

New Oral Anticoagulants for the Treatment of Venous Thromboembolism: Understanding Differences and Similarities

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Abstract Venous thromboembolism (VTE) is a major cause of morbidity, mortality, and healthcare expenditure. In the United States, approximately 0.1 % of the population experiences an initial VTE event each year. Anticoagulation therapy is the cornerstone of acute VTE treatment and for prevention of recurrent VTE events. Conventional anticoagulants, including heparin, low-molecular-weight heparins, fondaparinux, and vitamin K antagonists are widely used but have limitations. Newer oral anticoagulant agents, including direct thrombin inhibitors (e.g., dabigatran etexilate) and direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban) have been developed to attempt to overcome some of the limitations of conventional anticoagulant therapy. These new oral agents have been evaluated for safety and efficacy in large, randomized clinical trials in the treatment and secondary prevention of VTE with results that are comparable to conventional therapy. Dabigatran, rivaroxaban, apixaban, and edoxaban are important new treatment options for patients with VTE. In this review, we compare these new agents and their associated clinical trials in VTE treatment.

1 Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant healthcare concern resulting in substantial morbidity, mortality, and resource expenditure. A first VTE event occurs in approximately 0.1 % of people in the United States (US) each year [1]. In 2006, the incidences of patients admitted to hospital for DVT and PE were 52 per 100,000 and 49 per 100,000 persons, respectively [2], which is consistent with a community VTE incidence reported at 104 events per 100,000 population [3]. Patients with a first episode of VTE are at an increased risk of recurrence [1, 4, 5]. In a study of 1,626 patients, the cumulative incidence of recurrent VTE was 11.0, 19.6, 29.1, and 39.9 % after 1, 3, 5, and 10 years, respectively [6], and in a systematic review, the rate of recurrence of VTE at 24 months was 3.3 % per patient-year for all patients with a transient risk factor and 7.4 % per patient-year after unprovoked VTE [7]. Risk factors associated with the development of recurrent VTE include the presence of reversible provoking risk factors (e.g., recent surgery, use of estrogen-based oral contraception), previous unprovoked VTE, and the presence of active cancer [7, 8]. In almost 25 % of patients stricken with PE, the initial clinical manifestation is sudden death, with mortality exceeding 15 % in the first 3 months after diagnosis [9, 10]. A study evaluating short- and long-term mortality after 67,354 definite and 35,123 probable cases of VTE found 30-day and 1-year case fatality rates of 10.6 and 23.0 %, respectively [11].

Initial and recurrent VTE episodes are associated with high healthcare costs. A study assessing administrative claims from 30 managed care organizations found the average total annualized healthcare cost of a patient with a

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primary diagnosis of DVT was US\$10,804 and US\$16,644 for a patient with PE [12]. Most of the costs can be attributed to hospitalization, facility and professional costs, and outpatient procedure costs. Recurrent episodes of VTE were also associated with increased costs. Total hospitalization costs for patients readmitted with DVT were US\$2,057 more than the initial hospitalization [12]. This increase was primarily due to a longer length of hospital stay for the recurrent episode. Another medical center study reported treating an average of 160 hospitalized patients with PE per year and incurring annual treatment expenses ranging from approximately US\$900,000 to US\$1.9 million [13].

Anticoagulant therapy is necessary to prevent early and late episodes of recurrent VTE [4]. Currently available therapies include conventional anticoagulants, such as unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux, and vitamin K antagonists (VKAs). Each conventional anticoagulant is associated with intrinsic limitations, such as unpredictable pharmacokinetics and pharmacodynamics, monitoring requirements, parenteral administration, drug–food or drug–drug interactions, and potentially severe adverse events. New oral anticoagulants (NOACs) have advantages that make them beneficial treatment options for patients with acute VTE as well as for prevention of recurrent events. Here, we examine the data on the direct thrombin inhibitor dabigatran etexilate, and direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban to gain a better understanding of how each agent fits into the landscape of therapeutic options for VTE management. Currently, rivaroxaban, apixaban, and dabigatran are approved by the US Food and Drug Administration (FDA) for the treatment of acute VTE and prevention of recurrence. Edoxaban has been studied in phase III studies and is currently under evaluation by the FDA.

2 New Oral Anticoagulants

Dabigatran has been evaluated for the acute treatment of VTE in the RE-COVER (Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism) I and II trials [14, 15]. To increase the robustness of the data supporting the use of dabigatran in acute VTE treatment, the RE-COVER II trial was conducted using the same trial design and outcome measures as the RE-COVER I trial [15]. The efficacy and safety of rivaroxaban in the acute treatment of VTE was assessed in two separate trials, EINSTEIN-DVT and EINSTEIN-PE (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism) [16, 17]. Aside from

the index event in the patients enrolled in each trial, the study designs were identical. Apixaban has been evaluated in the acute treatment of VTE in the AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) trial [18]. The efficacy and safety of edoxaban for the acute treatment of VTE was evaluated in the Hokusai-VTE trial [19]. An overview of these trials is presented in Table 1.

3 Study Design

3.1 Treatment Protocols

The RE-COVER I and II, AMPLIFY, and Hokusai-VTE trials were all conducted in a double-blinded fashion, with international normalized ratio (INR) testing incorporated through an encrypted point-of-care device providing accurate and sham results [14, 15, 18, 19]. In contrast, the EINSTEIN trials had an open-label design (Table 1) [16, 17]. All of the studies had a comparator arm reflecting standard of care—parenteral anticoagulant administered along with a VKA. However, the approaches to parenteral anticoagulant use in the investigational treatment arms differed among the trials. The RE-COVER and Hokusai-VTE trials both incorporated initial treatment with a heparin agent for at least 5 days [14, 15, 19]. The second approach, employed in the EINSTEIN and AMPLIFY trials, was NOAC monotherapy. The rationale for initial parenteral therapy originated from a prior trial using the investigational direct thrombin inhibitor ximelagatran. Here, the recurrent VTE rate was elevated during the early treatment period in patients receiving a fixed-dose oral anticoagulant compared with standard of care [20]. To address this, the EINSTEIN and AMPLIFY studies initiated treatment with a higher dose of their respective agents, without initial parenteral anticoagulation, before reducing to a lower maintenance dose [16–18].

An additional difference in dosing strategies, unique to the edoxaban trial, was the incorporation of predetermined dose reductions in response to the presence of certain characteristics that could lead to increased drug exposure [19]. In the Hokusai-VTE trial, patients with a creatinine clearance (CrCl) ≥ 30 to ≤ 50 mL/min, a body weight of ≤ 60 kg, or those receiving concomitant treatment with a potent P-glycoprotein (P-gp) inhibitor were given a dose of edoxaban of 30 mg once daily instead of 60 mg once daily [19, 21]. After randomization, if the patient's CrCl changed to ≥ 30 to ≤ 50 mL/min (confirmed by repeat measurement at least 1 week apart) and the CrCl change was $>20\%$ from baseline, the edoxaban dose was reduced permanently [19]. Similarly, if the patient's body weight dropped to ≤ 60 kg (confirmed by repeat measurement at least 1 week

