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# Low-molecular-weight heparin in patients with renal insufficiency

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## Summary

*Background:* Low-molecular-weight heparins (LMWH) have been shown to be safer, more effective and more convenient than unfractionated heparin (UFH) in many clinical situations. However, their use is limited in patients with renal insufficiency (RI) due to bioaccumulation.

*Method:* The literature is critically reviewed and known pharmacokinetic properties are summarised. An approach to using LMWH in patients with RI is proposed on the basis of currently available evidence.

*Results and discussion:* Pharmacokinetic data of commonly used LMWH and of UFH are summarised in respect of RI. Most data are known on enoxaparin. A dose reduction is recommended in patients with severe RI. Limited data on dalteparin and tinzaparin suggest that there is less bioaccumulation. However, further studies are needed, in respect of long-term use and clinical end-points in particular. There are no data on certoparin and only very limited data on nadroparin. A detailed approach is suggested for the use of LMWH in patients with severe RI. Briefly: (1) before using LMWH, evaluate the patient's renal function, its expected course, imminent interventions, and general bleeding risk; (2) prefer LMWH to UFH in view of better efficacy and lower bleeding risk in general; (3) however, prefer i.v. UFH to s.c. LMWH if a patient is unstable, is awaiting emergency interventions, or has a high bleeding risk, since UFH can be stopped more quickly due to i.v. administration, has a shorter half-life time, and can be effectively antagonised; (4) prefer a well documented LMWH; use established dosing schemes; (5) monitor LMWH with peak anti-Xa levels in patients with severe RI regularly, and adjust dose to be in target range; (6) do not use LMWH in patients with severe RI if there is no possibility of measuring anti-Xa levels.

*Conclusions:* LMWH may be considered for patients with severe RI. However, experience, judicious choice and careful monitoring of patients with severe RI treated with LMWH are necessary.

*Key words: kidney disease; low-molecular-weight heparin; pharmacokinetics; renal insufficiency; unfractionated heparin*

## Introduction

Low-molecular-weight heparins (LMWH) have been shown to be at least as efficient and safe as, and more convenient than, unfractionated heparin (UFH) for prophylaxis and treatment of venous thromboembolism (VTE) and for therapy of acute cardiovascular diseases [1–8]. LMWH have been shown to be associated with better outcome and/or less risk of bleeding than UFH in VTE prophylaxis for orthopaedic, surgical and medical patients [2], in treatment of VTE [3, 9] and acute coronary syndrome (ACS) [10, 11], and in special patient groups such as cancer patients [12]. Long-

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**Abbreviations**

| | |
|---|---|
| ACS | acute coronary syndrome |
| anti-Xa | anti-factor Xa activity |
| APTT | activated partial thromboplastin time |
| AUC | area under the curve |
| CI | confidence interval |
| CrCl | creatinine clearance |
| DVT | deep vein thrombosis |
| eq. | equation |
| ICU | intensive care unit |
| i.v. | intravenously |
| LMWH | low-molecular-weight heparin |
| MDRD | modification of diet in renal disease |
| R | bioaccumulation factor |
| RI | renal insufficiency |
| s.c. | subcutaneously |
| $\tau$ | tau, dosing interval |
| $t_{½}$ | apparent elimination half-life time |
| U | international units |
| UFH | unfractionated heparin |
| VTE | venous thromboembolism |

term administration of LMWH has been shown to be advantageous for VTE prophylaxis in surgical [13] and medical [14] inpatients, and in patients with cancer [12].

LMWH have excellent bioavailability of >85% after s.c. injection; in contrast, s.c. administered UFH has low bioavailability of only 15–40% with wide interindividual variability [15]. Furthermore, LMWH have a linear elimination pharmacokinetics [15] which renders their pharmacodynamic effect highly predictable and therefore safe in most situations, without the need for coagulation tests to monitor efficacy or safety [16]. The risk of heparin-induced thrombocytopenia is lower for LMWH than for UFH [17, 18]. Therefore, LMWH have replaced UFH in most situations [8, 19, 20]. LMWH are among the most used drugs in hospitals, e.g. about 60% of medical inpatients should have a VTE prophylaxis [21] according to current guidelines [2, 22].

However, there are situations such as renal insufficiency (RI, see table 1), under- or overweight, pregnancy, or childhood, in which the pharmacokinetics of LMWH is less well known and the benefit of the use of LMWH less clear. This review focuses on the use of LMWH in patients with RI. Renal insufficiency is a frequent condition in hospitalised patients. About a quarter of medical in-house patients of a tertiary care hospital have been found to have at least moderate RI; about 10% have severe RI [23].

