Anticoagulation

Low-Molecular-Weight Heparins in Renal Impairment and Obesity: Available Evidence and Clinical Practice Recommendations Across Medical and Surgical Settings

Edith A Nutescu, Sarah A Spinler, Ann Wittkowsky, and William E Dager

OBJECTIVE: To develop practical recommendations for the use of low-molecular-weight heparins (LMWHs) as prophylaxis and treatment of venous thromboembolism and acute coronary syndromes in patients with impaired renal function or obesity.

DATA SOURCES: Multiple MEDLINE searches were performed (November 2008) to identify studies for inclusion, using a comprehensive list of search terms including, but not limited to, LMWH, enoxaparin, dalteparin, tinzaparin, obesity, weight, renal, kidney, elderly, monitoring, and anti-Xa.

STUDY SELECTION AND DATA EXTRACTION: Only articles published in English that were relevant for this review were included.

DATA SYNTHESIS: In the majority of patients, standardized prophylaxis or treatment doses of LMWHs can be used without the need for monitoring and adjusting regimens. For patients with severe renal impairment (estimated creatinine clearance [CrCl] <30 mL/min), doses of some LMWHs should be adjusted or unfractionated heparin should be used instead. CrCl should be estimated using the Cockcroft-Gault method. Differences are noted in the degree of accumulation of various LMWHs in patients with moderate-to-severe renal impairment, and thus, the degree of dose adjustment may differ among the various LMWHs. Increasing the prophylactic doses of LMWH may be appropriate in morbidly obese patients (body mass index ≥40 kg/m²). The use of total body weight is appropriate for therapeutic doses of LMWH in obese patients. Laboratory monitoring of the anticoagulation effect of LMWHs is generally not necessary, but should be considered in patients with morbid obesity (weight >190 kg), those with severe renal impairment, and those with moderate renal impairment with prolonged (>10 days) LMWH use. When anti-Xa activity is monitored, it should be determined using a chromogenic method and a calibration curve based on the LMWH used.

CONCLUSIONS: Additional data are needed for specific dose guiding in obese and renally impaired patients, who are often excluded from larger clinical trials. Practice recommendations are made based on available evidence and authors' clinical opinions.

KEY WORDS: anti-Factor Xa activity, chronic kidney disease, dalteparin, dosing, enoxaparin, low-molecular-weight heparin, monitoring, obesity, practice recommendations, renal impairment, tinzaparin.

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Standardized prophylaxis or treatment doses of low-molecular-weight heparins (LMWHs) can be used in most patients without dose adjustment. However, there are concerns about whether dose adjustments are needed to optimize anticoagulation in certain patient populations. Specifically, these concerns relate to the potential for increased bleeding due to LMWH accumulation in patients with impaired renal function and about whether and when dose adjustments are needed for obese patients. However, unwarranted down-adjustment of dosing could compromise clinical efficacy.[1]

This article reviews currently available information on the use of LMWHs in patients with impaired renal function or obesity and formulates practical recommendations for dosing and monitoring in these specific subpopulations (Table 1).

LMWH Use in Renally Impaired Patients

LMWHs are excreted via the kidney, resulting in a potential for accumulation in patients with impaired renal function. Due to pharmacologic and pharmacokinetic differences, variation may exist in the rate of accumulation of the different LMWH compounds in patients with renal impairment.[2] LMWH accumulation may increase the risk of major bleeding

Author information provided at the end of the text.

Table 1. Summary of LMWH Dosage Recommendations

Patients	Recommendations	Dalteparin PI	Enoxaparin PI	Tinzaparin PI
Renal impairment	CrCl should be estimated in all pts. who are prescribed LMWH. Pts. with renal impairment require careful observation for signs and symptoms of bleeding. Anti-Xa monitoring can be considered in pts. with severe renal impairment who do not undergo renal replacement therapy.	Anti-Xa may be used to monitor the anticoagulant effect in pts. with severe renal impairment. Use with caution in pts. with severe renal impairment.	Anti-Xa may be used to monitor the anticoagulant effect in pts. with severe renal impairment. Dose reduction in severe renal impairment (CrCl <30 mL/min) is needed.	
VTE prophylaxis	Dose adjustment is generally not needed in pts. with mild-to-moderate renal impairment. Dalteparin and tinzaparin may not need dose adjustment in pts. with severe renal impairment.		30 mg once daily	not indicated
VTE treatment	Use UFH in pts. with severe renal impairment (CrCl <20 mL/min). Extended use (>10 days) of LMWH (enoxaparin) in pts. with moderately impaired renal function (CrCl 30–60 mL/min) may require anti-Xa measurement and close vigilance to rule out drug accumulation.	Monitor anti-Xa levels in pts. with severe renal impairment to dose-adjust to anti-Xa target range of 0.5–1.5 IU/mL.[a]	1 mg/kg once daily	Pts. with severe renal impairment should be dosed with caution.
Treatment NSTEMI	Use UFH in pts. with severe renal impairment (CrCl <20 mL/min).		1 mg/kg once daily	not indicated
Treatment STEMI	Use UFH in pts. with severe renal impairment (CrCl <20 mL/min).	not indicated	Use initial 30 mg iv bolus, followed by 1 mg/kg once daily. Dose reduction is needed in elderly pts.; no initial iv bolus, 0.75 mg/kg every 12 h.	not indicated
Obesity	Anti-Xa monitoring and treatment dose adjustments are generally not necessary for pts. weighing ≤190 kg. Anti-Xa monitoring can be considered in pts. with morbid obesity (BMI >40 kg/m^2).			
VTE prophylaxis	Increase prophylaxis doses in pts. with morbid obesity (BMI >40 kg/m^2).			not indicated
VTE treatment	LMWH dosing should be based on body weight. Dose capping is not recommended. Twice-daily dosing may be preferable for enoxaparin.	Use weight-based dosing, with dose capping at 18,000 IU.[a]		Weight-based dosing is appropriate for heavy/obese pts.
Treatment NSTEMI	LMWH dosing should be based on body weight.	Use weight-based dosing, with dose capping at 10,000 IU.		not indicated
Treatment STEMI	LMWH dosing should be based on body weight.	not indicated	Use weight-based dosing, with dose capping of the first 2 doses at 100 mg.	not indicated
Monitoring	Monitoring of anti-Xa levels is not needed in clinically stable or uncomplicated pts. treated with LMWH. Peak anti-Xa levels should be drawn 4 h after sc injection. Trough anti-Xa monitoring may be used to evaluate accumulation at the end of the dosing interval in pts. with renal impairment. Anti-Xa activity should be determined using a chromogenic method and a calibration curve based on the LMWH used.			

BMI = body mass index; CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; NSTEMI = non–ST-segment elevation myocardial infarction; PI = product information; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin; VTE = venous thromboembolism.
[a]Dalteparin indication for long-term treatment of patients with cancer.

complications.[3] Thus, patients with severe renal impairment treated with LMWHs require careful monitoring for bleeding. It is for this reason that clinical trials of LMWHs generally exclude patients with severe renal impairment (Table 2).[4-24]

Renal function has been classified as: normal glomerular filtration rate (GFR) (≥90 mL/min); mildly decreased GFR (60–89 mL/min); moderately decreased GFR (30–59 mL/min); or severely decreased GFR (15–29 mL/min). Patients with a GFR less than 15 mL/min or on dialysis are considered to have end-stage renal disease and are a separate group from patients with severe renal impairment (Table 3).[25] Creatinine clearance (CrCl) is used as a correlate of GFR and is usually estimated from the Cockcroft-Gault equation, which accounts for serum creatinine (SCr), age, weight, and sex. More recently, the Modification of Diet in Renal Diseases (MDRD) equation[25] has been developed to estimate GFR; this equation takes SCr, age, race, and sex into account (Table 3). However, this method is not accurate for individuals with an estimated GFR greater than 60 mL/min.[26,27] SCr alone is not an accurate method of predicting renal function,[25] especially in the elderly.[28,29] Different studies included in this review used various definitions for groups of patients with reduced renal function. As a result of differences in methods of estimating GFR, variations in the severity scoring of renal failure may arise, resulting in divergent dosing approaches. For dose adjustments, CrCl should be estimated using the Cockcroft- Gault method, in accordance with most clinical trials.[30]

Another controversy in this context is the accuracy of measured anti-Xa activity as a marker for LMWH antithrombotic activity or for risk of bleeding. Recent studies exploring this concept suggest that it may not be reliable in patients requiring renal replacement therapy.[31] Measured anti-Xa activity in patients with renal dysfunction may have wide variability when correlated to estimates of renal function.[32]

PROPHYLACTIC DOSES OF LMWH

Pharmacodynamic Considerations

Pharmacodynamic studies with prophylactic doses of LMWH have generally shown no evidence of LMWH accumulation in patients with mild or moderate impaired renal function. Details of these studies are given in Table 4a.[33-39] Accumulation of enoxaparin has been reported in patients with CrCl less than or equal to 30 mL/min. In a pharmacodynamic study of 12 healthy volunteers and 36 patients with renal impairment given subcutaneous enoxaparin, patients with CrCl less than or equal to 30 mL/min showed a 65% increase in anti-Xa activity at day 4 compared with healthy volunteers.[33] None of the available studies with dalteparin[36-40] or tinzaparin[35] showed evidence of accumulation in patients with renal impairment. However, in most of these studies, patients receiving continuous renal replacement therapy (hemodialysis or peritoneal dialysis) were excluded. In the DIRECT (Dalteparin's Influence on the Renally Compromised: Anti-Ten-A) study with dalteparin, 13 of 138 patients had a CrCl level at baseline of 10 mL/min or less or were on chronic dialysis.[39]

Clinical Evidence

Limited evidence is available on clinical outcomes in patients on prophylactic LMWH doses with renal impairment compared with those who had no renal impairment. Currently available studies of LMWH use in renally impaired patients do not have enough subjects to demonstrate a relationship between anti-Xa levels, bleeding, and thrombosis (Table 4a).[34-37,39]

Consolidation of Data on Prophylactic Doses of LMWH

The available data indicate that the need for adjustment of the prophylactic doses of LMWH may be limited to enoxaparin in patients with severe renal impairment. When enoxaparin is used, a lower prophylactic dose of 30 mg subcutaneously once daily is recommended in patients with severe renal impairment (CrCl <30 mL/min) instead of the typical dose for medical patients or those undergoing abdominal surgery (40 mg once daily), in knee replacement surgery (30 mg every 12 hours), or in hip replacement surgery (30 mg every 12 hours or 40 mg once daily).[41] Dosing adjustments do not appear to be necessary when dalteparin or tinzaparin is used in prophylactic doses. Data on the use of LMWHs in patients with CrCl less than 20 mL/min and on hemodialysis are limited. The above studies are based on short treatment periods (typically 4–10 days). As such, it is unclear whether accumulation in patients with moderate renal impairment can occur when LMWHs are given for extended periods (ie, >10 days). The extended use (>10 days) of any LMWH in patients with moderately impaired renal function (CrCl 30–50 mL/min) may require close monitoring and anti-Xa measurements to rule out drug accumulation.

