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## Issues in Venous Thromboembolism

Patient Safety

Bridging Therapy

Cancer-Associated Thrombosis

Thromboprophylaxis in High-Risk Patients

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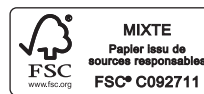
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### Current Issues in Anticoagulation

Hector Baillie MD



#### About the Author

Hector Baillie is a specialist in complex adult medicine in Nanaimo, British Columbia, and the editor-in-chief of *Canadian Journal of General Internal Medicine*.

Internists have long been asked to comment on disorders of blood coagulation. Whether in the prevention of deep vein thrombosis in our sick in-patients or minimizing the risk of cardioembolic stroke in atrial fibrillation, we have to deal with issues of blood clotting on a daily basis. We have to be familiar with current and newly minted antithrombotic and anticoagulant medications, and know when and how to use them. This supplement to *Canadian Journal of General Internal Medicine* affords a valuable overview of four areas of antithrombosis.

Anne McLeod and William Geerts discuss the safety of anticoagulation, particularly newer agents, and the importance of prescribing these valuable drugs in the right clinical setting: “Fewer than half of general surgical patients and even a smaller proportion of medical patients receive appropriate thromboprophylaxis.” We can all learn how to discharge a patient with greater safety, by giving written instructions and by implementing reliable monitoring strategies.

Charles Mahan and Alex Spyropoulos focus on a common issue: how to bridge between long-term anticoagulation and surgery for moderate and high-risk patients. By understanding the kinetics of drug action (particularly drug half-lives), we can advise our surgical colleagues when to stop and restart platelet and coagulation inhibitors.

Algorithms to stratify risk (e.g., CHADS-VASc and HAS-BLED) are discussed, and a practical approach to bridging outlined. The future will involve more specific agents that promise efficacy, ease of use, and lower bleeding risk.

“The natural history of VTE in patients with cancer is more aggressive and unpredictable than in patients without cancer”; the prevention and treatment of VTE in our cancer patients has its own challenges, as are clearly outlined by Agnes Lee. Standard and novel agents are described, although the latter are largely investigational. The CLOT trial, among others, is reviewed, and one learns that “one episode of recurrent VTE is prevented for every 13 patients treated with dalteparin.”

Andrew Aw and Marc Carrier address the importance of thromboprophylaxis in medically ill patients, a practice that is generally underutilized in our hospital wards. Various strategies using unfractionated heparin, low molecular weight heparin, and fondaparinux are described, as are mechanical methods for those with a high bleeding risk. More specifically, anticoagulation options for orthopedic patients following hip and knee arthroplasty are reviewed. Again, direct thrombin inhibitors and factor Xa inhibitors offer promise in the postoperative management of this at-risk population.

## Questions d'anticoagulation

Hector Baillie MD

### Au sujet de l'auteur

Médecin spécialiste dans le domaine de la médecine complexe de l'adulte, Hector Baillie exerce sa profession à Nanaimo en Colombie-Britannique; il est le rédacteur en chef de La Revue canadienne de médecine interne générale.



Depuis longtemps, on fait appel à l'interniste pour se pencher sur les troubles de la coagulation sanguine. Qu'il s'agisse de la prévention de la thrombose veineuse profonde chez le malade hospitalisé ou de la réduction du risque d'accident vasculaire cérébral dû à une embolie d'origine cardiaque en cas de fibrillation auriculaire, l'interniste aborde couramment le sujet de la coagulation sanguine. Il se doit de connaître les modalités d'utilisation des antithrombotiques et des anticoagulants, si nouveaux soient-ils. Le présent supplément de *La Revue canadienne de médecine interne générale* offre une vue d'ensemble utile de quatre aspects de la démarche antithrombotique.

Anne McLeod et William Geerts examinent le sujet de l'anticoagulation en toute innocuité, notamment l'emploi des nouveaux médicaments, et soulignent l'importance de prescrire ces médicaments dans le cadre clinique approprié : « Moins de la moitié des patients des unités de chirurgie générale et une proportion plus faible encore des patients des unités de médecine sont soumis à la thromboprophylaxie indiquée. » Il nous revient de connaître les mesures à adopter pour accorder au patient son congé en toute sécurité, en lui remettant des directives écrites et en mettant en application des stratégies de surveillance fiables.

Charles Mahan et Alex Spyropoulos se penchent sur une situation courante : le passage de l'anticoagulation à long terme à la chirurgie chez le patient présentant un risque modéré ou élevé. Forts de la connaissance de la pharmacocinétique du médicament (particulièrement de sa demi-vie), nous pouvons conseiller nos collègues chirurgiens à propos du moment opportun pour interrompre et reprendre l'antiplaquettaire ou

l'anticoagulant. Les auteurs présentent des algorithmes de stratification du risque, dont CHADS-VASc et HAS\_BLED, ainsi qu'une méthode pratique de détermination des modalités de la transition. L'avenir nous réserve des médicaments plus spécifiques encore, efficaces, d'usage facile et de risque hémorragique moindre.

« L'histoire naturelle de la thromboembolie veineuse (TEV) en présence de cancer est plus fulgurante et imprévisible que celle de la TEV en l'absence de cancer ». La prévention et le traitement de la TEV chez nos patients atteints de cancer posent leurs propres défis, comme le fait ressortir Agnes Lee. Elle décrit les médicaments d'usage courant ainsi que des médicaments inédits en usage expérimental pour la plupart. Elle passe en revue l'étude CLOT entre autres, et le lecteur en retire que « le traitement par la daltéparine débouche sur la prévention d'un épisode de TEV récurrente par groupe de 13 patients traités ainsi ».

Andrew Aw et Marc Carrier soulignent l'importance de la thromboprophylaxie chez les malades hospitalisés dans les unités de médecine, une pratique marquée par la sous-utilisation dans nos hôpitaux. Plusieurs stratégies s'offrent au praticien : l'héparine non fractionnée, l'héparine de bas poids moléculaire, le fondaparinux ainsi que des moyens mécaniques en cas de risque hémorragique élevé. Plus précisément, les auteurs passent en revue les options d'anticoagulation en orthopédie à la suite d'une arthroplastie de la hanche ou du genou. Encore là, les inhibiteurs directs de la thrombine et les inhibiteurs du facteur Xa se révèlent prometteurs dans la prise en charge postopératoire de la population à risque.

## Patient Safety in Thromboembolism and Anticoagulation

Anne G. McLeod MD MSc, William Geerts MD



### About the Authors

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### Abstract

The underuse and improper use of anticoagulants are common patient safety issues leading to increased morbidity, mortality, and health care costs. The widespread replacement of unfractionated heparin and, in some cases warfarin, by low molecular weight heparins has been a major advance in effective and safe anticoagulation. A high proportion of patients with atrial fibrillation remain at risk for devastating stroke because they are not anticoagulated. However, careful use of warfarin and the new oral thrombin and factor Xa inhibitors can have a major impact on the management of atrial fibrillation and lead to improved outcomes. Despite overwhelming evidence that primary thromboprophylaxis safely and inexpensively reduces thromboembolic complications, there continue to be large gaps in the provision of this key safety intervention to most hospitalized patients. Implementation of quality improvement strategies is able to increase adherence to thromboprophylaxis guidelines and to decrease both clinically important thromboembolic events and hospital costs.

### Résumé

La sous-utilisation et l'usage inapproprié des anticoagulants compromettent la sécurité des patients et contribuent à accroître la morbidité, la mortalité et les coûts liés aux soins de santé. La pratique répandue du remplacement de l'héparine non fractionnée et de la warfarine dans certains cas par une héparine de bas poids moléculaire constitue une percée majeure dans l'anticoagulation efficace et sûre. Toutefois, une grande proportion des personnes aux prises avec de la fibrillation auriculaire courent un risque d'accident vasculaire cérébral dévastateur pour cause d'absence d'anticoagulation. La warfarine et les nouveaux inhibiteurs oraux de la thrombine et du facteur Xa, utilisés dans les règles, peuvent occuper une place majeure dans la prise en charge de la fibrillation auriculaire et améliorer les résultats cliniques. Alors que d'abondantes données probantes concluantes confirment que la thromboprophylaxie primaire représente un moyen sûr et peu coûteux de réduire les complications thromboemboliques, cette importante intervention sûre demeure d'application restreinte dans la plupart des hôpitaux. La stratégie d'amélioration de la qualité permettrait de rehausser la conformité aux lignes directrices sur la thromboprophylaxie et de diminuer tant les incidents thromboemboliques de portée clinique que les coûts hospitaliers.

Without question, anticoagulants save lives by the prevention and treatment of arterial and venous thromboembolism. In 1986, the first American College of Chest Physicians (ACCP) clinical practice guidelines on antithrombotic therapy were developed.<sup>1</sup> Most recently, the 8th edition of the ACCP guidelines, outlining the appropriate use of antithrombotic agents in the management of atrial fibrillation, acute coronary syndromes, valvular and other heart disease, and venous thromboembolism (VTE), were published.<sup>2</sup> More than 200,000 Canadians receive warfarin through publicly funded programs,<sup>3</sup> and many more receive unfractionated heparin (UFH) or low molecular weight heparin (LMWH). At the same time, both heparin and warfarin appear on the

“Top 10” list of prescription drugs involved in medication errors as reported to the Center for the Advancement of Patient Safety in the United States,<sup>4</sup> emphasizing the difficult balance between thrombosis and bleeding. It is our duty as physicians to offer these efficacious medications to our patients when indicated but also to provide the supervision and education needed to keep them safe.

In 2009, the Canadian Medical Protective Association (CMPA) analyzed 85 cases involving anticoagulants that were closed between 2002 and 2007.<sup>5</sup> These cases demonstrated that, in comparison to the overall CMPA experience with legal actions, anticoagulant cases were less likely to be settled in favour of the physician. Analysis of CMPA legal cases showed

that 60% of all legal cases were dismissed and 7% resulted in judgment for the physician. However, in cases involving anticoagulants, only 48% were dismissed and only 2% resulted in judgment for the physician. Two predominant risks were identified in these cases: (1) delay or failure to prescribe an anticoagulant where indicated and (2) inadequate monitoring once the anticoagulant was prescribed. These cases were nearly equally divided between thromboembolic and bleeding adverse events. Key issues that led to adverse outcomes were communication failure between physicians during the transfer of care (usually from the in-patient to the outpatient setting), delay or failure to consult a specialist if problems occurred, failure to reverse warfarin prior to an invasive procedure, and not considering the effect of potential interactions between anticoagulants and other medications such as antibiotics. In the majority of the patients involved, the adverse event resulted in significant disability or death. *Therefore, we must anticoagulate, but we must do it well.*

### Patient Safety Issues with the Use of Heparin

Heparin provides rapid-onset and short-acting anticoagulation in the management of arterial and venous thrombosis. In the past, UFH has been perceived as the safest method of anticoagulating patients in whom there is an increased risk of bleeding because of its rapid clearance from the body and the availability of protamine as a reversal agent. However, LMWHs provide significant advantages over UFH including greater bioavailability and a much more predictable anticoagulant response (which makes outpatient subcutaneous administration possible), decreased bleeding, no laboratory monitoring, and a greatly reduced incidence of heparin-induced thrombocytopenia (HIT).<sup>2</sup>

### Advantages of LMWH over UFH

LMWHs are derived from UFH through a process of fractionation that results in molecules with reduced binding to plasma proteins, macrophages, and endothelial cells.<sup>6</sup> This allows for a longer half-life and more predictable dose-response relationship. Therefore, LMWHs can be administered subcutaneously with once- or twice-daily dosing based on body weight without laboratory monitoring. Many randomized controlled trials have demonstrated the efficacy and safety of LMWHs in the treatment of venous thrombosis and in acute coronary syndromes.<sup>2</sup> The risk of HIT is threefold lower with therapeutic LMWH than with UFH.<sup>2</sup> Although the risk of HIT is dose dependent, even small amounts of UFH used in line flushes or for VTE prophylaxis carry a risk of HIT. In our experience, measures to eliminate the use of UFH can reduce the number of adverse patient outcomes and the health care costs of HIT.

The risk of osteopenia is greater with UFH than LMWHs, likely because of increased binding to bone cells. Animal studies suggest that LMWHs have the potential to cause osteopenia, and this should be taken into consideration in patients being considered for long-term use.<sup>7,8</sup>

Although the risk of heparin-associated bleeding increases with heparin dose,<sup>9</sup> the efficacy of heparin in reducing recurrence is dependent on adequate early anticoagulation.<sup>10</sup> Therapeutic UFH given intravenously requires frequent monitoring, usually by the activated partial thromboplastin time (APTT). Despite the use of heparin dosing nomograms, over- and under-dosing in the critical period after initiation of anticoagulation are very common. Significant delays often occur between the phlebotomy for the APTT and the reporting of the result,

complicating dosing and leading to prolonged delays in stabilization of the dose. In addition, the use of infusion pumps for intravenous (IV) heparin has been frequently associated with anticoagulant medication errors.<sup>11</sup> All of this makes IV heparin dosing unpredictable and increases the risk of major bleeding. Several meta-analyses of UFH versus LMWH in the initial treatment of VTE have demonstrated that LMWH is associated with less major bleeding than IV UFH.<sup>12-14</sup>

### Special Considerations for LMWH: Renal Impairment and Obesity

One limitation of LMWH is its clearance by the kidneys, which can result in bioaccumulation and an associated increased risk of bleeding in patients with renal insufficiency. Options for the treatment of acute arterial or venous thrombosis in patients with creatinine clearance of less than 30 mL/min include IV UFH or LMWH with an initial dose reduction of 50% and monitoring of anti-Xa levels.<sup>2</sup>

There has been concern about the use of LMWHs in obese patients because of instructions in the product monograph to not exceed a maximum dose. However, weight-based dosing without a dosage cap is important to avoid inadequate anticoagulation of obese patients.<sup>2</sup>

### Long-Term Use of LMWH: Cancer and Pregnancy

For most patients requiring anticoagulation, the use of LMWH is temporary until they are transitioned to warfarin. Two patient groups in which long-term use of LMWH is indicated in preference to warfarin are cancer patients and pregnant patients. LMWH has been shown to reduce the rate of breakthrough thrombosis in cancer patients by 50% compared with warfarin and is recommended for at least the first 6 months of treatment for venous thromboembolic disease.<sup>15</sup> Due to the association of warfarin with fetal embryopathy between 6 and 12 weeks of development, and the risks of intracranial bleeding in the developing baby, LMWH is recommended for anticoagulation of pregnant patients.<sup>16</sup> LMWHs can be safely used in pregnancy and while breastfeeding.<sup>17</sup> The components of a safe hospital or office discharge for patients remaining on long-term LMWH include the following:

1. A discussion of the medical indication for anticoagulation and the benefits and risks of LMWH
2. Instructions for management of bleeding and interventions such as surgery or delivery
3. Follow-up appointments to regularly review the indication for the medication and any possible side effects

### Patient Safety Issues with the Use of Vitamin K Antagonists

Few drugs have had as robust and productive an existence as warfarin and other vitamin K antagonists. Although some patients are surprised that warfarin is also used to kill rodents, it is an extremely effective drug with few side effects other than a small increase in bleeding. While more information about the safety and efficacy of the new oral anticoagulants accumulates across all indications, warfarin will remain in widespread use for years to come.

In a Canadian study of high-risk patients with known atrial fibrillation admitted with a first stroke, 29% of patients were on no antithrombotic

agent and, in the 40% of patients prescribed warfarin, 75% had an International Normalized Ratio (INR) <2.0 at the time of their stroke.<sup>18</sup> In this patient group, 60% of strokes were disabling and 20% were fatal. Many excellent studies from countries around the world have demonstrated this same knowledge-to-care gap.<sup>19–26</sup> While it would be unethical to deny a patient with a large pulmonary embolism (PE) anticoagulation because of physician concern about potential bleeding complications, despite overwhelming evidence of the efficacy of warfarin in preventing stroke and death, many eligible atrial fibrillation patients do not receive warfarin.<sup>18</sup>

Vitamin K antagonists have a narrow therapeutic index and require frequent, at least monthly, INR monitoring even in the most stable patients. The pharmacokinetics of vitamin K antagonists are altered by several factors, including other prescription and over-the-counter medications, dietary intake, alcohol use, and concurrent illness. In addition, the delay in the effect of warfarin dosing on the INR often leads to inappropriate dosing changes that can put patients at risk. The skills required to safely monitor and dose warfarin in the in-patient and outpatient setting are often not taught. Studies have demonstrated that patient education and involvement in their own anticoagulant supervision are important in reducing the risk of bleeding and breakthrough thrombosis.<sup>27</sup> Several studies have demonstrated that specialized anticoagulant clinics,<sup>28</sup> patient self-testing and self management,<sup>29</sup> and pharmacy-managed dosing clinics<sup>30</sup> are all advantageous in reducing the risks of anticoagulation. Even with the extensive resources available to health professionals and patients about warfarin management and dosing, the incorporation of this information into routine care requires commitment, time, and effort.

