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Safety Profile of Different Low-Molecular Weight Heparins Used at Therapeutic Dose

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Contents

Abstract

Low-molecular weight heparins (LMWHs) have been shown to be as safe and effective as unfractionated heparin (UFH) for the treatment of acute venous thrombosis and non-life-threatening pulmonary embolism. Different reports have shown that LMWHs may also be used to treat patients with unstable angina or non-Q-wave infarction. The safety of LMWHs used at therapeutic dose has been widely studied in pivotal clinical trials and analysed in several meta-analyses. However, despite the wide development and use of LMWHs, several issues regarding the safety and optimal use of LMWHs remain unanswered.

The main adverse effect of LMWHs is bleeding and it is uncertain whether a weight-adjusted dosage regimen without laboratory monitoring can be used in patients with a high risk of bleeding, such as patients with renal failure, elderly patients, obese patients or pregnant women. These patients are usually excluded from clinical trials and only a few studies, not sufficiently powered to estimate efficacy and safety, have been carried out in these special populations. Most of the available data comes from pharmacokinetic or population pharmacodynamic studies or clinical reports. Results in patients with renal impairment who are not undergoing haemodialysis suggest that a reduction in calculated creatinine clearance levels is associated with an increased risk of accumulation of anti-Xa activity, the extent of which differs depending on the individual LMWH and the extent to which the compound is cleared by the kidney. The limited data available regarding the use of therapeutic doses of LMWHs in obese patients suggest that there is no need to cap the dose at a maximal allowable dose. Long-term (3-month) treatment with LMWHs appears to be as effective and safe as oral anticoagulant therapy for the treatment of venous thromboembolism. It appears that each LMWH is a distinct compound with unique pharmacokinetic and pharmacodynamic profiles. Until more data are available regarding these special populations, periodic monitoring of anti-Xa activity levels may be recommended to detect accumulation and/or an overdose and minimise the bleeding risk.

The non-haemorrhagic adverse effects of the LMWHs include heparin-induced thrombocytopenia (HIT) and osteoporosis. The incidence of HIT appears to be lower with LMWHs than with UFH; there is currently not enough data to compare the frequency of HIT between the various LMWHs. LMWHs also appear to carry a lower risk of causing osteoporosis than UFH.

In conclusion, studies that include special population patients are required to make conclusive recommendations concerning the safety and monitoring of the different LMWHs.

It is many years now since low-molecular weight heparins (LMWHs) became the treatment of choice for venous thrombosis. They have been shown to be as safe and effective as unfractionated heparin (UFH) for the treatment of acute venous thrombosis and non-life-threatening pulmonary embolism. They offer the potential for treating selected patients in an outpatient setting, without the need for laboratory monitoring or dose adjustment in the majority of cases.[1] Different reports show that LMWHs may also be used to treat patients affected by unstable angina or non-Q-wave infarction.[2] In all these settings, LMWHs have replaced UFH.

Despite the wide development and use of LMWHs, several issues regarding the safety and optimal use of LMWHs remain unclear, but could be answered with properly designed studies. The main adverse effect of LMWHs is haemorrhage and it is uncertain whether a weight-adjusted dosage regimen without laboratory monitoring can be used in patients with a high risk of bleeding, such as patients with renal failure, obese patients or pregnant women. These patients are usually excluded from clinical trials and only a few studies, not sufficiently powered to estimate efficacy and safety, have been carried out in these special populations. Recommendations are necessary for these clinical subgroups. Heparin-induced thrombocytopenia (HIT) and osteoporosis are some of the relevant non-haemorrhagic adverse effects of LMWHs.

This article reviews the current literature with respect to the safety of LMWHs used at therapeutic dose in the general population, excluding children, as well as in special populations with a high risk of bleeding. However, as LMWHs have usually been compared with UFH and not head-to-head, it is difficult to evaluate the comparative safety of the

Table I. Currently available low-molecular weight heparin preparations

Drug	Production method	Molecular weight (Da)	Anti-Xa/IIa ratio[3]
Ardeparin sodium	Peroxidative depolymerisation	5500–6500	2.0
Bemiparin sodium	Alkaline depolymerisation	3000–4200	6–9
Certoparin sodium	Isoamylic nitrate degradation	6000	2.0
Dalteparin sodium	Nitrous acid depolymerisation	5000–5950	2.5
Enoxaparin sodium	Benzylation and alkaline depolymerisation	3500–5500	3.6
Nadroparin calcium	Nitrous acid depolymerisation	4200–4800	3.2
Parnaparin sodium	Peroxidative depolymerisation	4000–5000	2.4
Reviparin sodium	Nitrous acid depolymerisation	3550–4650	3.2
Tinzaparin sodium	Digestion by heparinase	5800–6750	1.9

different LMWHs. Only indirect comparisons are available.

A search was conducted on Medline between 1990 and November 2004 for articles containing the keywords 'low molecular weight heparins' and 'renal insufficiency', 'renal failure', 'older patients', 'obese', 'pregnant women', 'heparin induced thrombocytopenia', 'osteoporosis', 'thrombocytosis', 'serum potassium', 'monitoring', as well as the names of the available products. Only studies published in English during this period were selected. We also searched the Cochrane Library and reviewed abstracts from major international meetings.

1. Low-Molecular Weight Heparin (LMWH) Preparations and Pharmacodynamic Properties

The pharmacodynamic and pharmacokinetic differences between UFH and LMWHs can be explained by the relatively lower binding properties to proteins or cells of LMWHs. This reduced binding is responsible for the more predictable dose-response relationship of LMWHs compared with UFH.[1] LMWH preparations are derived from UFH by chemical or enzymatic depolymerisation to yield fragments with a mean molecular weight ranging from 3000 to about 6500Da (table I). Because they are prepared by various methods of depolymerisation, they differ to some extent in pharmacokinetic and pharmacodynamic properties. LMWHs exert their anticoagulant activity mainly by inhibiting factor Xa and thrombin. The relative anti-Xa and antithrombin (IIa) activity of LMWHs, expressed as the anti-Xa/anti-IIa ratio, depends on the distribution of molecular weight of each molecule. Anti-IIa activity requires long heparin molecules of at least 18 saccharide units (>5400Da), whereas heparin molecules of any length can catalyse the inactivation of factor Xa.[1] Moreover, the clearance of heparin chains is influenced by the chain length of the molecules, with the higher molecular weight fractions cleared mostly through the reticulo-endothelial system and the lower molecular weight species cleared mostly through the kidney.

Monitoring of the anticoagulant effect of LMWHs is generally not thought to be necessary in clinically stable patients. To date, it has not been clearly demonstrated in any clinical trial that measuring plasma anti-Xa activity levels correlates with the outcome. Nevertheless, dose-finding studies with LMWHs have shown that increasing the dose is associated with high anti-Xa activity levels and an increased rate of major bleeding.[4,5] Thus, anti-Xa activity monitoring may detect an overdose and/or accumulation of LMWHs in special populations.

2. Bleeding Risk with LMWHs in Patients Included in Clinical Trials

In clinical trials, bleedings are usually reviewed as major bleedings, whereas minor bleedings are not always reported. However, the definitions for major haemorrhages are heterogeneous. Depending on the studies, they include different criteria: bleeding that led to interruption of treatment, bleeding associated with a decrease in haemoglobin level (≥2 g/dL), fatal, retroperitoneal or intracranial bleeding, or bleeding resulting in a transfusion of ≥2 units of blood. In this review, we will focus only on major bleeding.

