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Review

New oral anticoagulants in the ED setting: a review

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Abstract

Background: Emergency department (ED) clinicians are not typically involved in the long-term management of patients' anticoagulation therapy, but they are responsible for decision making for emergency conditions requiring anticoagulation, such as acute venous thromboembolism (VTE). In addition, emergency physicians are often faced with patients who present first to the ED with conditions that may prompt long-term anticoagulation upon hospital discharge, such as atrial fibrillation (AF), or who have acute or potential bleeding complications from anticoagulation.

Objective: In this review, clinical trials of new oral anticoagulants evaluated for treatment of VTE and stroke prophylaxis in AF, as well as practical management aspects, will be discussed. In addition, clinical trials evaluating the adjunctive use of the new oral anticoagulants with antiplatelet therapy in patients who have experienced acute coronary syndrome will be explored.

Discussion: Both dabigatran etexilate and rivaroxaban have successfully completed phase III trials for acute VTE treatment and are currently approved for the reduction of risk of stroke and systemic embolism in patients with nonvalvular AF. In a recently completed phase III trial, apixaban also demonstrated promising efficacy and safety in that indication. Rivaroxaban represents the only new anticoagulant to date to have shown promising phase III results as an adjunct to antiplatelet therapy after acute coronary syndrome.

Conclusion: Knowledge of the appropriate clinical use and safety concerns of the new anticoagulants is imperative as they become more frequently prescribed, and their potential uses in the ED setting represent an important aspect of continuing education for emergency physicians.

1. Introduction

New oral anticoagulants have been developed and evaluated for a variety of indications including prevention and treatment of venous thromboembolism (VTE), stroke prophylaxis in nonvalvular atrial fibrillation (AF), and acute coronary syndrome (ACS). Emergency department (ED) clinicians may not only be diagnosticians of acute VTE, AF, or ACS but also be presented with patients who are experiencing active bleeding events resulting from over-anticoagulation. Traditionally, a low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is used initially in the treatment of acute VTE, followed by long-term vitamin K antagonist (VKA) therapy. For stroke prophylaxis in AF, long-term anticoagulation with the VKA warfarin is the standard of care. Currently, the standard of care for the prevention of secondary ischemic events in ACS is dual-antiplatelet therapy after either percutaneous coronary intervention or conservative management.

The new oral anticoagulants address many of the practical management challenges associated with warfarin, and in some cases, they may have advantages in efficacy in VTE treatment and in AF. In the case of secondary prevention after ACS, the addition of the new oral anticoagulants to existing

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antiplatelet agents represents a new paradigm in the long-term care of these patients. In this review of the literature, clinical trials evaluating the new anticoagulants for indications of potential interest to ED clinicians will be discussed.

2. The new oral anticoagulants

Traditionally used anticoagulants such as warfarin, LMWHs, and fondaparinux are associated with a variety of challenges. There is a significant degree of interpatient variability with regard to clinical response to warfarin because of genetic polymorphisms, particularly upon initiating therapy. In addition, a large number of drug-drug and drug-food interactions necessitate more frequent monitoring of international normalized ratio (INR) and may complicate management. Major and non–major bleeding events, as well as expectant management of supratherapeutic INRs, represent a frequent cause for ED presentation for patients taking warfarin [1]. In older patients, warfarin is the most common cause of drug-related emergency hospitalization [2]. Although LMWHs and fondaparinux do not require routine laboratory monitoring and have few drug interactions, their main limitation as chronic agents is their subcutaneous route of administration.