The consequences of managing warfarin poorly can be dire. There is a strong relationship between INR control and complications.<sup>31</sup> For example, a large trial showed patients taking warfarin for atrial fibrillation who had poor (INR in range <60% of the time) or moderate control (INR in range 60–75% of time) had an increased risk of stroke, myocardial infarction (MI), bleeding, and death compared with patients whose time in range exceeded 75%.<sup>31</sup>

### Warfarin and Concomitant Antiplatelet Agent Use

The use of antiplatelet agents in combination with warfarin is an extremely common situation. Strong evidence exists that combinations of antiplatelet agents and warfarin significantly increase bleeding risk with no increased benefit in preventing stroke. In a large study of more than 100,000 Danish patients with atrial fibrillation, the risk of significant bleeding leading to hospitalization or death increased from 3.9% for warfarin alone and 3.7% for acetylsalicylic acid (ASA; Aspirin) alone to 6.8% for the combination of warfarin and ASA, with no change in the risk of stroke.<sup>32</sup> There are very few indications for the addition of an antiplatelet agent in patients with an indication for warfarin. These include only (1) acute MI, (2) percutaneous coronary intervention with stent placement, (3) high-risk mechanical heart valve, and (4) transient ischemic attack (TIA) or stroke on therapeutic warfarin. Unless one of these criteria is met, patients starting on warfarin should stop their antiplatelet agent.

The components of a safe hospital discharge for patients on vitamin K antagonists include the following:

1. Discussion and documentation of the indication for a vitamin K antagonist
2. Decision of who will be responsible for INR monitoring and warfarin dosing and documentation that the physician/clinic has accepted this responsibility (the only way to do this properly is to call and speak directly with the person or clinic and document this conversation)
3. Detailed patient education about the INR, the importance of regular testing, symptoms and signs of bleeding, drug interactions (especially antibiotics), whom to call with questions, and who is responsible for their warfarin dosing
4. Provision of accurate written information such as the warfarin patient information handout found at the Thrombosis Interest Group of Canada website ([www.tigc.org](http://www.tigc.org))
5. Documentation of dosing to date and when the next INR is needed and ensuring that a copy of this is given to the patient
6. Arrangement of periodic follow-up with the most relevant physician to reassess the indication for and duration of anticoagulation and potential side effects

### Issues for the Future

A pressing current question is the safety of the new oral anticoagulants, dabigatran and rivaroxaban, in the treatment of atrial fibrillation and VTE. Although the inconvenience of INR monitoring and the narrow therapeutic index make warfarin a challenge, we are accustomed to having the ability to monitor compliance and to rapidly reverse warfarin's effect with vitamin K and prothrombin complex concentrates. It seems likely that the predictability of dosing with the new oral agents will more than compensate for the lack of monitoring and no reversal agent. It is hoped that there will soon be more studies to demonstrate the role and safety of these agents in routine practice for our varied patient populations.

### Prevention of Venous Thromboembolism

The prevention of VTE is a key patient safety priority for internists and hospitalists based on four facts summarized in Table 1. Approximately 60% of the entire burden of VTE in the community is related to a current or recent hospitalization, and VTE is 130 times more common in hospital than community patients.<sup>33,34</sup> Almost all patients admitted to hospital have at least one (and usually multiple) risk factors proven to be associated with VTE, and VTE is one of the most common complications of hospital care and the commonest preventable cause of hospital death.<sup>35–37</sup> Although VTE is commonly considered to be a problem associated with surgery, the majority of symptomatic and fatal cases of hospital-acquired VTE actually occur in medical patients.<sup>38</sup>

#### Table 1. Rationale for the Importance of Thromboprophylaxis

- Venous thromboembolism is very **common** in hospitalized patients.
- Venous thromboembolism leads to increased **morbidity, mortality, and health care costs**.
- Venous thromboembolism is **preventable** with safe and inexpensive interventions.
- Thromboprophylaxis is the **standard of care** for almost all hospital patients.

**Table 2. Patient Groups and Recommended Thromboprophylaxis Options**

Patient Groups	Thromboprophylaxis Options*	Duration
Outpatient surgery	No specific thromboprophylaxis	
Minor surgery in mobile patients	Early and "aggressive" ambulation	
Medical patients who are fully mobile with expected length of stay <48 h		
Acute medical illness	Low molecular weight heparin Low-dose heparin	Discharge
Major, non-orthopedic surgery: general, gynecologic, thoracic, urologic, vascular, bariatric	Low molecular weight heparin Low-dose heparin Fondaparinux	Discharge
Hip and knee arthroplasty	Rivaroxaban, dabigatran Low molecular weight heparin Fondaparinux	2–4 wk
Hip fracture repair	Fondaparinux Low molecular weight heparin Low-dose heparin	2–4 wk
High bleeding risk	Mechanical method (graduated compression stockings, pneumatic compression device)	Until an anticoagulant method can start

\*In addition to encouraging patients to be as mobile as possible.

Source: Modified from the 8th American College of Chest Physicians guidelines on the prevention of venous thromboembolism (Geerts et al.).<sup>37</sup>

Since the first randomized trial showing that fatal PE could be reduced by the use of thromboprophylaxis was published in 1959, there have been more than 400 additional trials that unequivocally prove that this critical safety intervention reduces VTE and fatal PE by more than 60%, with a very low risk of adverse effects and in a cost-effective manner.<sup>37,39–41</sup> Furthermore, clinical practice guidelines have recommended routine use of thromboprophylaxis for the past 25 years.<sup>37,42</sup> For all of these reasons, the prevention of VTE has been ranked as the number one patient safety strategy for hospitalized patients.<sup>43</sup> Failure of physicians and hospitals to provide appropriate thromboprophylaxis to patients in whom it is indicated is also grounds for negligence and for medical legal claims and substantial settlements.<sup>5</sup>

### Thromboprophylaxis Recommendations

Since 1986, the ACCP guidelines have summarized all of the relevant studies related to the risks of VTE and its prevention and provided evidence-based recommendations for (or, in some cases, against) thromboprophylaxis in each of these groups.<sup>37</sup> These guidelines are useful since they provide three levels of assistance for clinicians and hospital patient safety leaders. The summary recommendations, including the grade of evidence, for each of 23 different patient groups can be reviewed quickly. At the next level, the text supporting each of the recommendations can be reviewed. Finally, the references to the primary evidence can be searched for more details. Since the volume of literature related to thromboprophylaxis is so massive, the ACCP guidelines help to focus clinicians and hospitals on the implementation of the recommendations rather than on repeating lengthy literature reviews. Non-pharmacological methods of thromboprophylaxis, including graduated compression stockings and pneumatic compression devices, are useful because they do not cause bleeding in vulnerable patients.

Although mechanical methods appear to provide some protection in some patient groups and may provide added protection when combined with anticoagulant-based prophylaxis options, there are many fewer studies of mechanical prophylaxis compared with anticoagulant methods, and many of these studies have poor methodology.<sup>37,44,45</sup> A recent large, rigorous study demonstrated that compression stockings provided no protection against deep venous thrombosis in patients with acute stroke compared with no prophylaxis.<sup>46</sup> Furthermore, substantial efforts are required to ensure that they are used properly since compliance is generally poor.<sup>47</sup> Therefore, we believe that mechanical thromboprophylaxis should be restricted to situations in which anticoagulant methods cannot be used because of high bleeding risk and only until anticoagulant prophylaxis can be started. Mechanical thromboprophylaxis methods are considered medical devices, and there is a legal obligation for clinicians and hospitals to ensure that they are properly fitted and that compliance is optimal. They need to be applied to both legs and used almost 24 hours per day. Several hundred clinical trials have demonstrated the effectiveness and safety of various anticoagulant options for thromboprophylaxis, including low-dose unfractionated heparin (LDUH), LMWH, fondaparinux, and the new oral anticoagulants rivaroxaban and dabigatran.<sup>37</sup> Currently recommended methods of thromboprophylaxis are safe, with bleeding risks similar to or only slightly greater than placebo. Compared with LDUH, LMWH has a much more predictable dose-response effect, a longer half-life, once versus two or three times per day dosing, equal or superior efficacy, equal or superior safety, and a 40-fold lower risk of HIT.<sup>37,41,48,49</sup> For these reasons and the shrinking cost differences between the two agents, LMWH has replaced LDUH in many hospitals. Also, with the availability of the oral factor Xa and thrombin inhibitors that are given in fixed doses and do not require laboratory monitoring, there is no longer any justification to use warfarin as primary prevention of VTE in

**Table 3. Local Strategies to Improve Thromboprophylaxis Success**

1.	Obtain the active support of hospital administration and clinical leadership.
2.	Create a multidisciplinary committee with the goal of optimizing thromboprophylaxis.
3.	Conduct a baseline assessment of appropriate use of thromboprophylaxis.
4.	Develop a written, hospital-wide hospital policy on thromboprophylaxis.
5.	Standardize thromboprophylaxis across the organization and keep it simple.
6.	Embed the hospital thromboprophylaxis policy into order sets that require a decision about thromboprophylaxis.
7.	Provide education to all front-line staff on the importance of venous thromboembolism and its prevention.
8.	Audit the provision of appropriate thromboprophylaxis on a regular basis and provide feedback to practitioners.
9.	Involve physicians, pharmacists, nurses, and patients in the implementation of best practices in thromboprophylaxis.

hospitalized patients since these new oral agents are more effective, safer, easier to use, and not more costly.<sup>37,50,51</sup>

A summary of current thromboprophylaxis options found in Table 2. Thromboprophylaxis should be started soon after admission or after surgery if it is safe to do so. For most medical and surgical patients, thromboprophylaxis should continue until discharge from hospital and should not be discontinued simply because the patient begins to ambulate. For major orthopedic surgery, thromboprophylaxis should continue for 2–4 weeks after surgery because most symptomatic thromboembolic events in these patients occur in the weeks after hospital discharge and there is strong evidence that clinically important VTE can be prevented by extended prophylaxis.<sup>37,52</sup>

**Adherence to Thromboprophylaxis**

Numerous studies confirm that major gaps exist between the evidence and guideline recommendations on the one hand and actual thromboprophylaxis use in hospitals on the other.<sup>53</sup> Thromboprophylaxis rates are highest in arthroplasty and critical care patients. The Canadian Joint Replacement Registry reports the use of recommended thromboprophylaxis in more than 99% of hip and knee arthroplasty patients in Canada.<sup>54</sup> However, post-discharge use of thromboprophylaxis is often overlooked in these high-risk patients.<sup>55</sup> Fewer than half of general surgical patients and even a smaller proportion of medical patients receive appropriate thromboprophylaxis.<sup>56</sup> A study of 1,894 consecutive medical patients in 29 Canadian hospitals showed that thromboprophylaxis was indicated in 90% but only 15% received appropriate thromboprophylaxis.<sup>57</sup> There is evidence of a strong link between suboptimal thromboprophylaxis and both increased symptomatic VTE rates and costs compared with thromboprophylaxis that is adherent with the ACCP guidelines.<sup>58</sup>

**Improving Thromboprophylaxis Success**

Several recent national initiatives promote thromboprophylaxis. The widespread use of surgical checklists helps to remind surgical teams to consider thromboprophylaxis for each of their cases.<sup>59</sup> Since January 2011,

**Table 4. Practical Actions for Internists to Reduce the Hospital Burden of VTE**

•	Assess all of your own in-patients for risk of VTE and ensure they receive optimal thromboprophylaxis.
•	Address thromboprophylaxis in preoperative assessments.
•	Assess the VTE risk and order thromboprophylaxis for patients you see in consultation.
•	Initiate, lead, or support efforts to develop and implement a hospital-wide thromboprophylaxis policy that is embedded into routine order sets.
•	Aim for 100% appropriate thromboprophylaxis for patients at risk.
•	Provide education for medical and surgical colleagues and other health professionals about VTE, its prevention, and treatment.

VTE = venous thromboembolism.

every hospital undergoing accreditation in Canada is expected to report on their commitment to ensuring appropriate thromboprophylaxis through a hospital-wide thromboprophylaxis policy, patient risk assessment for VTE, routine provision of evidence-based thromboprophylaxis, audit of adherence, and education of both staff and patients.<sup>60</sup> The prevention of VTE has also been embraced as a key patient safety intervention by Safer Healthcare Now! the national quality improvement arm of the Canadian Patient Safety Institute. Safer Healthcare Now! provides education, mentorship, and resources to assist hospitals to achieve high-quality thromboprophylaxis.<sup>61</sup>

At the local hospital level, a number of strategies have been identified to increase the success of thromboprophylaxis safety (Table 3).<sup>37,62–66</sup> Provision of group education and dissemination of guidelines on thromboprophylaxis alone are ineffective as interventions to improve the use of appropriate thromboprophylaxis, whereas multi-component quality improvement strategies are much more effective.<sup>62–64,66</sup> Making VTE prevention a hospital safety priority through the active support of the hospital board, senior administrators, department heads, and clinician leaders is essential. An evidence-based, hospital-wide written policy and guideline on thromboprophylaxis provides a reference framework for the entire organization. If thromboprophylaxis is standardized and simple, all health care providers can be involved in implementing the hospital policy. Since more than 90% of in-patients in most hospitals have an indication for thromboprophylaxis, it should routinely be considered on admission for almost all. The selection of thromboprophylaxis from a limited list of options that are embedded into routine paper or electronic order sets is highly effective in improving adherence with the hospital policy.<sup>67</sup> It is also essential that routine audits of appropriate thromboprophylaxis use be carried out as a means to determine where barriers to optimal adherence exist, to track success over time, and to guide various quality improvement initiatives. The objective must be to provide appropriate thromboprophylaxis to 100% of patients at risk. Providing feedback from these audits to health care providers is a very powerful method to influence change.

Despite overwhelming evidence that the morbidity, mortality, and costs

of VTE can be reduced, there remains a substantial underuse of thromboprophylaxis. Internists and hospitalists have an essential role in improving thromboprophylaxis rates and, thereby, in decreasing this important patient safety problem (Table 4).

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## Original Article

## Peri-operative Antithrombotic Management and Anticoagulant Bridging

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#### Abstract

Peri-operative antithrombotic management with anticoagulants and antiplatelet agents is an important field in which the risk-benefit balance of thrombosis and bleeding is carefully assessed in order to designate the best approach to the patient care plan. An increasing number of patients are requiring anticoagulant bridging and management. The primary therapeutic goals of bridging anticoagulation in the peri-operative period are to minimize the time patients are not receiving anticoagulant therapy, which minimizes the risk for thromboembolism, and to coordinate appropriate timing of antithrombotics to reduce the risk for bleeding. Two new bridging studies are under way and should provide new, important evidence in an emerging field. Novel oral anticoagulants and antiplatelets are now available, with several new agents on the horizon. These new antithrombotics will lead to new approaches for peri-operative management and may provide advantages over current standard-of-care therapies.

#### Résumé

La transition périopératoire repose sur l'évaluation minutieuse des avantages de l'anticoagulation et des risques de thrombose ou de saignement en prévision de la conception de la meilleure démarche thérapeutique. De plus en plus, il s'avère nécessaire d'établir un plan de transition postopératoire en matière d'anticoagulation. Les principaux buts thérapeutiques de l'anticoagulation de transition consistent à réduire au minimum la période sans anticoagulation, laquelle diminue le risque de thromboembolie, et à prévoir le moment opportun du traitement antithrombotique afin de réduire le risque d'hémorragie. Deux nouvelles études en cours devraient produire des données probantes utiles dans ce domaine émergent. Des anticoagulants et des antiplaquetaires oraux ont fait leur entrée sur le marché récemment et plusieurs autres se profilent à l'horizon. Ces nouveaux antithrombotiques faciliteront la prise en charge périopératoire et ils seront peut-être plus avantageux que les traitements usuels.

## Background and Introduction

Antithrombotics are composed of antiplatelets, anticoagulants, and fibrinolytics.<sup>1</sup> For patients on anticoagulants such as vitamin K antagonists (VKAs; e.g., warfarin, phenprocoumon) or antiplatelets, temporary interruption of these agents for procedures (i.e., invasive procedure or surgery) poses a significant challenge to clinicians managing these patients.<sup>2</sup> Approximately 3 million and 5 million patients in the United States and the European Union, respectively, are currently taking anticoagulants for atrial fibrillation (AF), mechanical heart valves (MHVs), or treatment of venous thromboembolism (VTE).<sup>2,3</sup> The number of AF patients in the United States is expected to rise to 5.6 million by 2050.<sup>4,5</sup> Taking into consideration that it is estimated that 1 in 10 of these patients undergo a procedure on an annual basis,<sup>2</sup> the number of patients that need to be assessed in these 26 countries is approximately 800,000 per year and will likely rise to over 1 million patients annually within the very near future.

