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LOW-MOLECULAR-WEIGHT HEPARIN (LMWH) IN THE TREATMENT OF THROMBOSIS

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Abstract: Thromboembolic complications are a common and costly medical problem, associated with significant morbidity and mortality, especially in postoperative patients. There have been reports of death due to thromboembolic complications even after short procedures, e.g. arthroscopy. Low-molecular-weight heparins (LMWHs) (e.g., certoparin, dalteparin, enoxaparin, nadroparin, reviparin, tinzaparin) have been tested for treatment of deep vein thrombosis in comparison to unfractionated heparin (UFH) in many patients being effective and safe alternative for treatment of deep vein thrombosis (DVT) and venous thromboembolism (VTE). Fixed-dose subcutaneous LMWH once daily is in most cases of equivalent efficacy and safety compared to conventional UFH therapy. There may be less risk for bleeding, less platelet activation together with a control of markers of haemostatic system activation, and either no progression or regression of thrombus size in patients treated with LMWH. The handling of LMWH is more comfortable for patients and less time consuming for nurses and laboratories compared to UFH. The cost-effectiveness analysis showed that LMWH are more cost effective than UFH. It has been calculated that outpatient treatment with LMWH may save $ 1641 per patient in comparison to hospital treatment. This economic benefit of outpatient treatment of DVT seems to be realized in different health systems. Women with antiphospholipid antibodies and a history of either prior thrombotic events or pregnancy loss are at high risk during pregnancy for either another fetal death or thrombosis and may benefit from treatment with LMWH. In patients with malignant tumors secondary prophylaxis or long-term treatment with LMWH is successful. Patients with a contraindication for oral anticoagulants may benefit from treatment with LMWH as do patients on chronic anticoagulation treatment scheduled for an operative intervention. In most instances LMWH (dalteparin, enoxaparin, nadroparin) treatment for DVT may be given once daily at a fixed dose without any harm, based on a prolonged antithrombin activity. Effectiveness and safety of LMWH (dalteparin, enoxaparin, nadroparin, tinzaparin) in comparison to UFH treatment on outpatient basis has been demonstrated in several studies. In summary, LMWHs have an established role in the treatment of DVT and pulmonary embolism (PE), on an in- and outpatient basis and could realize substantial savings. Most studies were performed with dalteparin, enoxaparin and nadroparin. There is evidence that LMWHs may help to prolong survival in cancer patients and to avoid complications of the acute coronary syndrome.

Key words: Deep vein thrombosis; pulmonary embolism; dalteparin; enoxaparin; nadroparin; tinzaparin; certoparin; reviparin; LMWH; acute coronary syndrome; cancer

INTRODUCTION

Thromboembolic complications are a common and costly medical problem, associated with significant morbidity and mortality, especially in postoperative patients. There have been reports of death due to thromboembolic complications even after trivial procedures, e.g. tumescent analgesia and liposuction (Rao et al. 1999). The cause of thrombosis is often unknown but is universally ascribed to part of Virchow's triad: stasis, hypercoagulability, and intimal injury (Quader et al. 1998; Burroughs 1999). In multiple studies LMWHs were successfully tested for prophylaxis of deep vein thrombosis (Holzheimer 2004). The diagnosis of deep vein thrombosis (DVT) requires both clinical assessment and objective testing because clinical features are nonspecific and investigations can be either false positive or negative. Initially the patients are stratified into high-, intermediate- and low-risk categories (Bick and Kaplan 2004). Once a patient is diagnosed with an acute DVT, low-molecular weight heparin (LMWH) is the agent of choice for the initial therapy and oral anticoagulant therapy may follow for long-term secondary prophylaxis. Therapy duration is usually at least three months and may be prolonged depending on the risk of recurrent thrombosis, anticoagulant-related bleeding, and the patient's preference (Hirsh and Lee 2002). Traditionally, treatment for DVT required patients to be hospitalized for administration of intravenous unfractionated heparin, but with years of experience of LMWH treatment, it has

been suggested to initiate or complete therapy in an outpatient setting (Rydberg et al. 1999; Yacovella and Alter 2000). It has been reported that LMWH are potentially superior to unfractionated heparin or warfarin (Hyers 2003). Whereas initial studies have excluded pregnant women and patients with acute pulmonary embolism or a known hypercoagulable disorder, there have been several studies successfully completed in special patient populations in the last decade (Kujovich 1999) and recently more patient populations who may benefit from treatment with LMWH have been identified, e.g., acute coronary syndrome, cancer, stroke, inflammatory bowel disease, pulmonary disease, pregnancy, pulmonary embolism and pediatric patients.