A number of compounds, administered once or twice daily, have been compared with UFH in the initial treatment of patients with venous thrombosis

Table II. Incidence of major bleeding during heparin treatment of venous thromboembolism and combined relative risk from different meta-analyses

Meta-analysis	No. of patients	Incidence of major bleeding (%)		Relative risk	p-Value
		Low-molecular weight heparin	Unfractionated heparin		
Lensing et al.[7]	1086	0.8	2.8	0.68 (95% CI 0.31, 0.85)	p < 0.005
Siragusa et al.[9]	1684	2.2	4.7	0.42 (95% CI 0.2, 0.9)	p = 0.01
Dolovich et al.[12]	4447	1.5	2.6	0.63 (95% CI 0.37, 1.05)	p = 0.08

and/or pulmonary embolism. Meta-analyses have been used to re-examine the results of these studies and, depending on the selection criteria, have reached varied conclusions.[6-12] The overall results of these studies show that the rates of major bleeding, for a treatment duration of up to 10 days, were similar for all LMWHs and ranged from 0.8% to 2.4%. In meta-analyses that included only truly randomised studies for which a combined relative risk was calculated, the results for major bleeding are in favour of LMWHs compared with UFH (table II).[7,9,12] In the Cochrane database review, which included 14 randomised trials (4754 patients), at the end of the initial treatment period (up to 10 days), major bleeding occurred in 1.3% and 2.1% of the patients receiving LMWH and UFH, respectively (odds ratio [OR] 0.60; 95% CI 0.39, 0.93).[13] Finally, in a meta-analysis including only patients with pulmonary embolism, major bleeding occurred in 1.3% and 2.1% of the patients receiving LMWH and UFH, respectively (OR 0.67; 95% CI 0.36, 1.27).[14]

Studies with bemiparin sodium as well as those with certoparin sodium, which is the only LMWH used at a fixed and bodyweight-independent dose, have not been included in the different meta-analyses presented here. These two LMWHs have been shown to be as effective and safe as UFH in the treatment of acute proximal deep venous thrombosis.[15,16]

Once-daily treatment is more convenient for the patient and may optimise home treatment. It was initially thought that once-daily administration of LMWHs would be associated with a higher risk of bleeding. In fact, although only a few studies have compared head-to-head once- and twice-daily regimens for the initial treatment of venous thromboembolism (VTE), results of the pooled data showed that once-daily treatment is as safe as twice daily, with a rate of major bleeding during the 10-day treatment of 1.3% and 1.2% for once- and twice-daily treatment, respectively.[12,17,18]

In the treatment of acute coronary syndromes (unstable angina or non-ST-segment elevation myocardial infarction), LMWHs have been compared with UFH or placebo in trials, including very large cohorts of patients:

- dalteparin sodium (120 IU/kg/12h for 6 days vs UFH, extended treatment with 7500 IU/24h for 40 days vs placebo)[19-21];
- nadroparin calcium (86 IU/kg bolus + 86 IU/kg/12h for 6 days vs UFH for 14 days vs placebo)[22];
- enoxaparin sodium (ESSENCE [Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events]: 1 mg/kg/12h for 2–8 days vs UFH, TIMI [Thrombolysis In Myocardial Infarction] 11B: 30 mg bolus + 1 mg/kg/12h for 4–6 days vs UFH, extended treatment with 40 mg/12h or 60 mg/12h for 43 days vs placebo).[23,24]

The results of these studies have been analysed in a critical review published by Husted et al.[25] The incidence of major bleeding at 6 days was similar for dalteparin sodium (1.1%), nadroparin calcium (0.7–1.3%) and UFH (1%). In the nadroparin calcium 14-day treatment group, the incidence was significantly higher (3.5%) than in the 6-day treatment group and the 14-day UFH group (1.6%). The incidence of major bleeding with enoxaparin sodium treatment was analysed either at 14 days (TIMI 11B) or at 35–45 days (ESSENCE) and was 1.5% versus 1% for UFH, and 6.5% versus 7% for UFH, respectively.[25]

One open-label study compared enoxaparin sodium (1 mg/kg twice daily) and tinzaparin sodium (175 IU/kg once daily) that was administered for 7 days in acute coronary syndromes; the rate of major bleeding at day 7 was similar with the two molecules.[26]

In this section, we have reviewed the rate of major bleeding in patients included in pivotal clinical trials. On a routine practice basis, in a recent prospective observational study, the bleeding rate was recorded during a 1-month period in hospitalised patients who were treated with different LMWHs.[27] Among the 99 patients who received a LMWH at therapeutic dose, seven bleeding events were recorded. Unfortunately, the authors did not provide any clear information related to the type of bleeding and the characteristics of the patients (age, renal function or other haemorrhagic risk factors).[27]

In conclusion, although no head-to-head comparative studies are available, in terms of safety there is no convincing evidence that LMWHs are clinically different when administered to 'non-high-risk patients' in the treatment of VTE or acute coronary syndrome.

3. Bleeding Risk in Special Populations

3.1 Patients with Renal Insufficiency

In contrast to UFH, the clearance of LMWHs is primarily via renal excretion. Thus, repeated administration of therapeutic doses of LMWH to patients with renal insufficiency may lead to an overdose and/or accumulation, with an increased risk of bleeding. The calculation of the creatinine clearance (CrCl) level using the Cockcroft and Gault formula is a useful and accurate way to quickly predict CrCl without collecting urine.[28] The use of the CrCl as a method for screening patients at high risk of over-anticoagulation is attractive because of its easy performance. However, it is not clear whether any particular cut-off in CrCl is a threshold below which there is a danger of accumulation of the anticoagulant effect of LMWHs.[29]

Renal function can be decreased either through renal disease or as a consequence of ageing. Since age-related reduction in glomerular filtration may not lead to the same degree of accumulation as acute glomerular disease does,[29] we will review the data concerning the safety of LMWHs in elderly patients separately (see section 3.2).

Owing to the low incidence of major bleeding in patients treated for VTE or acute coronary syndrome with LMWHs, an estimate of the safety requires a considerable number of patients. Such studies have not been carried out in patients with renal insufficiency and only clinical reports are available. The first published studies were pharmacokinetic studies with prophylactic doses in patients undergoing or not undergoing haemodialysis. These studies are of great interest since they evaluate the relationship between renal function and relevant pharmacokinetic parameters that should be used to establish specific dosage recommendations. However, because of the diversity of patients included in the studies (patients undergoing haemodialysis and patients with moderate or severe renal impairment) and of methodology (single dose or multiple dose), it is difficult to reach any conclusion about the use of LMWHs in these patients. These studies allow a crude assessment of the bleeding risk, but do not allow determination of the absolute incidence rate of major bleeding events in this special population.

The characteristics of the studies which included patients with renal failure who were treated with LMWHs are summarised in table III and table IV.

3.1.1 Enoxaparin Sodium

Among the different LMWHs, enoxaparin sodium has been the most widely studied in patients with renal failure (table III).

Several pharmacokinetic studies at different doses are available. Single-dose enoxaparin sodium (1 mg/kg) administered to eight patients with end-stage renal disease on an off-dialysis day showed a 2-fold prolongation in anti-Xa activity half-life compared with values reported in healthy volunteers.[32] At the single dose of 0.5 mg/kg in 12 patients not undergoing haemodialysis, with a mean CrCl of 11.4mL/min (range 5–21), the clearance of enoxaparin sodium was two times lower in patients with chronic renal failure.[30]

Multiple-dose enoxaparin sodium (40 mg/day for 4 days) administered to three groups of 12 patients with mild (mean CrCl 66.4 mL/min), moderate (mean CrCl 38.5 mL/min) or severe (mean CrCl 19.3 mL/min) renal impairment resulted in a statistically significant decrease in anti-Xa activity clearance on day 4 (−39%) only in patients with severe renal impairment compared with volunteers who had normal renal function (n = 12).[34] In a prospec-

Table III. Characteristics of studies including patients with renal failure treated with enoxaparin sodium classified according to the year of publication

