Treatment of Venous Thromboembolism: Challenging the Unfractionated Heparin Standard

Edith Nutescu, Pharm.D., Manider Singh-Khalsa, M.D., M.B.A., and the Heparin Consensus Group

Venous thromboembolism (VTE) is a major public health problem leading to high morbidity and mortality in the United States. Since more then 50% of patients with VTE may have asymptomatic disease, the start of appropriate therapy often is delayed. Traditionally, intravenous unfractionated heparin (UFH) has been used to manage the acute phase of VTE. Although an effective agent, numerous limitations are associated with the use of UFH therapy, such as the need for careful monitoring and frequent dosing adjustments. In addition, the assay used to monitor UFH—the activated partial thromboplastin time (aPTT)—does not correlate reliably with plasma heparin levels or antithrombotic activity. In the early 1990s, the low-molecular-weight heparins (LMWHs) emerged as alternative anticoagulants to UFH and began to successfully challenge the UFH standard for treatment of VTE. Clinical evidence has consistently demonstrated that LMWHs given subcutaneously are at least as safe and as effective, if not better, than intravenous UFH. This anticoagulant class has a much more predictable dose-response relationship, requires little or no monitoring, and provides cost-saving opportunities for outpatient management of VTE. The LMWHs are now considered the treatment of choice for many patients with VTE and are largely replacing UFH for this indication. In the last decade, additional agents, such as direct thrombin inhibitors and factor Xa inhibitors, have emerged as potential future alternatives for treatment of VTE. As clinical data regarding these new agents for treatment of VTE continue to evolve, their role in clinical practice will be elucidated.

Key Words: venous thromboembolism, unfractionated heparin, low-molecular-weight heparins, activated partial thromboplastin time, nomograms.

(Pharmacotherapy 2004;24(8 Pt 2):127S–131S)

Venous thromboembolism (VTE) accounts for about 250,000 hospitalizations and as many as 50,000 deaths/year in the United States.[1, 2] An Italian study estimated that the incidence of pulmonary embolism is approximately 100 cases/year/100,000 population.[3] Similar data have been reported based on statistics from the U.S. National Hospital Discharge Survey.[3] Of patients suspected of having pulmonary embolism, 30% are first seen in the emergency department. A retrospective population-based study, conducted in Olmsted County, Minnesota, revealed an annual incidence of 14.3–145.0 cases/100,000 for deep vein thrombosis (DVT) and 20.8–65.8 cases/100,000 for pulmonary embolism.[4]

Both DVT and pulmonary embolism are difficult to diagnose because of the poor sensitivity and specificity of clinical signs and

From the Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois (Dr. Nutescu); and Cigna HealthCare of Arizona, Phoenix, Arizona (Dr. Singh-Khalsa).

Address reprint requests to Edith A. Nutescu, Pharm.D., University of Illinois at Chicago, College of Pharmacy, 833 South Wood Street, MC 886, Room 164, Chicago, IL 60612; e-mail: enutescu@uic.edu.

symptoms.[5] A retrospective chart review found that swelling above or below the knee, recent immobility, cancer, and fever were the clinical findings most closely related to the presence of proximal DVT.[6] However, the presence of one or more of these findings had a specificity of only 20% in the diagnosis of DVT. Diagnosis of VTE in the critically ill patient may be further hampered by problems with communication, making the interpretation of signs and symptoms difficult.

In terms of objective diagnostics, venography has been used frequently in clinical trials since it is considered the gold standard for DVT detection. Its high sensitivity and specificity minimize the rate of false-positive diagnoses, providing an unbiased estimate of the relative treatment effects. However, this method may produce results that are not always applicable to clinical practice, particularly with distal, asymptomatic DVT rates.

A more practical and noninvasive diagnostic method is compression ultrasonography. The sensitivity of Doppler and duplex ultrasonography in asymptomatic patients is 40–60%. In patients with symptoms of DVT, the sensitivity of these methods increases to 90–97%. When ultrasonography is combined with venography to confirm positive results in clinical trials, ultrasonography can provide unbiased estimates of relative treatment effects and is more reflective of clinical practice.[7,8]

Treatment Overview

The goal of treating VTE is to prevent thrombus extension and embolization. This is most effectively achieved with early administration of anticoagulant agents.[9] The use of anticoagulants for treatment of VTE emerged approximately 60 years ago. Today, two major classes of drugs are prescribed to manage this disease: injectable heparins and oral vitamin K antagonists (e.g., coumarins). The heparins act rapidly in attaining an immediate anticoagulant effect, whereas the coumarins exert their effect much more slowly.[9] The treatment of VTE can be divided into the acute and chronic phases. The acute treatment phase of VTE is managed with an intravenous heparin product, the chronic phase with an oral coumarin derivative (e.g., warfarin).

