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PROPHYLAXIS OF THROMBOSIS WITH LOW-MOLECULAR-WEIGHT HEPARIN (LMWH)

R. G. Holzheimer

University of Halle-Wittenberg, Germany

Abstract: Deep vein thrombosis (DVT) and pulmonary embolism (PE) are a major cause of morbidity and mortality, affecting approximately 4 million people each year in the United States.

The identification of risk factors for the development of DVT and PE helped to develop a system for risk stratification. The risk to develop a deep vein thrombosis has been estimated to be up to 80% in some populations without prophylaxis. In multiple studies LMWHs demonstrated to be efficient and safe for reduction of DVT of patients in general and visceral surgery, orthopedic surgery, and trauma. Three compounds have been studied best, e.g., dalteparin, enoxaparin, nadroparin, which may help to decide which type of LMWH to use. There is clearly an expanding role for LMWHs in gynecology, cancer, intensive care, patients with acute medical illness and bedridden patients.

In summary, LMWHs have chemical, physical, and clinical similarities. They have greater bioavailability, longer half-lifes, more predictable pharmacological response, possible improved safety, and similar or greater efficacy compared with UH. However, the evaluation of clinical trials does not allow the determination of therapeutic equivalence due to different diagnostic methods, drug administration times, dose equivalencies, and outcome measurements The scoring of the quality of clinical trials for meta-analysis is problematic and it has been recommended to assess the methodological aspects individually.

Despite clear evidence of effectiveness, deep vein thrombosis prophylaxis is underused. This has been recognized by law firms as evidenced by internet advertisement where patients are informed on the prevention of venous thromboembolism or economy class syndrome. "If you or a family member has been injured, contact a personal injury attorney today. Just fill out Injury.Board.com's on-line questionnaire and have a personal injury lawyer review your potential personal injury claim – free of charge.". The medico legal implications of antithrombotic prophylaxis and treatment are well recognized.

Key words: LMWH; dalteparin; enoxaparin; nadroparin; deep vein thrombosis; pulmonary embolism; prophylaxis

INTRODUCTION

In 1980, unfractionated heparin (UFH) was the established agent for the prophylaxis of venous thromboembolic (VTE) disease in patients undergoing general surgery (Breddin 2000). The commercial use of low molecular weight heparins (LMWHs) began in the mid 1980s for hemodialysis and the prophylaxis of deep vein thrombosis (DVT). In the initial stages of development of these drugs only dalteparin, enoxaparin, and nadroparin were used. (Mousa 2002). Low-molecular-weight heparins (LMWH), mixtures of heparin molecules in the range of 3,000 to 10,000 daltons represent a major clinical advance in anticoagulation since the identification of unfractionated heparin (UFH) in 1922 and the introduction of the synthetic coumarin derivative, warfarin, in 1948. Their predictable pharmacokinetics, increased bioavailability, and longer plasma half-life allow for once- or twice-daily dosing and eliminate the need for routine laboratory monitoring (Huang and Shimamura 1998). At equipotent antithrombotic doses, LMWHs produce less bleeding than does unfractionated heparin. The pharmacokinetic characteristics of LMWHs permit their use in a fixed dose administered subcutaneously without monitoring, resulting in greater clinical utility than standard heparin (Turpie 1997). Each LMWH is viewed as a unique drug by regulatory agencies because of their differing physical and pharmacokinetic attributes (Kleinschmidt and Charles 2001). Their anti-Xa/anti-IIa ratio varies significantly, and the injection of the same dose generates different anti-Xa activities and activated partial thromboplastin time (APTT) prolongations (Boneu 2000). The type of prophylaxis varies largely: (1) standard low-dose heparin (5000 U administered subcutaneously 2-3 times per day); (2) adjusted-dose heparin (adequate to elevate the activated partial thromboplastin time to 5 seconds above the upper limit of normal); and (3) low-molecular-weight heparin (30 mg subcutaneously twice daily without monitoring) (Owings and Blaisdell 1996). Not every patient with major intra-abdominal surgery or orthopedic surgery has obtained prophylaxis against deep vein thrombosis: 84.3% hip replacement, 75.9% knee replacement, 45.2% hip fracture repair and 50.3% abdominal surgery pa-

tients received prophylaxis (Stratton et al. 2000), although the impact on the clinical acceptance of LMWH and the cost savings of prophylaxis are well understood (Geerts et al. 2001; Bick and Haas 2003).

Prophylaxis in General and Visceral Surgery

Incidence

Venous thromboembolism (VTE) continues to be an important cause of death in hospitalized patients undergoing major elective surgery. Approximately 500,000 cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) occur in the United States each year. Of those patients who suffer a massive PE, 70% die within the first hour of symptom onset. (Muntz 2000). A study of autopsy-proven pulmonary embolism in hospital patients showed that VTE accounted for 10% of deaths. Recognition of non-fatal thromboembolism continues to be a problem (Kakkar and de Lorenzo 1998; Lausen et al. 1995). Epidemiology, etiology and diagnosis of venous thromboembolism have been reviewed in another paper of this issue (Gathof et al. 2004).

Risk Factors

Several risk factors for thromboembolic events have been characterized in general surgery patients: previous thromboembolism, obesity, varicose veins, malignancy, preoperative hospitalization, estrogen therapy, chronic cardiac disease, bronchitis, leg fracture or arthroplasty, present leg ulcer, operating times longer than 150 minutes, preoperative transfusion (Samama et al. 1988; Flordal et al. 1996; Miller et al. 2002). Three levels of risk to develop DVT were identified: low level (less than 10%), moderate (10-40%) and high (40-80%) (Bergqvist et al. 1992). Together with acquired risks conditions of thrombophilia, caused by deficiencies in coagulation inhibitors (antithrombin III, protein C, protein S) or alteration of the anticoagulation system as resistance to activated protein C or antiphospholipid antibodies may increase the risk for DVT (Storti et al. 1996). The aging process is associated with increased coagulation and fibrinolysis parameters, which may multiply the risk of thromboembolism in this population (van Gorp et al. 1998). Certain types of operations, e.g., hip or knee arthroplasty, are at highest risk for DVT or PE (Muntz 2000). Risk stratification and thromboprophylaxis modalities are reviewed by Bick and Kaplan (2004).