Table 1 General overview of clinical trial design

Criteria	RE-COVER I [14]	RE-COVER II [15]	EINSTEIN-DVT [16]	EINSTEIN-PE [17]	AMPLIFY [18]	Hokusai-VTE [19]
Study design	Randomized, double-blind, non-inferiority, parallel group		Randomized, open-label, event-driven, non-inferiority, parallel group		Randomized, double-blind, parallel group	Randomized, double-blind, non-inferiority, parallel group
Intervention	Dabigatran etexilate 150 mg bid (<i>n</i> = 1,274)	Dabigatran etexilate 150 mg bid (<i>n</i> = 1,279)	Rivaroxaban 15 mg bid for 3 weeks, followed by 20 mg od <i>n</i> = 1,731	Rivaroxaban 15 mg bid for 3 weeks, followed by 20 mg od <i>n</i> = 2,419	Apixaban 10 mg bid for 7 days, followed by 5 mg bid <i>n</i> = 2,676	Edoxaban 60 mg od or edoxaban 30 mg od in patients with a CrCl of 30–50 mL/min, body weight ≤60 kg or receiving strong P-gp inhibitors <i>n</i> = 4,118
Comparator	Warfarin dose-adjusted to INR 2.0–3.0 <i>n</i> = 1,265	Warfarin dose-adjusted to INR 2.0–3.0 <i>n</i> = 1,289	Enoxaparin 1 mg/kg bid (≥5 days)/VKA (warfarin or acenocoumarol) dose-adjusted to INR 2.0–3.0 <i>n</i> = 1,718	Enoxaparin 1 mg/kg bid (≥5 days)/VKA (warfarin or acenocoumarol) dose-adjusted to INR 2.0–3.0 <i>n</i> = 2,413	Enoxaparin 1 mg/kg bid (≥5 days)/warfarin dose-adjusted to INR 2.0–3.0 <i>n</i> = 2,689	Warfarin dose-adjusted to INR 2.0–3.0 <i>n</i> = 4,122
Parenteral anticoagulation	Mandatory, at least 5 days		Optional, maximum 48 h		Optional, maximum 36 h	Mandatory, at least 5 days
Inclusion criteria	Symptomatic uni- or bilateral proximal DVT or PE (with or without DVT)	Symptomatic proximal DVT or PE (with or without DVT)	Symptomatic proximal DVT without symptomatic PE	Symptomatic PE with or without symptomatic DVT	Symptomatic proximal DVT or PE (with or without DVT)	Symptomatic proximal DVT or PE (with or without DVT)
Anatomical definition	Proximal defined as trifurcation area, popliteal, superficial femoral, deep femoral, common femoral, and iliac veins		Proximal defined as the iliac vein, common femoral vein, superficial femoral vein, and popliteal vein	PE defined as an intraluminal filling defect in segmental or more proximal branches	Proximal defined as involving at least the popliteal vein or a more proximal vein	Proximal defined as involving the popliteal, femoral, or iliac veins
Objective testing for suspected PE	Confirmed by ventilation-perfusion lung scan, pulmonary angiography, or spiral CT Additional baseline exams (bilateral CUS) were performed no later than 72 h after randomization to facilitate adjudication of suspected recurrence		Intraluminal filling defect in segmental or more proximal branches on spiral CT, or a (new) intraluminal filling defect or extension of an existing defect or a new sudden cutoff of vessels ≥2.5 mm in diameter on pulmonary angiogram, or a (new) perfusion defect of at least 75 % of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy Or inconclusive spiral CT, pulmonary angiography, ventilation-perfusion lung scan evidence of a new or recurrent PE, with demonstration of a new or extended DVT in the lower extremities by CUS or venography			
Objective testing for suspected DVT	Confirmed by venous CUS or venography Additional baseline exams (CUS in symptom-free leg, bilateral CUS when the initial DVT diagnosis was made by venography, perfusion lung scan or lung spiral CT) were performed no later than 72 h after randomization to facilitate adjudication of suspected recurrence		Confirmed by an abnormal CUS or an intraluminal filling defect on venography	Confirmed by abnormal CUS, including grey-scale or color-coded Doppler, or an intraluminal filling defect of venography	Confirmed by a noncompressible venous segment on ultrasonography, or an intraluminal filling defect on venography, or an intraluminal filling defect on spiral CT of the leg	Objective testing for suspected DVT (no prior testing) or an extension of an intraluminal filling defect on spiral CT/contrast of the leg
Primary efficacy endpoint	Recurrent symptomatic VTE or death related to VTE		Recurrent symptomatic VTE	Recurrent symptomatic VTE	Recurrent symptomatic VTE or death related to VTE	Recurrent symptomatic VTE

Table 1 continued

Criteria	RE-COVER I [14]	RE-COVER II [15]	EINSTEIN-DVT [16]	EINSTEIN-PE [17]	AMPLIFY [18]	Hokusai-VTE [19]
Primary safety endpoint	Major bleeding		Major or CRNM bleeding	Major or CRNM bleeding	Major bleeding	Major or CRNM bleeding
Treatment duration	6 months		3, 6, or 12 months (pre-specified)		6 months	3–12 months (flexible)

bid twice daily, *CrCl* creatinine clearance, *CRNM* clinically relevant non-major, *CUS* compression ultrasound, *DVT* deep vein thrombosis, *INR* international normalized ratio, *od* once daily, *PE* pulmonary embolism, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

apart) and the change was >10 % of baseline, the edoxaban dose was reduced permanently. While verapamil, quinidine, and dronedarone were the only P-gp inhibitors allowed at the time of randomization, concomitant use of any protease inhibitor was prohibited. The P-gp inhibitors erythromycin, azithromycin, clarithromycin, ketoconazole, and itraconazole were prohibited at the time of randomization, but subsequent use was permitted after randomization. When verapamil, quinidine, dronedarone, erythromycin, azithromycin, clarithromycin, ketoconazole, or itraconazole were used concurrently, the edoxaban dose was reduced to 30 mg daily. Conversely, the edoxaban dosing regimen was returned to 60 mg daily when the patient was no longer taking the concomitant medication [19].

Another difference in study designs was treatment duration. Both the RE-COVER and AMPLIFY trials had treatment durations of 6 months [14, 15, 18]. In the EINSTEIN trials, patients could have received treatment for 3, 6, or 12 months based on the discretion of the investigator, but the desired duration of therapy had to be determined at the time of randomization. A 3-month duration was intended in patients with a transient risk factor (recent surgery, trauma, immobilization, estrogen use, puerperium). A 6- or 12-month duration was intended for patients with idiopathic VTE or permanent risk factors (active cancer, previous VTE, thrombophilia) [16, 17]. In the Hokusai-VTE trial, treatment duration was for a minimum of 3 months and up to a maximum of 12 months, as determined by the investigator. In the Hokusai-VTE trial, unlike the other clinical trials, efficacy outcomes were assessed over the entire study treatment period of 12 months regardless of the duration of treatment (3–12 months) [19]. Safety and net clinical benefit were assessed only during the on-treatment period.

3.2 Inclusion and Exclusion

Except for the EINSTEIN trials, each trial had similar inclusion criteria, requiring the presence of symptomatic proximal DVT with or without PE (Table 1). The EINSTEIN-DVT trial required symptomatic proximal DVT

without PE, and the EINSTEIN-PE trial required the presence of symptomatic PE, with or without DVT [16, 17]. All trials required objective testing for diagnosis of initial and recurrent events (Table 1).

While venography is considered the standard diagnostic study against which all others are judged, the primary diagnostic method for DVT in the US is compression ultrasound (CUS). CUS has high sensitivity (>92 %), specificity (>97 %), and high interobserver agreement ($\kappa = 1$) for first-episode proximal DVT [22]. However, CUS-evident abnormalities continue to be present in approximately 80 % of patients at 3 months and in 50 % of patients after 1 year following a proximal DVT. Regardless of the ultrasound method used, proximal DVT is more accurately diagnosed than distal DVT [22]. Similarly, residual pulmonary thrombi can be detected on CT scan up to 11 months after the index PE [23]. Therefore, it becomes difficult to determine whether a suspected event in the same leg or pulmonary vein is new or residual thrombosis from the index event.

Each trial employed venography and CUS for DVT diagnosis. Only RE-COVER I and II mandated baseline exams and imaging of the symptom-free extremity to facilitate adjudication of recurrent events [14, 15]. This more stringent investigation could, in part, explain the numerically higher recurrent symptomatic DVT event rates when comparing RE-COVER I and II with EINSTEIN-DVT and AMPLIFY trials. The AMPLIFY trial included duplex ultrasonography (grey-scale or color-coded Doppler), a more comprehensive exam [18, 24]. In the Hokusai-VTE trial, diagnostic testing also included spiral computed tomography (CT) of the lower extremities [19]. In the EINSTEIN, AMPLIFY, and Hokusai-VTE trials, recurrent events were diagnosed when thrombosis was detected in a new or previously normal segment [16–19]. Similarly, recurrent DVT was diagnosed by measuring changes in vein diameter over time, defined as an increase in thrombus diameter to 4 mm in a previously affected vein segment, as opposed a reduction or no change in size [25]. All trials utilized a blinded central adjudication committee for the evaluation of all suspected efficacy and safety outcome events. In the RE-COVER trials, autopsies were conducted

