2.7	2.5
Anatomical extent of PE (%)*							
Limited	Not applicable	12.6	Not indicated	Not indicated	Not indicated	9.1	7.6
Intermediate	Not applicable	58.3	Not indicated	Not indicated	Not indicated	42.9	41.0
Extensive	Not applicable	24.3	Not indicated	Not indicated	Not indicated	37.2	45.8
Not assessable	Not applicable	4.9	Not indicated	Not indicated	Not indicated	10.8	5.6
Study outcomes (NOAC vs. VKA)							
Recurrent VTE							
Absolute rate (%)	2.1 vs. 3.0	2.1 vs. 1.8	2.4 vs. 2.1	2.3 vs. 2.2	1.8 vs. 1.3	2.3 vs. 2.7	3.2 vs. 3.5
HR [95 % CI]	0.68 [0.44–1.04]	1.12 [0.75–1.68]	1.10 [0.65–1.84]	1.08 [0.64–1.80]	1.44 [0.78–2.64]	RR 0.84 [0.60–1.18]	0.89 [0.70–1.13]
p value	$p < 0.001$ for NI	$p = 0.003$ for NI	$p < 0.001$ for NI	$p < 0.001$ for NI	$p = 0.01$ for NI	$p < 0.001$ for NI	$p < 0.001$ for NI
Major bleeding							
Absolute rate (%)	0.8 vs. 1.2	1.1 vs. 2.2	1.6 vs. 1.9	1.2 vs. 1.7	0.9 vs. 1.8	0.6 vs. 1.8	1.4 vs. 1.6
HR [95 % CI]	0.65 (0.33–1.30)	0.49 (0.31–0.79)	0.82 [0.45–1.48]	0.69 [0.36–1.32]	0.52 [0.27–1.02]	RR 0.31 [0.17–0.55]	0.84 (0.59–1.21)
p value	$p = 0.21$	$p = 0.003$			$p = 0.06$	$p < 0.001$ for Sup	$p = 0.35$ for Sup

Table 5 continued

	EINSTEIN-DVT [21]	EINSTEIN-PE [22]	RE-COVER I [23]	RE-COVER II [27]	RE-MEDY [24]	AMPLIFY [25]	Hokusai-VTE [26]
Major or CRNM bleeding							
Absolute rate (%)	8.1 vs. 8.1	10.3 vs. 11.4	5.6 vs. 8.8	5.3 vs. 8.5	5.6 vs. 10.2	4.3 vs. 9.7	8.5 vs. 10.3
HR [95 % CI]	0.97 [0.76–1.22]	0.90 [0.76–1.07]	0.63 [0.47–0.84]	0.62 [0.50–0.76]	0.54 (0.41–0.71)	0.44 (0.36–0.55)	0.81 [0.71–0.94]
p value	$p = 0.77$	$p = 0.23$			$p < 0.001$	$p < 0.001$	$p = 0.004$ for Sup
Minor bleeding	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Any bleeding							
HR [95 % CI]	Not indicated	Not indicated	0.71 [0.59–0.85]	0.67 [0.56–0.81]	0.71 [0.61–0.83] ARR −6.8%	HR not calculated	0.82 [0.75–0.90] ARR −3.9%
Total deaths							
HR [95 % CI]	0.67 [0.44–1.02]	1.13 [0.77–1.65]	0.98 [0.53–1.79]	Not indicated	0.90 [0.47–1.72]	0.79 [0.53–1.19]	HR not calculated

ARR absolute risk reduction, *CI* confidence interval, *CRNM* clinically relevant non-major, *DVT* deep-vein thrombosis, *HR* hazard ratio, *LMWH* low molecular weight heparin, *NI* non-inferiority, *NOAC* new oral anticoagulant, *PE* pulmonary embolism, *RR* relative risk, *Sup* superiority, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