THERAPEUTIC ANTICOAGULATION

Pharmacodynamic Considerations

At treatment doses, LMWH regimens have the potential to accumulate in the tissues and serum, leading to higher peak and trough anti-Xa levels, especially in severe renal impairment (Table 4b).[3,24,32,40,42-53] A number of studies have consistently demonstrated higher anti-Xa activity in patients with severe renal impairment who are on treatment doses of enoxaparin. In the TIMI-11A (Thrombolysis in Myocardial Infarction) trial in patients with non–ST-

Table 2. Exclusion Criteria for Renal Function and Body Weight in LMWH Trials

Study	LMWH	Pts., N	Age, y	Renal Function Exclusion	Body Weight, kg			Dose Capping
					Exclusion	Median	Maximum	
VTE prophylaxis								
Hull (2000)[4]	dalteparin	1472	63 ± 13[a]	Cr >1.7 mg/dL	≤40	80[b]		
CLOT Lee (2003)[5]	dalteparin	672	50–76	Cr ≥3 × upper limit of normal range	≤40			18,000 IU
PREVENT Leizorovicz (2004)[6]	dalteparin	3706	68 ± 11[a,c]	Cr >2 mg/dL				
ONCENOX Deitcher (2006)[7]	enoxaparin	122	35–87	CrCl ≤30 mL/min	>120			
MEDENOX Samama (1999)[8]	enoxaparin	1102	73 ± 11[a,c]	Cr >1.7 mg/dL				
Comp (2001)[9]	enoxaparin	873	28–90[c]	insufficiency[d]		85[b]	150	
VTE treatment								
Merli (2001)[10]	enoxaparin	900	18–92	Cr >2 mg/dL		80[b]	155	
THESEE Simonneau (1997)[11]	tinzaparin	612	67 ± 16[a]	severe renal failure[d]		74[b]		
Hull (2000)[12]	tinzaparin	200	71, <60 129, ≥60	severe impairment necessitating dialysis				
NSTE-ACS								
FRISC FRISC Study Group (1996)[13]	dalteparin	1506	821, ≤70 677, ≥71	Cr >2 mg/dL		75	125	10,000 IU
FRISC-II FRISC Investigators (1999)[14]	dalteparin	2289	37–91	insufficiency[d]				
FRIC FRIC Investigators (1997)[15]	dalteparin	1482	25–92	insufficiency[d]		73	125	
ESSENCE Cohen (1997)[16]	enoxaparin	3171	mean 64[c] median 65[c]	CrCl <30 mL/min		78	159[e]	
TIMI 11-B Antman. (1999)[17]	enoxaparin	3910	median 66, IQR 56–73[c]	Cr ≥2 mg/dL		77	159[e]	
A to Z Blazing (2004)[18]	enoxaparin	3987	median 61, IQR 52–69[c]	Cr >2 mg/dL				
SYNERGY Ferguson (2004)[19]	enoxaparin	9978	median 68, IQR 61–75[c]	CrCl <30 mL/min		80	196	
EVET Michalis (2003)[20]	enoxaparin tinzaparin	438	enoxaparin 64.4 ± 11.8[a] tinzaparin 65.2 ± 11.3[a]	Cr >200 µmol/L	<40 and >110			
STE-ACS								
ExTRACT Antman (2006)[21]	enoxaparin	20,506	median 59, IQR 51–69[c]	men: Cr >2.5 mg/dL women: >2.0 mg/dL[f]		76		first 2 sc doses after iv 30-mg bolus; maximum 100 mg if <75 y, 75 mg if ≥75 y
ASSENT-3 ASSENT-3 Investigators (2001)[22]	enoxaparin	6095	12.6% >70	men: Cr >221 µmol/L women: >177 µmol/L				first 2 sc doses after iv 30-mg bolus; maximum 100 mg
ASSENT-3-Plus Wallentin (2003)[23]	enoxaparin	1639	62 ± 13[a]	men: Cr >2.5 mg/dL women: >2.0 mg/dL				first 2 sc doses after iv 30-mg bolus; maximum 100 mg

Cr = creatinine; CrCl = creatinine clearance; IQR = interquartile range (Q1-Q3); LMWH = low-molecular-weight heparin; NSTE-ACS = non–ST-segment elevation acute coronary syndromes; STE-ACS = ST-segment elevation acute coronary syndromes; VTE = venous thromboembolism.

[a]Mean ± SD.

[b]Mean body weight.

[c]Data refer to treatment group only.

[d]Not defined in terms of CrCl in study.

[e]Maximum body weight in enoxaparin group for meta-analysis of ESSENCE/TIMI 11-B.[24]

[f]Dose adjustment in patients with CrCl <30 mL/min.

segment elevation acute coronary syndrome (NSTE-ACS) who received enoxaparin, a small substudy of 11 patients with an estimated CrCl of 40 mL/min or less showed a reduction in enoxaparin clearance compared with those with normal renal function (mean CrCl 88 mL/min) (Table 4b).[42] Twice-daily dosing of enoxaparin (1.0 mg/kg) was associated with higher mean anti-Xa activity in patients with estimated CrCl 31–50 mL/min and 11–30 mL/min, compared with those with adequate renal function (estimated CrCl >50 mL/min). This effect was not seen in patients given once-daily enoxaparin (1.5 mg/kg) (Table 4b).[32] A number of studies with treatment doses of enoxaparin have demonstrated an inverse correlation between CrCl and anti-Xa concentrations.[42,45]

One study using data from a trial with tinzaparin for the treatment of patients with deep vein thrombosis found that tinzaparin clearance decreased by about 24% in patients with estimated CrCl less than 30 mL/min compared with those with normal renal function.[48] In contrast, other studies with tinzaparin did not demonstrate a correlation between anti-Xa activity and CrCl (Table 4b).[46,47]

For dalteparin, no significant difference in peak anti-Xa activity was observed between 11 patients with estimated CrCl less than 40 mL/min and 11 control subjects with CrCl greater than 80 mL/min 3–5 hours after the last of 5–6 doses (Table 4b).[40] A comparison of dalteparin (39 units/kg) with enoxaparin (0.7 mg/kg) in patients with end-stage renal disease found no evidence that either agent accumulated following 1–4 weeks of treatment. Anti-Xa activity with dalteparin declined faster than with enoxaparin, suggesting greater dependence of enoxaparin on renal function for removal.[54] Again, these studies did not enroll patients receiving renal replacement therapy.

Clinical Evidence

Renal insufficiency is associated with worse outcomes for patients with venous thromboembolism (VTE) or for those with ACS.[24,49,51-53] In the RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry of patients with acute symptomatic deep vein thrombosis or pulmonary embolism, 1037 patients with CrCl less than 30 mL/min had an increased incidence of fatal bleeding (2.2% vs 0.5%; $p < 0.001$), fatal initial pulmonary embolism (5.2% vs 0.8%; $p < 0.001$), and overall death (25% vs 7.3%; $p < 0.001$) 3 months after diagnosis, compared with 17,214 patients with CrCl greater than 30 mL/min, respectively.[55] Approximately 90% of the patients were initially treated with LMWH.