Peri-operative “bridging” may be defined as an overlap of a shorter-acting parenteral agent, currently unfractionated heparin (UFH), the pentasaccharide fondaparinux, or low molecular weight heparin (LMWH), to best cover the patient during the offset and onset of VKA therapy when this interruption is required.<sup>2</sup> Other oral or parenteral anticoagulants may become available as future options.<sup>1</sup> Bridging provides an alternative, shorter-acting anticoagulant to cover the patient while the International Normalized Ratio (INR) is not in its therapeutic range. Most bridging cases are currently managed with LMWH. It should be noted that peri-operative bridging is an emerging field with no well-designed randomized controlled trials yet available. Only within the past 3 years have international guidelines been developed to guide clinicians on best-recommended approaches.<sup>2,6</sup>

The primary therapeutic goals of bridging anticoagulation are to minimize the time patients are not receiving anticoagulant therapy, thereby minimizing the risk for thromboembolism, and to do this in a fashion that reduces patients’ risk for bleeding in the peri-operative timeline since antithrombotic use in the peri-operative period poses additional bleeding risk to the patients.<sup>2</sup> No intravenous (IV) or rapid-acting options currently exist for antiplatelet agents; however, goals exist to ensure that the antiplatelet timing of the offset after discontinuation, and onset after resumption, is taken into consideration to best balance the risk and benefit for the patient in the peri-operative period.

Anticoagulants and antiplatelets are primarily used in patients with AF or MHV to prevent arterial thromboembolism (ATE), which can cause severe morbidity and have fatal consequences.<sup>1</sup> Similarly with VTE, the primary goal of anticoagulation is to prevent recurrent VTE, which can also cause serious sequelae and manifest as fatal pulmonary embolism (PE).<sup>1</sup> Because these patients on anticoagulants and antiplatelets are at high risk of developing ATE or VTE, if the need for a procedure arises, detailed consideration needs to be given for how the clinician should manage antithrombotic therapy. The clinician must carefully consider the balance of thrombosis and bleeding, using risk stratification for both, to determine the appropriate approach to patient care. Some procedures may have a low enough bleed risk that patients may not require anticoagulant or antiplatelet interruption. On the contrary, for procedures that carry a high risk of bleeding, bridging in the peri-procedural period may not be warranted and VKAs may be stopped and restarted later without overlap of a parenteral agent. However, for many patients at moderate or high risk of thromboembolism and at low bleed risk, bridging is likely warranted.<sup>2</sup>

As applicable, anticoagulant and antiplatelet therapies should be managed carefully. Communication among physicians and clinicians as well as the *timing* of this management are critical, in both the days leading up to the procedure and after the procedure has occurred so that both bleeding and ATE/VTE risks are minimized.<sup>2</sup>

## Critical Points Offset of Agents

To best understand the execution of bridging, in addition to taking into consideration the thromboembolic and bleeding risks of the individual patient scenario, the clinician must understand the onset and offset of the various agents used. For onset of antithrombotics, it is important to understand when the initial peak anticoagulant effect occurs after the administration of an agent. For offset, it is typically agreed that after 5–7 elimination half-lives of an agent, it has minimal pharmacological effect.<sup>2</sup> Although warfarin affects various factors in the coagulation cascade, the half-life is typically accepted to be in the range of 36–42 hours.<sup>2</sup> Although used to a lesser extent in Canada, phenprocoumon has a longer half-life, in the range of 96–140 hours, and should be discontinued earlier than warfarin, at approximately 10 days pre-procedure, and possibly earlier in the elderly.<sup>2</sup> An INR range of 1.5 or less is acceptable in order to perform the necessary procedure in most cases.<sup>2</sup> Thus, when discontinuing the VKA prior to the procedure, offset of warfarin is typically 5–7 days. In the elderly or in those with hepatic dysfunction, this may be longer, in the range of 7–10 days.<sup>2</sup> The half-lives of fondaparinux, LMWH, and UFH are approximately 14–17 hours, 4–7 hours, and 1–2 hours, respectively.<sup>7</sup> Fondaparinux’s longer half-life likely contributes to the low use of this agent in peri-procedural bridging studies and clinical use. This may be primarily driven from fondaparinux’s long offset time pre-procedure. In patients with impaired renal function, the half-lives and elimination of fondaparinux and LMWH are prolonged. Antiplatelets such as acetylsalicylic acid (ASA, or aspirin), ticlopidine, clopidogrel, and prasugrel are irreversible inhibitors and exert an effect until platelets are regenerated, which is typically in the range of 7–10 days.<sup>1,2</sup> This range also approximates the platelet lifespan.

Nonsteroidal anti-inflammatory drugs (NSAIDs) also need to be taken into consideration as these drugs inhibit platelet-mediated cyclooxygenase activity. To minimize the bleeding risk and ensure that there is no residual antiplatelet effect at the time of the procedure, the NSAID should be held 5–7 elimination half-lives prior to the procedure. NSAIDs with longer half-lives, such as piroxicam, nabumetone, meloxicam, with half-lives greater than 20 hours, should be stopped at a minimum of 10 or more days prior to surgery.<sup>2</sup> For NSAIDs with intermediate half-lives of 7–15 hours including celecoxib, diflunisal, sulindac, these agents should be stopped at a minimum of 2 to 4 days prior to the procedure.<sup>2</sup> NSAIDs with shorter half-lives of 2–6 hours, such as ibuprofen, ketoprofen, indomethacin, and diclofenac, should be stopped at a minimum of 1–2 days prior to surgery.<sup>2</sup>

## Onset of Agents

When resuming VKA therapy post-procedure, the clinician should take into consideration that it takes a minimum of 2–3 days for the anticoagulant effect to begin after re-initiation, with variable effects on different factors.<sup>2</sup> Subcutaneous (SC) LMWHs and UFH take approximately 3–5 hours for a peak anticoagulant effect to be reached after re-initiation.<sup>2,7</sup> IV UFH has an almost immediate anticoagulant effect.

Antiplatelets vary in their onset, with only minutes needed for an antiplatelet effect to begin after the administration of ASA, and 3–7 days for peak inhibition of platelet aggregation to be reached after the start of a 75 mg maintenance dose of clopidogrel. If loading doses (i.e., 300–900 mg) of clopidogrel are given, the time to peak inhibition of platelet aggregation is 4–6 hours.<sup>2</sup> Compared with clopidogrel, the conversion of prasugrel to its active metabolite is much quicker (around 30 minutes) and more efficient and occurs via single-step oxidation in the liver.<sup>1</sup> For this reason, time to peak platelet aggregation inhibition is less than 4 hours with a prasugrel loading dose of 60 mg. Therefore, platelet inhibition induced by prasugrel at 30–60 minutes after administration is similar to that of clopidogrel at 4–6 hours.<sup>1</sup>

### Recent Clinical Data

Approximately 14, 10, and eight prospective cohort studies have assessed bridging anticoagulation in around 1,300 patients with MHV, 1,400 with AF, and 500 with VTE, respectively.<sup>2</sup> From these studies, it can be determined that approximately 75% of these patients were bridged for minor procedures and that about 80% of the bridging regimens involved therapeutic-dose UFH or LMWH.<sup>8</sup> In addition, all studies used standardized protocols and follow-up periods that were typically around 1 month.<sup>8</sup> An important point is that it would likely be beneficial for institutions or health systems to standardize protocols for antiplatelet and anticoagulant management when peri-procedural interruption is required. This would be contiguous with the Joint Commission national patient safety goals on anticoagulation and VTE performance measures.<sup>9,10</sup>

### Thromboembolic Risks

The thromboembolic risk helps guide the decision as to whether bridging with a parenteral agent should be used. International bridging guidelines categorize patients into low, moderate, or high risk for thromboembolism.<sup>2,6</sup> Crude rates of thromboembolism in bridging studies for MHV, VTE, and AF are 0.83% (95% confidence interval [CI] 0.43–1.5), 0.6% (95% CI 0.13–1.7), and 0.57% (95% CI 0.26–1.1), respectively.<sup>2</sup> In patients with MHV or AF, mathematical modelling has been used from estimated 17% and 5% annual thromboembolic rates, respectively, for when these patients are not treated with VKAs.<sup>11,12</sup> These annual rates correspond to daily thromboembolic risk rates of 0.046% (MHV) and 0.013% (AF) or around 0.4% (MHV) and 0.1% (AF) for the approximate 8-day period (i.e., the period in which peri-procedural bridging may or may not be performed) if a patient is *NOT* therapeutically anticoagulated in this timeframe.<sup>2</sup> The finding of higher rates of peri-procedural thromboembolism in actual bridging studies versus this mathematical modelling suggests that the true risk of thromboembolism in patients with MHV or AF is higher than expected in “real world” scenarios.<sup>2</sup>

### Bleeding Risks

It appears that there is emerging evidence that the clinical impact of major bleeding is possibly more than was previously recognized.<sup>2</sup> If bleeding occurs, this can also delay the resumption of the antithrombotic therapy that is important to minimize the thrombotic risk for patients.<sup>2</sup> Current recommendations are to categorize patients' bleeding risks into low and high.<sup>13</sup> Understandably, the introduction of anticoagulants for bridging in the peri-procedural period, especially post-procedure, may expose patients to additional and unnecessary bleeding risks. Moreover for VKA

bridging, using two anticoagulants upon offset and onset during the respective pre- and post-procedural periods also increases the bleeding risk compared with single anticoagulant administration. If the patient is on antiplatelets or NSAIDs, this may also introduce an additional risk of bleeding and needs to be taken into consideration by the clinician.

### Costs of Bridging Anticoagulation

Several different cost analyses have concluded that outpatient administration of SC LMWH for bridging is less expensive than in-patient administration of IV UFH.<sup>2</sup> For this reason, the American College of Chest Physicians (ACCP) guidelines recommend outpatient use of SC LMWH over in-patient administration of IV UFH when feasible.<sup>2</sup> The patient, a family member, or a health care provider must administer the SC LMWH. Patients should be appropriately educated to properly administer the medication.<sup>10</sup>

### Key Questions

Four important questions should be asked for all patients currently on antiplatelets or anticoagulants who are scheduled to undergo a procedure. **First, can the procedure be delayed to a time when the patient may not be on antithrombotics?** Many times due to various barriers, communication among professionals is not optimal. When the perceived need for a procedure arises, this should be the first point addressed. If the procedure is not urgent or emergent and can be delayed, it should be in order to not expose the patient to unnecessary thromboembolism and bleeding risks that could potentially be catastrophic.

**Second, if the procedure is necessary, does the patient require interruption of antithrombotic therapy during the peri-procedural period?** For patients undergoing minor procedures, interruption of antithrombotic therapy may not be warranted because the thrombotic risk outweighs the bleeding risk. Examples of such minor procedures include simple dermatological, dental, or ophthalmic procedures. On the contrary, in patients who require a major procedure, interruption of antithrombotic agents is typically warranted due to the risk of peri-procedural bleeding. Additionally, patients who have a low risk of thromboembolism may be temporarily interrupted without the need for bridging therapy. Therapeutic levels of antiplatelets (e.g., ASA, prasugrel, or clopidogrel), VKA, or LMWH/UFH during a major procedure expose the patient to a significantly increased risk for bleeding.<sup>2</sup> For certain patients, such as those with bare metal coronary stents placed within 6 weeks or drug-eluting coronary stents placed within 12 months, it is recommended that ASA and clopidogrel be continued through the peri-procedural period when possible.<sup>2</sup> For a more detailed discussion of peri-procedural antiplatelet management, we refer readers to the ACCP guidelines.<sup>2</sup>

**Third, if the interruption of antithrombotic therapy is deemed necessary, is bridging with a parenteral anticoagulant required?** In regards to the peri-procedural management of anticoagulants, both patient and procedural risk factors for thrombosis and bleeding should be assessed and the patient should be risk stratified.<sup>8</sup> The delicate balance of the risk-benefit profile of both thrombosis and bleeding is the key determinant that guides whether parenteral anticoagulant bridging will be used. It is important to understand that ATE can carry a 15% case-fatality rate for heart valve thrombosis or as high as a 70% case-fatality or serious morbidity rate for stroke.<sup>8</sup> DVT purveys a 6% rate of permanent disability or death, whereas PE purveys up to a 25% case-fatality rate.<sup>8</sup> The

**Table 1. ACCP Thromboembolic Risk Stratification for Perioperative Anticoagulation Management**

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
<b>Low:</b> <4% per year risk of ATE Or <2% per month risk of VTE	Bileaflet AVR <i>without</i> major risk factors for stroke	CHADS <sub>2</sub> score of 0–2 (and no prior stroke or TIA)	VTE >12 months ago
<b>Moderate:</b> 4–10% per year risk of ATE Or 4–10% per month risk of VTE	Bileaflet AVR <i>with</i> major risk factors for stroke	CHADS <sub>2</sub> score of 3 or 4	VTE within past 3–12 months Recurrent VTE Non-severe thrombophilia Active cancer
<b>High:</b> >10% per year risk of ATE Or >10% per month risk of VTE	Any mechanical mitral valve Caged ball or tilting disc valve in mitral/aortic position Recent (<6 month) stroke or TIA	CHADS <sub>2</sub> score of 5 or 6 Recent (<3 months) stroke or TIA Rheumatic valvular heart disease	Recent (<3 months) VTE Severe thrombophilia Deficiency of protein C, protein S, or antithrombin Antiphospholipid antibodies Multiple thrombophilias

ACCP = American College of Chest Physicians; ATE = arterial thromboembolism; AVR = aortic valve replacement; CHADS<sub>2</sub> = see text for details; TIA = transient ischemic attack; VTE = venous thromboembolism.

Source: Adapted from Douketis et al.<sup>2</sup>

**Table 2. CHADS-VASc Risk Assessment Model**

Risk Factor	Score*
Congestive heart failure/left ventricular dysfunction	1
Hypertension	1
Age ≥75 years of age	2
Diabetes mellitus	1
Stroke/transient ischemic attack/thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65–74 years	1
Sex category (i.e., female gender)	1
Maximum	9 points

\*0 = low; 1 = intermediate; ≥2 = high risk.

Source: Reproduced with permission from Lip et al.<sup>14</sup>

**Table 3. HAS\_BLED Risk Assessment Model for Bleeding**

Risk Factor	Score*
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum	9 points

INR = International Normalized Ratio.

Source: Reproduced with permission from Pisters et al.<sup>15</sup>

common problem of recurrent PE carries an additive case-fatality rate, with up to a 25% case-fatality rate. Major bleeding typically carries an overall case-fatality rate of between 8 and 11%.<sup>8</sup> Table 1 provides a suggested schema for risk stratifying patients' *thromboembolic risk* into low, moderate, or high.<sup>2</sup> Only the CHADS<sub>2</sub> score has been validated at this time within the AF population. CHADS<sub>2</sub> scores congestive heart failure, hypertension, age ≥75, and diabetes mellitus as 1 point and prior stroke or transient ischemic attack as 2 points. The scores therefore range from 0 to 6. Novel risk-assessment models (RAMs) have been developed, including the CHADS-VASc (Table 2) and HAS\_BLED (see Table 3 for acronym expansion and scoring) to predict thromboembolic and bleeding risks, respectively, within the AF population.<sup>14,15</sup> CHADS-VASc adds on vascular disease (1 point), another age category (1 point), and sex category (1 point for female) as additional points onto CHADS<sub>2</sub> and has now also been validated and shown to be more predictive than the CHADS<sub>2</sub>. It will be interesting to evaluate the introduction of the new RAMs including CHADS-VASc and HAS\_BLED and to see how they will be used in the peri-procedural bridging field. Table 4 provides a schema to separate patients into low or high *bleeding risks*; the 2-day risk of major bleed is 0–2% and 2–4%, respectively, for low- and high-risk patients.<sup>16</sup>

Table 5 provides an overall assessment schema to assist in determining the patient care plan. For patients on only antiplatelets, parenteral overlap with UFH, LMWH, or the pentasaccharide fondaparinux is typically not used. However, for patients on VKA at moderate or high thrombosis risk, AND low bleeding risk, bridging therapy with a parenteral agent is likely warranted. For patients on VKA who are at low bleeding risk, such as with gastrointestinal endoscopy, cardiac catheterization, simple dental extractions, etc., the parenteral LMWH/UFH/fondaparinux may be resumed approximately 24 hours post-procedure.<sup>2</sup> For patients on VKA with a high bleeding risk who have undergone major procedures but in whom the physician has deemed the patient to have achieved adequate hemostasis, parenteral LMWH/UFH/fondaparinux may likely be resumed 48–72 hours post-procedure.<sup>2</sup> For patients on VKA with a high bleeding risk – for example, from major surgeries such as neurosurgical, cardiac,

**Table 4. Bleeding Risk Stratification**

<b>High Risk (2-day risk of major bleed 2–4%)</b>
Heart valve replacement
Coronary artery bypass
Abdominal aortic aneurysm repair
Neurosurgical/urological/head and neck/abdominal/breast cancer surgery
Bilateral knee replacement
Laminectomy
Transurethral prostate resection
Kidney biopsy
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
PEG placement
Endoscopically guided fine-needle aspiration
Multiple tooth extractions
Vascular and general surgeries
Any major surgery (procedure duration >45 min)
<b>Low Risk (2-day risk of major bleed 0–2%)</b>
Cholecystectomy
Abdominal hysterectomy
Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endosonography without fine-needle aspiration
Pacemaker and cardiac defibrillator insertion and electrophysiological testing
Simple dental extractions
Carpal tunnel repair
Knee/hip replacement and shoulder/foot/hand surgery and arthroscopy
Dilatation and curettage
Skin cancer excision
Abdominal hernia repair
Hemorrhoidal surgery
Axillary node dissection
Hydrocele repair
Cataract and non-cataract eye surgery
Non-coronary angiography bronchoscopy ± biopsy
Central venous catheter removal
Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies

PEG = percutaneous endoscopic gastrostomy.