Study	Type of study	Treatment		Subjects		
		dose (route)	duration	renal status	no.	CrCl (mL/min)
Cadroy et al.[30]	PK	0.5 mg/kg (SC)	Single dose	Normal	12	105
				CRF	12	11.4 (5–21)
Gerlach et al.[31]	Retrospective	30 mg/12h (SC) or 1 mg/kg/12h (SC) or 40 mg/24h (SC)	≥2 doses	Normal	50	ND
				RI	53	ND
Brophy et al.[32]	PK	1 mg/kg (SC)	Single dose	ESRD	8	ND
Collet et al.[33]	Prospective	1 mg/kg/12h (SC) then adjustment to the anti-Xa activity	4d (mean)	Normal	55	>60
				Moderate RI	28	30–60
				Severe RI	28	<30
Sanderink et al.[34]	PK/PD	40 mg/24h (SC)	4d	Normal	12	120.7 ± 11.3
				Mild RI	12	66.4 ± 2.8
				Moderate RI	12	38 5 ± 1.4
				Severe RI	12	19.3 ± 2.0
Becker et al.[35]	PK/PD from TIMI 11A	30mg (IV) bolus then 1 mg/kg/12h or 1.25 mg/kg/12h (SC)	3d (median)	Normal	273	>80
				Moderate RI	149	40–80
				Severe RI	11	<40
Bruno et al.[36]	PK/PD from TIMI 11A	30mg (IV) bolus then 1 mg/kg/12h or 1.25 mg/kg/12h (SC)	3d (median)	Normal	393	>50
				Moderate RI	51	30–50
				Severe RI	4	<30
Chow et al.[37]	Prospective	1 mg/kg/12h (SC)	≥3 doses	Normal to mild RI	7	>60
				Mild RI	6	31–60
				Moderate RI	4	11–30
				Severe RI	1	≤10
Spinler et al.[38]	Retrospective analysis from TIMI 11B and ESSENCE	30mg (IV) bolus then 1 mg/kg/12h (SC)	≤8d	Normal	3432	86.7 ± 66.0
				RI	69	24.8 ± 5.1
Collet et al.[39]	Prospective	1 mg/kg/12h, or 0.65 mg/kg/12h (SC) in severe RI patients with dose adjustment to the anti-Xa activity	≥4d	Non-severe RI	453	>30
				Severe RI	62	≤30
Montalescot et al.[40]	Prospective	1 mg/kg/12h (SC) or less in severe RI patients	≥4d	Non-severe RI + normal	723	>30
				Severe RI	80	≤30
Hulot et al.[41]	Population, PK	1 mg/kg/12h (SC) or less	36h (mean)	Severe RI to normal	60	56 ± 24

CrCl = creatinine clearance; **CRF** = chronic renal failure; **ESRD** = end-stage renal disease; **ESSENCE** = Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events study; **IV** = intravenous; **ND** = not determined; **PD** = pharmacodynamic; **PK** = pharmacokinetic; **RI** = renal insufficiency; **SC** = subcutaneous; **TIMI** = Thrombolysis In Myocardial Infarction study.

Table IV. Characteristics of studies including patients with renal failure treated with low-molecular weight heparins (LMWHs) excluding enoxaparin sodium

Study	Type of study	Treatment			Subjects		
		LMWH	dose (route)	duration	renal status	no.	CrCl (mL/min)
Goudable et al.[42]	PK	Nadroparin calcium	100 anti-Xa IC units/kg (IV)	Single dose	Normal	12	75–200
					ESRD	7	<10
					RI	7	10–20
					RI	5	30–50
Baumelou et al.[43]	PK	Reviparin sodium	55 IU/kg (SC) between 2 dialysis sessions	Multiple dose	Normal	6	ND
					ESRD	10	ND
Hainer et al.[44]	Crossover PK/PD	Tinzaparin sodium	75 IU/kg (SC and IV)	Single dose	ESRD	12	ND
Polkinghorne et al.[45]	PK	Dalteparin sodium	2500IU (IV)	4wk	ESRD	15	ND

Anti-Xa IC = anti-Xa Institut Choay; **CrCl** = creatinine clearance; **ESRD** = end-stage renal disease; **IV** = intravenous; **ND** = not determined; **PD** = pharmacodynamic; **PK** = pharmacokinetic; **RI** = renal insufficiency; **SC** = subcutaneous.

tive multiple-dose study evaluating 18 patients with varying degrees of renal function initiated on enoxaparin sodium (1mg/kg/12h), the median anti-Xa activities measured at peak level were higher in patients with CrCl ≤30 mL/min.[37] A linear correlation was found between CrC1 and anti-Xa activity concentrations at peak level. On the basis of these data, the authors believe that a dose adjustment is necessary in patients with CrCl ≤30 mL/min who receive repeated therapeutic doses of enoxaparin sodium.[37]

In routine practice, enoxaparin sodium was shown to result in increased bleeding complications in 53 patients with renal impairment compared with 50 patients with normal renal function (30% vs 2%).[31] However, these results have to be interpreted with caution since this is a retrospective study that included 103 patients, some of whom underwent dialysis, some received different doses of enoxaparin sodium for different indications, and only serum creatinine levels and not CrCl was determined.

TIMI 11A, 11B and ESSENCE studies provide relevant population pharmacodynamic data. The results of the TIMI 11A study have been re-examined to evaluate the impact of renal function on factor Xa inhibition pharmacodynamics and pharmacokinetics after enoxaparin sodium administration (1 mg/kg/12h or 1.25 mg/kg/12h) for a median duration of 3 days in 433 patients with acute coronary syndrome.[35] Patients with marked renal impairment (CrCl <40 mL/min, n = 11) had higher plasma trough and peak anti-Xa activity levels compared with those with normal renal function and were more likely to have major haemorrhagic events. Moreover, a significant correlation between apparent clearance of enoxaparin sodium and CrCL was found (r = 0.85). Using population pharmacodynamic and pharmacokinetic/pharmacodynamic models in the TIMI 11A study, patients with CrCl <50 mL/min (n = 55) had a mean decrease of 21% in enoxaparin sodium clearance and a 2.4-fold increase in the risk of major haemorrhagic events.[36] The authors suggest that either dose modification (0.5 to 0.75 mg/kg/12h) or anti-Xa activity measurements may be necessary in these patients to avoid potentially dangerous levels of anticoagulation.[35] An analysis of data from ESSENCE and TIMI 11B

studies of patients with acute coronary syndrome treated with enoxaparin sodium 1 mg/kg/12h for up to 8 days versus UFH showed that patients with severe renal impairment (mean CrCl 24.8 mL/min) experienced more major haemorrhages than patients without renal impairment (6.6% vs 1.1%), whether they were treated with UFH or enoxaparin sodium.[38]

A dose-adjustment proposal according to renal function in patients with acute coronary syndrome treated with enoxaparin sodium has been investigated by Collet et al.[33,39] and Montalescot et al.[40] In the most recent study by Collet et al.,[39] among 515 consecutive patients, 174 would have been excluded from randomised pivotal trials performed with enoxaparin sodium.[39] Heart failure and CrCl ≤30 mL/min were the most frequent exclusion criteria. Patients with CrCl ≤30 mL/min were initially treated with 65% of the recommended dosage (1 mg/kg/12h). A subsequent dose adjustment was made when needed, aiming for a peak anti-Xa activity level between 0.5 and 1.0 IU/mL. The bleeding rates (major and minor) were similar in both groups at 30 days. Compared with the non-excluded patients, excluded patients had a 4-fold increased rate of death or myocardial infarction. However, does the enoxaparin sodium dose reduction explain this higher rate or is this poor prognosis a result of the baseline characteristics of the patients? In an another study of 803 patients, Montalescot et al.[40] showed that low anti-Xa activity (<0.5 IU/mL) was strongly and independently associated with early mortality. The authors concluded that physicians must be aware that a dose reduction leading to lower anti-Xa levels may increase the risk of mortality and recurrent ischemic events.[40] Finally, a population pharmacokinetic study of enoxaparin sodium performed in a group of 60 patients, including patients with renal failure, showed that bodyweight and determinants of renal function (i.e. serum creatinine level and gender) influence enoxaparin sodium clearance.[41] Based on these results, the authors suggested an individualisation of the dosage of enoxaparin sodium. However, the dose adjustment has to be validated in terms of efficacy and safety.[41]