Therapeutic Efficacy and Safety of LMWH and UFH

LMWHs (certoparin, dalteparin, enoxaparin, nadroparin, reviparin, tinzaparin) have been tested for treatment of deep vein thrombosis in comparison to UFH in many patients and can be recommended as an effective and safe alternative for treatment of DVT/VTE. Fixed-dose subcutaneous dalteparin once daily is of equivalent efficacy and safety to conventional UFH therapy. There may be less risk for bleeding, less platelet activation together with a control of markers of hemostatic system activation, and no progression of thrombus size. It has been recommended to walk with medical compression stockings which will increase the rate of resolution of pain and swelling (Bratt et al. 1985; Bratt et al. 1988; Albada et al. 1989; Bratt et al. 1990; Hull et al. 1992; Thery et al. 1992; Lindmarker et al. 1994; Meyer et al. 1995; Luomanmaki et al. 1996; Columbus Investigators 1997; Simonneau et al. 1997; Holmstrom et al. 1997; Decousus et al. 1998; Kirchmaier et al. 1998; Partsch and Blattler 2000; Merli et al. 2001; Peternel et al. 2002) .

Enoxaparin is at least as effective and safe as UFH. The handling of LMWH is more comfortable for patients and less time consuming for nurses and laboratories (Simonneau et al. 1993; Levine et al. 1996; Xiao and Theroux 1998; Merli et al. 2001). Subcutaneous fixed dose nadroparin is safe and at least as effective as UFH in the treatment of deep vein thrombosis. It significantly inhibits the thrombin and fibrin generation (Lopaciuk et al. 1992; Diquelou et al. 1995). However, UFH may control markers of the hemostatic system more rapidly than once-daily subcutaneously administered weight-adjusted nadroparin (Stricker et al. 1999). LMWH (ardeparin) may exhibit less binding to plasma proteins than unfractionated heparin (Young et al. 1994). In addition to comparability to UFH, LMWHs (reviparin, bemiparin, certoparin) may be more effective in reduction of thrombus size and prevention of recurrent thromboembolism (Kirchmaier et al. 1998; Harenberg et al. 2000; Breddin et al. 2001; Harenberg et al. 2001; Kakkar et al. 2003) (Table 1)

Therapeutic Efficacy and Safety of LMWH and Coumarin/Warfarin

Most studies comparing LMWH (dalteparin, enoxaparin, nadroparin) with oral anticoagulants (coumarin, warfarin) at least similar efficacy in preventing recurrent DVT (Das et al. 1996; Leroyer et al. 1998; Lopaciuk et al. 1999). Some studies came out with better results for LMWH: less late valvular communicating vein insufficiency (nadroparin) (Lopez-Beret et al. 2001), lower recurrence rate (enoxaparin) of symptomatic venous thromboembolism and lower incidence of bleeding (Gonzalez-Fajardo et al. 1999). However, long-term administration of LMWH (enoxaparin) did not result in lower recurrence rate (Pini et al. 1994) or the findings in elderly patients treated with LMWH (enoxaparin) were inconclusive due to a wide confidence interval for differences between outcomes (Veiga et al. 2000) (Table 2).

Are All LMWH Equal?

There is insufficient evidence to determine the therapeutic equivalence of LMWHs. Evaluation of clinical trials, also by meta-analysis, is limited because of differing diagnostic methods, drug administration times, dose equivalencies, and outcome measurements. (van der Heijden et al. 2000; McCart 2002).

LMWH Versus UFH

Several review papers deal with the question whether LMWH should replace unfractionated heparin in the treatment of adults with DVT. Most authors agree that LMWH are at least as effective than UFH but may have less bleeding complications and do not require monitoring (Brewer 1998; Litin 1998; Merli 2000). LMWH preparations vary considerably in their methods of preparation and pharmacological properties, but whether these differences have clinical importance or may help to reduce complications associated with the use of UFH may depend on future trials (Hirsh 1998; Pineo and Hull 1998). Some authors doubt that heparin may prevent recurrence or may decrease thrombus propagation (Egermayer 2001).

Cost-effective Analysis LMWH Versus UFH/OA

The cost-effectiveness analysis showed that LMWH are more cost effective than UFH. Inpatient LMWH treatment became cost saving when it reduced the yearly incidence of late complications by at least 7%, when as few as 8% of patients were treated entirely as outpatients, when at least 13% of patients were eligible for early discharge. It has been suggested that on an outpatient's basis cost of $1641 per patient could be saved (Rodger et al. 1998; Gould et al. 1999).

Table 1. Randomized studies comparing LMWH and UFH in the treatment of deep vein thrombosis.

