Anticoagulation Therapy

Jeffrey A. Ginsberg, Mark A. Crowther, Richard H. White, and Thomas L. Ortel

Despite refinements and standardization in the use of anticoagulants, many problems remain for clinicians. Dr. Crowther describes appropriate starting and maintenance doses of warfarin, factors accounting for inter- and intra-observer variability and importantly, the management of the over-anticoagulated patients and bleeding patients. Dr. White compares unfractionated heparin (UFH) and low molecular weight heparin (LMWH) and addresses whether there truly are differences in the efficacy and safety of different LMWH's for both arterial and venous indications. Dr. Ortel discusses the management of the problem patient who requires anticoagulants, the management of heparin-induced thrombocytopenia, the pregnant patient, the obese patient, patients who have renal insufficiency and/or liver disease, patients with malignant disease, and other challenging patient populations.

I. Initiation and Control of Oral Anticoagulant Therapy

Mark A. Crowther, MD, MSc*

Warfarin Initiation

Warfarin is effective for the prevention and treatment of venous and arterial thrombosis. As additional indications are studied, the number of patients receiving warfarin increases. As a result, more physicians and allied health care professionals are called upon to guide the initial days of warfarin therapy. A lack of experience with warfarin initiation and maintenance therapy can lead to inappropriate dosing, which results in over-anticoagulation (and a risk of hemorrhage) or under-anticoagulation (which might prolong the need for parenteral anticoagulants, and be associated with an increased risk of thrombosis). To reduce the risk of inappropriate anticoagulant therapy during the initial days of warfarin therapy, a number of warfarin dosing algorithms have been evaluated. Algorithm guided warfarin initiation results in more rapid achievement of a therapeutic international normalized ratio (INR) than simple physician guided warfarin initiation, and may result in shorter hospital stays for some patients.[1]

Oral anticoagulant therapy (OAC) has been traditionally initiated with fixed loading doses which are larger than those required for maintenance of an adequate anticoagulant effect. Historically, loading doses as large as 1 mg/kg were used because these doses produce prothrombin times exceeding the lower limit of the therapeutic range within 24 to 36 hours of the first dose. Seminal work carried out by O'Reilly and Aggeler in the 1960s[2] demonstrated that these very large loading doses were unnecessary; over the ensuing 30 years the initial dose of warfarin was gradually reduced until, in the 1990s, most physicians initiated warfarin with a dose two- to threefold higher than average maintenance doses (10 to 15 mg).

Recently, the use of a warfarin loading dose has been called into question. Two randomized clinical trials suggest that warfarin therapy should be initiated in most patients with a 5 mg dose and adjusted according to the INR response.[3,4] Use of a 5 mg warfarin loading dose appears to reduce the likelihood of excessive early anticoagulation, ameliorates precipitous declines in protein C in the first days of warfarin therapy (which might be associated with the development of a hypercoagulable state), and does not appear to prolong the time required to achieve an INR of 2.0-3.0. Furthermore, the associated reliable early anticoagulation may reduce the need for INR determinations during warfarin initiation, since the probability of excessively prolonged INR values is reduced. Reducing the number of INR determinations required in the initial days of warfarin therapy is desirable as it simplifies treatment, particularly of outpatients. The effectiveness of smaller initial warfarin doses was confirmed in a recent paper published by O'Connell and associates.[5] In this retrospective review of charts identified from computerized pharmacy records at a county

* Department of Hematology, St. Joseph's Hospital, 50 Charlton Ave E, Hamilton ONT L8N 4A6, Canada

teaching hospital, the time to first INR of 2.0 or greater, bleeding complications, number of warfarin doses held, and vitamin K use were compared in elderly patients who received an initial warfarin dose of about 5 mg or an initial warfarin dose of about 10 mg. The mean time to first INR of 2.0 or greater was similar in the two groups, 3.4 and 3.0 days, respectively (p = 0.38). The low-dose group showed trends towards less bleeding (7 vs. 13, p = 0.28), and required fewer doses of warfarin held (11 vs. 18 patients, p = 0.27, 30 vs. 50 doses). The authors conclude that hospitalized elderly patients achieved therapeutic INRs in a similar time irrespective of their initial dose of warfarin, but that a lower initial warfarin dose was more effective.

In some patient populations, a 5 mg initial dose of warfarin is excessive. In a retrospective study, Ageno and Turpie studied the anticoagulant response of patients undergoing elective heart valve replacement.[6] In this study, the mean daily dose of warfarin required to achieve a therapeutic INR was 3.29 +/- 1.29 mg, while the mean daily dose of warfarin in a comparable group of patients initiating warfarin for other reasons was 4.96 +/- 1.76 mg (p < 0.001). Heart valve replacement patients were overly-anticoagulated more frequently than the comparison group (48.8% vs 21.8%, p = 0.014) and, during initiation, doses of warfarin were withheld due to excessive anticoagulation more frequently (54.7% versus 28.1%, p = 0.015). The authors conclude that patients starting oral anticoagulation after heart valve replacement are more sensitive to warfarin than non-surgical patients, and that initial warfarin doses of less than 5 mg is indicated in many such patients.

Warfarin Maintenance Therapy

The effectiveness and safety of warfarin is critically dependent on maintaining the INR in the therapeutic range. The importance of maintaining good anticoagulant control was demonstrated by an "on-treatment" re-analysis of the primary prevention trials in atrial fibrillation.[7] The results of this analysis showed that both thromboembolic and bleeding events occurred when warfarin's anticoagulant effect was outside the therapeutic range and that both the safety and efficacy of warfarin was increased by maintaining good anticoagulant control. Subgroup analyses of other studies have shown a sharp increase in the risk of bleeding when the INR is above than the upper limit of the therapeutic range[8-11] and the risk of a thromboembolic event increases when the INR falls below the lower limit.[9,12] Therefore, every effort should be made to maintain the INR result within the therapeutic range. This is facilitated by targeting an INR level in the mid-level of the INR range (e.g. 2.5 for a designated range of 2.0-3.0 and 3.0 for a designated range of 2.5-3.5).

To increase the "time in the therapeutic range" (TTR) a variety of aids have been developed. Large anticoagulant clinics may benefit from the use of computerized warfarin dosing systems, which track previous warfarin use, and predict future requirements based on both patient-specific and patient-independent factors. Anticoagulant monitoring clinics (AMCs) with dedicated personnel, or widespread use of point-of-care monitors may also increase the TTR and thus, improve the safety, efficacy and cost effectiveness of warfarin therapy. Recently, Ansell et al have published a comprehensive review of the benefits of both maximizing TTR and the potential benefits of both point of care anticoagulant monitoring and AMCs.[13] These authors conclude that, in select circumstances, AMCs or patient self-testing and monitoring reduce the costs of anticoagulation, when compared with physician directed care (by reducing the frequency of bleeding and its associated hospitalization), increase the TTR (thus reducing the risk of recurrent thromboembolism) and are more acceptable to patients.

Computerized programs that direct warfarin dosing have also been developed (for example, see [14-17]). In one randomized trial of patients followed in an outpatient clinic, the reliability of three established computerized dosage programs was compared with warfarin dosing by experienced medical staff.[18] The INR control achieved by the computerized programs was similar to that achieved by clinic staff for patients whose target INR was 2.0-3.0, but the computerized programs achieved significantly better control than empiric dosage adjustment in patients with a higher target INR (3.0-4.5). In a second randomized study[19] 101 long-term anticoagulated patients with prosthetic cardiac valves were assigned to monitoring by a computerized system or to empiric management by trained personnel. The computer program was comparable to the empiric system in maintaining the percentage of INRs in range, but achieved a 50% reduction in the number of dose adjustments. More recently, a large multicenter randomized study of 285 patients performed by the European Concerted Action on Anticoagulation[20] showed that a computer assisted dosage program was significantly more effective than traditional dosing in achieving a targeted therapeutic range. Thus, computerized dosage adjustment appears to have an advantage over traditional physician-based dosing, particularly if the personnel using the latter approach are inexperienced. By increasing time in the therapeutic range, it is likely that computerized dosing adjustment will reduce the risk of bleeding (attributable to excess anticoagulation) and thrombosis (attributable to inadequate anticoagulation). However, none of the studies completed to date comparing traditional and computerized dosing have been powered to detect differences in the rates of clinical outcomes.

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Table 1. Suggested treatment strategies for various international normalized ratio (INR) values in patients receiving warfarin administered to achieve a target INR of 2.0 to 3.0. For patients receiving warfarin with a higher target INR, the ranges presented should be adjusted upwards. In all cases, the cause of the excessive prolongation of the INR should be sought, and corrected.