The novel oral anticoagulants belong to 2 main classes: direct thrombin inhibitors (DTIs) and selective factor Xa inhibitors. The DTI dabigatran etexilate prevents the conversion of fibrinogen to fibrin, whereas the selective factor Xa inhibitors rivaroxaban and apixaban work on the previous step in the coagulation cascade by preventing the conversion of prothrombin to thrombin (Figure). Dabigatran etexilate and rivaroxaban have both been approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF; in addition, rivaroxaban has been approved for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing knee or hip replacement surgery. None of the novel anticoagulants have been approved by the US Food and Drug Administration (FDA) for VTE treatment or use in ACS to date; however, several phase III clinical trials have been completed. These agents share fixed oral dosing, a wide therapeutic window, and minimal drug and food interactions and require no routine laboratory monitoring (Table 1) [3-6]. In fact, for the most part, there is no reliable laboratory monitoring possible for these agents, which some clinicians following up anticoagulated patients for the long term view as a disadvantage.

3. Venous thromboembolism treatment

Acute VTE comprises DVT, typically in the lower extremities, and PE, which is potentially fatal. Postthrombotic syndrome and high rates of recurrence (secondary VTE) are significant complications of VTE, with their incidence being highly dependent on concomitant risk factors [7].

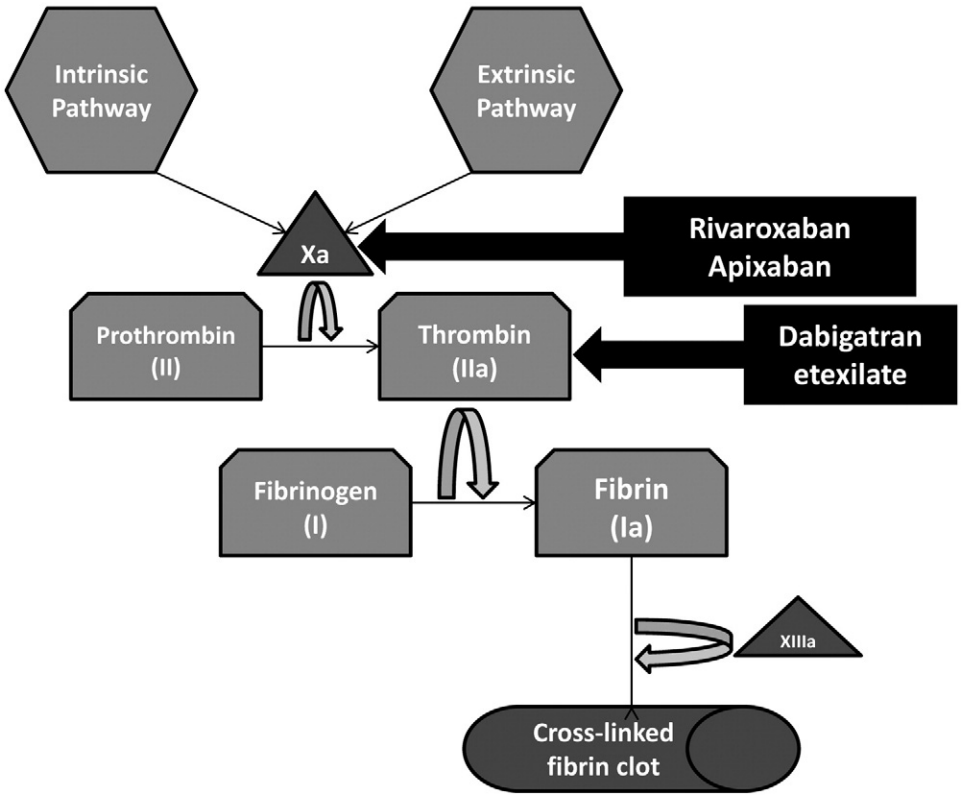

Figure. Abbreviated coagulation cascade.