Author	Year	Type of LMWH	Efficacy	Comments	Safety
Bratt et al.	1985	Dalteparin	+	No progression of thrombus size in LMWH group (second study)	+
Bratt et al.	1988	Dalteparin	+		+
Albada et al.	1989	Dalteparin	+	Trend in risk reduction for bleeding	+
Bratt et al.	1990	Dalteparin	+	2x/d	+
European multicentre study	1991	Nadroparin	+ +		+
Prandoni et al.	1992	Nadroparin	+		+
Lopaciuk et al.	1992	Nadroparin	+		+
Hull et al.	1992	Tinzaparin	+ +		+ +
Thery et al.	1992	Nadroparin	+	at 400 anti-Xa	+
DVTENOX study group	1993	Enoxaparin		Hemostatic activation system	
Simonneau et al.	1993	Enoxaparin	+ +		+
Young et al.	1994	Ardeparin	+	Less plasma protein binding	
Lindmarker et al.	1994	Dalteparin	+	Fixed dose 1/d	+
Diquelou et al.	1995	Nadroparin	+ +	Similar anticoagulant activity	
Meyer et al.	1995	Dalteparin	+		+
Fiessinger et al.	1996	Dalteparin	+		+
Partsch et al. *	1996	Dalteparin	+	100IU/kg 2x/d better than 200IU/kg 1x/d	+
Luomanmaki et al.	1996	Dalteparin	+	Fixed dose 1x/d	+
Levine et al.	1996	Enoxapain	+	In- vs out-patient	+
Koopman et al.	1996	Nadroparin	+	In- vs out-patient	+
Holmstrom et al.	1997	Dalteparin	+	1x/d	+
Columbus Investigators	1997	Reviparin	+		+
Simonneau et al.	1997	Tinzaparin	+		+
Xiao and Theroux	1998	Enoxa-parin/argatroban	+ +	UFH is associated with platelet activation	
Kirchmaier et al.	1998	Certoparin	+	s.c. and i.v.	+
Goldhaber et al.	1998	Ardeparin	+ +	In- vs out-patient	+
Decousus et al.	1998	Enoxaprin	+	Vena cava filter	+
Stricker et al.	1999	Nadroparin		Markers of hemostatic system are more rapidly controlled by UFH	
Belcaro et al.	1999	Nadroparin	+	In- vs out-patient	+
Pernerstorfer et al.	1999	Dalteparin	+ +	LMWH blunts LPS-induced coagulation activation	
Partsch and Blattler *	2000	Dalteparin		Walking and medical compression stockings improve outcome when added to LMWH	
Harenberg et al.	2000	Certoparin	+ +		+
Hull et al.	2000	Tinzaparin	+ +		+
Von Tempelhoff	2000	Certoparin	+ +	long-term survival breast cancer	+
Harenberg et al.	2001	Certoparin	+ +	Composite outcome and thrombus size better	+ +
Merli et al.	2001	Enoxaparin	+	1x/d and 2x/d vs UFH	+
Breddin et al.	2001	Reviparin	+ +	Better in thrombus reduction and prevention of recurrence	+
Peternel et al.	2002	Dalteparin	+	F1+2, TAT, D-dimers similar	+
Kakkar et al.	2002	Reviparin	+ +	More effective in inhibiting in vivo thrombin generation than UFH	+
Kakkar et al.	2003	Bemiparin	+ +	Reduction in thrombus size by bemi-parin	+

\+ LMWH similar to UFH + + LMWH better than UFH * no UFH

Table 2. Randomized studies comparing LMWH and warfarin/coumarine in the treatment of deep vein thrombosis.

Author	Year	LMWH vs C or W	Efficacy	Comments	Safety
Pini et al.	1994	Enoxaparin vs W	+		+ +
Das et al.	1996	Dalteparin vs W	+		+ +
Leroyer et al.	1998	Enoxaparin + C (fluindione) early vs delayed	+	Early and delayed coumarine application have similar outcome	+
Lopaciuk et al.	1999	Nadroparin vs C	+	Secondary prophylaxis	+
Gonzalez-Fajardo et al.	1999	Enoxaparin vs C	+ +		+ +
Veiga et al.	2000	Enoxaparin vs C	+	Less bleeding complications	+ +
Lopez-Beret et al.	2001	Nadroparin vs c	+	Better for recanalization	+

C coumarin
W warfarin
+ LMWH similar to C/W
+ + LMWH better than C/W

According to a cost-effective analysis of LMWH versus warfarin for the prevention of secondary thromboembolism LMWH might be a cost-effective drug - depending on the cost for the drug - for secondary prophylaxis, especially in patients at high risk of recurrence (Marchetti et al. 2001).

