# Novel Antiplatelet and Anticoagulant Agents in the Cardiac Care Unit

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**KEYWORDS**

• Acute coronary syndrome • Anticoagulants • Antiplatelet drugs • Atrial fibrillation
• Percutaneous coronary intervention • Stroke • Venous thromboembolism

**KEY POINTS**

- Prasugrel and ticagrelor are more effective than clopidogrel for preventing ischemic events in patients with acute coronary syndromes (ACS) at the cost of a slightly higher risk of bleeding.
- Prasugrel is approved by the U.S. Food and Drug Association (FDA) for use in patients with ACS undergoing percutaneous coronary intervention (PCI), whereas ticagrelor is approved for use with or without PCI.
- Dabigatran, rivaroxaban, and apixaban proved noninferior to warfarin for preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
- These novel anticoagulants were associated with much lower rates of intracerebral bleeding than warfarin.
- Rivaroxaban is the first novel anticoagulant to gain FDA approval for preventing and treating venous thromboembolism.
- The absence of validated reversal strategies to use in the event of major bleeding during treatment with a new antithrombotic agent is a potential limitation.

Atherothrombotic vascular disease causes most cases of acute coronary syndrome (ACS) and ischemic stroke, contributing substantially to cardiovascular morbidity and mortality worldwide.[1] Patients with ACS often require urgent treatment in the intensive care unit (ICU) for symptom relief, hemodynamic stabilization, and prevention and control of complications. Secondary thromboembolic events, including deep vein thrombosis and pulmonary embolism, and atrial fibrillation occur frequently in critically ill patients in the ICU. Comprehensive knowledge of conventional and novel antithrombotic drugs is therefore essential.

Platelets play a central role in thrombosis, leading to acute ischemic events in coronary, cerebral, and other vascular beds.[2] Dual antiplatelet therapy (DAPT) with aspirin plus a thienopyridine or $P2Y_{12}$ adenosine diphosphate (ADP) receptor inhibitor has become standard of care for patients with ACS, with clopidogrel the conventional agent.[3–5] Although this regimen is widespread, limitations inspired the development of alternative drugs.

Although the newer agents also target the ADP pathway, they cause more complete inhibition of platelet aggregation than clopidogrel. When given in combination with aspirin in clinical trials of ACS, prasugrel and ticagrelor displayed greater efficacy than clopidogrel at the cost of increased bleeding.[6,7] Novel oral anticoagulants approved as alternatives to warfarin for preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation and prevention and treatment

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of venous thromboembolism (VTE) showed comparable or greater antithrombotic efficacy, with an overall decrease in intracerebral bleeding, translating into net clinical benefit for appropriately selected patients.[8–11]

This article reviews the landmark studies of the novel antiplatelet and anticoagulant agents and discusses the clinical use of these drugs in the cardiac care unit (CCU).

## ANTIPLATELET AND ANTICOAGULANT THERAPY

### *Conventional Antiplatelet Agents*

Aspirin irreversibly inhibits cyclooxygenase-1 in the arachidonic acid pathway, reducing the formation of key activators, such as prostacyclin and thromboxane $A_2$, on platelet receptors (**Fig. 1**, **Table 1**). The benefits of aspirin in the prevention and treatment of ischemic events have been well established.[12–15] The United States Veterans Administration Cooperative study found a 51% reduction in the incidence of death or acute myocardial infarction in patients with ACS randomized to aspirin compared with placebo ($P = .0005$),[12] and investigations of aspirin for long-term secondary coronary prevention after myocardial infarction demonstrated its value well beyond the acute phase.

Clopidogrel irreversibly inhibits the platelet $P2Y_{12}$ ADP receptor, a mechanism distinct from that of aspirin, although both impede platelet activation and aggregation. Clopidogrel has fewer side effects than the thienopyridine ticlopidine, which more often caused bone marrow suppression. Clopidogrel has applications across a wide spectrum of acute and chronic cardiovascular disease states.[16–19] Dual antiplatelet therapy with aspirin and clopidogrel is recommended for patients with unstable angina (UA) and/or non–ST elevation myocardial infarction (NSTEMI).[3]

### *Limitations of Conventional Platelet Inhibitor Drugs*

Among the limitations of aspirin are a dose-dependent risk of gastrointestinal intolerance and allergy.[2,3] Clopidogrel is generally well tolerated but may cause allergic reactions, diarrhea, and, rarely, thrombocytopenia; like all antithrombotic agents, aspirin and clopidogrel can cause or exacerbate bleeding. Both agents also have variable platelet inhibition among individuals. Proposed mechanisms for clopidogrel involve genetic polymorphisms in the CYP450 enzyme, specifically CYP2C19, which decrease the amount of active metabolite available for platelet inhibition[2,20,21] in up to one-third of patients.[22,23]

### *Newer Antiplatelet Agents*

Prasugrel, a prodrug, requires one-step hepatic activation by CYP450 isoenzymes to irreversibly inhibit the $P2Y_{12}$ ADP receptor.[2] As a result, platelet inhibition is more rapid after administration of prasugrel (within 30 minutes) than after clopidogrel (6 hours).[24] Platelet inhibition is also more complete after a loading dose of prasugrel (60 mg) compared with high-dose clopidogrel (600 mg),[25] and the platelet inhibitory effects of a maintenance dose of prasugrel were greater than those with clopidogrel, even at a higher than conventional daily dosage (150 vs 75 mg, respectively).[26]

