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Clinical Controversy: Pulmonary Embolism Treatment and Prophylaxis with New vs Old Heparins

The introduction of low molecular weight heparin (LMWH) in the 1990s presented new options for prevention and treatment of venous thromboembolic (VTE) disease, deep vein thrombosis (DVT) and pulmonary embolism (PE). The various LMWHs added a dimension to heparin management of anticoagulation that was previously carried out with unfractionated heparin (UFH). As more was learned about the molecular basis for heparin's anticoagulant properties, pharmacologic research isolated the essential molecular activity and brought newer agents such as fondaparinux to market.

With the clinical availability of LMWHs and newer agents such as fondaparinux, is there still a place for UFH in PE prevention and treatment? The question is explored in this Clinical Controversy.

Before pharmacologic prophylaxis was available, options for prevention of DVT and PE were limited to pressure stockings or intermittent pneumatic compression (IPC) devices applied to the legs. Pressure stockings today may be considered for individual outpatients, but probably should not be relied upon to prevent DVT in inpatients. Pneumatic compression devices can be considered on the basis of their strengths and weaknesses in DVT prevention:

- Strengths—no bleeding risk, may complement efficacy of UFH or LMWH, used alone reduce cost of prophylaxis, require no puncture of the skin, and the patient's family can monitor correct positioning of the device.
- Weaknesses—a "most effective" pressure is not stated in the literature, different devices have different ranges of pressure, hypercoagulability is not treated by pressure application, and few well-designed studies of efficacy have been conducted.

A study in limited numbers of postoperative obstetric-gynecology patients found no significant difference in UFH versus IPC in prevention of DVT as assessed by venogram and fibrinogen leg scans.¹ Other studies also have found "no difference" in UFH versus IPC in DVT prophylaxis. A 2007 study of IPC alone or IPC plus fondaparinux in general surgery patients demonstrated on 30-day observation more

asymptomatic DVT (22 vs 7) in the IPC-alone group of 424 patients, and more major non-fatal bleeding (1 vs 8) in the IPC-plus fondaparinux group of 418 patients.²

A lesson of studies with 30-day observation is that because treatment skews the natural history of DVT, venography earlier in the 30-day period may not provide information of the best quality on which to base treatment.

Recommendations for use of IPC for VTE prophylaxis are stated in current American College of Chest Physician guidelines:³

- Mechanical prophylaxis should be used primarily in patients with high risk for bleeding (Grade 1A), or as an adjunct to pharmacologic therapy (Grade 1A);
- Proper use and optimal adherence should be carefully monitored (Grade 1A);
- Combine mechanical prophylaxis with pharmacologic therapy for general surgery patients at very high risk for VTE (Grade 1C); and
- When mechanical prophylaxis is used because of contraindication for drug prophylaxis, switch to drug prophylaxis when the contraindication remits (Grade 1C).

UFH for PE Prophylaxis and Treatment

There are strong arguments for retaining UFH in the armamentarium for prevention and treatment of PE. While LMWH and even newer agents have expanded treatment options, UFH should still be used when its use meets rational clinical criteria.

The mechanism of action of UFH and LMWH is important to understand when comparing the drugs for efficacy, safety and cost.

Action of the Heparins

Unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux do not have inherent anticoagulant activity. They have their anticoagulant effect by activating antithrombin (AT), which inhibits a number of clotting factors that target thrombin. Thrombin links platelet activation and clotting factors and converts fibrinogen into insoluble fibrin. The heparin/AT interaction is key to

understanding heparin activity. AT is sometimes referred to as ATIII, the definition given it upon its discovery 40 years ago.

The sequence of events by which heparin binds to AT has been thoroughly investigated and is well understood. Heparin binds to AT via a unique pentasaccharide and induces a change in AT conformation. This converts AT from a slow to a rapid inhibitor of clotting factors. The high-affinity pentasaccharide can be synthesized; it is the active molecule in fondaparinux, a follow-on drug to UFH and LMWH.