INR value	Clinical Data	Treatment strategy
Any elevation	Life threatening bleeding	1. Withhold warfarin. 2. Replace coagulation factors using plasma or complex concentrates. 3. Administer intravenous vitamin K (5 to 10 mg, with the dose depending on the INR). 4. Correct mechanical causes of hemorrhage. 5. Provide medical support, including transfusion, as required.
Any elevation	Major (non-life threatening bleeding)	1. Withhold warfarin. 2. Consider administration of plasma or complex concentrates. 3. Administer intravenous vitamin K (1 to 10 mg, with the dose depending on the INR). 4. Correct mechanical causes of hemorrhage. 5. Provide medical support, including transfusion, as required.
4.5 to 6.0	No bleeding	1. Withhold warfarin and recheck INR in 24 to 48 hours OR 1. Withhold warfarin, administer 1 mg oral vitamin K and recheck INR in 24 to 48 hours OR 1. Reduce warfarin dose, recheck INR in 24 to 48 hours
6.1 to 10.0	No bleeding	1. Withhold warfarin and recheck INR in 24 hours OR 1. Withhold warfarin, administer 1 mg oral vitamin K and recheck INR in 24 hours OR 1. Withhold warfarin, administer 1 to 2.5 mg of oral vitamin K, consider using plasma or complex concentrates ONLY IN PATIENTS AT HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours
10.1 and above	No bleeding	1. Withhold warfarin, administer 1 to 5 mg of oral vitamin K and recheck INR in 24 hours OR 1. Withhold warfarin, administer 0.5 to 1.0 mg of intravenous vitamin K and recheck INR in 24 hours OR 2. Withhold warfarin, administer 1 to 5 mg of oral vitamin K, consider using plasma or complex concentrates ONLY IN PATIENTS AT HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours OR 1. Withhold warfarin, administer 0.5 to 1.0 mg of intravenous vitamin K, consider plasma or complex concentrates ONLY IN PATIENTS WITH HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours.

An alternative strategy to centralized warfarin monitoring is management by patients of their own anticoagulation, using a portable warfarin monitor. The utility of this therapy was recently investigated by Cromheecke et al.[21] Fifty patients receiving long-term oral anticoagulant treatment were included in a randomized cross-over study in which patients self-managed warfarin or were managed by an AMC for periods of 3 months and then crossed-over to the other management strategy. The primary endpoint was the number of measurements within the therapeutic range (therapeutic target value +/- 0.5 INR units). The investigators found that self-managed patients had INR results within the desired range 55% of the time, while patients managed by the AMC were within this range 49% of the time (p = 0.06) and that patients were more satisfied with self-management than with clinic management. The authors conclude that, for selected patients, self-management of oral anticoagulant therapy is feasible and appears to result in anticoagulant control comparable to that achieved in an AMC.

Treatment of High INR Values:
Non-bleeding Patients
Bleeding is the main complication of oral anticoagulant therapy. Randomized studies have shown that the risk of bleeding is influenced by the intensity of anticoagulant therapy and that lowering the target intensity of warfarin reduces the risk of clinically important bleeding.[22,23]

Patients receiving warfarin frequently have excessively prolonged INR results. This can be due to the use of concomitant medications, the presence of co-morbid illnesses, dietary changes, or for no apparent reason.[24] Numerous studies have demonstrated that patients receiving warfarin frequently are found to have INR results above the therapeutic range, and that such elevations are an independent predictor for major bleeding.[22,25,26] A recent study by Hylek et al[27] has emphasized the risk of hemorrhage in patients with excessively prolonged INR values who receive oral anticoagulant therapy; in this study 5 of 114 (4%) asymptomatic patients with an INR > 6.0 developed life-threatening bleeding within 2 weeks of their elevated INR value, suggesting that timely intervention to reduce a prolonged INR value might reduce the risk of bleeding in these patients.

Patients receiving warfarin who present with an elevated INR should be screened for bleeding. In patients with active, major bleeding, plasma, in combination intravenous vitamin K should be given and quickly reduces the INR to the normal range (see **Table 1**). Because of the cost and risks of plasma therapy, it should only be used in patients with an acute indication for the immediate reversal of the anticoagulant effect of warfarin, and

it should be administered in concert with parenteral vitamin K. Plasma should not be used to correct a moderately prolonged INR in a non-bleeding patient, and its use in any non-bleeding patient should be discouraged given the effectiveness of oral and intravenous vitamin K for the rapid reversal of prolonged INR values.

There is no generally accepted method designed to reduce an excessively prolonged INR in non-bleeding patients receiving warfarin. The most simple and widely used approach is to withhold warfarin and allow the INR to fall into the desired range, at which point warfarin is re-instituted, often at a reduced dose. Two large case-series have examined the safety of this approach.[28,29] In these investigations, a total of 352 INR values above 6.0 occurred in 299 patients and only 2 patients (0.6%) suffered hemorrhage. The authors recommend that this strategy be considered in patients presenting with asymptomatic warfarin-associated coagulopathy. The study by Lousberg et al[29] also suggested that simply withholding warfarin was more cost-effective than administering vitamin K to patients with INR values between 6.0 and 10.0. Why the rates of hemorrhage in these papers (0.6% in aggregate) was lower than that observed by Hylek et al (4%) is unclear. Although study design and the characteristics of the patients enrolled in the two studies may account for some of the observed difference, additional prospective studies with sufficiently large numbers of patients are required to accurately judge the rate of hemorrhage in patients taking warfarin who present with excessively prolonged INR values.

To hasten the fall of the INR towards the desired range, vitamin K is often administered to patients with an elevated INR value. Vitamin K can be administered intravenously, subcutaneously or orally. Parenteral vitamin K can cause adverse experiences including warfarin resistance,[29-31] anaphylactoid reactions,[32-34] and skin reactions.[35] In addition, parenteral administration is inconvenient and requires a visit to a health care provider.

Intravenous vitamin K rapidly and reliably reduces excessively prolonged INR values towards normal. Shetty et al[31] administered 1.0 mg or 0.5 mg of vitamin K intravenously to consecutive patients presenting with excess warfarin effect. Ten patients received 1.0 mg of intravenous vitamin K (mean INR at presentation 10.5), while 21 patients received 0.5 mg intravenously (mean INR at presentation 10.3). Five patients receiving 1.0 mg had "over-reversal" of their anticoagulation (INR < 2.0 at 24 hours), while 2 patients had persistent prolongation of their INR at 24 hours. Of the 21 patients receiving 0.5 mg intravenously, 7 had an INR > 3.0 at 24 hours, while none was "over-reversed." No complications of therapy were reported. Similar results were also reported by Anderson et al.[36] Although this evidence suggests that intravenous vitamin K is both safe and ef-

fective for the treatment of excessively prolonged INR values in patients receiving warfarin, two concerns have led to intravenous vitamin K being underutilized. The first concern is the risk of anaphylactoid reactions. Although frequently reported, and likely more common in patients who receive large intravenous doses administered rapidly, the true frequency of this complication is likely low. Slow intravenous administration (i.e. 1-2 mg over 20-30 minutes) of vitamin K appears to be associated with a low risk of anaphylaxis. The second concern is warfarin resistance due to excessively large doses of vitamin K. Administration of doses larger than 1-2 mg by the intravenous route is likely to be associated with this complication, and thus should be avoided. There is no indication for larger doses of vitamin K, as even very prolonged INR values respond rapidly to small (0.5-1 mg) intravenous vitamin K doses.

Although widely used to treat warfarin associated coagulopathy, subcutaneous vitamin K is relatively ineffective. Nee et al[37] performed a randomized, double blind trial in which non-bleeding patients with INR values between 6.0-20.0 received either subcutaneous or intravenous vitamin K. Independent of route, patients with INR values between 6-10 received 0.5 mg of vitamin K, while those with values between 10-20 received 3 mg of vitamin K. Thirty-three patients were randomized to subcutaneous vitamin K, while 22 patients received intravenous vitamin K. Twenty-four hours following administration of the study drug, 45% of patients in the subcutaneous group had an INR less than 4.5, compared with 95% of patients in the intravenous group. Surprisingly, over-correction of the INR occurred more frequently in the subcutaneous group (42%) than the intravenous group (23%). Similarly, Raj et al[38] performed a single blind randomized trial that enrolled non-bleeding patients with INR values greater than 6.0 to receive either 1 mg of intravenous or subcutaneous vitamin K. Eight hours after administration of the study drug, 9% of patients in the subcutaneous group, and 82% of patients in the intravenous group had an INR less than 5.0. At 24 hours, 64% of the patients in the subcutaneous group, and 82% of the patients in the intravenous group had an INR value of less than 5.0. Taken together, these studies support the contention that if rapid reductions in the INR are desired, vitamin K administered by the intravenous route is appropriate because it begins to reduce the INR within 8 hours. Furthermore, these studies suggest that subcutaneous vitamin K is relatively ineffective and that its use is associated with over-correction of the INR.