Table 1 Comparison of key considerations for new oral anticoagulants [3-6]

Factor	Warfarin	Enoxaparin (LMWH)	Dabigatran etexilate	Rivaroxaban	Apixaban
Routine laboratory monitoring required	X				
Antidote available	X	X			
Dose adjustment for renal insufficiency		X	X	X	X
Rapid onset and offset of action			X	X	X

Low-molecular-weight heparins, UFH, or fondaparinux is recommended by guidelines for the acute treatment of VTE, overlapped with a VKA for at least 5 days and when the INR is 2.0 or greater for at least 24 hours [7,8]. Long-term therapy (ie, secondary VTE prophylaxis) with a VKA or LMWH is recommended for at least 3 months and up to 6 to 12 months or even longer in certain scenarios [7,8]. The 2012 guidelines from the American College of Chest Physicians now recommend the use of rivaroxaban for the treatment of VTE [8]. Ambulatory patients typically present to the ED after symptoms of VTE, making ED clinicians responsible for initiating anticoagulant treatment.

3.1. Dabigatran etexilate

Dabigatran etexilate has been evaluated for acute VTE and secondary VTE prophylaxis in the RE-VOLUTION program, which consists of 3 completed phase III trials to date.

3.1.1. Acute VTE treatment

In the Dabigatran vs Warfarin in the Treatment of Acute Venous Thromboembolism trial, patients with proximal DVT or PE and for whom 6 months of anticoagulation was deemed appropriate were enrolled [9]. All patients were initially treated with UFH or LMWH and were then randomized to receive either warfarin titrated to an INR of 2.0 to 3.0 or dabigatran etexilate 150 mg twice daily. The primary efficacy outcome of recurrent VTE during the study period occurred at rates of 2.4% in the dabigatran etexilate group and 2.1% in the warfarin group (hazard ratio [HR], 1.10; 95% confidence interval [CI], 0.65-1.84), which met the prespecified noninferiority margin. Combined major and clinically relevant non–major bleeding events occurred at significantly higher rates in patients receiving warfarin (8.8%) compared with patients receiving dabigatran etexilate (5.6%; HR, 0.63; 95% CI, 0.47-0.94; $P = .002$).

3.1.2. Secondary VTE prevention

In Dabigatran vs Placebo for Extended Maintenance Therapy of Venous Thromboembolism trial, patients who had initially received 6 to 18 months of anticoagulation for VTE and had an indication for continued anticoagulation were randomized to receive either dabigatran etexilate 150 mg twice daily or placebo for 6 months [10]. Recurrent VTE occurred at a rate of 0.4% in patients receiving dabigatran etexilate and 5.6% in patients receiving placebo. There were 2 major bleeding events, both gastrointestinal and both occurring in patients receiving dabigatran etexilate. Clinically relevant non–major bleeding occurred at a rate of 5.3% in the dabigatran etexilate group and 1.8% in the placebo group (HR, 2.9; 95% CI, 1.5-5.6; $P = .001$). On-treatment cardiovascular events occurred in 3 patients receiving dabigatran etexilate and in 2 patients receiving placebo.

In the Dabigatran or Warfarin for Extended Maintenance Therapy of Venous Thromboembolism trial, patients who had initially received 3 to 12 months of anticoagulation for VTE were randomized to receive either dabigatran etexilate 150 mg twice daily or warfarin adjusted to an INR of 2.0 to 3.0 for an additional 6 to 36 months [11]. Recurrent VTE occurred at a rate of 1.8% in the dabigatran group and 1.3% in the warfarin group (HR, 1.44; 95% CI, 0.78-2.64; $P = .03$ for noninferiority). Major bleeding occurred at a rate of 0.9% in the dabigatran group and 1.8% in the warfarin group (HR, 0.52; 95% CI, 0.27-1.01). In addition, cardiovascular events occurred in 0.9% of patients receiving dabigatran etexilate and in 0.2% of patients receiving warfarin ($P = .02$).

3.2. Rivaroxaban

The EINSTEIN program was a series of 3 phase III clinical trials evaluating oral rivaroxaban. All 3, the Acute DVT Study, the Continued Treatment Study (also known as EINSTEIN-Extension, which included both DVT and PE), and the Acute PE Study have been completed [12,13].

