

# Novel Oral Anticoagulants

## *Implications in the Perioperative Setting*

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### ABSTRACT

Patients undergoing surgery receive anticoagulation for perioperative thromboprophylaxis or ischemic cardiovascular disease. Because anticoagulants may also potentiate bleeding, clinicians need to understand the implications of anticoagulation in perioperative and postoperative patient management. Many newer anticoagulants that are now available or are in clinical development do not require routine coagulation monitoring, have more predictable dose responses, and have fewer interactions with other drugs and food. The most advanced oral anticoagulants in clinical development are the direct factor Xa inhibitors rivaroxaban and apixaban, and the direct thrombin inhibitor dabigatran etexilate. These agents have been evaluated in the postoperative setting in patients undergoing total hip- or knee-replacement surgery with promising results, and it remains to be seen whether these results will translate into other surgical settings. The impact of the new agents will be influenced by the balance between efficacy and safety, improved convenience, and potential cost-effectiveness benefits.

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Received from the Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia, and the Department of Medicine, University of North Carolina, Chapel Hill, North Carolina. Submitted for publication February 8, 2010. Accepted for publication April 20, 2010. Support was provided from departmental sources, and additional editorial assistance was provided by Elizabeth Ng, B.Sc. (Chameleon Communications International, London, United Kingdom), supported by Bayer Schering Pharma AG (Berlin, Germany) and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (Raritan, New Jersey). The figures in this article were prepared by Annemarie B. Johnson, C.M.I., Medical Illustrator, Wake Forest University School of Medicine Creative Communications, Wake Forest University Medical Center, Winston-Salem, North Carolina.

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**S**URGICAL patients are increasingly receiving anticoagulation for perioperative thromboprophylaxis and as therapy for ischemic cardiovascular disease. Patients with atrial fibrillation, prosthetic valves, or coronary artery disease are also at risk for thrombosis and so may be receiving anticoagulation therapy when they present for surgery. All therapies that prevent clot growth or formation in pathologic states also interfere with normal hemostasis. As a result, patients often present for surgery with an acquired hemostatic imbalance because of preexisting preoperative anticoagulation.

Under physiologic conditions, there is a complex and delicate equilibrium between vascular endothelial cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system.<sup>1</sup> After vascular injury, surgical or trauma patients also develop additional acquired procoagulant changes that alter this complex balance.<sup>1</sup> Hemostasis is far more complex than the simplified coagulation cascade of intrinsic and extrinsic hemostatic activation taught in medical school, and clinicians are often presented with patients receiving one or more anticoagulation therapies. Multiple therapies are currently in use, and newer therapies are approved in other countries and are in development in North America. Because anticoagulants may also potentiate bleeding, it is important that clinicians understand the implications of perioperative and postoperative therapy for thromboembolic disease on the patient. Furthermore, with the introduction of low-molecular-weight heparin (LMWH), there were initial concerns regarding the management of regional anesthesia in patients on LMWH therapy, because standard coagulation assays were not appropriate to monitor its effects.<sup>2</sup> This review discusses the established therapies and novel anticoagulant agents for the prevention of venous thromboembolism (VTE) in the perioperative and postoperative management of surgical patients. The review will focus on anticoagulant agents without discussion of antiplatelet agents.

### VTE after Surgery

Venous thromboembolism comprises deep vein thrombosis and pulmonary embolism (PE), which are potentially life threatening but often preventable conditions. PE, the most

life-threatening manifestation of VTE, occurs in 1.7% of patients without *versus* 0.9% of patients with thromboembolic prophylaxis.<sup>3</sup> Approximately 10% of all cases of PE are rapidly fatal,<sup>4</sup> and VTE may be associated with long-term clinical consequences such as pulmonary hypertension, post-thrombotic syndrome, and recurrent thromboembolic events. There is also a significant healthcare resource burden associated with VTE.<sup>5–7</sup>

Nearly 65% of surgical patients are at risk of VTE according to the American College of Chest Physicians (ACCP) criteria.<sup>8</sup> Because thrombus formation is triggered by vascular trauma and venous stasis,<sup>9</sup> major surgery and postoperative immobility increase the risk of developing VTE.<sup>9,10</sup> In addition to the nonsurgical risk factors for VTE, such as increasing age or body mass index, or a history of VTE, perioperative risk factors include the type and duration of surgery, the type of anesthetic used, the degree and duration of immobility, and the occurrence of dehydration or sepsis.<sup>11</sup> The risk of VTE varies depending on the type of surgery; without thromboprophylaxis, the risk of deep vein thrombosis in most general, open gynecologic or urologic surgery patients is 10–40%, which rises to 40–80% in patients undergoing major orthopedic surgery.<sup>12</sup> The effectiveness of thromboprophylaxis for the prevention of postoperative VTE has consistently been demonstrated in clinical trials.<sup>12</sup> The internationally recognized guidelines produced by the ACCP and other national guidelines recommend the use of anticoagulants after most types of major surgery.<sup>12,13</sup>§,|| The difference in the risk of VTE is reflected in the varying proportion of patients receiving ACCP-recommended prophylaxis between different types of surgery, as demonstrated in the ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study; 88% of patients undergoing hip or knee replacement were receiving prophylaxis, compared with 69% of those undergoing colorectal surgery and 50% of those undergoing urologic surgery.<sup>8</sup> For surgical patients at low risk of VTE, early mobilization may be sufficient to prevent VTE. Patients at moderate or high risk, or those who are likely to have extended periods of immobilization, require thromboprophylaxis to prevent VTE. However, thromboprophylaxis after certain types of surgery, such as vascular, gynecologic, and urologic,<sup>12</sup> lack clinical trial or prospective data to make appropriate recommendations, or recommendations are based on limited data.

§ National Institute for Health and Clinical Excellence. Venous thromboembolism—reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. Available at: <http://guidance.nice.org.uk/CG92>. Accessed April 28, 2010.

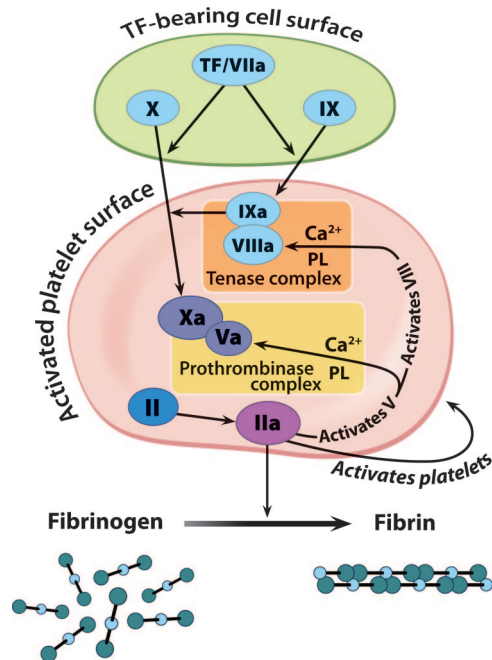
|| American Academy of Orthopaedic Surgeons. Clinical guideline on prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. Available at: [http://www.aaos.org/Research/guidelines/PE\\_guideline.pdf](http://www.aaos.org/Research/guidelines/PE_guideline.pdf). Accessed January 11, 2010.

The levels of recommendations made by the ACCP are based on an evaluation of benefit *versus* harm, burden, and cost. Strong (grade 1) recommendations are made if there is confidence that benefits do or do not outweigh harm, burden, and cost. If the magnitude of the benefits and risks is less certain, the weaker (grade 2) recommendations are made. Grade 1 recommendations can be applied to most patients; the application of grade 2 suggestions requires further evaluation of individual patient and resource requirements. The quality of the supporting randomized control trial evidence for these recommendations is graded as high (A), moderate (B), or low (C) quality, depending on factors such as the design and conduct of the trial and the precision and consistency of results.<sup>14</sup>

Patients undergoing major orthopedic surgery—hip or knee arthroplasty—are at significantly increased risk of developing VTE compared with patients undergoing other types of surgery.<sup>12,15</sup> The most recent ACCP guidelines recommend routine use of LMWH, fondaparinux, or a dose-adjusted vitamin K antagonist (VKA) for the prevention of VTE in all patients undergoing total hip or knee replacement or hip fracture surgery (grade 1A).<sup>12</sup> Thromboprophylaxis after these procedures is generally well accepted; however, adherence to guidelines with respect to start time, duration, and intensity of therapy is relatively low.<sup>16</sup> In addition, a significant proportion of venous thromboembolic events occur after discharge from hospital,<sup>15,17</sup> highlighting the importance of an appropriate duration of prophylaxis in these patients.