Combination Prophylaxis

Prophylaxis of venous thromboembolism is aimed at the prevention of thrombosis by pharmacological methods, e.g., unfractionated heparin (UH), low-molecular weight heparin (LMWH), oral anticoagulants, and physical methods, e.g., elastic graduated compression stockings (GCS) and systems of intermittent pneumatic calf compression. GCS are effective in diminishing the risk of DVT in hospitalized patients. The combination of physical and pharmacological methods seems to be the optimal prophylaxis (Wille-Jorgensen et al. 2003; Amarigiri and Lees 2000; Storti et al. 1996). The addition of other pharmacological compounds may be more effective than LMWH alone for preventing symptomatic thromboembolism (Tsimoyiannis et al. 1996); yet there is a need for cost-effective analysis. The significance of available methods for prophylaxis of DVT and PE has been reported in the recommendations of the sixth ACCP Consensus Conference on Antithrombotic Therapy (Geerts et al. 2001) and in another chapter of this issue (Bick and Kaplan 2004).

Efficacy and Safety of LMWH

With regard to reduction of venous thrombotic events efficacy has been demonstrated for LMWHs (dalteparin, enoxaparin, fraxiparin) in comparison to UH (The European Fraxiparin Study Group 1988; Bergqvist et al. 1990; Bergqvist et al. 1992; Ockelford et al. 1989; Nurmohamed et al. 1995). However, further clinical studies and meta-analyses did not unanimously report that LMWH are more efficient than UH in general surgery patients (Leizorovicz et al. 1993; Jorgensen et al. 1993; Bounameaux et al. 1993; Nurmohamed et al. 1992; Palmer et al. 1997; Koch et al. 1997). Simplified handling of the prophylaxis with LMWH when compared to UH is acknowledged, in general, but the assessment of safety has varied considerably (Kakkar 1993). Some authors reported a higher risk of bleeding complications with LMWH (Koch et al. 1997; Koch et al. 2001; Ho et al. 1999; Clagett and Reisch 1988; Bergqvist et al. 1988). It has been demonstrated that LMWHs may be associated with a higher risk for bleeding when administrated in higher doses (Samama et al. 1988; Flordal et al. 1996), whereas low-dose LMWH may have less bleeding episodes (Kakkar et al. 1997; Kakkar et al. 1993; Hartl et al. 1990; Mismetti et al. 2001; Kakkar et al. 1998). Although a correlation between plasma anti-Xa activity and body weight has been observed for some LMWH, the question for the right dosage has not been answered for all LMWHs and circumstances - LMWH at doses below 3400 anti-Xa unites seemed to be effective as and safer than UH (Leizorovicz et al. 1993; Mismetti et al. 2001). On balance, LMWH and low-dose unfractionated heparin appear to be equally efficacious in preventing DVT in general surgery patients with the advantage of a once daily administration of LMWH (Geerts et al. 2001).

Timing of Prophylaxis

Timing of prophylaxis is also an important issue. Late thromboembolic complications after cessation of postoperative prophylaxis are known to occur up to 7 weeks after surgery. The incidence may be

1%, but could be 10 times higher when special screening was performed (Wille-Jorgensen et al. 1993). Prevention of thromboembolism is not strictly limited to a 2-hour interval between start of prophylaxis and onset of surgery but may also be provided by starting prophylaxis with LMWH during the evening before surgery and continuing postoperatively (Haas and Flosbach 1993; Bergqvist et al. 1995). In Europe, prophylaxis is started pre-operatively and the usual duration for the post-operative period may be 7 days or until the patient is discharged from the hospital (Kakkar and De Lorenzo 1998). Patients with emergency abdominal surgery may benefit even when the prophylaxis is started 24 hours later (Bergqvist et al. 1996). The prolonged administration of LMWH seems not to be justified in general surgery (Sarasin and Bounameaux 1996; Lausen et al. 1998; Kakkar et al. 1993).

Costs of LMWH Prophylaxis

Although heparin and LMWH may be equally effective, low-dose heparin has been considered a more economically attractive choice for thromboembolism prophylaxis after colorectal surgery in North-America (Etchells et al. 1999; McLeod et al. 2001); this, however, is largely depending on the price of the LMWH and the costs for handling thromboprophylaxis in the hospital which may be different from country to country (Bergqvist et al. 1996).

Management of Patients with Chronic Anticoagulant Therapy or Special Disease

The management of patients who require temporary interruption of oral anticoagulant therapy because of surgery or other invasive procedures has to balance the patient's risk of thromboembolic event when anticoagulant therapy is interrupted and the risk of bleeding that is associated with the surgery or procedure (Douketis 2002). Dental procedures, cataract surgery and diagnostic endoscopy may be performed without discontinuing anticoagulation. Periprocedural thromboprophylaxis or bridging may be necessary for patients with prosthetic heart valves, atrial fibrillation, hypercoagulable states and chronic venous thrombosis. Consensus on the appropriate perioperative treatment of patients on long-term warfarin therapy is lacking. Low molecular weight heparins (LMWHs) may have an advantage over unfractionated heparin (UH) that perioperative conversion from warfarin with LMWH can be carried out in an outpatient setting (Spandorfer et al. 1999; Jafri 2004). Although LMWH offers many advantages over UH, in patients with renal dysfunction, obesity and pregnancy its use is less clearly defined and may involve further risks (Nagge et al. 2002; Howard 2003).

Prophylaxis in Laparoscopic Surgery

Indication for thromboprophylaxis may vary widely and not all surgeons do accept prophylaxis with LMWH as an option. Only 20% of the surgeons asked considered that thromboembolism, despite the risk of thromboembolic disease due to use of the laparoscopic pneumoperitoneum, was a problem (Bradbury et al. 1997; Lord et al. 1998; Filtenborg Tvedskov et al. 2001).