3.2.1. Acute VTE treatment

In the Acute DVT Study, patients with proximal DVT without symptomatic PE were randomized to receive either (*a*) rivaroxaban 15 mg orally twice daily for the first 3 weeks, followed by 20 mg once daily for 3, 6, or 12 months of treatment, or (*b*) enoxaparin 1 mg/kg subcutaneously twice daily, started with an oral VKA within 48 hours after randomization. Enoxaparin was discontinued when the patient had an INR of 2.0 or greater and had received at least 5 days of treatment [12]. The primary efficacy outcome of symptomatic recurrent VTE occurred at a rate of 2.1% in the rivaroxaban group and 3.0% in the enoxaparin/VKA group (HR, 0.68; 95% CI, 0.44-1.04; $P < .001$ for noninferiority). Rates of major bleeding and clinically relevant non–major bleeding were similar between groups. There were a greater number of deaths in the enoxaparin/VKA group, bordering on statistical significance ($P = .06$).

In the PE study, patients with acute symptomatic PE with or without DVT were randomized to receive rivaroxaban 15

mg twice daily for 3 weeks followed by 20 mg once daily, or standard therapy with enoxaparin followed by a VKA for 3, 6, or 12 months [13]. Both the rivaroxaban and standard therapy groups demonstrated similar efficacy and similar safety with regard to the first episode of major or clinically relevant non–major bleeding during treatment. It is of note, however, that patients receiving rivaroxaban had significantly fewer major bleeding events (1.1% vs 2.2%; HR, 0.49; 95% CI:0.31-0.79; $P = .003$.)

3.2.2. Secondary VTE prevention

In the Continued Treatment Study, patients with symptomatic DVT or PE who had been treated for 6 to 12 months with warfarin or rivaroxaban were randomized to receive either rivaroxaban 20 mg orally once daily or placebo for 6 or 12 months [12]. The primary efficacy outcome of recurrent VTE occurred at a rate of 1.3% in the rivaroxaban group and 7.1% in the placebo group (HR, 0.18; 95% CI, 0.09-0.39; $P < .001$). Combined major and clinically relevant non–major bleeding events occurred at a rate of 6.0% in the rivaroxaban group and 1.2% in the placebo group (HR, 5.19; 95% CI, 2.3-11.17; $P < .001$).

3.3. Apixaban

3.3.1. Acute VTE treatment

Apixaban has been evaluated for the treatment of acute VTE in a phase II dose-ranging study, Botticelli DVT (Efficacy and Safety of Oral Direct Factor Xa Inhibitor Apixaban for Symptomatic Deep Vein Thrombosis) [14]. Patients with either acute symptomatic proximal DVT or extensive calf vein thrombosis were randomized to receive either oral apixaban 5 mg or 10 mg twice daily, 20 mg once daily, or a subcutaneous LMWH and an oral VKA, with the LMWH discontinued after a minimum of 5 days, for an intended treatment duration of 84 to 91 days. The primary efficacy outcome, recurrent VTE, was similar among treatment groups and occurred at a rate of 4.2% in the LMWH/VKA group and 4.7% in patients receiving apixaban. The rate of combined major and clinically relevant non–major bleeding also occurred at similar rates among groups: 7.3% in patients receiving apixaban compared with 7.9% in the LMWH/VKA group.

3.3.2. Secondary VTE prevention

A phase III trial (NCT00643201) is currently under way, evaluating apixaban 10 mg twice daily for 7 days, followed by apixaban 5 mg twice daily, compared with enoxaparin/warfarin for 6 months, with an estimated completion date of December 2012 [15].

4. Stroke prophylaxis in AF

Atrial fibrillation affects roughly 1% to 2% of the general population, and its incidence is projected to increase 2.5-fold in the next 50 years, in part, because age is a strong risk factor [16,17]. Atrial fibrillation is a potent risk factor for stroke, and a diagnosis of paroxysmal or permanent AF imparts a 5-fold increased risk of stroke [16]. Emergency department visit rates for AF have increased through the years, and ~20% of all new-onset AF diagnoses occur in the ED; however, AF may also be incidentally diagnosed after presentation of stroke or transient ischemic attack [18,19].