There are few prospective studies in patients undergoing thoracic surgery.<sup>12</sup> However, VTE is not an uncommon complication in these patients, in that approximately 5% of patients develop postoperative PE,<sup>18</sup> and approximately 1.3% develop fatal PE.<sup>18,19</sup> Data from one study found that PE was the second most frequent reason for early postoperative death after lung resection,<sup>19</sup> a finding that may also be related to the high incidence of atrial fibrillation that can occur.<sup>20</sup> In addition, patients undergoing thoracic surgery are likely to have other underlying risk factors for VTE such as cancer or delayed mobilization.<sup>12</sup> Despite the lack of data regarding the risk of VTE in these patients, the ACCP recommends that physicians consider the use of LMWH, low-dose unfractionated heparin (UFH), or fondaparinux after thoracic surgery (grade 1C).<sup>12</sup>

The risk of VTE after cardiac surgery is based on retrospective studies with variable results. The incidence of postoperative PE is reported at between 0.75% and 10%.<sup>21</sup> Cardiac surgery patients are at high risk for developing both atrial fibrillation<sup>22</sup> and heparin-induced thrombocytopenia (HIT; a well-described prothrombotic adverse drug reaction),<sup>23,24</sup> which increase the risk of arterial and venous thrombosis.<sup>25,26</sup> Additional factors for the risk of VTE associated with cardiac surgery may not be due to the procedure *per se*<sup>15</sup> but to underlying patient characteristics, including preexisting atrial fibrillation, heart failure, valvular heart disease, prior myocardial infarctions, and the underlying disease



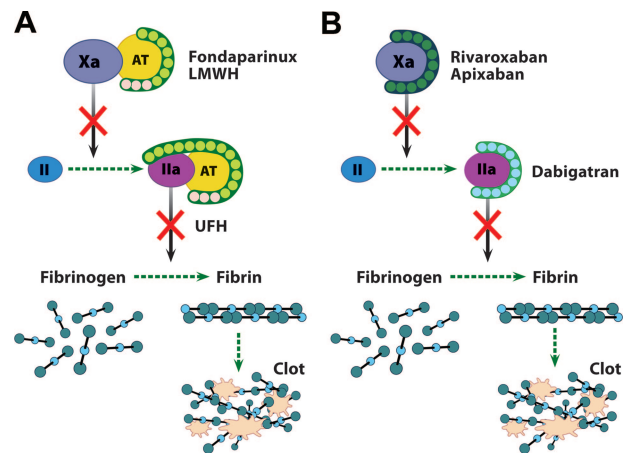
**Fig. 1.** The coagulation cascade. TF = tissue factor; PL = phospholipids.

state. It is estimated, based on extrapolated data, that 1,100–1,300 deaths occur in the United States each year as a result of VTE after coronary artery bypass grafting.<sup>27</sup> Although asymptomatic VTE occurs frequently,<sup>28</sup> symptomatic VTE can also go undetected after cardiac surgery, because symptoms—such as shortness of breath and leg discomfort or swelling—may be attributed to the expected consequences of the preexisting conditions or surgery (*i.e.*, saphenous vein harvest).<sup>27</sup>

The overall risk of clinically important VTE may be relatively low after coronary artery bypass grafting, but patients often require anticoagulation because of unstable angina or the presence of other risk factors.<sup>12</sup> Despite limited evidence, the ACCP recommends thromboprophylaxis with LMWH, UFH, or optimally used bilateral intermittent pneumatic compression or graduated compression stockings, to provide early thromboprophylaxis in patients who may have a more complicated postoperative course than usual (grade 1C).<sup>12</sup> They recommend the use of LMWH over low-dose UFH (grade 2B) based on the fact that LMWH is associated with a lower risk of HIT compared with UFH.<sup>12</sup>

## Current Options for Thromboprophylaxis

The mainstay of anticoagulant drugs—the heparins—target two major components of the coagulation cascade, factor Xa and thrombin, as shown in figures 1 and 2A. Classically, the coagulation cascade *in vitro* comprises two pathways: the intrinsic coagulation pathway, which is initiated when contact is made between blood and exposed negatively charged surfaces (exposed as a result of tissue damage), and the ex-



**Fig. 2.** The primary mechanism of action of the established anticoagulants (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], and fondaparinux) via antithrombin-dependent binding (A) and the new anticoagulants (rivaroxaban, apixaban, and dabigatran etexilate) via antithrombin-independent binding (B). UFH also inactivates factors Xa, IXa, XIa, and XIIa via antithrombin, but to a lesser extent than inactivation of thrombin. LMWH also inactivates thrombin via antithrombin, but to a lesser extent than inactivation of factor Xa. AT = antithrombin.

trinsic coagulation pathway, which is initiated upon vascular injury and exposure of tissue factor. These two pathways converge at the point where factor X is activated to factor Xa. The activation of factor X is catalyzed by factor IXa, through interaction with the protein cofactor VIIIa (intrinsic tenase) or by tissue factor and factor VIIa (extrinsic tenase; fig. 1). Factor Xa activates prothrombin to thrombin, which then activates factors XI, VIII, and V, amplifying the cascade. Thrombin converts soluble fibrinogen to fibrin and activates factor XIII to XIIIa, which cross-links fibrin polymers, solidifying the clot (fig. 1). However, a cell-based model of hemostasis is a better method of understanding the complex interactions of procoagulant and anticoagulant factors, the critical role of tissue factor, and the role of hemostatic-vascular interactions in hemostasis.<sup>29–31</sup>

## UFH and LMWH

UFH and LMWHs are widely used but are also associated with a number of limitations.<sup>32</sup> UFH inactivates both thrombin and factor Xa, catalyzed by binding to antithrombin (also called antithrombin III), whereas LMWH—also by binding to antithrombin—has a selective inhibitory effect on factor Xa (fig. 2A).<sup>32</sup> One advantage of UFH is that it can be completely neutralized with protamine sulfate—unlike LMWHs.<sup>32</sup> UFH requires regular coagulation monitoring, dose adjustments, and potential monitoring for HIT.<sup>32</sup> LMWH requires parenteral administration but monitoring is not required in patients with normal renal function (table 1). However, its half-life is prolonged in patients with renal dysfunction, therefore monitoring and/or dose reduction is recommended in these patients.<sup>32</sup>

**Table 1.** Properties of the Established Anticoagulants Used in the Surgical Setting

|                            | LMWH  | VKAs  | Fondaparinux   |
|----------------------------|---|---|--|
| Bioavailability, %         | ~90   | ~100  | 100  |
| Half-life, h               | 3–6   | 36–42   | 17–21  |
| Elimination                | Renal   | Renal   | Renal  |
| Management with anesthesia | <ul style="list-style-type: none"> <li>• Preoperative LMWH:               <ul style="list-style-type: none"> <li>- Low dose: needle placement at least 10–12 h after last dose</li> <li>- High dose: needle placement 24 h after last dose</li> <li>- Neuraxial techniques should be avoided in patients administered LMWH 2 h preoperatively</li> </ul> </li> <li>• Postoperative LMWH:               <ul style="list-style-type: none"> <li>- Twice-daily dose: Initiate 24 h after surgery. Remove catheter 2 h before first dose</li> <li>- Once-daily dose: Initiate 6–8 h after surgery. May leave catheter in. Remove catheter 10–12 h after last dose. Resume therapy 2 h after catheter removed</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• If prophylactic dose of warfarin is given &gt;24 h before surgery, check INR measurements before initiating neuraxial anesthesia</li> <li>• Remove neuraxial catheters at INR &lt;1.5</li> </ul> | <ul style="list-style-type: none"> <li>• Atraumatic needle placement and avoidance of indwelling catheters recommended</li> <li>• Postoperative therapy with indwelling catheter:               <ul style="list-style-type: none"> <li>- Initiate therapy 6–8 h after surgery</li> <li>- Remove catheter 36 h after last dose</li> <li>- Resume therapy 12 h after catheter removed</li> </ul> </li> </ul> |
| Monitoring required        | No  | Yes   | No   |
| Food/drug interactions     | None reported   | Multiple  | None   |
| Immunogenicity             | Can induce immune-mediated platelet activation. Risk of HIT   | Low risk of HIT   | Low risk of HIT  |

HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist.

### Fondaparinux

Fondaparinux is a synthetic pentasaccharide that binds to antithrombin, producing a conformational change at the reactive site of antithrombin, to selectively inhibit factor Xa by mechanisms identical to LMWHs, but without affecting thrombin activity (fig. 2A).<sup>32</sup> Fondaparinux also inhibits free factor Xa, but not factor Xa bound to the prothrombinase complex.<sup>33</sup> It is administered by subcutaneous injection and has a longer half-life than LMWHs, requiring a once-daily dose (table 1).<sup>32</sup> The risk of HIT is relatively low.<sup>34</sup> Fondaparinux does not require routine coagulation monitoring, except in patients with renal dysfunction, because fondaparinux is primarily eliminated renally (table 1).<sup>33</sup> There are no currently available reversal agents for fondaparinux, although partial reversal has been described.<sup>35</sup>

### VKAs

VKAs, of which warfarin is the most frequently used, interfere with the posttranslational carboxylation of coagulation factors II, VII, IX, and X, and other coagulation proteins,

resulting in a reduced coagulant effect.<sup>36</sup> Warfarin has unpredictable pharmacodynamic, pharmacokinetic and pharmacogenetic properties, causing major variability in patients' dose responses (table 1).<sup>36</sup> Initiating VKA therapy requires frequent therapeutic monitoring and dose adjustments using the international normalized ratio (INR), based on the prothrombin time.<sup>36</sup> Administration of vitamin K is recommended to reverse a mildly increased INR. Prothrombin complex concentrates are recommended for reversal in cases of life-threatening bleeding or intracranial hemorrhage<sup>36,37</sup>; however, fresh frozen plasma is still used if prothrombin complex concentrates are not available. Off-label use of recombinant factor VIIa has also been reported to reverse the INR effect.