The use of LMWH instead of UFH has been shown to be effective and safe in preventing extracorporeal circuit thrombosis during haemodialysis in patients with end-stage renal failure [24, 25], and LMWH have been widely used in dialysis centres for years. This intermittent use of LMWH has not been reported to involve increased bleeding complications compared to UFH used otherwise [24]. However, the adequate dosing of LMWH is less clear for non-dialysis patients with impaired renal function. Furthermore, there are scant data on the use of LMWH in patients on peritoneal dialysis.

UFH is eliminated by (i) a rapid dose-dependent saturable mechanism and (ii) a slower first-order clearance mechanism [15]. In contrast, LMWH are known to be metabolised less by the reticuloendothelial system (i) and to depend mainly on the non-saturable renal mechanism (ii) [15]. However, e.g. dalteparin, enoxaparin, and nadroparin have various ratios of renal drug clearance in relation to total drug clearance [15]: dalteparin 3%, enoxaparin 6–8%, nadroparin 4%.

Although an animal model has shown that kidneys clear 69% of the administered radioactively marked dalteparin [26], it should be borne in mind that most of this radioactivity detected in the urine is related to non-functional metabolites, since anti-Xa activity of the urine is less than 10% of the applied dose in healthy volunteers [27], which further decreases the influence of renal function on the risk of bioaccumulation.

The ratio of renal clearance in respect of total drug clearance is lower for LMWH with higher mean molecular weight. It can therefore be postulated that the clearance of LMWH with larger molecules such as dalteparin or tinzaparin is less dependent on renal function than it is for LMWH with lower mean molecular weight, such as enoxaparin or nadroparin [1].

In conclusion, LMWH must be individually analyzed and cannot be discussed as a group of drugs concerning pharmacokinetics in patients with RI.

## Bleeding risk versus drug efficacy

Bleeding is the major complication risk of both UFH and LMWH [28–31]. Renal function has been shown to decrease with age [23]. In addition, age has been shown to be an independent risk factor for major bleeding [28].

Bleeding risk is increased in patients with impaired renal function [32] regardless of the anticoagulant used [7, 30, 33]. Causes of bleeding in patients with severe RI are multifactorial and are incompletely understood [32]. A meta-analysis of enoxaparin studies showed a relative risk of major bleeding events in patients with severe RI of 2.25 (95% CI 1.19–4.27) compared to patients with better renal function [34].

Bleeding risk has been shown to be lower with LMWH than with UFH in general [28], but this is less evident in patients with severe RI. A meta-analysis has shown no difference in bleeding complications of LMWH and UFH for intermittent use in haemodialysis [24]. A registry study on therapy of VTE in patients with severe RI has reported no difference concerning fatal bleedings in patients anticoagulated with LMWH compared with those on UFH; however, the use of UFH has been associated with a significantly higher rate of fatal pulmonary embolism if compared to LMWH [9]. Another registry of patients with ACS has reported a trend to lower mortality and lower in-hospital major bleeding in patients with severe RI on LMWH compared to UFH [10]. A trend towards higher mortality with UFH compared to LMWH in patients with severe RI has also been reported by a sub-group analysis of two randomised controlled trials [7].

Thorevska et al. reported a significantly higher incidence of *minor bleeding* events (IDR 2.54, 95% CI 1.01–6.36) in patients with a GFR ≤20 ml/min anticoagulated with enoxaparin compared with UFH [33]. Nevertheless, the incidence of *major bleeding* events was comparable. Further,

enoxaparin with known bioaccumulation in RI and clear recommendations for dose reductions was used as the LMWH in this study. The study contained no information on dosage; a potential risk of overdosing may be due to missed dose adjustments. No pharmacokinetic data such as anti-Xa levels were shown which might help to verify this possibility. These results of increased bleeding rates may therefore not be transferable to other settings or other LMWH, in particular because other LMWH are known with less bioaccumulation in patients with severe RI.

In conclusion, there is no strong evidence concerning the bleeding risk with LMWH or UFH in patients with severe RI. However, there are several indicators that LMWH are not only equal to UFH but actually safer in patients with severe RI, as they have been shown to be in patients with better renal function.