* The same criteria for anatomical extent were used in EINSTEIN-PE and Hokusai-VTE: limited, involvement of ≤25% of the vasculature of a single lobe; intermediate, involvement of >25% of the vasculature of a single lobe or multiple lobes with involvement of ≤25% of the entire vasculature; and extensive, involvement of multiple lobes with ≥25% of the entire vasculature. The criteria used in AMPLIFY were: limited, involved ≤25% of the vasculature of a single lobe; extensive, there were two or more lobes involving ≥50% of the vasculature for each lobe; and intermediate if neither of these definitions were met

than warfarin at 12 months. Approximately 17.5% of the Hokusai-VTE study population qualified for dose reduction from edoxaban 60 mg to 30 mg. Among the dose-adjusted group, 22/733 (3.0%) edoxaban patients and 30/719 (4.2%) warfarin patients had recurrent VTE events (HR 0.73; 95 % CI 0.42–1.26), which correlated with results in the overall study population [26].

Extended Secondary Prevention Studies

The duration of treatment is an uncertain issue in VTE treatment because the benefit of preventing VTE recurrence and risk of bleeding must be balanced for each patient. Following on from the acute VTE treatment studies, continued long-term therapy with the NOACs dabigatran, rivaroxaban and apixaban have been performed and provided promising results. The RE-MEDY study (Tables 3, 5) compared dabigatran with warfarin in a 6- to 36-month extended treatment period after 3–12 months of initial VTE therapy [24]. Dabigatran showed non-inferior efficacy compared with warfarin in the primary outcome of symptomatic, recurrent VTE or VTE-related death and significantly fewer bleeding events and major or clinically relevant non-major bleeds were observed with dabigatran than warfarin [24]. However, patients in the dabigatran group had a significantly higher rate of acute coronary syndrome events than those in the warfarin group ($p = 0.02$) [20]. A similar observation was made in patients with atrial fibrillation who received dabigatran compared with warfarin during the RE-LY trial [35].

Placebo-controlled extension studies have also been performed with the NOACs to investigate benefits compared with treatment cessation (Tables 4, 6). The RE-SONATE study compared dabigatran with placebo in a 6- to 18-month extension period that followed 6–18 months of initial VTE treatment [24]. RE-SONATE showed that long-term treatment was significantly more effective than placebo ($p < 0.001$) in prevention of symptomatic recurrent VTE and related deaths. However, dabigatran treatment was associated with a significantly higher rate of any bleeding and major or clinically relevant bleeding. In the EINSTEIN-Extension study with a 6- or 12-month extension, rivaroxaban was associated with significantly fewer symptomatic, recurrent VTE events than placebo ($p < 0.001$) [21]. The rivaroxaban arm had a significantly higher incidence of major or clinically relevant non-major bleeding than placebo ($p < 0.001$), as well as comparable non-fatal major bleeding to placebo. In the 12-month AMPLIFY-Extension study in symptomatic DVT or PE patients [16], both of the apixaban 5 mg and 2.5 mg doses were superior to placebo in prevention of symptomatic, recurrent VTE or death from any cause ($p < 0.001$ for both comparisons). The rate of major bleeding was similar in the three treatment groups at 0.5% ($n = 4$) with placebo, 0.2% ($n = 2$) with apixaban 5 mg and 0.1% ($n = 1$) with apixaban 2.5 mg. Although the placebo group had the highest rate of major bleeds, no significant difference was observed and such fluctuations are likely to occur by chance. In addition, the rate of major or clinically relevant non-major bleeding was 2.7% in the placebo group, 4.3% in the apixaban 5 mg group and 3.2% in the apixaban 2.5 mg group [16]. Based on these bleeding data, some commenters have speculated that the intermediate dose of apixaban 2.5 mg may be most beneficial in extended treatment. Taken together, the placebo-controlled RE-SONATE, EINSTEIN-

Table 6 Comparison of results of placebo-controlled VTE extension studies with NOACs