### The Use of Anticoagulants and Neuraxial Anesthesia

Anticoagulant use with neuraxial anesthesia, including spinal/epidural puncture, can increase the risk of epidural or



spinal hematoma, which can lead to permanent paralysis. The risk of epidural hematoma with neuraxial anesthesia is increased 15-fold with the use of anticoagulant therapy without appropriate precautions.<sup>38</sup> This risk can be further increased with the use of postoperative indwelling epidural catheters. It is critical, therefore, to ensure that anticoagulated patients under anesthesia are appropriately and correctly managed, particularly with the continuing development of new, potentially more potent anticoagulants. The risk of hematoma associated with a specific anticoagulant is difficult to accurately assess because the low incidence of hematoma (one epidural hematoma per 150,000 epidural injections)<sup>38</sup> means that prospective randomized trials are not possible.<sup>39</sup> It is difficult, therefore, to assess the best strategy to balance the risk of hematoma with effective thromboprophylaxis.<sup>38</sup> Several national guidelines have been developed based on case reports and the pharmacokinetic properties of the relevant agents,<sup>38,40</sup> and recommendations are therefore drug specific. Patient management is based on appropriate timing of needle placement and catheter removal relative to the timing of anticoagulant drug administration, to ensure that drug concentration is at its lowest.<sup>39</sup> Delaying the initiation of anticoagulation after surgery can further reduce the risk of hematoma.<sup>38</sup> With all anticoagulants, the risk of hematoma is increased with concomitant use of medications such as nonsteroidal antiinflammatory drugs, clopidogrel, or other anticoagulants, therefore, management of patients taking these medications requires caution. In addition, all patients undergoing neuraxial anesthesia should be monitored for signs of neurologic impairment to enable prompt intervention.<sup>38,39</sup>

### UFH

The consensus statement from the American Society of Regional Anesthesia and Pain Medicine (ASRA) on regional anesthesia in the anticoagulated patient bases its recommendations for UFH on the initial recommendations established 20 yr ago, supported by reviews of case series and case reports of spinal hematoma.<sup>39</sup> ASRA recommends that UFH administration be delayed for 1 h after needle placement. Indwelling neuraxial catheters should be removed 2–4 h after the last UFH dose, and the next dose should be given 1 h after catheter removal. Patients should be carefully monitored for any signs of hematoma (table 1).<sup>39</sup>

### LMWH

**Preoperative LMWH.** Pharmacokinetic studies of the LMWH enoxaparin demonstrated that after a single bolus administration of 40 mg, anti-Xa activity had nearly returned to baseline after 12 h (in patients with normal renal function).<sup>40</sup> To ensure that trough levels are achieved, ASRA recommends that needle placement should occur at least 10–12 h after the last dose of LMWH<sup>39</sup>; most European guidelines recommend a delay of at least 12 h, but a delay of 20 h is recommended by French guidelines.<sup>38</sup> ASRA recommends that needle placement occur at least 24 h after the last

dose if a higher dose of LMWH is used (such as 1 mg/kg enoxaparin every 12 h or 1.5 mg/kg daily).<sup>39</sup> Neuraxial techniques should be avoided in patients administered LMWH 2 h preoperatively, because needle placement would occur during peak anticoagulant activity (table 1).<sup>39</sup>

**Postoperative LMWH.** The management of anesthesia with postoperative LMWH is based on the dosing regimen used. Twice-daily dosing may be associated with an increased risk of spinal hematoma.<sup>39</sup> The ASRA guidelines recommend that the first dose be administered no earlier than 24 h postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed before initiation of LMWH therapy. If a continuous technique is selected, the epidural catheter may be left indwelling overnight and removed the following day, with the first dose of LMWH administered at least 2 h after catheter removal.<sup>39</sup> For once-per-day dosing, as used in the European Union (EU), the first postoperative LMWH dose should be administered 6–8 h postoperatively. The second postoperative dose should occur no sooner than 24 h after the first dose.<sup>39</sup> Indwelling neuraxial catheters may be safely maintained but the catheter should be removed a minimum of 10–12 h after the last dose of LMWH according to ASRA<sup>39</sup> (this recommendation differs between countries, as described previously). Subsequent dosing should occur a minimum of 2 h after catheter removal according to the ASRA guidelines,<sup>39</sup> but European guidelines recommend a 4–6 h delay.<sup>38</sup>

### Fondaparinux

It is recommended that fondaparinux be started between 6 and 8 h after the end of surgery.<sup>38</sup> Indwelling epidural catheters should not be removed until 36 h (at least two half-lives) after the previous dose, and the next dose should not be given until 12 h after catheter removal (a more convenient time point than that suggested by the pharmacokinetics of the drug). The 48-h window required between two injections of fondaparinux is achieved by skipping one injection.<sup>38</sup> In the EXPERT (Evaluation of ariXtra for the Prevention of vEnous thromboembolism in daily practice) study, this regimen was shown to allow safe catheter removal without affecting the thromboprophylaxis efficacy. In patients receiving 2.5 mg fondaparinux daily for 3–5 weeks after major orthopedic surgery, the rate of symptomatic VTE was similar in patients with and without catheters, and no neuraxial hematomas were reported.<sup>41</sup> Although the risk of spinal hematoma is unknown, spinal hematoma has been reported in association with the use of fondaparinux.<sup>39</sup> Patients receiving fondaparinux with neuraxial anesthesia and postoperative indwelling epidural catheters should be closely monitored for signs and symptoms of neurologic impairment (table 1).<sup>38</sup>

### VKAs

The anesthetic management of patients receiving warfarin, either as a long-term therapy or as thromboprophylaxis perioperatively, has been controversial. The ASRA consensus

statement bases its recommendations on drug pharmacology, the clinical relevance of vitamin K coagulation factor levels, and case reports of spinal hematoma.<sup>39</sup> For patients who require long-term anticoagulation, VKA therapy should ideally be stopped 4–5 days before surgery, and the INR should be measured before initiation of neuraxial block. For patients receiving a prophylactic dose of warfarin more than 24 h before surgery, INR measurements should be checked before initiating neuraxial anesthesia. Neuraxial catheters should be removed when the INR is less than 1.5 (table 1)<sup>39</sup>; this value was derived from studies that correlate hemostasis with clotting factor activity levels greater than 40%.<sup>39</sup>

## Reversing the Effects of Anticoagulation

Anticoagulation is associated with an increased risk of bleeding, particularly after surgery, and clinicians must consider the risks and benefits of therapy in individual patients. The risk of experiencing a bleeding event is related to the intensity of the anticoagulant effect and the length of therapy (VKAs), the dosage used (UFH and LMWH), and underlying patient characteristics.<sup>42</sup> Patients may also experience bleeding events as a result of overdose. In the event of a bleeding episode, agents that are able to reverse the effects of anticoagulation may be required. In addition, patients receiving anticoagulants may suffer a major trauma or require emergency surgery for which rapid reversal of the effects of anticoagulation will be required. UFH can be rapidly and completely neutralized with protamine sulfate; LMWHs can be partially neutralized by protamine sulfate.<sup>32</sup> For patients receiving VKA therapy with serious or life-threatening bleeding, the ACCP recommends infusion of vitamin K supplemented with either fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa (rFVIIa).<sup>36</sup>

## New Options for Thromboprophylaxis

Because of specific limitations of the currently available anticoagulant agents, there has been a long-standing need for more convenient, effective anticoagulant therapies for clinical management of VTE, especially in the era of minimizing hospital stay after surgery. Newer agents may have an important impact on perioperative and postoperative care and patient management. Most current anticoagulant agents require parenteral administration, whereas VKAs have a slow onset, marked variability in effect, and need frequent coagulation monitoring. By targeting specific components of the coagulation cascade, the new small-molecule anticoagulants in development should have a more predictable pharmacologic profile and dose response than untargeted agents, potentially eliminating the requirement for routine coagulation monitoring.<sup>43</sup>

Oral inhibitors of factor Xa and thrombin are among the newer agents currently in development or under consideration by North American regulatory agencies. Factor Xa is an attractive target as the rate-limiting factor in the generation and amplification of thrombin.<sup>44</sup> Thrombin also has a piv-

otal role in hemostasis, converting soluble fibrinogen to fibrin, activating factors V, VIII, and XI (which generate more thrombin), and activating platelets (fig. 1).<sup>45</sup> Although there is considerable debate regarding the best target for anticoagulation, both of these types of inhibitor have been extensively studied in large randomized clinical studies. One theory is that factor Xa inhibition may cause less bleeding than direct inhibition of thrombin because residual thrombin can still be activated by critical feedback processes.<sup>44</sup> Because the coagulation cascade is an amplification pathway, one molecule of factor Xa catalyzes the formation of almost 1,000 thrombin molecules.<sup>44</sup> There are several new parenteral and oral agents in various stages of development that directly or indirectly inhibit factor Xa or thrombin.