Patients with ACS and renal impairment have been observed to have an increased risk of both bleeding and ischemic adverse outcomes compared with those with normal renal status, regardless of whether treatment included LMWH or unfractionated heparin (UFH) (Table 4b).[24,49,51-53] Multivariate logistic regression analysis of GRACE (Global Registry of Acute Coronary Events) data comprising 982 patients with ACS and severe renal impairment (estimated CrCl ≤30 mL/min), 3705 with moderate renal impairment (CrCl >30 to ≤60 mL/min), and 7194 with normal renal function found that moderate (adjusted odds ratio [OR_{adj}] 1.58; 95% CI 1.21 to 2.10) and severe (OR_{adj} 3.64; 95% CI 2.64 to 5.01) renal impairment were independent predictors of mortality and in-hospital major bleeding (OR_{adj} 1.32; 95% CI 1.01 to 1.71, and 2.51; 95% CI 1.82 to 3.54, respectively).[51] It is important to consider the cardiorenal syndrome when interpreting cardiovascular outcomes in patients with renal impairment. Cardiorenal syndrome refers to the reciprocal interdependency of the heart and kidney, most clearly seen when 1 of these 2 systems fails and leads to downstream problems in its sister system.[56] This was demonstrated in a trial in which patients with reduced CrCl (<60 mL/min) experienced increased mortality rates, particularly from cardiovascular events (relative risk [RR] 1.41; $p = 0.001$).[57]

The efficacy and safety of enoxaparin in patients with renal impairment have been compared with that of UFH, primarily in the setting of ACS (Table 4b).[24,49,51] In an analysis of data from 143 patients with NSTE-ACS and severe

Table 3. Definition of Renal Function and Assessing Renal Function According to the National Kidney Foundation[25]

Description of renal function	**GFR, mL/min**
Normal GFR	≥90
Mildly decreased GFR	60–89
Moderately decreased GFR	30–59
Severely decreased GFR	15–29
End-stage renal disease	<15 or pt. on dialysis
Method to estimate GFR	**Equation**
Measuring endogenous CrCl (24-h urine collection)	CrCl = (urine creatinine × urine volume)/(1440 × SCr)
Estimating CrCl by Cockcroft-Gault	CrCl = ([140 – age] × weight)/(72 × SCr) (multiply by 0.85 if female)
Modification of Diet in Renal Disease	$GFR = 186 \times SCr^{-1.154} \times age^{-0.203}$ (multiply by 0.742 if female; multiply by 1.210 if African American)

CrCl = creatinine clearance; GFR = glomerular filtration rate; SCr = serum creatinine.

renal impairment, rates of composite death, myocardial infarction (MI), and urgent target vessel revascularization (UTVR), as well as the rates of major bleeding, were similar between enoxaparin and UFH (Table 4b).[24] Another study showed no significant differences in the rates of major bleeding between enoxaparin and UFH in patients with mild, moderate, or severe renal impairment who were receiving full treatment doses of either subcutaneous enoxaparin or intravenous UFH for a variety of indications (Table 4b).[49] In the ExTRACT-TIMI 25 trial of ST-segment elevation MI (STEMI) patients treated with thrombolytics, a net clinical benefit of death, nonfatal repeat MI, or nonfatal major bleeding was demonstrated for subcutaneous enoxaparin over intravenous UFH in patients with estimated CrCl greater than 90 mL/min (5.9% vs 7.9%, respectively; $p < 0.001$) and those with CrCl greater than 60–90 mL/min (10.7% vs 13.0%; $p < 0.01$). However, no significant difference in patients with CrCl 30–60 mL/min (21.3% vs 20.6%; $p > 0.05$) or CrCl less than 30 mL/min (34.9% vs 37.7%; $p > 0.05$) was observed. The net clinical benefits were driven by a reduced rate of death or nonfatal repeat MI that offset higher major bleeding rates (Table 4b). In ExTRACT-TIMI 25, the dose of enoxaparin was prospectively reduced to 1 mg/kg/day for patients with CrCl less than 30 mL/min (pts. with SCr >2.0 mg/dL [women] or >2.5 mg/dL [men] were excluded), and the intravenous bo-

Table 4a. Pharmacodynamic and Clinical Studies on Use of LMWH for VTE Prophylaxis in Renal Impairment

						CrCl, mL/min		
Reference	**LMWH**	**Study n/N[a]**	**Design**	**Dosing**	**Mild Outcome**	**Moderate (50–80)**	**Severe (30–50)**	**(<30)**
Pharmacodynamic outcomes					**Anti-Xa levels**			
Sanderink (2002)[33]	enoxaparin	36/48	prospective cohort	40 mg/day, 4 doses	exposure vs healthy volunteers	20% higher (n = 12; p = 0.10)	21% higher (n = 12; p = 0.10)	65% higher (n = 12; p = 0.0001)
Mahé (2007)[34]	enoxaparin	125	prospective cohort	40 mg/day, <10 days	maximum (mean)	0.60 (n = 28)	0.61 (n = 58)	0.72 (n = 39; p > 0.05 vs all others)
Mahé (2007)[35]	enoxaparin	28	prospective open-label	40 mg/day, ≥8 days	accumulation day 1–8		1.22 (n = 28; p < 0.0001)	
					correlation with CrCl		no correlation (n = 28)	
	tinzaparin	27		4500 IU/day, ≥8 days	accumulation day 1–8		1.05 (n = 27; p = 0.29)	
					correlation with CrCl		no correlation (n = 27)	
Tincani (2006)[36]	dalteparin	115	prospective cohort	5000 IU/day or 2500 IU/day, ≥6 days	mean ± SD	0.030 ± 0.086 (n = 12)	0.033 ± 0.075 (n = 73)	0.048 ± 0.084 (n = 24; p = 0.72)
Rabbat (2005)[37]	dalteparin	19	prospective observational cohort	5000 IU/day	correlation with CrCl	no correlation (n = 19)		
Schmid (2007)[38]	dalteparin	38	prospective observational cohort	not specified, mean 7.5 days	mean (95% CI)	0.46 (0.21 to 0.57) (n = 8)	0.40 (0.19 to 0.87) (n = 13)	0.48 (0.33 to 0.63) (n = 8)
Douketis (2008)[39]	dalteparin	156	prospective open-label cohort	5000 IU/day, until discharge up to 30 days	pts. (n) with trough anti-Xa >0.40 IU/mL			0 (n = 120)
Clinical outcomes					**VTE or major bleeding**			
Mahé (2007)[35]	enoxaparin	28	prospective open-label	40 mg/day, ≥8 days	symptomatic VTE		none (n = 28)	
					major bleeding		1 (n = 28)	
	tinzaparin	27		4500 IU/day, ≥8 days	symptomatic VTE		none (n = 27)	
					major bleeding		2 (n = 27)	
Mahé (2007)[34]	enoxaparin	125		40 mg/day, <10 days	serious bleeding	anti-Xa levels similar between pts. with and without bleeding (n = 125; p = 0.77)		
Tincani (2006)[36]	dalteparin	115	prospective cohort	5000 IU/day or 2500 IU/day, ≥6 days	major bleeding or VTE	none (n = 115)		
Rabbat (2005)[37]	dalteparin	19	prospective observational cohort	5000 IU/day	VTE	1 (n = 19)		
					major bleeding	1 (n = 19)		
Douketis (2008)[39]	dalteparin	156	prospective open-label cohort	5000 IU/day, until discharge up to 30 days	DVT (95% CI)			5.1 (2.5 to 10.2) (n = 156)
					major bleeding (95% CI)			7.2 (4.0 to 12.8) (n = 156)

CrCl = creatinine clearance; DVT = deep-vein thrombosis; LMWH = low-molecular-weight heparin; VTE = venous thromboembolism.
[a]n/N = renally impaired patients/total study population. If the total study population included only renally impaired patients, just 1 number is given.

Table 4b. Pharmacodynamic and Clinical Studies on Use of Treatment Doses of LMWH in Renal Impairment

Reference	LMWH (or comparator)	n/N[a]	Dosing	Study Design	Outcome	CrCl, mL/min			
						Normal (>80)	Mild (50–80)	Moderate (30–50)	Severe (< 30)
Pharmacodynamic outcomes					**Anti-Xa**				
Bazinet (2005)[32]	enoxaparin	233	1.5 mg/kg once daily	prospective, open-label	mean (95% CI)	1.10 (1.00 to 1.20) (n = 38)		1.21 (1.09 to 1.33) (n = 27)	1.18 (0.92 to 1.44) (n = 14)
					supra-target (>2.0 IU)	0%		4%	0%
			1 mg/kg q12h		mean (95% CI)	1.06 (0.99 to 1.14) (n = 68)		1.25 (1.12 to 1.39) (n = 27)	1.27 (1.15 to 1.40) (n = 22)
					supra-target (>1.1 IU)	40%		63%	77%
Becker (2002)[42]	enoxaparin	445	initial 30-mg iv bolus, 1 or 1.25 mg/kg sc q12h	RCT subgroup	peak level ± SD (3rd dose)	1.25 ± 0.37 (n = 273)	1.41 ± 0.44[b] (n = 149)		1.58 ± 0.58[c] (n = 11)
					trough level ± SD (3rd dose)	0.58 ± 0.35	0.71 ± 0.42[b]		0.83 ± 0.49[c]
Bruno (2003)[43]	enoxaparin		initial 30-mg iv bolus, 1 or 1.25 mg/kg sc q12h	modeling study	LMWH clearance vs normal			17% decrease	27% decrease
Hulot (2005)[44]	enoxaparin	350/532	mean 0.83 ± 0.19 mg/kg q12h	retrospective analysis	LMWH clearance vs normal	(n = 182)	17% decrease (n = 192)	31% decrease (n = 103)	44% decrease (n = 55)
Chow (2003)[45]	enoxaparin	18	1 mg/kg q12h	prospective cohort	mean	0.91 (n = 13)			1.34 (n = 5) (p < 0.05)
					correlation with CrCl	yes			
Pautas (2002)[46]	tinzaparin	200	175 IU/kg once daily	prospective cohort	correlation with CrCl	no			
Shprecher (2005)[40]	dalteparin	11/22	100 IU/kg q12h	prospective, open-label cohort	anti-Xa	0.55 ± 0.20 (n = 11)			0.47 ± 0.25[b] (n = 11)
Siguret (2000)[47]	tinzaparin	30	175 IU/kg	prospective cohort	correlation anti-Xa and CrCl?	no			
Barrett (2001)[48]	tinzaparin	131/187	175 IU/kg once daily		LMWH clearance				24% decrease
Clinical outcomes					**Ischemic events or major bleeding**				
VTE/ACS treatment									
Lim (2006)[3]	enoxaparin		therapeutic dose adjusted to CrCl or anti-Xa	meta-analysis	major bleeding	2.4%			8.3%
					major bleeding	1.9%			0.9%

ACS = acute coronary syndromes; CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; RCT = randomized clinical trial; VTE = venous thromboembolism.