Meta-analysis : LMWH Versus UFH

A significant reduction in the incidence of thrombus extension but non-significant trends in favour of LMWH were observed for recurrence of thromboembolic events and total mortality in earlier reports on meta-analysis (16 studies) (Leizorovicz et al. 1994). There were relative risk reductions for symptomatic thromboembolic complications (53%), clinically important bleeding (68%), and mortality (47%) when 19 studies were analyzed (Lensing et al. 1995). These results were confirmed in another meta-analysis (Siragusa et al. 1996). However, when inclusion criteria for three major outcomes and randomization procedures were included for evaluation the results were not so straightforward in favor of LMWH. Compared with UFH, LMWH reduced mortality rates over 3 to 6 months of patient's follow-up, but there was no significant difference for bleeding complications and prevention of thromboembolic recurrences (Gould et al. 1999). Clot improvement in venography, recurrence, total mortality and major hemorrhages were assessed in 4,472 patients with DVT from 21 studies treated with LMWH or UFH. LMWH resulted in a significant improvement in clot reduction, a decrease in total mortality, and a lower incidence of hemorrhage. There was no difference in the rate of recurrences (Rocha et al. 2000).

LMWH and Direct Thrombin Inhibitors or Synthetic Xa-inhibitor

LMWHs have been compared to direct thrombin inhibitors and synthetic Xa-inhibitor.

Direct thrombin inhibitor (ximelagatran) shows similar effectiveness in reducing the size of thrombus in patients with deep vein thrombosis when compared to LMWH (dalteparin, enoxaparin) followed by warfarin (Harenberg et al. 2002; Eriksson et al. 2003). Patients treated with a synthetic Xa-inhibitor (fondaparinux) had 2.4% recurrent thromboembolic complications versus 5.0% in the LMWH (dalteparin) group, although not statistically significant. Primary outcome (change in thrombus mass, occurrence of pulmonary embolism (PE)) and safety (bleeding) were similar in both groups (The Rembrandt investigators 2000).

Effects of LMWH in Different Clinical Situations

LMWHs may show activity not only in the haemostatic system, but also in the immune system, which may open new treatment options for these compounds (Pineo and Hull 2004).

In a randomized study comparing LMWH (enoxaparin) versus UFH D-Dimer levels decreased during the first days of treatment and indicated a thromboembolic recurrence, but there was no relationship between antifactor Xa activities and any biological marker (DVTENOX Study Group 1993). Due to the short half-life of the anti-IIa activity of LMWH the effectiveness of LMWH has been difficult to explain (Iorio et al. 1994). The antithrombin III (AT III) mediated anti-Xa and anti-IIa effects have been regarded as the sole determinants of the antithrombotic actions of LMWHs. However, this did not explain the greater than 100% bioavailability of subcutaneously administered LMWH as measured by the chromogenic based antiXa-method. Recently it has been demonstrated that tissue factor pathway inhibitor (TFPI) may explain some of the effects of LMWHs, which induce a distinct TFPI release profile. Long leg compression may also induce an increase in TFPI levels (Hoppensteadt et al.

1995). In a more recent study, LMWH (reviparin) demonstrated to be more effective in inhibiting in vivo thrombin generation compared to UFH plus vitamin K antagonist, and it also produced a significantly higher TFPI release and a greater reduction in thrombin activatable fibrinolysis inhibitor (TAFI) and fibrinogen levels (Kakkar et al. 2002). Some patients may not benefit from treatment with LMWH, which may be reflected by a failure of improvement in coagulation parameters, markers of in-vivo thrombin generation, TFPI-release and phlebography (Breddin et al. 2003).

Inflammation, Sepsis and Intensive Care

LMWHs may demonstrate distinctive anti-inflammatory activities. Lipopolysaccharide (LPS) is a major trigger of sepsis-induced disseminated intravascular coagulation (DIC) via the tissue factor (TF)/factor VIIa-dependent pathway of activation. LMWH may decrease the activation of coagulation caused by LPS, as F (1+2) and polymerized soluble fibrin, termed thrombus precursor protein (TpP) levels were only slightly increased in the LMWH group (Pernerstorfer et al. 1999). LMWH (dalteparin) may attenuate the organ injury after trauma and sepsis by downregulation of TNF-alpha (Tsukuda et al. 2003).

Anticoagulants can influence production of cytokines in whole blood, but the effects vary depending on the type of anticoagulant and the immunological stimulus (Call and Remick 1998). In acute lung injury the protective effects of LMWH may be associated with altered neutrophil adhesion, TNF-alpha and thromboxane activity (Darien et al. 1998). Together with other compounds, e.g., pentoxifylline and dexamethasone, LMWH (enoxaparin) may limit the central nervous system local inflammatory responses and could improve the effort towards reducing the detrimental outcome of patients with pneumococcal meningitis (Schwartz et al. 1998). In acute neurodegenerative diseases LMWH (enoxaparin) may reduce brain edema and the size of lesions, improving motor and cognitive functional recovery (Stutzmann et al. 2002), which may have clinical significance for ischemia and brain trauma. It has been demonstrated that LMWH possesses anti-inflammatory properties distinct from its anticoagulant properties, which may have an effect in ischemia-reperfusion injuries and systemic inflam-matory response (Downing et al. 1998; Kruse-Eliott et al. 1998).