Until the early 1980s, unfractionated heparin (UFH) and coumarin derivatives were the only effective therapeutic anticoagulation agents available for treatment of VTE. The low-molecular-weight heparins (LMWHs) were introduced in the 1980s and achieved widespread use in VTE treatment in the 1990s.[10] In the last decade, additional agents, such as direct thrombin inhibitors and factor Xa inhibitors, emerged as potential future alternatives in the treatment of VTE. As clinical data with these new agents in the treatment of VTE continue to evolve, their role in clinical practice will be elucidated.

UFH: Evidence and Issues

The benefits of anticoagulation therapy in patients with VTE were first documented in the early 1960s.[11] If left untreated, patients with VTE have a high recurrence and mortality rate. The first randomized trial of treatment with UFH versus placebo in patients with pulmonary embolism clearly demonstrated the benefit of anticoagulant therapy. Patients in the placebo group had a 25% mortality rate compared with 0% in the group receiving active treatment. Further studies confirmed the benefit of UFH in reducing disease recurrence and mortality in patients with VTE.[12–15]

Subsequent clinical trials concentrated on UFH dosage, duration of infusion, and mode of administration. Thus, traditional therapy for management of acute VTE involves in-hospital administration of continuous intravenous UFH, followed by long-term secondary prophylaxis with oral anticoagulants for a minimum of 3–6 months to prevent VTE recurrence.[16] The initial UFH induction period is usually 5–7 days. Using this approach, an additional 4–5 days of hospitalization can be avoided. However, it is now well accepted that a shorter UFH induction period of 4–5 days is just as effective as a longer period of 9–10 days.[17,18] Warfarin, begun early in VTE therapy, is routinely administered jointly with UFH for at least 4–5 days. The UFH infusion is stopped once the international normalized ratio exceeds 2.0.

Though an effective anticoagulant, UFH requires careful monitoring and dosing adjustment when used as treatment of active VTE. Laboratory monitoring and heparin dosage adjustments are necessary due to marked variability in anticoagulant response among patients, as well as the day-to-day dosage variations in the same patient.[19,20] A certain level of heparin anticoagulation needs to be maintained to halt the continuing thrombotic process. Heparin levels of 0.2–0.4 international

units (IU)/ml as measured by protamine titration are necessary to attain an effective antithrombotic state.[21]

In clinical practice, the frequently used activated partial thromboplastin time (aPTT) has shortcomings as a monitoring parameter since it does not correlate reliably with plasma heparin levels or antithrombotic activity.[16] Both intravenous and subcutaneous UFH have demonstrated efficacy in the treatment of VTE when appropriate dosages are administered and the aPTT is prolonged into the therapeutic range.[20, 22–24] Various UFH dosing schemes have been evaluated for initial VTE therapy, such as a standard intravenous bolus of UFH 5000 U followed by an intravenous infusion of 1000 U/hour, a weight-adjusted dosing nomogram, or a subcutaneous injection of approximately 17,500 U twice/day.[16] When the subcutaneous route for UFH administration is selected, the dosage must be sufficient to overcome the lower bioavailability associated with this route. For an immediate anticoagulant effect, an intravenous bolus of UFH is required.

Audits of physician-conducted therapy with UFH have demonstrated a large variation in dosing decisions and ability to maintain a therapeutic aPTT.[25, 26] Due to these dosing limitations and an unpredictable anticoagulant effect, monitoring protocols for UFH needed to be developed and optimized. Several dosing nomograms have been evaluated to help clinicians attain and maintain a therapeutic heparin range.[27–29] All of these nomograms are based on frequent aPTT monitoring and a corresponding quick response to low or high aPTT values.[16]

Although UFH dosing nomograms can increase the likelihood of attaining therapeutic aPTT within the first 24–48 hours of therapy, audit data show that in many institutions at least 25% of patients do not achieve adequate levels of anticoagulation.[10] In summary, these complex dosing schemes and nomograms developed for UFH still do not produce the desired anticoagulant response in many patients. Studies have confirmed that inadequate levels of anticoagulation result in unacceptably high rates of recurrent VTE. Therefore, therapeutic levels of anticoagulation must be consistent throughout the treatment period.[16, 30]

One study demonstrated that patients with subtherapeutic anticoagulation had significantly higher VTE rates (19.3%) than patients who received adequate anticoagulation (5.2%).[20] Other investigators have confirmed these findings, indicating that the efficacy of UFH for treatment of VTE is significantly correlated with degree of anticoagulation.[19, 31] In addition to attaining and maintaining therapeutic heparin levels during VTE treatment, the time it takes to achieve these therapeutic levels is also crucial.