Table 2 Comparison of clinical trial exclusion criteria

Criteria	RE-COVER I, II [14, 15]	EINSTEIN-DVT [16]	EINSTEIN-PE [17]	AMPLIFY [18]	Hokusai-VTE [19]
Exclusion	Symptoms >14 days	Not defined			
Prior intervention	Thrombolytic therapy within 14 days IVC filter, or anticipated use	Thrombolysis, thrombectomy, or insertion of IVC filter for current episode			
Parenteral anticoagulation prior to randomization	UFH, LMWH, fondaparinux >72 h	UFH, LMWH, fondaparinux >48 h		UFH >36 h, daily LMWH, or fondaparinux >2 doses, twice daily LMWH >3 doses	UFH, LMWH, fondaparinux >48 h
Oral anticoagulation	VKA for another indication				
Prior oral anticoagulation	>2 doses	>1 dose		>2 doses	>1 dose
Contraindications	Contraindication to heparins or alternative therapies for initial treatment and warfarin	Contraindication to enoxaparin, warfarin, and acenocoumal		Contraindication to UFH, LMWH, or any VKA	
Renal function	Estimated CrCl ≤ 30 mL/min	CrCl <30 mL/min		CrCl <25 mL/min, serum creatinine >2.5 mg/dL	Calculated CrCl <30 mL/min
Uncontrolled hypertension	N/A	Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg		Systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg	Systolic blood pressure >170 mmHg or diastolic blood pressure >100 mmHg
Hepatic function	Hepatic disease (ALT or AST $2 \times$ ULN, RE-COVER I, $3 \times$ ULN, RE-COVER II)	Hepatic disease, ALT or AST $3 \times$ ULN		Hepatic disease, ALT or AST $2 \times$ ULN, total bilirubin $1.5 \times$ ULN	Hepatic disease, ALT $\geq 2 \times$ ULN, total bilirubin $\geq 1.5 \times$ ULN
Life expectancy	<6 months	<3 months		<6 months	<3 months
Cancer	Not defined			Subjects with cancer who will be treated with LMWH for ≥ 6 months	Active cancer where long-term treatment with LMWH is anticipated
Child-bearing potential	Pregnancy or risk of becoming pregnant	Pregnancy, child-bearing potential without contraception, breast feeding		Pregnancy, child-bearing potential unable/willing to use contraception, breast feeding	Pregnancy, breast feeding, child-bearing potential without proper contraceptive methods
Cardiovascular disease	Endocarditis, myocardial infarction within last 3 months	Endocarditis			Not defined
Bleeding risk	High bleeding risk	Active bleeding or high risk of bleeding		Active bleeding or high risk of bleeding	Active bleeding or high bleeding risk contraindicating treatment with UFH or LMWH
Laboratory parameters	Hemoglobin <10 mg/dL, platelet count <100,000/mm ³	Not defined		Hemoglobin <9 mg/dL, platelet count <100,000/mm ³	Not defined
Trauma or major surgery	Within last month	Not defined		Within last 2 months	Not defined
Intracranial, intraocular bleed	Any history	Not defined		Within last 6 months	Not defined
GI bleed	Within last 3 months	Not defined		Within last 6 months	Not defined

Table 2 continued

Criteria	RE-COVER I, II [14, 15]	EINSTEIN-DVT [16]	EINSTEIN-PE [17]	AMPLIFY [18]	Hokusai-VTE [19]
Hemorrhagic disorder	Any history	Not defined		Any history	Not defined
Concurrent aspirin excluded	>100 mg per day			>165 mg per day	>100 mg day
Concurrent antiplatelet therapy	Clopidogrel, ticlopidine, G2b3a inhibitors prohibited	Clopidogrel 75 mg daily allowed		Dual antiplatelet therapy prohibited, monotherapy eligible	Dual antiplatelet therapy (oral or IV) prohibited
Anti-inflammatory agents	NSAID with $t_{1/2}$ <12 h with treatment for <1 week allowed	NSAID use discouraged		NSAIDs acceptable in doses not exceeding approved labeling	Chronic use of NSAIDs, COX-1, COX-2 inhibitors \geq 4 days/week prohibited
Concomitant therapies	N/A	CYP-4503A4 inhibitors (HIV protease inhibitors, ketoconazole) or inducers (rifampin) prohibited		CYP-4503A4 inhibitors (azole antifungals: ketoconazole, itraconazole; macrolide antibiotics: clarithromycin, telithromycin; protease inhibitors: ritonavir, indinavir, nelfinavir, atazanavir, saquinavir, nefazadone)	Treatment with P-gp inhibitors, ritonavir, nelfinavir, indinavir, saquinavir Use of dronederone at randomization Systemic use with P-gp inhibitors, ketoconazole, itraconazole, erythromycin, azithromycin, clarithromycin at randomization
Competing clinical trials or investigational drugs	Within last 30 days	Within 30 days of screening		Within last 30 days	Within 30 days prior to randomization
Other	Contraindication to radio contrast, chronic use of corticosteroids, unsuitable for follow up	None		Prisoners, psychiatric, physical illness	None

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *COX* cyclo-oxygenase, *CrCl* creatinine clearance, *CYP-4503A4* cytochrome P450 isoenzyme 3A4, *G2b3a* glycoprotein IIb/IIIa, *GI* gastrointestinal, *IVC* inferior vena cava, *LMWH* low-molecular weight heparin, *N/A* not available, *NSAID* non-steroidal anti-inflammatory drug, *P-gp* P-glycoprotein, $t_{1/2}$ half life, *UFH* unfractionated heparin, *ULN* upper limit of normal, *VKA* vitamin K antagonist

when possible to determine cause of death; for all other trials, cause of death was adjudicated by objective test, autopsy, documented cause, or when VTE could not be ruled out.

Exclusion criteria were similar across the studies (Table 2). Each study allowed a window for conventional parenteral anticoagulation therapy prior to enrollment with heparins or fondaparinux. Patients were excluded if life expectancy was <3 months (EINSTEIN-DVT, -PE; Hokusai-VTE) or <6 months (RE-COVER I, II, AMPLIFY) [14–19]. Patients with cancer were excluded if LMWH use was anticipated in AMPLIFY and Hokusai-VTE, whereas cancer was not exclusionary in the RE-COVER or EINSTEIN trials. All trials excluded patients with a $CrCl \leq 30$ mL/min, except AMPLIFY, which used a $CrCl < 25$ mL/min or a serum creatinine >2.5 mg/dL. Pregnancy excluded patients in all trials. Exclusions for high bleeding risk were better defined in RE-COVER I and

II and AMPLIFY with limitations based on hemoglobin, platelet count, recent surgery, and bleeding episodes or disorders. Only EINSTEIN allowed concomitant use of dual antiplatelet therapy.

3.3 Bleeding Definitions

There was concordance in the definitions of major bleeding across the trials (Table 3). The RE-COVER I and II, AMPLIFY, and Hokusai-VTE trials used the International Society of Thrombosis and Hemostasis (ISTH) definition of bleeding, while the EINSTEIN trials used a definition from the van Gogh trial that is nearly identical [26, 27]. Clinically relevant non-major (CRNM) bleeding was defined as those episodes that did not meet the criteria for major bleeding but still required medical attention (Table 3). This definition was identical in the EINSTEIN trials, AMPLIFY, and Hokusai-VTE trial [16, 17, 19, 28].

Table 3 Comparison of clinical trial major and clinically relevant nonmajor bleeding definitions

Outcome	RE-COVER I, II ^a [14, 15]	EINSTEIN-DVT [16]	EINSTEIN-PE [17]	AMPLIFY [18]	Hokusai-VTE [19]
Major bleeding					
Citation	ISTH [26]	van Gogh trial [27]		ISTH	
Description	Bleeding must be symptomatic	Bleeding must be overt		Bleeding must be symptomatic	
Hemoglobin requirement	Associated with a fall in hemoglobin of 2 g/dL or more				
Transfusion requirement	Leading to transfusion of ≥ 2 U of whole blood or red cells ^b				
Site requirement	Critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome)				
Mortality	Contributing to death				
Non-major bleeding					
Citation	Original	van Gogh trial			
Definition	Bleeding not meeting the criteria for major bleeding				
Intervention	Bleeding leading to hospitalization and/or requiring surgery	Associated with compromised hemodynamics, medical intervention, unscheduled physician contact, cessation of treatment, or associated with any other discomfort, pain, or impairment of activities of daily life			
Transfusion	Bleeding leading to transfusion of < 2 U of whole blood or red cells	Not included			
Hematoma	Spontaneous skin hematoma of ≥ 25 cm	Subcutaneous hematoma > 25 or > 100 cm ² if provoked by traumatic cause Intramuscular hematoma documented by ultrasonography			
Epistaxis	Nose bleed > 5 min duration	Epistaxis > 5 min, if it is repetitive, or leads to intervention			
Gingival	Gingival bleeding > 5 min duration	Gingival bleeding if it occurs spontaneously, or it lasts for > 5 min			
Hematuria	Macroscopic hematuria, either spontaneous or lasts for > 24 h after instrumentation, or of the urogenital tract				
Gastrointestinal	Not included	Macroscopic gastrointestinal hemorrhage, including at least 1 episode of melena or hematemesis, or rectal blood loss			
Rectal	Spontaneous rectal bleeding (more than blood spots on toilet paper)				
Hemoptysis	Undefined	Hemoptysis if more than a few speckles in the sputum and not occurring within context of pulmonary embolism			
Other	Any bleeding considered clinically relevant by investigator	Not included			

^a For RE-COVER I and II at least one of the criteria had to be fulfilled

^b Red cell unit corresponds to 500 mL of whole blood

ISTH International Society of Thrombosis and Hemostasis

In the RE-COVER I and II trials, the definition of CRNM bleeding was more stringent, requiring hospitalization and/or surgery, and transfusion of < 2 U of whole blood or red cells. It did not include parameters for hemoptysis and gastrointestinal bleeding [14, 15]. The RE-COVER I and II trials also included an option that allowed the investigator to designate these events.