## New Anticoagulants and Neuraxial Anesthesia

As with the established anticoagulants, the management of patients with new anticoagulants and neuraxial anesthesia will be based on the pharmacokinetic properties of the anticoagulant. Needle or catheter placement and removal should be timed to take place when anticoagulant concentrations are at their lowest, and patients should be monitored closely for signs of hematoma in the initial days after catheter removal. Rosenthal *et al.*<sup>38</sup> suggest allowing at least two half-lives (for the specific anticoagulant) to pass before catheter removal, at which point only 25% of the drug remains active. Allowing a longer interval would only slightly reduce the drug concentration, because elimination slows after this point.<sup>38</sup> The risk of the residual anticoagulant activity and neuraxial hematoma needs to be weighed against the risk of VTE. They suggest that anticoagulation should be restarted after 8 h minus the time to reach maximum activity ( $T_{max}$ ), on the basis of the fact that it takes 8 h to establish a stable clot but allowing time for the peak of anticoagulation to be reached.<sup>38</sup> Although this approach does not guarantee extremely low anticoagulant levels over the entire time interval indicated, it is suggested that this is a reasonable compromise between the risk of bleeding and the risk of VTE.<sup>38</sup> In the following section, specific recommendations are outlined according to the manufacturers' instructions, where available, for managing each agent when used with neuraxial anesthesia.

## Factor Xa Inhibitors

### Indirect Factor Xa Inhibitors

**Idraparinux and Idaraparinux.** The synthetic pentasaccharide idraparinux is a chemically modified version of fondaparinux that inhibits factor Xa through binding to antithrombin, but its affinity for antithrombin is 34-fold greater than that of fondaparinux. Because of this high affinity, it has a half-life of ~80 h, making once-weekly dosing feasible.<sup>46,47</sup> However, because there is no antidote, this long half-life may be problematic if bleeding occurs or urgent surgery is required.<sup>47</sup> Idraparinux is administered subcutaneously and does not require routine coagulation monitor-

ing.<sup>47</sup> In patients with deep vein thrombosis, idraparinix demonstrated efficacy similar to that of standard therapy but was less efficacious than standard therapy in patients with PE.<sup>48</sup> Idraparinix was effective in preventing recurrent VTE for 6 months but increased the risk of major bleeding compared with standard therapy.<sup>49</sup> In the Amadeus trial, idraparinix demonstrated similar efficacy for the prevention of stroke in patients with atrial fibrillation but significantly increased the risk of bleeding compared with VKAs, and the study was discontinued.<sup>50</sup> A biotinylated version of idraparinix (idrabiotaparinix) has subsequently been developed that has a specific neutralizing agent; it also can be administered once per week.<sup>51</sup> There are no further trials planned with either idraparinix or idrabiotaparinix.

**Danaparoid Sodium.** Danaparoid sodium is a subcutaneous, low-molecular-weight heparinoid with a long half-life<sup>32,52</sup> that, like LMWH, requires antithrombin to inactivate factor Xa. Although approved for HIT in several countries other than the United States, it was initially approved to prevent postoperative VTE but is more expensive than LMWHs, so it is no longer marketed in this indication.<sup>32,52</sup> Danaparoid is seldom used.<sup>32,52</sup>

### Direct Factor Xa Inhibitors

**Rivaroxaban.** Rivaroxaban is an oral, direct factor Xa inhibitor with more than 10,000-fold greater selectivity for factor Xa than for other related serine proteases.<sup>53</sup> In contrast to LMWH and similar agents, rivaroxaban does not require antithrombin as a cofactor.<sup>54</sup> Direct factor Xa inhibitors, including rivaroxaban, can inhibit free factor Xa, clot-bound factor Xa, and factor Xa bound to the prothrombinase complex (fig. 2B),<sup>44,55</sup> unlike indirect factor Xa inhibitors, such as fondaparinux, which are unable to inhibit factor Xa within the prothrombinase complex. Rivaroxaban is also a non-heparin-like molecule that may be suitable for the management of patients with HIT.<sup>56</sup> It has an oral bioavailability of 80–100% (for a 10-mg dose),<sup>#</sup> and approximately two-thirds of the administered dose undergoes metabolic degradation in the liver.<sup>57</sup> Of this, half is excreted *via* the kidneys and half *via* the fecal route. The remaining third is eliminated as unchanged drug in the urine (table 2).<sup>57</sup>

Rivaroxaban has been approved in the EU, Canada, and several other countries for the prevention of VTE in adult patients after elective hip- or knee-replacement surgery, based on the results of the extensive phase III RECORD (REGulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) program. The program included more than 12,500 patients in four trials comparing once-daily rivaroxaban with either 40 mg enoxaparin once daily (the regimen approved in the EU) or 30 mg enoxaparin twice daily (a regimen approved in the

United States in patients undergoing total hip- or knee-replacement surgery). In all four trials, rivaroxaban therapy demonstrated superiority to the enoxaparin regimens tested for the prevention of VTE, without a significant increase in the rate of major bleeding (table 3).<sup>58–61</sup> In a pooled analysis of these studies, rivaroxaban regimens significantly reduced the incidence of the composite of symptomatic VTE and death compared with enoxaparin regimens.<sup>62</sup>

When used with neuraxial anesthesia for total hip- or knee-replacement surgery, an epidural catheter should not be removed earlier than 18 h after the last administration of rivaroxaban, and the next rivaroxaban dose should be administered no earlier than 6 h after the removal of the catheter (table 2).# Rivaroxaban is not recommended in patients undergoing total hip- or knee-replacement surgery who have creatinine clearance (CrCl) rates of <15 ml/min and may be used with caution in patients with CrCl of 15–29 ml/min. No dose adjustment is necessary in patients with mild (CrCl 50–80 ml/min) or moderate (CrCl 30–49 ml/min) renal impairment.# Rivaroxaban is contraindicated in patients undergoing hip- or knee-replacement surgery who have hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It may be used with caution in patients with cirrhosis who have moderate hepatic impairment (Child–Pugh B) if not associated with coagulopathy. No dose adjustment is necessary in patients with other hepatic diseases or those aged over 65 yr.# Rivaroxaban is metabolized *via* cytochrome P3A4 (CYP3A4), cytochrome P2J2, and cytochrome P450-independent mechanisms and is a substrate of the transporter proteins P-glycoprotein (P-gp) and the breast cancer resistance protein. Its use is therefore not recommended in patients undergoing total hip- or knee-replacement surgery who are receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole, and ritonavir.# Fluconazole can be coadministered with caution. Moderate inhibitors of CYP3A4 and P-gp (such as erythromycin), and strong inhibitors of either CYP3A4 or P-gp (such as clarithromycin) can be used. Strong CYP3A4 inducers (such as phenytoin, carbamazepine, and phenobarbital) should be coadministered with caution.# In studies in healthy subjects, no clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was coadministered with acetylsalicylic acid or clopidogrel, although an increase in bleeding time was observed with clopidogrel in some subjects.<sup>63,64</sup> Patients undergoing total hip or knee replacement who are receiving rivaroxaban can concomitantly receive nonsteroidal antiinflammatory drugs and platelet aggregation inhibitors, but care should be taken because of the increased risk of bleeding. Care should also be taken if patients are to receive other anticoagulants.# There is no antidote to reverse the anticoagulant effect of rivaroxaban, and standard methods should be used to control bleeding events should they occur.# Discontinuation or delaying the next dose may be sufficient, because rivaroxaban has a half-life of 7–11 h. Other strategies include mechanical

# Xarelto®. Summary of product characteristics—EU. Bayer HealthCare. Available at: [http://www.xarelto.com/html/downloads/Xarelto\\_Summary\\_of\\_Product\\_Characteristics\\_May2009.pdf](http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_May2009.pdf). Accessed March 29, 2010.