Dose reductions may be considered to decrease bleeding risk [1]. However, reducing the risk of bleeding may increase the risk of losing therapeutic efficacy. Reduced enoxaparin doses with peak anti-Xa levels below 0.5 U/ml involve a higher risk of death and recurrent myocardial infarction at 30 days in patients with ACS [35]. A certain level of anti-Xa activity must be achieved, since too low doses of enoxaparin have been shown to be as ineffective as placebo in preventing thromboembolic complications [36]. Furthermore, a registry on patients with severe RI treated for VTE has documented that the risk was higher for a fatal thromboembolic event than for fatal bleeding [9]. Dose adjustment algorithms must therefore aim to minimise both the risk of bleeding and the risk of thromboembolic complications. Additionally, regular monitoring of anti-Xa levels is necessary [37].

## Evaluation of renal function

Official guidelines [38] stratify renal function into 5 stages (table 1). Glomerular filtration rate (GFR) or creatinine clearance (CrCl) can be estimated in steady state situations although there is ongoing discussion concerning the use of measured CrCl instead [39–41], and which formula is best in which situation [42, 43]. It is well known that renal function cannot be evaluated by serum creatinine alone.

The equation by Cockcroft and Gault [44] (adjusted to SI units) is very often used to estimate CrCl:

$$\text{(eq. 1)}\quad CrCl\ [ml/min] = gender \cdot \frac{(140 - age\ [years]) \cdot weight\ [kg]}{serum\ creatinine\ [\mu mol/l]}$$

with *gender* = 1.04 for women and *gender* = 1.23 for men

Its accuracy may be increased for under- or overweight people by adjusting it to standard body surface 1.73 m² using a formula by Du Bois and Du Bois to calculate body surface [45]:

$$\text{(eq. 2)}\quad std.\ CrCl\ [ml/min/1.73m^2] = \frac{1.73 \cdot 10\,000}{71.84\ (weight[kg])^{0.425} \cdot (height[cm])^{0.725}} \cdot CrCl$$

A newer equation by the Modification of Diet in Renal Disease (MDRD) Study Group [38] (adjusted to SI units) has been shown to estimate GFR more accurately, especially when GFR is <60 ml/min/1.73 m²:

$$\text{(eq. 3)}\quad GFR\ [ml/min/1.73m^2] = 32{,}788\ (serum\ creatinine\ [\mu mol/l])^{-1.154} \cdot (age\ [years])^{-0.203} \cdot (0.742\ if\ female) \cdot (1.210\ if\ African\text{–}American)$$

The GFR estimated at hospital admission may not remain stable. Renal function needs to be regularly re-evaluated. Pharmacokinetic studies of LMWH should therefore consider changes of renal function over time, especially if they are designed to study a longer period.

**Table 1**

Official classification of chronic kidney disease of the National Kidney Foundation (NKF) [38].

| Stage | GFR (ml/min/1.73 m²) | Description |
|---|---|---|
| 1 | ≥90 | Kidney damage with normal or increased GFR |
| 2 | 60–89 | Kidney damage with mildly decreased GFR |
| 3 | 30–59 | Moderately decreased GFR |
| 4 | 15–29 | Severely decreased GFR |
| 5 | <15 or dialysis | Kidney failure |

GFR, glomerular filtration rate

## Monitoring of LMWH

The use of LMWH need not be monitored by anticoagulation tests in most situations due to their predictable pharmacokinetic properties [1, 8, 16, 46]. Coagulation tests such as thrombin time or activated partial thromboplastin time (APTT) used for UFH cannot be used for LMWH monitoring. A chromogenic assay measuring the activity of UFH, LMWH or fondaparinux in patient plasma against activated coagulation factor X (anti-Xa activity) is commonly used to monitor treatment. This assay is used in almost all central laboratories in Swiss hospitals. It is noteworthy that the test must be calibrated for each drug specifically.

Peak values 3–5 h after s.c. injection may be used to monitor LMWH [1, 16, 47]. Typical target ranges are summarised in table 2. Adjusting peak anti-Xa levels to dose and body weight facilitates comparison of anti-Xa levels in pharmacokinetic studies [48, 49].

$$\text{(eq. 4)}\quad \textit{adjusted anti-Xa [kg/ml]} \cdot \frac{\textit{(anti-Xa [U/ml])} \cdot \textit{weight [kg]}}{\textit{dose [U]}}$$

Trough values before next injection may be used to evaluate safety alone (bioaccumulation). Anti-Xa activity is actually a pharmacodynamic effect that is used as a pharmacokinetic parameter [50]. Although there is discussion as to how it may be correlated to clinical events such as bleeding or thromboembolic complications [51–55], this surrogate parameter is the best available for clinical routine and used in most studies.