Prophylaxis in Urology

There is a lack of well-designed clinical studies that meet the methodological criteria as published by the American College of Chest Physician. Patients at normal risk may benefit from LMWH prophylaxis. In high-risk patients a combination with mechanical prophylaxis has been suggested (Geerts et al. 2001; Bick and Kaplan 2004).

Prophylaxis in Vascular Surgery

Carotid Artery Dissection

Extracranial internal carotid artery dissection can lead to occlusion of the artery and hence can cause an ischemic stroke. Antithrombotic agents (heparin, oral anticoagulants or antiplatelet drugs) may prevent arterial thrombosis. A Cochrane analysis of 26 studies including 327 patients found no evidence to support their routine use (Lyrer and Engelter 2003).

Infrainguinal Bypass, Arterial Reconstructive Surgery and Angioplasty

Chronic peripheral arterial disease (PAD) is frequently treated by implantation of either an infrainguinal autologous venous or artificial graft. To prevent graft occlusion - one-year occlusion rates vary between 15% and 75% - patients receive either an antiplatelet or antithrombotic drug, or a combination of both (Dorffler-Melly et al. 2003). There are only few studies investigating LMWH in the prophylaxis in arterial thrombosis. LMWH may be used successfully for maintenance of graft patency (Edmondson et al. 1994; Samama and Gigou 1995). Again, the use of high dose LMWH may be associated with increased bleeding rates (Kujath et al. 2002). The evidence is not conclusive which may be the best form to prevent occlusion (vitamin K antagonist, aspirin, LMWH) (Dorffler-Melly et al. 2003) and unfortunately many trials have significant deficiencies (Watson et al. 1999). In preliminary investigations extensive dissections after percutaneous transluminal angioplasty (PTA) might benefit from extended prophylaxis with LMWH (Schweizer et al. 2001). Postoperative deep vein thrombosis after aortic surgery may be prevented by LMWH, best by direct injection into the aorta (Farkas et al. 1993; Wilson et al. 1991).

Stent, Percutaneous Coronary Intervention (PCI), Coronary Angioplasty

Stents were successfully used for coronary revascularization in recent years, but have also been associ-

ated with a high rate of stent thrombosis. LMWH administered by subcutaneous injection may provide an effective alternative to the use of intravenous heparin after stent implantation (Stables and Sigwart 1996; Zidar 1997). LMWH may produce significantly fewer clinical events and vascular complications than the conventional warfarin anticoagulation (Zidar 1998; Pan et al. 1996; Kereiakes et al. 2001; Furman et al. 2001; Choussat et al. 2002; Bhatt et al. 2003; Moliterno et al. 2003; Batchelor et al. 2001). Intramural delivery may not improve the outcome after stent deployment (Meneveau et al. 2000) nor may do the prolonged administration of LMWH (Grassman et al. 2001). Stents used for transjugular intrahepatic portosystemic shunt (TIPS) may be thrombogenic and have a high risk of early shunt insufficiency, which may be prevented by periprocedural heparin (Siegerstetter et al. 1997).

Coronary Artery Bypass

The effect of preoperative administration of LMWH in patients undergoing coronary artery bypass has been studied with conflicting results with regard to hemoglobin values, postoperative bleeding or blood product transfusion when compared to UH (Kincaid et al. 2003; Medalion et al. 2003).

Prosthetic Valve Implantation

In contrast, in patients with mechanical heart valve implantation, LMWH may compare favorably with UH or acenocumarol (Montalescot et al. 2000; Ferreira et al. 2003) leading to a shorter length of stay and decreased postoperative costs (Fanikos et al. 2004).

Prophylaxis in Trauma Patients

Deep vein thrombosis and pulmonary embolism are major risks in patients experiencing major trauma. The reported incidence of deep venous thrombosis ranges from 20 to 90%. The reported incidence of pulmonary embolism varies between 2.3 and 22%. There may be an increased risk of thromboembolism due to the aging population and survival of more severely injured patients (Hak 2001). Color-flow duplex proved to be a sensitive method for detecting thrombi. Unfortunately there was no correlation of the risk assessment profile for thromboembolism (RAPT) scale with the occurrence of DVT (Greenfield et al. 1997).

Spinal Cord Injury

The incidence of DVT without prophylaxis in acute spinal cord injury patients varies from 49% to 100% in the first 12 weeks with the first 2 weeks having the highest rate following acute injury (Attia et al. 2001; Merli et al. 1993). Single agent pharmacological therapy with adjusted dose heparin is effective but carries some risk of bleeding. Combination prophylaxis may consist of external pneumatic compression sleeves, aspirin, dipyridamole, and low-dose heparin for 8 to 12 weeks (Merli et al. 1993). Several studies have demonstrated that LMWH compares favorably or may be even superior to UH (Green et al. 1990; Green et al. 1994; Harris et al. 1996; Chiou-Tan et al. 2003; Spinal Cord Injury Thromboprophylaxis Investigators 2003). In more recent studies a 3-month duration of prophylaxis has been recommended, in case of non-responders with vena cava filter (Anonymous 2002).

Brain Injury

Anticoagulant prophylaxis for patients with head injury who suffered intracranial bleeding or who need intracranial surgery has been debated. A diversity of practice and opinion together with a concern about the failure to implement even the simplest means of prophylaxis has been recently reported (Cupitt 2001).

Blunt Trauma

In contrast, LMWH were successfully applied in patients with closed head injuries and nonoperatively treated solid abdominal organ injuries (Norwood et al. 2001). LMWHs were equally safe or even more effective than low-dose heparin in preventing venous thromboembolism after major trauma (Geerts et al. 1996; Knudson et al. 1996; Haetjens 1996).