[a]n/N = renally impaired patients/total study population. If the total study population included only renally impaired patients, just 1 number is given.

[b]CrCl 40–80 mL/min.

[c]CrCl ≤40 mL/min.

(continued on page 1071)

lus dose of 30 mg was omitted for patients older than 75 years, which may have improved the safety of enoxaparin.[52]

In a subanalysis of the OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) study of patients with NSTE-ACS and renal impairment, enoxaparin was associated with similar rates of death, MI, or refractory ischemia compared with fondaparinux and higher rates of major bleeding at 9 days (Table 4b).[53] However, 56% of patients treated with enoxaparin received additional UFH during percutaneous coronary intervention (PCI), compared with 21% of patients treated with fondaparinux. The dual antithrombin therapy in the enoxaparin group may have contributed to the difference in bleeding rates observed between the 2 treatments.[58]

Consolidation of Data on Therapeutic Doses of LMWH

The importance of an increased risk of bleeding with decreasing renal function must be weighed against the benefits of LMWH treatment and the possible increased risk of death and ischemic events from underdosing. Alternative treatment options, such as UFH, should be considered in patients with severe renal impairment. UFH also has the potential benefit that its effects can be easily reversed by the use of protamine sulfate, which is only partially effective in reversing the effects of LMWHs.[59] Adjusted treatment doses of enoxaparin have been approved by the Food and Drug Administration (FDA) for use in patients with severe renal impairment (Table 1).

Table 4b. Pharmacodynamic and Clinical Studies on Use of Treatment Doses of LMWH in Renal Impairment (continued)

Reference	LMWH (or comparator)	n/N[a]	Dosing	Study Design	Outcome	CrCl, mL/min			
						Normal (>80)	Mild (50–80)	Moderate (30–50)	Severe (<30)
ACS									
Spinler (2003)[24]	enoxaparin	69/3501	1 mg/kg q12h	RCT retrospective subgroup	death, MI, urgent revascularization	15.7%			18.8%
					major bleeding	1.2%			7.5%
	UFH	74/3468	iv, dose adjusted		death, MI, urgent revascularization	18.4%			32.4%
					major bleeding	1.0%			5.8%
	enoxaparin/ UFH	143/ 6969			death, MI, urgent revascularization	17.0%			25.9%
					major bleeding	1.1%			6.6%
Thorevska (2004)[49]	enoxaparin	620	1 mg/kg sc q12h	retrospective cohort	major bleeding		12.4%[d]	22.5%[e]	36.6%[f]
	UFH		iv, dose adjusted				16.9%[d]	41.8%[e]	30.7%[f]
Collet (2003)[50]	enoxaparin	174/515	1 mg/kg q12h (65% of dose for CrCl ≤30 mL/min, adjusted to anti-Xa levels)	prospective cohort	death, MI	5.6%			25.0%
					major or minor bleeding	2.4%			4.7%
Collet (2005)[51]	enoxaparin	4687/ 11,881	NA, registry data	prospective cohort	death	1.75%[g]		4.30%[h]	15.35%
					major bleeding	1.24%[g]		2.03%[h]	5.9%
	UFH		NA, registry data		death	2.74%[g]		7.8%[h]	18.58%
					major bleeding	2.18%[g]		4.36%[h]	9.29%
Bruno (2003)[43]	enoxaparin	448	initial 30 mg iv bolus, 1 or 1.25 mg/kg sc q12h	modeling study	major bleeding			OR 2.4	OR 3.8
Fox (2007)[52,53]	enoxaparin		initial 30 mg iv bolus, 1 mg/kg sc q12h[i]		death, MI	5.1%[j]	9.6%[k]	19.4%[h]	33.0%
					major bleeding	1.2%[j]	2.3%[k]	3.5%[h]	5.7%
	UFH				death, MI	7.3%[j]	12.1%[k]	19.4%[h]	37.7%
					major bleeding	0.8%[j]	1.6%[k]	1.9%[h]	2.8%
	enoxaparin/ UFH				death, MI	6.2%[j]	10.9%[k]	19.4%[h]	35.4%
					major bleeding	1.0%[j]	1.9%[k]	2.7%[h]	4.2%

ACS = acute coronary syndromes; CrCl = creatinine clearance; GFR = glomerular filtration rate; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NA = not available; OR = odds ratio; RCT = randomized clinical trial; UFH = unfractionated heparin.

[a]n/N = renally impaired patients/total study population. If the total study population included only renally impaired patients, just 1 number is given.

[d]GFR 41–60 mL/min.

[e]GFR 21–40 mL/min.

[f]GFR ≤20 mL/min.

[g]CrCl >60 mL/min.

[h]CrCl 30–60 mL/min.

[i]Dose adjustments for CrCl <30 mL/min and ≥75 years of age.

[j]CrCl >90 mL/min.

[k]CrCl 60–90 mL/min.

Reduced Dosing Strategies

Several strategies for reducing treatment doses of enoxaparin have been proposed for renally impaired patients (Table 5).[21,41,44,50,60-62] A meta-analysis of clinical studies in patients with severe renal impairment has suggested that a reduced dose of enoxaparin in this group of patients avoids the excess of major bleeding events seen with standard doses (Table 4b).[3] Reduced dosing strategies focus on either reducing the frequency of dosing from twice daily to once daily[21,60] or reducing the amount of drug given each time with twice-daily dosing,[44,50,61,62] A reduced amount of drug will primarily lower peak anti-Xa activity, while reduced frequency of dosing will mainly lower the mean concentration. The practical application of a dosing strategy using slightly lower maintenance doses of enoxaparin (0.75 and 0.50 mg/kg every 12 hours in moderate and severe renal impairment, respectively) resulted in 80% of patients with moderate renal impairment and 60% of those with severe renal impairment being within the target anti-Xa range after the third dose (Table 5).[61] Doses were further adjusted when anti-Xa levels remained outside the target range.

The use of once-daily enoxaparin dosing (1.5 mg/kg) did not lead to significant accumulation of enoxaparin (as indicated by peak anti-Xa levels) in patients with moderate or severe renal impairment, whereas off-target anti-Xa levels were significantly more likely to occur during a twice-daily regimen (1 mg/kg twice daily) (OR 2.28; 95% CI 1.25 to 4.16).[32] This effect was also seen in patients who received a reduced twice-daily regimen (0.75 mg/kg twice daily). Because the number of patients in this latter group was small (n = 5), it remains unclear whether the apparent advantage of once-daily dosing (1.5 mg/kg) is due to the higher total daily dose with the twice-daily regimen (1.0 mg/kg twice daily) or the once-daily dosing interval.

The ExTRACT-TIMI 25 trial included a reduced dosing protocol for STEMI patients with severe renal impairment (CrCl <30 mL/min) and for the elderly (aged >75 y).[21] For patients with estimated CrCl less than 30 mL/min, the enoxaparin dose was modified to 1 mg/kg/day. In a subanalysis of patients with severe renal impairment in this trial, no statistically significant differences were shown between enoxaparin (n = 106) and UFH (n = 106) in death or nonfatal MI (33.0% vs 37.7%, respectively) or major bleeding (5.7% vs 2.87%, respectively).[52] However, more data on adjusted doses of LMWH in severe renal impairment are needed.

ELDERLY PATIENTS

As renal function deteriorates with age,[28,63] the use of LMWH in this population can be of concern. In a study of 854 outpatients aged 65 years or more, 28.9% had an estimated GFR of 50 mL/min or less, and a minority (6.4%) of elderly patients showed severe renal impairment (GFR ≤30 mL/min).[29]

The correlation between anti-Xa activity and CrCl was weak or nonexistent in elderly patients given prophylactic doses of enoxaparin or tinzaparin, or treatment doses of tinzaparin.[35,46,47] In a study of 189 patients older than 75 years treated with enoxaparin (40 mg once daily) for VTE prophylaxis (50% presented with renal impairment), 4% of patients had peak anti-Xa activity greater than 1.0 IU/mL.[64] The 1 patient in the study experiencing a major bleeding event was not from the high anti-Xa activity group. This does not rule out the possibility of accumulation of anti-Xa activity in elderly patients with severe renal impairment; therefore, renal function should be carefully assessed in this population.

In a subanalysis of the ExTRACT-TIMI 25 trial, efficacy and safety outcomes were analyzed for 17,947 STEMI patients less than 75 years old and 2532 patients aged 75 years or older.[65] Dose reductions were made for the elderly

Table 5. Various Reduced Dosing Strategies Employed by Diverse Studies for Treatment Doses of LMWH Enoxaparin in Patients with Severe Renal Impairment[a]

Study	CrCl, mL/min	Dosing Strategy
Treatment dose	normal	1 mg/kg q12h sc
Lovenox,[41] Lachish (2007)[60]	<30	1 mg/kg/day
Hulot (2005)[44]	<30	first dose 1 mg/kg sc, followed by 0.66 mg/kg q12h sc
Kruse (2004)[61]	<30	first dose 1 mg/kg sc, followed by 0.50 mg/kg q12h sc
Green (2005)[62]		1 mg/kg q12h sc for the first 48 h, then:
	10–19	0.3 mg/kg q12h sc
	20–29	0.4 mg/kg q12h sc
Collet (2003)[50]	≤30	65% of the recommended dose, with monitoring and dose-adjustment if needed
STEMI treatment dose	normal	first dose 30 mg iv, followed by 1 mg/kg q12h sc
ExTRACT Antman (2006)[21]	<30	first dose 30 mg iv, followed by 1 mg/kg/day sc

CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; STEMI = ST-segment elevation myocardial infarction.
[a]Creatinine clearance <30 mL/min.

patients by eliminating the initial 30-mg intravenous bolus dose and reducing the subcutaneous dose from 1 mg/kg to 0.75 mg/kg every 12 hours. The dose cap of 100 mg for the first 2 subcutaneous injections was also reduced in the elderly, to 75 mg. The relative risk of death or MI was lower in patients on enoxaparin compared with those on UFH, an effect that was more pronounced in the younger group (RR 0.80; 95% CI 0.72 to 0.87; $p < 0.0001$) compared with the older group (RR 0.94; 95% CI 0.82 to1.08; $p_{interaction} = 0.10$). A relative increase in TIMI major bleeding risk with enoxaparin compared with UFH was demonstrated in patients younger than 75 years (RR 1.67; 95% CI 1.31 to 2.13; $p < 0.0001$), but was not shown in the older patients (RR 1.15; 95% CI 0.74 to 1.78; $p = 0.53$). Thus, dose modification may ameliorate bleeding complications and may be routinely considered in elderly patients with STEMI.