To avoid the inconvenience and toxicity of parenteral vitamin K, recent interest has focussed on the use of oral vitamin K for the treatment of warfarin-associated coagulopathy. When used in doses of 1-2.5 mg, oral vi-

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tamin K does not appear to over-reverse the anticoagulant effect of warfarin, and its use has not been associated with anaphylactoid or skin reactions.[39,40] Further, oral vitamin K does not require injection and, in most jurisdictions, is an over-the-counter product. Therefore, it can be administered without a physician's prescription by the patient, nurse or pharmacist. The use of oral vitamin K to reduce the anticoagulant effect of warfarin was first reported by Cosgrif.[41] In the modern era, the first randomized trial of oral vitamin K was performed by Pengo et al.[40] This study demonstrated the effectiveness of oral vitamin K in patients with warfarin-associated coagulopathy. Two additional randomized controlled trials have confirmed the effectiveness of low dose oral vitamin K. Our group[42] has reported the results of a randomized trial in which 92 patients with INR values of 4.5-10.0 were randomly allocated to receive 1 mg of oral vitamin K or placebo. The primary endpoint was the proportion of patients with an INR value of 1.8-3.2 on the day following study drug. Twenty-five of 45 patients (56%) who received vitamin K, and 9 of 44 (20%) patients who received placebo, had INR values of 1.8-3.2 on the day following study drug administration (p = 0.001; OR 0.21, 95% CI: 0.07,0.57). No patient who received vitamin K, and 4 patients (9%) who received placebo, had an increase in their INR values on the day following study drug administration (p = 0.056), and 7 patients (16%) who received vitamin K, and none who received placebo, had an INR value of less than 1.8 on the day following study drug administration (p = 0.012). INR values were significantly higher in the placebo group than the vitamin K group on both the first and second study days but were comparable thereafter. The pooled results from our prospective studies that examined the utility of 1 mg of oral vitamin K for the treatment of warfarin associated coagulopathy are summarized in **Figure 1**. Similar results were reported by Patel et al.[43] One of the concerns expressed about the use of oral vitamin K for the treatment of warfarin associated coagulopathy is its impaired absorption in patients with liver disease. However, a recent study suggests that large doses of oral vitamin K (20 mg of menadiol orally daily for 3 days) are effective for the treatment of prolonged INR values in patients with cholestatic liver disease.[44]

Treatment of High INR Values: Bleeding Patients

The management of patients who bleed while receiving oral anticoagulants must be individualized and depends on several factors, including the severity and location of the hemorrhage and the INR when bleeding occurs. For patients who have relatively minor bleeding from an accessible site, such as epistaxis or wound bleeding, local compression with or without a reduction or discontinuation of warfarin may suffice. Patients with severe

hemorrhage or hemorrhage into a critical organ require more aggressive management. Administration of intravenous vitamin K, in combination with either fresh frozen plasma or prothrombin complex concentrate, will result in an immediate and sustained reduction in the INR value. Doses of vitamin K as small as 1 mg, used in combination with plasma or coagulation complexes, are effective for this indication.[31] For patients with life-threatening hemorrhage the use of prothrombin complex concentrates may be preferable to fresh frozen plasma. Thus, Cartmill et al[45] performed a prospective study in which the utility of prothrombin complex concentrate was compared with fresh frozen plasma in patients requiring neurosurgical intervention as a result of warfarin-associated hemorrhage. Patients receiving prothrombin complex concentrates had a more rapid and more complete reversal of their over-anticoagulation. Similar results were reported by Makris et al,[46] who demonstrated that clotting factor concentrates more effectively corrected an elevated INR than fresh frozen plasma. Three major issues have limited the use of prothrombin complex concentrates in patients presenting with life-threatening hemorrhage. The first is the fear of thrombotic complications, which have been reported to occur after its administration, particularly in patients with severe liver disease. The second is the limited availability of these products and the third is the lack of knowledge of their utility. The likelihood of thrombosis after administration of these products to patients who do not have severe liver impairment is not known; as a result, accurate estimates of this risk will have to await prospective studies. The lack of knowledge and limited access to these products will have only be corrected if adequately powered and methodologically rigorous studies are completed that demonstrate that coagulation factor concentrates are more effective than frozen plasma in patients on warfarin who present with life threatening bleeding.
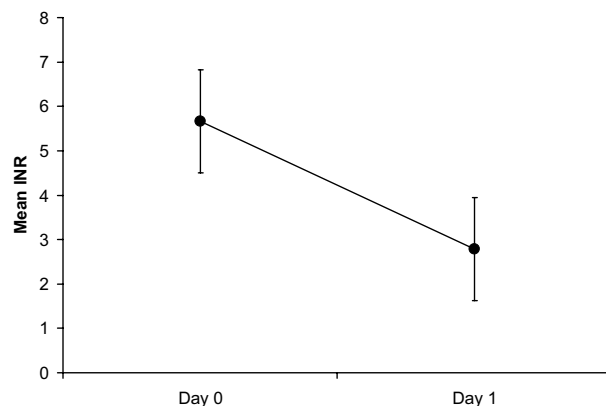
Figure 1. The results of three prospective trials performed by our group in which 134 patients presenting with INR values of 4.5 to 10.0 received 1.0 mg of oral vitamin K are presented. The mean INR prior to vitamin K was 5.7 (1 standard deviation [SD] 1.2), while it was 2.8 (1.2) on the day after vitamin K.

The long term management of patients who have bled while taking oral anticoagulants and who require protection against systemic embolism (e.g. patients with mechanical heart valves or with atrial fibrillation and other risk factors) is problematic. If bleeding occurs when the INR is above the therapeutic range, warfarin treatment can often be re-started when bleeding stops and the cause (if identified) is corrected. More careful attention to warfarin control might then reduce the risk of undesired, recurrent, prolongation of the INR. If bleeding occurs while the patient is in the therapeutic range, treatment is more problematic. For patients with mechanical prosthetic valves (and a persisting increased risk of bleeding) it is reasonable to aim for a less intense INR of 2.0-2.5 (rather than 2.5-3.5). For patients with atrial fibrillation (and a persisting risk of increased bleeding), the anticoagulant target range can be reduced from 2.0-3.0 to 1.5-2.0 with the expectation that efficacy will be reduced but not abolished.[47] Alternatively, aspirin can be used to replace warfarin in patients with atrial fibrillation.

Discontinuing Warfarin Therapy

Oral anticoagulant therapy may be discontinued temporarily or permanently. In either case, simply stopping oral anticoagulant intake should result in normalized coagulation within four to seven days of the last dose. As during the initiation phase of warfarin therapy, the INR in the period immediately after warfarin is discontinued may not accurately reflect the degree of impairment of coagulation because the initial fall in the INR is likely due to rising levels of coagulation factor VII despite continued depression of the levels of coagulation factors II and X. The clinical importance of this phenomenon is unknown. To determine the time-course of change in INR after warfarin discontinuation, White et al[48] performed a cohort study in which patients receiving warfarin who had an average INR of 2.6 stopped their warfarin, and their INR value was followed serially. The mean INR 2.7 days after warfarin was discontinued was 1.6, and 20 of 22 patients had INR values above 1.2, while after 4.7 days had passed, the mean INR was 1.1 with only 5 of 22 patients having INR values above 1.2. Five patients were studied in detail and demonstrated that the INR declined precipitously with a half-life of 0.5-1.2 days after the discontinuation of warfarin. The patient's age correlated inversely with the rate of fall of the INR. These authors conclude that normal coagulation is not achieved for a minimum of four days after discontinuation of warfarin, and there is substantial inter-individual variation in the rate of fall of the INR.

Conclusion

Oral anticoagulant therapy with vitamin K antagonists remains the mainstay of antithrombotic therapy. Better strategies to initiate and control this therapy should reduce the risk of both thrombosis and hemorrhage, while minimizing the need for laboratory monitoring. Effective strategies for the treatment of bleeding should simplify the care of these patients, reduce the likelihood of death or long-term morbidity attributable to hemorrhage, and reduce the need for costly, and potentially dangerous treatments. Finally, although alternate oral antithrombotic agents are showing promise in clinical trials, it is likely that vitamin K antagonists will remain the preeminent anticoagulant for the foreseeable future.

II. LOW MOLECULAR WEIGHT HEPARINS: ARE THERE ANY DIFFERENCES?

Richard H. White, MD*

The Issues

Three low molecular weight heparin (LMWH) products are now available for clinical use in the US: enoxaparin, dalteparin and tinzaparin There are, without question, differences in the chemical composition of these products, and the US FDA has classified them as distinct drugs. However, these heparin products share so many chemical characteristics and appear to have such a similar degree of clinical efficacy that it is commonplace for journal and book articles to simply refer to these products generically as LMWHs. In making recommendations for anticoagulant therapy, the American College of Chest Physicians consensus conference refers only generically to "LMWH," not to any one specific product for a particular indication.[1,2]

Nevertheless, there is a growing debate about whether these LMWHs are indeed therapeutically (or clinically) equivalent.[3-5] A major concern is whether the results of large clinical trials using a specific LMWH product for a specified indication, e.g. use of enoxaparin to prevent venous thromboembolism in trauma patients, can be extrapolated and applied to a different LMWH product.[6,7] The issues that motivate this debate in the health care community are, not surprisingly, 1) the cost of these products and 2) the appropriateness of judging these products as being therapeutically equivalent and interchangeable.