First-line use of warfarin is recommended for stroke prophylaxis in most patients with AF by evidence-based guidelines [16,20,21]. Warfarin has a 68% relative risk (RR) reduction of ischemic stroke compared with placebo; aspirin has a less-robust RR reduction of 21% compared with placebo [22,23]. Despite its excellent efficacy, the practical management challenges of warfarin, particularly in the largely older population afflicted by AF, have led to the clinical development of novel oral anticoagulants for this indication. Dabigatran etexilate is currently recommended in US guidelines as an alternative to warfarin in patients with AF who do not have prosthetic heart valves, hemodynamically significant valve disease, severe renal failure, or advanced liver disease [24]. In the 2012 edition of the guidelines by the American College of Chest Physicians, dabigatran is recommended over warfarin in patients at a high risk for stroke (ie, $CHADS_2$ score ≥ 2) [25].

4.1. Dabigatran etexilate

Dabigatran etexilate was the first new oral anticoagulant to be FDA approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF. The approved dose is 150 mg twice daily (or 75 mg twice daily for patients with a creatinine clearance [CrCl] of 15-30 mL/min) [4]. The approval of dabigatran etexilate was based on the landmark phase III Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study [26]. The open-label RE-LY study compared dabigatran etexilate 110 mg or 150 mg twice daily with warfarin (titrated to an INR of 2.0-3.0) in patients with AF. The primary efficacy outcome, the composite of stroke (ischemic and hemorrhagic), and systemic embolism occurred at a rate of 1.69% per year in the warfarin group, 1.53% per year in the dabigatran 110 mg group (RR, 0.91; 95% CI, 0.74-1.11; $P < .001$ for noninferiority), and 1.11% per year in the dabigatran 150 mg group (RR, 0.66; 95% CI, 0.53-0.83; $P < .001$ for superiority). The annual rate of major bleeding was 3.36% in the warfarin group, 2.71% in the 110 mg dabigatran group ($P = .003$ vs warfarin), and 3.11% in the 150 mg dabigatran group ($P = .31$ vs warfarin). Rates of intracranial hemorrhage were significantly lower in both dabigatran groups compared with warfarin. Although dabigatran etexilate 110 mg twice daily had a superior bleeding-event profile to dose-adjusted warfarin and had similar efficacy, the 150-mg twice-daily dose was more effective than warfarin and had a similar bleeding profile. Significantly higher rates of dyspepsia were observed among both dabigatran etexilate groups compared with warfarin. Rates of myocardial infarction (MI) were higher among both

dabigatran etexilate groups, but this only reached statistical significance in the 150 mg dosing group.

4.2. Rivaroxaban

Rivaroxaban was the first oral selective factor Xa inhibitor alternative to warfarin to be FDA approved for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular AF. The approved dose of rivaroxaban is 20 mg once daily with the evening meal (15 mg once daily with the evening meal in patients with a CrCl between 15 and 50 mL/min) [5]. Rivaroxaban is not recommended for use in patients with a CrCl less than 15 mL/min or with moderate or severe hepatic impairment.

The approval of rivaroxaban was based on the double-blind Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study [27]. The ROCKET AF study compared rivaroxaban 20 mg once daily (15 mg once daily in patients with renal insufficiency) with warfarin titrated to an INR of 2.0 to 3.0 in patients with AF. The primary efficacy outcome, the composite of stroke (ischemic and hemorrhagic), and systemic embolism occurred at a rate of 2.4% per year in the warfarin group and 2.1% in the rivaroxaban group in the intent-to-treat analysis (HR, 0.88; 95% CI, 0.75-1.03; $P < .001$ for noninferiority and $P = .12$ for superiority). The rate of major bleeding was 3.4% per year in the warfarin group and 3.6% in the rivaroxaban group (HR, 1.04; 95% CI, 0.90-1.20; $P = .58$). Rates of intracranial and fatal bleeding were significantly lower in patients receiving rivaroxaban; however, rates of gastrointestinal bleeding were higher in patients receiving rivaroxaban compared with patients receiving warfarin.