Clotting factors inactivated by the heparin/AT complex include thrombin (factor IIa) and factors Xa, IXa, Xla and XIIa. Thrombin is highly sensitive to heparin/AT action, as is factor Xa.

The function of heparin is influenced by the length of the saccharide chain. A chain that is too short does not link AT to thrombin, and is thus unable to inhibit thrombin. If the chain contains a pentasaccharide, however, it can act by inhibiting factor Xa. Only about one-third of heparin molecules carry the essential pentasaccharide, but at very high concentration the heparin molecules that lack the pentasaccharide can inhibit thrombin by other routes. The anticoagulant effect of heparin is usually monitored using activated partial thromboplastin time (aPTT). Risk for bleeding increases as the heparin dose is increased; thus, monitoring of UFH is usually considered essential.

LMWHs are derived from UFH by various patented methodologies. The LMWHs are smaller in chain length and molecular weight than UFH. They all contain the essential pentasaccharide sequence, but different methods of deriving them from UFH render them non-interchangeable in clinical use. Their mode of action is the same of that of UFH. Because the anticoagulant response is more predictable with LMWH than with UFH, coagulation monitoring is usually considered unnecessary, except perhaps in patients with very high risk for bleeding. LMWHs reduce formation of heparin-induced thrombocytopenia (HIT) antibodies and this reduces the incidence of HIT as compared with UFH.

The cost of LMWH is substantially more than that of UFH. At one hospital, for example, the cost of 1,000 units of UFH is \$0.04 and the cost of 1,000 units of the LMWH enoxaparin is \$4.10.

Other measures by which to compare the utility of UFH versus LMWH are:

- Efficacy/safety;
- Efficacy of subcutaneous administration;
- Predictability; and,
- Risk for HIT.

Studies have found comparable efficacy/safety of UFH and LMWH in treatment of DVT and PE. Studies comparing efficacy and safety of subcutaneously administered UFH and LMWH have not found any substantial difference between the agents. It has been pointed out that, while UFH administration is usually monitored and LMWH administration is not, the importance of monitoring is not clearly evident for patients in general.

The question of whether UFH or LMWH is more implicated in HIT is yet to be definitively settled; studies from 1992 to 1998 have shown about equal weight of evidence for both agents causing HIT.

Guidelines for treatment of acute PE are stated in detail in the 8th edition of ACCP Evidence-Based Clinical Practice Guidelines for Antithrombotic and Thrombolytic Therapy.⁴ Short-term treatment of acute PE with subcutaneous (SQ) LMWH and intravenous (IV) UFH are both grade 1A recommendations on the basis of high-quality evidence. Both monitored SQ UFH and fixed-dose UFH are also 1A recommendations for short-term treatment of acute PE.

The question of heparin versus thrombolysis in initial treatment of PE has been addressed in a number of studies. A 2004 meta-analysis showed thrombolysis somewhat more effective than heparin in preventing recurrent PE, and heparin somewhat more effective in improving survival.⁵

New Anticoagulants Versus UFH

Patients with asymptomatic or “silent” DVT/PE make up a preponderance of those who can benefit from prophylaxis and early treatment. The focus of DVT/PE prevention today is on primary prevention—prophylaxis in patients who have not had a prior episode of VTE. The goals of VTE prophylaxis are prevention of DVT and PE, improving survival, prevention of post-thrombotic complications and

avoidance of therapy-associated complications of bleeding, heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT).

Whereas pharmacologic VTE prophylaxis prior to the 1990s was limited to UFH, the choices are much more numerous today. In addition to UFH there are:

- LMWHs;
- Ultra-LMWHs;
- Pentasaccharide indirect factor Xa inhibition;
- Direct thrombin inhibition;
- Direct factor Xa inhibition; and,
- Others in trial or near trial.

Compared to UFH, LMWHs and pentasaccharide have high bioavailability and rapid antithrombotic effect when given SQ, excellent dose-response predictability, long elimination half-life, predominantly renal clearance, decreased effect on platelet aggregation, and increased anti-factor Xa and anti-factor IIa activity.