Hip Fracture

Dosage and optimal initiation of thromboembolic prophylaxis continue to be a matter of dispute (Monreal et al. 1989). LMWH may be as effective and safe compared to UH (Thaler et al. 2001; Kew et al. 1999; Jorgensen et al. 1992). In older patients a reduction of dose has been recommended (Barsotti et al. 1990). Efficacy or safety of LMWH in patients undergoing hip fracture surgery was not different (The TIFDED Study Group 1999), but new synthetic LMWH may have an advantage (Eriksson et al. 2001).

Leg Injury

Deep vein thrombosis is common in persons with leg injury requiring prolonged immobilization. The incidence may vary from 4.3% to 29%; LMWH prophylaxis demonstrated a significant reduction of thromboembolic events in most studies but one (Kock et al. 1995; Kujath et al. 1993; Spannagel and Kujath 1993; Lassen et al. 2002; Jorgensen et al. 2002).

Combined Prophylaxis

Intermittent pneumatic compression (IPC) devices or sequential treatment by Flowtron DVT garments have been reported to improve the outcome of thromboprophylaxis in trauma patients (Ginzburg et al. 2003; Eskander et al. 1997).

Long-term Prophylaxis

In patients with contraindications to coumarin prophylaxis LMWH may be successfully applied for long-term prophylaxis, especially when there is recent blood loss, gastroduodenal ulcer disease, psychological or physical inability or unwillingness for monitoring, chronic alcoholism, dementia, pregnancy, recent neurosurgery, pericardial effusion or age above 80 years (Monreal et al. 1994).

Cost-effectiveness

Cost-analysis studies on the use of LMWH prophylaxis in trauma patients came out with different conclusions. Prophylaxis may save costs provided the price for the compound is right (Wade et al. 2000) or concluded that no method was superior to any other or to no prophylaxis (Velmahos et al. 2000). Neither concerns about the higher cost of LMWH nor the financial implications of major bleeding should preclude the use of LMWH in trauma patients (Shorr and Ramage 2001). With rising health care cost, thromboprophylaxis with LMWH should be able to decrease the length of hospital stay without compromising care. The 1998 American College of Chest Physicians guidelines recommend thromboprophylaxis with LMWH and oral warfarin in trauma patients. The LMWH Expedited Anticoagulation Program (LEAP) has successfully decreased hospital days (Bridges et al. 2003).

Prophylaxis in Intensive Care and Acutely Ill Medical Patients

10% - 30% of medical and surgical intensive care patients develop DVT within the first week of intensive care treatment. Approximately 60% of trauma intensive care patients developed DVT within the first 2 weeks of admission. The estimated prevalence of DVT in neurosurgical intensive care patients not given prophylaxis ranges from 22% to 35%. Intensive care patients with spinal cord injury may develop DVT in 50% to 80% of cases (Attia et al. 2001). Both undetected and clinically evident DVT can seriously impact the prognosis in critically ill patients or prolong the recovery from the original illness. LMWH may be more effective than UH in critically trauma patients, high dose LMWH in seriously ill medical patients. LMWH appears to be superior to UH in acute stroke patients (Davidson 2000). All patients should be assessed for their risk of thromboembolism and then prophylaxis should be started individually with regard to initiation, monitoring, and dosage adjustment. When bleeding is expected, mechanical prophylaxis may be applied until the bleeding risk decreases; all others should receive UH or LMWH (Geerts et al. 2001).

Hemofiltration

Filter survival time in hemofiltration, e.g., high-volume continuous venovenous hemofiltration, may depend on baseline platelet count. LMWH provide identical filter life, comparable safety but increased costs compared to UH. Patients with higher platelet count may benefit from adjusted dosage of LMWH (Reeves et al. 1999; de Pont et al. 2000). LMWHs have been successfully applied in hemodialysis and hemofiltration, but there is an urgent need for more clinical evaluation (Sagedal and Hartmann 2004).

Acutely Ill Medical Patients

Medical patients represent the majority of hospitalized patients, and at least 75% of fatal pulmonary emboli occur in this group. Medical patients are at significant risk of DVT, yet the clinical benefit and cost-effectiveness of routine thromboprophylaxis in medical patients have been discussed controversially (Cohen 2002). In recent trials LMWH (dalteparin, enoxaparin, nadroparin) have been successfully tested in medical patients with heart failure, respiratory failure, infectious disease, rheumatic disorder, unstable angina, acute myocardial infarction and atrial fibrillation (Harenberg et al. 1990; Harenberg et al. 1993; Glick et al. 1996; Bijsterveld et al. 2002; Lamy et al. 2002; de Lissovoy and Subedi 2002; Kleber et al. 2003; Gardlund 1996; Samama et al. 1999; Fraisse et al. 2000; Turpie 2000; Lechler et al. 1996). Anticoagulation, UH and LMWH are used in patients with myocardial infarction. The effect of LMWH or UH on the development of VTE after myocardial infarction is not known (Geerts et al. 2001). Critically ill patients with normal renal function may have significantly lower anti-Xa levels in response to a single daily dose of subcutaneous LMWH when compared with medical patients in the normal ward (Priglinger et al. 2003). Rebound coagulation activation may occur shortly after discontinuation of UH and LMWH. A longer duration or weaning of treatment, or continuation with other anticoagulant treatment may reduce this effect (Bijsterveld et al. 2002). Economic analysis indicated that prophylaxis with LMWH may induce a small increase in current treatment cost but may avoid long-term costs, e.g., avoidance of incremental cost per VTE and/or future VTE treatment (de Lissovoy and Subedi 2002). Further improvement of prophylaxis will be available when the impact of LMWH on clinically important endpoints, e.g., objectively confirmed DVT, fatal or non-fatal PE, proximal DVT, sudden death, has been investigated (Vaitkus et al. 2002). Low-dose unfractionated heparin or LMWH significantly decrease the incidence of thromboembolic events when compared with no prophylaxis in medical patients, while LMWH is followed by less bleeding events (Geerts et al. 2001). Vaitkus has reviewed the results of recent trials in thromboprophylaxis in immobilized medical patients (2004).