Ticagrelor, neither a thienopyridine nor a prodrug, is a cyclopentyl-triazolo-pyrimidine that also inhibits the $P2Y_{12}$ ADP receptor. Unlike thienopyridines that inhibit the receptor site for the life of the platelet, ticagrelor reversibly changes the conformation of the receptor, allowing ADP

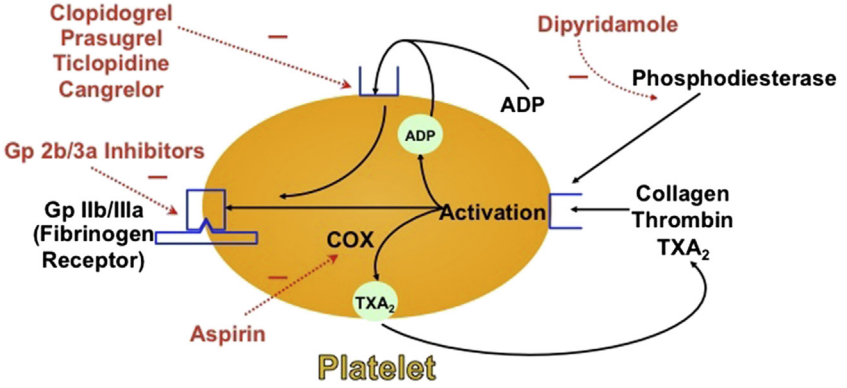


**Fig. 1.** Targets for antiplatelet therapy. COX, cyclooxygenase; Gp, glycoprotein; $TXA_2$, thromboxane $A_2$. (*Adapted from* Schafer AI. Antiplatelet therapy. Am J Med 1996;101:199–209; with permission.)

**Table 1**
**Comparison of oral antiplatelet agents**

| Antiplatelet Agents | Aspirin | Clopidogrel | Prasugrel | Ticagrelor |
|---|---|---|---|---|
| Target | Cyclooxygenase-1 | $P2Y_{12}$ ADP receptor | $P2Y_{12}$ ADP receptor | $P2Y_{12}$ ADP receptor |
| Chemical structure | Acetylsalicylic acid (NSAID) | Thienopyridine | Thienopyridine | Cyclopentyl-triazolo-pyrimidine |
| Receptor binding | Irreversible | Irreversible | Irreversible | Reversible |
| Prodrug | No | Yes | Yes | No |
| Bioavailability (%) | 50–75 | >50 (active metabolite) | 70–80 (active metabolite) | 30–40 |
| Time to peak | 1–3 h | 6 h* | 30 min–4 h* | 30 min–2 h* |
| Half-life (h) | 2.0–30.0 (dose-dependent) | 0.5 | 7.0–12.0 | 6.0–9.0 |
| Renal excretion (%) | 75 | 50 | 60–70 | 1–5 |
| FDA-approved | Primary and secondary prevention of stroke and MI; ACS +/− PCI; peripheral vascular disease | ACS +/− PCI; secondary prevention | ACS + PCI | ACS +/− PCI |
| Contraindications or warnings | Gastrointestinal bleeding; allergy; children/adolescents (Reye syndrome) | Allergy; known resistance | History of stroke/TIA or age >75 y; use lower dose (5 mg) for weight <60 kg | May have higher risk of stent thrombosis if missed doses |
| Hold before surgery (d) | 7 | 7 | 5 | 7 |

*Abbreviations:* MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.
* After loading dose.

to bind without inducing signaling.[2] This function, plus diminished inhibition after 12 hours, allows for more rapid reversal of the antiplatelet effect that, although potentially advantageous if an invasive procedure is required, might increase the risk of thrombotic complications after missed doses. Ticagrelor does not require hepatic activation and, like prasugrel, produces peak platelet inhibition 30 minutes after a loading dose.[27]

### *Anticoagulants*

Anticoagulation has been a mainstay for the management of patients with ACS, prevention of stroke and systemic embolism in patients with atrial fibrillation, and prevention and treatment of VTE. Several studies compared unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs; eg, enoxaparin, dalteparin), the parenteral antithrombin agent bivalirudin, and the factor Xa inhibitor fondaparinux, in patients with ACS.[15,26,28,29] Unfractionated heparin, enoxaparin, or fondaparinux is recommended for patients managed without initial revascularization.[4] For those undergoing percutaneous coronary intervention (PCI), bivalirudin is another option. For patients with nonvalvular atrial fibrillation, aspirin or an anticoagulant is prescribed based on the individual's risk profile.[30] For those with acute VTE, LMWHs and fondaparinux are alternatives to therapy with UFH followed by a vitamin K antagonist.[31]

### *Limitations of Conventional Anticoagulants*

Among the parenteral anticoagulants used in the ICU, UFH requires monitoring of the activated partial thromboplastin time (aPTT) to assure therapeutic dosing, whereas, except in cases of heparin-induced thrombocytopenia, bivalirudin, fondaparinux, and enoxaparin do not. Anticoagulation initiated with these agents is usually followed by a transition to oral warfarin for extended therapy. Among the limitations of warfarin are numerous interactions with foods and other drugs, requiring routine monitoring of anticoagulation

intensity.[32] These limitations stimulated development of newer anticoagulants.

