Prevention of venous thromboembolism: consensus, controversies, and challenges

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The last 50 years have witnessed a multitude of publications evaluating the efficacy, safety and cost effectiveness of many different thromboprophylaxis interventions. There is widespread consensus that thromboprophylaxis safely reduces morbidity and mortality. More than 25 evidence-based guidelines, published since 1986, also recommend routine thromboprophylaxis in the majority of hospitalized patients. As a result, thromboprophylaxis is recognized as a key safety priority for hospitals. Some of the remaining areas of controversy that will be discussed in this paper include the role of individual risk assessments to determine thrombosis risk and prophylaxis, replacement of low-dose heparin by low-molecular-weight heparin (LMWH), the optimal duration of prophylaxis, the role of combined thromboprophylaxis modalities, the safety of anticoagulant prophylaxis with regional analgesia, the use of LMWHs in chronic renal insufficiency, and the emerging role of new oral anticoagulants as thromboprophylactic agents. Despite the overwhelming evidence supporting thromboprophylaxis, rates of thromboprophylaxis use remain far from optimal. Successful implementation strategies to bridge this knowledge:care gap are the most important current challenges in this area. These strategies must be multifaceted, utilizing local, systems-based approaches as well as legislation and incentives that reinforce best practices.

Venous thromboembolism (VTE) is one of the most common complications of hospitalization and is associated with substantial short- and long-term morbidity, deaths and costs. The rationale for the routine use of thromboprophylaxis in most hospitalized patients is based on solid scientific evidence demonstrating its effectiveness and cost-effectiveness in preventing VTE.[1] Several hundred clinical trials of thromboprophylaxis, conducted over the past 50 years, have shown that the use of prophylaxis reduces the rates of deep vein thrombosis (DVT), proximal DVT, pulmonary embolism (PE), and fatal PE by more than 60% in a broad spectrum of hospitalized patients with a very low risk of adverse effects.[1,2] Anticoagulants are the mainstay of prophylaxis options in most of these patient groups with non-pharmacologic prophylaxis having a more limited role. When the Agency for Healthcare Research and Quality (AHRQ) systematically evaluated and ranked 79 safety practices based on the strength of evidence supporting each intervention and on their impact on patient outcomes, they determined that the appropriate use of thromboprophylaxis was "the number one patient safety practice" for hospitals.[3]

Thromboprophylaxis Guidelines—The Consensus

More than 25 evidence-based guidelines on the prevention of VTE have been published since 1986.[1,4] The American College of Chest Physicians (ACCP) sponsor and publish what are generally considered to be the most comprehensive and most commonly utilized of these guidelines.[1] A summary of the 2008 ACCP Guidelines on the Prevention of VTE is presented in **Table 1**. Most non-orthopedic surgical patients and sick medical patients have a moderate risk of VTE; the guidelines recommend the routine use of one of the following thromboprophylaxis modalities: low-molecular-weight heparin (LMWH), low-dose heparin (LDH), or fondaparinux. Patients who have undergone hip or knee arthroplasty or hip fracture surgery have a high VTE risk and the guidelines recommend the routine use of LMWH, fondaparinux or warfarin (target INR 2.0-3.0). LMWH is also recommended for patients who are recovering from major trauma. Most hospital patients at risk for VTE should continue thromboprophylaxis until discharge and not stop as soon as they start to ambulate. For major orthopedic surgery, the recommended duration of prophylaxis is at least 10 days, with a strong recommendation to continue for up to 5 weeks.

Table 1. Risk stratification, recommended thromboprophylaxis and optimal duration of prophylaxis by patient group.