Source: Reproduced with permission from Spyropoulos.<sup>16</sup>

major orthopedic, or urological surgeries – post-procedural parenteral LMWH/UFH/fondaparinux may not be warranted as the bleed risk is merely too high if an additional anticoagulant were to be used in the post-procedure period in close proximity to the procedure.<sup>2</sup> Using this technique, some studies have achieved a 1% incidence of major bleeding, with no fatal bleeds.<sup>3</sup> In these cases, warfarin is typically resumed within 1–3 days post-procedure, once adequate hemostasis has been achieved.

**Fourth, if parenteral anticoagulation is used for bridging, should prophylactic dosing or therapeutic dosing be employed?** Peri-operative bridging of anticoagulation is currently the administration of a short-acting anticoagulant, such as SC LMWH, fondaparinux or UFH, or IV UFH, administered typically as a therapeutic-dose regimen for approximately 8–10 days during the peri-procedural interruption of VKA therapy when the INR is outside the therapeutic range. Table 6 gives examples of parenteral overlap options, with LMWH being the preferred option for parenteral bridging. In general, for patients at high thromboembolic risk and in whom bridging therapy will be used, this is typically performed using therapeutic-dose LMWH, fondaparinux, or UFH. Similarly, for patients at moderate thromboembolic risk and in whom bridging therapy will be used, this may be executed with therapeutic-, intermediate-, or prophylactic-dose LMWH, fondaparinux, or UFH. While there are good data to demonstrate that prophylactic-dose LMWH or UFH is efficacious in the prevention of VTE, there are no current strong data supporting the idea that these agents, at prophylactic or intermediate doses, prevent ATE. This should be taken into consideration when risk stratifying patients as this regimen is likely more effective in patients with VTE as compared with patients with AF or MHV. It should also be noted that fondaparinux has been only used in very limited amounts within bridging studies.

### Execution of Bridging

Initially, patients should be risk stratified into low or high bleeding risk AND low, moderate, or high thromboembolic risk. Table 5 provides a visual scheme to the overall management of patients on VKAs, while Figure 1 provides visual guidance as to the chronological execution of bridging and peri-procedural management. Importantly, the key questions above need to be answered collaboratively in order to develop an individualized patient care plan.

**Table 5. Overall Suggested Approach to Peri-operative Vitamin K Antagonist Interruption**

Bleed Risk*	Thromboembolic Risk <sup>†</sup>		
	High (Annual ATE >10%; 1 Month VTE >10%)	Moderate (Annual ATE 5–10%; 1 Month VTE 2–10%)	Low (Annual ATE <5%; 1 Month VTE <2%)
<b>High</b> (2-day risk of 2–4%)	Bridging recommended/ post-procedural bridging considered	Bridging considered/ post-procedural bridging optional	Bridging not recommended/ post-procedural bridging not recommended
<b>Low</b> (2-day risk of 0–2%)	Bridging recommended/ post-procedural bridging recommended	Bridging considered/ post-procedural bridging considered	Bridging not recommended/ post-procedural bridging not recommended

ATE = arterial thromboembolism; VTE = venous thromboembolism.

\*Note: Timing for resumption of parenteral agent is based on individual patient factors and procedural factors.

<sup>†</sup>Includes theoretical 100-fold post-operative VTE risk and possible 10-fold post-operative ATE risk with major surgery.

**Table 6. Parenteral Regimens for Bridging Therapy**

Drug	Regimen
Unfractionated heparin subcutaneously	250 IU/kg q12h for therapeutic levels or 5,000 units q8h or q12h for VTE patients at moderate thromboembolic risk
Unfractionated heparin intravenously	Therapeutic dose per institutional protocol
Dalteparin sodium	100 IU anti-Xa/kg SC q12h or 200 IU anti-Xa/kg SC q24h
Enoxaparin sodium	1 mg/kg SC q12h or 1.5 mg/kg SC q24h

VTE = venous thromboembolism.

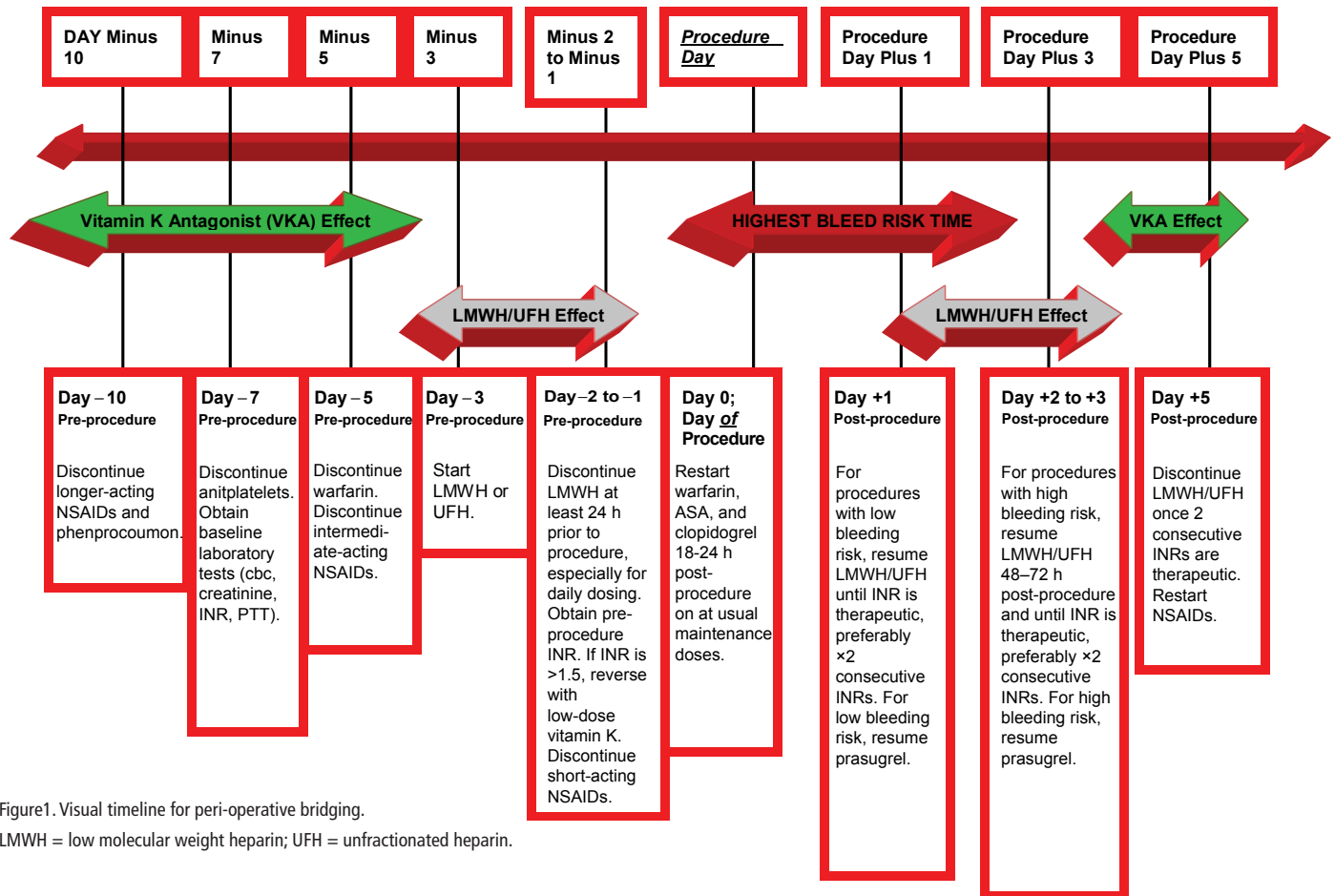


Figure 1. Visual timeline for peri-operative bridging.

LMWH = low molecular weight heparin; UFH = unfractionated heparin.

One of the *most critical points* of peri-procedural antithrombotic management, whether it be for bridging or anticoagulation or other clinical issues, is that communication between overlapping physicians and clinicians caring for the patients is of the utmost importance and should be prioritized. Patient care plans should be outlined and agreed upon with the key clinical stakeholders including the patients, with the patient input and preferences documented.

Offsets and onsets of all agents affecting coagulation need to be strongly considered as many patients are on dual or triple antithrombotic therapy, including at times one or two antiplatelets and one or two anticoagulants, including the parenteral bridging anticoagulant, if used, in addition to ancillary NSAID use. Agents should be stopped at the appropriate time, taking into consideration age and renal and hepatic issues. The elderly often eliminate drugs at a slower rate, so half-lives are lengthened; thus,

NSAIDs, antiplatelets, and anticoagulants should be stopped at a minimum of 5 half-lives and possibly as many as 7 half-lives prior to the procedure. NSAIDs can likely be stopped even earlier prior to the procedure because their indication is typically for pain and pain can be managed alternatively during the peri-procedural period. This further minimizes the bleeding risk. Warfarin should be stopped 5-7 days prior to the procedure and possibly earlier in the elderly and those with any hepatic dysfunction that may prolong the clearance of warfarin. The day prior to the procedure, a final INR should be taken in those patients on VKA. If INR is >1.5, appropriate, conservative, reversal with low-dose vitamin K (1-2.5 mg PO) should occur to ensure the INR is <1.5 for the procedure.<sup>2</sup>

If bridging therapy with parenteral anticoagulants is to be performed, it should be initiated as the INR drops below the therapeutic threshold. If

**Table 7. Characteristics and Background of New Anticoagulants**

Drug Features	Dabigatran Etxilate	Rivaroxaban	Apixaban
Target	Factor IIa	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Molecular weight	628	436	460
Dosing	Once or twice daily	Once or twice daily	Twice daily
Bioavailability (%)	6	80	60
Half-life (hours)	12–17	7–11	9–14
Renal excretion (%)	80	65	25
Populations being studied in	Medical and surgical VTE prophylaxis, atrial fibrillation, VTE treatment	Medical and surgical VTE prophylaxis, VTE treatment, and acute coronary syndromes	Medical and surgical VTE prophylaxis, atrial fibrillation, VTE treatment, and acute coronary syndromes
Drug interactions	Moderate and potent inhibitors/inducers of P-gp; caution should be used	Potent inhibitors/inducers of CYP3A4 or P-gp; caution should be used	Potent inhibitors/inducers of CYP3A4; caution should be used
Status	Approved in US for atrial fibrillation and in Canada and Europe for VTE prophylaxis after major orthopedic surgery	Approved in Canada and Europe for VTE prophylaxis after major orthopedic surgery	No approvals yet

CYP3A4 = cytochrome p450 3A4 protein; P-gp = P-glycoprotein 1; VTE = venous thromboembolism.

IV UFH is used, it should be at a therapeutic dose using a validated activated partial thromboplastin time (aPTT) or Xa, weight-based nomogram per institutional protocol if available. As the procedure approaches, the LMWH should be discontinued at a minimum of 24 hours prior to the procedure, whereas IV UFH may be stopped 4–6 hours prior to the procedure. For the last parenteral dose of LMWH, approximately half the *DAILY* dose should be administered. For daily dosing, the dose should be halved. For twice-daily dosing, the last dose should be the typical dose. It should be reiterated at this point that patients who are elderly or have renal insufficiency may need to be stopped earlier to appropriately clear the drug.

At approximately 24 hours post-procedure, VKAs, ASA, and clopidogrel can be resumed at their pre-procedure maintenance doses. Prasugrel should be initiated at approximately 24 hours for patients with a low bleeding risk and at 48–72 hours for patients with a high bleeding risk since its onset is quicker than that of clopidogrel (similar to LMWHs). NSAIDs should be resumed conservatively and in the later phases once the INR is therapeutic. If parenteral bridging is being used, LMWH and IV UFH may be resumed at 24 hours for patients with a low bleeding risk and at 48–72 hours for patients with a high bleeding risk. For both groups, adequate hemostasis should be achieved before LMWH/UFH resumption. Once the INR is therapeutic, LMWH/UFH may be discontinued.

For patients on VKA who are deemed to have too high a bleeding risk for parenteral bridging therapy, VKA should be stopped 5–7 days prior (or 10 or more days for phenprocoumon) to the procedure and resumed approximately 24 hours post-procedure. Pre-procedural VKA discontinuation may need to take place earlier in the elderly.

### The Future

Approximately 10 antiplatelets and 20 anticoagulants are currently in advanced phases of development.<sup>1</sup> New antiplatelets, such as cangrelor with a short half-life of 3–5 minutes and platelet function recovery within 1 hour, may provide new possibilities in the peri-operative setting. Novel oral anticoagulants (OACs), such as the recently approved direct thrombin (factor II) inhibitor dabigatran, may provide new approaches to peri-procedural management as their pharmacokinetic and pharmacodynamic

profiles offer new potentials such as rapid onset of action and short time to peak anticoagulation, short half-lives compared with VKAs, and no need for routine monitoring compared with VKAs.<sup>1</sup> A potential disadvantage of these agents is that there are no antidotes currently available for them, whereas vitamin K can be used with VKA agents.

Table 7 lists some key attributes of the new agents dabigatran, apixaban, and rivaroxaban. While already approved in Canada and the European Union for VTE prophylaxis following major orthopedic surgery, dabigatran is now also approved in the United States and Canada for stroke prevention in non-valvular AF patients due to the convincing results of the recent Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.<sup>17</sup> In addition, a second OAC, rivaroxaban, a direct factor Xa inhibitor, has recently been studied in the concluded ROCKET-AF trial (Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-central Nervous System Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation), with promising results in patients with AF; therefore, rivaroxaban will likely soon gain approval in the United States and Canada for this indication.<sup>18</sup> A third OAC, apixaban, is also a direct factor Xa inhibitor and is in advanced stages of testing.<sup>19</sup> All three agents have been or are being studied in VTE prophylaxis, AF, and VTE treatment, with rivaroxaban and apixaban also being studied in acute coronary syndromes.<sup>20</sup> These agents' shorter onset and offset, more predictable and consistent anticoagulant effect, and faster time to peak anticoagulant effect (within hours) compared with VKAs will likely eliminate the need for parenteral bridging therapies.<sup>13,20</sup> The short half-lives of the new OACs suggest that they may be stopped within 1–2 days prior to a procedure and resumed as soon as hemostasis has been achieved and the period of high bleeding risk has subsided.<sup>13</sup> For procedures with low bleeding risk, these agents may likely be resumed within 24 hours after the procedure; resumption after procedures with high bleeding risk may likely occur within 48–72 hours after the procedure has occurred.<sup>13</sup> This approach would minimize the time the patient spends without therapeutic levels of anticoagulation, thus minimizing the thromboembolic risks associated with peri-procedural interruption of anticoagulation. In addition, use of these novel OACs will likely minimize the use of two concurrent

anticoagulants, which will likely lead to less overall bleeding associated with peri-procedural management of anticoagulants. It may also be possible to convert patients from warfarin to these agents prior to elective procedures.