* Division of General Medicine, University of California at Davis Medical Center, Suite 2400, PSSB, 4150 V Street, Sacramento CA 95817

Pharmaceutical firms, and to some extent investigators, have invested time and millions of dollars completing many large randomized trial using a specific product, assuming that the results of their studies should be applied only to their specific LMWH product.[8] Hospitals and health care systems, on the other hand, are burdened by exponentially mounting drug acquisition costs and face extreme pressure to minimize drug expenditures by using the least expensive effective product available.[9] The physicians and pharmacy administrators who conclude that LMWHs are therapeutically interchangeable call attention to the fact that there is scant literature showing any 'clinically meaningful' difference between the drugs; hence, they are 'clinically interchangeable.' Clinicians can be caught in the middle, wanting to use the most effective drug and, at the same time, the cheapest drug. Whereas the literature may support the efficacy of one specified LMWH, the hospital may select a different LMWH for their formulary. So, what are the differences, if any, among the currently available LMWH products? The following issues will be discussed: 1) What are the biochemical and pharmacological differences among the currently available LMWHs and what is the basis for these differences? 2) Do these differences translate into different biologic effects in humans? 3) Do these differences (if any) result in clinically meaningful differences in efficacy and safety?

Unfractionated Heparin

Unfractionated heparin is a heterogenous group of glycosaminoglycans made in mast cells, consisting of a basic structure of alternating saccharide residues of uronic acid and glucosamine.[10] The saccharides are modified by a number of enzymes that change the molecular structure by making chemical modifications at specific sites, such as adding a sulfate or glucuronic acid moiety. The essential core of heparin that functions as an anticoagulant resides in short polysaccharide fragments that interact with antithrombin (AT), and the exact biologic effect varies depending on the number of polysaccharides in the fragment. Very short fragments of heparin, as short as a pentasaccharide, are capable of enhancing the effect of AT, leading to inhibition of activated factor X. This effect is measured as anti-Xa activity. Longer polysaccharide molecules of over 16 units are needed in order to effectively catalyze AT's inhibition of thrombin.[11] Thus, if heparin is broken down into smaller sized

molecules, the relative inhibition of factor Xa and factor IIa will vary depending on the relative abundance of saccharide fragments with over 16 units (more antithrombin effect) and under 16 units (more anti-Xa effect). It is not clear which effect, if either, is more important to maximally inhibit thrombosis.

Native heparin purified from bovine or porcine sources is quite heterogeneous, with the mean molecular weight ranging from 11,000 to 17,000 daltons, and fragments ranging in size from 6,000 to 25,000 daltons.

Low Molecular Weight Heparins

LMWHs are collections of heparin molecules with considerably lower mean molecular weight than regular unfractionated heparin.[10] All LMWH products are administered subcutaneously with excellent bioavailability. Four LMWH products have been approved by the FDA for use in the US. The three that are commercially available at this time, and their method of preparation, are shown in **Table 2**. Other LMWH products in use in Europe and in other countries include reviparin, nadroparin and certoparin.

Because these products isolate shorter heparin fragments using different chemical methods, there are size and molecular differences among them. Chemical or enzymatic methods of cleaving native heparin lead to differences in the size and the chemical structure of the saccharide molecules, which are subsequently isolated.[12]

The principal anticoagulant properties of LMWH are a result of the ability of the small fragments to bind to AT and inactivate factors Xa and IIa. There is, however, evidence that LMWHs, like unfractionated heparin, release tissue factor pathway inhibitor (TFPI), which also acts as an anticoagulant.[13] The relative potencies of the different LMWH products, when measured using anti-Xa or anti-IIa (aPTT) assays, are likely due to differences in the relative abundance of polysaccharide fragments with fewer than 16 residues compared with those with more than 16 residues. The plasma level of anti-Xa activity does not appear to correlate with antithrombotic effectiveness in either a rabbit model[14] or in humans.[15] **Table 3** summarizes some of the key characteristics of the different LMWH products.

Fareed and coworkers have demonstrated in vitro and in vivo differences between theses LMWH products.[16,17] For instance, 30% of enoxaparin is neutralized by protamine sulfate compared with 40% for dalteparin

Table 2. Commercially available low molecular weight heparin products.

Drug name	Trade name(s)	Manufacturer	Method of Preparation
enoxaparin	Lovenox, Clexane	Aventis	Benzylation followed by alkaline hydrolysis
dalteparin	Fragmin	Pharmacia & Upjohn	Controlled nitrous acid depolymerization
tinzaparin	Innohep, Logiparin	Dupont (now BristolMeyer Squibb)	Heparinase digestion

Table 3. Characteristics of comercially available low molecular weight heparins.

Drug name	Mean Molecular Wt	Anti-Xa/ aPTT ratio	Subcutaneous Treatment Dose (venous thrombosis)
enoxaparin	4,300	3.8	100 anti-Xa IU/kg bid or 150 anti-Xa IU/kg qd
dalteparin	5,800	4.0	100 anti-Xa IU/kg bid or 200 anti-Xa IU/kg qd
tinzaparin	5,800	2.0	175 anti Xa IU/kg qd

and 60% for tinzaparin. Some pharmacokinetic differences also exist when studied in normal humans without thrombosis. For example, the half-life of elimination of anti-Xa activity for dalteparin is 2.4 hours, whereas for tinzaparin it is 3.0 hours and for enoxaparin it is 4.3 hours.[18] However, release of TFPI is comparable in normal male subjects given 50, 100 and 200 anti-Xa IU of either dalteparin or enoxaparin, even though resultant anti-Xa activities after 2 to 6 hours are significantly different.[19] Based on an array of in vitro analyses and in vivo comparisons in animal models *(United States Pharmacopeia* potency, glycosaminoglycan content, rabbit ear bleeding, rabbit jugular vein thrombosis, etc.) there are differences between LMWH preparations.[12,16] Some of the measured differences among preparations may reflect a difference in the dose administered, since there is no clear or universally accepted method of determining equivalent doses. For example, products with equal anti-Xa potency on a weight basis may have unequal anti-IIa potency.

Although differences exist, LMWH products appear to be remarkably similar in antithrombotic effect as measured in various animal models and in humans. For example, in a dog model of acute deep vein thrombosis, when 100 anti-Xa IU/kg of enoxaparin given twice a day is compared to 200 anti-Xa IU/kg of dalteparin given once a day, the measured suppression of thrombus propagation measured using a sensitive radiolabeled anti-fibrin antibody is almost identical.[20] Indeed, it is surprising that there have been no reports of major differences in the measured in vivo efficacy or safety of any of these products. A recent study by Montalescot et al suggests that, among patients with unstable angina, there may be greater inhibition of von Willebrand factor release during the first 48 hours among patients treated with enoxaparin as opposed to dalteparin,[21] and that higher levels of von Willebrand factor predict adverse outcomes. However, these data were collected retrospectively from subjects enrolled in several different clinical trials, and the analysis included no adjustment for demographic variables, illness severity or trial design. Observations such as these reinforce the conclusion that the only way of determining if there are clinically significant differences in available LMWH preparations is to directly compare them in randomized clinical trials. Unfortunately, few such studies have been reported in the literature and most are underpowered to determine differences in efficacy or safety. Thus, one is left with indirect comparisons of trials that mainly compare unfractionated heparin or warfarin with LMWH, and these trials are heterogeneous with regard to patient population, therapeutic indication, evaluable outcomes, and statistical power.

Drug Interchange and Drug Substitution

The FDA treats each LMWH product as a separate drug. Thus, these products cannot be legally substituted for one another. In order to get FDA approval for a specific indication, each manufacturer has to provide rigorous evidence of efficacy based on appropriately conducted clinical trials. Products that contain the exact same drug in the same strength, dosage form and route of administration can be interchanged and substituted as generic equivalents (after the patent expires).

The fact that two products are classified by the FDA as separate drugs does not prevent hospitals or health care plans from deciding that two different products are essentially the same and interchanging them on their formulary. In most hospitals, the substitution of one formulary product for another is usually made by a pharmacy and therapeutics committee, with approval of the medical staff. The American Medical Association has a list of criteria needed in order for a formulary "therapeutic interchange" to be deemed acceptable (www.ama-assn.org/apps/pf_online/pf_online). Such an interchange should be contrasted with a "therapeutic substitution," which is defined as the act of dispensing an alternate drug without prior authorization, and is strongly opposed by the AMA.