	EINSTEIN-Extension [21]	AMPLIFY-Extension [20]	RE-SONATE [24]
Study population (%)			
Unprovoked	73.7	91.7	Not indicated
Proximal DVT	62.0	65.4	64.9
PE	38.0	34.6	33.0
Previous VTE	16.1	12.7	Not indicated
Active Cancer	4.5	1.7	0.2
Anatomical extent of PE (%)*			
Limited	Not indicated	Not indicated	Not indicated
Intermediate	Not indicated	Not indicated	Not indicated
Extensive	Not indicated	Not indicated	Not indicated
Not assessable	Not indicated	Not indicated	Not indicated
Study outcomes (NOAC vs. placebo)			
Recurrent VTE			
Absolute rate (%)	1.3 vs. 7.1	Apixaban 5 mg BID: 1.7 vs. 8.8;	0.4 vs. 5.6
HR [95 % CI]	0.18 [0.09–0.39]	ARR 7.0% [4.9–9.1]	0.08 [0.02–0.25]
p value	$p < 0.001$	$p < 0.001$ for Sup	$p < 0.001$ for Sup
		Apixaban 2.5 mg BID:	
		1.7 vs. 8.8	
		ARR 7.2% [5.0–9.3]	
		$p < 0.001$ for Sup	
Major bleeding			
Absolute rate (%)	0.7 vs. 0	Apixaban 5 mg BID	0.3 vs. 0
HR [95 % CI]	HR not estimable	0.1 vs. 0.5	HR not estimable
p value	$p = 0.11$	RR 0.25 [0.03–2.24]	$p = 1.0$
		Apixaban 2.5 mg BID	
		0.2 vs. 0.5	
		RR 0.49 [0.09–2.64]	
Major or CRNM bleeding			
Absolute rate (%)	6.0 vs. 1.2	Apixaban 5 mg BID: 4.3 vs. 2.7	5.3 vs. 1.8
HR [95 % CI]	5.19 [2.3–11.7]	1.62 [0.96–2.73]	2.92 [1.52–5.60]
p value	$p < 0.001$	Apixaban 2.5 mg BID:	$p = 0.001$
		3.2 vs. 2.7	
		1.20 [0.69–2.10]	

Table 6 continued

	EINSTEIN-Extension [21]	AMPLIFY-Extension [20]	RE-SONATE [24]
Minor bleeding	Not indicated	Not indicated	Not indicated
Any bleeding	Not indicated	Not indicated	1.82 [1.23–2.68]
Total deaths	Rivaroxaban $n = 1$ (0.2%)	Apixaban 2.5 mg BID: ARR −0.9%	HR not calculated
	Placebo $n = 2$ (0.3%)	Apixaban 5 mg BID: ARR −1.2%	

ARR absolute risk reduction, *BID* twice daily, *CI* confidence interval, *CRNM* clinically relevant non-major, *DVT* deep-vein thrombosis, *HR* hazard ratio, *NOAC* new oral anticoagulant, *PE* pulmonary embolism, *RR* relative risk, *Sup* superiority, *VTE* venous thromboembolism

Extension and AMPLIFY-Extension studies suggested that patients at clinical equipoise between treatment continuation and cessation may benefit from additional treatment. This was demonstrated because the benefit of the NOACs with an 80% reduction in preventing recurrent venous thromboembolic events exceeded the risk of major bleeding and because the net clinical benefit was evident for rivaroxaban and apixaban compared with placebo [20, 21]. However, the optimal duration of extended therapy with NOACs still requires further clarification as only dabigatran was compared with a VKA in RE-MEDY, the other extension studies had a limited duration of 12–18 months and patients were not followed up after stopping anticoagulant treatment in the EINSTEIN-Extension the AMPLIFY-Extension studies [17, 20, 21].

Balancing VTE Recurrence and Bleeding Rates

To help ascertain the benefit of the NOACs in clinical practice, it is important to analyze observed rates of VTE recurrence in relation to bleeding (Figs. 1, 2). In the extended treatment studies, rates of VTE recurrence were very low in the anticoagulant groups (rivaroxaban, apixaban and dabigatran) and were significantly higher, around 10% in the placebo groups. However, rates of clinically relevant bleeding with rivaroxaban and dabigatran were higher than placebo. The lowest bleeding rate in this group of studies was seen with apixaban. Although the extended treatment RE-MEDY study found less bleeding with dabigatran than warfarin, VTE recurrence rates were slightly higher with dabigatran than with warfarin. In the acute VTE studies, bleeding rates with the NOACs were all less than with VKA treatment. The AMPLIFY study with apixaban, the EINSTEIN-DVT study with rivaroxaban and Hokusai-VTE with edoxaban suggested lower absolute rates of both VTE recurrence and bleeding compared with VKA treatment (Fig. 1).