Nephrotic Syndrome and Chronic Renal Failure

The nephrotic syndrome carries a high risk of thrombotic complications, which has lead to an-

tithrombotic prophylaxis in patients at risk (albuminemia < 20g/l and membranous nephropathy) either by LMWH or antivitamin K (Rostoker et al. 1995). LMWH may suppress macroscopic clot formation and fibrinopetide A (Ryan et al. 1991). Concomitant coumarin use may enhance the effect (Janssen et al. 1996) A recombinant tissue plasminogen activator has been successfully tested as alternative treatment (Schenk et al. 2000).

Geriatric Patients

Bedridden elderly patients with an acute medical illness are at increased risk to develop DVT. Just recently studies have shown that LMWH may successfully reduce the risk to develop DVT (Bergmann and Neuhart 1996; Harenberg et al. 1996).

Prophylaxis in Patients with Malignant Tumors

Cancer Patients Undergoing Surgery

Patients undergoing major abdominal or pelvic surgery for malignancy are at particularly high risk of developing VTE. About 40% of VTE occur after discharge from the hospital (Khusal et al. 2002). Certain malignant tumors are prone to support the development of DVT, e.g., breast and pelvic cancer, ovarian cancer, head and neck cancer (Maxwell et al. 2001; von Tempelhoff et al. 2000; von Tempelhoff et al. 1997; Gondret et al. 1995). Several studies in patients in cancer patients undergoing surgery demonstrated that the use of LMWH is as effective as UH but with a major advantage in handling (once daily versus three times daily application) (Fricker et al. 1988; Enoxacan Study Group 1997; Boncinelli et al. 2001). Hemorrhage was not seen to be an adverse event in these patients (Bergqvist et al. 1990; Baykal et al. 2001), these patients may even benefit from a higher dosage of LMWH which may be weight adjusted (Wiig et al. 1995; Baykal et al. 2001). Prolonged prophylaxis may help to avoid the occurrence of post discharge VTE (Bergqvist 1996; Khusal et al. 2002; Rasmussen 2002) and may even have an effect on cancer survival (von Tempelhoff et al. 2000). Postoperative prophylaxis may be improved by simultaneous application of LMWH and external pneumatic compression (Maxwell et al. 2001).

Prophylaxis in Cancer Patients

Patients with cancer who present with both a greater thrombus burden and more pronounced derangement of the coagulation system are at increased risk to develop DVT, venous thromboembolism (VTE) and PE. Central venal catheters used for the administration of chemotherapy have been associated with a number of complications, thrombosis and infection. LMWH reduced the rate of upper extremity thrombosis to 6% in comparison to 62% without prophylaxis (Monreal et al. 1996). Whereas some investigators reported a similar benefit-to-risk ratio for warfarin and LMWH (Mismetti et al. 2003), the use of UH may not reach this level of protection (Klerk et al. 2003). In general LMWH may be superior to oral anticoagulants with regard to a reduction of the risk to develop VTE or bleeding rates (Lee et al. 2003; Meyer et al. 2002). The administration may not prevent the disseminated intravascular coagulation syndrome (DIC) (Chojnowski et al. 2002) but may help to prevent the recurrent VTE, which is more likely to occur in patients with cancer, chronic cardiovascular disease and chronic respiratory disease (Douketis et al. 2000). It has been successfully demonstrated that the prolonged administration of LMWH reduces the incidence of venographically demonstrated thrombosis (Bergqvist et al. 2002) and is at least as effective but safer than oral anticoagulation (Meyer et al. 2002; Levine 2003). Lastly, the potential antineoplastic effects of LMWHs make these more attractive options in cancer patients (Bergqvist 2002; Kakkar 2003; Lee 2003). Pathogenesis, epidemiology of venous thromboembolism and the available prophylaxis/treatment modalities were reviewed by Petralia and Kakkar (2004).

Prophylaxis in Gynecology

Incidence and Risk

VTE are a major cause of maternal mortality and morbidity. The reported overall risk of deep venous thrombosis in gynecological surgery ranges from 7-45%. Fatal pulmonary embolism may occur in nearly 1% of these women (Gates et al. 2002; Oates-Whitehead et al. 2003). The risk for VTE is higher in pregnant than in non-pregnant patients (Laurent et al. 2002). Risk factors for VTE may be cesarean section, a personal or family history of VTE, and inherited or acquired thrombophilias (Gates et al. 2002; Heilmann et al. 2000; Greer 2003). VTE may lead to adverse events such as intrauterine growth restriction, stillbirth, severe early onset preeclampsia and placental abruption (Walker et al. 2003). Anticoagulative prophylaxis seems to be reasonable for women at risk (Friederich et al. 1996). A comprehensive review of the prevention of venous thromboembolism in pregnancy has been presented by Greer (2004).

Indication

LMWH has been recommended for prophylaxis of deep vein thrombosis in pregnancy, for prevention of fetal loss, and for decreasing the risk of premature delivery in pregnant women with antiphospholipid syndrome (Makatsaria et al. 2003) and when cesarean section is planned (Burrows et al. 2001). LMWH may be an alternative for patients with a contraindication to coumarin therapy (Monreal et al. 1994).

Pregnancy, Late Pregnancy

Several LMWHs (dalteparin, enoxaparin, nadroparin) have been successfully tested in pregnancy

(Nelson-Piercy et al. 1997; Gibson et al. 1998; Pettila et al. 1999; Blomback et al. 1998; Makatsaria et al. 2003).

Pharmacokinetics during Pregnancy

Increased renal clearance during pregnancy may influence the pharmacokinetics of LMWH (Casele et al. 1999;Jacobsen et al. 2003).

Bleeding and Dose

The incidence of bleeding complications is often related to the dose of LMWH; at a lower dose this may be avoided (Ellison et al. 2000; Borstad et al. 1992; Borstad et al. 1988). LMWH and simultaneous administration of epidural analgesia should be used with caution (American College of Obstetricians and Gynecologists 2002).

