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Current State of Anticoagulants to Treat Deep Venous Thrombosis

Timothy Vo[1], **Sara Vazquez**[2], and **Matthew T. Rondina**[3,4]

[1]SUNY Upstate Medical University, Syracuse, New York, 13210

[2]University of Utah Health Care Thrombosis Center, Department of Pharmacy Services, Salt Lake City, UT 84132

[3]Division of General Internal Medicine and University Healthcare Thrombosis Service, Department of Internal Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah, 84132

[4]Program in Molecular Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah, 84132

Abstract

Anticoagulation remains the cornerstone of treatment in patients with deep vein thrombosis (DVT). While parenteral anticoagulants and oral vitamin K antagonists (e.g. warfarin) have been used for many decades, the recent development of novel oral anticoagulants have provided clinicians with an expanding set of therapeutic options for DVT. This review summarizes the pharmacology and clinical trial results of these new oral anticoagulants. Several practical considerations to the use of these oral anticoagulants including issues related to adherence, monitoring, and reversal are also discussed.

Keywords

deep vein thrombosis; anticoagulants; rivaroxaban; dabigatran; apixaban; edoxaban; warfarin

Introduction

Deep venous thrombosis (DVT) is common and occurs in 1 adult per 1000 each year, increasing to 7 adults per 1000 per year past age 75 [1–3]. It is an expensive disease to treat, estimated to cost between $7.5 to $39 billion per year in the US alone[4]. DVT is also associated with post-thrombotic syndrome (PTS), which occurs in 20–60% of patients with prior DVT, increases the cost of treatment by up to 75%, and greatly diminishes quality of life[5–9]. Death occurs in approximately 6% of patients within one month of diagnosis, primarily due to association with pulmonary embolism (PE)[3]. DVT and PE, together

Corresponding Author: Matthew T. Rondina, M.D. University of Utah, Department of Internal Medicine, Eccles Institute of Human Genetics, 15 North 2030 East, Bldg 533, Suite 4220, Salt Lake City, Utah 84112, (801) 585-0950 (phone), (801) 585-1393 (fax), matt.rondina@u2m2.utah.edu.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Timothy Vo declares that he has no conflict of interest.

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termed venous thromboembolic events (VTE), are the third most common cause of vascular death after myocardial infarction and stroke[1]. The timely and effective treatment of DVT decreases the rates of these complications [5, 6].

As one approach, the treatment of DVT may be divided into three general phases: an acute phase, a long-term phase, and an extended phase[10]. In the acute phase, parenteral anticoagulants such as heparinoids or fondaparinux have traditionally been used for rapid anticoagulation. For more than 50 years, vitamin K antagonists (e.g. warfarin, titrated to an INR goal of 2–3) are often then initiated for the long-term and extended treatment phases although in some cases, such as cancer-associated DVT, at least three months of monotherapy with low-molecular weight heparins (LMWHs) may be preferred. While used extensively, warfarin has numerous potential limitations. These include a slow onset and offset of anticoagulation, a narrow therapeutic window, unpredictable pharmacokinetics with significant food and drug interactions, and the requirement for regular monitoring and dose-adjustments [11–13].

The novel oral anticoagulants (NOACs) have advantages over warfarin in many of these respects, including more predictable pharmacokinetics which eliminate the need for routine monitoring, a rapid onset of action and shorter half- life, and fewer drug and food interactions[14, 10, 15, 16]. The NOACs that are either approved or in late stage development include the direct factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban, as well as the direct thrombin inhibitor dabigatran. Of these, rivaroxaban is currently the only NOAC currently FDA-approved for the treatment of DVT, having been approved for this indication in November 2012. Rivaroxaban is also approved for VTE prevention following total knee and total hip arthroplasty and in stroke prevention in atrial fibrillation. Dabigatran and apixaban are both approved in the United States for the single indication of stroke prevention in atrial fibrillation, though approval for DVT treatment is being sought for dabigatran in the United States.

To date, several large, multicenter studies have been conducted examining each of these drugs (rivaroxaban, dabigatran, apixaban, and edoxaban) for the acute and/or extended treatment of DVT. The pharmacology and key clinical trials for these drugs will be discussed below.

Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor (Table 1). It reaches maximum plasma concentration and anticoagulation effect 2–4 hours after administration with a half-life of 7–13 hours. Of a given dose of rivaroxaban, approximately one third is cleared unchanged by the kidneys, one-third is excreted by the kidneys as inactive metabolites, and the remaining one-third is metabolized by the liver. The influence of renal dysfunction, even when severe, on rivaroxaban clearance is only minimal to moderate, with area under the concentration curve (AUC) increases of 1.44, 1.52, and 1.64 in patients with mild (CrCl 50 – 80 mL/min), moderate (CrCl 30 – 49 mL/min), and severe (CrCl < 15 mL/min) renal impairment, respectively[17]. Nevertheless, in accordance with the manufacturer's guidelines, rivaroxaban is not recommended for DVT patients with an estimated creatinine clearance < 30mL/min. In contrast, advanced liver disease (e.g. Child-Pugh class B and C) is associated with significant increases in the AUC and, accordingly, is a contraindication to rivaroxaban use [14].

While rivaroxaban has far fewer drug-drug interactions than warfarin, there are several that clinicians should be aware of. These interactions are related primarily to concomitant use of CYP3A4 and P-glycoprotein (P-gp) inducers and/or inhibitors[14]. For example, co-administration of rivaroxaban with strong CYP3A4 and P-gp inducers (e.g. rifampin,

phenytoin) may decrease rivaroxaban exposure up to 50%, potentially also reducing systemic anticoagulation and thus, rivaroxaban's efficacy. As such, rivaroxaban use in patients who are also taking strong CYP3A4 and P-gp inducers, including rifampin, phenytoin, carbamazepine, and St. John's wort, should be avoided. Drugs that are weak or moderate inhibitors of CYP3A4 and P-gp, such as the azole antifungals, the HIV protease inhibitors, and rifampin, increase rivaroxaban exposure. Rivaroxaban should be avoided in patients who are concomitantly taking these agents, particularly if these patients also have renal dysfunction, which may synergistically increase rivaroxaban exposure and the associated risk of bleeding. Drugs which inhibit or induce only CYP3A4 or P-gp (e.g. diltiazem) have not been associated with clinically significant increases in total rivaroxaban exposure and may be safely used, although clinical prudence is still warranted.

EINSTEIN-DVT was the major phase III trial evaluating rivaroxaban for the treatment of DVT (Table 2). EINSTEIN-DVT was an open-label, randomized, event-driven, non-inferiority study comparing rivaroxaban alone to enoxaparin followed by a vitamin K antagonist (LMWH-VKA, adjusted to achieve an INR goal of 2–3) in 3449 patients with acute, symptomatic DVT[18]. Rivaroxaban was initially dosed at 15mg twice daily for three weeks followed by 20mg once daily thereafter. The primary outcome was recurrent VTE and the principal safety outcome was major or clinically relevant non-major bleeding. Patients with concurrent PE were excluded, and were instead evaluated in the EINSTEIN-PE study. In EINSTEIN-DVT, the non-inferiority endpoint was met. Recurrent VTE occurred in 2.1% of patients receiving rivaroxaban (36 events) and in 3.0% of patients receiving LMWH-VKA (51 events), with a hazard ratio (HR) of 0.68 (95% confidence interval [CI], 0.44 to 1.04; $p<0.001$ for non-inferiority). Rates of major or clinically relevant non-major bleeding were equal between the two treatment arms (8.1% in each arm). Other adverse events, such as increased liver function tests, vascular events, and dyspepsia, were similar between the two groups. A secondary outcome of net clinical benefit, defined as recurrent VTE plus major bleeding, favored rivaroxaban (2.9% versus 4.2%, $p=0.03$). Safety and efficacy outcomes were similar for subgroups of age, gender, weight, and renal function.