3.1.2 Tinzaparin Sodium

A crossover pharmacokinetic study evaluated tinzaparin sodium 75 IU/kg administered as a single dose by two different routes (subcutaneous [SC] on an off-dialysis day and intravenous [IV] with dialysis) to 12 patients undergoing long-term haemodialysis at least 2 weeks apart.[44] The anti-Xa activity clearance following tinzaparin sodium administration was reduced by 28% relative to patients with normal renal function. The anti-Xa activity returned to baseline values within 12 hours following the IV dose and 16–24 hours following the SC dose. These results suggest an absence of accumulation after one single dose of tinzaparin sodium in patients with end-stage renal disease.[44]

3.1.3 Nadroparin Calcium

Pharmacokinetic parameters of nadroparin calcium in various stages of chronic renal failure have been studied after a single IV bolus injection of 100 anti-Xa Institut Choay units/kg.[42] Three groups of patients were tested: seven haemodialysed patients, seven patients with a CrCl ranging from 10 to 20 mL/min and five patients with a CrCl ranging from 30 to 50 mL/min, and were compared with a group of 12 healthy volunteers (CrCl 75–200 mL/min). In the three groups of patients, there was no significant difference between the pharmacokinetic parameters and no correlation between these parameters and the CrCl. However, compared with the healthy volunteers, the anti-Xa activity half-life was significantly prolonged in the three groups of patients. These results suggest an accumulation effect of nadroparin calcium in patients with renal insufficiency.[42]

3.1.4 Dalteparin Sodium

In a prospective randomised study, the pharmacokinetics of dalteparin sodium (2500IU, IV) and enoxaparin sodium (40mg, IV) were compared in 15 patients with end-stage renal disease undergoing long-term haemodialysis.[45] No accumulation of anti-Xa activity of either drug was noted over the 4-week treatment period.

3.1.5 Reviparin Sodium

In ten haemodialysed patients, no meaningful prolongation in elimination of anti-Xa activity relative to healthy volunteers was found after administration of 55 IU/kg reviparin sodium to patients between two dialysis sessions.[43]

3.1.6 Conclusion

These results support the notion that non-haemodialysis patients who have a reduction in calculated CrCl are at risk of accumulation of anti-Xa activity to different extents depending on which LMWH they are treated with. However, the results do not allow determination of a cut-off at which the risk of accumulation increases, especially when no relationship is found between the CrCl and the clearance of heparin anti-Xa activity. As concluded by Nagge et al.,[29] there appears to be no justification for the use of a 30 mL/min cut-off in CrCl to select patients who are at increased risk of accumulation; using this cut-off point might be dangerous for some LMWH preparations or might be overly cautious for others. The importance of an increased risk of haemorrhage with decreasing renal function must be systematically weighed against the benefit of treatment when the use of a LMWH in patients with impaired renal function is considered. Moreover, the decision to use reduced initial dosages for LMWHs has not been evaluated in the treatment of acute VTE and should be considered with great caution since it could be beneficial in terms of safety but deleterious in terms of efficacy. The development of specific dosage algorithms requires clinical trials and further investigation of patients with advanced renal insufficiency.

3.2 Older Patients With or Without Renal Insufficiency

A fall in glomerular filtration rate with age has been clearly demonstrated. In addition to increased age, polypharmacy and co-morbid conditions, which are frequently encountered in the elderly, contribute to the renal failure in this population. Renal failure is not being detected in many elderly patients because of the absence of an inappropriate evaluation. Serum creatinine level alone shows a poor sensitivity for the detection of renal failure in elderly patients.[46] Although the calculation of CrCl using the Cockcroft and Gault formula underestimates the CrCl by 20–30% in patients over 80 years of age, this is currently the most accurate way to estimate the renal function in these patients.[47,48] On one hand, the risk of bleeding is potentially higher in the elderly and on the other hand, more older patients have diseases requiring treatment with LMWHs. Thus, reliable evidence concerning the bleeding rate in older patients treated with repeated therapeutic doses of LMWH and the safety profile of LMWHs in the frail elderly population is needed. Unfortunately, most clinical trials include too few very elderly patients and there are only a few studies specifically devoted to the elderly.[49]

By pooling data on older patients treated with therapeutic doses of various LMWHs included in clinical trials, Merli[50] came to the conclusion that there was no evidence of an increased risk of major bleeding based on the age of the patient. However, this was a review that analysed subgroups of patients and not studies aimed at evaluating the bleeding risk in older patients.

Among LMWHs, only nadroparin calcium and tinzaparin sodium at therapeutic dose have been specifically studied in older patients.[51-53]

In a pharmacokinetic study, nadroparin calcium 180 IU/kg was administered once daily for 6–10 days to 12 healthy young volunteers (mean age 25 ± 4 years, mean CrCl 114 ± 15 mL/min), 12 healthy elderly volunteers (mean age 65 ± 3 years, mean CrCl 62 ± 6 mL/min) and to 12 older patients who were hospitalised for acute deep vein thrombosis (DVT) [mean age: 65 ± 11 years, mean CrCl 71 ± 24 mL/min].[51] After repeated administration, a significant accumulation of the anti-Xa activity (assessed by measurement of maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) was observed in the healthy elderly volunteers and in the older patients, but not in the healthy young volunteers. There was no evidence of accumulation of anti-thrombin activity. In contrast to the study conducted in patients with renal failure treated with nadroparin calcium,[42] in this study there was a significant correlation between the CrCl and the clearance of anti-Xa activity.[51]

The two studies conducted with tinzaparin sodium included much older patients than the latter one with nadroparin calcium. In the first study, 30 patients with acute VTE or atrial fibrillation (mean age 87 ± 6 years, mean CrCl 41 ± 15 mL/min [range 20–72]) received tinzaparin sodium 175 IU/kg once daily for up to 10 days.[52] No progressive increase of the anti-Xa or anti-IIa activities measured at peak level was noted after repeated administration of tinzaparin sodium over the 10-day treatment period.

No correlation between CrCl and anti-Xa or anti-II activity was found. Since no patient had an anti-Xa activity above 1.5 IU/mL, the dose of tinzaparin sodium remained fixed over 10 days. The second trial was a prospective study to evaluate the safety profile of tinzaparin sodium given at a therapeutic dosage (175 IU/kg once daily) to very elderly patients treated for up to 30 days.[53] 200 inpatients with a mean age of 85 ± 7 years and a mean CrCl of 51 ± 23 mL/min (range 20–161) were included. The main indications for treatment were acute VTE or atrial fibrillation and the mean duration of treatment was 19 days. Three major bleedings were reported, one of which was fatal. It was likely that antithrombotic drug interactions contributed to two of these bleeding events (overdosage in warfarin and tinzaparin sodium in one case and a combination of warfarin, aspirin [acetylsalicylic acid, dipyridamole with tinzaparin in the second case]). This rate of major bleeding (1.5%) was comparable to that in younger patients who have been included in clinical trials. Anti-Xa activity was regularly measured at peak level and a similar dispersion of these values was noted in the four groups of patients according to their CrCl (20–34 mL/min, 35–49 mL/min, 50–64 mL/min and ≥65 mL/min). Confirming the results of the first study,[52] no correlation between CrCl and anti-Xa activity was found.[53] Of the 200 patients, 26 patients had their dose changed because of an anti-Xa activity above the upper limit of the therapeutic range (≥1.4 IU/mL); they were distributed throughout the four groups of CrCl. Six of them had received an overdose (>190 IU/kg/24 hours) and thus had their dose corrected. These results suggest that tinzaparin sodium appears to be safe at therapeutic dosage in very elderly patients.