CONTINUOUS RENAL REPLACEMENT THERAPY

Multiple forms of renal replacement therapy exist, ranging from intermittent procedures lasting 3–4 hours to continuous approaches. Different filters may be used that can influence drug removal or impact platelet activity. Patients on continuous renal replacement therapy (CRRT) are considered to have end-stage renal disease and are a separate group from patients with severe renal impairment. LMWH is infrequently used for therapeutic anticoagulation in patients who require CRRT; these patients generally receive UFH because of frequent changes in the treatment approach and the ability to control any bleeding complications. A meta-analysis of small studies indicated that for the prevention of thrombosis of the extracorporeal dialysis circuit in CRRT, LMWH could be as safe and effective as UFH.[66] Some removal of enoxaparin from the CRRT circuit does occur, but it is not yet clear whether dose adjustments for the treatment of critically ill patients undergoing CRRT are needed.[67]

DIFFERENCES BETWEEN AGENTS

One study suggested that tinzaparin is less sensitive to renal function compared with enoxaparin.[35] The anti-Xa accumulation factor (ratio of maximal anti-Xa activity on days 1 and 8) of a prophylactic dose over 8 days in 55 patients aged 75 years or older with estimated CrCl 20–50 mL/min was 1.05 ($p = 0.29$) in patients given tinzaparin (4500 IU/day) and 1.22 ($p < 0.0001$) in patients given enoxaparin (40 mg/day). Potential changes in renal function over time were not determined. Insufficient data are available on dalteparin and tinzaparin for a meta-analysis on the relationship between renal impairment, anti-Xa activity, and major bleeding risk.[3] Although limited, current data suggest that in contrast with enoxaparin, other LMWHs such as dalteparin and tinzaparin may result in limited or no accumulation in patients with severe renal impairment.

DOSING RECOMMENDATIONS IN PATIENTS WITH RENAL IMPAIRMENT

Prophylaxis or Treatment Doses

1. Patients with renal impairment given LMWH require careful assessment for potential bleeding risks and observation for signs and symptoms of bleeding.[3,24,49,51-53]
2. Data on the use of LMWH in patients with CrCl less than 20 mL/min and hemodialysis are very limited.[a]
3. We suggest that CrCl should be estimated using the Cockcroft-Gault equation in all patients who are prescribed LMWH.[30] The use of estimated GFR for dosing calculations should be avoided until experience with this approach in clinical trials and outcomes on efficacy and risk have been done.[a]
4. Extended use (>10 days) of enoxaparin in patients with moderately impaired renal function (CrCl 30–60 mL/min) may require anti-Xa measurement, close vigilance, and adjustment of dose if accumulation is noted.[51,a]

Prophylaxis Doses

1. For patients with mild-to-moderate renal impairment (CrCl 30–90 mL/min), adjustment of prophylaxis doses of LMWH is generally not needed.[33,34,36,37]
2. When using LMWH for prophylaxis in patients with severe renal impairment (CrCl <30 mL/min) with enoxaparin, consider a lower dose of 30 mg subcutaneously once daily.[41] With dalteparin or tinzaparin, dose adjustment may not be needed with short-term use (<10 days); for longer-term use, consider monitoring of anti-Xa activity and adjust dose if accumulation is noted.[a]

Treatment Doses

1. For treatment doses in patients with CrCl less than 20 mL/min, consider weight-based, adjusted-dose intravenous UFH, titrated to a target activated partial thromboplastin time. Although UFH has not shown better safety or efficacy in patients with renal impairment compared with LMWH,[24,49,51] clinical data on adjusted doses of LMWH are limited in this patient group.[3,52,53,65]
2. For treatment doses of enoxaparin in patients with CrCl less than 30 mL/min, significant accumulation of LMWH can occur if doses are not adjusted.[32,42-45,48] The doses can be adjusted according to manufacturer-recommended dosage regimens for patients with CrCl less than 30 mL/min[41] and greater than 20 mL/min.[a]

[a]This recommendation is based on the authors' experience and clinical practice, because published data to support this recommendation are lacking.

3. For use of enoxaparin in elderly patients (≥75 y) with STEMI, we recommend dose adjustment to 0.75 mg/kg every 12 hours in addition to a maximum dose limit of 75 mg.[30,65]
4. For treatment doses of dalteparin or tinzaparin in patients with CrCl less than 30 mL/min, limited data suggest no or a lower degree of accumulation.[40,47]

LMWHs in Obese Patients

Patients at extremes of body weight are rarely reported in clinical trials and registries involving LMWHs for the treatment of VTE or ACS and are sometimes excluded from trials.[68] Some clinical trials have included patients weighing more than 150 kg and up to a maximum reported weight of 196 kg (Table 2).[69-71] Pharmacodynamic studies have included patients weighing up to 190 kg.[72] Obesity is defined by the US National Institutes of Health as a body mass index (BMI) of 30 or more, and morbid obesity as BMI greater than or equal to 40. The appropriate dosing of LMWHs in these patients is a controversial issue.

A retrospective study of enoxaparin for VTE prophylaxis found, in a logistic regression analysis, that although the relationship between body weight and thrombosis did not reach significance (p = 0.07), there was a strong relationship between BMI and thrombosis (p = 0.0002).[73] Although this finding exemplifies the importance of distinguishing between body weight and BMI wherever possible, many studies of LMWHs discuss body weight rather than BMI and may, therefore, include different patients.

Table 6a. Pharmacodynamic and Clinical Studies on Use of LMWH for Venous Thromboembolism Prophylaxis in Obese Patients

Study	Pts.	LMWH	n/N[a]	Dosing	Study Design	Definition of Obese	Outcome	Nonobese	Obese
Pharmacodynamic outcomes							**Anti-Xa levels**		
Frederiksen (2003)[74]	surgical	enoxaparin	NA/19	40 mg (single)	prospective cohort		correlation with body weight	negative correlation	
Simone (2008)[75]	bariatric surgery	enoxaparin		40 mg q12h vs 60 mg q12h, 3 doses	prospective cohort		mean subtherapeutic (<0.18 units/mL) supratherapeutic (>0.44 units/mL)		0.21 units/mL vs 0.43 units/mL p < 0.001 44% vs. 0% p = 0.02 0% vs 57%
Borkgren-Okonek (2008)[76]	bariatric surgery	enoxaparin	223	40 mg bid if BMI ≤50 kg/m² vs 60 mg bid if BMI >50 kg/m²	prospective open-label		4 h after 3rd dose		0.32 IU/mL vs 0.26 IU/mL
Clinical outcomes							**VTE or major bleeding**		
Kucher (2005)[77]	medically ill	dalteparin placebo	558/3706 560/3706	5000 units/day	RCT retrospective subgroup	men: BMI ≥30 kg/m² women: BMI ≥28.6 kg/m²	VTE major bleeding VTE major bleeding	2.8% 1.6% 5.2% 0.3%	2.8% 0% 4.3% 0.7%
Samama (1995)[73]	orthopedic surgery	enoxaparin	NA/817	40 mg/day	retrospective analysis	BMI >32 kg/m²	VTE bleeding[b]	16.7% no relationship with body weight	31.8% (p < 0.001 vs nonobese)
Scholten (2002)[78]	bariatric surgery	enoxaparin	481	30 mg q12h 40 mg q12h	prospective cohort	mean BMI 50–51 kg/m²	VTE major bleeding VTE major bleeding		5.4%[c] 1.1% 0.6%[c] 0.3%
Escalante-Tattersfield (2008)[79]	bariatric surgery	enoxaparin	618	40 mg q12h	retrospective	BMI >35 kg/m²	VTE postoperative bleeding		0.16% 1.6%
Kardys (2008)[80]	bariatric surgery	enoxaparin	31	40 mg q12h	retrospective chart review	mean BMI 71 kg/m² (38–107)	VTE		9.5%

BMI = body mass index; LMWH = low-molecular-weight heparin; NA = not available; RCT = randomized clinical trial; VTE = venous thromboembolism.

[a]n/N = obese patients/total study population. If the total study population included only obese patients, just 1 number is given.

[b]Bleeding not defined as major or minor.

[c]Significant difference in VTE rate with 30-mg dose versus 40-mg dose; p < 0.01.