**Table 2.** Properties of the New Oral Anticoagulants for Potential Use in the Surgical Setting

|  | Apixaban                                      | Rivaroxaban  | Dabigatran  |
|--|---|--|---|
| Target   | Factor Xa                                     | Factor Xa  | Thrombin  |
| Bioavailability, %                             | 34–88*  | 80–100   | 6.5   |
| Half-life, h                                   | 8–11 with twice-daily dosing                  | 7–11   | 12–14 (healthy subjects)  |
| Dosing for thromboprophylaxis after THR or TKR | Twice daily†                                  | <ul style="list-style-type: none"> <li>Initiate (full dose) 6–10 h after surgery (provided hemostasis has been established)</li> <li>Once daily, fixed dose (10 mg)</li> </ul>   | <ul style="list-style-type: none"> <li>Initiate with half the daily dose (single 110-mg capsule) within 1–4 h of surgery; continue with full 220-mg dose (two 110-mg capsules) once daily thereafter</li> <li>Fixed dosing</li> </ul>   |
| Dosing in special populations after THR or TKR | —   | <ul style="list-style-type: none"> <li>CrCl &lt;15 ml/min: not recommended</li> <li>CrCl 15–29 ml/min: use with caution</li> <li>CrCl 30–49 ml/min: no dose adjustment</li> <li>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk: not recommended</li> <li>Cirrhotic patients with moderate hepatic impairment not associated with coagulopathy: use with caution</li> <li>Other hepatic diseases: no dose adjustment</li> <li>Age over 65 yr: no dose adjustment</li> <li>Approximately one-third excreted as unchanged active substance in urine</li> <li>Of the two-thirds metabolized, half is renally, and half is eliminated via hepatobiliary route in feces</li> </ul> | <ul style="list-style-type: none"> <li>CrCl &lt;30 ml/min: not recommended</li> <li>CrCl 30–50 ml/min: reduced dose (150 mg od [two 75-mg capsules])</li> <li>Hepatic impairment (elevated liver enzymes at &gt;2× ULN): not recommended</li> <li>Age over 75 yr: reduced dose (150 mg od [two 75-mg capsules])</li> </ul>  |
| Elimination                                    | Fecal, 56%; renal, ~25%                       | <ul style="list-style-type: none"> <li>Age over 65 yr: no dose adjustment</li> <li>Approximately one-third excreted as unchanged active substance in urine</li> <li>Of the two-thirds metabolized, half is renally, and half is eliminated via hepatobiliary route in feces</li> </ul>   | Renal (85% after i.v. administration)   |
| Management with anesthesia                     | No information available                      | Neuraxial anesthesia: epidural catheter should not be removed earlier than 18 h after the last dose; next dose no earlier than 6 h after catheter removal  | <ul style="list-style-type: none"> <li>Not recommended in patients undergoing anesthesia with postoperative indwelling epidural catheters</li> <li>First dose should occur a minimum of 2 h after catheter removal</li> </ul>   |
| Monitoring required                            | No  | No   | No  |
| Antidote available                             | No  | No   | No  |
| Drug interactions                              | Minimal, but no recommendations yet available | <ul style="list-style-type: none"> <li>Not recommended: Potent inhibitors of CYP3A4 or P-gp (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors)</li> <li>Use with caution: Fluconazole; strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital)</li> <li>Use with care: NSAIDs; PAIs; other anticoagulants</li> </ul>  | <ul style="list-style-type: none"> <li>Dose adjustment required: amiodarone (a P-gp inhibitor)</li> <li>Not recommended: quinidine; other anticoagulants; certain antiplatelet agents (GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, and sulfinpyrazone)</li> <li>Use with caution: Strong P-gp inhibitors (e.g. verapamil, clarithromycin); potent P-gp inducers (e.g. rifampicin, St John's wort)</li> <li>Use with care: NSAIDs</li> </ul> |
| Immunogenicity                                 | No information available                      | Not immunogenic for HIT antibodies   | No information available  |

\* Animal studies. † Not yet approved in any country.

CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; HIT = heparin-induced thrombocytopenia; HIV = human immunodeficiency virus; i.v. = intravenous; NSAID = non-steroidal anti-inflammatory drug; od = once daily; PAI = platelet aggregation inhibitor; P-gp = P-glycoprotein; THR = total hip replacement; TKR = total knee replacement; ULN = upper limit of normal.



**Table 3.** Phase III Trial Results for Dabigatran, Rivaroxaban, and Apixaban after Total Hip- or Knee-Replacement Surgery

|                                 |                               | Primary Efficacy Endpoint* |  | Major Bleeding† |  |
|---------------------------------|-------------------------------|----------------------------|--|-----------------|--|
|                                 | Duration of Therapy           | % (n/N)                    | p-Value for Difference from Enoxaparin | % (n/N)         | p-Value for Difference from Enoxaparin |
| Dabigatran                      |                               |                            |  |                 |  |
| RE-NOVATE (THR),<br>N = 3,494   | 28–35 days                    | —                          | —                                      | —               | —                                      |
| Dabigatran 220 mg od            | —                             | 6.0 (53/880)               | <0.0001                                | 2.0 (23/1,146)  | —                                      |
| Dabigatran 150 mg od            | —                             | 8.6 (75/874)               | <0.0001                                | 1.3 (15/1,163)  | —                                      |
| Enoxaparin 40 mg od             | —                             | 6.7 (60/897)               | —                                      | 1.6 (18/1,154)  | —                                      |
| RE-MOBILIZE (TKR),<br>N = 2,615 | 12–15 days                    | —                          | —                                      | —               | —                                      |
| Dabigatran 220 mg od            | —                             | 31.1 (188/604)             | 0.0234                                 | 0.6 (5/857)     | —                                      |
| Dabigatran 150 mg od            | —                             | 33.7 (219/649)             | 0.0009                                 | 0.6 (5/871)     | —                                      |
| Enoxaparin 30 mg bid            | —                             | 25.3 (163/643)             | —                                      | 1.4 (12/868)    | —                                      |
| RE-MODEL (TKR),<br>N = 2,101    | 6–10 days                     | —                          | —                                      | —               | —                                      |
| Dabigatran 220 mg od            | —                             | 36.4 (183/503)             | 0.0003                                 | 1.5 (10/679)    | —                                      |
| Dabigatran 150 mg od            | —                             | 40.5 (213/526)             | 0.017                                  | 1.3 (9/703)     | —                                      |
| Enoxaparin 40 mg od             | —                             | 37.7 (193/512)             | —                                      | 1.3 (9/694)     | —                                      |
| Rivaroxaban                     |                               |                            |  |                 |  |
| RECORD1 (THR),<br>N = 4,541     | 31–39 days                    | —                          | —                                      | —               | —                                      |
| Rivaroxaban 10 mg od            | —                             | 1.1 (18/1,595)             | <0.001                                 | 0.3 (6/2,209)   | 0.18                                   |
| Enoxaparin 40 mg od             | —                             | 3.7 (58/1,558)             | —                                      | 0.1 (2/2,224)   | —                                      |
| RECORD2 (THR),<br>N = 2,509     | —                             | —                          | —                                      | —               | —                                      |
| Rivaroxaban 10 mg od            | 31–39 days                    | 2.0 (17/864)               | <0.0001                                | <0.1 (1/1,228)  | —                                      |
| Enoxaparin 40 mg od             | 10–14 days                    | 9.3 (81/869)               | —                                      | <0.1 (1/1,229)  | —                                      |
|                                 | (with placebo for 31–39 days) |                            |  |                 |  |
| RECORD3 (TKR),<br>N = 2,531     | 10–14 days                    | —                          | —                                      | —               | —                                      |
| Rivaroxaban 10 mg od            | —                             | 9.6 (79/824)               | <0.001                                 | 0.6 (7/1,220)   | 0.77                                   |
| Enoxaparin 40 mg od             | —                             | 18.9 (166/878)             | —                                      | 0.5 (6/1,239)   | —                                      |
| RECORD4 (TKR),<br>N = 3,148     | 10–14 days                    | —                          | —                                      | —               | —                                      |
| Rivaroxaban 10 mg od            | —                             | 6.9 (67/965)               | 0.0118                                 | 0.7 (10/1,526)  | 0.1096                                 |
| Enoxaparin 30 mg bid            | —                             | 10.1 (97/959)              | —                                      | 0.3 (4/1,508)   | —                                      |
| Apixaban                        |                               |                            |  |                 |  |
| ADVANCE-1 (TKR),<br>N = 3,195   | 10–14 days                    | —                          | —                                      | —               | —                                      |
| Apixaban 2.5 mg bid             | —                             | 9.0 (104/1,157)            | 0.06                                   | 0.7 (11/1,596)  | 0.05                                   |
| Enoxaparin 30 mg bid            | —                             | 8.8 (100/1,130)            | —                                      | 1.4 (22/1,588)  | —                                      |
| ADVANCE-2 (TKR),<br>N = 3,057   | 10–14 days                    | —                          | —                                      | —               | —                                      |
| Apixaban 2.5 mg bid             | —                             | 15.1 (147/976)             | <0.001                                 | —               | —                                      |
| Enoxaparin 40 mg od             | —                             | 24.4 (243/997)             | —                                      | —               | —                                      |

\* Composite of any deep vein thrombosis, pulmonary embolism, and death from any cause. † Different definitions of major bleeding were used in each study program.

bid = twice daily; n = number of patients in which the particular outcome occurred; N = total number of patients in the group; od = once daily; RECORD = REgulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism; THR = total hip replacement; TKR = total knee replacement.

compression, surgical interventions, fluid replacement and hemodynamic support, or transfusions. If these methods are unable to control a bleeding episode, rFVIIa may be considered, but this recommendation is based on data from preclinical studies. In these studies, rFVIIa partially reversed the

anticoagulant effects of rivaroxaban in *in vitro* and primate models.<sup>65,66</sup> The activated prothrombin complex concentrate factor VIII inhibitor bypassing activity (FEIBA) has also demonstrated ability to partially neutralize the effect of high-dose rivaroxaban in studies in baboons and rats.<sup>66,67</sup> The

prothrombin complex concentrate Beriplex® (CSL Behring, Marburg, Germany) was also able to reverse effects of high-dose rivaroxaban in rats, and plasma-derived and recombinant factor Xa have also demonstrated potential as antidotes for factor Xa inhibitors.<sup>68–70</sup> There is, however, no clinical data for the use of these agents in patients receiving rivaroxaban. Although routine monitoring is not required, several clotting assays have been investigated for their potential to monitor levels of rivaroxaban should this be required in the event of an overdose, for example. These preliminary tests indicate that prothrombin time (using a rivaroxaban calibrator), dilute Russell's viper venom test, one-step PiCT® (Pentapharm, Basel, Switzerland), and HepTest® (American Diagnostica, Stamford, CT) assays seem to be the most useful.<sup>71</sup> However, commercially available prothrombin time tests should not be used for factor Xa inhibitors; for rivaroxaban, prothrombin time assay results should be expressed in rivaroxaban plasma concentration in micrograms per milliliter with calibrated plasma concentrations.<sup>71</sup> Factor Xa chromogenic assays may also be a useful measure of rivaroxaban activity in human plasma, using rivaroxaban as a calibrator.<sup>71,72</sup>

Rivaroxaban is also under investigation for the treatment of VTE and the prevention of recurrent VTE in the phase III EINSTEIN program (table 4). The EINSTEIN Extension study assessed the relative efficacy and safety of rivaroxaban *versus* placebo in patients who had completed 6 or 12 months of anticoagulant treatment for an acute episode of VTE. Rivaroxaban (20 mg once daily) was associated with an 82% relative risk reduction in the recurrence of VTE and a low incidence of major bleeding (0.7% in the rivaroxaban group, 0% with placebo).<sup>\*\*</sup> A phase II study of rivaroxaban in patients with acute coronary syndrome (ACS) identified tolerable doses, which will be investigated in phase III trials.<sup>73</sup> Other ongoing studies are shown in table 4. Overall, rivaroxaban represents one of the first new oral anticoagulant agents to be approved in different markets.