The appropriateness of a therapeutic interchange of one LMWH for another rests on a formal drug evaluation by unbiased experts. This process centers on a thorough evaluation of all available literature that relate to the clinical efficacy, safety and cost-effectiveness of the each drug for each indication. In the absence of direct comparative studies, a judgement must be made based on indirect comparison of results of clinical trials that involve patients with the same indication. The same control or comparison drug (e.g., unfractionated heparin) must be used, comparable doses of the LMWH must be used, and similar methodology and outcome measures must be employed. It has to be kept in mind that results between studies may differ if the comparison drug, such as intravenous heparin, is not dosed in the exact same fashion. The results of meta-analyses that pool the results of studies involving use of LMWH preparations depend heavily on all of these assumptions. Therapeutic

interchange is made more difficult in the case of LMWHs because it may require some guesswork in selecting the optimal dose of a LMWH to use if there have been no clinical studies (e.g., tinzaparin for DVT prophylaxis after trauma).

Comparison of LMWHs in the Prevention of Venous Thromboembolism

A large number of studies have assessed the efficacy of LMWH in the prevention of venous thromboembolism after surgery, particularly elective total hip replacement and elective total knee replacement.[1] In fact, prophylaxis of venous thromboembolism is the only clinical indication for which clinical trials have been completed that directly compare different LMWH products.[22] In the vast majority of these clinical trials, LMWHs have been compared to subcutaneously administered regular unfractionated heparin, warfarin, or placebo for varying time periods. Most recent clinical trials have used radiographic evidence of thrombosis 7-12 days after surgery as a surrogate measure for the outcome of interest, clinically important thromboembolism. Meta-analyses have generally shown that LMWHs are superior to unfractionated heparin and placebo.[23-26]

Planes et al in France conducted a large multicenter trial that compared enoxaparin 4000 anti-factor IU Xa once daily to tinzaparin 4500 anti-factor IU Xa once daily, started preoperatively and given daily thereafter after total hip replacement until a venogram was performed 12-14 days after surgery.[22] This dosing protocol does not reflect the practice pattern of most orthopedic surgeons in the US, but it is typical of current practice in Europe. Of 499 patients enrolled, 440 underwent venography (results are shown in **Table 4**).

Using a predefined statistical definition of equivalence, the results of the study showed that the two LMWH preparations were equivalent. Interestingly, significantly higher anti-factor IIa levels were found among the patients receiving tinzaparin, whereas significantly higher anti-factor Xa levels were found in the enoxaparin group.[27] This is consistent with other reports showing that tinzaparin has greater anti-IIa activity and less anti-Xa activity relative to enoxaparin.

In another small, randomized study, enoxaparin was compared to dalteparin in patients with hip fracture.[28] Small doses (2000 anti-Xa IU enoxaparin, 2,500 anti-Xa IU dalteparin) were given prior to surgery, and larger daily doses (4000 anti-Xa IU enoxaparin, 5000 anti-Xa IU dalteparin) were given post-operatively. Patients randomized to each group had similar sex, age, body mass index, history of prior thromboembolism and history of malignancy. The principal outcome was deep vein thrombosis detected

on venogram 9 to 11 days after surgery (results are shown in **Table 5**).

The study was very small, but the findings indicate that a large clinical trial would be necessary in order to detect a significant difference between drug treatment groups.

Comparison of LMWHs in the Treatment of Venous Thromboembolism.

No clinical trials in humans that have directly compared different LMWH preparations in the treatment of acute venous thromboembolism have been published. However, an interim analysis of a large clinical trial has been reported in an abstract. Using a single blind protocol, Wells et al directly compared dalteparin, 200 IU/kg once daily to tinzaparin, 175 IU/kg once daily in patients with symptomatic venous thrombosis or pulmonary embolism (Wells PS et al, abstract at www.cartesian-secure.com/isth2001/index_isth.htm). After enrollment of 370 patients, no significant differences were noted between groups in the incidence of recurrent thromboembolism or bleeding.

Several carefully performed meta-analyses of a large number of clinical trials have analyzed the effect of different LMWH products on the specific outcomes of recurrent thrombosis and major bleeding.[29,30] In an analysis by Gould et al, the LMWH product did not account for significant variation in the observed reduction in mortality or recurrent thromboembolism.[29] However, different LMWH preparations did influence the risk of major bleeding. Tinzaparin, dalteparin and nadroparin were associated with lower odds of bleeding, whereas enoxaparin and reviparin were associated with a higher

Table 4. Tinzaparin versus enoxaparin after total hip replacement.[22]

Drug	Thrombosis			Major Bleeding
	Proximal	Distal	Total*[#]	
enoxaparin (n = 219)	23	21	44	4
tinzaparin (n = 221)	21	27	48	2

*Risk Difference = 1.6% (95% CI = - 6.0% - 9.2%); interpreted as showing *equivalence*.

[#] Only 5 of 92 (5.4%) were clinically manifest.

Table 5. Comparison of enoxaparin and dalteparin in patients with hip fracture.[28]

Drug	Thrombosis			Major Bleeding
	Proximal	Distal	Total	
dalteparin (n = 52)	3	3	5	1
enoxaparin (n = 53)	2	6	8	2

OR = 0.53 (95% CI, 0.14- 1.96), p = 0.29.

risk of bleeding than unfractionated heparin. However, no single LMWH preparation was found to be significantly better or worse than another.

Dolovich et al performed a similar meta-analysis of 13 published studies and reached similar conclusions.[30] They found no significant difference between the LMWH preparations in the incidence of death or recurrent thromboembolism. Only nadroparin was associated with a significantly lower odds of bleeding compared to unfractionated heparin.

Van der Heijden et al recently reported the results of a slightly different analysis of 16 clinical trials completed through the year 2000.[3] They used a methodology called meta-regression analysis, which is a multivariate technique that allows for statistical adjustment for potential confounders, such as the type LMWH used. They found that compared to other LMWH products, dalteparin was associated with significantly higher odds of developing recurrent thromboembolism (as compared to intravenous heparin), but it was also the only LMWH product associated with a significantly lower odds of major hemorrhage. These findings suggest that the dose of dalteparin used in the studies (N = 3), 200 anti-Xa IU/kg as a single dose, may be low compared to the doses of the other LMWH products. However, these findings could also be explained by systematic differences in the study protocols that compared dalteparin to unfractionated heparin. The authors conclude that the limited number of studies using different LMWHs precludes making a firm conclusion regarding clinically meaningful differences among the LMWH products.

Comparison of LMWHs in the Treatment of Patients with Unstable Angina

Numerous studies have assessed the efficacy of LMWH in preventing death or myocardial infarction in patients with unstable angina, and most of the studies have compared use of a LMWH to placebo or to unfractionated heparin for a short period of time (5-7 days) or have compared LMWH to placebo for an extended period of time. No studies have been published that directly compared different LMWH products in the setting of unstable angina (or acute coronary syndrome without ST elevation). One study of 438 patients randomized to 100 IU/kg of enoxaparin given twice a day to 175 IU/kg of tinzaparin once a day has been published in abstract form, but details regarding study design are incomplete. In this abstract, Michalis et al reported a statistically significant benefit of enoxaparin to tinzaparin in the incidence of recurrent unstable angina at 7 days, but there were no differences in the incidence of death, myocardial infarction or recurrent angina. After 30 days there was no difference in the in the incidence of rehospitalization or death, but there was a greater need for acute revascular-

ization in the tinzaparin group. The observed differences in the 'soft' endpoints of recurrent angina and revascularization could be due to the different dosing schedule, once a day dosing versus twice a day, and it is unclear if this was a double blind study.

In a meta-analysis of clinical trials published prior to 2000, Eikelboom et al specifically analyzed 5 trials that compared LMWH to intravenous unfractionated heparin and analyzed results by the LMWH product used.[31] They found that use of LMWH led to a modest but not statistically significant reduction in the risk of death or myocardial infarction compared to unfractionated heparin, and there were no significant differences among the LMWH products. They noted that a reduction in the short term risk of recurrent angina was reported in some studies but that there was no difference in the need for revascularization. These authors acknowledge that two clinical trials that studied enoxaparin (ESSENCE and TIMI IIB) suggested superiority of this LMWH compared to regular heparin, whereas the trials that studied dalteparin and nadroparin did not show a difference. Because of differences in study design, however, the authors concluded that there the only method of determining if one drug is superior to the other is to directly compare them in a clinical trial.

Kaul and Shah thoroughly reviewed the same literature and reached similar conclusions.[32] They noted that the most convincing evidence for superiority of LMWH compared to unfractionated heparin was limited to studies that included the "softer" endpoints of recurrent angina and urgent revascularization, rather than recurrent myocardial infarction or mortality, and the benefits of LMWH were limited to high risk patients. They caution that the benefit of LMWH may be exaggerated because of the use of the more subjective soft endpoints. Studies that incorporated an aggressive interventional strategy (ESSENCE and TIMI IIB-enoxaparin) obviously impacted the rate of revascularization (as well as pharmaco-economic outcomes) compared to the studies that used a more conservative strategy (FRIC-dalteparin). The authors also concluded that the only way to determine if one LMWH is better than another is to conduct a randomized trial.