4.3. Apixaban

Apixaban was the only one of the new oral anticoagulants to undergo a head-to-head trial against aspirin in patients with AF who were considered unsuitable candidates for warfarin (low stroke risk, contraindications, etc) [28]. This trial was ended early due to apixaban's superior efficacy in preventing stroke and systemic embolism, with a similar risk of bleeding events. This trial was followed by a second phase III trial, Apixaban vs Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) [29]. The ARISTOTLE study compared apixaban 5 mg twice daily (2.5 mg twice daily in patients with renal insufficiency) with warfarin titrated to an INR of 2.0 to 3.0 in patients with AF. The primary efficacy outcome, the composite of stroke (ischemic or hemorrhagic), and systemic embolism occurred at a rate of 1.60% per year in the warfarin group and 1.27% per year in the apixaban group (HR, 0.79; 95% CI, 0.66-0.95; $P < .001$ for noninferiority and $P = .01$ for superiority). The rate of major bleeding was 3.09% per year in the warfarin group and 2.13% per year in the apixaban group (HR, 0.69; 95% CI, 0.60-0.80; $P < .001$). In addition, mortality and the rate of intracranial hemorrhage were both significantly lower in patients receiving apixaban.

5. Considerations when comparing the trials of the new anticoagulants for stroke prevention in AF

Although direct comparisons among agents cannot be made, given the lack of a randomized clinical trial comparing the 3 agents, there are some key differences in the design and the study population of RE-LY, ROCKET AF, and ARISTOTLE. Patients enrolled in RE-LY and ARISTOTLE had a mean $CHADS_2$ score of 2.1, compared with 3.5 in ROCKET AF (in which patients were at a substantially higher risk for stroke) [26,27,29].

A summary of the phase III clinical trials for the new anticoagulants is provided in Table 2 [26,27,29]. Time-in-therapeutic range (TTR), which is a numerical mean for time spent in a therapeutic INR of 2.0 to 3.0, was different among the trials. In addition, both ARISTOTLE and ROCKET AF were double blind and double dummy and used sham INR measurements. In contrast, RE-LY was an open-label trial.

Table 2 Comparison of RE-LY, ROCKET AF, and ARISTOTLE trial interventions, mean $CHADS_2$ scores, and TTR achieved [26,27,29]

Study	Intervention	Inclusion	Mean $CHADS_2$ score at randomization	Mean TTR (%)
RE-LY	Warfarin (INR 2.0-3.0) Dabigatran 110 mg twice daily Dabigatran 150 mg twice daily	$CHADS_2 \geq 1$	2.1	64
ROCKET AF	Warfarin (INR 2.0-3.0) Rivaroxaban 10 mg once daily	$CHADS_2 \geq 3$ or previous stroke/TIA	3.5	55
ARISTOTLE	Warfarin (INR 2.0-3.0) Apixaban 5 mg twice daily	$CHADS_2 \geq 1$	2.1	62

TIA, transient ischemic attack.

6. Acute coronary syndrome

Acute coronary syndrome, comprising either MI with or without ST-segment elevation or unstable angina, is responsible for more than 1.5 million hospitalizations annually [30]. Because of the strong association between ischemic discomfort and ACS, the ED is typically the first point of medical interaction for ambulatory patients experiencing an ACS event. Once patients are stabilized, antiplatelet agents (typically aspirin or clopidogrel) are indicated for various durations, depending on the type of intervention (bare metal or drug-eluting stent or conservative management) for the prevention of secondary ischemic events. Emergency department clinicians are not typically involved in managing oral antiplatelet therapy once patients are stabilized; however, a history of ACS is a strong risk factor for recurrence, and ED clinicians may be faced with patients already on antiplatelet therapy having secondary ischemic events.