3.4 Assessment of Non-Inferiority

All of the acute VTE treatment trials with the NOACs have had the primary efficacy outcome of non-inferiority compared with standard therapy. Non-inferiority studies are

designed to show that a treatment is 'as good as' current therapy, and are commonly employed when the use of placebo would be unethical. Non-inferiority margins must be chosen in a manner that considers both the uncertainty associated with the estimated treatment benefit and a tolerable margin for similarity between the tested and established therapy. A narrower margin is a reflection of greater certainty that the finding by the non-inferiority testing is true, and is also partly a reflection of sample size.

While each of these agents demonstrated non-inferiority in their respective trials, the definition of non-inferiority was not consistent between the trials. The RE-COVER trials had the highest boundaries for non-inferiority, with

the hazard ratio (HR) for non-inferiority being out to 2.75. The outer 95 % confidence interval (CI) achieved with dabigatran was 1.84 and 1.80 in the RE-COVER I and II trials, respectively, and 1.57 in the pooled analysis [14, 15]. In the EINSTEIN trials, the definition of non-inferiority was an HR of 2.0. In the EINSTEIN-DVT trial, the outer 95 % CI achieved with rivaroxaban was 1.04, and was 1.68 in the EINSTEIN-PE trial [16, 17]. In the pooled analysis of the EINSTEIN trials, the HR for non-inferiority was 1.75 and the upper 95 % CI achieved with rivaroxaban was 1.19 [29]. In the more recent AMPLIFY and Hokusai-VTE trials, the non-inferiority margins were decreased to a relative risk (RR) of 1.80 and an HR of 1.50, respectively [18, 19]. The upper 95 % CI achieved with apixaban was 1.18 and was 1.13 with edoxaban. The broad definition of non-inferiority in the RE-COVER and EINSTEIN trials may cause clinicians to question the utility of the efficacy outcome results. While the upper 95 % CI boundary in the EINSTEIN-PE trial may raise questions, the HR and 95 % CI in the pooled analysis provides some support to the

efficacy of rivaroxaban, which was approved for treatment of acute VTE and prevention of recurrent events by the FDA in 2012. In addition, dabigatran was just recently approved for this indication in early 2014. The more conservative non-inferiority boundaries in the apixaban and edoxaban trials are less likely to be a concern in regards to approval by the FDA.

4 Acute Treatment Clinical Trial Results

Demographics for patients in the individual trials are detailed in Table 4. Efficacy and safety outcomes are presented in Table 5.

4.1 Dabigatran Etxilate

The RE-COVER I ($n = 2,564$) and II ($n = 2,589$) trials shared a similar design [14, 15]. Patients were randomized to dabigatran 150 mg twice daily or warfarin to a

Table 4 Comparison of patient characteristics in acute venous thromboembolism trials

Characteristic	RE-COVER I [14]	RE-COVER II [15]	EINSTEIN-DVT [16]	EINSTEIN-PE [17]	AMPLIFY [18]	Hokusai-VTE [19]
Patients (n)	2,539	2,568	3,449	4,832	5,395	8,240
Mean age (years)	55	57 ^a	56	58	57	56
Male sex (%)	58	61	57	53	59	57
Mean weight (kg)	85	83	82	83	85	82
CrCl 30–50 mL/min (%)	4.7	4.9	6.8	8.2	5.7	6.6
Index event (%)						
Patients with DVT only	68.9	68.1	98.7	0	65.5	59.7
Patients with PE only	21.3	23.2	0	75.2	25.2	30.4
Patients with PE and DVT	9.6	8.6	0.1	24.8	8.8	9.9
Unprovoked VTE (%)	NR	NR	62.0	64.5	89.8	65.7
Patients with active cancer (%)	4.8	3.9	6.0	4.6	2.7	2.5
History of VTE (%)	25.6	17.5	19.3	19.5	16.2	18.4
Median duration of parenteral anticoagulation in the VKA group (days)	9 ^a	10	8	8	6.5	7
Patients receiving parenteral anticoagulation in the NOAC group (%)	100	100	73	93	86	100
Median duration of parenteral anticoagulation in the NOAC group (days)	9 ^b	9	1	1	1	7
INR control ^c						
TTR [% (range ^d)]	60 (53–66)	57 (51–62)	58 (54–66)	63 (58–73)	61 (NR)	64 (NR)
% above INR of 3.0	19	19	16	16	16	18
% below INR of 2.0	21	24	24	22	23	19

CrCl creatinine clearance, DVT deep vein thrombosis, INR international normalized ratio, NOAC novel oral anticoagulant, NR not reported, PE pulmonary embolism, TTR time in therapeutic range, VKA vitamin K antagonist, VTE venous thromboembolism

^a Median reported instead of mean

^b Total duration before and after randomization

^c For patients randomized to vitamin K antagonist therapy

^d Represents the time in therapeutic range during the first month of therapy compared with the end of the trial

Table 5 Efficacy and safety outcomes in acute venous thromboembolism treatment trials

Outcome	RE-COVER-I [14] ^a		RE-COVER-II [15] ^a		EINSTEIN-DVT [16] ^b		EINSTEIN-PE [17] ^b		AMPLIFY [18] ^a		Hokusai-VTE [19] ^b	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban	Warfarin
Primary efficacy endpoint (%) ^a	2.4	2.1	2.3	2.2	2.1	3.0	2.1	1.8	2.3	2.7	3.2	3.5
Symptomatic DVT only (%)	1.3	1.4	2.0	1.3	0.8	1.6	0.7	0.7	0.8	1.3	1.4	1.5
Symptomatic nonfatal PE (%)	1.0	0.6	0.5	1.0	1.2	1.0	0.9	0.9	1.0	0.9	1.2	1.4
VTE mortality (%)	0.1	0.2	0.2	0.0	0.2	0.3	0.4	0.2	0.4	0.6	0.6	0.6
Total mortality (%)	1.6	1.7	2.0	1.9	2.2	2.9	2.4	2.1	1.5	1.9	3.2	3.1
Major bleeding (%)	1.6	1.9	1.2	1.7	0.8	1.2	1.1 ^c	2.2	0.6 ^c	1.8	1.4	1.6
CRNM bleeding (%)	4.0	6.9	3.8	6.2	7.3	7.0	9.5	9.8	3.8 ^c	8.0	7.2 ^c	8.9
Major and CRNM bleeding (%)	5.6 ^c	8.8	5.0 ^c	7.9	8.1	8.1	10.3	11.4	4.3 ^c	9.7	8.5 ^c	10.3
Any bleeding (%)	16.1 ^c	21.9	15.6 ^c	22.1	NR	NR	NR	NR	15.5 ^c	25.8	21.7 ^c	25.6

CRNM clinically relevant nonmajor, DVT deep vein thrombosis, NR not reported, PE pulmonary embolism, VTE venous thromboembolism

^a Incidence of recurrent symptomatic VTE and related deaths

^b Incidence of recurrent VTE

^c Represents a statistically significant reduction with the use of the new oral anticoagulant

therapeutic INR (2.0–3.0). All patients received initial therapy with an injectable anticoagulant for a median of 9 days. In both trials, dabigatran was non-inferior to warfarin in the prevention of the primary endpoint (RECOVER I: HR 1.10; 95 % CI 0.65–1.84; $p < 0.001$; RECOVER II: HR 1.08; 95 % CI 0.64–1.8; $p < 0.001$) (Table 5). Major bleeding was not significantly different between the groups (HR 0.82; 95 % CI 0.45–1.48), but there was a significant 36 % relative reduction (HR 0.63; 95 % CI 0.47–0.84; $p = 0.002$) in RECOVER I and a 38 % relative reduction in the combination of major and CRNM bleeding with the use of dabigatran compared with warfarin (HR 0.62; 95 % CI 0.45–0.84) in RECOVER II (Table 5). While all other adverse effects were similar between the groups, patients receiving dabigatran were more likely to experience dyspepsia during the study compared with patients receiving warfarin (2.9 vs 0.6 %; $p < 0.001$) in RECOVER I. There was no difference in events leading to the discontinuation of study drug between the groups in RECOVER II. Due to the shared trial design and defined endpoints, a pooled analysis of 5,107 patients from the RECOVER I and II trials was completed [15]. In this combined analysis, dabigatran maintained its non-inferiority to standard of care in terms of the primary efficacy outcome (2.4 vs 2.2 %; HR 1.09; 95 % CI 0.76–1.57; $p < 0.001$ for non-inferiority). The incidence of major bleeding was not significantly different between the dabigatran and warfarin groups (1.4 vs 2.0 %; HR 0.73; 95 % CI 0.48–1.11), but there was a significant reduction in the combination of major bleeding and CRNM bleeding (5.3 vs 8.5 %; HR 0.62; 95 % CI 0.50–0.76) and with any bleeding (HR 0.70; 95 % CI 0.61–0.79) [15]. Furthermore, when bleeding events are compared from the start of the oral study drug only, there is a significant reduction in major bleeding (HR 0.60; 95 % CI 0.36–0.99), major or CRNM bleeding (HR 0.56; 95 % CI 0.45–0.71), and any bleeding (HR 0.67; 95 % CI 0.59–0.77) favoring dabigatran [15].