Allergy, Autoimmune and Inflammatory Bowel Disease.

Evidence has now accumulated that heparin can significantly affect immune response including allergic inflammation. LMWH may have an inhibitory role in mast cell-mediated allergic inflammation (Baram et al. 1997). Patients with inflammatory bowel disease, in which mast cells play a key role, may benefit from adjuvant treatment with LMWH (He 2004). LMWH (enoxaparin) may ameliorate the severity of colitis (Dotan et al. 2001). It is suggested that LMWHs exert an anti-allergic action by inhibiting infiltration of inflammatory cells, by reducing the release and antagonizing the activities of inflammatory mediators (Wang et al. 2000). Experimental data indicate that antiallergic activity of inhaled heparin is independent of its anticoagulant action and resides in the $<2{,}500$ ULMW chains. The antiallergic activity of NAF-heparins is mediated by an unknown biological action and may have therapeutic potential (Campo et al. 1999). Low-molecular-weight heparins may decrease the pathology of T cell-infiltrative autoimmune disease (Christopherson et al. 2002) The enhancement of endothelial cell procoagulant activity by antiphospholipid antibodies has been inhibited by LMWH (Oosting et al. 1992). Women with antiphospholipid antibodies (aPL = IgG anticardiolipin and/or lupus anticoagulants) and a history of either prior thrombotic events or pregnancy loss are at high risk during pregnancy for either another fetal death or thrombosis and may benefit from treatment with LMWH (Cowchock 1998).

Heart and Vascular

LMWH may interact with smooth muscle cell migration and proliferation and may alter the accumulation of components of the extracellular matrix after arterial injury. Together with cyclosporine it reduced the frequency and severity of accelerated graft coronary disease and the extent of parenchymal rejection (Aziz et al. 1993). The Factor Xa induced mitogenic response in smooth muscle cells has been inhibited by LMWH (Bretschneider and Schror 2001). LMWH decreased vein wall profibrotic mediators and post-DVT vein wall fibrosis (Thanaporn et al. 2003). Statins and angiotensin converting enzyme (ACE) inhibitors are well known compounds for treatment of coronary artery disease. It has been demonstrated for the first time that a statin, an ACE-inhibitor and a LMWH (dalteparin) suppress tissue factor up-regulation in the cellular micro-environment which may lead to improved treatment of acute coronary syndrome (Lindmark and Siegbahn 2002; Moons et al. 2002). In addition, LMWH (dalteparin) may have further lipolytic effects on serum lipid levels (Myrmel et al. 1992; Monreal et al. 1995).

LMWH and Special Populations

LMWHs have been studied in special populations, e.g., elderly or obese patients, which may have clinical implications. The incidence of deep vein thrombosis and pulmonary embolism increases exponentially with age. Careful evaluation of the individual hemorrhagic risk, dose adaptation, and careful laboratory monitoring may help to avoid bleeding complications. LMWH may

offer an advantage but further studies are needed in this population (Gensini et al. 1998). LMWHs may exert a renoprotective effect and cause a reduced platelet activation (Weigert et al. 2001; Stefonie et al. 2002). Obesity and impaired renal function may influence the levels of anti-Xa, although the clinical effect is not yet fully understood. LMWHs have an established role in hemodialysis and hemofiltration, but the reports on their efficacy and safety during continuous renal replacement therapy are scarce (Sagedal and Hartmann 2004). Population analysis in patients with disease and heterogeneity indicated similar pharmacody-namics as in volunteers, supporting weight-based dosing and identified the dependence of clearance on obesity and severe renal function, although the magnitude of these effects are probably not clinically significant (Barrett et al. 2001; Sanderink et al. 2002).

Patients with a contraindication for coumarin use (e.g., recent blood loss, active gastroduodenal ulcer, psychological or physical inability or unwillingness to comply with the laboratory monitoring needs, chronic alcoholism, dementia, pregnancy, recent neurosurgery, pericardial effusion or over 80 years of age) may benefit from LMWH (dalteparin) administration (Monreal et al. 1994). Patients with chronic anticoagulation and the need for an operative intervention may receive LMWH (enoxaparin) treatment (Spandorfer et al. 1999).