Comparison of Indications for LMWH

The manufacturer of enoxaparin has aggressively sought FDA approval for use of this LMWH for many indications including prophylaxis of venous thromboembolism after hip and knee replacement, after hip fracture, after general surgery, treatment of venous thromboembolism, and prevention of acute thrombosis in patients with unstable angina. In comparison, the manufacturer of dalteparin has FDA approval for only three indications: for prophylaxis of venous thromboembolism after hip

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replacement and after general surgery and for prevention of arterial thrombosis in patients with unstable angina (**Table 6**). No published studies have evaluated the efficacy of dalteparin in patients undergoing total knee replacement. Currently, tinzaparin has approval only for treatment of acute venous thromboembolism.

In the absence of studies comparing different LMWH products, and when there have been no clinical trials that have assessed the efficacy of a specific LMWH product in patients with a specific indication, what dose of the LMWH should be used and what dosing regimen should be used? This is not a major problem for treatment of deep vein thrombosis because there have been published studies using enoxaparin (FDA approved), tinzaparin (FDA approved) and dalteparin (not FDA approved). However, for the indication of prophylaxis after total knee replacement there is little information to guide the selection of the optimal doses of tinzaparin or dalteparin.

Tinzaparin has been studied in patients undergoing total knee replacement, with a dose of 75 anti-Xa IU/kg daily. In the major study by Hull et al, this resulted in a lower incidence of venographically defined thrombosis but a higher incidence of bleeding compared to warfarin prophylaxis.[33] This raises the possibility that a lower dose of tinzaparin may be optimal.

Is the dose of dalteparin used to prevent thromboembolism after hip replacement surgery (5,000 anti-Xa IU once daily) the correct dose to use after knee replacement? No published studies provide the data needed to make an informed decision. A similar dilemma exists regarding the dosing of tinzaparin among patients with unstable angina. Essentially all of the studies that have assessed the use of LMWH in the prevention of venous thromboembolism for other conditions (e.g., trauma, neurosurgery, medical patients) have used enoxaparin. What is the appropriate dose of dalteparin and tinzaparin in these patients? Is the efficacy of LMWHs so robust all one has to do is simply select a dose proportionate to the dose of enoxaparin dose?

Clearly the biggest challenge when making a therapeutic interchange is to determine the correct dose of a LMWH preparation. This is difficult when there are no published studies and no FDA approved dosing guidelines. Amplifying this dilemma even more are the facts that 1) the most commonly used drug LMWH used in the US, enoxaparin, is usually dosed every 12 hours, whereas tinzaparin is usually dosed once a day, and dalteparin is dosed once or twice a day; 2) preoperative prophylactic regimens used in Europe are not used in the US; and 3) different studies using the same LMWH may use different dosing regimens.

For example, what dose of dalteparin or tinzaparin should be used to prevent thromboembolism after total knee replacement? If one assumes that the prophylactic dose of each preparation should be proportionate to the prophylactic dose of enoxaparin, and using the FDA approved recommended daily dose of each LMWH for the treatment of venous thromboembolism as the referent ratio, the best dose of dalteparin is 6000 anti-Xa IU/day and the best dose of tinzaparin is 5250 anti-Xa IU/day. However, for dalteparin, it is more logical to select the same dose recommended for after hip replacement, which is 5000 anti Xa IU/day. The only study of tinzaparin that has been performed in North America used 75 anti-Xa IU/kg, which for an 80 kg patient is 6000 IU.

Conclusions

Based on this review, certain conclusions can be made:

1. Many in vitro test systems and some in vivo thrombosis models demonstrate measurable differences in the three currently available LMWH preparations.

2. There is a paucity of clinical trials that have directly compared LMWH preparations, and it is unlikely that there will be enthusiasm to conduct such studies. The small studies that have been done have shown no clinically meaningful differences in the LMWH preparations, but most have been underpowered.

3. Using FDA approved dosing recommendations, the three products that are commercially available at this time appear to have comparable efficacy in the treatment of venous thromboembolism; dalteparin and enoxaparin have similar efficacy in the prevention

Table 6. Current FDA approved indications for use of low molecular weight heparins (LMWHs).

Drug	Treatment of Venous Thromboembolism	Prophylaxis – Total Knee	Prophylaxis – Total Hip	Unstable Angina
enoxaparin	100 IU/kg/ q 12 hr or 150 IU/kg qd	3000 IU/day bid	3000 IU/day bid	100 IU/kg q 12 hr
dalteparin	(200 IU/kg once daily)*	???	5000 IU/day	120 IU/kg q 12 hr
tinzaparin	175 IU/kg/once daily	??? ? 75 IU/kg/day	??? ? 75 IU/kg/day ? 4,500 IU/day	???

Indication for LMWH

 * Not FDA approved, but used in other countries at this dose.

of venous thrombosis after general surgery and after total hip arthroplasty; enoxaparin and dalteparin have comparable efficacy in the prevention of death or myocardial infarction among patients with unstable angina.

4. For all remaining indications, there is more abundant evidence-based literature to support the use of enoxaparin; therapeutic interchange of dalteparin and tinzaparin for enoxaparin may be possible, but selecting the optimal dose for each indication is difficult.

III. Anticoagulation Management of the "Problem Patient"

Thomas L. Ortel, MD, PhD*

Every field of medicine has a subset of patients who do not fit into the standard mold, who need to be considered differently because of comorbid conditions, adverse drug reactions, or other variables. Although there are many broad rules that apply to patients on anticoagulant therapy, there are many instances where patients are not 'following the rules.' In some instances, this can lead to complex management decisions for which relatively little data are available. This discussion will focus on several of the more common problems that are not infrequently encountered in patients needing anticoagulant therapy.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a drug-induced, immune-mediated syndrome that occurs in ~3% of patients receiving heparin for 5 or more days.[1] The major target antigen is a multimolecular complex of platelet factor 4 (PF4) and heparin. Immune complexes interact with the platelet FcγII receptor, which leads to platelet activation, formation of prothrombotic microparticles, and generation of thrombin.[1] These antibodies can also interact with heparan-PF4 complexes on endothelial cells, resulting in the expression of a prothrombotic surface.

Diagnosis of HIT. HIT is a clinicopathologic diagnosis. Clinical suspicion should be raised in any patient who has been receiving heparin for at least 5 days who develops an otherwise unexplained thrombocytopenia. At that time, the physician should stop heparin, initiate anticoagulation with an alternative antithrombotic agent

* Hematology/Oncology Division, Duke University Medical Center, Box 3422, Durham NC 27710

(see below), and send appropriate testing to confirm the diagnosis. If testing is negative, alternative diagnoses should be considered, but additional testing for HIT may be indicated.

Diagnostic tests for HIT are divided into functional and immunologic assays. Functional assays include the ^{14}C-serotonin release and platelet aggregation assays.[1] Optimal sensitivity and specificity with either assay are obtained by using washed platelets rather than platelet rich plasma.[1] Recently, several flow cytometric methods have been described that may approach the level of sensitivity obtained with the ^{14}C-serotonin release assay.[2] In contrast to the functional assays, the immunologic assays detect the binding of antibodies to immobilized heparin-PF4 complexes.[3] The immunoassay may have less diagnostic specificity for the clinical syndrome of HIT, however, since it appears to detect antibody development in some patients who do not develop thrombocytopenia or other manifestations of the syndrome.[4]

Management of HIT. Once HIT is clinically suspected, therapeutic management consists of two steps: (1) removal of the immune stimulus, by discontinuing heparin therapy; and (2) inhibition of thrombin, either directly or by blocking the generation of new thrombin. Although cessation of heparin is essential, it is insufficient for the prevention of thrombosis in patients with isolated thrombocytopenia. In one study, over half the patients with isolated thrombocytopenia sustained a thromboembolic complication during the first 30 days after heparin was stopped.[5] Consequently, some authorities recommend that patients with isolated thrombocytopenia receive an alternative anticoagulant, at least until the thrombocytopenia has resolved.

There are currently available four parenteral anticoagulants that can be used in patients with HIT (**Table 7**). Lepirudin is a recombinant hirudin analog that received FDA approval in 1998 for patients with HIT. Dosing is weight-based, with a desired target aPTT ratio of 1.5 to 2.5.[6] Since the drug is renally cleared, dose adjustments need to be made for patients with renal insufficiency, and it is not recommended if the serum creatinine exceeds 6.0 mg/dl. One problem that can occur with lepirudin is that anti-hirudin antibodies develop in about 40% of patients treated with lepirudin.[7] In some patients, this can result in an increased anticoagulant effect due to delayed renal elimination of active lepirudin-anti-hirudin complexes.[7]

Argatroban is a synthetic direct thrombin inhibitor that received FDA approval for the treatment of patients with HIT (Table 7). Dosing is weight-based, and the aPTT is used for monitoring. The PT is also prolonged in patients on argatroban, which can complicate the initiation of warfarin in these patients. In contrast to lepirudin, argatroban is hepatically metabolized and can

Table 7. Alternative parenteral anticoagulants for patients with heparin-induced thrombocytopenia (HIT).