Prostethic Heart Valves

The efficacy of LMWH at preventing valve thrombosis remains uncertain (Rowan et al. 2001), although this may not be the case for all LMWHs (Makatsaria et al. 2003). The use of LMWHs is not recommended for pregnant women with prostethic heart valves (American College of Obstetricians and Gynecologists 2002).

Osteoporosis

Long-term prophylaxis with UH may bear a risk for osteoporosis; this may be avoided by the use of LMWH (Pettila et al. 2002).

Pregnancy Loss

Patients with recurrent pregnancy loss associated with factor V Leiden mutation may benefit from LMWH prophylaxis (Younis et al. 2000).

Controversy

Inherited Thrombophilia

While the majority of women with thrombophilia will have an uneventful gestation, it has been demonstrated that thrombophilia is more prevalent in women with pregnancy loss, early onset preeclampsia, placental abruption, and severe intrauterine growth retardation (Brenner and Kupferminc 2003). There is a dire lack of randomized trials on the efficacy of heparin or other coagulation modulators on pregnancy in patients with inherited thrombophilias (Gebhardt and Hall 2003; Walker et al. 2003).

Antiphospholipid Syndrome

There is a consensus on thromboprophylaxis for antiphospholipid syndrome: LMWH and low dose aspirin are recommended (Gebhardt and Hall 2003; Tincani et al. 2003; Triolo et al. 2003).

Warfarin, Unfractionated Heparin, LMWH, Aspirin

Thromboprophylaxis should be offered, but there is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period (Gates et al. 2002; Hague et al. 2001). Evidence suggests that UH and LMWH are equally effective in preventing DVT and warfarin may be equally effective as UH. There is no evidence to suggest that warfarin, heparin or aspirin reduce the incidence of PE (Oates-Whitehead et al. 2003). In prophylaxis settings, dalteparin and enoxaparin have been most widely studied and priority should be given to those products (Laurent et al. 2002; Greer 2002).

Prostethic Heart Valves

The ideal anticoagulation regimen in pregnant patients with prosthetic heart valves is uncertain. Oral dicoumarol anticoagulants, LMWH, subcutaneous high dose heparin and continuous high-dose intravenous heparin have their advantages and disadvantages (Mahesh et al. 2002). Oral anticoagulants may cross the placental barrier and have been accused to cause embryopathy and other adverse effects to the fetus (Bates 2002). Evidence for LMWH prophylaxis is scarce and there may be a high rate of treatment failure (Leyh et al. 2003). The report on treatment failures and concerns about teratogenicity with use of LMWH has been heavily criticized by experts (Ginsberg et al. 2003).

Anti-Xa Activity and Antithrombotic Properties of LMWHs in Pregnancy

LMWHs may differ in their effects on haemostatic parameters, but this may not necessarily lead to clinical differences of these agents (Ellison et al. 2001). During pregnancy, differences in the pharmacokinetics of LMWH were observed, with an overall reduction in anti-Xa activity (Sephton et al. 2003).

Prophylaxis in Neurology and Neurosurgery

Neurosurgery Patients

VTE is a frequent complication following craniotomy for brain tumors. Several studies in elective neurosurgery patients with LMWH prophylaxis were successfully performed without major bleeding events which may be attributable to the LMWH (Iorio and Agnelli 2000; Walsh and Kakkar 2001); one study was terminated because of the increased incidence of adverse events, e.g., intracranial hemorrhage (Dickinson et al. 1998). The combination with intermittent pneumatic compression (IPC) may attribute to the reduction of VTE (Goldhaber et al. 2002; Macdonald et al. 2003; Agnelli et al. 1998; Nurmohamned et al. 1996). In traumatic intracranial hemorrhagic injuries or intracranial

aneurysm ruptures a routine LMWH should be avoided during the early postoperative period (Sironen et al. 2003; Norwood et al. 2002). Preliminary studies showed that preoperative blood tests for haemostatic markers, e.g., soluble fibrin polymers (SFP) or D-dimer, might help to identify patients at risk (Sonaglia et al. 1999; Vukovich et al. 1997). Patients undergoing operations at the vertebral disc may benefit from antithrombotic prophylaxis with LMWH (Voth et al. 1992).

Stroke

The results of studies with LMWH prophylaxis in acute stroke are controversial. LMWH may be superior to aspirin in preventing DVT but may result in a higher rate of symptomatic intracranial hemorrhage (Sandset et al. 1990; Berge et al. 2000; Bath et al. 2001). In other studies LMWH has been successful in preventing DVT without the induction of bleeding (Prins et al. 1989; Hillbom et al. 2002). Low-dose unfractionated heparin, LMWH have been recommended for patients with acute stroke. In case of hemorrhagic stroke, the situation is less clear and mechanical prophylaxis may be better than LMWH (Geerts et al. 2001). Thromboprophylaxis and antithrombotic therapy in patients with ischemic stroke and cerebral venous/sinus thrombosis have been reviewed by Busch and Masuhr (2004).

Prophylaxis in Pediatric Patients

Although thrombosis is less frequent in children than adults, multiple factors, genetic and acquired, may contribute to the development of thrombosis in children (Hoppe and Matsunaga 2002). In children peripheral venous catheters may be a cause of complications. Heparin has been shown to be effective in prolonging the patency of peripheral catheters. The effect of heparin on the duration of these catheters varied across the studies. Because of heterogeneity in clinical outcome recommendations for heparin use in neonates with catheters cannot be made (Shah et al. 2002). LMWH have been applied for prophylaxis and appeared to be safe and efficacious (Dix et al. 2000; Streif et al. 2003; Massicotte et al. 2003). However, the evidence for recommendations for prophylaxis in children is small and there are no general recommendations available.