The EINSTEIN-Extension study was a double-blind, randomized, event-driven, superiority study that evaluated rivaroxaban 20mg once daily versus placebo for extended anticoagulation (Table 3). Patents were treated for an additional 6 or 12 months after completing treatment for at least 6 months in the EINSTEIN-DVT study[18]. The median duration of treatment was 264 days for rivaroxaban and 265 days for placebo. The primary efficacy outcome was recurrent VTE, as in EINSTEIN-DVT, and the primary safety outcome was major bleeding. Recurrent VTE occurred less commonly in patients receiving rivaroxaban (1.8% vs. 7.1%, HR: 0.18; 95% CI 0.09 to 0.39; $p<0.001$). Nonfatal major bleeding occurred in 0.7% of patients in the rivaroxaban arm (n=4 patients) and zero patients in the placebo arm, but this did not meet statistical significance ($p=0.11$).

Dabigatran

Dabigatran etexilate is an oral direct thrombin inhibitor (Table 1). Dabigatran is administered as a pro-drug and reaches peak anticoagulant effect approximately 1–3 hours after ingestion [19]. The half-life of dabigatran is 12–14 hours in patients with normal renal function. Dabigatran undergoes approximately 80% renal clearance, and the average half-life of dabigatran increases progressively to 15.3 hours, 18.4 hours, and 27.2 hours in patients with mild (CrCl 50 – 80 mL/min), moderate (CrCl 30 – 49 mL/min), and severe (CrCl < 15 mL/min) renal insufficiency, respectively. For patients in the United States, the current FDA-approved dose of dabigatran for AF (e.g. 150mg BID) should be reduced to 75mg BID if the creatinine clearance is 15–30 mL/min. Dabigatran should be avoided in patients with a creatinine clearance < 15 mL/min. In patients with class Child Pugh B

hepatic impairment, the AUC of dabigatran does not change relative compared to healthy control subjects. Nevertheless, patients with elevated liver enzymes were generally excluded in clinical trials of dabigatran.

Dabigatran's major drug interactions are solely related to concomitant use of P-gp inducers and inhibitors. The pro-drug of dabigatran, but not its active metabolite, is a substrate for P-gp. Thus, the absorption of the pro-drug can be significantly altered by the co-administration of medications that are P-gp inducers or inhibitors. For example, rifampin, a strong P-gp *inducer*, decreases the AUC of dabigatran by approximately 66%. Separation of the rifampin and dabigatran dosing is unlikely to significantly reduce this interaction. Rifampin is currently the only drug in the United States with an absolute contraindication to concomitant dabigatran use. Caution should also be exercised with concomitant use of other, more moderate P-gp inducers, such as St. John's wort and carbamazepine. P-gp *inhibitors*, including amiodarone, ketoconazole, quinidine, verapamil, clopidogrel, and dronedarone, increase the AUC of dabigatran anywhere from 50 to >200%. Immediate-release verapamil, given 1 hour prior to dabigatran, had the largest effect (243%). Administering dabigatran 2 hours prior to verapamil, however, eliminated this interaction. Taken together, these studies suggest that in in patients taking concomitant P-gp inducers or inhibitors, clinical prudence with dabigatran prescription is warranted. If unfamiliar with these potential drug interactions, providers should consult the package insert, clinical guidelines, and/or seek expert consultation from anticoagulation providers.

While dabigatran is currently only FDA-approved for patients with non-valvular AF, dabigatran may eventually be approved for the treatment of DVT and thus a brief review of the clinical trials is warranted. RECOVER was a randomized, double-blind, non-inferiority study evaluating dabigatran for the treatment of acute DVT and/or PE [20]. In contrast to the EINSTEIN studies, patients in RE-COVER (n=2564 patients) were initially treated with a minimum of 5 days (median 9 days, interquartile range 8–11 days) of heparin and then randomized in double-blind, double-dummy fashion to dabigatran 150mg twice daily or warfarin titrated to an INR of 2–3. The primary outcome in RE-COVER was the 6-month incidence of recurrent, symptomatic VTE and VTE-related death. Overall, the RE-COVER study demonstrated that dabigatran was non-inferior to warfarin for the acute treatment of VTE ($p<0.001$). The 6-month incidence of recurrent VTE and VTE-related deaths occurred in 2.4% of the dabigatran group and 2.1% of the warfarin group. Rates of adverse events, including major bleeding, acute coronary syndrome, and abnormal liver function tests, were similar between dabigatran and warfarin treated groups. Minor bleeding was decreased in the dabigatran arm compared to warfarin (hazard ratio 0.71, 95% CI [0.59 to 0.85]), but dyspepsia and all-cause drug discontinuation was higher in patients treated with dabigatran (2.9% versus 0.6%, $p<0.001$ and 7.9% versus 6.5%, $p=0.05$, respectively).