### *Newer Anticoagulant Agents*

The novel oral anticoagulants directly inhibit thrombin (coagulation factor IIa) or factor Xa (**Fig. 2**, **Table 2**). They have a wide therapeutic window, and minimal food interaction or interpatient variability, allowing administration in fixed doses without routine coagulation monitoring. Dabigatran etexilate, a prodrug, inhibits thrombin, reaches peak plasma concentrations 30 minutes to 2 hours after ingestion, has a half-life of 12 to 17 hours,[33,34] and is approximately 80% cleared by the kidneys.[35] Potent P-glycoprotein (P-gp) inhibitors, such as quinidine, increase plasma concentrations of dabigatran and should be avoided.[36]

Rivaroxaban and apixaban, oral direct factor Xa inhibitors, block free and clot-bound factor Xa activity. Both reach peak plasma concentrations within 1 to 3 hours but, unlike dabigatran, are highly protein-bound in the active form and are only 25% to 33% cleared renally.[37] Concurrent therapy with CYP3A4 or P-gp inhibitors, such as ketoconazole or ritonavir, increases serum drug concentrations and should be avoided.

## ANTITHROMBOTIC THERAPY IN THE CCU: ACS

Plaque rupture and platelet activation and aggregation are involved in most cases of ACS. Initial management involves DAPT with parenteral anticoagulation, regardless of whether an invasive or conservative treatment strategy is planned. Although clopidogrel is conventional, prasugrel and ticagrelor (each combined with aspirin) are increasingly chosen, and the LMWHs or fondaparinux are reasonable alternatives to UFH and bivalirudin.[12]

The TRITON-TIMI 38 trial compared prasugrel with clopidogrel in 13,608 patients with moderate-to-high risk ACS on aspirin scheduled for PCI, stratified based on UA/NSTEMI (10,074 patients) or ST elevation myocardial infarction (STEMI) (3534 patients).[6] Patients were randomized to prasugrel (60 mg load, 10 mg/d) or clopidogrel (300 mg load, 75 mg/d). Drug-eluting and bare metal stents were balanced; approximately 50% of patients were treated with platelet glycoprotein $II_b/III_a$ inhibitors during index hospitalization. The primary end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 12.1% of patients in the clopidogrel group versus 9.9% in the prasugrel group (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.73–0.90; $P<.001$). Patients with UA/NSTEMI on prasugrel showed a reduction in the primary end point (HR, 0.82; 95% CI, 0.73–0.93; $P = .002$); the advantage was similar for patients with STEMI (HR, 0.79; 95% CI, 0.65–0.97; $P = .02$). A 52% reduction in stent thrombosis and a reduction in the secondary end point of cardiovascular death, nonfatal myocardial infarction, or urgent target vessel revascularization were seen with prasugrel.

Prasugrel was associated with a higher risk of fatal (0.4% vs 0.1%; $P = .002$) and nonfatal (1.1% vs 09%; $P = .23$) life-threatening bleeding and greater requirement for blood transfusion (4% vs 3%; $P<.001$). Several post hoc analyses suggested a net harm of prasugrel in patients who had a previous stroke or transient ischemic attack (TIA; HR, 1.54; 95% CI, 1.02–2.32; $P = .04$) and no benefit among patients older than 75 years or weighing

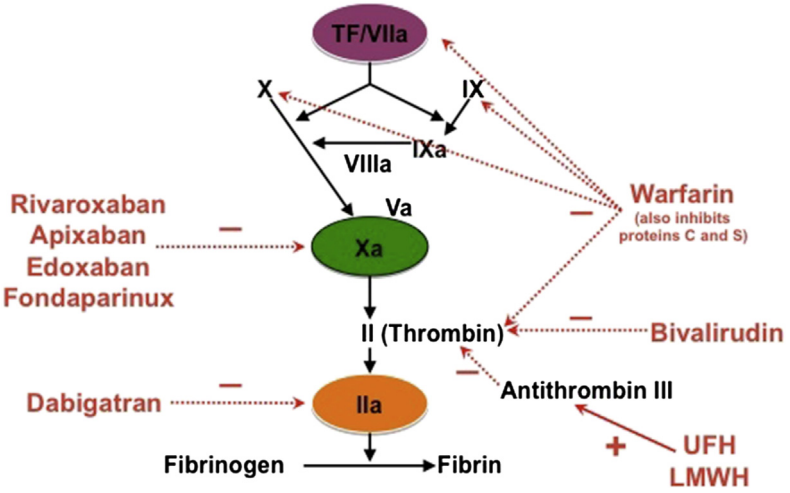


**Fig. 2.** Targets for anticoagulant therapy. TF, tissue factor. (*Data from* Refs.[62–64])

**Table 2**
**Comparison of oral anticoagulant agents**

| Oral Anticoagulant Agent | Warfarin | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|---|
| Target | Vitamin K | IIa | Xa | Xa |
| Prodrug | No | Yes | No | No |
| Bioavailability (%) | 95 | 6–8 | 60–80 | 50 |
| Time to peak (h) | 24 | 2 | 3–4 | 1–3 |
| Half-life (h) | 36–38 | 12–17 | 8–9 | 7–8 |
| Renal excretion (%) | 90 | 80 | 35 | 25 |
| FDA-approved indications | Standard of care anticoagulation for various conditions (eg, AF, DVT, PE, mechanical heart valves, LV thrombus) | Nonvalvular AF | Nonvalvular AF; acute VTE (DVT, PE); prophylaxis of VTE after elective knee or hip replacement | Nonvalvular AF |
| Contraindications or warnings | Pregnancy, especially first trimester (fetal warfarin syndrome); several food and drug interactions | Black box warning for use with mechanical heart valves; avoid concurrent use with P-gp inhibitors (quinidine) | Avoid concurrent use with CYP3A4 or P-gp inhibitors (ketoconazole, ritonavir) | |