Prophylaxis in Long Distance Flights

Traveler's thrombosis, also known as "economy class syndrome", has been recognized as a possible complication of long distance flights. In high-risk subjects after long (>10 hours) flights, the incidence of DVT may be between 4% and 6%. High-risk subjects without prophylaxis suffered in 4.82% from DVT, in the aspirin group 3.6% DVT, and none in the LMWH group. DVT was asymptomatic in 60% of subjects. A single dose of LMWH seems to be sufficient for prophylaxis of DVT in long distance flights (Cesarone et al. 2002). There may be an association of PE and ischemic stroke in passengers with a patent foramen ovale (Lapostolle et al. 2003). However, the etiology of these adverse events needs further clarification before a final recommendation for prophylaxis can be done. High-risk passengers may benefit from a single injection of LMWH (Royal College of Obstetricians and Gynecologists 2001). Epidemiological data, clinical presentation, pathophysiology, and possibilities for prevention were reviewed by Ferrari and Morgan (2004).

Prophylaxis in Orthopedic Surgery

Incidence and Risk

Thrombosis, affecting approximately 4 million people per year, is the most common cause of mortality in the United States, resulting in more than 2 million deaths per year (Skinner and Schulz 2002). In patients with hip replacement surgery calf vein thrombosis may occur in 40-60% of cases, proximal vein thrombosis in 20% of cases, and fatal pulmonary embolism in 1-2% of cases when prophylaxis is not used (Turpie 1991). Among other risk factors, e.g., inherited thrombophilia, female gender is considered a strong risk factor for venous thrombosis (Svensson et al. 1997). The prevalence of asymptomatic deep vein thrombosis remains high despite 7 to 10 days prophylaxis, as recommended by the American College of Chest Physicians, with a post prophylaxis incidence of nonfatal venous thromboembolism of 2.2% and 0.05% incidence of fatal pulmonary embolism. The post prophylaxis incidence is higher after hip than knee replacement (2.5% versus 1.4%). However, the prevalence of deep vein thrombosis identified by venographic studies was higher after knee than hip replacement (Willan and Crowther 2002; Kearon 2003). In 2000, 53% of hip replacement patients and 47% of knee replacement patients received prophylaxis for longer than 21 days (Anderson et al. 2002). The high risk of DVT has made orthopedic surgery the ideal discipline to test the efficacy and safety of LMWH.

In elective hip replacement LMWH (enoxaparin 40 mg/day) has been successfully tested for prophylaxis of VTE (Planes et al. 1988; Planes et al. 1990; Planes et al. 1991). A comprehensive review on the prevention of deep vein thrombosis in orthopedic surgery has been presented by Eichinger and Kyrle (2004).

Timing

Fixed-dose LMWH may even be started postoperatively (Turpie 1990; Turpie 1991). Postoperative enoxaparin administration has been successfully used in elective knee arthroplasty (Colwell et al. 1995; Leclerc et al. 1996) Enoxaparin 30 mg twice daily was effective and safe as low dose unfractionated heparin to prevent deep venous thrombosis after hip arthroplasty (Colwell and Spiro 1995). Pre-

operative prophylaxis with LMWH (dalteparin) was more effective than that with warfarin, but there seems to be an increased need for postoperative transfusions and an increase in wound-related bleeding complications (Francis et al. 1997). A modified regimen in close proximity to surgery resulted in substantive risk reductions for all and proximal deep vein thrombosis without increased overt bleeding when initiated postoperatively (Hull et al. 2000).

Side Effects and Dosage

LMWH may cause similar or less hemorrhagic events than UH, with a similar rate of deep vein thrombosis (Levine et al. 1991; Warwick et al. 1995). Hemorrhagic side effects may depend on dosage (Spiro et al. 1994). In spinal anesthesia a dose reduction (20mg) has been recommended (Planes et al. 1991).

Cost Effectiveness

In comparison to standard heparin and warfarin, enoxaparin may be cost effective and it can reduce hospital stay (O'Brien et al.1994; Drummond et al. 1994; Menzin et al. 1994).

Prolonged Administration

The risk of late-occurring DVT remains high at least until day 35 after surgery (Planes et al. 1996) and several studies demonstrated a beneficial effect when the enoxaparin prophylaxis was prolonged for nine days to one month (Bergqvist et al. 1996;Nilsson et al. 1997;Leclerc et al. 1998). The cost-effectiveness of prolonged enoxaparin prophylaxis after elective hip replacement surgery has been demonstrated (Detournay et al. 1998;Friedman and Dunsworth 2000); this benefit has not been demonstrated for knee replacement (Comp et al. 2001). In several studies LMWHs demonstrated to be safe, effective with major effects on hemostasis (Arnesen et al. 2003; Andersen 1997; Lassen et al. 1998; Dahl et al. 1997; Hull et al. 2000; Hull et al. 2000). It may be interesting to further study the lipolytic effect of LMWH (dalteparin) under these conditions (Myrmel et al. 1992).

Comparison with other LMWH or Direct Thrombin Inhibitors

In recent years enoxaparin prophylaxis in hip and knee replacement surgery has been compared to a synthetic pentasaccharide (Fondaparinux), direct thrombin inhibitor (ximelagatran), and tinzaparin (Planes 2000;Turpie et al.2001; Heit et al. 2001). Tinzaparin and ximelagatran were found to be equally effective than enoxaparin in these studies; however, other investigators could not repeat the effect of ximelagatran (Eriksson et al. 2003). Fondaparinux was equal or more effective in preventing deep vein thrombosis in several studies in hip or knee replacement surgery (Bauer et al. 2001; Turpie 2001; Lassen et al. 2002; Turpie et al. 2002). In a metaanalysis a superior effect of fondaparinux has been demonstrated in comparison to enoxaparin (Turpie et al. 2002; Turpie et al. 2002).