Although antiplatelet therapy is the current standard of care for reducing secondary ischemic events after ACS, patients are still at risk for recurrent events. Excessive thrombin generation that persists after the acute event may explain this [31]. Despite its efficacy in reducing secondary ischemic events, the addition of warfarin to antiplatelet regimens after ACS has not been widely accepted for the reduction of secondary ischemic events because of a perceived excessive risk of bleeding; however, patients at low or intermediate risk for bleeding may possess a favorable risk-benefit profile [32]. A number of novel oral anticoagulants have been evaluated as adjuncts to the standard antiplatelet therapy in ACS, but none is currently approved for use in the United States. Promising results in ACS were first seen with the DTI ximelagatran, but reports of idiosyncratic hepatotoxicity ended the agent's further clinical development [33].

6.1. Dabigatran etexilate

Dabigatran etexilate was evaluated in the Dabigatran vs Placebo in Patients with Acute Coronary Syndromes on Dual Antiplatelet Therapy trial [34]. In this phase II dose-escalation trial, the composite of major or clinically relevant minor bleeding events was significantly greater in all dabigatran dosing groups, compared with placebo. With regard to efficacy, the composite of cardiovascular death, nonfatal MI, and nonhemorrhagic stroke occurred at numerically lower rates in the 2 higher dabigatran dosing groups, but this was similar to placebo. No phase III trial evaluating dabigatran etexilate in ACS has commenced.

6.2. Rivaroxaban

After showing promising safety and efficacy in the phase II study Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 46, rivaroxaban became the first of the new anticoagulants to successfully complete a phase III trial in ACS [35]. In the phase III trial Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51, patients stabilized after an ACS event were randomized to receive rivaroxaban 2.5 or 5 mg twice daily or placebo in addition to the standard medical therapy, which included either low-dose aspirin or a thienopyridine (clopidogrel or ticlopidine) [36]. The primary efficacy outcome, the composite of death from cardiovascular causes, MI, and stroke occurred at a rate of 8.9% in the combination of both rivaroxaban arms and 10.7% in the placebo arm (HR, 0.84; 95% CI, 0.74-0.96; P = .008). The low 2.5-mg twice-daily dose significantly reduced rates of all-cause mortality (2.9% vs 4.5%, P = .002) and cardiovascular-related death (2.7% vs 4.1%, P = .002). In addition, both doses significantly reduced the risk of stent thrombosis (2.3% vs 2.9%, P = .008). With regard to safety, rivaroxaban increased the risk of thrombolysis in MI major bleeding (not related to coronary artery bypass graft) at rates of 2.1% in the combination of both rivaroxaban arms and 0.6% in the placebo arm (HR, 3.96; 95% CI, 2.46-6.38; P < .001); however, there was no significant difference in fatal bleeding between rivaroxaban and placebo.

6.3. Apixaban

Apixaban was evaluated for ACS in the phase III trial Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) after completion of a phase II trial (APPRAISE-1) that warranted further investigation [37,38]. In APPRAISE-2, apixaban 5 mg twice daily was compared with placebo in addition to standard antiplatelet therapy in patients stabilized after an ACS event and who had at least 2 additional risk factors for ischemic events. The trial was terminated early due to a disproportionately higher rate of major bleeding events in the apixaban group, with no apparent advantage in reduction of recurrent ischemic events.

7. Practical management aspects of the new anticoagulants

7.1. Drug interactions

The new oral anticoagulants have few clinically significant drug interactions compared with warfarin [4-6]. Dabigatran, rivaroxaban, and apixaban are all substrates for the drug transporter protein P-glycoprotein (P-gp). Furthermore, rivaroxaban and apixaban are partially metabolized by the clinically important cytochrome P450 isoenzyme 3A4. Clinically relevant drug interactions with dabigatran are with P-gp inducers or inhibitors such as rifampin; combined P-gp and strong cytochrome P450 isoenzyme 3A4 inducers or

inhibitors interact with apixaban and rivaroxaban. Patients who have renal insufficiency may be particularly sensitive to drug interactions with all of these agents due to reduced CrCl. There may also be an increased risk of bleeding if any of these new agents is coadministered with agents that affect hemostasis.