4.2 Rivaroxaban

In the EINSTEIN-DVT trial, patients ($n = 3,449$) were randomized to rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily or traditional therapy with enoxaparin 1 mg/kg twice daily and a VKA to an INR of 2.0–3.0 [16]. Patients randomized to conventional therapy had a median duration of parenteral treatment of 8 days. In the EINSTEIN-DVT trial, patients receiving rivaroxaban demonstrated a 30 % relative reduction in the primary endpoint compared with standard of care (HR 0.68; 95 % CI 0.44–1.04) (Table 5). This met the trial’s qualifications for non-inferiority ($p < 0.001$) but not for superiority ($p = 0.08$) [16]. The primary safety outcome (composite of

major or CRNM bleeding) occurred in 8.1 % of patients in both groups, with a numerical decrease in major bleeding and an increase in CRNM bleeding with the use of rivaroxaban compared with standard of care (Table 5). Net clinical benefit, which included the combination of the primary efficacy outcome and major bleeding, was also a prespecified outcome. Net clinical benefit favored rivaroxaban compared with standard of care (2.9 vs 4.2 %; $p = 0.03$) [16].

In the EINSTEIN-PE trial, patients ($n = 4,833$) were randomized to rivaroxaban and conventional therapy, as in the EINSTEIN-DVT trial [17]. Patients randomized to conventional therapy had a median duration of parenteral treatment of 8 days. The EINSTEIN-PE trial also demonstrated the non-inferiority of rivaroxaban compared with warfarin (HR 1.12; 95 % CI 0.75–1.68) (Table 6). In this trial, major bleeding was significantly reduced by 50 % with the use of rivaroxaban compared with standard of care (HR 0.49; 95 % CI 0.31–0.79; $p = 0.003$). The incidence of CRNM bleeding or the combination of major and CRNM bleeding were similar between the groups

(Table 5). Net clinical benefit was not different between the groups in the EINSTEIN-PE trial (3.4 vs 4.0 %; $p = 0.28$) [17].

Due to the shared trial design and defined endpoints, a combined analysis of the EINSTEIN-DVT and EINSTEIN-PE trials was conducted [29]. In this combined analysis of 8,282 patients, rivaroxaban (2.1 %) maintained its non-inferiority to standard of care (2.3 %) in terms of the primary efficacy outcome (HR 0.89; 95 % CI 0.66–1.19; $p < 0.001$ for non-inferiority), but was not superior ($p = 0.41$). While there was no difference in the incidence of major and CRNM bleeding (9.4 vs 10.0 %; $p = 0.27$), there was a >45 % relative reduction in major bleeding with the use of rivaroxaban compared with standard of care (1.0 vs 1.7 %; $p = 0.002$). This reduction in major bleeding drove the significant reduction on net clinical benefit of rivaroxaban over standard of care (HR 0.77; 95 % CI 0.61–0.97). Patients presenting with a history of VTE in the EINSTEIN trials demonstrated a significant 55 % reduction in recurrent VTE with rivaroxaban use compared with standard of care (1.4 vs 3.1 %; HR 0.45; 95 % CI

Table 6 Comparison of patient characteristics in long-term secondary venous thromboembolism prevention trials

Characteristic	RE-MEDY [30]	RE-SONATE [30]	EINSTEIN-Extension [16]	AMPLIFY-EXT [28]	
	Dabigatran	150 mg bid	Rivaroxaban 20 mg daily	Apixaban 2.5 mg bid	Apixaban 5 mg bid
Patients (n)	1,430	681	602	840	813
Mean age (years)	55.4	56.1	58.2	56.6	56.4
Male sex (%)	60.9	55.9	58.8	58	57.7
Mean weight (kg)	86.1	83.7	82.2	85.7	85.7
CrCl <30 mL/min (%)	0	NR	0	0.1	0.4
CrCl 30–50 mL/min (%)	4.1	6.0	6.1	5.6	5.0
Patients with DVT (%)	65.6	63.3	64.1	64.8	64.8
Patients with PE (%)	22.7	26.9	35.9	35.2	35.2
Patients with PE and DVT (%)	11.7	6.9	NR	NR	NR
Unprovoked VTE (%)	NR	NR	73.1	93.2	90.7
Patients with active cancer (%)	4.2	0.1 ^a	4.7	1.8	1.1
History of VTE (%)	NR	NR	17.9	11.8	14.5
Mean treatment duration before randomization (days)	198	293	NR	NR	NR
			VKA pre-treatment 6–12 months: 429 (71.3 %)		
			Rivaroxaban pre-treatment 6–12 months: 173 (28.7 %)		
Mean duration of study drug (days)	473	165	NR	NR	
			Median 181 days–6 months	2 (0.2%) <6 months	
			Median 264 days–12 months	828 (98.6 %) 6–12 months	
				10 (1.2%) >12 months	

bid twice daily, *CrCl* creatinine clearance, *DVT* deep vein thrombosis, *NR* not reported, *PE* pulmonary embolism, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

^a active cancer was an exclusion criterion, and the numbers represent protocol violations

0.22–0.91) with similar rates of major bleeding (HR 0.51; 95% CI 0.21–1.27) [29].

Patients enrolled in EINSTEIN-DVT had slightly higher rates of recent surgery, trauma, and active cancer compared with patients enrolled in EINSTEIN-PE [16, 17]. Patients with recent surgery or trauma equaled 19.5 % of the patients receiving rivaroxaban and 19.5 % of the patients receiving enoxaparin/VKA in EINSTEIN-DVT compared with 17.2 % of the patients receiving rivaroxaban and 16.5 % of the patients receiving enoxaparin/VKA in EINSTEIN-PE. Patients with cancer made up 6.8 and 5.2 % of the patients receiving rivaroxaban and enoxaparin/VKA, respectively, in EINSTEIN-DVT in contrast to 4.7 and 4.5 % for rivaroxaban and enoxaparin/VKA, respectively, in EINSTEIN-PE. Statistically, these numbers were not different in the pooled analysis [29]; however, it is possible that the higher prevalence of cancer and surgery or trauma may have predisposed the EINSTEIN-DVT population towards more bleeding.

4.3 Apixaban

In the AMPLIFY trial, patients ($n = 5,395$) were randomized to apixaban 10 mg twice daily for 7 days followed by apixaban 5 mg twice daily or injectable anticoagulant followed by warfarin titrated to an INR of 2.0 to 3.0. Patients randomized to conventional therapy had a median duration of parenteral treatment of 6.5 days. Patients randomized to apixaban had a 16 % relative reduction in the primary endpoint compared with standard of care (RR 0.84; 95 % CI 0.60–1.18) (Table 5) [18]. This met the trial's qualifications for non-inferiority ($p < 0.001$) but not for superiority. Apixaban demonstrated similar efficacy in the 66 % of patients enrolled with DVT (2.2 vs 2.7 %; RR 0.83; 95 % CI 0.54–1.26) and the 34 % of patients enrolled with PE (2.3 vs 2.6 %; RR 0.90; 95 % CI 0.50–1.61) compared with standard of care. Major bleeding was significantly reduced by over 65 % with the use of apixaban compared with standard of care (RR 0.31; 95 % CI 0.17–0.55). There were also significant reductions in CRNM bleeding and major or CRNM bleeding with the use of apixaban (Table 5). Net clinical benefit significantly favored treatment with apixaban compared with standard of care (2.8 vs 4.5 %; $p = 0.001$) [18].

4.4 Edoxaban

In the Hokusai-VTE trial, patients ($n = 8,292$) were randomized to edoxaban 60 mg once daily or warfarin titrated to an INR of 2.0 to 3.0 [19]. Among those randomized to receive edoxaban, 733 (17.8 %) received a reduced dose of 30 mg once daily while the remainder received 60 mg once daily. Patients in both groups had a median duration of

parenteral treatment of 7 days. Patients receiving edoxaban in the Hokusai-VTE trial demonstrated an 11 % relative reduction in the incidence of the primary efficacy endpoint (HR 0.89; 95 % CI 0.70–1.13) (Table 5). This met the trial's qualifications for non-inferiority ($p < 0.001$) but not for superiority [19]. Among the 40 % of patients enrolled with PE, edoxaban seemed to have a signal of improved efficacy compared with warfarin (2.8 vs 3.9 %; HR 0.73; 95 % CI 0.50–1.06), while in the 60 % of patients enrolled with DVT, efficacy was equivalent to warfarin (3.4 vs 3.3 %; HR 1.02; 95 % CI 0.75–1.38). The primary safety outcome (major or CRNM bleeding) was significantly reduced with the use of edoxaban compared with warfarin (HR 0.81; 95 % CI 0.71–0.94; $p = 0.004$) [19]. Major bleeding was not significantly reduced with the use of edoxaban, while CRNM ($p = 0.004$) and any bleeding ($p < 0.001$) were lower compared with warfarin (Table 5). The edoxaban 30-mg once-daily dose maintained efficacy (HR 0.73; 95 % CI 0.42–1.26) and preserved safety (HR 0.62; 95 % CI 0.44–0.86) compared with warfarin therapy [19].