New reversal agents for LMWH and UFH are entering phase II studies and may have fewer adverse effects than protamine.<sup>21</sup> This may be in part because the agents are smaller molecules and also not anticoagulants like protamine. PMX-60056's mechanism of action is to bind directly to the pentasaccharide group of UFH or LMWH. This agent may provide an opportunity to also minimize patients' time without therapeutic anticoagulation if LMWH can be used in closer proximity to the procedure. It may also provide other opportunities for reversal during cardiac and vascular surgeries, for which protamine is currently being used intra-operatively.

Two large, placebo-controlled, peri-operative bridging trials are under way and geared to determine the safety and efficacy of bridging therapy in patients with AF or MHV.<sup>22,23</sup> The Effectiveness of Bridging Anticoagulation for Surgery (BRIDGE study) is a randomized, double-blind, placebo-controlled trial evaluating the LMWH dalteparin (given twice daily) for peri-procedural bridging in patients with AF.<sup>22</sup> The design requires AF patients to have a minimum of one additional major stroke risk factor, previous warfarin use for at least 3 months, and the need for temporary interruption of warfarin for a procedure. The primary efficacy outcome is ATE, and secondary efficacy outcomes are MI, DVT, and PE. The primary safety outcome is major bleeding, and the secondary safety outcome is minor bleeding.<sup>22</sup> The PERIO 2 (Safety and Effectiveness Study of LMWH Bridging Therapy versus Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin) is a multi-center, randomized, double-blind, placebo-controlled trial that is aimed to assess whether bridging therapy reduces the risk of peri-operative thromboembolism.<sup>23</sup> Patients with MHV or AF who have a minimum of one additional risk factor for major stroke will discontinue warfarin treatment 5 days prior to the procedure and receive once-daily dalteparin or placebo for a minimum of 4 days depending on bleed risk. Thromboembolism and bleeding rates will be observed for 3 months.<sup>23</sup> Combined, these two studies aim to enrol more than 5,000 patients and should help to further determine which patient groups will best benefit from bridging therapy and should provide valuable data in the moderate-risk thromboembolic patient population, for which there is currently the greatest clinical equipoise.<sup>8</sup> Patient enrollment is projected to be completed by 2014.

### Conclusions

Clinicians must carefully risk stratify patients' thromboembolic and bleeding risks based on both individual patient risk factors as well as procedure-related risks. Clinical decisions must carefully be communicated between decision makers so that timing can be coordinated for both the discontinuation and resumption of various antiplatelets and anticoagulants. Peri-operative bridging is a leading example of the careful risk-benefit assessment that must take place in order to maximize patient care. In this case, it is the delicate balance between thromboembolic and bleeding risks that needs to be weighed. The introduction of new OACs may simplify the peri-operative management of patients, without the need for overlap of a parenteral agent. In addition, these agents may be used pre-procedure in closer proximity to VKA use, due to their shorter half-lives, and resumed when

deemed safe with an almost immediate peak anticoagulant effect. Although these agents are currently approved for various indications in Canada, the United States, Australia, and the European Union, uptake has been slow. Therefore, bridging for patients on VKA will continue to be a challenging clinical issue for years. New randomized, placebo-controlled trials will likely provide novel, higher-quality data to this field that will be especially useful in patients with moderate thromboembolic risk.

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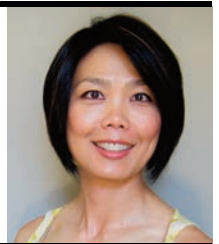
## Original Article

## Evidence-Based Treatment of Cancer-Associated Thrombosis

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**Abstract**

Anticoagulants remain the treatment of choice in patients with cancer-associated thrombosis (CAT). Once-daily injection of a low molecular weight heparin (LMWH) is the preferred monotherapy for treatment of CAT, and dalteparin is the only LMWH with regulatory approval for this indication. Currently, warfarin remains the only other option for long-term therapy as new oral anticoagulants such as dabigatran and rivaroxaban have not been studied in cancer patients. All anticoagulants are associated with bleeding, and this risk must be weighed against the benefits of reducing recurrent thrombosis. This is particularly important in patients with a short life expectancy in whom symptom relief from venous thromboembolism is the primary goal for anticoagulation. Recurrent thrombosis can be treated with higher doses of LMWH, and inferior vena cava filter insertion should be avoided. Anticoagulation in those with bleeding concerns remains challenging without evidence to guide practice. The optimal duration of anticoagulation has not been studied in CAT.

### Résumé

L'anticoagulant est toujours le traitement de choix de la thrombose chez le patient atteint de cancer. Une héparine de bas poids moléculaire en injection unquotidienne constitue la monothérapie de prédilection de cette thrombose, et la daltéparine est la seule héparine de bas poids moléculaire d'usage approuvé dans cette indication. À l'heure actuelle, la warfarine demeure la seule autre option dans le traitement au long cours, car les nouveaux anticoagulants oraux, tels le dabigatran et le rivaroxaban, n'ont pas été étudiés chez les personnes atteintes de cancer. Le risque de saignement est présent pour tous les anticoagulants et il doit être soupesé comparativement à l'effet bénéfique de la réduction de la thrombose récurrente. Cela revêt d'autant plus d'importance pour le patient dont l'espérance de vie est brève, chez qui l'atténuation des symptômes de la thromboembolie veineuse représente le principal but de l'anticoagulation. La thrombose récurrente peut être traitée par une héparine de bas poids moléculaire à une dose élevée et l'insertion d'un filtre dans la veine cave inférieure est à éviter. L'anticoagulation en présence d'un risque de problème hémorragique pose des difficultés en l'absence de données probantes pour encadrer la pratique. La durée optimale de l'anticoagulation en cas de thrombose chez un patient atteint de cancer est inconnue.

Patients with cancer often develop venous thromboembolism (VTE). In fact, VTE is the second leading cause of death in oncology patients.<sup>1</sup> Deep vein thrombosis (DVT) and pulmonary embolism (PE) can also delay or interfere with first-line cancer therapy, precipitate or prolong hospitalization, and increase health care resource utilization. Thrombotic complications are burdensome to the patients and their families and have a negative impact on quality of life. It is also recognized that the incidence of venous and arterial thrombotic events in cancer patients is rising because of the aging population and the use of more effective but often more thrombogenic cancer treatments.<sup>2,3</sup>

To date, few studies have evaluated the efficacy and safety of anticoagulants in cancer-associated thrombosis (CAT), and clinical research investigating duration of therapy, prognostic stratification, and other interventions is needed. Major national and international consensus guidelines support the use of low molecular weight heparin (LMWH) as the preferred class of agents for the initial and long-term treatment of CAT and therapeutic options remain limited. Novel oral anticoagulants may offer more effective and convenient strategies for minimizing the burden of VTE but clinical trials evaluating these new agents have not been conducted in the oncology population.

### Therapeutic Goals in Cancer-Associated Thrombosis

The major objectives in the treatment of VTE are to diminish the acute symptoms of DVT and/or PE, and to reduce the incidence of long-term sequelae, such as recurrent thrombosis, fatal PE, pulmonary hypertension, and post-thrombotic syndrome. In patients with cancer, convenience of treatment, interference with anti-cancer therapy, and quality of life are also critically important considerations when making a decision regarding thrombosis treatment. In patients with a short life expectancy, it is sometimes questionable whether anticoagulation offers net benefits, considering the cost of LMWH, the inconvenience of laboratory monitoring for warfarin, and the potential risk of bleeding.

### Anticoagulant Regimens

The standard treatment for an acute episode of VTE in the general population consists of initial therapy with a heparin followed by long-term therapy with warfarin or another vitamin K antagonist (VKA). But this regimen does not meet the needs of cancer patients, in whom warfarin

is usually poorly tolerated and the risk of recurrent thrombosis remains high despite anticoagulation. It is now recognized that the natural history of VTE in patients with cancer is more aggressive and unpredictable than in patients without cancer, and that treatment with heparin followed by warfarin is associated with a high incidence of treatment failure.<sup>4,5</sup> Other complications, such as bleeding, are also significantly higher in cancer patients. Prospective studies have reported that up to 21% of patients with cancer develop recurrent VTE and up to 13% develop major bleeding while receiving warfarin.<sup>4,5</sup>

### Initial Therapy

Traditional treatment divides the course of anticoagulant therapy into initial and long-term phases. This is largely due to the delayed therapeutic action of warfarin and other VKAs because it depends on the clearance of circulating, carboxylated vitamin K-dependent factors II, VII, IX, and X. To “bridge” this gap, a fast acting anticoagulant is required for the first 5–7 days. Currently, the anticoagulants available for the initial treatment of acute VTE are unfractionated heparin (UFH), LMWH, fondaparinux, and argatroban. Heparins and fondaparinux indirectly inhibit serine proteases in the clotting cascade by binding to antithrombin via a unique pentasaccharide sequence and accelerating antithrombin's inhibitory action. While UFH and LMWH indirectly inhibit both thrombin and activated factor X (fXa), fondaparinux is a selective inhibitor of fXa with no activity against thrombin. Argatroban is a direct thrombin inhibitor mainly reserved for patients with heparin-induced thrombocytopenia. Most of the new oral anticoagulants being developed are direct inhibitors of thrombin (e.g., dabigatran) or fXa (e.g., rivaroxaban, apixaban). Their rapid onset of action and stable pharmacokinetics make them suitable for once- or twice-daily dosing at fixed doses and attractive alternatives to traditional anticoagulants.

### Unfractionated Heparin, Low Molecular Weight Heparins, and Fondaparinux

Of the parenteral anticoagulants, LMWH is most widely used for initial therapy. This reflects the advantages offered by LMWH over UFH: simple weight-based dosing; no need for routine laboratory monitoring; availability of outpatient treatment; lower risk of heparin-induced

thrombocytopenia; and lower health care costs from avoided hospitalization.<sup>6,7</sup> A well-designed randomized trial has shown that UFH can be given subcutaneously using weight-based dosing on an outpatient basis.<sup>8</sup> However, the twice-daily, large-volume injections make this less desirable than once-daily LMWH. LMWH also comes in prefilled syringes, which simplify administration and reduce the risk of dosing errors. The vast majority of patients are able to perform self-injections when they are given adequate support and appropriate education, and cohort studies have shown that cancer patients can self-inject LMWH safely at home.<sup>9–11</sup> The major disadvantage of outpatient LMWH treatment is drug cost. Depending on the provincial and private drug reimbursement programs available, the cost is a barrier for some patients. However, many hospitals offer outpatient programs that cover the cost of LMWH, provided that patients return to the emergency department or medical day care on a daily basis. The avoided admission for 5–7 days makes this economically attractive to hospital administration, albeit burdensome to patients who must return for daily visits.

Pooled evidence from the literature also shows that LMWH therapy provides better efficacy, safety, and survival than UFH.<sup>12</sup> According to a Cochrane Database of Systematic Reviews published in 2004 that compared LMWH with UFH, weight-adjusted LMWH given subcutaneously once or twice daily reduces the risk of recurrent thrombosis by 43% (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.44–0.75), lowers the risk of major hemorrhage by 50% (OR 0.50, 95% CI 0.29–0.85), and reduces overall mortality by 38% (OR 0.62, 95% CI 0.46–0.84).<sup>12</sup> Consequently, LMWH should be considered superior to UFH for initial treatment of VTE. The only patient groups in whom UFH remains the drug of choice are those with hemodynamic instability, severe renal insufficiency, or a very high risk of bleeding so that rapid reversal of the anticoagulant effect is critical.

Less evidence is available for fondaparinux but it does show that fondaparinux has comparable efficacy and safety with the heparins.<sup>13,14</sup> Its once-daily dosing does not provide additional convenience over LMWH but it is rarely associated with heparin-induced thrombocytopenia. It is contraindicated in patients with significant renal insufficiency. Unlike heparins, fondaparinux cannot be reversed with protamine sulfate and it has a long half-life of approximately 18 hours.

None of the anticoagulants have been formally studied in oncology patients for the initial therapy of VTE. Because these patients usually represent only 10–15% of the total study population in clinical trials, the efficacy and safety of anticoagulants are not well established in patients with cancer. Based on limited published data from trials that reported on the outcomes of this subgroup, weighted-adjusted, subcutaneous doses of LMWH and activated partial thromboplastin time (aPTT)-adjusted intravenous infusions of UFH have similar efficacy in patients with cancer.<sup>15,16</sup> However, fondaparinux may be less efficacious than LMWH in cancer patients with DVT while it may be more efficacious than UFH in cancer patients with PE.<sup>17</sup> This evidence comes from a single post-hoc subgroup analysis, so it should be interpreted with caution. Data on the bleeding risk of UFH, LMWH, and fondaparinux for initial therapy of VTE in cancer patients are not available.

### **Novel Oral Anticoagulants**

None of the new oral anticoagulants being developed are available for VTE

treatment at this time but recent clinical trials show these agents hold great promise in replacing traditional anticoagulants for treatment of VTE in the general population.<sup>17,18</sup> These agents are attractive to clinicians and patients because they are given in fixed doses and do not require laboratory monitoring. Their major limitation is the lack of readily available assays to measure the anticoagulant effect when needed, for example, when patients present with bleeding. This also means that compliance cannot be readily assessed when treatment failure is encountered. Lastly, the lack of specific antidotes for these agents has raised concerns.

To date, rivaroxaban has been reported to be comparable in efficacy and bleeding compared with heparin followed by warfarin but few patients with cancer were included in the study.<sup>17</sup> Dabigatran has not been compared with UFH or LMWH for initial treatment.<sup>18</sup> The only new agent with cancer patient-specific data is apixaban. In 125 patients with advanced or metastatic cancer on first- or second-line chemotherapy, apixaban given for 12 weeks was found to be well tolerated. These patients did not have VTE and did not experience bleeding.<sup>19</sup> Overall, there are insufficient data to support efficacy and safety of the new oral agents for treatment of CAT. Because patients with cancer have more aggressive thrombosis and they are more likely to experience drug interactions and organ dysfunction, clinical trials in oncology patients are needed to evaluate new anticoagulants.

### **Long-Term Therapy**

Anticoagulant therapy must be continued for a minimum of 3 months to reduce the risk of recurrent thrombosis. For decades, VKA therapy was the only feasible treatment option, but LMWH is now the preferred treatment of choice for long-term anticoagulant therapy in patients with cancer. New oral anticoagulants are attractive for long-term treatment but more data are needed on their efficacy and safety with prolonged exposure.

### **Vitamin K Antagonists**

Warfarin is the most commonly used VKA worldwide. When a patient is diagnosed with an acute DVT or PE, warfarin is started and is continued for 3 months or longer. Due to differences in the anticoagulant response between patients and within patients over time, dose adjustments are needed based on the international normalized ratio (INR). For the treatment of VTE, the target therapeutic INR range is 2.0–3.0. When VKA therapy is used following therapeutic doses of UFH, LMWH, or fondaparinux, the 3-month risk of symptomatic recurrent VTE is approximately 3–4% for patients without cancer.<sup>20</sup>

But warfarin therapy is problematic in patients with cancer. Due to its pharmacology, unpredictable anticoagulant response can result from drug interactions, changes in vitamin K status, liver dysfunction, and gastrointestinal disturbances such as vomiting and diarrhea. All of these are common events in cancer patients. Furthermore, because vitamin K antagonists have a delayed onset of action and prolonged clearance of the anticoagulant effect, they are difficult to manage in patients who require periodic invasive procedures or experience frequent episodes of chemotherapy-induced thrombocytopenia.

Cancer patients also develop recurrent VTE despite having therapeutic INR levels. Studies have reported the annual risk of recurrent VTE is

**Table 1. Clinical Trials of Long-Term Anticoagulation for the Prevention of Recurrent VTE in Cancer Patients**

Study	No.*	Treatment Regimens	Recurrent VTE <sup>†</sup>	Major Bleeding <sup>†</sup>	Death	p Value for Primary Outcome <sup>‡</sup>
Lee <sup>21</sup>	336	Dalteparin (200 IU/kg for 5–7 d) + coumarin (INR 2–3 × 6 m)	17%	4%	41%	.002 <sup>a</sup>
	336	Dalteparin (200 IU/kg OD for 1 m) then dalteparin (~150 IU/kg OD × 5 m)	9%	6%	39%	
Hull <sup>24</sup>	100	IV UFH (aPTT adjusted for 6 d) + warfarin (INR 2–3 × 3 m)	10%	7%	19%	NS <sup>b</sup>
	100	Tinzaparin (175 IU/kg OD for 3 m)	6%	7%	20%	
Meyer <sup>22</sup>	71	Enoxaparin (1.5 mg/kg OD for at least 4 d) + warfarin (INR 2–3 × 3 m)	21.1%	21.1%	22.7%	.09 <sup>c</sup>
	67	Enoxaparin (1.5 mg/kg OD for 3 m)	10.5%	10.5%	11.3%	
Deitcher <sup>23</sup>	30	Enoxaparin (1 mg/kg BID for 5 d) + warfarin (INR 2–3 for 180 d)	10.0%	2.9%	8.8%	NS <sup>d</sup>
	29	Enoxaparin (1 mg/kg BID for 5 d) then enoxaparin (1 mg/kg OD for 175 d)	6.9%	6.5%	6.5%	
	32	Enoxaparin (1 mg/kg BID for 5 d) then enoxaparin (1.5 mg/kg OD for 175 d)	6.3%	11.1%	19.4%	

aPTT = activated partial thromboplastin time; BID = twice daily; d = day; INR = international normalized ratio; IU = international units; IV = intravenous; m = month; NS = not significant; OD = once daily; UFH = unfractionated heparin; VTE = venous thromboembolism.