Following completion of RE-COVER, a replica study (RE-COVER II) was completed given the low rate of recurrent VTE in RE-COVER. RE-COVER II was a double-blind, double-dummy, non-inferiority study treating 2568 patients with acute VTE[21]. The design was similar to RE-COVER in that all patients were initially treated with heparin for 5–11 days and then randomized to either dabigatran 150mg twice daily or dose-adjusted warfarin (INR 2–3). Patients were treated for 6 months and followed for the primary outcome of recurrent, symptomatic VTE. The overall results confirmed the non-inferiority of dabigatran for the treatment of acute VTE.

RE-MEDY and RE-SONATE examined the efficacy and safety of extended treatment with dabigatran 150mg twice daily for VTE patients[22]. Both studies enrolled patients who had received ≥ 3 months of anticoagulation treatment for VTE. In RE-MEDY, an active-control study comparing dabigatran to adjusted dose warfarin, recurrent VTE occurred in 1.8% of

patients receiving dabigatran and 1.3% of patients receiving warfarin (p=0.01 for the pre-specified endpoint of non-inferiority). Major bleeding was less common in dabigatran-treated patients (0.9% versus 1.8%, p=0.06). Major bleeding plus clinically relevant bleeding was significantly lower with dabigatran (5.6% of versus 10.2%, p<0.001). Similarly, any bleeding was lower with dabigatran (19.4% versus 26.2%, p<0.001). Rates for ACS were higher in dabigatran-treated patients, at 0.9% versus 0.2% for warfarin (p=0.02). In RE-SONATE, the placebo-control study, recurrent VTE was lower with dabigatran (0.4% versus 5.6%, p<0.001). Rates of major bleeding were similar between the two groups (0.3% versus 0%), while major plus clinically relevant bleeding was increased for dabigatran (5.3% versus 1.8%). Rates for ACS were equal between the two arms, occurring in only one patient each.

Apixaban

Apixaban is an oral direct, reversible factor Xa inhibitor. While not yet FDA-approved for the treatment of DVT, a brief review of the pharmacology and clinical trials for apixaban is provided here. Apixaban is rapidly absorbed, reaching maximum plasma concentrations about 3–4 hours after ingestion, and has a half-life of approximately 8–15 hours in healthy subjects. Approximately 25% of apixaban is excreted by the kidneys and 75% through the hepatobiliary system [14]. Although apixaban has not been well-studied in patients with DVT and a CrCl less than 25 mL/min[14], clinical correlates may be drawn from the AVEROES study, a trial comparing apixaban to aspirin in patients with atrial fibrillation. In this trial, patients having two out of the three criteria (weight<60kg, age≥80, or serum creatinine > 1.5mg/dL) were given a 50% lower dose of apixaban (2.5mg twice daily rather than 5mg twice daily) [23]. Recommendations on dose adjustment for DVT patients with renal impairment may accompany FDA-approval. Hepatic impairment associated with coagulopathy or other conditions that may substantially increase a patient's bleeding risk (e.g. esophageal varices) is a contraindication for apixaban use. Caution is advised for patients with Child Pugh class A and B liver disease. Major drug interactions stem primarily from interactions with both CYP3A4 and P-gp, similar to those described above for rivaroxaban.

The AMPLIFY trial was a randomized, double-blind, non-inferiority study comparing apixaban (10mg twice daily for 7 days followed by 5mg twice daily for 6 months) against standard therapy (enoxaparin followed by adjusted dose warfarin) in patients with acute DVT or PE [24]. The primary efficacy outcome was recurrent VTE or VTE-related death and the primary safety outcomes were major bleeding and major plus clinically relevant non-major bleeding. Apixaban was non-inferior to standard therapy (2.3% vs. 2.7%, respectively; p<0.001 for non-inferiority). Major bleeding and the composite of major bleeding plus clinically relevant non-major bleeding were significantly lower with apixaban (0.6% vs. 1.8% and 4.3% vs. 9.7%, respectively; p<0.001 for superiority for both comparisons).