5 Extended Secondary Prevention Trials

Demographics for patients in the individual trials are detailed in Table 6. Efficacy and safety outcomes are presented in Table 7.

5.1 Dabigatran

The safety and efficacy of dabigatran for long-term secondary prevention of VTE has been evaluated in two trials, which enrolled patients with objectively confirmed symptomatic proximal DVT or PE who completed at least 3 months of treatment with warfarin or dabigatran [30]. Patients in the RE-MEDY (Secondary Prevention of Venous ThromboEmbolism) trial were considered to still be at risk of recurrent VTE and were therefore randomized in a double-blinded fashion to dabigatran 150 mg twice daily or active control with warfarin to an INR of 2.0–3.0 for 6–36 months (mean 15.8 months) [30]. In the RE-SONATE (Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxilate in the Long Term Prevention of Recurrent Symptomatic VTE) trial, investigators had to have equipoise regarding the need for continued anticoagulant therapy. Patients in the RE-SONATE trial were randomized to dabigatran 150 mg twice daily or placebo for up to 12 months (mean 5.5 months) [30]. Of the 2,856 patients in the RE-MEDY trial, 40 % were initially enrolled in the RE-COVER I or II trials, while only 2 % of the 1,343 patients in the RE-SONATE trial had been enrolled in these trials. The primary efficacy outcome was

Table 7 Comparison of efficacy and safety outcomes in long-term secondary venous thromboembolism prevention trials

Outcome	RE-MEDY [30]		RE-SONATE [30]		EINSTEIN-Extension [16]		AMPLIFY-EXT [28]		
	Dabigatran 150 mg bid	Warfarin	Dabigatran 150 mg bid	Placebo	Rivaroxaban 20 mg daily	Placebo	Apixaban 2.5 mg bid	Apixaban 5 mg bid	Placebo
Primary endpoint (%)	1.8	1.3	0.4 ^a	5.6	1.3 ^a	7.1	3.8 ^a	4.2 ^a	11.6
Symptomatic DVT only (%)	1.2	0.9	0.3	3.3	0.8	5.2	0.7	1.0	6.4
Symptomatic nonfatal PE (%)	0.7	0.4	0.1	2.1	0.3	2.2	1.0	0.5	1.8
VTE mortality (%)	0.1	0.1	0	0	0.2	0.2	0.2	0.4	0.8
Total mortality (%)	1.2	1.3	0	0.3	0.2	0.3	0.8	0.5	1.7
Major bleeding (%)	0.9	1.8	0.3	0.0	0.7	0.0	0.2	0.1	0.5
CRNM bleeding (%)	4.7	8.4	5.0	1.8	5.4	1.2	3.0	4.2 ^b	2.3
Major and CRNM bleeding (%)	5.6 ^a	10.2	5.3 ^b	1.8	6.0 ^b	1.2	3.2	4.3	2.7
Any bleeding (%)	19.4 ^a	26.2	10.5 ^b	5.9	17.4 ^b	10.7	NR	NR	NR

bid twice daily, *CRNM* clinically relevant nonmajor, *DVT* deep vein thrombosis, *NR* not reported, *PE* pulmonary embolism, *VTE* venous thromboembolism

^a Represents a statistically significant reduction with the use of the new oral anticoagulant

^b Represents a statistically significant increase with the use of the new oral anticoagulant

the incidence of recurrent, objectively confirmed symptomatic VTE or VTE-related death. The RE-MEDY trial was designed as a non-inferiority trial, while the RE-SONATE trial was designed to demonstrate superiority of dabigatran [30]. Bleeding outcomes included major and CRNM bleeding using the same definitions as the RECOVER I and II trials.

In the active-control RE-MEDY trial, dabigatran demonstrated non-inferiority ($p = 0.01$) compared with warfarin for the primary efficacy endpoint (HR 1.44; 95 % CI 0.78–2.64) (Table 7). While major bleeding was reduced by 50 % with dabigatran compared with warfarin, it did not achieve statistical significance ($p = 0.06$). As in the RECOVER trials, major or CRNM bleeding was significantly lower with the use of dabigatran compared with warfarin (HR 0.54; 95 % CI 0.41–0.71). There was also an increased risk in the incidence of acute coronary syndrome (ACS) in patients randomized to dabigatran in this trial (0.9 vs 0.2 %; $p = 0.02$) [30].

In the placebo-controlled RE-SONATE trial, dabigatran demonstrated a significant 92 % reduction in the primary endpoint, representing superiority over placebo (HR 0.08; 95 % CI 0.02–0.25) (Table 7). While major bleeding was not significantly increased with the use of dabigatran, there were significant increases in both major or CRNM bleeding (HR 2.92; 95 % CI 1.52–5.60) and any bleeding (HR 1.82; 95 % CI 1.23–2.68) with the use of dabigatran compared with placebo (Table 7). The incidence of ACS was not different between the groups (0.1 vs 0.2 %). Although there was a difference in the incidence of ACS in the active-control RE-MEDY trial, this may reflect a protective effect of warfarin more than than a harmful effect of dabigatran [30].

5.2 Rivaroxaban

The long-term use of rivaroxaban for secondary prevention of VTE was evaluated in the EINSTEIN–Extension trial [16]. Patients with objectively confirmed, symptomatic VTE who had completed treatment of 6–12 months with a VKA or rivaroxaban were randomized in a double-blinded fashion to rivaroxaban 20 mg once daily or placebo for an additional 6 (60 %) to 12 (40 %) months. Randomization to placebo was considered ethical as investigators had to have equipoise with respect to the need for continued anticoagulant therapy. Of the 1,196 patients in the EINSTEIN–Extension trial, 34.1 % were initially enrolled in the EINSTEIN–DVT trial and 19.1 % were in the EINSTEIN–PE trial [16]. At the time of randomization, 72 % of patients had completed treatment with a VKA and 28 % with rivaroxaban for a median of approximately 7 months. The primary efficacy outcome of recurrent symptomatic VTE was significantly reduced by 82 % with the use of rivaroxaban compared with placebo (HR 0.18; 95 % CI 0.09–0.39) (Table 7). While the primary safety outcome of major bleeding was not different between the groups, there was a significant increase in major or CRNM bleeding with the use of rivaroxaban compared with placebo (HR 5.19; 95 % CI 2.3–11.7) (Table 7). This increase was mainly due to increases in hematuria (9 vs 0 events), epistaxis (8 vs 1 event), and rectal bleeding (7 vs 2 events) [16].

5.3 Apixaban

Apixaban was evaluated for long-term prevention of VTE in the AMPLIFY-EXT (AMPLIFY-Extended Treatment)

trial [28]. Patients with objectively confirmed symptomatic VTE who had completed 6–12 months with warfarin or apixaban were randomized in a double-blinded fashion to apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, or placebo for an additional 12 months. As in the EINSTEIN-Extension trial, investigators had to have equipoise with respect to the need for continued anticoagulant therapy. Of the 2,482 patients in the AMPLIFY-EXT trial, 33.7 % were initially enrolled in the AMPLIFY trial. The primary efficacy outcome of recurrent symptomatic VTE or death from any cause was significantly reduced by 67 % with apixaban 2.5 mg twice daily (RR 0.33; 95 % CI 0.22–0.48) and 64 % with apixaban 5 mg twice daily (RR 0.36; 95 % CI 0.25–0.53) compared with placebo (Table 7) [28]. When the primary outcome from the AMPLIFY trial is used (recurrent symptomatic VTE or VTE-related death), both apixaban groups demonstrated an 80 % reduction compared with placebo (1.7 % for both groups vs 8.8 %; $p < 0.001$). These results suggest that, after the initial treatment period for acute VTE, an even lower dose may be able to be used for long-term secondary prevention of VTE. The rate of CRNM bleeding was higher in the apixaban 2.5-mg twice-daily group (RR 1.29; 95 % CI 0.72–2.33), but was only significantly higher in the apixaban 5-mg twice-daily group compared with placebo (RR 1.82; 95 % CI 1.05–3.18) [32]. As with rivaroxaban, most of the increase in CRNM bleeding was due to numerical increases in hematuria, epistaxis, and rectal bleeding. There was no difference between the two apixaban doses for efficacy or safety (Table 7).