VTE PROPHYLAXIS

For VTE prophylaxis, fixed doses of enoxaparin, dalteparin, and tinzaparin are typically used, regardless of total body weight. Concerns have been expressed that these fixed doses may be inadequate in obese patients (Table 6a).[73-80]

Pharmacodynamic Considerations

An inverse correlation between anti-Xa levels and body weight was shown during the first 10 hours after dosing with a fixed prophylactic dose of enoxaparin (40 mg subcutaneously) in patients undergoing surgery whose weights were approximately 50–150 kg. This suggested that patients at extremes of body weight may not develop adequate anti-Xa levels.[74]

Clinical Evidence

Some clinical studies with dalteparin or enoxaparin have suggested that higher fixed doses may be appropriate in morbidly obese patients and that weight-based dose adjustments should be investigated (Table 6a).[73-80] In a retrospective subgroup analysis of 1118 obese, hospitalized, medically ill patients, a fixed dose of dalteparin prophylaxis was effective in reducing VTE compared with placebo in nonobese patients (RR 0.53l; 95% CI 0.34 to 0.82) and seemed effective in obese patients, although the confidence interval indicated this not to be significant (RR 0.64; 95% CI 0.32 to 1.38).[77] This was largely due to no reduction in VTE with dalteparin in the highest weight group (BMI ≥40 kg/m^2; RR >1.0). Dalteparin was not associated with an increase in major bleeding compared with placebo in obese patients ($p > 0.99$), but did show a trend for increased bleeding in nonobese patients ($p = 0.07$) (Table 6a). Similarly, a study of patients undergoing orthopedic surgery and given enoxaparin prophylaxis found a higher thrombosis rate in obese patients compared with nonobese patients ($p < 0.001$).[73] There was no relationship between weight and bleeding (Table 6a). A higher dose of enoxaparin was more effective in reducing VTE in patients undergoing bariatric surgery; only 1 patient in each group developed bleeding complications (Table 6a).[78] In another analysis of 668 morbidly obese patients undergoing bariatric surgery, a strategy of early administration of thromboprophylaxis perioperatively given 40 mg every 12–24 hours postoperatively, followed by extended use of 30 mg/day for an additional 10 days, was associated with the fewest thromboembolic events.[81] These studies indicate that the use of a slightly higher fixed prophylactic dose of LMWH or longer duration of prophylaxis in patients with morbid obesity may be warranted.

Therapeutic Anticoagulation

For treatment doses, weight-based dosing of enoxaparin, dalteparin, and tinzaparin is used. However, debate has arisen whether dosing based on total body weight may lead to over-anticoagulation and an increased bleeding risk in patients with a high body weight. Adjusting LMWH doses in these patients through techniques such as capping of body weight at the higher extremes of weight and adjustments according to anti-Xa monitoring has been investigated.

Pharmacodynamic Considerations

The distribution of LMWHs to the intravascular compartment, instead of tissues and body fat, suggests that ideal body weight or lean body mass rather than total body weight may be better predictors of appropriate LMWH treatment doses.[82,83] However, the majority of pharmacodynamic studies (with dalteparin, enoxaparin, and tinzaparin), suggest that weight-based dosing of LMWH for treatment of VTE should be based on total body weight (Table 6b).[10,13,15,24,32,48,72,84-89] In a dalteparin pharmacodynamic analysis, total body weight ($r^2 = 0.39$) and adjusted body weight ($r^2 = 0.32$) were found to correlate better with dalteparin clearance than did lean body weight ($r^2 = 0.01$) in a linear regression analysis.[85] Several pharmacokinetic studies have also indicated that capping weight–based doses of dalteparin, tinzaparin, or enoxaparin in obese patients is inappropriate, as there was little or no indication of a cumulative effect when patients were given uncapped doses of dalteparin with body weights up to 190 kg,[72] tinzaparin with weights up to 165 kg (BMI 61 kg/m^2),[48,87] or enoxaparin with weights to up 159 kg.[32]

Clinical Evidence

In the RIETE registry of patients with acute VTE, most (82%) of whom were initially treated with LMWH, there were no significant differences between obese and nonobese patients in rates of recurrent VTE or major bleeding during the first 15 days of treatment (Table 6b).[89] However, mean daily doses of LMWH (per kg total body weight) were substantially lower in those weighing more than 100 kg (mean dose 148 IU/kg) compared with those weighing 50–100 kg (mean dose 181 IU/kg). This suggests that, in practice, doses appear to have been capped.

A retrospective chart review of 193 obese patients with acute VTE suggested that dalteparin dosing can be based on total body weight without dose-capping, although this study had no comparator group (Table 6b).[10] In a prespecified subgroup analysis of obese patients with VTE, VTE seemed to recur more often among those treated with enoxaparin once daily than twice daily, although this was not statistically significant. This difference in recurrence rates suggests that obese patients should not be treated with a once-daily dosing strategy of enoxaparin, although this also may reflect the benefits of a higher total daily dose (2 mg/kg total per day) in high-risk patients.

Table 6b. Pharmacodynamic and Clinical Studies on Use of Treatment Doses of LMWH in Obese Patients

Study	LMWH (or comparator)	n/N[a]	Dosing	Study Design	Definition of Obese	Outcome	Nonobese	Obese
Pharmacodynamic outcomes						**Anti-Xa levels**		
Smith (2003)[84]	dalteparin	21	196.5 units/kg once daily 126.2 units/kg q12h	retrospective open-label	>90 kg	mean		0.9 SD ± 1.1 1.1 SD ± 0.23
Yee (2000)[85]	dalteparin	10/20	200 IU/kg/day or 120 IU/kg q12h	pharmacodynamic	BMI ≥30 kg/m^2	volume of distribution	8.36 (n = 10)	12.36 (n = 10; p = 0.11 vs nonobese)
Wilson (2001)[72]	dalteparin	37	200 IU/kg once daily	prospective cohort	100–120% ideal body weight 120–140% ideal body weight >140% ideal body weight	mean		1.01 (95% CI 0.89 to 1.13) (n = 13) 0.97 (95% CI 0.85 to 1.09) (n = 14) 1.12 (95% CI 0.96 to 1.28) (n = 10)
Sanderink (2002)[86]	enoxaparin	24/48	1.5 mg/kg sc once daily	pharmacodynamic	BMI 30–40 kg/m^2		(n = 24)	14–19% higher vs nonobese (n = 24; p < 0.05)
Bazinet (2005)[32]	enoxaparin	81/233	1.5 mg/kg once daily 1 mg/kg bid	prospective open-label	BMI >30 kg/m^2	mean	1.13 (95% CI 1.04 to 1.22) 1.12 (95% CI 1.03 to 1.20)	1.15 (95% CI 1.02 to 1.28) 1.17 (95% CI 1.08 to 1.25)
Hainer (2002)[87]	tinzaparin	35 37	175 IU/kg 75 IU/kg	pharmacodynamic	100–160 kg	mean	0.87 (95% CI 0.78 to 0.96) 0.30 (95% CI 0.28 to 0.32)	0.81 (95% CI 0.76 to 0.86) 0.34 (95% CI 0.303 to 0.375)
Barrett (2001)[48]	tinzaparin	NA/425	175 IU/kg once daily	data analysis of 2 RCTs	BMI >30 kg/m^2	LMWH clearance		22% decrease
Clinical outcomes								
VTE treatment						**VTE or major bleeding**		
Al-Yaseen (2005)[88]	dalteparin	193	200 IU/kg once daily 100 IU/kg q12h	retrospective chart review	>90 kg kg/m^2	recurrent VTE major bleeding recurrent VTE major bleeding		1.6% (95% CI 0.2 to 5.8) 0.8% (95% CI 0.02 to 4.5) 1.4% (95% CI 0.03 to 7.6) 1.4% (95% CI 0.03 to 7.6)
Merli (2001)[10]	enoxaparin	900	1 mg/kg once daily 1.5 mg/kg q12h	RCT	men: BMI >26.9 kg/m^2, women: BMI >27.2 kg/m^2	recurrent VTE	4.4% 2.9%	7.3% 3.4%
	UFH		adjusted				4.1%	2.5%
RIETE registry Barba (2005)[89]	NA	294/8845	different doses	registry analysis	>100 kg	recurrent VTE major bleeding	1.0% 1.3%	0.7% (OR 0.7; 95% CI 0.2 to 2.7 vs nonobese) 1.0% (OR 0.8; 95% CI 0.2 to 2.5 vs nonobese)
ACS						**Ischemic events or major bleeding**		
Klein (1997)[15]	dalteparin	NA/1482	days 1–6: 120 IU/kg q12h days 7–45: 7500 IU once daily	RCT subgroup analysis	BMI >26	death, MI, UR	15.7%	8.4%
	placebo						13.3%	11.4%
FRISC FRISC Investigators (1996)[13]	dalteparin	731/1497	120 IU/kg q12h (10,000 IU cap)	RCT subgroup analysis	BMI >26	death, MI	0.8%	2.5%
	placebo						5.5%	4.0%
Spinler (2003)[24]	enoxaparin	921/3516	1 mg/kg q12h	RCT subgroup analysis	BMI ≥30	death, MI, UR major bleeding	16.1% 1.6%	14.3% 0.4%
	UFH	918/3481	adjusted doses			death, MI, UR major bleeding	19.2% 1.0%	18.0% 1.2%
	enoxaparin/UFH					death, MI, UR major bleeding	16.2% 0.8%	17.6% (p = 0.39 vs nonobese) 1.3% (p = 0.12 vs nonobese)

ACS = acute coronary syndromes; BMI = body mass index; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NA = not available; OR = odds ratio; RCT = randomized clinical trial; UFH = unfractionated heparin; UR = urgent revascularization; VTE = venous thromboembolism.
[a]n/N = obese patients/total study population. If the total study population included only obese patients, just 1 number is given.