Evidence from clinical trials has shown newer agents superior to UFH in VTE prophylaxis in patients with hip and knee arthroplasty, hip fracture, and non-hemorrhagic stroke. Safety data from trials and meta-analyses of trials have shown a trend for LMWH superiority to UFH in bleeding episodes. Comparison of LMWH and UFH in cardiopulmonary patients in the PRINCE trial showed superiority of LMWH in VTE prevention.⁶

For discussion and recommendations regarding treatment and prevention of HIT, the authoritative reference is the relevant chapter in 2008 ACCP guidelines for antithrombotic and thrombolytic therapy.⁷ Data cited in the chapter show HIT incidence to be higher with UFH versus LMWH.

When VTE occurs, it must be treated, and rational goals for therapy established:

- Prevention of VTE extension, embolism, recurrence and post-thrombotic complications, and

- Avoidance of bleeding and HIT/HITT.

Activated partial thromboplastin time (aPTT) is the standard test for assessing adverse events in patients with VTE, but PPT does not necessarily correlate with clinical events when monitoring heparinized patients. This may be cited as a negative aspect of UFH versus LMWH, as LMWH usually requires no monitoring, whereas UFH is usually considered to require monitoring. The intrinsic difficulties with monitoring are found in the standard practices of physicians and hospitals:

- Physicians may not be as proficient as they should be in selecting safe/effective UFH doses;
- Phlebotomists and nurses may not be timely or efficient in drawing blood samples for monitoring; and,
- Hospital laboratories may not be timely in returning PTT and other relevant results.

In a 1999 meta-analysis of VTE treatment studies, (1) no difference in efficacy was detected between IV-UFH and once-daily SQ LMWH, (2) SQ LMWH was safer than UFH as a cause of major bleeding, and (3) LMWH was associated with greater reduction of risk for death.⁷

The ACCP 2008 guidelines for antithrombotic and thrombolytic therapy recommend that in VTE patients with acute nonmassive PE, initial treatment should be with LMWH rather than UFH.⁴ Choices for initial treatment of VTE with LMWH or pentasaccharide are:

- Enoxaparin, 1mg/kg every 12 hours, or 1.5 mg/kg every 24 hours;
- Tinzaparin, 175 IU/kg every 24 hours;
- Daltaparin, 120 IU/kg every 12 hours, or 200 IU/kg every 24 hours; and,
- Fondaparinux, 5.0/7.5/10 mg every 24 hours.

ACCP guidelines recommend that when HIT risk is low (<0.1%) in medical patients, routine platelet count monitoring should not be used for patients receiving LMWH or fondaparinux.⁸

The summary of data for use of UFH versus LMWHs and newer anticoagulants in VTE prophylaxis indicate (1) similar efficacy, possible better efficacy of newer agents in high-risk patients, (2) lower bleeding risk associated with newer agents, and (3) lower risk for HIT/HITT associated with newer agents.

The summary of data for use of UFH versus LMWHs and newer anticoagulants in VTE treatment indicate (1) similar efficacy of UFH and newer agents, (2) possible lower risk for death with newer agents, (3) less risk for bleeding with newer agents, and (4) lower risk for HIT/HITT with newer agents.

Additional concerns may be expressed regarding pharmacologic VTE prophylaxis in patients receiving care in an intensive care unit. For example:

- Hemorrhage risk in patients with renal failure, liver failure, thrombocytopenia and disseminated intravascular coagulopathy (DIC);
- Procedure-related bleeding risk in patients undergoing surgery, epidural or lumbar puncture, and central line installation;
- ICU stress ulcers with bleeding risk;
- Bleeding risk associated with concomitant drugs—e.g., anti-platelet agents; and,
- Volume resuscitation induced clotting factor dilution.

Considerations when prescribing VTE prophylaxis in the ICU should include:

- Anticoagulant dose;
- Anticoagulant drug metabolism, clearance and route of elimination—e.g., renal function when kidneys are the route of elimination;
- Risk for hypotension and possible need for vasopressors;
- Soft-tissue edema;
- Reversibility (and availability of antidote); and,
- Risk in special populations—e.g., obese, cachectic, pregnant patients (data for risk in these populations may be sparse).