\*No. denotes number of patients evaluable for the primary outcome in the respective treatment groups.

<sup>†</sup>Event rates reported during treatment period.

<sup>‡</sup>Notes:

a. Primary outcome of cumulative incidence of objectively documented recurrent VTE was assessed at 6 months. Hazard ratio in the dalteparin group compared with the coumarin group was 0.48 (95% CI 0.30 to 0.77), log-rank  $p = .002$ .

b. Primary outcome measure of objectively documented recurrent VTE or death was assessed at 3 and 12 months. There was no significant difference between treatment groups at the end of study treatment at 3 months (difference  $-4.0%$  [95% CI  $-12.0%$  to  $4.1%$ ]).

c. Primary outcome was a composite end point of objectively documented recurrent VTE or major bleeding. There was no significant difference between treatment groups with a relative risk of 2.02 (95% CI 0.88 to 4.65).

d. Primary objective was to evaluate the feasibility of recruitment and compliance with long-term (180 days) injections of enoxaparin. No difference was observed in overall compliance with an average rate of 95% among all groups.

21–27% in cancer patients while on warfarin therapy.<sup>4,5</sup> This is two- to three-fold higher than in patients without cancer. Cancer patients on warfarin also have an annual risk of major bleeding of 12–13%, versus 3–4% for patients without cancer.<sup>4,5</sup> The risk of bleeding does not correlate with the INR level and it continues to increase over the course of therapy. Lastly, the psychosocial burden of warfarin is significant in patients with cancer. Having to undergo weekly venopuncture is painful for patients who have poor venous access after many cycles of chemotherapy, and going to a laboratory or the hospital for monitoring is burdensome because many of these patients have fatigue, chronic pain, restricted mobility, or limited access to transportation. The frequent dosing changes are also confusing, frustrating, and potentially dangerous for elderly patients, who are often on many other medications, such as narcotics for pain control.

### Low Molecular Weight Heparins

In contrast to VKAs, LMWHs do not require routine laboratory monitoring and have minimal drug interactions. Although uncomfortable, subcutaneous injection also ensures drug delivery, which is a benefit in patients who are unable to tolerate oral intake or have significant gastrointestinal problems. Finally, dose adjustments or

withholding of LMWH can be made readily to accommodate thrombocytopenia or invasive procedures. However, LMWH should be avoided in patients with severe renal dysfunction. It is also associated with a low risk of heparin-induced thrombocytopenia and higher costs.

To date, a number of open-label trials have compared different LMWHs with VKAs for the long-term treatment of CAT (Table 1).<sup>21–24</sup> The largest of these studies is the CLOT trial.<sup>21</sup> This study randomized 676 cancer patients with acute VTE to standard treatment with dalteparin followed by VKA therapy or to experimental therapy with dalteparin alone for 6 months. Patients in the dalteparin group received therapeutic doses at 200 IU/kg once daily for the first month followed by a maintenance dose of 75–80% of the full dose for the next 5 months. Patients in the control group received dalteparin 200 IU/kg once daily for a minimum of 5 days and a VKA at doses to target the INR value at 2.5 for 6 months. All patients were followed for symptomatic recurrent VTE, bleeding, and death. Over the 6-month treatment period, 27 of 338 in the dalteparin group and 53 of 338 in the VKA group had symptomatic, recurrent VTE. The cumulative risk of recurrent VTE was reduced from 17% in the VKA group to 9% in the dalteparin group, resulting in a statistically significant risk reduction of 52% (log-rank  $p$  value .002). Accordingly, one episode of recurrent VTE is prevented for every 13 patients treated with dalteparin.

There were no differences in major or any bleeding (6% of patients in the dalteparin group versus 4% of the control group experienced major bleeding), or overall survival (40% of the patients in each group died; 90% were due to progressive cancer). Similar results were obtained in a prospective cohort study using a fixed dose of dalteparin for long term-treatment. The study included 203 patients with metastatic cancer who received an initial 7-day course of weight-adjusted dalteparin followed by dalteparin 10,000 IU once daily, regardless of the patients' weight. During 3 months of follow-up, 18 patients (9%) developed recurrent VTE and 11 patients (5%) had major bleeding.<sup>25</sup>

Smaller trials have studied other LMWHs. The CANTHANOX trial compared 3 months of standard warfarin therapy with enoxaparin in cancer patients with proximal DVT, PE, or both.<sup>22</sup> After 3 months of treatment, 15 of 71 patients in the warfarin group had recurrent VTE or major bleeding, as compared with seven of 67 patients assigned to receive enoxaparin ( $p = .09$ ). There were six fatal bleeding events in patients receiving warfarin and none in the enoxaparin group. Another trial, the ONCENOX study, evaluated enoxaparin for long-term treatment in 101 cancer patients with VTE. Two different doses of enoxaparin (1 mg/kg or 1.5 mg/kg once daily) were tested, but the study was underpowered to demonstrate any difference between warfarin and enoxaparin.<sup>23</sup> A randomized trial has also compared tinzaparin with warfarin for long-term use in cancer patients.<sup>24</sup> In the Main-LITE cancer study, 100 patients were randomized to receive 3 months of tinzaparin 175 units/kg once daily and 100 were assigned to receive usual care with intravenous UFH then warfarin. At the end of the 3-month treatment period, 6% of patients in the tinzaparin group versus 10% of the usual care group had symptomatic recurrent VTE. This difference was not statistically significant ( $-4.0\%$ ; 95% CI  $-12.0$  to  $4.1\%$ ). Both groups had similar incidences of major bleeding and overall mortality. A larger randomized trial, the CATCH trial, is now ongoing internationally to compare tinzaparin with warfarin for extended treatment for CAT.

Based on the above results, LMWH is recommended for extended treatment in cancer patients by the American College of Chest Physicians Consensus Guidelines,<sup>20</sup> the British Society of Haematology,<sup>26</sup> the National Comprehensive Cancer Network,<sup>27</sup> and the American Society of Clinical Oncology<sup>28</sup> as the treatment of choice for cancer patients with VTE. Currently, dalteparin is the only LMWH to receive regulatory approval for the extended treatment of CAT. Enoxaparin and tinzaparin are also used worldwide but they are not approved for long-term treatment. All LMWH products are available in pre-filled syringes, which ease self-administration and reduce the risk of dosing error. The major limitation of using LMWH is the cost. This is prohibitive for many patients, especially if they are already paying for expensive chemotherapeutic regimens. The American Society of Clinical Oncology guidelines have taken this into consideration and recommend the use of warfarin therapy if LMWH is not available.<sup>28</sup> This is sensible and practical advice, and tailors therapy to meet patients' medical and financial needs. In patients with a particularly high risk of recurrent thrombosis, such as those with progressive metastatic disease, those with very thrombogenic tumour histologies (e.g., pancreas, glioblastoma, lung), and those with a previous history of thrombosis or multiple risk factors, it may be beneficial to provide LMWH for at least the first month of treatment, when the risk of thrombosis is highest, and then continue with warfarin therapy thereafter,

if the cost of LMWH is a problem.

LMWH is relatively contraindicated in patients with renal dysfunction. However, if VKA therapy is also problematic in a patient with renal insufficiency, then the better option is to use LMWH with anti-factor Xa monitoring and adjust the dose accordingly. With once-daily regimens, the target peak anti-Xa level at 3–4 hours after an injection is 1.0–1.5 IU/mL, and the trough level prior to the next dose should be 0.2–0.5 IU/mL. Provided that the renal function is stable and does not deteriorate, it is not necessary to measure the anti-Xa level more than once monthly. Alternatively, some physicians use twice-daily, subcutaneous injections of UFH in those with renal compromise. This is not an attractive approach as the aPTT must be meticulously followed, and the dose and volume required tend to be rather large. The large dose of UFH required also raises the concern for heparin-induced thrombocytopenia and osteoporosis. In some areas, the cost of UFH on an outpatient basis is comparable to LMWH.

### Novel Oral Anticoagulants

Novel oral agents are very attractive for long-term treatment of VTE. Major concerns include compliance and toxicity with chronic exposure and drug cost.

To date, large randomized controlled trials have been completed to study dabigatran and rivaroxaban for long-term use. The trials vary in design making cross-comparisons difficult. In the RECOVER trial, all patients with either DVT or PE received a 1-week course of UFH or LMWH followed by either warfarin or dabigatran,<sup>18</sup> while the EINSTEIN DVT trial started rivaroxaban in the initial treatment phase and continued it for 3 months or longer.<sup>17</sup> In the dabigatran trial, the risk of recurrent thrombosis and major bleeding were comparable between dabigatran and warfarin.<sup>18</sup> In the rivaroxaban trial, no differences in efficacy and bleeding were observed between rivaroxaban alone versus heparin followed by warfarin. In both trials, cancer patients made up approximately 5% of the study population and their results have not been reported separately. Given the higher risk of recurrent thrombosis and bleeding in patients with cancer, it is important that further research is done to understand the antithrombotic impact of these new agents in cancer patients.

### Therapy for Recurrent Thrombosis

Up to 9% of patients with CAT treated with LMWH or 20% treated with warfarin can develop recurrent VTE. Studies have suggested that presence of metastasis, younger age, or a short interval between VTE and cancer diagnosis (less than 3 months) are predictors of recurrent thrombosis despite anticoagulation.<sup>29,30</sup> Whether the risk factors that increased the risk of a first episode of thrombosis also contribute to a higher risk of recurrent thrombosis is unknown.

Although randomized controlled trial data are lacking to guide optimal management in oncology patients with recurrent thrombosis, observational data and increasing clinical experience support the use of LMWH in this setting. In patients who developed a recurrence while on warfarin therapy, the recommended practice is to switch these patients to LMWH because it is more efficacious than warfarin. Raising the intensity of warfarin therapy is not recommended because of the potential for increasing bleeding without a benefit in reducing recurrent VTE. Patients with cancer have a high risk of bleeding as well as a high risk of recurrent

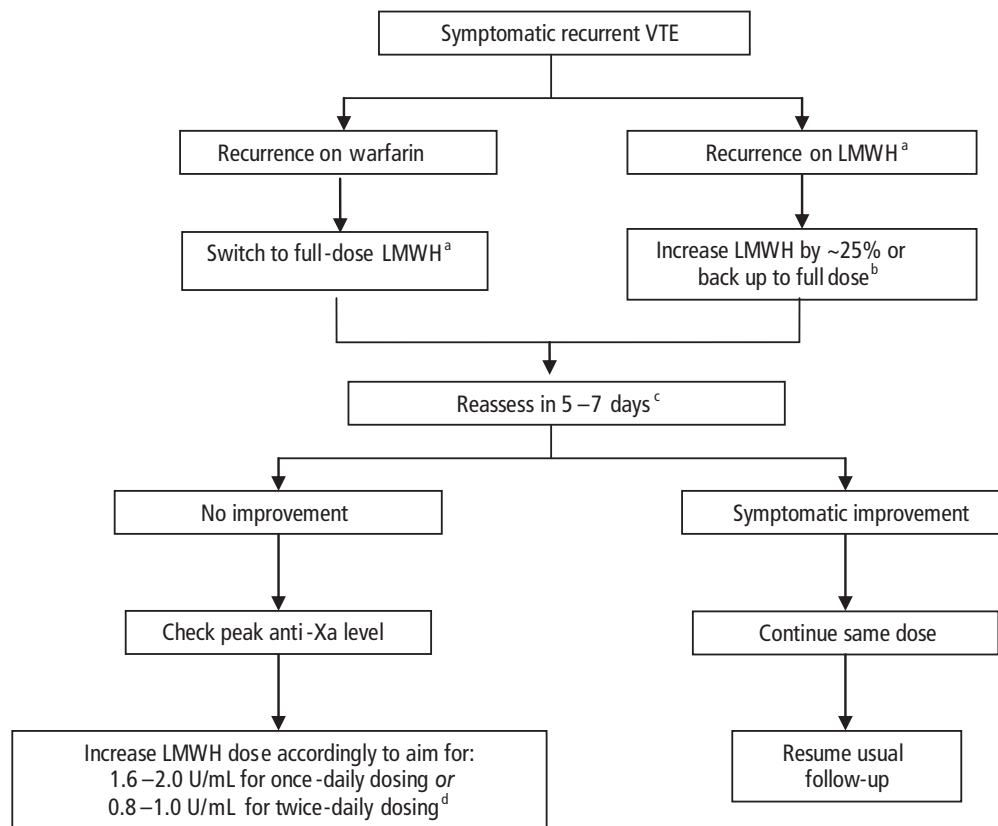


Figure 1. Suggested approach in treating recurrent VTE in patients with cancer. Notes: a. Only dalteparin has regulatory approval for extended treatment of cancer-associated thrombosis. b. Full dose refers to the recommended weight-adjusted dose of LMWH for the initial therapy of VTE. c. Reassessment should consist of clinical evaluation of symptoms. Radiological imaging is not required except when deterioration is noted and further extension or new thrombosis is suspected. d. These are empiric target levels set for patients who had recurrent thrombosis while on standard weight-based doses of LMWH. LMWH = low molecular weight heparin; VTE = venous thromboembolism.

thrombosis despite achieving therapeutic and even higher levels of INRs.<sup>5</sup> For patients who developed a recurrence while on LMWH, dose escalation of LMWH is often effective (Figure 1). In a small cohort study of oncology patients with recurrent thrombosis while on LMWH or warfarin, escalating the dose of LMWH by 20–25% or switching to LMWH, respectively, was effective in preventing further thrombotic episodes.<sup>31</sup> During 3 months of follow-up, six of 70 (8.6%) patients developed another recurrence while one patient had a major bleeding event and two had minor bleeding. The success of escalated doses of LMWH suggests that the standard weight-adjusted dose regimens are insufficient in some patients with cancer. This is not surprising given the heightened prothrombotic state of these patients. Anecdotal experience has found that higher LMWH doses might be required to achieve therapeutic anti-Xa levels.

### Inferior Vena Cava Filter

Insertion of a vena cava filter has been recommended for oncology patients with recurrent VTE despite adequate long-term LMWH therapy. However, adequate studies have not been done to evaluate or document the outcomes. Retrospective series have reported that up to 32% of oncology patients with filters inserted for thrombosis develop recurrent

VTE.<sup>32</sup> The high recurrence rate is not surprising since filters do not treat the underlying hypercoagulable state in patients with cancer. The single randomized trial studying the efficacy of filters in patients who were also treated with anticoagulation showed a reduction in symptomatic pulmonary embolism but higher rates of recurrent deep vein thrombosis in the filter group.<sup>33</sup> Overall, the total VTE rates were the same and a difference in overall survival was not observed. Considering the cost and invasiveness of filters and the lack of proven efficacy, they should be used only in situations where anticoagulant therapy is contraindicated because of serious, active bleeding.

### Therapy for Patients with Active or High Risk of Bleeding

Factors unique to cancer patients that may contribute to bleeding include the type and location of the tumour and its metastases, cancer treatments that cause rapid shrinkage of tumour mass resulting in friable vessels, chemotherapy-induced thrombocytopenia, and the need for invasive, diagnostic, or therapeutic procedures. Liver dysfunction may cause decreased production of clotting factors, and disseminated intravascular coagulopathy leads to uncontrolled consumption of coagulant proteases. Both thrombocytopenia and clotting factor derangement can also result

from other causes, such as sepsis. Adding anticoagulant therapy to these comorbid conditions certainly increases the risk of serious and potentially fatal hemorrhage.