*Abbreviations:* AF, atrial fibrillation; DVT, deep vein thrombosis; LV, left ventricle; PE, pulmonary embolism; P-gp, P-glycoprotein.

less than 60 kg. The U.S. Food and Drug Administration (FDA) approval for prasugrel warns against use in patients with previous stroke, TIA, or bleeding risk and in patients older than 75 years because of an increased risk of fatal intracranial hemorrhage. For those weighing less than 60 kg, the increased bleeding risk is attributed to an increased exposure to active metabolites. A lower dosage (5 mg/d) has been cautiously recommended but not investigated in prospective trials.[4]

The PLATO trial compared ticagrelor and clopidogrel in patients with ACS with and without ST-segment elevation.[7] A total of 18,624 patients were randomized to ticagrelor (180 mg load, 90 mg twice daily) or clopidogrel (300 or 600 mg load, 75 mg/d) plus aspirin (75–100 mg/d; for those not previously receiving aspirin, the preferred loading dosage of 325 mg/d was permitted for up to 6 months). PCI was performed in 64.3% of patients. After 1 year, the primary end point of death from vascular causes, myocardial infarction, or stroke occurred in 9.8% of patients randomized to ticagrelor versus 11.7% with clopidogrel. The difference in efficacy appeared 30 days after randomization and continued to the end of the study. Ticagrelor was associated with a reduction in all-cause mortality (4.5% vs 5.9% per year; $P<.001$). Bleeding unrelated to coronary artery bypass graft (CABG) surgery, specifically fatal intracranial hemorrhage, was higher with ticagrelor. Other adverse effects included dyspnea (13.8% vs 7.8%; $P<.001$) and increased serum uric acid and creatinine levels. Outcomes for those with prior stroke or TIA were not reported. Subgroup analyses found that the benefit of ticagrelor was attenuated in patients weighing less than average, those not taking lipid-lowering medication, and those from study centers in North America ($P = .045$), where the dose of aspirin was often higher than in other regions.[38]

Of the novel antiplatelet therapies, only ticagrelor is FDA-approved for patients with ACS managed without revascularization. Among 5216 patients in PLATO (28% of the study population) who did not undergo PCI, ticagrelor was associated with a reduction in primary events (12% vs 14.3% per year; HR, 0.85; 95% CI, 0.73–1.00; $P = .04$) and mortality.[39] For the management of ACS without PCI, antiplatelet therapy with clopidogrel or ticagrelor is recommended for 12 months.

Prasugrel was investigated in 9326 patients with UA or NSTEMI managed without revascularization in the Targeted Platelet Inhibition to Clarify Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study.[40] The results were inconclusive, because divergence in rates of primary events (cardiovascular death, myocardial infarction, or stroke) after 12 months did not reach significance ($P = .07$).

The CHAMPION-PCI and CHAMPION-PLATFORM trials compared cangrelor, an intravenous $P2Y_{12}$ ADP receptor inhibitor, with clopidogrel in patients with ACS undergoing PCI. Both studies were terminated early based on futility assessments regarding the primary end point (death, myocardial infarction, revascularization, or stent thrombosis 48 hours after randomization).[41] The CHAMPION-PHOENIX trial involving 11,145 patients, using a more restricted definition of myocardial infarction, found a primary end point rate of 4.7% with cangrelor versus 5.9% with clopidogrel ($P = .005$).[42] Adverse events were low in both arms, but stent thrombosis was less frequent in the cangrelor group.

### *Timing of Antiplatelet Drug Therapy*

Either clopidogrel or ticagrelor can be administered in patients with ACS before an invasive or conservative strategy is determined, but prasugrel is not recommended this early. Before PCI, timing of loading is crucial: clopidogrel (600 mg) or ticagrelor (180 mg) should be given as early as possible before PCI is performed, and prasugrel (60 mg) should be given after coronary anatomy is defined when PCI is planned. After deployment of bare metal stents, antiplatelet therapy should continue for up to 1 year (clopidogrel, 75 mg/d; prasugrel, 10 mg/d; or ticagrelor, 90 mg twice daily). With drug-eluting stents for ACS, DAPT should generally continue for at least 12 months, although earlier interruption may be safe with later-generation (eg, everolimus-eluting) stents.

### *Concurrent Anticoagulation*

Patients with ACS should be treated with parenteral anticoagulation (UFH, LMWH, or fondaparinux). Bivalirudin is generally restricted to the catheterization laboratory. In the ATLAS ACS-2-TIMI-51 trial, rivaroxaban, 2.5 mg twice daily, plus DAPT reduced cardiovascular death, myocardial infarction, and stroke compared with DAPT alone in patients with ACS. Increased bleeding in patients receiving rivaroxaban was comparable to that with prasugrel or ticagrelor in the TRITON and PLATO trials.[6,7,43] Rivaroxaban was approved in Europe in March 2013 for use in conjunction with antiplatelet therapy in patients with ACS; however, a few weeks earlier, the FDA deferred approval pending further review.