A subgroup analysis comparing obese and nonobese patients with NSTE-ACS from the ESSENCE and TIMI 11-B trials showed comparable rates of composite death, MI, UTVR, and major bleeding (Table 6b).[24] When comparing enoxaparin dosed according to actual body weight with UFH, rates of the composite of death, MI, and UTVR were lower with enoxaparin, both in nonobese and obese patients. Major bleeding was similar between enoxaparin and UFH for both nonobese and obese patients (Table 6b). Based on these results, dosing of LMWHs according to total body weight seems to be appropriate in the management of NSTE-ACS.

It has been suggested that the dose of enoxaparin used for patients with NSTE-ACS who weigh more than 100 kg should be capped,[90] but clear evidence to support this view is limited. In the FRISC trial, dalteparin was compared with placebo in patients with NSTE-ACS whose total body weight ranged from 47 to 125 kg, but with a maximum dose of 10,000 IU every 12 hours.[13] At 6 days, patients weighing less than 76 kg demonstrated a 1.3% incidence of death or MI, compared with 2.2% in patients weighing more than 76 kg. A similar relationship was seen for patients with BMI less than 26 versus those with BMI greater than 26 kg/m² (Table 6b). Major bleeding rates were not reported for the subgroups. These data suggest that dose capping is inappropriate in such patients. These trials were performed prior to the widespread use of several important agents, such as clopidogrel, and increased use of PCI, limiting their validity to determine dose relationship to efficacy and safety in the contemporary management era.[91]

Dosing Recommendations in Obese Patients

1. Increasing VTE prophylactic doses of LMWHs by 30% may be appropriate in morbidly obese patients (BMI ≥40 kg/m²).[73,74,77,78]
2. Until further information is available, LMWH dosing should be based on total body weight for the treatment of obese patients.[24,85]
3. Until further information is available, once-daily treatment dosing strategies for enoxaparin in obese patients (BMI >27 kg/m²) with VTE may be best avoided.[10]
4. Once-daily treatment dosing strategies for dalteparin (200 IU/kg daily) and tinzaparin (175 IU/kg daily) in obese patients with VTE appear to be appropriate.[a]
5. Capping of LMWH doses does not appear to be needed in the treatment of VTE.[a] For appropriate dose capping when using LMWH in ACS, refer to the specific product specification.[13,21,41,92]
6. Anti-Xa monitoring for dosing adjustments is not necessary for patients weighing up to 190 kg.[32,48,72,87,a]
7. For patients weighing more than 190 kg,[b] if anti-Xa monitoring is *available*, we suggest initiating LMWH dosing based on total body weight and consider adjusting dosing based on anti-Xa levels.[a]
8. For patients weighing more than 190 kg,[b] if anti-Xa monitoring is *unavailable*, we suggest initiating LMWH dosing based on total body weight, and adjusting doses downward if bleeding complications occur.a

Plasma Anti-Xa Activity for Laboratory Monitoring of LMWHs

LMWHs have predictable pharmacodynamic profiles and therapeutic windows wide enough to standardize dosing, without adjustments necessary based on serum concentrations, in most cases. In select circumstances, however, monitoring of plasma anti-Xa concentrations may be helpful to determine whether dosing is achieving concentrations within target ranges.

POPULATIONS IN WHOM LABORATORY MONITORING OF LMWH MAY BE CONSIDERED

Studies have suggested that laboratory monitoring may help to achieve optimal enoxaparin dosing in subsets of patients in settings such as renal impairment[93-95]; pregnancy[94,96]; morbid obesity or low body weight[94,95]; coronary interventional procedures[97,98]; LMWH needed for prolonged periods; thrombosis in those who are refractory to or unable to tolerate warfarin; those who are at particularly high risk of bleeding; neonates and children; and recurrent thrombosis despite LMWH therapy.[94]

ANTI-XA MONITORING

As a result of the higher Xa:IIa ratio of LMWHs, plasma anti-Xa levels have been used as markers of LMWH activity. Although correlation data with clinical outcomes are still limited, anti-Xa levels have been related to survival and efficacy in patients with NSTE-ACS. In 803 patients with NSTE-ACS who were treated with enoxaparin (1 mg/kg subcutaneously every 12 hours, with dose reductions at the discretion of the physician), those with anti-Xa levels below 0.5 IU/mL 4–6 hours after 2 or more injections were more than 3 times as likely to die within the first 30 days than were those whose peak anti-Xa levels were in the target range (0.5–1.2 IU/mL; p = 0.004).[1] In this study, the low anti-Xa levels were related to inappropriate low dosing.

It has been suggested that the incidence of bleeding is increased when anti-Xa levels are high. When patients

[a]This recommendation is based on the authors' experience and clinical practice, because published data to support this recommendation are lacking.

[b]The 190-kg weight limit is based on pharmacodynamic studies that have included patients weighing up to 190 kg.

with acute VTE were treated with dalteparin for 5–10 days, bleeding occurred in 11% (21/188) of those with a mean peak anti-Xa level (over the study period) of 0.8 IU/mL or less and in 40% (2/5) of those with a mean anti-Xa level greater than 0.8 IU/mL (p = 0.05).[99] However, other studies have failed to demonstrate a relationship between anti-Xa levels and bleeding, although this may also be partly the result of limited data.[1,100]

Determination of anti-Xa levels has not been standardized, and there is large variability in reported anti-Xa values between laboratories.[101] Clot-based anti-Xa assays may underestimate anti-Xa activity relative to results derived using chromogenic methods,[102,103] and some assays may be influenced by the anti-IIa activity of the LMWH being measured.[104] Additional variability between available assays may result from including antithrombin in the method, should low antithrombin levels be present, or from administration of sources of antithrombin, such as fresh frozen plasma. Results for specific LMWH products can vary considerably depending on the method and instrument used. A comparison of 3 different chromogenic methods for determining anti-Xa levels in 41 patients on dalteparin, for example, gave different values with each method: mean values were 0.27, 0.30, and 0.21 U/mL.[105] Anti-Xa levels further depend on time of assessment after LMWH administration.

Several authors have proposed alternative methods of measuring enoxaparin anticoagulation to allow rapid point-of-care testing, which are largely based on clotting times rather than anti-Xa activity.[31,97,98,106-108] However, while point-of-care tests offer potential clinical and economic benefits, there have been concerns regarding the accuracy of these devices[109] and many have been removed from the market or are otherwise unavailable in the US.[110,111]

TARGET ANTI-Xa RANGES FOR LMWHS

Anti-Xa activities measured at the time of peak plasma concentration yield the best correlation with clinical effect, assuming a dosing interval of every 12–24 hours. The time to maximal concentration for the LMWHs dalteparin, tinzaparin, or enoxaparin (given once or twice daily) is between 3 and 5 hours in healthy individuals, but can range from 1 to 5 hours,[94,112-115] coinciding closely with peak antithrombotic activity.[112]

Target anti-Xa levels for LMWHs are not well defined, but some studies have suggested target levels (Table 7).[1,94,95,104,116] Target prophylactic anti-Xa concentrations may be based on the thrombotic risk (Table 7).[104] A target peak anti-Xa of 0.6–1.0 IU/mL (4 h after subcutaneous injection) is suggested for twice-daily administration of LMWH, and 1.0–2.0 IU/mL for once-daily administration of LMWH in VTE treatment.[94,95]

A study of enoxaparin in patients with NSTE-ACS that demonstrated increased mortality at low anti-Xa activities reinforced the view that an anti-Xa level of at least 0.5 IU/mL should be attained in these patients.[1] This study did not provide a corresponding reinforcement of the upper limit of the target anti-Xa range, as high anti-Xa levels were unrelated to bleeding events.

Trough anti-Xa monitoring may be used to evaluate accumulation at the end of the dosing interval in patients with severe renal impairment.[93] For twice-daily dosing, the sample should be taken 12 hours after a dose, immediately preceding the next dose, and may be considered to be elevated if it exceeds 0.5 IU/mL. In a retrospective study of 72 patients with NSTE-ACS and severe renal impairment (CrCl <30 mL/min), mean trough anti-Xa level was 0.72 IU/mL with twice-daily dosing (1 mg/kg) and 0.40 IU/mL

Table 7. Target Anti-Xa Ranges

Indication	LMWH	Standard Dosing	Peak Level Range, IU/mL	Mean at 4 h, IU/mL
VTE prophylaxis	dalteparin	2500 IU/day 5000 IU/day	moderate risk: 0.01–0.25 high risk: 0.2–0.5	
	enoxaparin	30 mg q12h 40 mg/day	highest risk: 0.5–1.2[104]	
	tinzaparin[a]			
VTE treatment	enoxaparin	1 mg/kg q12h 1.5 mg/kg/day	0.6 –1.0[94,95] 1.0 –2.0[94,95]	
	dalteparin			1.05[95]
	tinzaparin	175 IU/kg/day		0.85[95]
NSTE-ACS	enoxaparin	1 mg/kg q12h	0.5 –1.20[1]	1.20 ± 0.17[116]
	dalteparin	120 IU/kg q12h (maximum dose 10,000 IU)		0.59 ± 0.25[116]
	tinzaparin[a]			

LMWH = low-molecular-weight heparin; NSTE-ACS = non–ST-segment elevation acute coronary syndromes; VTE = venous thromboembolism.
[a]Not indicated.

with once-daily dosing, suggesting that once-daily dosing is appropriate in patients with severe renal impairment.[93] Although trough levels may be more indicative of accumulation of anti-Xa activity, their clinical significance is not yet clear and needs further investigation.