Patient groups	Recommended thromboprophylaxis options*	Optimal duration of prophylaxis
Low VTE Risk: ▪ Medical – fully mobile, brief admission, no additional risk factors ▪ Surgical – procedure < 30 minutes, patient mobile, no additional risk factors	▪ No prophylaxis ▪ Early and frequent ambulation	Not applicable.
Moderate VTE Risk: ▪ Acute medical illness ▪ Major general surgery ▪ Major gynecologic surgery ▪ Major urologic surgery ▪ Thoracic surgery ▪ Bariatric surgery	▪ Low-molecular-weight heparin ▪ Low-dose heparin ▪ Fondaparinux ▪ Combinations of a mechanical method and an anticoagulant	Continue until discharge for the majority of patients. Selected patients may benefit from post-discharge prophylaxis.
High VTE Risk: ▪ Hip or knee arthroplasty ▪ Hip fracture surgery	▪ Low-molecular-weight heparin ▪ Fondaparinux ▪ Rivaroxaban or dabigatran ▪ Warfarin (target INR 2-3)	Minimum of 10 days and up to 35 days.
High VTE Risk: ▪ Major trauma, (including spinal cord injury)	▪ Low-molecular-weight heparin ▪ Combinations of a mechanical method and an anticoagulant	Continue until discharge for the majority of patients. Prophylaxis should be continued for the inpatient rehabilitation period.
High bleeding risk	▪ Mechanical method of prophylaxis (GCS, PCD, VFP) ▪ Consider anticoagulant prophylaxis when bleeding risk decreases	Duration appropriate for the specific patient risk group.

*The recommended options may differ somewhat for specific patient groups based on available evidence. See the 8th ACCP Guidelines on the Prevention of VTE.[1]
GCS indicates graduated compression stocking; PCD, pneumatic compression device, VFP, venous foot pump.

Controversies in Thromboprophylaxis

Risk Stratification for Thromboembolism

Two general approaches are used to stratify the risk of thromboembolism in hospitalized patients (and thereby to help select a prophylaxis option). The first approach uses one of a number of scoring systems that consider the risk of VTE in each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure. Thromboprophylaxis is then individually prescribed based on the composite risk estimate. Formal risk assessment models (RAMs) for DVT have been proposed to assist with this process.[1,5] Although we can support the concept of individualized patient risk assessment, this approach has not been adequately validated, is cumbersome to use, and there is little formal understanding of how the various risk factors interact in a quantitative manner to decide where a particular patient lies along the continuous spectrum of thromboembolic risk. Finally, individual RAMs may not be worth the effort because there are only a small number of thromboprophylaxis options to choose from and one of the principles of effective prevention strategies is to reduce complexity in decision making. The second approach involves routine implementation of standardized thromboprophylaxis to all patients in a large group, for example, major orthopedic surgery or major general surgery, unless a particular patient has a contraindication to the standard option. We support this approach for most patients for several reasons. Although a number of patient-specific factors contribute to the variability in VTE rates, the principal factor is the patient's primary reason for hospitalization, whether because of a surgical procedure or an acute medical illness. Furthermore, we are not able to confidently identify the relatively small proportion of patients within each target group that may not require thromboprophylaxis. Individualized risk assessment has not been subjected to rigorous clinical evaluation, while group risk assignment is the basis for most thromboprophylaxis intervention trials and clinical practice guidelines.[1,2] Finally, the complexity of individualized risk assessment may reduce compliance unless an intensive and sustained, systematic implementation strategy is in place. The group prophylaxis model still

requires clinical judgment to determine whether the group-specified prophylaxis modality and dose are appropriate for the individual patient. For example, while the usual prophylaxis for major trauma is LMWH, mechanical prophylaxis is appropriate if a particular patient has a high bleeding risk. **Table 1** provides a simple classification scheme to assign risk levels and the recommended thromboprophylaxis options for each level. A further simplification of the assignment of thromboprophylaxis is to use the same dose of the same LMWH for almost every patient at risk (medical, general surgical, orthopedic, critical care, trauma, etc) unless there are specific contraindications or unless individual patient factors such as weight, renal dysfunction or bleeding risk warrant consideration of an alternative approach. For example, at our center, we recommend reducing the LMWH dose by half for patients who weigh less than 40 kg and doubling the usual dose if they are heavier than 100 kg. We have successfully adopted this simplified approach to prophylaxis in our own medical center.

Replacement of Low-dose Heparin by LMWH

LDH is the traditional thromboprophylaxis modality and has been shown to effectively reduce VTE in a wide variety of patients for more than 35 years.[6] Although LDH and LMWH have similar efficacy and safety in medical and non-orthopedic surgery patients, LMWH has been shown to be more efficacious than LDH after hip and knee arthroplasty and major trauma.[1] In order to improve the use of thromboprophylaxis, LMWH is attractive since it is a recommended option for each major patient group, while LDH has some restrictions. Additional advantages of LMWH over LDH include less frequent dosing and a 40-fold lower risk of heparin-induced thrombocytopenia.[7] Furthermore, in most countries, the cost difference between these two classes of drugs is small. Therefore, we believe that, unless there is a large cost difference between LDH and LMWH, LMWH should be the preferred prophylaxis option for most hospital patients.