## ATRIAL FIBRILLATION

Atrial fibrillation is associated with, on average, a 5-fold increased risk of ischemic stroke. When atrial fibrillation develops after coronary intervention, after cardiac or noncardiac surgery, or during critical illness, the initial focus is on controlling the ventricular rate, unless hemodynamic instability or an accessory bypass tract requires cardioversion. Anticoagulation is not an immediate concern. In patients at high risk of thromboembolism, however, UFH is most often used in the ICU to prevent thromboembolism, although the safety and efficacy of this approach are not validated. In patients with ongoing or recurrent atrial fibrillation for whom long-term antithrombotic prophylaxis is necessary, warfarin is the conventional anticoagulant, but several novel agents (dabigatran, rivaroxaban, and apixaban) have been approved for patients with nonvalvular atrial fibrillation.[8,9,11,44] A fourth agent, edoxaban, is under investigation.[45]

The oral direct thrombin inhibitor dabigatran (110 or 150 mg twice daily) was compared with warfarin (goal international normalized ratio [INR], 2–3) in 18,113 patients (mean age, 71 years; mean $CHADS_2$ score, 2.1) with nonvalvular atrial fibrillation in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.[8] The primary end point (all stroke, ischemic or hemorrhagic) or systemic embolism occurred at a rate of 1.69% per year with warfarin versus 1.53% per year with dabigatran, 110 mg twice daily (relative risk [RR], 0.91; 95% CI, 0.74–1.11; noninferiority $P<.001$), and 1.11% per year with dabigatran, 150 mg twice daily (RR, 0.66; 95% CI, 0.53–0.82; superiority $P<.001$). Annual rates of major bleeding were 3.36% with warfarin, 2.71% with dabigatran 110 mg twice daily ($P = .003$), and 3.11% with dabigatran 150 mg twice daily ($P = .31$). Hemorrhagic stroke rates were lower in both dabigatran groups than the warfarin group. Dabigatran, 150 mg twice daily, was FDA-approved in 2010 for patients with nonvalvular atrial fibrillation, stroke risk factors, and creatinine clearance of 30 mL/min or greater. A dosage of 75 mg twice daily was approved for patients with creatinine clearance of 15 to 30 mL/min, but the agent should not be used in patients with creatinine clearance less than 15 mL/min or who are undergoing dialysis. Dabigatran at a dosage of 110 mg twice daily was not approved for use in the United States.[46]

The 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) randomized 14,264 patients (median age, 73 years; mean $CHADS_2$ score, 3.5) with nonvalvular atrial fibrillation to rivaroxaban (20 mg/d; 15 mg/d for those with creatinine clearance of 30–49 mL/min) or warfarin (goal INR, 2–3).[9] Rivaroxaban was noninferior for preventing ischemic or hemorrhagic stroke and systemic embolism (1.7 vs 2.2 events per 100 patient-years; HR, 0.79; 95% CI, 0.66–0.96; $P<.001$). No difference was seen in major and nonmajor clinically relevant bleeding rates. Patients taking rivaroxaban developed intracranial hemorrhage (0.5% vs 0.7%; $P = .02$) and fatal bleeding (0.2% vs 0.5%; $P = .003$) less often than those on warfarin. Rivaroxaban was FDA-approved in 2011 for this indication.

The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, randomized 5599 patients to apixaban (5 mg twice daily) or aspirin (81–324 mg/d) over a mean of 1.1 years.[44] The study was terminated when it became apparent that the rate of stroke or systemic embolism was significantly lower with apixaban (1.6% vs 3.7% per year), bleeding risk was similar in the 2 groups, and mortality was lower with apixaban.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, 18,201 patients were randomized to apixaban (5 mg twice daily, reduced to 2.5 mg twice daily in patients with 2 of the following factors: age $\geq$80 years, weight <60 kg, or serum creatinine >1.5 mg/dL) or warfarin (goal INR, 2–3). The median age was 70 years and the mean $CHADS_2$ score 2.2. The primary event rate was lower (1.27% vs 1.6% per year; HR, 0.79; 95% CI, 0.66–0.95; superiority $P = .01$), major bleeding was 2.1% versus 3.1% per year ($P<.001$), and all-cause mortality was 3.52% versus 3.94% per year ($P = .047$) with apixaban, which was approved for this indication in December 2012.

### *Anticoagulation for Cardioversion*

Anticoagulation is recommended for 3 or more weeks before and after cardioversion, unless transesophageal echocardiography is used to exclude thrombus in the left atrium or left atrial appendage. With either approach, anticoagulation must be maintained during and after cardioversion for a period based on the intrinsic thromboembolic risk.

A subgroup analysis evaluated dabigatran in 1270 patients undergoing 1983 cardioversion procedures (647 on warfarin, 672 on dabigatran at 110 mg twice daily, and 664 on dabigatran at 150 mg twice daily) performed during the RE-LY trial, with most taking the assigned drug for 3 or more weeks.[45] In those undergoing transesophageal echocardiography, the incidence of spontaneous echo contrast or intracardiac thrombus was similar in all groups. By 30 days, stroke or systemic embolism occurred in 0.60% of patients cardioverted on warfarin, compared with 0.77% treated with dabigatran at 110 mg twice daily ($P = .71$) and 0.30% treated with dabigatran at 150 mg twice daily ($P = .40$). The rate of major bleeding was low in all groups (0.6%, 0.6%, and 1.7%, respectively).