In the AMPLIFY-EXT trial, apixaban was studied for the extended treatment of VTE [25]. Patients (n=2486) were initially treated for 6–12 months following acute VTE with either apixaban or warfarin (in the AMPLIFY study) and were then randomized in a 1:1:1 ratio to one of two doses of apixaban (either 5mg twice daily or 2.5mg twice daily) or placebo. Treatment was administered for 12 months. Recurrent VTE or VTE-related death, the primary efficacy outcome, occurred in 1.7% of patients who received apixaban 2.5 mg, 1.7% of patients who received apixaban 5 mg, and 8.8% of patients who received placebo (p<0.001 for superiority). Major and clinically relevant non-major bleeding rates were similar across all arms.

Edoxaban

Edoxaban is an oral direct Xa inhibitor currently in late-stage development. While results have not yet been reported, the HOKUSAI-VTE study (NCT00986154) is a randomized, double-blind, non-inferiority trial comparing edoxaban 60mg once daily to warfarin in patients with acute, symptomatic DVT and/or PE[26]. All patients initially receive parenteral treatment with LMWH. The primary efficacy outcome is the incidence of symptomatic recurrent VTE and the principal safety outcome is clinically relevant bleeding (major or non-major) occurring during or within 3 days of stopping study treatment. One unique aspect of the HOKUSAI-VTE study design is that treatment duration (with either edoxaban or warfarin) may vary between 3 and 12 months, at the treating provider's discretion. This design was chosen to better mimic clinical practice. All patients will be followed for 12 months and will be included in the primary efficacy analysis, regardless of the duration of therapy chosen. HOKUSAI-VTE has just completed enrollment and results are expected in late 2013 or 2014.

Practical Considerations for NOAC Use in the Treatment of DVT

Taken together, these clinical trial results represent an exciting time in the field of DVT treatment. While only one NOAC is currently FDA-approved for the treatment of DVT (rivaroxaban), FDA-approval is being sought for both dabigatran and apixaban. The developers of edoxaban will likely follow similar suit. This, it is anticipated that within a year or two providers may have several NOACs approved for the treatment of DVT. Understanding the practical aspects of choosing an anticoagulant in patients with DVT will be critical for the safe use of these novel agents. While a comprehensive discussion of the advantages and disadvantages of these agents is beyond the scope of the current article, we have identified several key aspects below related to patient selection that should be considered when using the NOACs in routine clinical practice. A discussion of other issues related to NOAC use, such as monitoring and reversal, is beyond the scope of this article and the reader is referred to several recent reviews[27, 28, 13, 29–31, 16].

Patient Selection

Taken together, the large, phase III clinical trial results described above are encouraging and have led to the approval of novel anticoagulation therapies for patients with DVT. These agents certainly herald a new era in anticoagulation management and, for many patients and providers, may be preferred to warfarin or parenteral anticoagulation. Nevertheless, until Phase IV studies are completed, we should be cognizant that clinical trial participants may not be truly representative of patients we encounter in routine clinical practice. For example, patients with advanced age, with active cancer, at extremes of body weight, with significant renal or hepatic disease, and those on concomitant therapy with CYP3A4 and p-gp inhibitors or inducers were generally underrepresented or overtly excluded in the clinical trials[32, 16, 33]. As such, until further post-marketing data is available, clinicians may be prudent to approach the use of NOACs in these more complicated patients with some caution.

One group of patients that deserve brief discussion is the elderly. The incidence of deep vein thrombosis (without or without PU) rises exponentially in older adults [1, 3, 34–37]. Older patients are also more likely to have comorbid conditions (e.g. renal impairment, cancer, the use of CYP3A4 or P-gp inhibitors/inducers) and a higher risk of bleeding. As the average age of patients in EINSTEIN-DVT, AMPLIFY, and RE-COVER ranged from 54–57 years [18, 20, 24], the relative safety and efficacy of these NOACs in the elderly remains incompletely examined. Although sub-group analyses of the clinical trials studying NOACs in AF suggests that these agents may be effective and safe across ages in AF [38], until more data are available, the use of NOACs in older adults with DVT should be done prudently. In

all patients, a discussion of treatment options (including the advantages and disadvantages of either warfarin or a NOAC), estimation of bleeding risk, regular follow-up for assessment of side effects, interval monitoring of renal function, and continued patient education has been recommended [33, 32].