7.2. Laboratory monitoring

Although none of the new oral anticoagulants require routine laboratory monitoring due to their wide therapeutic window, the ability to monitor these agents may be useful in emergency situations such as overdose or active bleeding. Ecarin clotting time has shown to be a reliable assay to assess coagulation in patients taking dabigatran etexilate; however, the widespread availability of this assay is limited [39]. Prothrombin time assays may be useful for assessing coagulation in patients receiving rivaroxaban or apixaban (dilute prothrombin time), but because of a lack of standardization, as is the case with INR, results may be difficult to interpret [39,40]. Anti–factor Xa assays used for nonroutine monitoring of LMWHs may prove to be the best method to monitor rivaroxaban or apixaban; in addition, calibration with either of these agents may not be necessary [40,41]. Laboratory tests should always be interpreted in the context of best knowledge of the time interval between last oral dose and assay.

7.3. Dose adjustments

The new oral anticoagulants do not require routine monitoring, and unlike with anticoagulants such as warfarin, dose adjustments are not made based on laboratory measures. Because dabigatran, rivaroxaban, and apixaban all have some degree of renal excretion, dose adjustments may be necessary in the setting of renal insufficiency to offset drug accumulation, but this is largely dependent on the indication and dose used.

7.4. Management of bleeding events

The new oral anticoagulants do not have specific antidotes, but their effects can potentially be attenuated by a variety of strategies, depending on the clinical situation. For non–major bleeding events, temporary cessation may be an option because these agents all share relatively short half-lives and a linear pharmacokinetic-pharmacodynamic profile. Activated prothrombin complex concentrates (PCCs) and recombinant factor VII have been explored in early studies as reversal agents for the new anticoagulants, but data are limited; in addition, recombinant factor Xa is currently being explored as a reversal agent for factor Xa inhibitors [42-45]. A study in healthy human subjects demonstrated that 4-factor PCCs that are available in Europe immediately and completely reverse the effect of rivaroxaban, but they did not have any influence on dabigatran at the dose studied [46]. The question of how this translates to the 3-factor PCCs available in the United States remains.

Development of bleeding management protocols for these agents represents an important objective for emergency physicians at an institutional level. A recent care report of an older patient taking dabigatran for stroke prevention highlights this [47]. After experiencing a ground-level fall, non-contrast computed tomography (CT) revealed a right temporal intraparenchymal hemorrhage, a small right subdural hematoma, and a small area of subarachnoid hemorrhage. A repeat CT revealed significant progression of the hemorrhages, and the neurosurgical team decided to administer a weight-based dose of recombinant factor VII because of its rapid onset. A final CT revealed extensive progression of hemorrhage that encompassed most of the left hemisphere.

Many issues need to be considered when addressing emergency bleeding events with the new oral anticoagulants or when developing institutional protocols for managing them. For instance, in this patient, emergency dialysis might have been considered because the drug is partially dialyzable, while cautiously maintaining renal perfusion with intravenous fluids.

8. Conclusions

Emergency department clinicians are often faced with patients presenting for reasons related to their anticoagulant therapy, such as active bleeding, but they are also responsible for the initial emergency management of patients who may require anticoagulation, such as in AF and acute VTE. Dabigatran etexilate, rivaroxaban, and apixaban represent potential alternatives to traditionally used anticoagulants for a variety of indications. Both dabigatran etexilate and rivaroxaban have successfully completed phase III trials for acute VTE treatment, and both are currently approved for the reduction of risk of stroke and systemic embolism in patients with nonvalvular AF. Apixaban demonstrated superior efficacy and safety compared with warfarin for stroke prophylaxis in AF in a recently completed phase III trial. Furthermore, rivaroxaban represents the only new anticoagulant to have shown promising phase III results as an adjunct to antiplatelet therapy after ACS.

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