**Apixaban.** Apixaban is another oral, direct factor Xa inhibitor with good bioavailability, low potential for drug–drug interactions, and a half-life of approximately 12 h (table 2).<sup>74</sup> It has a high affinity for factor Xa and inhibits free factor Xa, factor Xa in the prothrombinase complex, and factor Xa bound to platelets (fig. 2B).<sup>74,75</sup> In animal studies, apixaban has a bioavailability of 34–88%.<sup>75</sup> In humans, it is eliminated *via* multiple pathways, predominantly *via* the fecal route (56%), with 25–29% of the recovered dose eliminated *via* urinary excretion.<sup>74</sup> Concomitant administration of apixaban and platelet inhibitors has only been studied in animal arterial thrombosis models. Apixaban in combination with acetylsalicylic acid or acetylsalicylic acid plus clopi-

dogrel demonstrated enhanced antithrombotic efficacy without excessive increases in bleeding time and will be investigated further in clinical trials.<sup>76</sup> Preliminary *in vitro* studies indicate that metabolic drug–drug interaction potential between apixaban and coadministered cytochrome P450 substrates or inhibitors is minimal, indicating that dose adjustments may not be required.<sup>77</sup> Although routine monitoring is not required, there are limited data available regarding effective methods of monitoring the effect of apixaban should this be required. An anti-Xa assay has demonstrated potential for predicting apixaban plasma concentration,<sup>78</sup> but apixaban produces only modest changes in INR and activated partial thromboplastin time, so these tests are not thought to be useful for monitoring.<sup>75</sup> There is no specific antidote for apixaban, and there is currently no information available on studies of potential reversal agents, except for preclinical studies of plasma-derived and recombinant factor Xa, which showed dose-dependent reversal of the anticoagulant effect of apixaban.<sup>69,70</sup>

Apixaban, administered twice daily, has been evaluated for the prevention of VTE after total knee-replacement surgery in two phase III studies. In the ADVANCE-1 study, apixaban failed to meet the noninferiority criteria compared with 30 mg enoxaparin twice daily for the prevention of VTE. However, apixaban was associated with lower rates of clinically relevant bleeding and had an adverse event profile similar to that of enoxaparin (table 3).<sup>79</sup> In ADVANCE-2, apixaban was more effective than 40 mg enoxaparin once daily for the prevention of VTE and was associated with a lower risk of major and clinically relevant bleeding (table 3).<sup>80</sup> ADVANCE-3 is ongoing and will compare apixaban with 40 mg enoxaparin once daily after total hip-replacement surgery (table 4). In a phase II placebo-controlled study, apixaban was evaluated for the prevention of acute ischemic and safety events in patients with ACS on antiplatelet therapy (AP-PRASE). Apixaban for 6 months was associated with a dose-related increase in major or clinically relevant nonmajor bleeding and lower rates of ischemic events compared with placebo. The two higher-dose apixaban arms were discontinued because of excess total bleeding.<sup>81</sup> Ongoing clinical trials of apixaban are shown in table 4.

**Other Direct Factor Xa Inhibitors under Investigation.** Several other direct factor Xa inhibitors have been studied, including YM150, which has completed studies in patients undergoing total hip replacement (ONYX and ONYX-2),<sup>82,83</sup> and phase II studies evaluating the efficacy and safety of once- and twice-daily dosing after knee replacement (PEARL and PEARL-1; table 4). Further studies are currently ongoing (table 4). Another oral, direct factor Xa inhibitor in phase II/phase III development is DU-176b (edoxaban), which inhibits both free and prothrombinase-bound factor Xa. DU-176b reduced the incidence of VTE after total knee replacement without increasing the risk of major or clinically relevant bleeding. It is noteworthy that this is the only placebo-controlled study conducted with one of the newer oral anticoagulants, and the rate of major bleeding in the placebo

<sup>\*\*</sup> Buller HR, on behalf of the Einstein investigators: Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism. The Einstein-Extension study. December 8, 2009. Available at: <http://ash.confex.com/ash/2009/webprogram/Paper25669.html>. Accessed January 11, 2010.

**Table 4.** Key Ongoing Clinical Trials of New Anticoagulant Agents\*

| Trial Name   | Purpose of Investigation  |
|--|---|
| Dabigatran etexilate<br>RE-NOVATE II   | Dabigatran etexilate for extended thromboprophylaxis compared with enoxaparin after THR (NCT00657150)   |
| RE-MEDY  | Placebo-controlled trial of long-term therapy with dabigatran etexilate for the prevention of recurrent VTE (NCT00329238)   |
| RE-COVER, RE-COVER II  | Dabigatran etexilate compared with warfarin for the 6-month treatment of acute symptomatic VTE (NCT00680186)  |
| RE-SONATE  | Dabigatran etexilate in the long-term prevention of recurrent symptomatic VTE (NCT00558259)   |
| RELY-ABLE  | Long-term safety of dabigatran etexilate for the prevention of stroke in patients with AF (NCT00808067)   |
| Rivaroxaban<br>EINSTEIN PE   | Rivaroxaban compared with enoxaparin plus a VKA for 3, 6, or 12 months' treatment in patients with confirmed acute symptomatic PE with or without symptomatic DVT (NCT00439777) |
| EINSTEIN DVT   | Rivaroxaban compared with enoxaparin plus a VKA for 3, 6, or 12 months' treatment in patients with confirmed acute symptomatic DVT without symptomatic PE (NCT00440193)         |
| ROCKET AF (Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation)  | Rivaroxaban compared with warfarin for the prevention of stroke in patients with AF (NCT00403767)   |
| ATLAS ACS TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51) | Rivaroxaban in addition to ASA with/without thienopyridine therapy to reduce the risk of cardiovascular events in patients with ACS (NCT00809965)                               |
| MAGELLAN (Multicenter, rAndomized, parallel Group Efficacy superiority study in hospitalized medically ill patients comparing rivaroxaban with enoxaparin)   | Rivaroxaban compared with enoxaparin for the prevention of VTE in hospitalized medically ill patients (NCT00571649)   |
| Apixaban<br>ARISTOTLE (Apixaban for Reduction In STroke and Other Thromboembolic Events in atrial fibrillation)<br>AVERROES  | Apixaban compared with warfarin for the prevention of stroke in patients with AF (NCT00412984)  |
|  | Apixaban compared with antiplatelet therapy for the prevention of stroke prevention in patients with AF unable to take warfarin (NCT00496769)                                   |
| ADOPT  | Apixaban compared with enoxaparin for the prevention of VTE in hospitalized medically ill patients (NCT00457002).   |
| AMPLIFY  | Apixaban compared with enoxaparin plus a VKA for the treatment and secondary prevention of VTE (NCT00643201)  |
| ADVANCE-3  | Apixaban compared with enoxaparin 40 mg once daily for the prevention of VTE after THR  |
| YM150<br>PEARL, PEARL-1  | YM150 compared with enoxaparin for the prevention of VTE in patients undergoing elective TKR (NCT00408239, NCT00595426)   |
| ONYX-3   | YM150 compared with enoxaparin in subjects undergoing THR (NCT00902928)   |
| OPAL-2   | Safety of YM150 compared with warfarin in patients with AF (NCT00938730)  |
| n.a.   | YM150 for the prevention of VTE in patients undergoing hip fracture surgery or surgery in the lower extremities (NCT00937911)   |
| n.a.   | YM150 compared with mechanical prophylaxis for the prevention of VTE in patients undergoing major abdominal surgery (NCT00942435)   |

(continued)

Table 4. Continued

| Trial Name                 | Purpose of Investigation  |
|----------------------------|---|
| DU-176b (edoxaban)<br>n.a. | DU-176b compared with dalteparin for the prevention of VTE in patients undergoing THR (NCT00398216)                                   |
| n.a.                       | DU-176b for the prevention of VTE in patients undergoing THR (NCT00107900)  |
| n.a.                       | DU-176b compared with warfarin for the prevention of stroke in patients with AF (NCT00806624, NCT00781391, NCT00504556)               |
| Betrixaban<br>EXPLORE-Xa   | Betrixaban compared with warfarin for the prevention of stroke in patients with AF (NCT00742859)                                      |
| Otamixaban<br>SEPIA-ACS1   | Otamixaban compared with unfractionated heparin and eptifibatide in patients with non-ST elevation ACS (NCT00317395)                  |
| Odiparcil<br>n.a.          | Odiparcil for the prevention of VTE after TKR (NCT00041509)   |
| n.a.                       | Pharmacokinetic/pharmacodynamic study of odiparcil with ASA in patients with AF with low or intermediate risk of stroke (NCT00240643) |

\* <http://clinicaltrials.gov>. Accessed 18 April 2010.