	Lepirudin (Refludan®)	Argatroban (Novastan®)	Danaparoid (Orgaran®)	Bivalirudin (Angiomax™)
Mechanism of action:	Direct thrombin inhibitor	Direct thrombin inhibitor	ATIII-dependent inactivation of factor Xa and thrombin	Direct thrombin inhibitor
Half-life:	1.5 hr	40 min	19 hr	25 min
Route of administration:	IV or SQ	IV	IV or SQ	IV
Elimination:	Renal	Hepatic	Renal	Renal
Monitoring:	aPTT or ECT	aPTT	Anti-factor Xa assay	ACT or aPTT
Effect on INR:	Prolonged	Prolonged	None	Prolonged
FDA-approved indication:	HIT	HIT	Thromboprophylaxis for orthopedic patients	PCI

Abbreviations include: ATIII, antithrombin III; IV, intravenous; SQ, subcutaneous; ECT, ecarin clotting time; ACT, activated clotting time; HIT, heparin-induced thrombocytopenia; PCI, percutaneous coronary intervention.

be used in patients with renal insufficiency. Dose adjustments may be needed in patients with hepatic failure, however.

Danaparoid is a heterogenous mixture of non-heparin glycosaminoglycans that have predominantly anti-factor Xa activity (Table 7). Cross-reactivity with heparin-dependent antibodies from patients with HIT can be demonstrated in in vitro assays in ~10% to 40% of patients tested (depending on the sensitivity of the assay), but this is usually clinically insignificant.[8] Danaparoid has a long half-life and is renally cleared, so it must be used cautiously in patients with renal insufficiency. In contrast to lepirudin and argatroban, however, it does not affect the PT, which is an advantage in patients converting to warfarin.

Bivalirudin is a synthetic hirudin-based 20 amino acid peptide that binds to both the anion-binding exosite and enzyme catalytic site of thrombin. Bivalirudin has been approved for use as an anticoagulant in patients with unstable angina undergoing percutaneous coronary intervention (PCI). It has also been used successfully in patients with HIT. In contrast to lepirudin, bivalirudin is a reversible thrombin inhibitor, which may account for the lower rate of hemorrhage observed with bivalirudin compared to heparin.[9] Dosing is weight-based, and most available information provides recommended target ACTs for patients undergoing PCI. The PT and aPTT are also prolonged with bivalirudin,[10] and dose adjustments are recommended for renal insufficiency.

Several additional issues are relevant to the management of patients with HIT. First, warfarin therapy should not be used in patients with *acute* HIT unless they are being concomitantly treated with one of the antithrombotic agents discussed above. In this setting, warfarin can be associated with a devastating event known as venous limb gangrene (discussed below). Second, the incidence of HIT with LMWH is substantially less than for unfractionated heparin, but once HIT has developed all LMWHs are contraindicated. Lastly, the heparin-dependent antibodies appear to be transient, with a median time to antibody disappearance from the serum of 50 to 85 days, depending on the assay used.[11] The importance of this observation is that a patient with a history of HIT but no evidence for circulating antibodies may be briefly re-exposed to heparin for a necessary procedure, such as cardiac or vascular surgery. If anticoagulation is needed for a longer period of time, then one of the alternative anticoagulants listed in Table 7 should be selected instead.

The Pregnant Patient and Anticoagulant Therapy

The risk of acute deep venous thrombosis (DVT) during pregnancy has been estimated at 0.6 per 1000 women younger than 35 years and 1.2 per 1000 women older than 35 years.[12] The diagnosis and management of venous thromboembolism in pregnancy can be complicated, however, and there is a relative lack of information concerning the optimal approach to prevention of DVT in high-risk patients.

Diagnosis of Venous Thromboembolism. The diagnosis of DVT and pulmonary embolism (PE) during pregnancy is complicated by several variables, including that clinical diagnosis is inaccurate and some of the diagnostic tests are potentially harmful to the fetus. On the other hand, diagnosis of DVT or PE in a pregnant patient has major implications for her care during the pregnancy and will also affect subsequent decisions regarding oral contraceptives and estrogen replacement therapy. Therefore, it is essential that an accurate diagnosis be made.

A rational approach for the diagnosis of a DVT in a pregnant patient would begin with either impedance plethysmogragphy (IPG) or ultrasonography.[13] If negative, and the patient remains symptomatic, either serial non-invasive testing or venography with abdominal shielding can be used. If pelvic vein thrombosis is sus-

pected, magnetic resonance imaging can be used. For the diagnosis of a PE, a ventilation-perfusion scan should be performed first.[13] Patients with non-diagnostic perfusion scans may benefit from ultrasonography of the legs, although this approach would miss pelvic vein thrombosis. If necessary, spiral CT or pulmonary arteriography should be performed.

Anticoagulant Therapy. Pregnancy in a patient who is on chronic anticoagulant therapy presents several issues. From the fetal standpoint, coumarin derivatives cross the placenta and are capable of causing teratogenic as well as hemorrhagic complications in the developing fetus. Warfarin embryopathy ('fetal warfarin syndrome') refers to a specific teratogenic effect that occurs in ~6.4% of live births exposed to warfarin between 6 to 12 weeks gestation.[14] Characteristic abnormalities in this syndrome include nasal hypoplasia and/or stippled epiphyses. CNS abnormalities, on the other hand, may reflect intracranial hemorrhage that can occur throughout the pregnancy. Neither unfractionated heparin nor LMWH cross the placenta, and several studies have shown that these drugs are safe for the fetus.[15]

From the maternal standpoint, the use of heparin throughout pregnancy is associated with several potential problems, including hemorrhage, HIT, and osteoporosis, which can be associated with an increased fracture risk.[15] For patients with prosthetic valves, a systematic review of the literature indicated that the risk of a thromboembolic event during pregnancy is significantly higher with heparin (low-dose or adjusted dose) than with warfarin.[14] This may, in part, reflect insufficient heparin dosing. LMWHs have been used successfully in women with venous thromboembolism as well as prosthetic valves and have a lower risk for developing HIT and osteoporosis, but this has not been studied carefully in patients with prosthetic valves.[15]

In the setting of an unexpected pregnancy, the optimal approach would be to discontinue warfarin as soon as pregnancy is recognized and convert the patient to heparin or LMWH.[15] For a planned pregnancy, two approaches can be taken: (1) continue warfarin, perform frequent pregnancy tests, and convert to therapeutic heparin or LMWH when pregnancy occurs; or (2) replace warfarin with therapeutic heparin or LMWH prior to attempts at conception.[15] In either situation, patients can continue with heparin or LMWH, or convert back to warfarin after the 12th week of gestation and continue warfarin until the middle of the third trimester, when they should resume heparin or LMWH until delivery.[15] Not all authorities agree with this approach, however, and some recommend that warfarin should be avoided throughout pregnancy.[13] In addition, a recent study revealed that children exposed to coumarins in utero had an increased risk for 'minor neurological dysfunction'

and a lower intelligence quotient (IQ < 80).[16]

Management of anticoagulant therapy at the time of parturition can be complicated. The LMWHs have been associated with the development of spinal hematoma following neuraxial anesthesia, and some advocate that an epidural catheter should not be placed within 24 hours of the last LMWH injection. For nursing mothers, heparin and LMWHs are not secreted into breast milk and can be used safely in the post-partum setting.[15] Warfarin does not induce an anticoagulant effect in the breast-fed infant and can also be used safely in this setting.[15]

Prevention of Venous Thromboembolism in High-Risk Patients. High-risk patients include individuals who have sustained one (or more) prior thromboembolic events and/or have one (or more) thrombophilic disorders. Obviously, risk assessment for each patient needs to be individualized, but two general approaches can be taken with these patients: (1) active prophylaxis with heparin or LMWH; or (2) clinical surveillance. Variables that would favor a more aggressive approach include whether the prior thromboembolic event(s) were idiopathic, severity of the event (PE vs. DVT), and the presence of certain thrombophilic disorders (e.g., antithrombin III deficiency, antiphospholipid antibodies). In contrast, clinical surveillance would be appropriate for an individual with a single prior DVT sustained in the setting of a transient risk factor. Because of the increased risk for thromboembolism in the postpartum setting, these patients should receive a brief course of therapeutic anticoagulation following delivery.

Comorbid Diseases and Anticoagulant Therapy

The Obese Patient. The obese patient presents potential problems for decisions regarding weight-based dosing of several anticoagulants. Relatively little data are available concerning dosing of the LMWHs in morbidly obese patients, especially those who weigh > 150 kg. It has been recommended that patients in this category should have periodic monitoring of anti-factor Xa activity during treatment with LMWHs.[17] The initial recommended dose for lepirudin is valid to a weight of 110 kg, and patients above that weight should receive the 110 kg-based dose with subsequent adjustment based on the aPTT.