## ACUTE VTE

Approximately 500,000 patients are hospitalized with acute VTE annually in the United States.[47] In the CCU, acute VTE typically presents secondary to immobilization during critical illness or intrinsic coagulopathy.[48–50] Conventional management begins with parenteral followed by oral anticoagulation for periods varying based on severity and likelihood of recurrence. Rivaroxaban is approved in the United States for treating patients with acute symptomatic deep vein thrombosis or pulmonary embolism, to improve outcomes and reduce risk of recurrence. In the RE-MEDY and RE-SONATE trials, extended dabigatran therapy after initial warfarin management showed lower rates of VTE but more bleeding and drug discontinuation in patients treated with dabigatran.[51]

### *Acute Deep Vein Thrombosis*

The EINSTEIN-DVT study involved 3449 patients randomized to oral rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg/d) versus subcutaneous enoxaparin followed by warfarin or acenocoumarol for 3, 6, or 12 months. The Continued Treatment Study evaluated rivaroxaban (20 mg/d) versus placebo for 6 or 12 additional months in 1196 patients after completing 6 to 12 months treatment. Recurrent VTE occurred in 2.1% in the rivaroxaban group versus 3% with enoxaparin and vitamin K antagonist (HR, 0.68; 95% CI, 0.44–1.04; $P<.001$). Rates of major bleeding were similar. Compared with placebo for extended treatment, fewer recurrences occurred with rivaroxaban (1.3% vs 7.1%; HR, 0.18; 95% CI, 0.09–0.39; $P<.001$).[10]

### *Acute Pulmonary Embolism*

In EINSTEIN-PE, 4832 patients with acute symptomatic pulmonary embolism were randomized to rivaroxaban (15 mg twice daily for 3 weeks, then

20 mg/d) or enoxaparin followed by vitamin K antagonist for 3, 6, or 12 months to prevent recurrence.[52] Rivaroxaban (2.1% per year) was noninferior to standard therapy (1.8% per year; HR, 1.12; 95% CI, 0.75–1.68; noninferiority $P = .003$) was associated with less frequent instances of major bleeding (superiority $P = .003$). The FDA approved rivaroxaban for VTE treatment in 2012.

### *Thromboprophylaxis During Acute Medical Illness*

Rivaroxaban (10 mg/d) was compared with subcutaneous enoxaparin (40 mg/d) in preventing asymptomatic or symptomatic VTE for up to 10 (for noninferiority) or 35 days (for superiority) in 8101 patients hospitalized with acute medical illnesses.[53] The median hospital stay was 11 days. The primary efficacy outcome occurred in 2.7% of patients in each arm (RR, 0.97; 95% CI, 0.71–1.31; noninferiority $P = .003$ at day 10). After 35 days, a reduction was seen in VTE (RR, 0.77; 95% CI, 0.62–0.96; superiority $P = .02$), but more bleeding occurred in the rivaroxaban group. Although rivaroxaban is approved for thromboprophylaxis in adults undergoing elective hip or knee replacement surgery, it is not approved for preventing VTE in medically ill patients.[54]

## SPECIAL CONSIDERATIONS

### *Mechanical Heart Valve Prostheses*

The dabigatran package insert carries a black-box warning against use in patients with mechanical heart valves based on the phase II RE-ALIGN study, which was terminated because of excess thromboembolism and bleeding with dabigatran compared with vitamin K antagonist therapy.[30] Research is ongoing to establish a safer and more effective dabigatran regimen for this indication.

### *Triple Therapy*

The combined use of clopidogrel, aspirin, and an oral anticoagulant (so-called triple therapy) in patients undergoing PCI is associated with significantly higher rates of bleeding than antithrombotic monotherapy. The combination of clopidogrel and an oral anticoagulant (without aspirin) as an alternative to triple therapy was evaluated in the open-label, multicenter WOEST trial that randomized 573 patients on an oral anticoagulant undergoing PCI to either clopidogrel alone or clopidogrel plus aspirin.[55] The primary outcome was the rate of major, minor, and minimal bleeding over a year, based on the Thrombolysis in Myocardial Infarction score. Significantly less bleeding was seen in the clopidogrel plus oral anticoagulant group than in the triple therapy group (HR, 0.36; 95% CI, 0.26–0.50; $P<.001$). The combination of death, myocardial infarction, stroke, target vessel revascularization, and stent thrombosis (safety end point) was also significantly lower in the dual-therapy group than the triple therapy group (11.3% and 17.7%, respectively; $P = .025$). All-cause mortality was 2.5% per year with dual therapy versus 6.4% with triple therapy ($P<.03$). Although underpowered for efficacy end points, and the primary end point included minimal, minor, and major bleeding (some of which is subjectively assessed), the results suggest a potential role for therapy with clopidogrel rather than triple therapy in patients on oral anticoagulants undergoing PCI.

Rivaroxaban is currently under investigation in patients with atrial fibrillation undergoing PCI in the 3-arm PIONEER AF-PCI trial which will randomize an anticipated 2100 patients to (1) rivaroxaban, 15 mg/d plus clopidogrel, 75 mg/d; (2) rivaroxaban, 2.5 mg twice daily plus DAPT; or (3) vitamin K antagonist (goal INR, 2–3) plus DAPT for a treatment duration of 12 months. The primary end point is major and minor bleeding events.

### *Control of Bleeding*

Compared with no antithrombotic therapy, aspirin is associated with a 60% greater risk of major bleeding, clopidogrel with a 38% greater risk, and prasugrel with a 32% greater risk.[6,16] In the PLATO trial of patients receiving aspirin concurrently, major bleeding unrelated to CABG surgery, including intracranial hemorrhage, was 25% higher with ticagrelor than with clopidogrel.[7] If excessive bleeding develops during treatment with prasugrel or ticagrelor, the drug should be stopped and platelets transfused as necessary. Off prasugrel, platelet inhibition resolves within 7 to 10 days.[55] Ticagrelor is more reversible, but metabolites may interfere with transfused platelets. Interruption of antiplatelet therapy during the first several months after coronary intervention increases the risk of stent thrombosis.

