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So that we can take advantage of electronic distribution efficiencies and reduce publication expenses, this will be the last paper issue of the *P&T News*. Beginning with the next issue, access to the *P&T News* will be through the on-line *Formulary and Handbook* and The Point. When each issue is published, a broadcast will be sent that contains a link to the document, as well as a brief index of the issue's content. Previous issues will also be available via the *Formulary and Handbook* and The Point.

THE SAFE USE OF ANTICOAGULANTS

Jeffrey Wilson, MD

Anticoagulants are commonly prescribed medications. In 2004, more than 30 million warfarin prescriptions were dispensed in the United States. Bleeding complications are the most frequent serious adverse effect of anticoagulants. In 2003 and 2004 United States death certificate data ranked anticoagulants first in total mentions for deaths from drugs causing adverse effects in therapeutic use. Responding to data indicating the increasing use and adverse effects of warfarin, the Food and Drug Administration (FDA) placed a "black box" warning in the drug's product information in 2006.¹

The failure to use anticoagulants when indicated is also associated with serious adverse effects. Pulmonary embolism (PE) is one of the most frequent causes of preventable in-hospital death. Prophylactic treatment with anticoagulants is effective in preventing deep venous thrombosis (DVT) and PE, but is underutilized. Approximately one half of hospitalized patients are at increased risk of DVT/PE, but appropriate prophylactic therapy is given to less than 50% of patients at increased risk.^{2,4}

In 2008 The Joint Commission issued National Patient Safety Goal 3E which states: "Reduce the likelihood of patient harm associated with the use of anticoagulation therapy."⁵ The purpose of this *P&T News* article is to review steps that healthcare professionals should take to promote the safe use of anticoagulants. This discussion will be limited to warfarin and heparins, including low molecular weight heparin (LMWH) and unfractionated heparin (UFH).

Warfarin

Warfarin is used primarily to prevent stroke and other systemic emboli in patients with atrial fibrillation, prosthetic heart valves and myocardial infarction, and in patients with venous thromboembolism (VTE) to prevent recurrent disease. Bleeding is the most common adverse event associated with warfarin use with intracranial bleeding causing the highest morbidity and mortality.¹ In one study, of 40 patients who died from warfarin-associated hemorrhage, 35 (88%) died from intracranial hemorrhage.⁶ The intensity of anticoagulation is the dominant risk factor for intracranial hemorrhage in patients taking warfarin.⁷ Thus, maintaining the international normalized ratio (INR) in a stable therapeutic range is an important safety goal. Multiple factors influence stability of the INR and are reviewed below. Additional information can be found in the "Guide to Warfarin Therapy for Adult Patients" (<http://www.healthcare.uiowa.edu/pharmacy/formulary/Pocketguide/WarfarinTherapy.doc>).

Many drugs alter the pharmacokinetics of warfarin and may either inhibit or potentiate the anticoagulant effect. All new medications prescribed to a patient should be reviewed for their potential to alter warfarin's effects. Similarly, common over-the-counter medications, nutritional supplements, and herbal products may alter the effect of warfarin, but their use is often not routinely reported by patients. Aspirin and other nonsteroidal anti-inflammatory drugs increase the risk of warfarin-associated bleeding, by inhibiting platelet function and by causing gastric erosions. An extensive list of drug and dietary supplement interactions with warfarin can be found on page 166S of the 2008 ACCP Guidelines on Antithrombotic and Thrombolytic Therapy.¹⁸

Warfarin produces an anticoagulant effect by inhibiting vitamin K synthesis and blocking the production of vitamin K dependent coagulation factors II, VII, IX and X in the liver. Fluctuating dietary intake of vitamin K may lead to variability in the anticoagulant effect of warfarin. An increased intake of dietary vitamin K may reduce the anticoagulant effect of warfarin. Patients prescribed warfarin should receive education on the need to maintain a consistent level of vitamin K in their diet. Poor oral intake and treatment with antibiotics (which reduce endogenous vitamin K production by gut flora) may lead to vitamin K deficiency and potentiate the effects of warfarin.

The education of patients regarding their medications can help prevent adverse drug events.²⁹ In addition to education regarding drug and dietary interactions, patients should have a clear understanding of why they are on warfarin, how the drug works, the expected duration of treatment, and the importance of regularly monitoring their INR. They should understand the common symptoms and signs of bleeding and who to contact if they occur. This information should be given well in advance of discharge home so that the patients' understanding of what they have been taught can be re-assessed, and they have ample opportunity to ask questions.