Patients with Renal Insufficiency. Thromboembolic complications that can occur in patients with renal insufficiency include spontaneous events as well as recurrent occlusion of vascular access catheters and grafts. Anticoagulant therapy in these patients is complicated by an increased hemorrhagic risk, however, because of the need for repeated vascular access for hemodialysis and the qualitative platelet defect associated with uremia. In addition, several parenteral anticoagulants are cleared by the kidneys, including the LMWHs, dana-

paroid, hirudin, and bivalirudin, and these agents need to be dose-adjusted and monitored very closely in these patients (if used at all).

Patients with Hepatic Insufficiency. Patients with hepatic impairment who need anti-coagulant therapy are particularly difficult to manage because of their underlying coagulopathy. Warfarin is extremely difficult to manage, and the risk of a significant hemorrhagic complication is high. The parenteral anticoagulant argatroban should not be used in patients with severe liver dysfunction.

Patients with Malignancy. Clinically significant thromboembolic disease affects ~15% of patients with cancer, and autopsy series suggest an even higher incidence.[18] Several studies have also documented that patients with cancer are at a higher risk for recurrent DVT and PE.[19,20] Consequently, it has been recommended that patients with venous thromboembolism and active malignancy receive an extended (≥ 12 months) course of therapy.[21] On the other hand, several studies have identified these patients as being at a higher risk to sustain a hemorrhagic complication while on warfarin therapy.[22,23] Multiple variables contribute to both the prothrombotic as well as the hemorrhagic risk in these patients, and the approach to prophylaxis and treatment of thromboembolism must be individualized.

Peri-operative thromboprophylaxis with heparin or LMWH can decrease the risk of post-operative DVT in patients with cancer.[18] In certain patients at high-risk for PE, pre-operative placement of an inferior vena cava (IVC) filter may be useful. "Low-dose" warfarin or LMWH can decrease thrombotic complications associated with indwelling central venous catheters[24] and may decrease the risk of spontaneous thromboembolism in certain patient subsets.[25]

Treatment of a thromboembolic event should include therapeutic anticoagulation, if possible. An extended course of therapeutic LMWH may be useful in patients with malignancy who are not eating well or are receiving cycling chemotherapy, since warfarin can be extremely difficult to manage in these patients. For individuals with an absolute contraindication to anticoagulation or with recurrent pulmonary emboli despite adequate anticoagulation, an IVC filter should be considered. In a randomized study investigating the role of IVC filters in patients with DVT, the device reduced the rate of pulmonary embolism but was associated with an increased risk for recurrent DVT.[26] The rate of thrombotic complications related to IVC filters may be even higher in patients with cancer,[27] and it has been recommended that these patients should also be anticoagulated, if possible.

The Patient with Recurrent Thrombosis While on Anticoagulant Therapy

Several clinical situations are associated with the development of thrombotic complications in the setting of apparently therapeutic oral anticoagulation. Management decisions in these patients may include discontinuation of the oral anticoagulant, initiation of a parenteral anticoagulant, and/or adjustment of the target INR.

Malignancy ("Trousseau's syndrome"). "Trousseau's syndrome" refers to a relatively rare complication in patients with malignancy, characterized by recurrent, migratory superficial thrombophlebitis.[18,28] Fortunately, these patients represent a minority of all patients with cancer and thrombosis. Management can be exceedingly difficult, and warfarin has been reported to be inadequate for the prevention of recurrent thrombosis.[28] Therapeutic modalities that have been used successfully in this subset of patients include unfractionated heparin and LMWH,[28,29] but the long-term outcome in these patients is poor.

Warfarin-Induced Skin Necrosis. Warfarin-induced skin necrosis has been estimated to occur in between 1:100 to 1:10,000 of patients on oral anticoagulant therapy.[30] This complication represents a transient imbalance in the procoagulant/anticoagulant pathways, leading to small vessel thrombosis and subsequent dermal necrosis.[30] The lesions generally appear within the first week of oral anticoagulant therapy and may be associated with large loading doses of warfarin. Areas rich in subcutaneous fatty tissue are typically involved, particularly the breasts, thighs, and buttocks. Many of these patients have a congenital deficiency of protein C, and other hypercoagulable states have also been described.[30] Acute management includes vitamin K and plasma supplementation, as well as a parenteral anticoagulant until the necrotic lesions have healed. In some patients, it may be possible to use warfarin for chronic anticoagulation, but this needs to be done slowly, with low doses of warfarin and concomitant heparin therapy until the INR is therapeutic and stable.[31]

Venous Limb Gangrene. This entity has a similar pathophysiology as warfarin-induced skin necrosis (procoagulant/anticoagulant imbalance) but primarily affects acral tissues such as the feet, toes, hands, and fingers.[32] Venous limb gangrene occurs in the setting of an acute DVT, typically involving the affected limb.[32] The disorder was first described in patients with acute HIT who were on warfarin therapy, generally with a supratherapeutic INR, and without concomitant thrombin inhibition.[32] Acute management includes vitamin K and initiation of an alternative parenteral anticoagulant agent (Table 7). Warfarin can generally be safely used in these patients after the thrombocytopenia has resolved (resolution of the acute HIT).

"Purple Toe Syndrome." The purple toe syndrome is a rare complication of warfarin therapy that occurs most frequently in males with underlying severe atherosclerotic disease.[30] It is felt that the mechanism is related to warfarin-induced bleeding into atherosclerotic plaques resulting in distal cholesterol embolization. Re-initiation of oral anticoagulation can potentially lead to recurrent symptoms, and some authorities recommend avoiding warfarin in these patients.[30]

Antiphospholipid Antibody Syndrome. A subset of patients with antiphospholipid antibodies will have a prolonged PT in the absence of an acquired hypoprothrombinemia or other underlying coagulopathy.[33] Consequently, the INR may not accurately reflect the intensity of oral anticoagulant therapy for these patients.[33] This effect has been most frequently noted with the recombinant thromboplastin Innovin®.[34] Optimal management of warfarin therapy may require using a thromboplastin that is 'insensitive' to the presence of a lupus anticoagulant or an alternative test such as the chromogenic factor Xa assay, if necessary.[33,34]

"Warfarin Failure." A small subset of patients who do not have any of the above diagnoses will have a recurrent thromboembolic event in the setting of an apparently therapeutic INR. It is important to confirm that these patients are truly 'therapeutic' before applying the label 'warfarin failure.' Several studies have demonstrated that depression of factor II is most important for warfarin's clinical antithrombotic efficacy,[35] whereas the factor II level may be the least significant of the three factors measured in determining the INR.[36] Patients with similar INR values show significant variations in their coagulation profiles on detailed testing.[37] Prior to labeling a patient as a 'warfarin failure,' it would be reasonable to confirm adequate anticoagulation by concomitantly checking a factor II level.

The Patient with Hemorrhagic Complications While on Anticoagulant Therapy

The major complication associated with anticoagulant therapy is hemorrhage. Variables associated with hemorrhagic complications include: (1) intensity of anticoagulation; (2) concomitant use of drugs that interfere with normal hemostasis, particularly antiplatelet agents; (3) length of anticoagulant therapy; and (4) patient-specific characteristics.[38] Patient characteristics associated with an increased hemorrhagic risk include advanced age, prior gastrointestinal bleeding, and other comorbid conditions, including cerebrovascular disease, hypertension, renal insufficiency, and malignancy.[38] Predictive models that incorporate these factors have been used to estimate hemorrhagic risk in patients on oral anticoagulants.[38]

Acute management in a patient with severe hemorrhage consists of stabilizing the patient, controlling the bleeding, and reversing the anticoagulant effect. For the patient with recurrent bleeding but with no apparent etiologic risk factors, it is reasonable to evaluate for possible underlying hemorrhagic abnormalities, such as von Willebrand disease or dysfunctional platelets. Menorrhagia can be particularly problematic in the menstruating woman; in the absence of an underlying anatomic abnormality, we have used hormonal therapy in a subset of these patients. Chronic management may require adjustment of the target INR or more frequent monitoring, discontinuation of concomitant anti-platelet medications, and consideration of the relative risk-benefits of continued anticoagulant therapy.

Peri-operative Management of Patients on Chronic Anticoagulation

Peri-operative management of a patient on chronic anticoagulation must be individualized and includes assessment of the patient's thromboembolic risk while off anticoagulation and the complexity of the surgical procedure to be performed (which can affect both hemorrhagic as well as thromboembolic risk). For most patients, the risk of a thromboembolic event is low enough that stopping warfarin for four days prior to the procedure should be sufficient to safely achieve an INR of 1.5 or less by the time of surgery.[39] For patients who have sustained a DVT or PE within the preceding month, however, or those who have sustained a thromboembolic complication when anticoagulation was held in the past, a more aggressive approach consisting of preoperative heparin or LMWH would be warranted. In addition, a recent survey revealed that most physicians would prefer parenteral anticoagulation in the peri-operative setting for selected high-risk patients.[40] For patients converted pre-operatively to LMWH as an outpatient, it is important to consider the types of surgery and anesthesia being planned to determine when the LMWH should be discontinued. Similarly, the decision as to when anticoagulation can be resumed post-operatively requires input from the surgeon regarding relative hemorrhagic risks.

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