DISCUSSION

VTE is a major burden on healthcare systems around the world and traditional treatment regimens with heparin and VKAs have a number of significant limitations that have limited their effectiveness in clinical practice for several decades. An aging population will most likely result in increase in the future burden of VTE. The NOACs dabigatran, rivaroxaban, apixaban and edoxaban have demonstrated a potential to provide effective

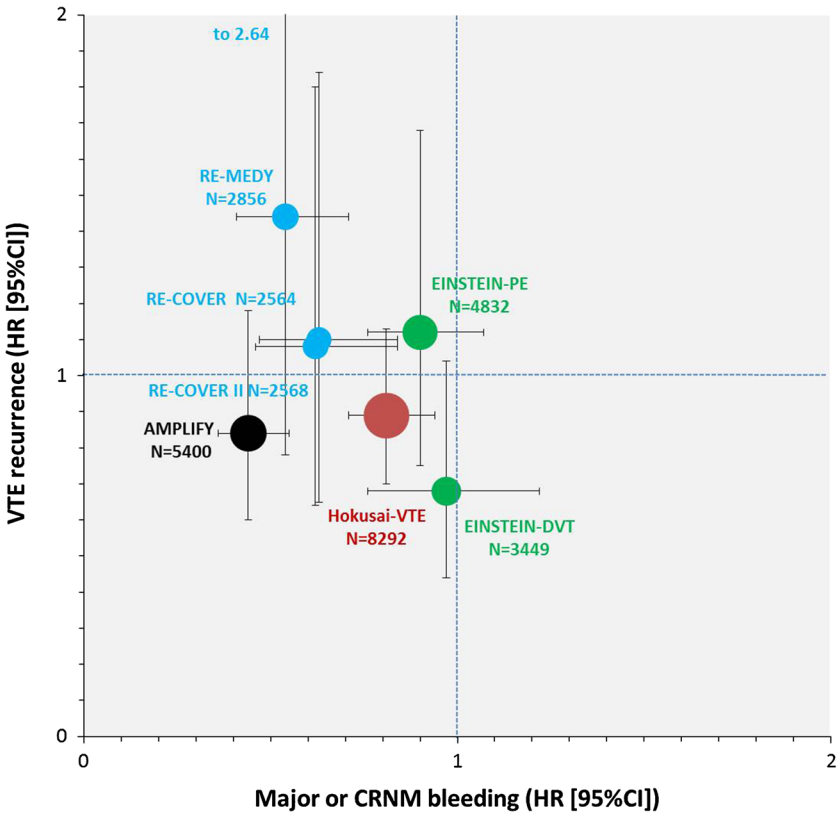

Fig. 1 VTE recurrence and rates of major or CRNM bleeding in VTE studies that compared NOACs with either LMWH and VKAs or VKAs. *CI* confidence interval, *CRNM* clinically relevant non-major. *DVT* deep-vein thrombosis, *HR* hazard ratio, *LMWH* low molecular weight heparin, *NOAC* new oral anticoagulant, *VKA* vitamin K antagonist, *VTE* venous thromboembolism [21–27]

alternative treatment in VTE patients. However, clinical studies with the NOACs had a number of limitations relating to the patients enrolled and study designs. All of the studies enrolled mostly Caucasian patients, had a very low proportion of both young and elderly patients, had few very obese patients, as well as patients with few comorbidities and a relatively low risk of VTE recurrence. In addition, very little information on possible drug interactions has been published. Most of the acute VTE studies had short, limited follow-up periods that have meant limited information on the appropriate duration of VTE treatment was obtained. The Hokusai-VTE study of edoxaban is the most recent study and aimed to address some weaknesses of previous trial designs. The study was large, had a flexible treatment duration which is more in line with clinical practice and had a longer follow-up with all patients analyzed at 12 months to aid treatment duration comparisons. Dose adjustments were allowed throughout the study as patient characteristics and concomitant treatments may change at any point in clinical practice [26]. In addition, central tracking of INR for each participating center and feedback to the investigators were also undertaken to ensure that a high TTR was achieved in the warfarin group [26].