The study cited above demonstrated the importance of reaching therapeutic anticoagulation within the first 24 hours of UFH therapy.[20] Patients with subtherapeutic aPTT values during this period had a significantly higher VTE recurrence rate (23%) than patients with a therapeutic aPTT (5%).[32] In contrast, during the initial period of UFH therapy, the association between supratherapeutic aPTT responses and bleeding is weak.[20, 30, 32]

Challenging the Standard: LMWH

The availability of LMWHs has transformed the treatment of VTE. These agents obviate many of the shortcomings encountered with UFH. The LMWH anticoagulant class has a much more predictable dose-response relationship and can be given, in most cases, without concern for dosing adjustments or routine laboratory monitoring. When administered subcutaneously, LMWHs demonstrate superior bioavailability, allowing therapeutic anticoagulation by this route. In addition, due to the dose-independent clearance and extended half-life of the LMWHs, therapeutic anticoagulation can be achieved with once- or twice-daily subcutaneous injections.[16] However, not all LMWH products currently available have equivalent efficacy and safety data for the treatment of VTE, or equivalent Food and Drug Administration labeling.

The use of LMWHs permits outpatient treatment of VTE, saving an average of 5–6 hospital days/patient.[16] Successful outpatient programs optimize LMWH safety and efficacy through implementation of evidence-based patient selection criteria and risk stratification. Over the years, due to the demonstrated safety of LMWHs in this setting, inclusion criteria for outpatient eligibility continue to expand, offering even greater cost savings. Thus, clinicians should evaluate home treatment first and consider inpatient treatment when certain conditions are present, such as excessive bleeding risk, significant comorbid conditions, or physical or mental disabilities.[33] Using LMWHs for outpatient management of VTE can contribute to a savings of approximately $250 million/year in

the United States.[16]

The efficacy and safety of LMWHs administered subcutaneously have been compared with continuous intravenous UFH for the initial treatment of patients with VTE. The results have indicated that LMWHs administered subcutaneously are at least as safe and as effective, if not better than, intravenous UFH.[34, 35] Several meta-analyses also have suggested that LMWH therapy results in lower rates of VTE recurrence, bleeding, and mortality rates than UFH (Table 1).[36–41]

Additional major advantages of LMWHs over UFH are rapid and predictable anticoagulation, ease and convenience of administration, low frequency of heparin-induced thrombocytopenia, and cost savings associated with home therapy.[16] These findings clearly support the use of LMWHs over UFH in the treatment of VTE preferentially and have revolutionized the initial management of this disease. The simplicity, convenience, and potential economic savings to health care systems associated with the use of LMWHs have made this anticoagulant class the preferred option for outpatient treatment.

Table 1. Treatment of VTE: Meta-Analyses of LMWH versus UFH

	Risk Reductiona		
Year of Publication	Recurrent VTE	Major Bleeding	Mortality
1994[39]	0.34	0.35	0.28
1995[40]	0.53	0.68	0.47
1996[41]	0.23	0.41	0.30
1996[38]	0.39	0.42	0.51
2000[36]	0.85	0.63	0.76

VTE = venous thromboembolism; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.
[a]All risk reductions favor LMWH.

Conclusion

Venous thromboembolism is a major cause of morbidity and mortality in the United States. Since both DVT and pulmonary embolism are difficult to diagnose, the start of appropriate therapy is often delayed. Traditionally, intravenous UFH has been used to manage the acute phase of VTE. Although UFH is an effective agent, numerous limitations are associated with its use, such as the need for careful monitoring and frequent dosing adjustments. In addition, the assay used to monitor UFH, the aPTT, does not correlate reliably with plasma heparin levels or antithrombotic activity.

In the 1980s, a new class of anticoagulants, the LMWHs, began to successfully challenge UFH as the standard treatment of VTE. Clinical evidence has consistently demonstrated that LMWHs administered subcutaneously are at least as safe and effective, if not more so, than intravenous UFH. The LMWH anticoagulant class has a much more predictable dose-response relationship, requires little or no monitoring, and provides cost-saving opportunities for outpatient management of VTE. The LMWHs are now considered the treatment of choice for many patients with VTE, and are largely replacing UFH for this indication. Recommendations of the Heparin Consensus Group for the treatment of VTE with injectable anticoagulants are provided in Appendix 1.

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Appendix 1. Recommendations for the Treatment of VTE with Injectable Anticoagulants

1. In VTE treatment it is critical to attain a therapeutic heparin anticoagulant effect within 24 hours of the start of treatment, and to maintain this effect throughout the course of therapy.
2. The therapeutic range for aPTT should be determined by each laboratory and revalidated for each change in reagent, reagent lot, and reagent-instrument combination.
3. The UFH dosing nomograms in VTE treatment should be based on the aPTT therapeutic range determined for each institution.
4. Once a therapeutic effect has been achieved in a patient receiving an injectable anticoagulant, VTE treatment should be converted to an oral anticoagulant for a minimum of 3–6 months after an appropriate period of overlap.
5. Due to issues related to UFH dosing, monitoring, administration, safety, and economics in VTE treatment, LMWHs represent a preferred alternative.
6. When feasible, outpatient management of VTE is more cost-effective than inpatient therapy.