Note in Conclusion

Physicians should be wary of information and recommendations offered by “expert authorities” in review papers, lectures, webinars, etc. Rather, the physician should approach all data critically and make decisions based upon critical review.

References

1. Clarke-Pearson DL, Synan IS, Dodge R et al. A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. *Am J Obstet Gynecol* 1993; 168:1146-1153.
2. Turpie AG, Bauer KA, Caprini JA et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. *J Thromb Haemost* 2007; 5:1854-1861.
3. Geerts WH, Bergqvist D, Pineo GF et al. Prevention of venous thromboembolism. *Chest* 2008; 133:381S-453S.
4. Kearon C, Kahn SR, Agnelli A et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2008; 133:454S-545S.
5. Wan S, Quinlan DJ, Agnelli G et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation* 2004; 110:744-749.
6. Kleber FX, Witt C, Vogel G et al. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. *Am Heart J* 2003; 145:614-621.
7. Gould MK, Dembitzer AD, Doyle RL et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of deep venous thrombosis. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999; 130:800-809.
8. Warkentin TE, Greinacher A, Koster A et al. Treatment and prevention of heparin-induced thrombocytopenia. *Chest* 2008; 133:340S-380S.

Standard of Practice

Prophylaxis and treatment of venous thromboembolism (VTE) and its sequelae of deep-vein thrombosis (DVT) and pulmonary embolism (PE) require major allocation of manpower, hospital and financial resources. Pulmonary embolism is one of the most common causes of death in hospitalized patients; it is present in 10-25% of patients who die while hospitalized.

Mechanical compression devices and anticoagulant drugs are standard approaches to prevention of VTE. Treatment of PE is by means of anticoagulants and less frequently with thrombolytic drugs. The heparins—unfractionated heparin (UFH) and the derivative low molecular weight heparins (LMWHs)—are commonly used for both prevention and treatment of PE. More recently the pentasaccharide fondaparinux has come into general use for prevention and treatment of PE.

Both UFH and LMWHs are indirect parenteral anticoagulants. UFH may be given intravenously (IV) or subcutaneously (SC); the LMWHs are given SC. The LMWHs, derived from UFH, are drugs available beginning in the 1990s, while UFH has been established for much longer for preventing and treating thromboembolic disease.

Since their introduction, the LMWHs have been shown to require no monitoring of anticoagulant effect, except possibly in presence of special conditions such as morbid obesity. UFH anticoagulant effect has by long-standing clinical tradition been monitored by activated partial thromboplastin time (aPTT).

Although monitoring of UFH effect is a standard of practice, its necessity may be questioned on the basis of both knowledge and experience. What is the evidence to justify routine monitoring of UFH? What is the experience of outcomes of monitoring versus no monitoring?

There is only weak evidence to support aPTT monitoring to indicate need for UFH dose adjustment to maintain a therapeutic range. However, risk of UHF-associated bleeding increases with UHF dose. In addition, pharmacokinetic properties of UHF can induce immune-mediated platelet activation leading to heparin-induced thrombocytopenia (HIT). The frequency of HIT is substantially lower in patients treated with LMWHs.

On a dose-for-dose comparison, UFH is significantly less costly than LMWHs, if drug cost is the only mode of comparison. When the lower frequency of HIT is considered, the added costs of further treatment and hospitalization favor the LMWHs.

Decreased LMWH clearance in patients with renal insufficiency has been associated with increased bleeding risk. UFH may be the drug of choice in this setting, to assure maintenance of a therapeutic range of anticoagulation and lower risk of bleeding.

The standard of practice in many if not most hospitals is to routinely choose LMWHs for prevention of venous thromboembolic disease. LMWHs may be, as well, an initial choice for treatment of early PE. However, UFH remains a useful anticoagulant that may make it a better choice than LMWHs in some patients and under some conditions. The physician should be familiar with evidence-based recommendations for uses, risks and monitoring of both UFH and the LMWHs.