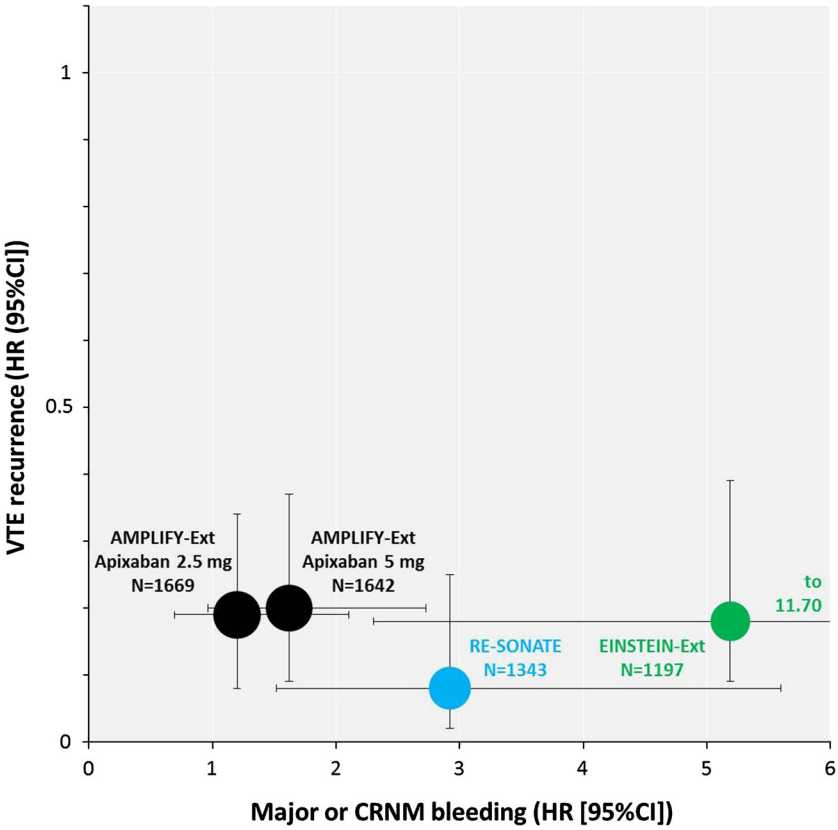

Fig. 2 VTE recurrence and rates of major or CRNM bleeding in placebo-controlled VTE extension studies of NOACs. *CI* confidence interval, *CRNM* clinically relevant non-major, *HR* hazard ratio, *NOAC* new oral anticoagulant, *VTE* venous thromboembolism [20, 21, 24]

In conclusion, all NOACs have shown similar efficacy to the standard of care: heparins and VKA, they have also shown a better safety profile than standard of care with respect to the important outcome of bleeding. The NOACs have their "pros and cons" with respect to each other, some are once daily, others are twice daily, and some require the use of a parenteral heparin lead in, others do not. The generalizability of results, the characterization of the patients treated, the extent of disease, the flexibility of dosing, and the evidence for extended therapy also vary between the studies. All these factors will need to be considered when deciding which of the NOACs to use in individual patients.

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Conflict of interest. Dr. Cohen reports receiving consulting fees from Bayer, Boehringer-Ingelheim, BMS, Daiichi Sankyo, GSK, Johnson & Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi, Schering Plough, Takeda, XO1; advisory board membership with Bayer, BMS, Daiichi Sankyo, Johnson & Johnson, Pfizer, Portola, Sanofi, XO1; payments for lectures including speakers bureau services, payments for preparation of reports and payment for development of educational presentations from Bayer, Boehringer-Ingelheim, BMS, Daiichi Sankyo, GSK, Johnson and Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi, and Schering Plough.

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Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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