Prior to initiating anticoagulant therapy, it is important to assess the severity and source of bleeding in those who are at risk, and weigh that against the burden or severity of the thrombotic event. The degree of “aggressiveness” of interventions should also depend on the quality of life and life expectancy. Bleeding in patients with cancer can range from nose bleeds to nuisance oozing from tumour invasion of mucosal sites, to life-threatening events from intracranial hemorrhage, to fatal events from tumour erosion into large vessels. In patients with minor bleeding, anticoagulant therapy may be tolerated. Careful monitoring for exacerbation of the bleeding is important. In a patient with serious or potentially life-threatening sources of bleeding, it may be prudent to withhold anticoagulation and follow with serial imaging if the thrombotic event was non-life threatening. In patients with serious bleeding and life-threatening thrombosis, filter insertion is often the default therapeutic option. Although this is a seemingly sensible approach, filters may contribute to thrombus extension and precipitate thrombus formation in the vena cava on the proximal side of the filter. Fatal PE has been reported in cancer patients after filter placement. Another “side effect” of filter placement is the false sense of security that anticoagulant therapy can be delayed or is no longer needed, even when the bleeding event has resolved. In patients with severe thrombocytopenia and an acute, serious thrombotic event, platelet transfusion support to maintain the platelet count above  $50 \times 10^9/L$  may be sufficient to allow full therapeutic anticoagulation. When the platelet count is between 20 and  $50 \times 10^9/L$ , reducing the dose of LMWH by half is reasonable. Below a platelet count of  $20 \times 10^9/L$ , most physicians would discontinue anticoagulant therapy. Of note, it has been reported that prophylactic doses of LMWH can be tolerated even in patients with platelet counts below  $20 \times 10^9/L$  and that symptoms of VTE can improve without using full therapeutic doses. Since there is very little literature on the management of these difficult patients, each case must be handled individually with thorough education and involvement of the patient in treatment management decisions.

### Duration of Anticoagulant Therapy

The length of treatment with an anticoagulant after a first episode of VTE has not been studied in patients with cancer. However, based on the consensus that patients with ongoing or irreversible risk factors for VTE need an extended duration of anticoagulant therapy, many cancer patients receive anticoagulation for longer than 6 months because they have evidence of cancer or are receiving chemotherapy. Beyond this period, “indefinite” therapy is conventionally recommended in patients with known metastases because their risk of recurrent VTE is high.<sup>28</sup> To date, biochemical markers or imaging assessment have not been evaluated to help guide duration of anticoagulation in oncology patients.

Patients should be re-evaluated frequently to assess the risk-benefit ratio of continuing anticoagulant therapy. The decision should also be based on the patient’s quality of life, life expectancy, and preference. Without evidence from randomized trials or validated methods of identifying patients who would benefit from extended secondary prevention, anticoagulant therapy beyond the usual 6-month period must be carefully assessed and tailored for each individual patient.

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## Original Article

### Thromboprophylaxis in High-Risk Patients: Medically Ill Hospitalized Patients and Major Orthopedic Surgery

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#### Abstract

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is a common medical problem with significant associated morbidity and mortality. Hospitalization for medical illness, major orthopedic surgery in the form of total hip and total knee arthroplasty, and hip fracture are important transient risk factors for the development of venous thromboembolic disease. Recommended

options for thromboprophylaxis in hospitalized medically ill patients and in major orthopedic surgery, as well as their underlying evidence, are discussed herein.

## Résumé

La maladie thromboembolique veineuse, qui englobe la thrombose veineuse profonde et l'embolie pulmonaire, est un problème de santé fréquent qui comporte son lot important de morbidité et de mortalité. L'hospitalisation pour cause de maladie, l'intervention chirurgicale majeure de nature orthopédique, plus précisément l'arthroplastie totale de la hanche ou du genou, et la fracture de la hanche sont des facteurs de risque de maladie thromboembolique veineuse. Les auteurs examinent la thromboprophylaxie recommandée chez le malade hospitalisé et chez la personne devant subir une intervention chirurgicale orthopédique majeure, ainsi que les données probantes à l'appui de ces recommandations.

Venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common, potentially fatal yet preventable and treatable medical problem. VTE is the third leading cause of cardiovascular mortality with one in 20 experiencing VTE in their lifetime.<sup>1-7</sup> VTE is associated with acute morbidity as well as with long-term consequences, such as post-thrombotic syndrome and recurrent VTE.<sup>8</sup> Major orthopedic surgery and hospitalization for medical illness are known transient risk factors that increase the risk for DVT or PE. This article will outline risk factors for the development of VTE as well as the types and duration of thromboprophylaxis recommended in these high-risk populations.

## Thromboprophylaxis in Medically Ill Patients

VTE remains a frequent cause of preventable morbidity and mortality in patients hospitalized with medical illness. More than 15 million medical patients are admitted to hospital in North America annually,<sup>9</sup> many of whom are at risk of developing DVT and PE. Indeed, an estimated 50–75% of VTE in hospitalized patients occur in those admitted to a medical service.<sup>10</sup> Although thromboprophylaxis in medically ill patients has been shown to be safe and effective, its practice remains underused in Canada.<sup>11</sup>

## Risk Factors

The risk of developing VTE is affected by a patient's underlying medical condition as well as the presence of other comorbidities. There are several risk factors for VTE in the medically ill patient (Table 1), and it is felt that this risk increases if multiple risk factors are present. Every hospitalized patient should be assessed for risk upon admission and this assessment should be re-evaluated regularly based on the patient's hospital course and changes in clinical status. Although models to estimate risk of developing VTE in medical patients have been proposed, there is no prospectively validated model for risk assessment of such patients. Nonetheless, thromboprophylaxis is suggested for medical patients older than 40 years who have limited mobility for 3 days or more and who have at least one risk factor<sup>12</sup> (see Table 1). In addition, all patients admitted to intensive care units are considered high risk for the development of VTE.<sup>13</sup>

## Pharmacological Thromboprophylaxis

In patients without a contraindication to prophylaxis with an anticoagulant, effective pharmacological thromboprophylaxis can be provided with low-dose unfractionated heparin (UFH), prophylactic dose low molecular weight heparin (LMWH), or the selective factor Xa inhibitor fondaparinux (Table 2).

## Unfractionated Heparin

Unfractionated heparin has been shown to be an effective thromboprophylactic agent in hospitalized medical patients. A recent meta-analysis including 36 trials investigating the use of UFH for thromboprophylaxis in medical patients showed a significant risk reduction in DVT (67%; relative risk [RR] 0.33, 95% confidence interval [CI] 0.26–0.42) and PE (36%; RR 0.64, 95% CI 0.50–0.82) compared to observation or placebo.<sup>14</sup> Furthermore, another trial showed that in-patients receiving thromboprophylaxis with UFH 5,000 U every 8 hours had a lower mortality than those receiving no treatment (7.8% vs. 10.9%,  $p = .03$ ).<sup>15</sup>

There is some debate with regards to optimal dosing of UFH for thromboprophylaxis. The two most commonly used regimens of UFH in the literature are 5,000 U every 8 hours and 5,000 U every 12 hours. A meta-analysis suggests that a UFH dosage of 5,000 U every 8 hours is more effective in preventing DVT than a UFH dosage of 5,000 U every 12 hours when compared with the control (RR 0.27, 95% CI 0.20–0.36; vs. RR 0.52, 95% CI 0.28–0.96).<sup>14</sup> Furthermore, another study with 11,693 patients with infectious diseases found no significant differences in mortality during hospitalization or in autopsy-verified fatal pulmonary embolism when comparing patients who received UFH at twice daily dosing versus no treatment (5.3% vs. 5.6%,  $p = .39$ ).<sup>16</sup> Thus, while no studies have directly compared the two dosing regimens, 8-hour dosing is recommended.<sup>12</sup>

**Table 1. Risk Factors for Venous Thromboembolism in Medical Patients**

Immobility
Previous venous thromboembolism
Active cancer*
Recent surgery
Lower limb paralysis or paresis
Congestive heart failure†
Sepsis or acute infectious disease
Active inflammatory bowel disease
Acute respiratory disease
Stroke with paralysis
Rheumatic disease
Older age
Nephrotic syndrome or other chronic renal disease

\*Treated within the past 6 months or palliative.

†Defined as New York Heart Association Class III or IV disease.

**Table 2. Anticoagulant Regimens for Prophylaxis against Venous Thromboembolism in Hospitalized Medically Ill Patient**

Drug	Dosing Regimen
Unfractionated heparin	5,000 units subcutaneously every 8 hours
Low molecular weight heparin	
Enoxaparin	40 mg subcutaneously once daily
Dalteparin	5,000 units subcutaneously once daily
Fondaparinux	2.5 mg subcutaneously once daily

**Low Molecular Weight Heparin and Fondaparinux**

Three important randomized, placebo-controlled trials have been performed to investigate thromboprophylaxis in hospitalized patients with the use of enoxaparin, dalteparin, and fondaparinux, respectively (see Table 2). Each has been shown to be effective in thromboprophylaxis in medical patients compared to placebo. In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, 1,102 medical patients were randomized to receive enoxaparin (at 20 mg or 40 mg subcutaneously once daily) or placebo. Patients receiving enoxaparin at 40 mg daily were found to have significantly lower rates of the primary end point (DVT or PE) (5.5% vs. 14.9%,  $p < .001$ ) and of proximal DVT (4.9% vs. 1.7%,  $p = .04$ ) as compared to the placebo group. No difference was seen when comparing those receiving the 20 mg dose to placebo.<sup>17</sup> The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients (PREVENT) trial randomized 3,706 nonsurgical patients to receive either dalteparin 5,000 U subcutaneously once daily or placebo for 14 days.<sup>18</sup> Similarly, patients receiving dalteparin had significantly lower rates of the primary end point (symptomatic DVT, PE, and asymptomatic DVT as determined by ultrasonography by day 21) (2.8% vs. 5.9%,  $p = .002$ ) and of proximal DVT as compared to placebo. Finally, the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS) investigated the use of fondaparinux at 2.5 mg subcutaneously daily for 6–14 days as compared to placebo for thromboprophylaxis in 849 medical patients.<sup>19</sup> The incidence of any VTE (5.6% vs. 10.5%,  $p = .03$ ) and of symptomatic VTE was significantly reduced amongst those patients randomly assigned to receive fondaparinux as compared to placebo.<sup>19</sup>

**Unfractionated Heparin versus LMWH**

In a meta-analysis of eight trials assessing the effectiveness of various heparin preparations for thromboprophylaxis in medical patients, no significant difference was found in the incidence of VTE or mortality between those receiving UFH and those receiving LMWH.<sup>20</sup> However, LMWH reduced the risk of major bleeding by 52% ( $p = .049$ ). Further, a recent trial of 3,239 medical patients demonstrated that certoparin at a dose of 3,000 U once daily was non-inferior to UFH 5,000 U every 8 hours.<sup>21</sup> As there is evidence to support both options, UFH 5,000 U every 8 hours and prophylactic doses of LMWH are reasonable choices for thromboprophylactic agents in hospitalized medically ill patients.

**Other Agents**

Little evidence exists to support the use of aspirin or other antiplatelet

drugs, such as clopidogrel, for thromboprophylaxis in hospitalized patients. A few studies suggest some benefit for the use of aspirin, though aspirin appears to be less efficacious than LMWH in small trials.<sup>22</sup> Thus, the most recent ACCP guidelines in 2008 recommend against the use of aspirin alone for thromboprophylaxis.<sup>23</sup> Further, warfarin is not an appropriate agent to initiate for immediate and short-term thromboprophylaxis in hospitalized medical patients who are not already taking the medication upon admission. However, patients who are anticoagulated with warfarin for another indication (i.e., atrial fibrillation, mechanical valve replacement), who have a therapeutic international normalized ratio (INR  $>2.0$ ) generally do not require additional thromboprophylaxis with UFH, LMWH, or fondaparinux. Finally, while the new antithrombotic agents rivaroxaban and dabigatran etexilate have been approved for use in thromboprophylaxis after total hip and/or knee arthroplasty, their use in VTE prophylaxis in hospitalized medical patients has not yet been established. The MAGELLAN study, a multi-centre, randomized controlled trial designed to assess the use of rivaroxaban as a thromboprophylactic agent in medically ill patients, was recently presented at the American College of Cardiology 2011 Scientific Session.<sup>24,25</sup> A total of 8,101 patients were randomized to either rivaroxaban for 35 days or enoxaparin for 10 days followed by placebo. The primary efficacy end point (composite of asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE-related death) has demonstrated that rivaroxaban is not inferior to enoxaparin for short term (10 days) thromboprophylaxis (2.7% in both groups,  $p = .0025$ ) and is superior to enoxaparin and placebo in extended-duration (35 days) thromboprophylaxis (4.4% vs. 5.7%,  $p = .0211$ ). However, rivaroxaban was associated with significantly higher rates of clinically relevant bleeding at 10 (2.8% vs. 1.2%,  $p < .001$ ) and 35 days (4.1% vs. 1.7%,  $p < .0001$ ). Rivaroxaban did not show a net clinical benefit across the whole population.

**Mechanical Thromboprophylaxis**

Medical patients should be assessed for any contraindications to pharmacological thromboprophylaxis. Hospitalized medically ill patients who are at increased risk for developing VTE, but in whom pharmacological thromboprophylaxis is contraindicated, should be considered for mechanical thromboprophylaxis. Such patients include those with active bleeding, such as from a peptic ulcer or intracranial hemorrhage, or those who are deemed at high risk for bleeding. In these patients, intermittent pneumatic compression (IPC) devices and/or graduated compression stockings (GCS) can be used. However, few studies have addressed the efficacy of such mechanical prophylactic devices in medical patients. There is in fact little evidence to support the use of GCS as a sole method of thromboprophylaxis. Indeed, in a meta-analysis involving patients who have had a stroke, GCS was found to be ineffective in the prevention of VTE.<sup>26</sup> In a recent systematic review of mechanical devices in surgical patients, the crude cumulated DVT rate for all the trials was 5.9% for GCS versus 2.8% for IPC, suggesting a difference in performance between the two types of devices.<sup>27</sup> Thus, in patients with contraindications to pharmacological thromboprophylaxis who would derive benefit from mechanical thromboprophylaxis, IPC devices should be considered (with or without the addition of GCS) as opposed to GCS alone.<sup>23</sup> However, mechanical methods of thromboprophylaxis need to be used continuously, for at least 23 hours a day. The use of these methods

can also be limited by improper fit and patient non-adherence. In addition, IPC devices cannot be used in patients with leg ischemia due to peripheral vascular disease. Further, a recent systematic review including 11 trials comparing compression alone to compression with pharmacologic prophylaxis found that combined prophylactic modalities significantly decreased the incidence of both symptomatic PE (from about 3% to 1%; odds ratio [OR] 0.39, 95% CI 0.25–0.63) and DVT (from about 4% to 1%; OR 0.43, 95% CI 0.24–0.76).<sup>28</sup> Thus, once a patient's contraindication to thromboprophylaxis with an anticoagulant resolves, the addition of pharmacologic prophylaxis or a switch to pharmacologic prophylaxis should be considered.

### ***Duration of Pharmacological Thromboprophylaxis***

The optimal duration of thromboprophylaxis in medical patients is unclear. This uncertainty is partly due to the difficulty that exists in defining the time period in which medical patients are at increased risk for developing VTE. Indeed, many medically ill patients have increased risk prior to admission and some investigations suggest that this increased risk extends beyond discharge date. Further, with increasing pressure on hospitals to expedite discharges in order to liberate beds, length of stay in hospital is often minimized, raising the question as to whether or not there would be potential benefit for extended-duration thromboprophylaxis. There is some evidence that extended-duration prophylaxis with enoxaparin reduces the incidence of VTE compared with placebo.<sup>29</sup> However, this benefit was limited to females, patients older than 75 years, and those completely bed bound or sedentary without bathroom privileges, and extended-duration enoxaparin also increased major bleeding events. Similarly, the MAGELLAN trial has shown that extended-duration thromboprophylaxis using rivaroxaban reduces the overall incidence of VTE compared to placebo but also significantly increased the rate of clinically relevant bleeding.<sup>24</sup> Thus, it is currently recommended that patients remain on thromboprophylaxis only during their hospitalization, although there may also be a subset of medical patients who could derive some potential benefit from extended-duration thromboprophylaxis. This area remains controversial and further studies are needed to better elucidate the risk factors that would define that particular subset of patients.