6 Subpopulations

Several specific subpopulations were represented in these acute VTE treatment trials. Standard of care for the acute treatment of VTE in patients with cancer is different from that in patients without cancer. In patients with cancer, treatment of VTE with a LMWH for 3–6 months has demonstrated better efficacy than and similar safety to treatment with an injectable anticoagulant transitioned over to warfarin for a similar duration. Based on these data, acute treatment of VTE in patients with cancer with a LMWH for 3–6 months is recommended in most clinical guidelines [8, 31, 32]. Patients with active cancer were included in all of the acute VTE treatment trials of the NOACs. The percent of patients with active cancer in these trials was low, ranging from 2.5 % in the Hokusai-VTE trial to 6.0 % in the EINSTEIN-DVT trial (Table 5) [18, 19]. While the overall percentage of patients with active cancer in these trials was small, there were 430 patients with active cancer in the EINSTEIN trials and over 1,000 patients with active cancer enrolled collectively in these

trials. The largest LMWH trial for prevention of VTE in patients with active cancer had only 672 randomized patients [33]. VTE and bleeding rates were higher in patients with active cancer compared with those without active cancer [14–19]. In each of these trials, the primary efficacy outcome was numerically lower in the NOAC group compared with the standard of care group in patients with active cancer (3.5 % dabigatran vs 4.7 % warfarin; 5.1 % rivaroxaban vs 7.1 % VKA; 3.7 % edoxaban vs 7.1 % warfarin; not reported in AMPLIFY) [18, 19, 29]. A recent meta-analysis of dabigatran, rivaroxaban, and apixaban studies suggests that these NOACs have the same efficacy and safety as conventional treatment for patients with cancer, and no difference in efficacy and safety was observed between patients with and without cancer [34]. Although these data may give some reassurance in the use of these new agents compared with warfarin, until a trial evaluating the NOACs compared with LMWH in cancer is conducted, LMWH should remain the treatment of choice. The American Society of Clinical Oncology Clinical Practice Guidelines, based on informal consensus, do not support the use of NOACs for either VTE prevention or treatment [34]. Similarly, the National Comprehensive Cancer Network Clinical Practice Guidelines for Venous Thromboembolic Disease recognizes rivaroxaban and apixaban, but they are not included among the recommendations for acute treatment or secondary VTE prevention [35]. There are patients who do not receive LMWH due to the cost of 3–6 months of therapy, and it is unlikely that the NOACs will provide a significant advantage in this regard. Until appropriate clinical trials are conducted, only patients with active cancer who refuse to receive subcutaneous injections and will not comply with warfarin therapy restrictions or monitoring should be considered candidates for NOAC treatment of their VTE event.

The EINSTEIN and Hokusai-VTE trials also looked at outcomes in fragile patients, which are patients with CrCl ≤ 50 mL/min, age ≥ 75 years of age, and body weight ≤ 50 kg. In the pooled analysis of the EINSTEIN trials, 1,573 patients were considered fragile, while there were 1,421 in the Hokusai-VTE trial. No differences were noted in efficacy of rivaroxaban compared with standard of care in fragile patients compared with non-fragile patients (HR 0.68; 95 % CI 0.39–1.18). As might be expected, major bleeding was higher in fragile patients ($p = 0.01$ for interaction) [29]. However, there was a significant (73 %) relative reduction in major bleeding with the use of rivaroxaban compared with standard of care in these fragile patients (1.3 vs 4.5 %; HR 0.27; 95 % CI 0.13–0.54). This reduction in major bleeding was consistent for all of the groups that made up the fragile patient subgroup (older age [1.2 vs 4.5 %], reduced CrCl [0.9 vs 4.1 %], and light body weight [0 vs 4.6 %]). Conversely, the rate of recurrent VTE

in fragile patients receiving edoxaban compared with standard of care favored edoxaban, and this was not observed in non-fragile patients ($p = 0.408$). No significant difference was noted in the rates of clinically relevant bleeding between fragile and non-fragile patients receiving edoxaban compared with standard of care [19].

All of the NOACs have some degree of renal elimination. A reduction in CrCl ranging from <25 to <30 mL/min was among exclusion criteria for the VTE treatment trials. However, all of the trials included patients with moderate renal insufficiency (CrCl 30–50 mL/min). In the pooled analysis of the RE-COVER trials, none of the 117 dabigatran-treated patients with a calculated CrCl 30–50 mL/min experienced the primary efficacy outcome compared with 5 of the 128 (3.9 %) warfarin-treated patients [15]. In the dabigatran secondary prevention trials (RE-MEDY and RE-SONATE), the incidence of the primary efficacy endpoint was similar to that of warfarin and placebo, respectively, but the incidence of bleeding outcomes was not reported [29]. The EINSTEIN-DVT trial reported 4 of 121 (3.3 %) rivaroxaban-treated patients with CrCl <50 mL/min with the primary efficacy endpoint of recurrent symptomatic VTE, while 13 of 120 (10.8 %) of the patients experienced the primary safety endpoint of major or CRNM bleeding [16]. There was no difference between patients treated with standard of care. In the EINSTEIN-PE trial, 7 of 211 (3.3 %) and 26 of 209 (12.4 %) rivaroxaban-treated patients with calculated CrCl <50 mL/min experienced the primary efficacy endpoint of recurrent symptomatic VTE or the primary safety endpoint of major or CRNM bleeding, respectively [17]. There was no difference compared with standard of care. In the pooled analysis of the EINSTEIN trials, compared with standard of care, patients with moderate renal insufficiency receiving rivaroxaban had similar efficacy and significantly lower rates of major bleeding (0.9 vs 4.1 %) [29]. The AMPLIFY trial reported that 7 of 169 (4.1 %) apixaban-treated patients with CrCl <50 mL/min developed recurrent VTE or experienced a VTE-related death. The AMPLIFY trial also reported that 5 of 175 (2.9 %) apixaban-treated patients with CrCl <50 mL/min developed the composite of major or CRNM bleeding [18]. Among patients with a CrCl of 30–50 mL/min who received edoxaban in the Hokusai-VTE trial, many of whom would have received the reduced dose of 30 mg once daily, rates of the primary efficacy and safety endpoints were numerically lower compared with standard of care (3.0 vs 5.9 % and 10.4 vs 14.3 %, respectively) [19]. In a recent meta-analysis, rivaroxaban, apixaban, and dabigatran were associated with lower major or CRNM bleeding in patients with mild renal insufficiency, and were comparable to conventional agents in patients with moderate renal insufficiency [36].

The overall percentage of patients with moderate renal insufficiency is only about 6–8 % in these trials (Table 5).

While clinicians may disregard these data due to the small percentage of patients, these data represent outcomes from several hundred patients with moderate renal insufficiency. For example, patients with moderate renal insufficiency made up 649 patients in the pooled analysis of the EINSTEIN trials and 541 patients in the Hokusai-VTE trial [19, 29]. Few trials evaluating the use of anticoagulants in patients with renal insufficiency have this number of patients. Therefore, these data should provide some confidence on the efficacy and safety of the use of the new oral anticoagulants in patients with moderate renal insufficiency.

In the NOAC trials, there was a wide variation in thrombus burden. In EINSTEIN-DVT, 1,200 of 1,731 (69 %) rivaroxaban-treated patients had extensive (involving iliac or common femoral veins) DVT [16]. In AMPLIFY, 753 of 1,749 (43 %) apixaban-treated patients had extensive DVT [18]. In Hokusai-VTE, 1,035 of 2,468 (42 %) edoxaban-treated patients had extensive DVT [19]. The extensiveness of clot burden did not have a significant impact on outcomes in the EINSTEIN and AMPLIFY trials, while these data have not been reported in the Hokusai-VTE trial. The RE-COVER I and II trials did not report the anatomical extent of the DVT.

In RE-COVER I and RE-COVER II, 270 (21.2 %) and 298 (23.3 %) of the dabigatran-treated patients had PE only [14, 15]. In EINSTEIN-PE, 597 (24.7 %) rivaroxaban-treated patients had extensive (multiple lobes and >25 % of the entire vasculature) thrombosis [17]. In AMPLIFY, 357 (38.4 %) of the apixaban-treated patients with pulmonary embolism had extensive (≥ 2 lobes involving ≥ 50 % of the vasculature for each lobe) thrombosis [18]. In Hokusai-VTE, 743 (45 %) edoxaban-treated patients had extensive (multiple lobes and ≥ 25 % of the vasculature) PE [19]. Hokusai-VTE was the only trial to report high-mortality risk features (right ventricular dysfunction, elevations in cardiac biomarkers, or severity indices). There were 454 patients (27.5 %) with elevations in N-terminal pro-brain natriuretic peptide (NT-proBNP) and 172 patients (34.5 %) with right ventricular dysfunction identified on CT scan. Venous thromboembolism recurrence was reduced in edoxaban-treated patients with PE and elevated NT-proBNP or with right ventricular dysfunction compared with patients who received standard of care [19].