Patient adherence to anticoagulant treatment, regardless of whether warfarin or NOACs are prescribed, is important to assess. While the NOACs are a fixed dose and thus may simplify medications regimens and improve adherence, missed or skipped doses of NOACs may place patients at risk for sub-therapeutic anticoagulation and an increased risk of recurrent VTE. Moreover, because of their shorter half-life, missing a NOAC dose may result in a higher risk of recurrent thrombosis than missing a dose of warfarin. As such, patient compliance to medication regimens should be closely evaluated both at drug initiation and at regular intervals during the treatment course [32].

Conclusion

Deep venous thrombosis is a common and costly disease and NOACs provide alternatives to traditional therapy with warfarin and parenteral anticoagulants. While the pharmacology and clinical trial results of NOACs in patients with DVT are encouraging, careful patient selection is paramount when using these new agents. Assessment of an individual patient's risk for drug accumulation, bleeding, interacting medications, and compliance is important for the prudent and safe use of the NOACs in routine clinical practice.

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References

1. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost. 2000; 83(5):657–60. [PubMed: 10823257]
2. Spencer FA, Emery C, Lessard D, Anderson F, Emani S, Aragam J, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med. 2006; 21(7):722–7.10.1111/j.1525-1497.2006.00458.x [PubMed: 16808773]
3. White RH. The epidemiology of venous thromboembolism. Circulation. 2003; 107(23 Suppl 1):I4–8.10.1161/01.CIR.0000078468.11849.66 [PubMed: 12814979]
4. Mahan CE, Holdsworth MT, Welch SM, Borrego M, Spyropoulos AC. Deep-vein thrombosis: a United States cost model for a preventable and costly adverse event. Thromb Haemost. 2011; 106(3):405–15.10.1160/TH11-02-0132 [PubMed: 21833446]
5. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis. 2009; 28(4):465–76.10.1007/s11239-009-0309-3 [PubMed: 19224134]
6. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Archives of internal medicine. 2004; 164(1):17–26.10.1001/archinte.164.1.17 [PubMed: 14718318]
7. Vazquez SR, Freeman A, VanWoerkom RC, Rondina MT. Contemporary issues in the prevention and management of postthrombotic syndrome. Ann Pharmacother. 2009; 43(11):1824–35.10.1345/aph.1M185 [PubMed: 19737994]
8. Fanikos J, Piazza G, Zayaruzny M, Goldhaber SZ. Long-term complications of medical patients with hospital-acquired venous thromboembolism. Thromb Haemost. 2009; 102(4):688–93.10.1160/TH09-04-0266 [PubMed: 19806254]

9. Piazza G, Seddighzadeh A, Goldhaber SZ. Deep-vein thrombosis in the elderly. Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2008; 14(4):393–8.10.1177/1076029608317942 [PubMed: 18593747]
10. Becattini C, Vedovati MC, Agnelli G. Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: a review of the literature. Thromb Res. 2012; 129(3):392–400.10.1016/j.thromres.2011.12.014 [PubMed: 22264937]
11. Brenner B, Hoffman R. Emerging options in the treatment of deep vein thrombosis and pulmonary embolism. Blood reviews. 2011; 25(5):215–21.10.1016/j.blre.2011.04.003 [PubMed: 21605928]
12. Cohen AT, Dobromirski M. The use of rivaroxaban for short- and long-term treatment of venous thromboembolism. Thromb Haemost. 2012; 107(6):1035–43.10.1160/TH11-12-0859 [PubMed: 22371186]
13. Franchini M, Mannucci PM. New anticoagulants for treatment of venous thromboembolism. European journal of internal medicine. 2012; 23(8):692–5.10.1016/j.ejim.2012.10.001 [PubMed: 23095463]
14. Poulsen BK, Grove EL, Husted SE. New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function. Drugs. 2012; 72(13):1739–53.10.2165/11635730-000000000-00000 [PubMed: 22931521]
15**. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e419S–94S. These evidence-based guidelines discuss the treatment of DVT. 10.1378/chest.11-2301 [PubMed: 22315268]
16**. Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012; 119(13):3016–23. This outstanding review highlights patient characteristics important to consider when choosing between new or established anticoagulants. 10.1182/blood-2011-10-378950 [PubMed: 22302737]
17. Kubitza D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. British journal of clinical pharmacology. 2010; 70(5):703–12.10.1111/j.1365-2125.2010.03753.x [PubMed: 21039764]
18. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363(26):2499–510.10.1056/NEJMoa1007903 [PubMed: 21128814]
19. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug metabolism and disposition: the biological fate of chemicals. 2008; 36(2):386–99.10.1124/dmd.107.019083 [PubMed: 18006647]
20. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009; 361(24):2342–52.10.1056/NEJMoa0906598 [PubMed: 19966341]
21. Schulman, S.; Kakkar, AK.; Schellong, S.; Goldhaber, SZ.; Henry, E.; Mismetti, P., et al., editors. Presented at the 53rd Annual American Society of Hematology Meeting. 2011. A Randomized Trial of Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER II).
22. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013; 368(8):709–18.10.1056/NEJMoa1113697 [PubMed: 23425163]
23. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011; 364(9):806–17.10.1056/NEJMoa1007432 [PubMed: 21309657]
24. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med. 201310.1056/NEJMoa1302507
25. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013; 368(8):699–708.10.1056/NEJMoa1207541 [PubMed: 23216615]