Optimal Duration of Thromboprophylaxis

The optimal duration of prophylaxis and the related issue of whether prophylaxis should be continued after hospital discharge are both unknown for the majority of hospitalized patients because of the paucity of studies examining this question. Furthermore, with shorter lengths of hospital stay (and, therefore, shorter durations of prophylaxis) than previously, as well as the greater morbidity of patients being discharged, some patients are at increased risk of VTE unless some post-discharge thromboprophylaxis is considered. Major orthopedic surgery constitutes one of the highest risk groups for VTE and is also an area where the duration of prophylaxis has been subjected to rigorous study. At least nine randomized controlled trials and at least four systematic reviews in patients who underwent hip and knee arthroplasty and hip fracture surgery have confirmed the benefit of post-hospital discharge thromboprophylaxis.[1,8-11] Patients who undergo total hip replacement (THR) appear to derive greater protection from symptomatic VTE with extended prophylaxis (pooled OR, 0.33; 95% CI, 0.19 to 0.56; number needed to treat [NNT], 62) than patients who undergo total knee replacement (TKR) (pooled OR, 0.74; 95% CI, 0.26 to 2.15; NNT, 250).[9] In another meta-analysis restricted to blinded THR trials, the rates of symptomatic VTE among patients who received in-hospital thromboprophylaxis and those who were administered post discharge LMWH were 2.7% and 1.1%, respectively (absolute risk reduction, 1.6%; 95% CI, 0.2 to 3.3; NNT, 64).[12] The absolute risk reduction for symptomatic PE was 0.4% (95% CI, - 0.3 to 1.4; NNT, 278). The benefit of post-hospital discharge thromboprophylaxis with oral vitamin K antagonists (VKA) has also been confirmed in at least one study in which more than 350 patients who underwent THR were randomized to warfarin (target INR, 2 to 3) until hospital discharge (mean duration, 9 days) or to warfarin that continued for 4 weeks after discharge.[13] VTE occurred in 5.1% of the patients who stopped warfarin at hospital discharge and in 0.5% of those who continued warfarin, a relative risk of 9.4 (95% CI, 1.2 to 73.5; NNT, 22) with only one major bleed in the extended prophylaxis group. However, compared to extended LMWH prophylaxis, the rates of major bleeding appear to be higher with a VKA[13-15] and considerable effort is required to maintain patients in the target INR range as outpatients. Extended prophylaxis with fondaparinux has also been shown to be highly protective in patients who underwent hip fracture surgery (HFS), with 96% and 89% relative risk reductions in asymptomatic and symptomatic DVT, respectively, and no increase in bleeding.[16] When examining the cost implications of longer versus shorter duration of VTE thromboprophylaxis after major orthopedic surgery, most investigators have concluded that prolonged thromboprophylaxis was either cost saving[17,18] or more costly but a good value in consideration of net benefits.[19,20] The relative value of prolonged thromboprophylaxis may substantially diminish when drug acquisition cost is high[19] or when the cost of administration increases (as when nursing care is needed to provide injections at home).[20] The recommendations for duration of prophylaxis for all major hospitalized patient groups are summarized in **Table 1** and incorporate the above considerations.

Role of Combined Thromboprophylaxis Modalities

Mechanical thromboprophylaxis modalities such as graduated compression stockings and intermittent pneumatic compression devices have a number of disadvantages

over anticoagulant prophylaxis. As a group, they have not been as intensively studied as pharmacologic prophylaxis, the studies have been unblinded and therefore subject to bias,[21,22] the devices have no established standards for size, pressure or physiologic features, compliance with mechanical prophylaxis is poor in routine care,[23] and they require substantial effort and resources to ensure their proper use. However, since they are not associated with bleeding, and some methods have demonstrated efficacy as DVT prevention in clinical trials, the use of mechanical prophylaxis in combination with pharmacological prophylaxis may be helpful in certain situations.[24,25] For example, in major trauma patients who have a high risk of bleeding at presentation (as after head injury), we use mechanical prophylaxis initially followed by anticoagulant prophylaxis with LMWH when safe, This strategy could be adopted in any postoperative situation in which the initial risk of bleeding is high.