Among the advantages of the novel oral anticoagulants are their pharmacokinetic profiles, with half-lives of 12 to 17 hours for dabigatran, 8 to 9 hours for rivaroxaban, and 7 to 8 hours for apixaban, compared with 36 to 38 hours for warfarin.[35] Withholding the drugs may be sufficient in cases of minor or non–life-threatening bleeding, and activated charcoal may reduce drug absorption within 2 to 3 hours of ingestion. For more severe bleeding, treatment includes transfusion of fresh frozen plasma or packed erythrocytes, although the efficacy of plasma is unconfirmed. No specific

antidotes are available to reverse the anticoagulation effects of the new agents. Activated 4-factor prothrombin complex concentrate (not available in the United States) corrected the aPTT in normal subjects taking rivaroxaban ($P<.001$) but did not reverse the dabigatran effect on aPTT.[56] Dialysis may reduce plasma concentrations of dabigatran but will not reverse rivaroxaban or apixaban. To manage bleeding during treatment with a novel anticoagulant, intravenous fluid should be given. Factor VIII inhibitor–binding activator or recombinant factor VII may be useful, but these have not been investigated clinically and carry a risk of thrombosis.

On an investigational level, a humanized monoclonal antibody fragment against dabigatran is in preclinical development as a specific reversal agent. The compound proved effective in vitro and in vivo in monkeys, and reduced dabigatran-related blood loss in a rat tail bleeding model.[34,57,58] Specific factor Xa antidotes currently under development include factor Xa derivatives lacking binding activity. These agents reversed laboratory markers of anticoagulation induced by rivaroxaban and apixaban in vitro and in animal models,[59,60] and reduced rivaroxaban-induced blood loss in a rabbit liver laceration model.[61] Human studies are in formative stages, made complex because of the importance of showing a reduction of clinical bleeding rather than simply a correction of laboratory coagulation measurements.

### *Perioperative Use*

Elective surgery should be deferred for at least 4 to 6 weeks after PCI with bare metal stents and at least 6 months after drug-eluting stents.[5] Prasugrel should be discontinued at least 7 days and ticagrelor or clopidogrel 5 days before surgery. For urgent CABG surgery, the risk of bleeding must be weighed against the benefit of continuing $P2Y_{12}$ therapy. The use of intravenous cangrelor after cessation of oral antiplatelet therapy before CABG surgery is associated with a greater degree of platelet inhibition but no excess in major bleeding compared with placebo.[58] Cangrelor is not currently available for clinical use. In patients undergoing urgent noncardiac surgery, antiplatelet therapy should generally be continued unless the risk of stent thrombosis and myocardial infarction is lower than the risk of bleeding. Vitamin K antagonists should be stopped 5 days preoperatively, and in patients with mechanical heart valves, bridging therapy with UFH or LMWH is recommended. Less evidence exists for bridging in anticoagulated patients with atrial fibrillation or VTE.

## SUMMARY

The development of novel antiplatelet and anticoagulant agents has broadened therapeutic options with favorable benefit to risk ratios compared to conventional agents. When combined with aspirin in patients with ACS, prasugrel and ticagrelor are more effective than clopidogrel in preventing ischemic events but carry a slightly high risk of bleeding, particularly intracranial hemorrhage. Dabigatran, rivaroxaban, and apixaban are all noninferior to warfarin in preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation, apixaban caused less major bleeding, and all agents caused less intracranial hemorrhage than warfarin. Although statistical significance varied, the new anticoagulants reduced all-cause mortality by approximately 10% compared with warfarin, an indicator of net clinical benefit. Only rivaroxaban is approved in the United States for preventing and treating VTE, but evidence with the others is accumulating. Although fixed oral dosing without routine coagulation monitoring, relatively few drug and food interactions, and the potential to reduce hospital length of stay make these agents appealing, the lack of reversal strategies and high cost are limitations.

Future investigation should focus on gaps in clinical applications and alternative pathways for inhibition of platelet function or coagulation.[2] Among the uncertainties is how to manage patients with recurrent ischemic events during treatment, with an aim to better understand the mechanisms of events, such as a ceiling effect limiting $P2Y_{12}$ inhibition, genetic polymorphisms affecting platelet reactivity, or thrombophilia. An urgent need exists for specific reversal agents to terminate the antithrombotic effects and for accurate ways to assess effects when patients require surgery or other invasive procedures. On balance, however, the new antiplatelet and anticoagulant agents have significant therapeutic advantages, offering substantial value in the management of patients with a variety of acute and chronic cardiovascular disease states before, during, and after their care in the CCU.