### ***Critically Ill Patients and Patients with Renal Impairment***

Critically ill patients often have multiple risk factors for the development of VTE, including immobility from sedation and the need for mechanical ventilation, exposure to central venous catheterization, and their underlying acute illness. This high risk is complicated by a concomitant high bleeding risk in this population, highly attributable to coagulopathy and thrombocytopenia. Two trials have specifically investigated pharmacological thromboprophylaxis using low-dose UFH in the intensive care unit. In a randomized controlled trial involving 119 critically ill patients, the efficacy of twice daily UFH in the prevention of DVT was compared to placebo.<sup>30</sup> Low-dose UFH was found to significantly decrease the incidence of DVT as compared to placebo (13% vs. 29%,  $p < .05$ ). In another randomized trial with 223 patients with an acute exacerbation of chronic obstructive pulmonary disease requiring mechanical ventilation for at least 2 days, the efficacy of nadroparin once daily for thromboprophylaxis was compared to placebo.<sup>31</sup> The DVT rate

as screened by venography on day 21 was 16% in the treatment group compared to 28% in the placebo group (relative risk reduction of 0.45). The recently published Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT) compared the use of prophylactic dose dalteparin (5,000 U subcutaneously daily) to low-dose UFH (5,000 U subcutaneously twice daily) in medical-surgical critical care patients.<sup>32</sup> This multicentre trial showed that dalteparin was not superior to UFH in decreasing the rates of the primary outcome of proximal leg DVT in critically ill patients. However, dalteparin was associated with a significant reduction in the secondary outcome of PE (1.3% vs. 2.3%,  $p = .01$ ). In addition, there was no significant difference between the two groups in the rates of major bleeding or death in hospital, suggesting similar safety profiles, and the per-protocol analysis also demonstrated that those patients receiving dalteparin had a significantly lower rate of heparin induced thrombocytopenia. While PROTECT sheds new light on this particular patient population, the results of the primary end point are not clinically directive. In summary, all medical patients admitted to the critical care unit are considered high risk for developing VTE and should be given thromboprophylaxis with an anticoagulant if no contraindications exist. Recommended prophylactic regimens in the critical care unit include low-dose UFH and prophylactic dose LMWH.

Conventionally, UFH is used for VTE prophylaxis in patients with renal impairment because its clearance is not affected by renal function. There is concern about bioaccumulation of LMWH in this patient population, which can lead to excessive anticoagulant effects. Limited data are available in this population given that prior studies investigating the use of LMWH for thromboprophylaxis have typically excluded patients with renal impairment. One multicentre trial of 138 critical care patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) assessed the safety of prophylactic dose dalteparin (5,000 U subcutaneously daily for up to 30 days) and showed that this regimen is not associated with excessive anticoagulant effect due to drug bioaccumulation, at least in the short term, and is unlikely to contribute towards bleeding.<sup>33</sup> Importantly, studies with other LMWH preparations, which differ in size and potential for bioaccumulation, have not been performed in this context. Indeed, pharmacokinetic studies suggest that bioaccumulation may occur with enoxaparin at a dose of 40 mg daily in those patients with moderate to severe renal dysfunction.<sup>34</sup> Further studies are required to better characterize the safety of LMWH in patients with renal impairment.

Venous thromboembolism in the hospitalized medically ill patient remains a common problem. Effective pharmacological thromboprophylaxis can prevent the development of DVT in medical patients, although it is underutilized in clinical practice. Pharmacologic options for thromboprophylaxis include UFH given subcutaneously every 8 hours, as well as prophylactic dose LMWH and fondaparinux given subcutaneously once daily. Patients with active bleeding or who are at high risk for bleeding may be administered mechanical prophylaxis in the form of intermittent pneumatic compression devices. Further work is required to improve the utilization of prophylaxis against VTE in Canadian hospitals.

### ***Thromboprophylaxis in Major Orthopedic Surgery***

Major lower extremity orthopedic surgery and hip fracture are highly associated with the development of post-operative VTE. Without thromboprophylaxis, patients undergoing primary total hip arthroplasty

**Table 3. Options for Thromboprophylaxis in Total Hip or Knee Arthroplasty**

Drug	Dosing Regimen*	Initiation and Duration <sup>†</sup>	Comment
Dalteparin	2,500 U subcutaneously then 5,000 U subcutaneously daily	4–8 hours after surgery	LMWH
Enoxaparin	30 mg subcutaneously twice daily	12–24 hours after surgery	LMWH
Tinzaparin	75 U/kg subcutaneously once daily	18–24 hours after surgery	LMWH
Fondaparinux	2.5 mg subcutaneously once daily	6–8 hours after surgery	Synthetic pentasaccharide
Warfarin	Variable, to maintain INR between 2.0 and 3.0	Night of surgery	VKA

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

\*Dosing and timing as per product monograph.

<sup>†</sup>Thromboprophylaxis should be continued for at least 10 days post-operatively. Extension to 28–35 days can be considered, particularly after total hip arthroplasty.

(THA) or total knee arthroplasty (TKA) have demonstrated a total prevalence of DVT from 41 to 85% and that of proximal DVT from 5 to 36%.<sup>35</sup> Prior to routine thromboprophylaxis, the incidence of PE ranged from 5 to 10%, while fatal pulmonary embolism, which was the most common cause of death in this population, occurred in up to 2% of patients. Thus, pharmacological thromboprophylaxis has become the standard of practice in patients undergoing major orthopedic surgery.

### **Thromboprophylaxis in Total Hip and Knee Arthroplasty**

Several options are available for effective pharmacological thromboprophylaxis in patients undergoing THA and TKA. Traditionally, LMWH, fondaparinux, and warfarin have been used as thromboprophylactic agents. More recently, dabigatran etexilate, a direct thrombin inhibitor, and rivaroxaban, a direct Xa inhibitor, have also been shown to be effective methods of thromboprophylaxis post TKA and THA.

### **Low Molecular Weight Heparins**

The LMWHs dalteparin, enoxaparin, nadroparin, and tinzaparin have been approved for use in Canada for thromboprophylaxis following elective THA and/or TKA (Table 3).<sup>36,37</sup> While studies using symptomatic VTE as end points suggest that LMWH and warfarin provide similar benefit in both THA and TKA, LMWH preparations have been shown to be superior to warfarin when venography was used as the end point.<sup>36</sup> Because of decreased need for monitoring blood work, LMWH has become a popular alternative to vitamin K antagonists. Although many studies assessing the efficacy of LMWH preparations in this patient population involved regimens with at least one dose of preoperative LMWH, this is not always practical in many Canadian hospitals in which patients are admitted the day of their elective surgery. Thus, thromboprophylaxis with a LMWH is generally initiated post-operatively (i.e., 4–24 hours after surgery) as per the various routine dosing regimens summarized in Table 3.

### **Fondaparinux**

In a meta-analysis of four randomized controlled trials including 7,344 patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture, 2.5 mg of fondaparinux subcutaneously daily initiated 6 hours post-operatively was found to significantly reduce incidence of VTE as compared to enoxaparin (6.8% vs. 13.7%).<sup>38</sup> The incidence of clinically relevant bleeding did not differ between the two groups. Further, in a review of four large trials, fondaparinux initiated 4–8 hours post-operatively was shown to be superior to enoxaparin in preventing VTE in patients undergoing major orthopedic surgery.<sup>39</sup> This

benefit was evident regardless of the established composite outcomes used, although it may be, at least in part, ascribed to earlier administration of fondaparinux in the post-operative setting.

### **Warfarin**

Warfarin is the historical choice for thromboprophylaxis after major orthopedic surgery and its use has been shown to be an effective strategy for VTE prophylaxis.<sup>40,41</sup> In a meta-analysis of 52 trials comparing various prophylactic regimens, the risk of proximal DVT and symptomatic PE in patients undergoing elective THA was significantly lower in those receiving warfarin as compared to placebo (6.3% vs. 25.8%,  $p < .0001$ , and 0.15% vs. 1.51%,  $p < .05$ , respectively).<sup>42</sup> Typically, a first dose of 5.0–7.5 mg is given on the night of surgery, though dose adjustment should be considered depending on the individual patient's age, size, comorbidities, and medication list. Warfarin doses should then be adjusted to achieve and maintain a therapeutic international normalized ratio (INR) between 2.0 and 3.0, preferably within 4 days post-operatively.

### **Oral Direct Thrombin Inhibitors and Xa Inhibitors**

Both dabigatran etexilate, an oral direct thrombin inhibitor, as well as rivaroxaban, an oral direct Xa inhibitor, have been approved for the use of thromboprophylaxis in THA and/or TKA in Canada (Table 4). The RE-NOVATE trial was a non-inferiority study randomizing 3,494 patients undergoing THA to receive 28–35 days of dabigatran etexilate initiated post-operatively (220 mg or 150 mg) or enoxaparin 40 mg daily initiated preoperatively.<sup>43</sup> Both doses were found to be non-inferior to enoxaparin for the primary outcome of total VTE and mortality from all causes, and there was no significant difference in major bleeding rates with either dose as compared to enoxaparin. The RE-MODEL trial was a similar study performed in 2,076 patients undergoing TKA. Again, both doses of dabigatran were found to be non-inferior to enoxaparin in terms of a primary end point of total VTE and all cause mortality.<sup>43</sup> However, the RE-MOBILIZE trial, which included patients undergoing TKA and compared dabigatran etexilate (220 mg or 150 mg) to 30 mg of enoxaparin twice daily initiated post-operatively, showed that dabigatran was inferior in the composite end point of total VTE and all cause mortality.<sup>44</sup> In summary, using venographic end points, dabigatran is equivalent to 40 mg of enoxaparin once daily initiated preoperatively; however, dabigatran is inferior to enoxaparin used at a dose of 30 mg twice daily initiated post-operatively. Thus, the recommended regimen for dabigatran etexilate for thromboprophylaxis after major orthopedic surgery is 110 mg or 75 mg orally initiated 1–4 hours post-operatively, followed by 220 mg or 150 mg orally once daily. Because dabigatran is

**Table 4. Oral Agents for Thromboprophylaxis in Total Hip or Knee Arthroplasty**

Drug	Dosing Regimen	Initiation and Duration*	Comment
Dabigatran etexilate	110 or 75 mg orally followed by 220 mg or 150 mg orally daily	1–4 hours after surgery	Direct thrombin inhibitor
Rivaroxaban	10 mg orally daily	6–8 hours after surgery	Direct Xa inhibitor

\*Thromboprophylaxis should be continued for at least 10 days post-operatively. Extension to 28–35 days can be considered, particularly after hip arthroplasty.

largely renally excreted, the lower dosing regimen should be considered for patients with moderate renal dysfunction and in the elderly.

Rivaroxaban is also approved for use in thromboprophylaxis after THA and TKA. The RECORD1 and RECORD2 trials were large studies in which patients undergoing THA were randomized to receive 10 mg of rivaroxaban daily or 40 mg of enoxaparin daily.<sup>45,46</sup> While the two trials differed in terms of duration of prophylaxis, both demonstrated that rivaroxaban was superior to enoxaparin in significantly reducing the composite end point of all DVT, nonfatal PE, and all cause mortality at 36 days. Similarly, the RECORD3 and RECORD4 trials involved patients undergoing TKA and compared 10 mg of rivaroxaban daily to two separate dosing regimens of enoxaparin, respectively.<sup>47,48</sup> The RECORD3 trial demonstrated superiority of rivaroxaban to 40 mg of enoxaparin daily for 10–14 days in the composite of all DVT, non-fatal PE, and death from any cause. The RECORD4 trial demonstrated superiority of rivaroxaban to 30 mg of enoxaparin given twice daily for 10–14 days in the same composite end point. In summary, using both venographic end points as primary outcomes and clinical events as secondary outcomes, rivaroxaban is superior to enoxaparin administered either once or twice daily. The recommended regimen is rivaroxaban 10 mg orally, initiated 6–8 hours post-operatively, followed by 10 mg orally once daily.

### Other Agents and Mechanical Thromboprophylaxis

The use of aspirin or low-dose UFH for thromboprophylaxis after THA or TKA is not recommended as their efficacy as sole agents has not been established.<sup>23</sup> While IPC devices and GCS may provide some protection, evidence for their efficacy is also limited. Thus, IPC devices and GCS should not be used as sole methods of thromboprophylaxis except in patients with contraindications to prophylaxis with an anticoagulant, and they should be replaced by pharmacologic means as soon as the contraindication resolves.

### Duration of Thromboprophylaxis

Historically, thromboprophylaxis was administered for the duration of a patient's hospital stay, which generally lasted from 7 to 14 days.<sup>35</sup> However, with continuing efforts to decrease length of stay, limiting post-operative thromboprophylaxis to only those days in which the patient remains hospitalized may not be sufficient. There is evidence that the prevalence of asymptomatic DVT after major orthopedic surgery is lower in patients who have received 10 days of thromboprophylaxis as opposed to 5 days.<sup>49</sup> A meta-analysis of four prospective studies investigating clinical outcomes suggests that relatively few symptomatic venous thromboembolic events occur if thromboprophylaxis is continued for at least 10 days post-operatively after major orthopedic surgery.<sup>50</sup> Therefore, while the optimal duration of post-operative thromboprophylaxis in patients undergoing THA or TKA is not known, studies suggest that VTE prophylaxis should

be continued for at least 10 days post-operatively in this population.<sup>23</sup> Multiple studies have investigated the efficacy of extended-duration thromboprophylaxis for up to 35 days. A meta-analysis of randomized trials comparing extended-duration prophylaxis to placebo or no treatment in patients undergoing THA or TKA found that extended prophylaxis significantly reduced the frequency of symptomatic VTE (1.3% vs. 3.3%, OR 0.38, 95% CI 0.24–0.61).<sup>51</sup> There was greater risk reduction in patients undergoing THA as compared to TKA. In addition, trials comparing extended-duration prophylaxis with LMWH to in-hospital use for only roughly 7 days demonstrated that patients receiving extended prophylaxis developed half the number of asymptomatic DVT as determined by routine screening venography. Moreover, in a randomized controlled trial comparing extended-duration rivaroxaban to short-term enoxaparin for the prevention of VTE after THA, extended-duration rivaroxaban was found to significantly decrease the composite end point of DVT, non-fatal PE, and all-cause mortality.<sup>46</sup> Thus, expert opinion favours continuation of thromboprophylaxis for at least 10 days post-operatively after major orthopedic surgery, and up to 35 days, particularly after THA.<sup>23</sup>

### Thromboprophylaxis in Hip Fracture

Hip fracture is also highly associated with the development of VTE and hip fracture patients should routinely receive post-operative pharmacological thromboprophylaxis unless contraindicated. Although there are fewer studies in this patient population, recommendations similar to those for VTE prophylaxis after THA and TKA are generally also applicable after hip fracture.

Recommended post-operative thromboprophylactic options for hip fracture patients include LMWH, fondaparinux, low-dose UFH, and warfarin (adjusted to target an INR of 2.0–3.0).<sup>23</sup> In a systematic review of 26 trials involving 2,600 patients that assessed efficacy of UFH, LMWH, and physical means for thromboprophylaxis following surgery for hip fractures, UFH and LMWH were found to significantly decrease incidence of DVT compared to control (24% vs. 39%, OR 1.39, 95% CI 0.86–2.23).<sup>52</sup> There was insufficient evidence to distinguish between the various applications of heparins. In a large double-blind, randomized controlled trial involving 1,711 patients undergoing surgery for hip fracture comparing 2.5 mg of fondaparinux once daily initiated post-operatively, to 40 mg of enoxaparin once daily initiated at least 5 days preoperatively, the incidence of VTE was significantly reduced in the fondaparinux group (8.3% vs. 19.1%,  $p < .001$ ).<sup>53</sup> There was no difference between the two groups in the incidence of death or clinically relevant bleeding. Rivaroxaban and dabigatran have not been assessed for safety and efficacy in patients with hip fractures and should not be used for thromboprophylaxis in this population until further studies are conducted.

As is the case with patients undergoing THA or TKA, the optimal duration of thromboprophylaxis in hip fracture patients is not known. However, expert opinion recommends post-operative thromboprophylaxis be administered for at least 10 days and continued until improved mobilization, or up to 35 days.<sup>23</sup> In a multi-centre, randomized, placebo-controlled trial with 656 hip fracture patients, extended-duration prophylaxis with 2.5 mg of fondaparinux daily for 3 weeks significantly reduced the risk of VTE by 96% ( $p < .001$ ) as compared to placebo.<sup>54</sup> There was no difference between the two groups in clinically relevant bleeding. Although similar studies assessing efficacy of extended-duration prophylaxis in hip fracture patients with LMWH and warfarin have not been performed, their use is likely beneficial. Importantly, if surgery is to be delayed post-hip fracture, the patient should receive preoperative prophylaxis during this delay. Because the timing of a patient's operation can be unpredictable, which complicates the use of agents with longer half lives, thromboprophylaxis in this particular context should be administered with low-dose UFH or prophylactic dose LMWH.<sup>23</sup>

Venous thromboembolism is a common post-operative complication of major orthopedic surgery and hip fracture, and routine thromboprophylaxis for these patients is the standard of care. Pharmacologic options for thromboprophylaxis in this population include LMWH, fondaparinux, and warfarin. For patients undergoing THA or TKA, the newer oral agents dabigatran etexilate and rivaroxaban are also suitable options. VTE in the setting of major orthopedic surgery and hip fracture is a challenging field. With novel agents being developed to address the need for anticoagulation, the importance of evidence-based practice will be paramount.

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