Timing and Dosing of LMWH

In most instances LMWH (dalteparin, enoxaparin, nadroparin) treatment for DVT may be given once daily at a fixed dose without any harm, which may be possible by a prolonged antithrombin activity (Holmostrom et al. 1992; Alhenc-Gelas et al. 1994; Agnelli et al. 1995; Boneu et al. 1998; Charbonnier et al. 1998; Couturaud et al. 2001; Merli et al. 2001).

In- Versus Out-patient Treatment of DVT

Effectiveness and safety of LMWH (ardeparin, dalteparin, enoxaparin, nadroparin, tinzaparin) in comparison to UFH treatment on outpatient basis has been demonstrated in several studies; however, due to exclusion criteria many patients did not participate (Levine et al. 1996; Goldhaber et al. 1998; Harrison et al. 1998; Wells et al. 1998; Belcaro et al. 1999). The potential savings associated with outpatient DVT treatment are substantial. During a 2-year program evaluation, total cost savings of $1,108,587 were realized when 391 patients were enrolled in an outpatient treatment program (Tillman et al. 2000). Clinical care pathway using patient selection, an integrated multidisciplinary approach, and the outpatient bleeding risk index may help to provide effectiveness and safety (Vinson and Berman 2001; Wells et al. 2003). Eight studies (three randomized trials and five cohort studies) compared outpatient use of low molecular weight heparin with inpatient use of unfractionated heparin in 3762 patients. The incidence of recurrent deep venous thrombosis was similar in the two groups (4%), as was major bleeding (0,5%). Use of low molecular weight heparin was associated with shorter hospitalization (median, 2.7 days) versus 6.5 days and lower costs (median difference, 1600 dollars) (Segal et al. 2003). Half of the delays in hospital discharge may be avoided by the outpatient use of LMWH (Dunn et al. 2004). This economic benefit of outpatient treatment of DVT seems to be realized in different health systems (Spyropoulos et al. 2002).

Upper Limb Thrombosis and LMWH

Upper limb vein thrombosis has been under-recognized, although this disease may pose a significant risk for pulmonary embolism and death. There are only a few reports available dealing with this entity and the use of LMWH (Ellis et al. 2000; Shah and Black-Schaffer 2003).

Pulmonary Embolism and LMWH

Pulmonary embolism may occur in 50% or more of patients with proximal deep vein thrombosis. Even in patients with known proximal DVT symptoms of PE are unspecific (Girard et al. 2001; Pforte 2004). A comparison of LMWH (enoxaparin, tinzaparin, certoparin; nadroparin; reviparin, dalteparin, tinzaparin) with unfractionated heparin or UFH followed by warfarin demonstrated similar effectiveness and safety of LMWH in the treatment of pulmonary embolism (Thery et al. 1992; Meyer et al. 1995; The Columbus Investigators 1997; Simonneau et al. 1997; Decousus et al. 1998; Kirchmaier et al. 1998; Hull et al. 2000; Merli et al. 2001; Findik et al. 2002; Beckman et al. 2003). Fourteen trials investigating the effect of LMWH (nadroparin, tinzaparin, dalteparin, reviparin, certoparin, enoxaparin) were analyzed in a recent meta-analysis. There seems to be a trend for a decrease in recurrent symptomatic venous thromboembolism at the end of treatment and at three months in the LMWH treated patients. Symptomatic and asymptomatic pulmonary embolism and major bleeding complications were reduced, but not statistically significant (Quinlan et al. 2004).

Superficial Thrombophlebitis

Superficial thrombophlebitis may bear a risk for deep vein thromboembolic events. However, treatment studies with LMWHs are rare. In a randomized controlled study the following treatment modalities were compared in 562 patients: compression only, early surgery, low-dose subcutaneous heparin, LMWH, and oral anticoagulant treatment. There was no significant difference in DVT incidence at 3 months among the treatment groups. Whereas the cost including LMWH were

the highest in this study, the highest social costs (lost working days, inactivity) were observed in patients treated only with stockings (Belcaro et al. 1999). In a study comparing LMWH (enoxaparin) versus saphenofemoral disconnection no statistically significant differences between the surgery and the LMWH group were discovered (Lozano and Almazan 2003). LMWH (enoxaparin) may reduce the incidence of deep and superficial venous thromboembolism from 30,6% in the placebo group to 8,3%/6,9% in the enoxaparin group (40mg/1,5 mg/kg) (Superficial Thrombophlebitis Treated by Enoxaparin Study Group 2003).