The different studies reviewed in this section illustrate the heterogeneity of the pharmacodynamics of LMWHs. Indeed, the clearance of heparins is influenced by the chain length of the molecules, with the higher molecular weight fraction cleared mostly through the reticulo-endothelial system and the lower molecular weight fraction cleared mostly through the kidney. Consequently, the relative proportion of the renal elimination of LMWHs and the risk of accumulation depends on the proportion of high- and low-molecular weight chains of each molecule. This could explain the different pharmacokinetic profiles of nadroparin calcium, tinzaparin sodium and enoxaparin sodium and the different results obtained in the studies conducted in the elderly.[37,51,52] Indeed, the higher proportion of high-molecular weight chains in tinzaparin sodium compared with other LMWHs accounts for the lower contribution of the kidney in the elimination process of this compound.

As it has been suggested that very high anti-Xa activity levels are associated with an increased bleeding risk, it seems reasonable to recommend monitoring of anti-Xa activity in older patients with renal failure treated by LMWHs, in order to avoid an overdose resulting from accumulation.

3.3 Obese Patients

In obese patients, the question is whether the dose should be increased linearly with the weight or 'capped' at a maximum allowable dose. Unfortunately, data evaluating the safety of using weight-based dosage of LMWHs in obese patients are limited. Too few studies have been carried out in obese patients treated with therapeutic and repeated doses of LMWHs. The results of the single-dose phamacodynamic or pharmacokinetic studies or of studies including only healthy obese volunteers should be interpreted with caution when applied to obese patients who will be treated for at least 5 days.

3.3.1 Enoxaparin Sodium

Enoxaparin sodium 1.5 mg/kg SC, was administered once daily for 4 days to 24 obese volunteers (mean weight 99 ± 15kg [range 78–144]; mean body mass index [BMI] 35 ± 5 kg/m^2 [range 29–48]) and to 24 age-, sex- and height-matched, non-obese volunteers.[54] Concerning the anti-Xa activity, exposure at steady-state (AUC_{ss}) was 16% higher in obese than in non-obese volunteers, but maximum anti-Xa activity was similar in both groups. The authors concluded that there appears to be no need to modify the currently recommended dosage of enoxaparin sodium (1.5 mg/kg once daily) when treating obese volunteers with a BMI of up to 40 kg/m^2. Similar results were obtained by Spinler et al.[38] in their analysis of the data from the ESSENCE and TIMI11B studies; there was no difference in the rate of major haemorrhages between patients who were

obese (mean BMI 34 ± 4 kg/m^2) or those who were not obese (0.8% vs 1.3%).

3.3.2 Tinzaparin Sodium

A single-dose pharmacodynamic study was carried out with tinzaparin sodium at therapeutic dose (175 IU/kg) in 37 heavy/obese healthy volunteers (mean weight 129 ± 20kg [range 101–165]; mean BMI 43 ± 9 kg/m^2 [range 26–61]).[55] The pharmacodynamic parameters based on anti-Xa activity were consistent over the bodyweight and BMI ranges. These results suggest that the dose of tinzaparin sodium does not need to be capped at a maximal absolute dose in obese patients. However, this study is a single-dose study in healthy volunteers and no data are available after repeated administrations of tinzaparin sodium to this special population.

3.3.3 Dalteparin Sodium

Dalteparin sodium 200 IU/kg based on actual bodyweight was administered once daily for VTE treatment for a minimum of 5 days to obese patients stratified into three weight classes: 20% above ideal bodyweight (n = 13), 20–40% above ideal bodyweight (n = 14) and >40% above ideal bodyweight (n = 10).[56] The weight range was from 56kg to 190kg. Mean peak and trough anti-Xa activity values measured on days 3 and 5 were similar in the three groups of patients. These results suggest that body mass did not have a significant influence on the response to treatment with dalteparin sodium, measured as anti-Xa activity.

In a retrospective study that included 21 patients (mean weight 118kg [range 94–176]) treated for VTE or acute coronary syndrome with dalteparin sodium twice daily at the mean daily dose of 126 IU/kg (n = 11) and once daily at the mean daily dose of 196 IU/kg (n = 21), the measured anti-Xa activity at peak level was used to assess the efficacy and safety of the two treatment regimens.[57] The results showed that the twice-daily regimen was effective in producing anti-Xa activity in the target range (0.5–1.0 IU/mL). When given as a single daily dose, the anti-Xa activity was below the target range (1.0–2.0 IU/mL) in four of ten patients, which suggests that the clearance of dalteparin sodium might be higher in obese patients.

3.3.4 Certoparin Sodium

In a pharmacodynamic study with certoparin sodium administered at a fixed and bodyweight-independent dose (8000IU anti-Xa) to 13 patients with DVT and 18 healthy volunteers, no correlation was found between bodyweight (55–100kg) and the AUC of the anti-Xa activity.[15]

3.3.5 Conclusion

Although the use of therapeutic doses of LMWHs in obese patients has not been studied extensively, the few available data suggest that there is no need to cap the dose for the molecules studied in these patients. The well predictable dose-response relationship of LMWHs administered to non-overweight patients cannot be applied to obese patients without specific studies. Therefore, monitoring of the anticoagulant effect of the treatment might be recommended in these patients in order to avoid overdoses.

3.4 Pregnant Women

VTE is a rare, but important, complication of pregnancy that remains a leading non-obstetric cause of maternal death. LMWHs are an attractive alternative to UFH in the acute treatment of VTE because of their ease of use and their association with a lower incidence of osteoporosis and HIT, but their evaluation in pregnancy has been limited to small case series. When determining the optimal therapeutic regimens for treatment of VTE during pregnancy, as well as the efficacy of the treatment, the safety of the drug for the fetus and mother, and the dosage regimen during delivery and post-partum, should be considered.[58,59]

LMWHs and UFH do not cross the placenta and, therefore, do not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the uteroplacental junction is possible. Several studies strongly suggest that LMWH therapy is safe for the fetus.[59] The rate of bleeding complications with therapeutic doses of LMWHs during pregnancy has not been clearly determined. Very few studies on LMWH use for the treatment of VTE during pregnancy have been published, but the safety of LMWH use in this setting appears to be good. These studies mostly concern enoxaparin sodium and, to a lesser extent, dalteparin sodium and nadroparin calci-

um.[58,59] Because of the change in the volume of distribution and weight gain in pregnant women, a dose adjustment based on the weight change or a monitoring of anti-Xa activity may be considered. However, these practices are not based on properly designed trials.

To avoid an unwanted anticoagulant effect and an excessive bleeding risk during delivery in women receiving therapeutic doses of LMWHs, it is recommended that LMWH therapy be discontinued 24 hours prior to elective induction of labour.[58]

3.5 Long-Term Treatment

In patients with permanent or temporary contraindications to oral anticoagulants, LMWHs may be an alternative. However, the safety of LMWHs in this setting has been rarely addressed, since the duration of treatment in clinical trials does not usually exceed 10 days. Different dosages have been used in long-term treatment: some studies used reduced dosages compared with that of the acute phase (enoxaparin sodium 40 mg/day, dalteparin sodium 5000IU once or twice daily, nadroparin calcium 85 IU/kg/day, dalteparin sodium 10 000 IU/day), with similar or better safety than with UFH or warfarin,[60-65] while others administered a therapeutic dosage of tinzaparin sodium 175 IU/kg/day for at least 3 months.[66,67]