Concomitant Use of Regional Anesthesia Techniques and Anticoagulant Prophylaxis

Neuraxial blockade (spinal or epidural anesthesia and continuous epidural analgesia) results in a significant reduction in cardiopulmonary morbidity compared with general anesthesia and narcotic-based systemic analgesia, as well as better pain control and patient satisfaction.[26] However, concerns have been raised about a possible increased risk of epidural or spinal hematoma and spinal cord ischemia or paraplegia with use of concomitant anticoagulant prophylaxis.[27,28] We believe that anticoagulant thromboprophylaxis with LMWH or LDH can safely be given along with neuraxial blockade with proper patient selection and timing of doses. Further details can be found in Section 1.5 of the 8th ACCP Prevention of VTE guidelines.[1] In summary:

1. Neuraxial blockade should be avoided in patients with systemic bleeding disorders and if hemostasis is impaired by an anticoagulant. The spinal needle or epidural catheter should be inserted at a time when there is minimal or no anticoagulant effect present.
2. Anticoagulant prophylaxis should be delayed if a hemorrhagic aspirate ("bloody tap") is encountered during initial needle or catheter placement.
3. Removal of an epidural catheter should be done when the anticoagulant effect is at a minimum (usually just before the next scheduled injection) and anticoagulant prophylaxis should be delayed for at least 2 hours after spinal needle or epidural catheter removal.
4. In patients with an indwelling epidural catheter, we suggest that warfarin be avoided altogether or that the catheter be removed less than 48 hours after starting warfarin because of its unpredictable anticoagulant effect.
5. The safety of continuous epidural analgesia with concomitant administration of fondaparinux or one of the new oral anticoagulants is not known and this combination is best avoided at this time.
6. Patients with epidural catheters who are given anticoagulant thromboprophylaxis should be carefully monitored for symptoms and signs of spinal cord compression. If spinal hematoma is suspected, diagnostic imaging and surgical decompression should be performed rapidly to reduce the risk of permanent spinal cord damage.
7. Every hospital using neuraxial blockade along with anticoagulant prophylaxis should develop a written protocol.
8. For patients receiving deep peripheral nerve blocks along with anticoagulant prophylaxis, it is reasonable to use the same cautions described above.

Anticoagulant Use in Chronic Renal Insufficiency

Renal clearance is the primary mode of elimination for several anticoagulants, including LMWH, fondaparinux, and the new oral factor Xa and IIa inhibitors. Therefore, with reduced renal function, these drugs may accumulate and may increase the risk of bleeding, particularly in elderly patients and those at high risk for bleeding.[29] The relationship between renal impairment and drug accumulation for the various LMWHs appears to be variable and may be related to the chain length distribution of the different LMWH preparations.[30] Two recent studies in hospitalized patients, the majority of whom were critically ill and had creatinine clearances less than 30 mL/min, have shown no bioaccumulation of dalteparin 5000 U once daily based on serial anti-factor Xa levels.[31,32] Therefore, we do not reduce the prophylaxis dose of dalteparin in patients with renal insufficiency. In patients receiving intermittent hemodialysis, we suggest that the LMWH be administered after the dialysis session. With enoxaparin thromboprophylaxis, we suggest that 30 mg once daily be used. We also suggest that fondaparinux, rivaroxaban and dabigatran be avoided unless future evidence demonstrates that these agents can be used safely in patients with severe renal insufficiency.

Role of New Oral Anticoagulants in Thromboprophylaxis

A number of new oral anticoagulants (direct factor Xa inhibitors and direct thrombin inhibitors) are undergoing evaluation as thromboprophylaxis. The advent of oral agents that do not need laboratory monitoring represents a significant advance in the field of thrombosis prevention. From these two classes of anticoagulants, rivaroxaban (an oral factor Xa inhibitor) and dabigatran (an oral thrombin inhibitor) have been assessed in large randomized trials of prophylaxis in hip and knee arthroplasty and found to have

similar or greater efficacy compared with standard LMWH with similar safety.[33-35] Both rivaroxaban and dabigatran have recently been approved for this indication in Europe and Canada. With once daily oral administration and avoidance of daily injections or INR monitoring, these agents are more convenient for patients and simplify prophylaxis, particularly in the post-hospital discharge phase.[35] Assessment of the safety, effectiveness and cost-effectiveness of these anticoagulants in large numbers of patients in real-life settings will add to the data provided in the clinical trials and will influence the extent of their adoption.