Ischemic Stroke and Atrial Fibrillation

Deep venous thrombosis (DVT) in the leg occurs in 23% to 75% of patients with acute ischemic stroke, and pulmonary embolism accounts for about 5% of deaths (Bornstein et al. 1988). For patients with ischemic stroke treated within 48 hours of the onset of symptoms, LMWH (nadroparin) was effective in improving outcomes at six months (Kay et al. 1995). The significance of LMWHs for recurrent stroke prevention and for the treatment of stroke-in-progress has been doubted (Sherman 1998). The frequency of recurrent ischemic stroke during the first 14 days was similar in the LMWH (dalteparin) treatment group compared to the aspirin treatment group (Berge et al. 2000). Treatment with other LMWH (tinzaparin), at high or medium dose, within 48 hours of acute ischemic stroke did not improve functional outcome compared with aspirin. Although high-dose tinzaparin was superior in preventing deep-vein thrombosis, it was associated with a higher rate of symptomatic intracranial hemorrhage (Bath et al. 2001). Antithrombotic therapy with LMWH in patients with ischemic stroke needs further evaluation to find out which population may benefit (Busch and Masuhr 2004). Although unproven by randomized studies, LMWH is used as a protective anticoagulant for atrial fibrillation, which may be responsible for a reduction in the length of hospital stay (Kim et al. 2003).

Cancer and LMWH

Cancer cells may be capable of both thrombin formation and induction of fibrin degradation, which may be essential prerequisites for the development of DVT as well as the spread of malignancy. The development of DVT may be indicated by D-dimer and fibrinogen levels may be predictive for the development of DVT (von Tempelhoff et al. 1997; Vukovich et al. 1997). Recurrent venous thromboembolism is more likely to occur in cancer patients (63%) while being treated with warfarin compared to non-cancer patients (30%). It has been suggested that long-term therapy with LMWH (dalteparin) may be effective in managing warfarin-failure thromboembolic disease (Luk et al. 2001). Warfarin may be associated with a high bleeding rate in patients with VTE and cancer - 6 deaths owing to hemorrhage in the warfarin group compared with none in the LMWH (enoxaparin) group (Meyer et al. 2002). The probability of recurrent thromboembolism at six months was 17% in the oral-anticoagulant group and 9% in the LMWH (dalteparin) group (Lee et al. 2003). Activation of coagulation appears to play a role in tumor progression and time to progression, which may be prolonged by LMWH (enoxaparin) administration (Robert et al. 2003). Certain types of cancer, e.g., breast cancer with unfavorable prognosis, seem to respond positively in terms of survival advantage from treatment with LMWH (certoparin)(von Tempelhoff et al. 2000). Beyond the established use of LMWH in the treatment of thrombosis, recent studies have demonstrated that LMWH therapy can prolong survival in patients with solid tumour malignant disease (Petralia and Kakkar 2004).

LMWH in Pregnancy

Anticoagulant therapy is indicated during pregnancy for treatment of VTE, systemic embolism in patients with mechanical heart valves, for prevention of pregnancy loss in women with APLAs or previous thrombophilia and previous pregnancy losses(Fiedler and Würfel 2004; Greer 2004). Warfarin may cause embryopathy and CNS abnormalities. There is also a risk of serious perinatal bleeding caused by the trauma of delivery to the anticoagulated fetus (Ginsberg et al. 2001). Especially in anticoagulant factor-deficient women there is an 8-fold risk for venous thromboembolism compared to non-deficient women (Friederich et al. 1996). Consequently, LMWH has been introduced as an alternative treatment option for VTE in pregnancy. Effectiveness and safety of several LMWHs (dalteparin, enoxaparin, tinzaparin) has been evaluated in retrospective or observational studies. Women with a history of venous thromboembolic events have thromboxane dominance during and after pregnancy, which may be eliminated through LMWH (dalteparin) (Kaaja et al. 2001). LMWH (dalteparin) can be used for treatment of acute venous thromboembolism in pregnancy, but at approximately 10-20% higher doses as compared to non-pregnant individuals (Jacobsen et al. 2003). The mean anti-Xa levels may be significantly reduced at 12, 24 and 36 weeks gestation at 2 hours post injection of the LMWH (dalteparin) as compared with the nonpregnant state (Sephton et al. 2003) This has been confirmed for other LMWHs (tinzaparin, enoxaparin) (Casele et al. 1999; Smith et al. 2004), but not all investigators could find a relationship between peak plasma anti-Xa levels of LMWH (enoxaparin) and gestational age (Ellison et al. 2000) There are some reports on side effects, but in most instances they were not related to the use

of LMWH (enoxaparin) (Dulitzki et al. 1996; Ellison et al. 2000; Rodie et al. 2002; Lepercq et al. 2001). Treatment with LMWH plus low-dose aspirin has been proposed as standard therapy for recurrent pregnancy loss due to aPL (Triolo et al. 2003). Despite poorer outcome there was no evidence of greater endothelial cell activation in the treated antiphospholipid syndrome pregnancies (Stone et al. 2003), but there is evidence that LMWH reduce the in vitro binding of antiphospholipid antibodies (Franklin and Kutteh 2003). Problematic is the treatment of VTE with LMWH (enoxaparin) in pregnant women with mechanical heart valves (Lev-Ran et al. 2000; Rowan et al. 2001; American College of Obstetrician and Gynecologists 2002) but this critique has not unanimously been accepted and there is an urgent need for clarification of this unresolved issue (Ginsberg et al. 2003). Another unresolved issue is the optimum dosing of LMWH therapy in pregnancy (Bates and Ginsberg 2002).