A recent review summarised the results from seven of the above-mentioned randomised trials that compared long-term treatment with LMWH versus oral anticoagulants (1379 patients). When all studies were combined, a statistically non-significant reduction in the risk of VTE (OR 0.66; 95% CI 0.41, 1.07) and in the risk of major bleeding (OR 0.45; 95% CI 0.18, 1.11) in favour of LMWH treatment was found. The results of this meta-analysis indicate that a 3-month course of LMWH therapy is as effective and safe in the treatment of VTE as a corresponding period of oral anticoagulant treatment and may thus be considered as a valuable alternative option for patients with contraindications to oral anticoagulants.[68]

4. Monitoring Patients Treated with LMWHs

Because the favourable pharmacokinetics of LMWHs result in a more predictable dose-response anticoagulant effect compared with UFH, monitoring of the anticoagulant effect of LMWHs is generally not thought to be necessary in clinically stable patients. In none of the pivotal trials in which LMWHs were administered once or twice daily at a therapeutic dose, were the anti-Xa activity levels monitored. That is why, to date, it has not been clearly demonstrated in any clinical trial that testing of activity correlates with the outcome. Nevertheless, consistent data and expert recommendations suggest that anti-Xa activity monitoring could improve the safety of LMWHs, especially in select populations with high haemorrhagic risk.[69] Thus, the need for monitoring of LMWH therapy remains a matter of debate.[70,71] To our knowledge, only one prospective study has tested whether dose adjustment of dalteparin sodium 100 IU/kg/12 hours administered for 10 days to patients with DVT to a range of 0.5–1.0 anti-Xa IU/mL does improve efficacy and safety.[72] This study failed to demonstrate that adjustment improves efficacy or safety; unfortunately, it included a small number of patients (60 patients in each arm) and could have been more informative with a greater sample size.

Thus, monitoring of anti-Xa activity may be recommended to detect an overdose and/or accumulation in patients with renal impairment, older patients, patients at the extreme of bodyweight, pregnant women, or in cases of prolonged treatment.[69,73,74]

Monitoring of anti-Xa activity may also allow the detection and correction of misuse, as shown in an observational study of patients receiving tinzaparin sodium; six patients had an anti-Xa activity above the upper limit of the therapeutic range and were receiving a dosage higher than 190 IU/kg/24 hours.[53] The overdose may be associated with an increased risk of bleeding. In the retrospective study of Cestac et al.,[27] three of seven patients who developed a bleeding event had received tinzaparin sodium at a higher dose than is recommended.

Since LMWHs minimally inhibit thrombin activity and cause only mild prolongation of the activated

partial thromboplastin time (aPTT), this test is inappropriate for monitoring anticoagulant effect. If such monitoring is warranted, the only tests currently available are those that measure the plasma anti-Xa activity by chronometric or chromogenic assays.[69,73,75] Consensus guidelines recommend a chromogenic anti-Xa activity assay.[69]

Therapeutic ranges of anti-Xa activity have long been controversial, but are now more clearly defined, with an individual target for each molecule (table V). They are usually defined on the basis of peak anti-Xa activity rather than trough activity. Appropriate timing for blood sampling should thus be respected: 3–4 hours after LMWH injection (in patients receiving two injections daily) and 4–6 hours after injection (in patients receiving one injection daily).

Because the aim of laboratory monitoring is to detect overdoses that are a result of possible accumulation phenomenon, the first blood sample should be obtained after the third or fourth administration (with a regimen of two injections daily), and after the second or third administration (in the case of a regimen with a single daily injection). Repetition of the sampling should be individually discussed according to the clinical status of the patient, the results of the first monitoring and the duration of treatment.[73]

Since each LMWH molecule has a specific phamacodynamic profile, the same dose of two distinct LMWHs generates different plasma anti-Xa activity. The mean peak plasma anti-Xa activity that is generated by some LMWHs used at therapeutic dose is detailed in table V. The upper limit of the therapeutic range for anti-Xa activity levels has been defined for some LMWHs: 1.0 IU/mL for dalteparin sodium (100 IU/kg twice daily), 1.5 IU/mL for tinzaparin sodium (175 IU/kg/day) and 1.8 IU/mL for nadroparin calcium (172 IU/kg/day).

Table V. Mean plasma anti-Xa activities at peak level of some low-molecular weight heparins (LMWHs)[73,76]

LMHW	Anti-Xa activity (IU/mL)
LMWHs administered twice daily (80–100 anti-Xa IU/kg/12h)	
Dalteparin sodium	0.59 ± 0.25
Nadroparin calcium	1.01 ± 0.18
Enoxaparin sodium	1.20 ± 0.17
Certoparin sodium[a]	0.74 ± 0.37
LMWHs administered once daily (175–200 anti-Xa IU/kg/24h)	
Dalteparin sodium	1.05
Nadroparin calcium	1.34 ± 0.15
Tinzaparin sodium	0.87 ± 0.15

a Certoparin sodium was given at a fixed dosage of 8000 anti-Xa IU/12h.[77]

5. Non-Haemorrhagic Adverse Effects of LMWHs

5.1 Heparin-Induced Thrombocytopenia

HIT is a serious, potentially life-threatening, adverse effect of heparins and the diagnosis can be difficult. It is a distinct clinicopathological syndrome, which is caused by platelet-activating antibodies that recognise complexes of platelet factor 4-heparin, and leads to a hypercoagulable state. It represents a unique hypercoagulable state with a spectrum of localised or disseminated intravascular thrombosis that is related to endothelium damage, as well as activated circulating platelets and clotting factors.[78] Its strong association with venous and arterial thrombosis represents a striking paradox.[79] The platelet count typically begins to fall after between 5 and 10 days of heparin treatment.[80] An earlier fall in platelet count on starting heparin therapy can also represent acute HIT, but only if a patient has circulating HIT antibodies resulting from recent heparin exposure. HIT antibodies are transient and become undetectable at a median of 50 days after first testing positively.[80] On rare occasions, HIT begins several days after discontinuing heparin therapy or persists for several weeks even though heparin administration has been stopped.[80]

The frequency of HIT has been shown to be variable and partly depends on the patient population, the type of heparin used and the duration of treatment.[79] LMWHs are usually considered to be less likely to cause HIT than UFH. The strongest evidence that LMWH is associated with a lower frequency of HIT was provided by a randomised trial that directly compared the frequency of HIT between enoxaparin sodium and porcine UFH that was given for postoperative orthopaedic patients.[79] A recent study has investigated the clinical and biological features of HIT caused by LMWHs; the interval between the initiation of heparin and onset of thrombocytopenia was longer with LMWHs than

with UFH, and severe thrombocytopenia (<15g/L) was more frequent with LMWHs.[81]

Thrombocytopenia occurring during treatment was reported in the published clinical trials that compared LMWHs with UFH in the treatment of VTE, but the true incidence of HIT is difficult to assess since criteria for definition and techniques of diagnosis are not always defined. The frequency ranges from 0% to 2.8% for LMWHs and from 0% to 3.5% for UFH.[15,16,82-90] Among the different LMWHs, the frequency for one LMWH changes from one study to another study, making the comparison impossible.

5.2 Osteoporosis

Only long-term use of heparins carries a risk of osteoporosis, with LMWHs carrying a lower risk than UFH. Osteoporosis has mostly been studied in pregnant women receiving UFH for the prevention of VTE. It was shown that bone mineral density of the lumbar spine was significantly lower in patients treated with UFH compared with LMWH (dalteparin sodium) for long-term thromboprophylaxis during and after pregnancy.[91]

In a study of long-term use (3–6 months) of dalteparin sodium (5000IU twice daily) compared with UFH (10 000IU twice daily), 1 of 40 patients and 6 of 40 patients developed spinal fractures, respectively.[64]

5.3 Other Adverse Effects

Elevated transaminase levels associated with the use of LMWHs have been described in a few series. Elevation (2- to 5-fold) was maximal within the first 7 days of therapy and returned to normal within 7–14 days. The incidence rate was found to be between 2% and 5% of patients receiving LMWHs.[92]

Thrombocytosis during treatment with LMWH has been reported in asymptomatic patients.[93]

Conflicting data regarding the effect of LMWHs on serum potassium levels exist. Some show increased levels, whereas others fail to show similar results. To date, the limited numbers of studies of this effect do not warrant routine monitoring of potassium levels in patients receiving LMWH therapy.[94,95]

6. Conclusions

In terms of safety, the use of LMWHs in patients with renal impairment or older patients is the main concern. In these patients, the degree of accumulation varies among the different compounds and may be explained by the specific pharmacodynamic profile of each molecule. In this setting, the decision whether to use reduced initial doses and specific dosage algorithms for LMWHs has yet to be validated in terms of efficacy.