ACS = acute coronary syndrome; AF = atrial fibrillation; ASA = acetylsalicylic acid; DVT = deep vein thrombosis; n.a. = not applicable; PE = pulmonary embolism; THR = total hip replacement; TKR = total knee replacement; VKA = vitamin K antagonist; VTE = venous thromboembolism.

group was higher than the rate seen with a 5-mg dose of DU-176b.<sup>84</sup> Two studies evaluating DU-176b for the prevention of VTE after hip-replacement surgery have been completed, but no data are currently available (table 4). A dose-finding study in patients with atrial fibrillation found two doses of DU-176b with safety profiles similar to standard therapy,<sup>85</sup> and additional efficacy and safety studies are ongoing (table 4).

An additional oral, direct factor Xa inhibitor, betrixaban, is also in phase II development and has been evaluated after total knee replacement in patients in the United States and Canada.<sup>86</sup> Additional studies include the EXPLORE-Xa study, which will compare the efficacy and safety of three doses of betrixaban with warfarin for the prevention of stroke in patients with atrial fibrillation (table 4). Eribaxaban (PD0348292) has been evaluated in patients undergoing total knee replacement and demonstrated a significant dose response for efficacy, and a trend for an increase in bleeding, although this was not significant.<sup>87</sup> Otamixaban is another noncompetitive, direct inhibitor of factor Xa that is given parenterally and has a half-life of 1.5–2 h.<sup>88,89</sup> It has been evaluated in a phase II dose-ranging study of patients undergoing percutaneous coronary intervention (PCI), in which it demonstrated a positive risk–benefit profile compared with UFH.<sup>89</sup> Further studies, such as the SEPIA-ACS1 study (table 4), will help to determine the potential role of otamixa-

ban in ACS; no studies of this agent in the postoperative setting are currently under way.

### Direct Thrombin Inhibitors

**Ximelagatran.** Ximelagatran, a prodrug of the active metabolite melagatran, is an oral, direct thrombin inhibitor.<sup>43</sup> Initially approved and marketed in the EU for the prevention of VTE after total hip- and knee-replacement surgery in 2004, it also demonstrated potential for preventing thromboembolic events after myocardial infarction and in patients with atrial fibrillation.<sup>90–94</sup> However, it was withdrawn from the market in 2006 because of concerns over potential liver toxicity. Ximelagatran provided proof of principle that direct inhibition of thrombin was an effective mode of action for new anticoagulants.

**Dabigatran Etxilate.** Dabigatran etexilate is an oral, direct thrombin inhibitor (fig. 2B) in advanced clinical development, with a rapid onset of action, no reported drug or food interactions, and no requirement for routine coagulation monitoring (table 2).<sup>95,96</sup> Dabigatran has a half-life of 12–14 h (in healthy subjects) and a bioavailability of 6.5%.<sup>††</sup> Unchanged dabigatran is predominantly excreted *via* the kidneys, with approximately 80% of an intravenous dose excreted unchanged in the urine. Dabigatran has been approved in the EU, Canada, and several other countries for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip- or knee-replacement surgery. In this indication, it is not recommended for use in patients with severe renal impairment, or hepatic impairment (increased liver enzymes at more than

<sup>††</sup> Pradaxa® prescribing information. Boehringer-Ingelheim. Available at: [http://www.pradaxa.com/Include/media/pdf/Pradaxa\\_SPC\\_EMEA.pdf](http://www.pradaxa.com/Include/media/pdf/Pradaxa_SPC_EMEA.pdf). Accessed March 29, 2010.



two times the upper limit of the normal range). A reduced dose is recommended in patients with moderate renal impairment (CrCl 30–50 ml/min) or aged more than 75 yr.<sup>††</sup> The cytochrome P450 system has a limited role in the metabolism of dabigatran; therefore, drugs metabolized by this system have low potential for clinically relevant interactions and are not contraindicated.<sup>††</sup> Dabigatran is a substrate of P-gp, so when used with amiodarone (a P-gp inhibitor) in patients undergoing total hip- or knee-replacement surgery, the dabigatran dose should be reduced to 150 mg once daily.<sup>††</sup> The P-gp inhibitor quinidine is contraindicated, and strong P-gp inhibitors (such as verapamil and clarithromycin) should be coadministered with caution. Caution is also advised for concomitant use of potent P-gp inducers such as rifampicin or St. John's wort. No clinically relevant interaction between digoxin (a substrate of P-gp) and dabigatran was observed in studies in healthy subjects, and digoxin is not contraindicated.<sup>††</sup> Although delayed absorption of dabigatran was reported when coadministered with proton pump inhibitors, no effect on bleeding or efficacy was observed in clinical trials.<sup>††</sup> Dabigatran is not recommended for concomitant use with other anticoagulants and certain antiplatelet agents (GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, and sulfapyrazone).<sup>††</sup> In phase III trials in patients undergoing total hip- or knee-replacement surgery, concomitant use with acetylsalicylic acid and nonsteroidal antiinflammatory drugs demonstrated a safety profile similar to that of enoxaparin, a standard of care,<sup>97</sup> but it is advised to monitor patients receiving dabigatran with nonsteroidal antiinflammatory drugs closely for signs of bleeding.<sup>††</sup> Dabigatran is not recommended in patients undergoing anesthesia with postoperative indwelling epidural catheters for total hip- or knee-replacement surgery. Administration of the first dose should occur a minimum of 2 h after the catheter is removed, and patients should be observed for neurologic signs and symptoms.<sup>98</sup>

There is no specific antidote to reverse the effect of dabigatran.<sup>††</sup> *In vitro* studies showed that rFVIIa is not able to reverse the effects of thrombin inhibitors,<sup>65</sup> but there is limited information available regarding the effects of other potential reversal agents. Routine coagulation monitoring is not required, and there are difficulties in measuring the anticoagulant effect of dabigatran using standard clotting assays, should this be needed. The effect on activated partial thromboplastin time is not dose dependent, and the sensitivity of INR assays is too low (as for all direct thrombin inhibitors). The thrombin time assay responds in a linear fashion, but lacks standardization and may be too sensitive for clinically relevant plasma concentrations. Ecarin clotting time seems to be the most accurate assay<sup>95</sup> but is not widely available. In the phase III clinical program, dabigatran etexilate administered once daily demonstrated efficacy and safety similar to that of 40 mg enoxaparin once daily for the prevention of VTE after total hip- or knee-replacement surgery (RE-MODEL, RE-NOVATE; table 3).<sup>99,100</sup> However, compared with the North American enoxaparin regimen of

30 mg twice daily, dabigatran failed to meet the noninferiority criteria for efficacy (RE-MOBILIZE; table 3).<sup>101</sup> It has demonstrated efficacy superior to that of dose-adjusted warfarin for the prevention of stroke in patients with atrial fibrillation, with a similar rate of major bleeding (RE-LY).<sup>102</sup> Dabigatran 150 mg twice daily demonstrated noninferiority to dose-adjusted warfarin (INR 2.0–3.0) for the 6-month treatment of acute symptomatic VTE (RE-COVER).<sup>103</sup> An additional study will evaluate further the efficacy and safety of dabigatran compared with warfarin for the 6-month treatment of acute symptomatic VTE (RE-COVER II; table 4). Other ongoing clinical studies are listed in table 4.

**Parenteral Agents.** Bivalirudin is a parenteral, bivalent direct thrombin inhibitor that, unlike heparin, inhibits both free and fibrin-bound thrombin and has low immunogenic potential.<sup>104</sup> It is an oligopeptide of hirudin, and its affinity for thrombin is intermediate between hirudin and argatroban (see paragraphs 3–5 of this section).<sup>104</sup> It has a rapid onset of action and is predominantly metabolized *via* proteolysis with subsequent renal excretion.<sup>104</sup> Bivalirudin is approved for use in patients with unstable angina who are undergoing percutaneous transluminal coronary angioplasty or for the treatment of patients with, or at risk for, HIT or HIT and thrombosis syndrome undergoing PCI. It is also indicated for PCI with provisional use of glycoprotein IIb/IIIa antagonist therapy.<sup>104</sup> In these indications, bivalirudin is intended for concomitant use with acetylsalicylic acid.<sup>105</sup> In patients with moderate- or high-risk ACS undergoing invasive treatment with glycoprotein IIb/IIIa inhibitors, bivalirudin was associated with similar rates of ischemia and significantly lower rates of bleeding compared with heparin.<sup>106</sup> In patients with ST-elevation myocardial infarction undergoing primary PCI, anticoagulation with bivalirudin alone significantly reduced 30-day rates of major bleeding and net adverse clinical events (major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke) compared with heparin plus glycoprotein IIb/IIIa inhibitors.<sup>107,108</sup>

Bivalirudin is the most extensively studied agent in patients requiring cardiac surgery who are HIT positive,<sup>109–111</sup> although it is not formally approved in this setting. Prospective studies have compared bivalirudin with heparin in patients without HIT who are undergoing cardiac surgery with or without cardiopulmonary bypass.<sup>109,112–114</sup> Bivalirudin dosing for off-pump cardiac surgery is similar to that used in PCI, as listed in table 5. Standard activated clotting times are used to monitor its anticoagulant effects.