7 Discussion

Four oral anticoagulants have migrated through drug development and completed phase III trials in acute VTE treatment. These trials had strikingly similar inclusion and exclusion criteria (Tables 1, 2). The primary efficacy

endpoints, the incidence of recurrent VTE, and the objective evaluations to determine those endpoints were nearly identical (Tables 1, 4, 5). The major bleeding safety endpoint was determined by standardized definitions that were also nearly identical. Not surprisingly, there was not a wide variation (2.1–3.2 %) in the incidence of the primary efficacy endpoint nor a wide range (0.5–1.2 %) in the incidence of symptomatic PE across trials. Similarly, major bleeding was quite comparable with the new agents, ranging from 0.6 to 1.6 % across the trials. Because of different CRNM bleeding definitions, there was a wide variation in event rates, ranging from a low incidence in RE-COVER II (3.8 %) to a much higher incidence in EINSTEIN-PE (9.5 %). Finally, while this information was not in the trials and prescription benefit coverage may vary, we found the current average wholesale price for the acute VTE treatment dosing to be: (i) dabigatran US\$11.67 per day, (ii) rivaroxaban US\$11.45 per day, and (iii) apixaban \$11.67 per day, further signaling the similarities between the agents [37].

Major and CRNM bleeding was significantly reduced in those receiving dabigatran, apixaban, and edoxaban in their respective trials, but not with rivaroxaban when compared with standard of care. The incidence of CRNM bleeding was, however, similar in the RE-COVER I (4.0 %), RE-COVER II (3.8 %), and AMPLIFY (3.8 %) trials. The incidences of CRNM bleeding between EINSTEIN-DVT (7.3 %), EINSTEIN-PE (9.5 %), and Hokusai-VTE (7.2 %) were similar as well [18, 19, 29].

In the EINSTEIN-DVT trial, there were actually more suspected VTE events in the rivaroxaban group compared with the standard-of-care group (13.3 vs 12.5 %), which suggest against a diagnostic-suspicion bias [16]. Of these suspected events, all of which were confirmed by the adjudication committee, 15.7 % were in the rivaroxaban group and 23.7 % occurred in the standard-of-care group. The same was found in the EINSTEIN-PE trial, where there were more suspected VTE events in the rivaroxaban group (20.3 vs 18.8 %) [17]. Of these suspected events, 10.2 % were confirmed by the adjudication committee in the rivaroxaban group compared with 9.7 % in the standard-of-care group. Therefore, it does not seem that the open-label design of the EINSTEIN trials produced a diagnostic-suspicion bias that favored rivaroxaban.

Early trials have shown that symptomatic, recurrent VTE is common in the first month of treatment, especially if anticoagulation is subtherapeutic [38, 39]. To overcome the slow onset of warfarin, standard practice has evolved to overlap adjusted-dose UFH or LMWH with warfarin for a minimum of 5–10 days to prevent thrombus extension or recurrence. The optimal intensity and duration of this initial anticoagulation period has been elusive [40, 41]. Both AMPLIFY and EINSTEIN trials compensated for this

uncertainty by employing an escalated dose for 7 and 21 days, respectively. These regimens may help identify that optimum time period.

Approximately 70–90 % of patients receiving rivaroxaban or apixaban received an injectable anticoagulant for up to 2 days (Table 4). While this may lead some clinicians to conclude that a short course of an injectable anticoagulant is still needed with these agents, only a minority in the EINSTEIN-DVT (4 %), EINSTEIN-PE (35 %), and AMPLIFY (31 %) trials received more than 24 hours of parenteral anticoagulation treatment [16–18]. This finding may actually reflect the delay in evaluating and enrolling a patient in a clinical trial, as patients are typically initiated on treatment as part of routine care before identification as a potential study subject. Efficacy and safety outcomes in these trials were not different based on patients receiving an injectable anticoagulant or the duration of use. In the Hokusai-VTE trial, no differences in the primary efficacy and safety outcomes were observed when results were stratified by median duration of parenteral anticoagulation [19]. These data are not available from the RE-COVER trials. In the EINSTEIN-DVT trial, the primary efficacy outcome was similar for patients not receiving an injectable anticoagulant before randomization (1.9 % rivaroxaban vs 2.0 % standard of care) to those receiving an injectable (2.1 % rivaroxaban vs 3.4 % standard of care) [16]. Similar results were demonstrated for those in the AMPLIFY trial not receiving an injectable (1.7 % apixaban vs 3.2 % standard of care) and those receiving an injectable (2.4 % apixaban vs 2.6 % standard of care) [18]. Because over 90 % of patients in EINSTEIN-PE received an injectable, the results have been presented as those receiving 1 day of an injectable (1.9 % rivaroxaban vs 1.6 % standard of care) or more than 1 day (1.9 % for both groups) [17]. Therefore, requiring 1–2 days of an injectable anticoagulant with rivaroxaban or apixaban does not seem justified. However, if patients are initially treated with an injectable anticoagulant, switching them to rivaroxaban or apixaban can be performed based on the experience from these trials.

Dabigatran, apixaban, and rivaroxaban safety and efficacy has been established for long-term secondary VTE prevention compared with placebo. Dabigatran has shown non-inferiority compared with warfarin for long-term secondary prevention of VTE. The NOACs represent therapeutic options for those patients deemed at continuous VTE risk. Furthermore, the option for tailoring therapy among agents exists: (i) compliance, favoring once-daily rivaroxaban; (ii) concern for bleeding, favoring reduced-dose apixaban (2.5 mg twice daily); and (iii) warfarin alternative, favoring dabigatran. While data on NOACs in VTE are emerging, recent studies with aspirin have become available as well. Two double-blind randomized trials have

Table 8 Practical considerations for novel anticoagulant selection

Co-morbidity or characteristic	Agent	Rationale
Initial parenteral therapy	Apixaban, dabigatran, edoxaban rivaroxaban	Allowance of 48–72 h initial treatment before randomization
Renal dysfunction CrCl \geq 25 mL/min to \leq 30 mL/min	Apixaban	Trial exclusion criteria
Low body weight, <60 kg	Edoxaban	Trial dosing adjustment
Cancers and thrombophilia	None	Limited trial data
Affordability	None, aspirin, or patient preference	Similar costs
Concurrent clopidogrel therapy	Rivaroxaban	Concomitant use allowed in trial
Chronic NSAID use	Apixaban	Concomitant use allowed in trial
PE with elevated biomarkers	Edoxaban	Trial sub-populations with high-risk features
Compliance challenges	Rivaroxaban, edoxaban	Once daily dosing
Prior MI	Apixaban, edoxaban, rivaroxaban	MI events associated with dabigatran
Propensity for bleeding	Apixaban, rivaroxaban	Clinical reductions in major bleeding
Multiple concomitant medications with potential drug interactions	Edoxaban, apixaban	Edoxaban and apixaban allow for a dose reduction

CrCl estimated creatinine clearance, MI myocardial infarction, NSAID non-steroidal anti-inflammatory drug, PE pulmonary embolism

shown efficacy and safety in patients with a first episode of unprovoked VTE. Patients who received low-dose aspirin (100 mg daily) after completing an initial course of anticoagulation had a reduction in VTE recurrence without an increase in major bleeding episodes when compared with placebo [42, 43]. It should be noted that the relative reduction in recurrent VTE with aspirin in these trials is between 25 and 40 % over 2–4 years, and the reduction in the NOAC trials is approximately 80–90 % in 1 year [16, 28, 30, 42, 43]. Therefore, aspirin may be a logical alternative for patients who cannot tolerate NOACs or warfarin, or have a high bleeding risk.

8 Conclusions

Clinicians now have three VTE treatment options to consider: conventional parenteral therapy with UFH, LMWH, or fondaparinux as a bridge to warfarin, monotherapy with an NOAC, or conventional parenteral therapy as a bridge to an NOAC. Use of NOACs can maintain efficacy compared with standard of care, while significantly reducing either major bleeding or major and CRNM bleeding. This safety benefit, along with the simplification of therapy compared with warfarin, make treatment of VTE with a NOAC an attractive option. While cost of the NOACs may be an issue, the potential ability to reduce hospitalizations and reduce length of stay could offset medication costs for third-party payers. The role of these new oral agents in the setting of cancer and VTE and their role in the treatment of massive DVT and high-risk PE where thrombolysis or mechanical intervention is required needs to be established.

Rivaroxaban and apixaban offer the advantage of no need for injectable therapy and a pure oral therapy approach to the treatment of VTE. A dose adjustment is needed at day 7 or 21 with the use of apixaban and rivaroxaban, respectively, which will require important communication between healthcare providers and patients during transition of care. Dabigatran and edoxaban do not require any dose alterations in the first weeks of therapy and may provide a simpler approach after patient discharge, but the need for a minimum of 5 days of injectable therapy may not be desirable.

NOACs have not been directly compared in clinical trials for VTE treatment. Despite pitfalls with cross-trial comparisons, inevitably clinicians will be forced to make treatment decisions [44]. While there were differences in NOAC study design and dosing regimens, enrollment criteria, population, and endpoint measures, ultimately outcomes were comparable. With efficacy, safety, and cost similar, tailoring selection based on patient co-morbidities, patient and clinician preference, dosing convenience, and adverse events becomes magnified. Practical considerations (Table 8) and patient preference may be deciding factors in drug selection and successful treatment.

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