The transition of care from inpatient to outpatient requires careful discharge planning to ensure appropriate follow up. Prior to discharge the indication for and duration of anticoagulant therapy, target INR and a date and location for INR monitoring should be determined. The healthcare provider responsible for monitoring and making necessary dosage adjustments should be clearly identified. The patient's ability to obtain the medication should be verified. Depending on the experience and willingness of the patient's primary care provider(s) to provide appropriate follow-up, consideration should be given to referral to an Anticoagulation Case Management Service (ACMS) (pager 7700) (<http://www.healthcare.uiowa.edu/Pharmacy/formulary/Hand/ACMSpoliciesprocedures.pdf>) for monitoring the INR and making adjustments in warfarin dosing. Specialized anticoagulation management clinics have been shown to increase the percentage of time a patients INR is in the therapeutic range. Some, but not all, studies have shown a decrease in the risk of hemorrhage and recurrent thrombotic events when compared with usual care.⁸⁻¹⁰

Unfractionated and Low Molecular Weight Heparin

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are used both to prevent venous thromboembolism and therapeutically treat patients with established DVT/PE, atrial fibrillation, myocardial ischemia, peripheral vascular disease and other conditions. LMWH exhibits less binding to cells and proteins than UFH leading to a more favorable pharmacokinetic and pharmacodynamic profile. Advantages of LMWH over UFH include: 1) no need for coagulation monitoring; 2) a lower incidence of heparin induced thrombocytopenia; 3) a lower risk of osteopenia; and 4) a longer half-life permitting less frequent dosing.¹⁸

Due to issues related to the distribution and clearance of LMWH, UFH is generally preferred in patients with obesity or severe renal insufficiency (estimated creatinine clearance < 30 mL/min). LMWH is also less predictably reversed with protamine when there is a bleeding complication.

In the setting of a high clinical suspicion of acute DVT and/or PE, strong consideration should be given to treatment with UFH or LMWH while appropriate diagnostic testing is being completed.

When using UFH in full treatment dosing, the use of a weight based dosing nomogram is recommended. When treating acute VTE, rapidly (within 24 hours) achieving a therapeutic activated partial thromboplastin time (aPTT) of 1.5 to 2.5 times control may lessen the likelihood of recurrent venous thromboembolism¹¹ and is a desirable goal.

Treatment with either UFH or LMWH may cause the heparin-induced thrombocytopenia (HIT) syndrome, an antibody-mediated condition associated with an increased risk of both venous and arterial thrombosis which is frequently life threatening. Routine platelet count monitoring of patients on heparin is indicated to aide in the detection of HIT. It is also important to recognize that a thrombotic event from HIT may precede a fall in platelet count. For more information refer to UIHC “Guidelines for Recognition and Management of HIT” (Heparin-Induced Thrombocytopenia Protocol).

Prevention of Venous Thromboembolism (VTE)

Venous thromboembolism (including DVT and PE) is one of the most frequent causes of preventable illness and death in hospitalized patients. It is estimated from autopsy studies that pulmonary embolism is responsible for 5 to 10% of deaths of hospitalized patients.^{3,12,13,14} Prophylaxis for venous thromboembolism is effective but underutilized, especially in patients on medical services. Three large randomized, double-blind, placebo-controlled trials have demonstrated the effectiveness of prophylactic anticoagulation in medical patients (Figure 1).³ However, it is important to recognize that prophylaxis is not 100% effective - DVT and PE can still occur in patients receiving appropriate prophylactic therapy.¹⁵

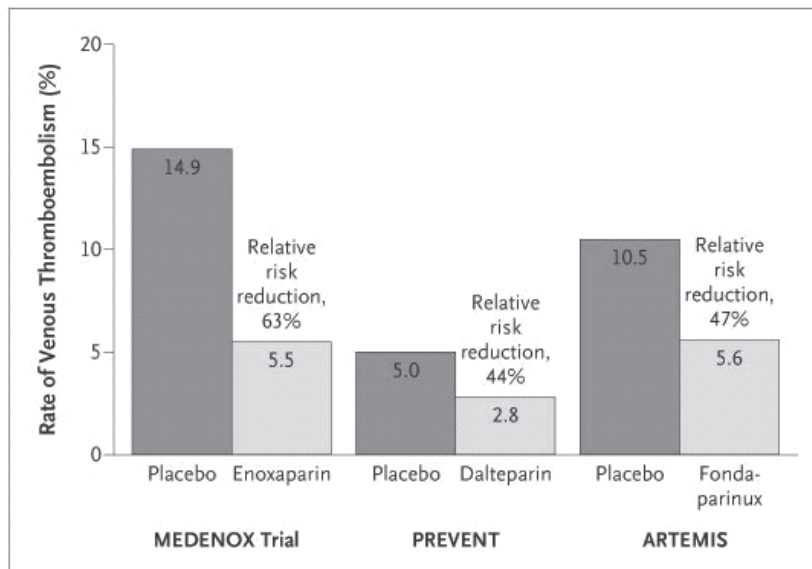


Figure 1. Results of Trials of Prophylaxis for Venous Thromboembolism in High-Risk Hospitalized Patients. *N Engl J Med* 2007; 356:1438-44