A direct comparison of three LMWH (certoparin, dalteparin, enoxaparin) showed all three were equally efficacious in the prophylaxis of DVT (Janni et al. 2001). Direct thrombin inhibitors (Ximelagatran and its subcutaneous form melagatran) showed similar results compared to dalteparin in the prophylaxis of DVT (Eriksson et al. 2002; Eriksson et al. 2002). In comparison to enoxaparin, dalteparin as first-line prophylaxis led to substantial cost savings (Krotenberg et al. 2001). Other LMWHs (ardeparin, clivarin, certoparin, nadroparine, tinzaparin, bemiparin, reviparin) have been studied in knee and hip arthroplasty for prophylaxis of DVT, mostly in comparison to enoxaparin (Levine et al. 1996; Heit et al. 1997; Planes 1993; Hamulyak et al. 1995; Planes et al. 1999; Adolf et al. 1999; Blanchard et al. 1999; Kakkar et al. 2000; Heit et al. 2000; Samama et al. 2002; Navarro-Quilis et al. 2003; Wang et al. 2004; Planes et al. 1998; Wirth et al. 2001). Some of the compounds were announced as new second generation LMWH. As inherent differences between LMWHs prevent the extrapolation of clinical outcomes from one trial to another further studies must be awaited before a final recommendation should be given (Deitelzweig et al. 2003).

Ambulatory Surgery

In patients undergoing ambulatory arthroscopic knee surgery perioperative and postoperative prophylaxis with a LMWH (dalteparin) was effective and safe (Michot et al. 2002).

Controversies

There is an ongoing discussion on several factors, which may have an effect on outcome of thromboprophylaxis.

Timing of initiation of prophylaxis with LMWH remains different in Europe and North America and it is not yet decided what would be the optimal time, although there is some evidence that administration 6 hours postoperatively may be protective without the risk of bleeding (Kher 2001; Dahl and Bergqvist 2002; Strebel et al. 2002; Hull et al. 2001; Hull et al. 1999; Raskob and Hirsh 2003).

The duration of prophylaxis has been studied in multiple randomized trials with success in hip arthroplasty, but not in knee arthroplasty. Adverse effects and cost-effectiveness remain an unsolved issue for some authors whereas others strongly advise the prolonged administration (Whang and Lieberman 2002; Friedman 2003; Hull et al. 2001).

A wide range of model estimates and assumptions identify LMWH (enoxaparin) compared to warfarin or no prophylaxis as the prophylaxis modality of choice for preventing venous thromboembolism and subsequent clinical complications following total knee replacement surgery (Nerurkar et al. 2002).

However, most trials evaluating heparins had methodological defects. UH and LMWH protect against lower limb DVT. There is, however, insufficient evidence to confirm either protection against pulmonary embolism or an overall benefit, or to distinguish between various applications of heparin (Handoll et al. 2002; Anderson et al. 1993). No statistically difference was noted between four prophylactic regimes (aspirin, warfarin, LMWH and pneumatic compression) due to the very small incidence of symptomatic PE (Westrich et al. 2000). For proximal DVT rates, LMWH was significantly better than warfarin - but not for total DVT (Brookenthal et al. 2001). One year earlier it has been stated that the best prophylactic agent in terms of both efficacy and safety was warfarin (Freedman et al. 2000). Another meta-analysis came to the conclusion that LMWH is significantly superior to both UH and warfarin (Palmer et al. 1997). This has led other authors to the conclusion that the absolute reduction in symptomatic venous thromboembolism attributed to extended prophylaxis in some studies and meta-analyses seem to have been overestimated (O'Donnell et al. 2003). It is unclear how much the radiologists experience and frequency of reporting on venograms may have influenced the outcome of these studies (Kalodiki et al. 1998). Furthermore the effect of the administration of LMWH may be influenced by weight and renal function. Weight-based dosing is recommended for some LMWH but not for all (Barrett et al. 2001). The decision to use warfarin or LMWH has then been considered to be a finely tuned trade-off, which is health care system dependent. It is accepted that the most significant parameters that influence the comparative cost-effectiveness are the cost of the drug, the cost of international normalized ratio monitoring and the costs associated with major bleeding (Hull et al. 1997). The prophylaxis with LMWH may also affect the decision which type of anesthesia will be performed. Reports of local bleeding after spinal or epidural analgesia/analgesia make anesthetists more reluctant to combine regional anesthesia with LMWH prophylaxis (Gallus 1999). 48% of orthopedic surgeons had to discontinue LMWH prophylaxis due to bleeding complications. 88% had witnessed excessive bruising around the wound and 53% had experienced increased wound bleeding or hematomas (McNally et al. 1997). A definition on surgical bleeding, which allows practical measurement procedures and quantification, is lacking. Clinical studies on vascular endpoints and standard scientific procedures for health economic analyses have been demanded (Dahl and Bergqvist 2002).

In most studies unfractionated heparin was monitored inappropriately which may be responsible for the reduced efficacy of UH (Raschke et al. 2003).

In summary, LMWHs have chemical, physical, and clinical similarities. They have greater bioavailability, longer half-lifes, more predictable pharmacological response, possible improved safety, and similar or greater efficacy compared with UH. However, the evaluation of clinical trials does not allow the determination of therapeutic equivalence due to different diagnostic methods, drug administration times, dose equivalencies, and outcome measurements (McCart and Kayser 2002). The scoring of the quality of clinical trials for meta-analysis is problematic and it has been recommended to assess the methodological aspects individually (Juni et al. 1999).

Despite clear evidence of effectiveness, deep vein thrombosis prophylaxis is underused. Law firms as evidenced by Internet advertisement have recognized this. Patients are informed on the prevention of venous thromboembolism or economy class syndrome. "If you or a family member has been injured, contact a personal injury attorney today. Just fill out Injury.Board.com's online questionnaire and have a personal injury lawyer review your potential personal injury claim - free of charge." (Injuryboard.com 2004). The medico legal implications of antithrombotic prophylaxis and treatment are well recognized (McIntyre 2001).

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Address for correspondence:
René Gordon Holzheimer MD PhD
Blombergstr. 5
D-82054 Sauerlach (Munich South)
Tel. +49-8104-887822
Fax +49-8104-887824
e-mail Gresser.holzheimer@t-online.de
www.praxisklinik-sauerlach.de