Lepirudin and desirudin are recombinant hirudins, synthetic analogs of hirudin manufactured by recombinant DNA technology. Lepirudin is approved for use in patients with HIT and associated thromboembolic disease to prevent further thromboembolic complications.<sup>26,115</sup> Lepirudin was initially reported for cardiac surgery and cardiopulmonary bypass; however, bleeding was a major problem.<sup>116–118</sup> HIT patients receiving lepirudin generate antibodies and require close monitoring (using activated partial thromboplastin

**Table 5.** Bivalirudin Dosing in Cardiac Surgery

|                                | Percutaneous Coronary Intervention <sup>104</sup> | Off Pump <sup>110,112,113</sup>    | On Pump <sup>111,114</sup>  |
|--------------------------------|---|------------------------------------|---|
| Initial bolus dose, mg/kg i.v. | 0.75  | 0.75                               | 1.0 (Priming dose of 50 mg added to the priming solution of the cardiopulmonary bypass reservoir) |
| Initial infusion rate, mg/kg/h | 1.75  | 1.75                               | 2.5   |
| Target ACT, s                  | —   | >300                               | 2.5× baseline   |
| Additional bolus dose, mg/kg   | 0.3   | 0.1–0.5 or increased infusion rate | 0.1–0.5   |

ACT = activated clotting time; i.v. = intravenous.

time) to avoid bleeding complications.<sup>119</sup> In patients with renal dysfunction, the drug may have a prolonged half-life.<sup>120</sup> No agents are currently available for reversing these direct thrombin inhibitors.

Desirudin (recombinant hirudin) is approved for use in the EU and now in the United States for the prevention of VTE after total hip- or knee-replacement surgery as a twice-daily subcutaneous dose, with the first dose given before surgery.<sup>121</sup> It reduced the risk of VTE after total hip replacement compared with enoxaparin, with a bleeding risk similar to that of enoxaparin despite the administration of desirudin immediately before surgery (compared with enoxaparin administration the night before),<sup>122,123</sup> and has demonstrated favorable efficacy and safety compared with heparin in patients with stable angina who are undergoing percutaneous transluminal coronary angioplasty.<sup>124</sup> It has also shown potential for the prevention of myocardial infarction in patients with ACS.<sup>125</sup> Antigenicity and anaphylaxis are also reported, although the risk of hypersensitivity to desirudin seems to be relatively low. Because desirudin is primarily eliminated by the kidneys, patients with moderate or mild-to-moderate renal impairment, and those receiving concomitant oral anticoagulant therapy, require monitoring using activated partial thromboplastin time.<sup>121</sup>

Argatroban is an injectable, synthetic, univalent direct thrombin inhibitor indicated for prophylaxis or treatment of thrombosis in patients with or at risk for HIT who are undergoing PCI.<sup>126–129</sup> Patients with HIT are likely to have reduced renal function; a potential advantage of argatroban is that, unlike bivalirudin and lepirudin, it is hepatically eliminated, so no dose adjustments are required in patients with renal impairment.<sup>130</sup> Because lepirudin is renally eliminated and bivalirudin is partially (approximately 20%) renally eliminated,<sup>104</sup> their use may require dose adjustment in renally impaired patients to avoid accumulation. In addition, unlike the use of lepirudin,<sup>119</sup> no antibodies that alter the anticoagulant activity of argatroban have been detected after prolonged or repeated use of argatroban.<sup>131</sup> Monitoring of argatroban is with the use of activated partial thromboplastin time, with a therapeutic goal of 1.5–3.0 times baseline values. The context-sensitive half-life of argatroban is 46 min, and no reversal agents are currently available.<sup>132</sup>

### Other Novel Agents in Early-phase Development

Odiparcil is an oral, indirect thrombin inhibitor in phase II development that exerts its anticoagulant effect through activation of antithrombin II (heparin cofactor II), a natural anticoagulant.<sup>133</sup> A study investigating odiparcil for the prevention of thromboembolism after total knee replacement has recently been completed (TEMPEST [ThromboEMbolism Prevention Efficacy and Safety Trial]); other ongoing trials are listed in table 4.

RB006 is a direct factor IXa inhibitor that is currently in early development as part of the REG1 anticoagulation system, which also comprises its antidote, RB007.<sup>134</sup> RB006 elicits its anticoagulant effect by selectively inhibiting the factor VIIIa/IXa-catalyzed activation of factor X.<sup>134</sup> It has demonstrated anticoagulant and antithrombotic activity in preclinical studies, and phase II dose-ranging studies are currently being conducted. A safety study of the REG1 anticoagulation system has recently been completed in which it was compared with UFH in subjects undergoing elective PCI after pretreatment with clopidogrel and acetylsalicylic acid.<sup>135</sup> A phase II comparison with heparin in subjects with ACS (RADAR), is currently ongoing. TTP889 is an oral inhibitor of factor IX in phase II clinical development that demonstrated antithrombotic potential in early studies. However, in a recent exploratory study in hip fracture patients, TTP889 started after 5–9 days of standard VTE prophylaxis was not effective in reducing thromboembolism compared with placebo.<sup>136</sup> Further studies of different doses and in different indications are warranted to assess the full potential of this agent.

Recombinant human soluble thrombomodulin (ART-123) is composed of the active extracellular domain of thrombomodulin, a thrombin receptor on the endothelial cell surface. It binds to thrombin to inactivate coagulation, and the thrombin–ART-123 complex activates protein C to produce activated protein C. Activated protein C, in the presence of protein S, inactivates factor VIIIa and factor Va, inhibiting further thrombin formation.<sup>137</sup> In a dose-ranging study in patients undergoing hip replacement surgery, ART-123 demonstrated efficacy for the prevention of VTE,<sup>137</sup> but further clinical studies are required to determine its potential for VTE prevention. It has also demonstrated potential in the

treatment of patients with disseminated intravascular coagulation associated with hematologic malignancy or infection compared with heparin, an established treatment method.<sup>138</sup>

SR123781A is the first synthetic hexadecasaccharide that inhibits both factor Xa and thrombin *via* antithrombin binding without binding to PF4.<sup>139</sup> It therefore maintains all the antithrombotic properties of heparin without the risk of developing HIT. It is an injectable agent and has demonstrated antithrombotic activity in preclinical studies.<sup>140</sup> In a dose-ranging study (DRIVE [Dose Ranging Study in Elective Total Hip Replacement Surgery]) in patients undergoing total hip replacement, a statistically significant dose–response effect was observed with SR123781A for both efficacy and safety outcomes.<sup>141</sup> A phase II study (SHINE) in patients with ACS has been completed, but no results are available to date.

## Summary

Clinicians need to be aware of new and emerging anticoagulants in development that have the potential to improve the efficacy, safety, and convenience of perioperative and postoperative anticoagulant management. The extent to which new anticoagulants will be applied into therapeutic algorithms will depend on the balance between efficacy and safety, the ease of administration and management, as well as pharmacoeconomic considerations. The new oral agents will potentially be more convenient to use in the perioperative and postoperative periods compared with the established injectable agents, helping to improve adherence to the guideline recommendations, particularly after hospital discharge. Because the new agents do not require routine coagulation monitoring, they carry an important practical advantage over warfarin and other VKAs that require frequent INR testing. The new agents have more predictable dose responses, fewer interactions with other drugs and food, and will not require dose adjustments based on age, weight, or renal function. Of the newer oral drugs, the agents most advanced in clinical development are the direct factor Xa inhibitors rivaroxaban and apixaban and the direct thrombin inhibitor dabigatran etexilate. Rivaroxaban and dabigatran are approved in the EU for the prevention of VTE in adult patients undergoing elective total hip- or knee-replacement surgery but are not approved in the United States for any indication. Apixaban is not yet approved in any country for any indication. These agents have been evaluated in the postoperative setting in patients undergoing total hip- or knee-replacement surgery, with promising results, and it remains to be seen whether these results will translate into other surgical settings. The impact of the new agents will be influenced by the balance between efficacy and safety, improved convenience for patient and physician, and any potential cost-effectiveness benefits.

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## ANESTHESIOLOGY REFLECTIONS

### Grandfather Crawford Long, M.D.



To my friend and physician, Dr. Charles Scott Venable,  
from  
Maude Long, grand-daughter of Dr. Crawford W. Long -  
January 25, 1935

In Jefferson, Georgia, on March 30, 1842, Crawford W. Long, M.D. (1815-1878), etherized James M. Venable to remove a neck tumor. In the Wood Library-Museum, a photograph of an oil portrait honoring Long is mat-inscribed to another Venable: "To my friend and physician, Dr. Charles Scott Venable, from Maude Long, grand-daughter of Dr. Crawford W. Long—January 25, 1935." As early as 1907, Dr. Venable had written about the safety of Crawford Long's anesthetic in an article titled "The Use of Adrenalin during Ether Anesthesia." (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at [www.anesthesiology.org](http://www.anesthesiology.org).)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. [UJYC@aol.com](mailto:UJYC@aol.com).