In pregnant women and obese patients, too few data are available to draw any conclusion concerning the comparative safety of the molecules.

Until more data are available concerning these special populations with a high risk of bleeding, monitoring of anti-Xa activity may be recommended in order to detect an overdose and/or accumulation.

It might not seem realistic to conduct clinical trials for each compound in all of the subpopulations mentioned. However, studies that include special population patients are required to make conclusive recommendations concerning the safety and monitoring of the different LMWHs.

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References

1. Hirsh J, Anand SS, Halperin JL, et al. AHA Scientific statement: guide to anticoagulant therapy. Heparin: a statement for healthcare professionals from the American Heart Association. Circulation 2001; 103: 2994-3018
2. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet 2000; 355 (9219): 1936-42
3. Samama MM, Desnoyers P, Gerotziafas GT. Low molecular weight heparins: a comparative review of pharmacodynamic, clinical pharmacology. In: Lugassy G, Brenner B, Schulman S, Samama MM, Cohen M, editors. Thrombosis and antithrombotic therapy. London: Martin Dunitz, 2001: 71-96
4. The Thrombolysis in Myocardial Infarction (TIMI) 11A Trial Investigator. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. J Am Coll Cardiol 1997; 29 (7): 1474-82
5. Bratt G, Tornebohm E, Granqvist S, et al. A comparison between low molecular weight heparin (KABI 2165) and standard heparin in the intravenous treatment of deep venous thrombosis. Thromb Haemost 1985; 54 (4): 813-7

6. Leizorovicz A, Simonneau G, Decousus H, et al. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. BMJ 1994; 309 (6950): 299-304
7. Lensing AW, Prins MH, Davidson BL, et al. Treatment of deep venous thrombosis with low-molecular-weight heparins: a meta-analysis. Arch Intern Med 1995; 155 (6): 601-7
8. Leizorovicz A. Comparison of the efficacy and safety of low molecular weight heparins and unfractionated heparin in the initial treatment of deep venous thrombosis: an updated meta-analysis. Drugs 1996; 52 Suppl. 7: 30-7
9. Siragusa S, Cosmi B, Piovella F, et al. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. Am J Med 1996; 100 (3): 269-77
10. Gould MK, Dembitzer AD, Doyle RL, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. Ann Intern Med 1999; 130 (10): 800-9
11. Rocha E, Martinez-Gonzalez MA, Montes R, et al. Do the low molecular weight heparins improve efficacy and safety of the treatment of deep venous thrombosis? A meta-analysis. Haematologica 2000; 85 (9): 935-42
12. Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000; 160 (2): 181-8
13. van Den Belt AG, Prins MH, Lensing AW, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev 2000; (2): CD001100
14. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med 2004; 140 (3): 175-83
15. Riess H, Koppenhagen K, Tolle A, et al. Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. Thromb Haemost 2003; 90 (2): 252-9
16. Planes A. Review of bemiparin sodium: a new second-generation low molecular weight heparin and its applications in venous thromboembolism. Expert Opin Pharmacother 2003; 4 (9): 1551-61
17. van Dongen CJ, Mac Gillavry MR, Prins MH. Once versus twice daily LMWH for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev 2003; (1): CD003074
18. Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism: a meta-analysis. Thromb Haemost 2001; 86 (4): 980-4
19. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Fragmin and fast revascularisation during instability in coronary artery disease investigators. Lancet 1999; 354 (9180): 708-15
20. Fragmin during instability in coronary artery disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. Lancet 1996; 347 (9001): 561-8
21. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). Circulation 1997; 96 (1): 61-8
22. The FRAXIS study group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX I.S. (Fraxiparine in ischaemic syndrome). Eur Heart J 1999; 20 (21): 1553-62
23. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events study group. N Engl J Med 1997; 337 (7): 447-52
24. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 1999; 100 (15): 1593-601
25. Husted S, Becker R, Kher A. A critical review of clinical trials for low-molecular-weight heparin therapy in unstable coronary artery disease. Clin Cardiol 2001; 24 (7): 492-9
26. Michalis LK, Katsouras CS, Papamichael N, et al. Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: the EVET trial. Am Heart J 2003; 146 (2): 304-10
27. Cestac P, Bagheri H, Lapeyre-Mestre M, et al. Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. Drug Saf 2003; 26 (3): 197-207
28. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16 (1): 31-41
29. Nagge J, Crowther M, Hirsh J. Is impaired renal function a contraindication to the use of low-molecular-weight heparin? Arch Intern Med 2002; 162 (22): 2605-9
30. Cadroy Y, Pourrat J, Baladre MF, et al. Delayed elimination of enoxaparin in patients with chronic renal insufficiency. Thromb Res 1991; 63 (3): 385-90
31. Gerlach AT, Pickworth KK, Seth SK, et al. Enoxaparin and bleeding complications: a review in patients with and without renal insufficiency. Pharmacotherapy 2000; 20 (7): 771-5
32. Brophy DF, Wazny LD, Gehr TW, et al. The pharmacokinetics of subcutaneous enoxaparin in end-stage renal disease. Pharmacotherapy 2001; 21 (2): 169-74
33. Collet JP, Montalescot G, Choussat R, et al. Enoxaparin in unstable angina patients with renal failure. Int J Cardiol 2001; 80 (1): 81-2
34. Sanderink GJ, Guimart CG, Ozoux ML, et al. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. Thromb Res 2002; 105 (3): 225-31
35. Becker RC, Spencer FA, Gibson M, et al. Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. Am Heart J 2002; 143 (5): 753-9
36. Bruno R, Baille P, Retout S, et al. Population pharmacokinetics and pharmacodynamics of enoxaparin in unstable angina and non-ST-segment elevation myocardial infarction. Br J Clin Pharmacol 2003; 56 (4): 407-14
37. Chow SL, Zammit K, West K, et al. Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. J Clin Pharmacol 2003; 43 (6): 586-90
38. Spinler SA, Inverso SM, Cohen M, et al. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J 2003; 146 (1): 33-41