26. Raskob G, Buller H, Prins M, Segers A, Shi M, Schwocho L, et al. Edoxaban for the long-term treatment of venous thromboembolism: rationale and design of the Hokusai-venous thromboembolism study - methodological implications for clinical trials. J Thromb Haemost. 2013; 11(7):1287–94.10.1111/jth.12230 [PubMed: 23574579]

27. Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay. Thromb Haemost. 2010; 104(6): 1263–71.10.1160/TH10-05-0328 [PubMed: 20978714]

28. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e326S–50S.10.1378/chest.11-2298 [PubMed: 22315266]

29*. Garcia D, Barrett YC, Ramacciotti E, Weitz JI. Laboratory assessment of the anticoagulant effects of the next generation of oral anticoagulants. J Thromb Haemost. 2013; 11(2):245–52. This review discussed important aspects of the laboratory assessment of novel oral anticoagulants. 10.1111/jth.12096 [PubMed: 23216682]

30*. Kaatz S, Kouides PA, Garcia DA, Spyropolous AC, Crowther M, Douketis JD, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol. 2012; 87 (Suppl 1):S141–5. This review discussed important aspects of the reversal of novel oral anticoagulants. 10.1002/ajh.23202 [PubMed: 22473649]

31. Nitzki-George D, Wozniak I, Caprini JA. Current state of knowledge on oral anticoagulant reversal using procoagulant factors. Ann Pharmacother. 2013; 47(6):841–55.10.1345/aph.1R724 [PubMed: 23695644]

32. Ageno W, Crowther M, Baglin T, Falanga A, Buller H, Palareti G, et al. Selection and assessment of patients treated with the novel oral anticoagulant drugs: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2013; 11(1):177–9.10.1111/jth.12038 [PubMed: 23419049]

33. Cushman M. Treating Acute Venous Thromboembolism: Shift with Care. NEJM. 2013 epub ahead of print.

34. Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM, et al. The epidemiology of venous thromboembolism in the community. Thromb Haemost. 2001; 86(1):452–63. [PubMed: 11487036]

35. Stein PD, Hull RD, Kayali F, Ghali WA, Alshab AK, Olson RE. Venous thromboembolism according to age: the impact of an aging population. Archives of internal medicine. 2004; 164(20): 2260–5.10.1001/archinte.164.20.2260 [PubMed: 15534164]

36. Ageno W, Squizzato A, Garcia D, Imberti D. Epidemiology and risk factors of venous thromboembolism. Semin Thromb Hemost. 2006; 32(7):651–8.10.1055/s-2006-951293 [PubMed: 17024592]

37. Spyropoulos AC, Merli G. Management of venous thromboembolism in the elderly. Drugs & aging. 2006; 23(8):651–71. [PubMed: 16964988]