## REFERENCES

1. Writing Group Members, Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010;121(7):e46–215.
2. Gurbel PA, Tantry US. Combination antithrombotic therapies. Circulation 2010;121(4):569–83.
3. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of

patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2011;123(18):e426–579.
4. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2012;60(7):645–81.
5. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(Suppl 2):53S–70S.
6. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357(20):2001–15.
7. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361(11):1045–57.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–51.
9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883–91.
10. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363(26):2499–510.
11. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981–92.
12. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative study. N Engl J Med 1983;309(7):396–403.
13. Popma JJ, Ohman EM, Weitz J, et al. Antithrombotic therapy in patients undergoing percutaneous coronary intervention. Chest 2001;119(Suppl 1):321S–36S.
14. Barnathan ES, Schwartz JS, Taylor L, et al. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. Circulation 1987;76(1):125–34.
15. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319(17):1105–11.
16. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345(7):494–502.
17. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. J Am Med Assoc 2002;288(19):2411–20.
18. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352(12):1179–89.
19. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366(9497):1607–21.
20. Fintel DJ. Oral antiplatelet therapy for atherothrombotic disease: overview of current and emerging treatment options. Vasc Health Risk Manag 2012;8:77–89.
21. Kim L, Charitakis K, Swaminathan RV, et al. Novel antiplatelet therapies. Curr Atheroscler Rep 2012;14(1):78–84.
22. Gurbel PA, Bliden KP, Hiatt BL, et al. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107(23):2908–13.
23. Serebruany VL, Steinhubl SR, Berger PB, et al. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol 2005;45(2):246–51.
24. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. Eur Heart J 2006;27(10):1166–73.
25. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the prasugrel in comparison to clopidogrel for inhibition of platelet activation and aggregation-thrombolysis in myocardial infarction 44 trial. Circulation 2007;116(25):2923–32.
26. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355(21):2203–16.
27. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50(19):1844–51.

28. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events study group. N Engl J Med 1997;337(7):447–52.
29. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354(14):1464–76.
30. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345(20):1444–51.
31. Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348(15):1425–34.
32. Rose AJ, Hylek EM, Ozonoff A, et al. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: results of the Veterans Affairs study to improve anticoagulation (VARIA). Circ Cardiovasc Qual Outcomes 2011;4(1):22–9.
33. Stangier J, Eriksson BI, Dahl OE, et al. Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. J Clin Pharmacol 2005;45(5):555–63.
34. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). Am Heart J 2012;163(6):931–7.e1.
35. Donadini MP, Ageno W, Douketis JD. Management of bleeding in patients receiving conventional or new anticoagulants: a practical and case-based approach. Drugs 2012;72(15):1965–75.
36. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361(24):2342–52.
37. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. Clin Pharm 2013;52(2):69–82.
38. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the platelet inhibition and patient outcomes (PLATO) trial. Circulation 2011;124(5):544–54.
39. James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised platelet inhibition and patient outcomes (PLATO) trial. BMJ 2011;342:d3527.
40. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012;367(14):1297–309.
41. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 2009;361(24):2330–41.
42. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368(14):1303–13.
43. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009;374(9683):29–38.
44. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364(9):806–17.
45. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J 2010;160(4):635–41.
46. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2011;123(10):1144–50.
47. Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations - United States, 2007-2009. MMWR Morb Mortal Wkly Rep 2012;61(22):401–4.
48. Marks PW. Coagulation disorders in the ICU. Clin Chest Med 2009;30(1):123–9, ix.
49. Pastores SM. Management of venous thromboembolism in the intensive care unit. J Crit Care 2009;24(2):185–91.
50. Rajasekhar A, Beyth R, Crowther MA. Newer anticoagulants in critically ill patients. Crit Care Clin 2012;28(3):427–51, vii.
51. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368(8):709–18.
52. EINSTEIN-PE Investigators, Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287–97.
53. Cohen AT, Spiro TE, Buller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med 2013;368(6):513–23.

54. Eriksson BI, Kakkar AK, Turpie AG, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. J Bone Joint Surg Br 2009;91(5):636–44.
55. Hirsh J, Guyatt G, Albers GW, et al. Antithrombotic and thrombolytic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133(Suppl 6):110S–2S.
56. Levy JH, Faraoni D, Spring JL, et al. Managing new oral anticoagulants in the perioperative and intensive care unit setting. Anesthesiology 2013;118(6):1466–74.
57. van Ryn J, Litzenberger T, Gan G, et al. In vitro characterization, pharmacokinetics and reversal of supratherapeutic doses of dabigatran-induced bleeding in rats by a specific antibody fragment antidote to dabigatran [abstract]. Presented at the 54th ASH Annual Meeting and Exposition. Atlanta, December 8–10, 2012. Abstract 3418.
58. Toth J, van Ryn J, Dursema H, et al. Reversal of dabigatran's anticoagulant activity in the monkey by a specific antidote and pharmacokinetic and pharmacodynamic modeling [abstract]. Presented at the 54th ASH Annual Meeting and Exposition. Atlanta, December 8–10, 2012. Abstract 22.
59. Lu G, DeGuzman FR, Lakhotia S, et al. Recombinant antidote for reversal of anticoagulation by factor Xa inhibitors [abstract]. Presented at the 50th ASH Annual Meeting and Exposition. San Francisco, December 6–9, 2008. Abstract 983.
60. Lu GP, Peng L, Hollenbach SJ, et al. Reconstructed recombinant factor Xa as an antidote to reverse anticoagulation by factor Xa inhibitors. J Thromb Haemost 2009;7:309.
61. Hollenbach SJ, Lu G, Tan S, et al. PRT064445 but not recombinant FVIIa reverses rivaroxaban induced anticoagulation as measured by reduction in blood loss in a rabbit liver laceration model [abstract]. Presented at the 54th ASH Annual Meeting and Exposition. Atlanta, December 8–10, 2012. Abstract 3414.
62. Weitz JI, Bates SM. New anticoagulants. J Thromb Haemost 2005;3:1843.
63. Turpie AG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2007;29:155.
64. Geurtin KR, Choi YM. The discovery of the Factor Xa inhibitor otamixaban: from lead identification to clinical development. Curr Med Chem 2007;14:2471.