39. Collet JP, Montalescot G, Fine E, et al. Enoxaparin in unstable angina patients who would have been excluded from randomized pivotal trials. J Am Coll Cardiol 2003; 41 (1): 8-14
40. Montalescot G, Collet JP, Tanguy ML, et al. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. Circulation 2004; 110 (4): 392-8
41. Hulot JS, Vantelon C, Urien S, et al. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. Ther Drug Monit 2004; 26 (3): 305-10
42. Goudable C, Saivin S, Houin G, et al. Pharmacokinetics of a low molecular weight heparin (Fraxiparine) in various stages of chronic renal failure. Nephron 1991; 59 (4): 543-5
43. Baumelou A, Singlas E, Petitclerc T, et al. Pharmacokinetics of a low molecular weight heparin (reviparine) in hemodialyzed patients. Nephron 1994; 68 (2): 202-6
44. Hainer JW, Sherrard DJ, Swan SK, et al. Intravenous and subcutaneous weight-based dosing of the low molecular weight heparin tinzaparin (Innohep) in end-stage renal disease patients undergoing chronic hemodialysis. Am J Kidney Dis 2002; 40 (3): 531-8
45. Polkinghorne KR, McMahon LP, Becker GJ. Pharmacokinetic studies of dalteparin (Fragmin), enoxaparin (Clexane), and danaparoid sodium (Orgaran) in stable chronic hemodialysis patients. Am J Kidney Dis 2002; 40 (5): 990-5
46. Swedko PJ, Clark HD, Paramsothy K, et al. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med 2003; 163 (3): 356-60
47. Goldberg TH, Finkelstein MS. Difficulties in estimating glomerular filtration rate in the elderly. Arch Intern Med 1987; 147 (8): 1430-3
48. Bliss MR, Vellupillai S, Julian PA, et al. Measured and predicted creatinine clearance [letter]. Lancet 1987; I (8536): 815
49. Siguret V, Pautas E, Gouin I. Low molecular weight heparin treatment in elderly subjects with or without renal insufficiency: new insights between June 2002 and March 2004. Curr Opin Pulm Med 2004; 10 (5): 366-70
50. Merli GJ. Treatment of deep venous thrombosis and pulmonary embolism with low molecular weight heparin in the geriatric patient population. Clin Geriatr Med 2001; 17 (1): 93-106
51. Mismetti P, Laporte-Simitsidis S, Navarro C, et al. Aging and venous thromboembolism influence the pharmacodynamics of the anti-factor Xa and anti-thrombin activities of a low molecular weight heparin (nadroparin). Thromb Haemost 1998; 79 (6): 1162-5
52. Siguret V, Pautas E, Fevrier M, et al. Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. Thromb Haemost 2000; 84 (5): 800-4
53. Pautas E, Gouin I, Bellot O, et al. Safety profile of tinzaparin administered once daily at a standard curative dose in two hundred very elderly patients. Drug Saf 2002; 25 (10): 725-33
54. Sanderink GJ, Le Liboux A, Jariwala N, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther 2002; 72 (3): 308-18
55. Hainer JW, Barrett JS, Assaid CA, et al. Dosing in heavyweight/obese patients with the LMWH, tinzaparin: a pharmacodynamic study. Thromb Haemost 2002; 87 (5): 817-23
56. Wilson SJ, Wilbur K, Burton E, et al. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. Haemostasis 2001; 31 (1): 42-8
57. Smith J, Canton EM. Weight-based administration of dalteparin in obese patients. Am J Health Syst Pharm 2003; 60 (7): 683-7
58. Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003; 1 (7): 1435-42
59. Bates SM, Greer IA, Hirsh J, et al. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126 Suppl. (3 Suppl.): 627S-44S
60. Lopaciuk S, Bielska-Falda H, Noszczyk W, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. Thromb Haemost 1999; 81 (1): 26-31
61. Das SK, Cohen AT, Edmondson RA, et al. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. World J Surg 1996; 20 (5): 521-6
62. Veiga F, Escriba A, Maluenda MP, et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. Thromb Haemost 2000; 84 (4): 559-64
63. Pini M, Aiello S, Manotti C, et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thromb Haemost 1994; 72 (2): 191-7
64. Monreal M, Lafoz E, Olive A, et al. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994; 71 (1): 7-11
65. Monreal M, Roncales FJ, Ruiz J. Secondary prevention of venous thromboembolism: a role for low-molecular-weight heparin. Haemostasis 1998; 28: 236-43
66. Hull RD, Pineo GF, Mah AF. Home-Lite: safety and efficacy results for a study investigating the long-term out-of-hospital treatment of patients with proximal venous thrombosis using subcutaneous low-molecular-weight heparin versus warfarin [abstract OC1647]. Thromb Haemost 2001 Jul
67. Hull RD, Pineo GF, Mah AF. A randomized trial evaluating long-term low-molecular-weight heparin therapy for three months versus intravenous heparin followed by warfarin sodium [abstract OC395]. J Thromb Haemost 2003 Jul
68. Iorio A, Guercini F, Pini M. Low-molecular-weight heparin for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants. J Thromb Haemost 2003; 1 (9): 1906-13
69. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119 (1 Suppl.): 64S-94S
70. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126 (3 Suppl.): 188S-203S
71. Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. J Thromb Haemost 2004; 2 (4): 551-4
72. Alhenc-Gelas M, Jestin-Le Guernic C, Vitoux JF, et al. Adjusted versus fixed doses of the low-molecular-weight heparin fragmin in the treatment of deep vein thrombosis. Fragmin-Study Group. Thromb Haemost 1994; 71 (6): 698-702
73. Boneu B, de Moerloose P. How and when to monitor a patient treated with low molecular weight heparin. Semin Thromb Hemost 2001; 27 (5): 519-22
74. Hirsh J. Laboratory monitoring of low-molecular-weight heparin therapy. J Thromb Haemost 2004; 2 (6): 1003
75. Duplaga BA, Rivers CW, Nutescu E. Dosing and monitoring of low-molecular-weight heparins in special populations. Pharmacotherapy 2001; 21 (2): 218-34
76. Boneu B, Nguyen F, Cambus J. Difficulties and pitfalls in the monitoring of heparin therapy. Sang Thrombose Vaisseaux 2003; 15 (3): 131-4

77. Harenberg J. Fixed-dose versus adjusted-dose low molecular weight heparin for the initial treatment of patients with deep venous thrombosis. Curr Opin Pulm Med 2002; 8 (5): 383-8
78. Messmore H, Jeske W, Wehrmacher W, et al. Benefit-risk assessment of treatments for heparin-induced thrombocytopenia. Drug Saf 2003; 26 (9): 625-41
79. Lee D, Warkentin T. Frequency of heparin-induced thrombocytopenia. In: Warkentin T, Greinacher A, editors. Heparin-induced thrombocytopenia. New York: Marcel Dekker, 2001: 87-122
80. Warkentin T. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin T, Greinacher A, editors. Heparin-induced thrombocytopenia. New York: Marcel Dekker, 2001: 43-86
81. Gruel Y, Pouplard C, Nguyen P, et al. Biological and clinical features of low-molecular-weight heparin-induced thrombocytopenia. Br J Haematol 2003; 121 (5): 786-92
82. Breddin HK, Hach-Wunderle V, Nakov R, et al. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. N Engl J Med 2001; 344 (9): 626-31
83. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. N Engl J Med 1997; 337 (10): 663-9
84. Koopman MM, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. N Engl J Med 1996; 334 (11): 682-7
85. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996; 334 (11): 677-81
86. Simonneau G, Charbonnier B, Decousus H, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Arch Intern Med 1993; 153 (13): 1541-6
87. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992; 326 (15): 975-82
88. Fiessinger JN, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Thromb Haemost 1996; 76 (2): 195-9
89. Lindmarker P, Holmstrom M, Granqvist S, et al. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thromb Haemost 1994; 72 (2): 186-90
90. Prandoni P, Vigo M, Cattelan AM, et al. Treatment of deep venous thrombosis by fixed doses of a low-molecular-weight heparin (CY216). Haemostasis 1990; 20 Suppl. 1: 220-3
91. Pettila V, Leinonen P, Markkola A, et al. Postpartum bone marrow mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMWHeparin. Thromb Haemost 2002; 87: 182-6
92. Hui CK, Yuen MF, OI-Lin Ng I, et al. Low molecular weight heparin-induced liver toxicity. J Clin Pharmacol 2001; 41 (6): 691-4
93. Liautard C, Nunes AM, Vial T, et al. Low-molecular-weight heparins and thrombocytosis. Ann Pharmacother 2002; 36 (9): 1351-4
94. Abdel-Raheem MM, Potti A, Tadros S, et al. Effect of low-molecular-weight heparin on potassium homeostasis. Pathophysiol Haemost Thromb 2002; 32 (3): 107-10
95. Gheno G, Cinetto L, Savarino C, et al. Variations of serum potassium level and risk of hyperkalemia in inpatients receiving low-molecular-weight heparin. Eur J Clin Pharmacol 2003; 59: 373-7

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