38. Pengo V, Crippa L, Falanga A, Finazzi G, Marongiu F, Moia M, et al. Phase III studies on novel oral anticoagulants for stroke prevention in atrial fibrillation: a look beyond the excellent results. J Thromb Haemost. 2012; 10(10):1979–87.10.1111/j.1538-7836.2012.04866.x [PubMed: 22827490]

Table 1

Key pharmacologic characteristics of the novel oral anticoagulants

	Rivaroxaban	Dabigatran	Edoxaban	Apixaban
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Mean half-life (t ½)	7–11 hours	12–17 hours	9–11 hours	8–15 hours
Tmax	2–4 hours	0.5–2 hours	1–2 hours	3–4 hours
Protein binding	93%	35%	55%	87%
Dosing Regimen	Daily	Twice Daily	Daily	Twice Daily
Major interactions	P-gp, CYP3A4	P-gp	P-gp	P-gp, CYP3A4
Estimated renal excretion	66%	80%	35%	25%
Food Effect	Delayed absorption	Delayed absorption	None	None

DVT: deep vein thrombosis, P-gp: p-glycoprotein.

Table 2

Outcomes of the published, phase III acute DVT treatment trials for the novel oral anticoagulants

	Rivaroxaban	Dabigatran	Dabigatran	Apixaban
Name of phase III treatment trial	EINSTEIN-DVT	RE-COVER	RE-COVER II	AMPLIFY
PE patients included	No	Yes	Yes	Yes
Initial therapy with heparinoids	Warfarin arm only	Both arms	Both arms	Warfarin arm only
Number of patients	3449	2564	2568	5395
Study drug dosing schedule	15mg twice daily for 3 weeks, then 20mg daily	150mg twice daily	150mg twice daily	10mg twice daily for 7 days, then 5mg twice daily
Primary outcome	Recurrent VTE	Recurrent VTE or VTE-related death	Recurrent VTE or VTE-related death	Recurrent VTE or VTE-related death
Primary outcome rate (study drug vs. standard therapy, p value for noninferiority)	2.1% vs 3.0% (p<0.001)	2.4% vs 2.1% (p<0.001)	2.4% vs 2.2% (p<0.0001)	2.3% vs 2.7% (p<0.001)
Major bleeding rate (study drug vs. standard therapy)	0.8% vs 1.2% [HR 0.65, 95% CI 0.33–1.30]	1.6% vs 1.9% [HR 0.82, 95% CI 0.45–1.48]	1.2% vs 1.7%, [HR 0.69, 95% CI 0.36–1.32]	0.6% vs 1.8% [RR 0.31, 95% CI 0.17–0.55; p<0.001 for superiority]

CI: confidence interval; HR: hazard ratio; PE: pulmonary embolism; RR: relative risk; VTE: venous thromboembolism.

Table 3

Outcomes of the published, phase III extended DVT treatment trials for the novel oral anticoagulants

	Rivaroxaban	Dabigatran	Dabigatran	Apixaban
Name of phase III secondary prevention trial	EINSTEIN-EXT	RE-MEDY	RE-SONATE	AMPLIFY-EXT
Comparator	Placebo	Warfarin	Placebo	Placebo
Number of patients	1196	2856	1343	2482
Study drug dosing schedule	20 mg daily	150 mg twice daily	150 mg twice daily	2.5 mg twice daily and 5 mg twice daily
Primary outcome	Recurrent VTE	Recurrent VTE	Recurrent VTE	Recurrent VTE and VTE-related death
Primary outcome rate (study drug vs. standard therapy)	1.3% vs 7.1% [HR 0.18, 95% CI 0.09–0.39; p<0.001]	1.8% vs 1.3% [HR with dabigatran 1.44, 95% CI 0.78–2.64; p=0.01 for noninferiority)	0.4% vs 5.6% [HR 0.08, 95% CI 0.02–0.25; p<0.001)	1.7% for 2.5 mg, 1.7% for 5 mg, 8.8% for placebo (p<0.001 for both comparisons)
Major bleeding (study drug vs. standard therapy)	0.7% vs 0% (p=0.11)	0.9% vs 1.8%	0.3% vs 0%	0.2% for 2.5 mg, 0.1% for 5 mg, 0.5% for placebo

CI: confidence interval; HR: hazard ratio; PE: VTE: venous thromboembolism.