Implementation of Appropriate Thromboprophylaxis: the Challenges

There is a strong link between suboptimal thromboprophylaxis and both symptomatic VTE rates and increased costs of care. However, audits demonstrate that many medical, surgical and cancer patients do not receive appropriate thromboprophylaxis. A high proportion of patients who develop VTE after a hospital admission have not received adequate prophylaxis during that admission.[36] An international, cross-sectional audit of 35,000 inpatients at risk for VTE found that only 59% of surgical patients and 40% of medical patients received recommended prophylaxis.[37] There were striking differences in prophylaxis use among the 32 participating countries. Similarly, an international registry of thromboprophylaxis use in medical patients found that only 37% of at-risk patients received any prophylaxis.[38] Both orthopedic surgery patients and cancer patients receiving thromboprophylaxis that was partially compliant with the ACCP guidelines had a higher risk of VTE and higher total hospital costs than patients whose prophylaxis was fully adherent with the guidelines.[39,40]

In order to change clinical practice and improve patient safety, a large number of strategies, both at the national level and at the local level, have been developed to increase the appropriate use of thromboprophylaxis.[41] At the national or system-wide level, several countries have enacted legislation or created financial incentives to induce hospitals to implement various patient safety practices, including the use of thromboprophylaxis. Other system-wide strategies include development of national standards of care, public reporting of hospital thromboprophylaxis rates, requiring documentation of a prophylaxis policy for hospital accreditation, and a number of national or international patient safety initiatives such as the Institute for Healthcare Improvement 5 Million Lives Campaign and the World Health Organization Surgical Safety Checklist.

At the local level, passive dissemination of thromboprophylaxis policies, optional availability of VTE risk assessment forms and group educational activities have little or no impact.[41] Adapting evidence-based practice guidelines into existing local policies and protocols has been shown to significantly increase the proportion of at-risk patients receiving appropriate thromboprophylaxis. The use of order sets that include thromboprophylaxis recommendations among the other admission or postoperative orders is a particularly useful tool for improving thromboprophylaxis rates. Implementation of daily safety checklists that include thromboprophylaxis reinforce the hospital's policy. Collecting local adherence rates and providing them to the patient care team has also been demonstrated to substantially improve thromboprophylaxis use. Computerized VTE risk assessment, based on the electronic medical record, and subsequent automatic physician alerts have been shown to both improve thromboprophylaxis use and to reduce thromboembolic complications in a randomized clinical trial that included 2500 at-risk hospital patients who were not initially ordered prophylaxis.[42] Order sets, whether paper or electronic, can be designed in a manner that requires clinicians to order thromboprophylaxis or to document the reason why prophylaxis is not needed or is contraindicated. A multifaceted quality improvement strategy, based on the use of preprinted admission or postoperative order sets, provider education, reminders, and audit and feedback, has been shown to increase thromboprophylaxis use from 63% to 95% and to reduce hospital-acquired DVT from 2.6 per 1000 discharges to 0.2 in one study.[43] Dramatic improvements in the use of thromboprophylaxis can be achieved using a combination of a written, institution thromboprophylaxis policy, provider education, reminders that are integrated with work flow, and default (or "opt out") order sets supplemented by periodic audit and feedback.

In summary, the effectiveness, safety and cost-effectiveness of appropriate thromboprophylaxis in preventing morbidity and death from VTE have been proven beyond reasonable doubt. Despite this, a high proportion of patients do not benefit from the accumulated knowledge in this field. The time has come for thromboprophylaxis to be incorporated into the culture of routine care so that every hospitalized patient receives evidence-based thromboprophylaxis in a timely manner and continued for the period of risk.

Disclosures

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Off-label drug use: While the direct factor Xa inhibitor rivaroxaban and the direct thrombin inhibitor dabigatran

are approved and are being used in a number of countries, neither have yet been approved by the FDA in the United States.

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