Recommendations for Laboratory Monitoring of LMWHs

1. Monitoring of anti-Xa levels is not needed in clinically stable or uncomplicated patients treated with LMWH.[95]
2. Laboratory monitoring of the anticoagulant effect of LMWH may be considered in patients with morbid obesity, severe renal impairment, pregnancy, pediatrics, and unexpected thromboembolic complications.[93-95] The usefulness of laboratory monitoring is undetermined in patients undergoing renal replacement therapy.
3. There is no clear consensus on the therapeutic range for anti-Xa activity in patients receiving prophylactic or treatment doses of LMWH for either venous or ACS indications. We suggest that generally, peak concentrations of 0.2–0.4 IU/mL for VTE prophylaxis, 0.5–1.0 IU/mL for VTE treatment with twice-daily dosing regimens and 1.0–2.0 IU/ml with once-daily dosing regimens, and 0.5–1.5 IU/mL for use in ACS should be the targets.[a]
4. Peak anti-Xa levels should be drawn 4 hours following subcutaneous injection.[94,112-115]
5. Trough anti-Xa monitoring may be used to evaluate accumulation at the end of the dosing interval in patients with renal impairment.[93,a]
6. Anti-Xa activity should be determined using a chromogenic method and a calibration curve based on the LMWH used.[94,102,103]
7. Once anti-Xa levels are obtained, there is no recommended method for adjusting doses to achieve a desired anti-Xa concentration. We suggest that the nomogram in Table 8 be applied for treatment doses of LMWH.[2,117,a]

[a]This recommendation is based on the authors' experience and clinical practice, because published data to support this recommendation are lacking.

Summary

Information on the use of LMWHs in patients with impaired renal function or obesity is incomplete. Available studies vary in methodology and outcomes, which complicates their interpretation. Clinical practice recommendations were lacking for these patients and clinical practice is highly inconsistent. Based on available information, we have formulated practical recommendations for dosing and monitoring of LMWH in these specific subpopulations (Table 1). Recommendations based on our experience and clinical practice remain to be confirmed in well-designed studies. These clinical practice recommendations may aid clinicians in the use of LMWHs in these difficult-to-manage patient populations.

Edith A Nutescu PharmD FCCP, Clinical Associate Professor; Director, Antithrombosis Center, Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago

Sarah A Spinler PharmD FCCP BCPS (AQ Cardiology), Professor of Clinical Pharmacy, Department of Pharmacy Practice, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, PA

Ann Wittkowsky PharmD CACP FASHP FCCP, Clinical Professor of Pharmacy, School of Pharmacy, University of Washington, Seattle, WA

William E Dager PharmD FCSHP, Pharmacist Specialist, University of California Davis Medical Center, Sacramento, CA

Reprints: Dr. Nutescu, Department of Pharmacy Practice, College of Pharmacy, The University of Illinois at Chicago, 833 S. Wood St., MC 886, Rm. 164, Chicago, IL 60612, fax 312/413 4805, enutescu@uic.edu

Dr. Nutescu is a consultant for Baxter and Eisai and a member of the speakers' panel for Eisai and sanofi-aventis.

Dr. Spinler is a consultant for sanofi-aventis and The Medicines Company and a member of the speakers' panel for Bristol-Myers Squibb, sanofi-aventis, and GlaxoSmithKline.

Table 8. Sample LMWH Dosing Nomogram for Treatment Doses of Enoxaparin

Anti-Xa Level (U/mL)	Hold Next Dose	Dosage Change	Next Anti-Xa Level
<0.35	no	increase by 25%	4 h after next dose
0.35–0.49	no	increase by 10%	4 h after next dose
0.5–1.0	no	no	next day, then in 1 wk, then monthly
1.1–1.5	no	decrease by 20%	before next dose
1.6–2.0	3 h	decrease by 30%	before next dose and 4 h after next dose
>2.0	until anti-Xa <0.5 U/mL	decrease by 40%	before next dose and q12h until anti-Xa <0.5 U/mL

LMWH = low-molecular-weight heparin.
Reproduced from Monagle et al. *Chest* 2001;119(suppl 1):344-70, with permission from the American College of Chest Physicians,[117] adapted according to Nutescu et al.[2]

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Uso de Heparinas de Bajo Peso Molecular en Insuficiencia Renal u Obesidad: Evidencia y Recomendaciones Clínicas para Pacientes de Medicina y Cirugía

EA Nutescu, SA Spinler, A Wittkowsky, y WE Dager

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EXTRACTO

OBJETIVO: Formular recomendaciones prácticas para el uso de heparinas de bajo peso molecular (LMWHs) para la profilaxis y tratamiento de tromboembolismo venoso y síndrome coronario agudo en pacientes con insuficiencia renal u obesidad.

FUENTES DE INFORMACIÓN: Se realizaron varias búsquedas en MEDLINE (noviembre 2008) para identificar estudios, utilizando una lista comprensiva de términos clave que incluyeron, pero no se limitó a: LMWH, enoxaparin, dalteparin, tinzaparin, obesity, weight, renal, kidney, elderly, monitoring y anti-Xa.

SELECCIÓN DE ESTUDIOS Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Sólo se incluyeron artículos publicados en el idioma inglés que fueran relevantes a esta revisión de la literatura.

SÍNTESIS DE LA INFORMACIÓN: La profilaxis o tratamiento con dosis estandarizadas de LMWHs puede ser utilizada en la mayoría de los pacientes sin necesidad de monitoreo o ajustes en el régimen. En pacientes con insuficiencia renal severa (depuración estimada de creatinina [CrCl] <30 mL/min) las dosis de algunas LMWHs deben ser ajustadas, o en su lugar utilizar heparina no fraccionada. La CrCl debe ser estimada utilizando el método Cockcroft-Gault. Se observaron diferencias en la acumulación de varias de las LMWHs en pacientes con insuficiencia renal moderada o severa, así como diferencias en la necesidad de ajuste en la dosis entre las distintas LMWHs. Un aumento en la dosis de LMWHs para la profilaxis de tromboembolismo venoso puede ser apropiado en pacientes con obesidad mórbida (índice de masa corporal ≥40 kg/m²). El uso del peso total del paciente es apropiado al determinar las dosis terapéuticas de LMWHs para pacientes obesos. Generalmente no es necesario el monitoreo del efecto en la anticoagulación con pruebas de laboratorio pero pudiera ser considerado en pacientes con obesidad mórbida (peso >190 kg), pacientes con insuficiencia renal severa y pacientes con insuficiencia renal moderada y uso prolongado (>10 días) de LMWHs. Cuando se provea monitoreo a la actividad del antifactor Xa, se debe utilizar el método cromogénico y una curva de calibración basada en la LMWH utilizada.

CONCLUSIONES: Se necesita información adicional para desarrollar guías específicas de dosificación para pacientes obesos y pacientes con insuficiencia renal, los cuales son excluidos frecuentemente de los estudios clínicos a gran escala. Las recomendaciones realizadas están basadas en la evidencia disponible y en la opinión clínica de los autores.

Traducido por Astrid J García-Ortiz

Données Probantes et Recommandations Quant à l'Utilisation des Héparines de Faible Poids Moléculaire dans un Contexte d'Insuffisance Rénale et d'Obésité

EA Nutescu, SA Spinler, A Wittkowsky, et WE Dager

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RÉSUMÉ

OBJECTIF: Développer des lignes directrices quant à l'utilisation des héparines de faible poids moléculaire (HFPM) pour le traitement et la prophylaxie des thromboembolies et du syndrome coronarien aigu chez des patients souffrant d'obésité ou d'insuffisance rénale.

SOURCES D'INFORMATION: Des recherches dans la banque de données MEDLINE ont été effectuées au mois de novembre 2008 pour identifier les études pertinentes selon les mots-clés suivants: héparine de faible poids moléculaire, énoxaparine, daltéparine, tinzaparine, obésité, poids, rénal, rein, personnes âgées, surveillance, et anti-Xa.

SÉLECTION DE L'INFORMATION: Seuls les articles publiés en langue anglaise et jugés pertinents ont été évalués pour cette revue.

RÉSUMÉ: L'utilisation des HFPM, quelle soit à titre prophylactique ou thérapeutique, ne requiert pas, pour la majorité des patients, un monitorage particulier et un ajustement posologique. Les patients souffrant d'insuffisance rénale sévère (telle que définie par une clairance de la créatinine estimée par la méthode de Cockcroft-Gault et inférieure à 30 mL/min) peuvent toutefois nécessiter, selon la nature de l'HFPM utilisé, un tel ajustement ou même requérir l'utilisation de l'héparine non fractionnée. Des différences dans le degré d'accumulation des HFPM ont été notées chez les patients souffrant d'insuffisance rénale modérée à sévère résultant en des ajustements posologiques différents selon la nature de l'HFPM utilisée. Il peut s'avérer appropriée d'augmenter les doses prophylactiques des HFPM chez les patients souffrant d'obésité morbide (tel que défini par un indice de masse corporelle supérieur ou égal à 40 kg/m²). L'utilisation du poids corporel total semble adéquate pour établir les doses thérapeutiques des HFPM chez les patients obèses. Le monitorage de l'effet anticoagulant des HFPM n'est pas généralement nécessaire mais devrait être considéré chez les patients souffrant d'insuffisance rénale sévère, d'obésité morbide, les patients pesant plus de 190 kg, et les patients avec une insuffisance rénale modérée devant recevoir un traitement de plus de 10 jours d'HFPM. L'activité anti-Xa devrait être déterminée selon une méthode chromogénique si la nécessité d'un tel monitoring est jugée nécessaire, et la courbe de calibration établie selon l'HFPM qui est utilisée par le patient.

CONCLUSIONS: Des données additionnelles sont requises afin de mieux guider l'établissement de la posologie optimale des HFPM chez les patients souffrant d'insuffisance rénale ou d'obésité, ces 2 populations ayant été souvent exclues des études cliniques. Les recommandations énoncées dans cette revue proviennent essentiellement des données probantes disponibles et des opinions cliniques des auteurs.

Traduit par Sylvie Robert