Every hospitalized patient should have assessment of their risk for venous thromboembolism, and their risk of bleeding from the use of prophylactic anticoagulation. Risk factors for VTE and bleeding are well described (See “Healthcare Provider’s Guide to the Prevention and Treatment of Venous Thromboembolism in Adults - <http://www.healthcare.uiowa.edu/pharmacy/formulary/Pocketguide/venousthrombo.doc>). Models to estimate the risk of VTE and bleeding have been proposed, but these have not been prospectively validated and are not used by most clinicians. Thromboprophylaxis recommendations are based on broad patient groups, for example, hip or knee replacement, trauma, stroke, and acute medical illness. Good clinical judgement is required in the decisions of when and how to use prophylactic therapy. Hospital-based, computerized reminder systems have been shown to increase the use of prophylactic treatment and lower the incidence of venous thromboembolism in inpatients.¹⁶

The specific recommended method of thromboprophylaxis varies by patient group, and is generally related to the patient’s primary reason for hospitalization, and the clinicians perceived risk of bleeding in each individual patient (See “Healthcare Provider’s Guide to the Prevention and Treatment of Venous Thromboembolism in Adults” – <http://www.healthcare.uiowa.edu/pharmacy/formulary/Pocketguide/venousthrombo.doc>).

Mechanical methods of thromboprophylaxis (graduated compression stockings, intermittent pneumatic compression (IPC) devices, and venous foot pumps) are frequently used in the United States. In a recent large study of acutely ill medical patients, intermittent pneumatic compression was the most frequently used form of prophylaxis.¹⁷ The major advantage of mechanical methods of thromboprophylaxis is the absence of bleeding risk. However, mechanical thromboprophylaxis has been less well studied compared to pharmacologic thromboprophylaxis and is generally considered to be less efficacious. Effective implementation of mechanical thromboprophylaxis is frequently limited by low compliance. For these reasons current ACCP recommendations are that mechanical methods of thromboprophylaxis be used primarily in patients with a high risk of bleeding.¹⁸

In many patient groups either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is recommended for pharmacologic prophylaxis. An exception to this are orthopedic patients with either hip fracture or total hip or knee replacement surgery where LMWH has been shown to be superior to UFH. In the United States UFH is used more in medical patients than LMWH,¹⁷ likely in part due to differences in pharmacy acquisition cost. At UIHC, pharmacy acquisition costs for LMWH are approximately 15 X more than for UFH (based on equivalent prophylactic dosing). However, additional factors to consider include: 1) LMWH has a longer half-life permitting once-a-day dosing for many patients, compared to 2 to 3 times per day dosing for UFH; and 2) thromboprophylaxis with LMWH is associated with a much lower rate of HIT compared with UFH.¹⁹ The development of HIT in a patient significantly increases length of stay and the total cost of hospitalization.^{20,21} Thus, LMWH may be more cost effective despite a higher initial acquisition cost.

In patients at high risk for VTE, combining mechanical and pharmacologic methods of thromboprophylaxis has been shown to be more effective than either method alone.²²⁻²⁴ Using both forms of prophylaxis together should be considered in patients at high risk for VTE.

Extending thromboprophylactic therapy to outpatient populations is receiving increasing study.²⁵ It is well established that an increased risk of VTE persists for four weeks or longer after hip fracture and hip and knee replacement surgery, and this risk can be safely lowered with outpatient thromboprophylaxis.²⁶ In these patient groups, extension of thromboprophylaxis is recommended for up to 35 days after surgery.¹⁸ Pregnant women with a prior history of VTE, especially in the presence of other ongoing risk factors, may also be appropriate candidates to receive thromboprophylaxis in the outpatient setting.²⁸ Much less is known about extending thromboprophylactic therapy in other outpatient groups. The utility of this approach in acutely ill medical outpatients is currently being studied.²⁷

Summary/Conclusion

The safe use of warfarin, enoxaparin, and heparin requires that both healthcare professionals and patients have a thorough understanding of the drugs indications, adverse drug reactions and need for appropriate monitoring. Every patient admitted to the hospital should be assessed for their risk of venous thromboembolism and risk of bleeding, with institution of thromboprophylaxis if indicated by this assessment.

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