Pediatric Patients and LMWH

Although thrombosis is less frequent in children than in adults, it represents a significant source of morbidity and mortality. Multiple factors, both genetic and acquired, contribute to the development of thrombosis in children (Hoppe and Matsunaga 2002). In a dose-finding study with two LMWH (enoxaparin) preparations compared to UFH in children with DVT/PE, thrombotic complications in the central nervous system, and congenital heart disease therapy with LMWH was effective and safe. Newborn infants, however, had increased dose requirements (Massicotte et al. 1996). When children with sinovenous thrombosis (SVT) were treated either with LMWH (enoxaparin) or UFH or oral anticoagulants (OA) there were no bleeding events in the LMWH group observed (de Veber et al. 1998). Resolution of thromboembolic events occurred in 94% of children receiving LMWH (enoxaparin); major bleeding in 5% of children receiving therapeutic doses. Recurrent or new thromboembolic events occurred in 1% of children (Dix et al. 2000). Thromboembolic events occurred predominantly in the lower and upper venous system in the presence of indwelling catheters (69%). Preterm infants required higher doses and a longer time to achieve an anti-Xa level in the target range than full term infants. The dose of LMWH (enoxaparin) may be influenced by other factors, e.g., congenital heart disease, impaired liver or renal function. Complete or partial resolution has been achieved in 69% of children with 0.9% of children experiencing a recurrent thromboembolic event and clot extension (Streif et al. 2003). In an open-label randomized trial comparing LMWH (reviparin) versus UFH/OA recurrent thromboembolic events occurred in 5.6% of children at 3 months compared to 10% of children in the UFH/OA group. The incidence of bleeding events was twofold in the UFH/OA group (Massicotte et al. 2003).

Acute Coronary Syndrome

Platelet aggregation and activation of coagulation have been recognized as key factors for the development of acute coronary syndromes. Patients suffering from this disease are at high risk of death or myocardial infarction. Heparin is able to reduce this risk in aspirin-treated patients, but is limited in its application by the risk of hemorrhage and thrombocytopenia and patients have to be monitored carefully. LMWHs may present a successful alternative treatment (Turpie and Antman 2001; Bechtold and Janssen 2004). LMWHs (dalteparin, enoxaparin, nadroparin) were found to improve clinical outcomes in acute coronary syndromes and provide a more predictable therapeutic response, longer and more stable anticoagulation, and a lower incidence of UFH-induced thrombocytopenia (Cohen 2003). The American Heart Association and the American College of Cardiology recommend lMWHs for treatment of unstable angina/non-ST-elevation myocardial infarction. Clinical trials with LMWHs showed promising results in patients with percutaneous coronary intervention and ST-elevation myocardial infarction (Wong et al. 2003). However, clinical trials of UFH and LMWH for the treatment of unstable angina may have limited generalizability to unselected patients, many of whom have characteristics that would exclude them from trial enrollment and put them at risk for adverse outcomes (Walsh et al. 2000). In addition, there is some concern about the difference in inclusion and exclusion criteria, and appropriate monitoring of heparin, which may influence outcome observed in some studies (Cohen et al. 1997; Lindahl et al. 2000; Collet et al. 2003; Raschke et al. 2003). Clinical studies demonstrated that lipid-modifying agents (e.g., statins), antiplatelet agents, (e.g., acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors), and low-molecular-weight heparin (e.g., dalteparin, enoxaparin, nadroparin) can reduce the occurrence of acute coronary events in patients with acute coronary syndromes. Angiographic studies suggest that statins may also promote regression of atherosclerosis (Kereiakes 2003; Monroe et al. 2003). There may be an association between atherosclerotic disease and spontaneous venous thrombosis. Atherosclerosis may induce venous thrombosis, or the two conditions may share common risk factors (Prandoni et al. 2003). The instruments for treating acute coronary syndromes, e.g., LMWH may soon be improved. An intensive lipid-lowering statin regimen may provide a greater protection against death or major cardiovascular events in patients with an acute coronary syndrome than does a standard regimen (Cannon et al. 2004).

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