**Table 2**

**Target ranges of peak anti-Xa levels 4 hours after s.c. injection.** Recommendations are shown for prophylaxis and therapy from the ACCP guidelines [1, 3] and from pharmacokinetic studies reporting typical values of specific LMWH [16, 27, 47, 84, 95, 118, 119].

| | Target range (U/ml) | | | | | |
|---|---|---|---|---|---|---|
| **Indication** | **ACCP guidelines** | **Tinzaparin** | **Dalteparin** | **Enoxaparin** | **Certoparin** | **Nadroparin** |
| Prophylaxis, injections 1× / 24h | – | 0.46 ± 0.19 | 0.49 ± 0.13 | 0.42 ± 0.11<br>0.55 ± 0.14 | 0.23 | 0.32 ± 0.09 |
| Therapy, injections 2× / 24h | 0.6–1.0 | – | 0.6<br>0.69 ± 0.26 | 0.6–1.0<br>1.0 | 0.61 ± 0.13 | 0.6–1.0<br>0.9<br>1.01 ± 0.18 |
| Therapy, injections 1× / 24h | 1.0–2.0 * | >0.85 *<br>0.87 ± 0.15 | >1.05 * | >1.0 *<br>1.20 ± 0.17 | – | >1.05 *<br>1.34 ± 0.15 |

Values are shown as range or as mean ± standard deviation (SD). ACCP, American College of Chest Physicians. U, international units.
* The ACCP guidelines list various minimum anti-Xa levels for specific LMWH [1, 3].

## Pharmacologic aspects

### A simple pharmacokinetic model

A simple pharmacokinetic model may be helpful to compare various results from studies such as bioaccumulation factor R or apparent elimination half-life time ($t_{½}$). Resorption of LMWH after s.c. injection is >85%, the distribution volume approximately corresponds to the plasma volume, and elimination has not been shown to be saturable [15]. A one-compartment model with first-order elimination kinetics may be described with a simple exponential term that allows calculation of R [56, 57] for an achieved steady-state situation dependent on $t_{½}$ and dosing interval ($\tau$).

$$\text{(eq. 5)}\quad R = \frac{1}{1 - \exp\left(-\ln(2) \cdot \frac{\tau}{t_{½}}\right)}$$

In return, $t_{½}$ may be estimated from known $\tau$ and R, if R > 1.

$$\text{(eq. 6)}\quad t_{½} = \tau \cdot \frac{-\ln(2)}{\ln\left(1 - \frac{1}{R}\right)}$$

### Dosing interval versus half-life time

It is noteworthy that the $t_{½}$ of most LMWH (3–4 h [15]) is rather short compared to the dosing interval in prophylaxis. This indicates that $t_{½}$ may be prolonged, e.g. due to RI, without clinically significant bioaccumulation. Furthermore, this may explain why dose recommendations for patients with severe RI do not necessarily have to be the same for prophylactic (low dose every 24 h) and therapeutic (lower dose every 12 h, higher dose every 24 h) use. Clinically significant bioaccumulation due to RI is more likely to occur if LMWH are used in therapeutic dosing schemes.

### Single dose versus long-term studies

Pharmacokinetic data of many studies are based on results after application of a single dose of the drug (see table 3). However, it is important to realize that the pharmacokinetic question of bioaccumulation and consequently the clinical questions of efficacy and safety cannot be answered by studies with a single dose design. This is best shown by the divergent $t_{½}$ determined on days 1 and 4 in the study by Sanderink et al. [58]. Studies with a short-term control period of only 2–3 days have a similar limitation. There is a need for long-term studies, best powered for clinical end-points, to acquire evidence.

**Table 3**
Published pharmacokinetic data on low-molecular-weight heparins (LMWH) in patients with renal insufficiency (RI) including two studies [27, 84] comparing pharmacokinetics of various LMWH in healthy volunteers.

| Authors | Dose | Population | Result |
|---|---|---|---|
| *Certoparin* | | | |
| No pharmacokinetic study in patients with RI published yet. | | | |
| *Dalteparin* | | | |
| Simoneau et al. 1992 [65] | 2500 U or 10 000 U s.c. single dose | Young volunteers, age <40 years, no RI, n = 12<br>Elderly subjects, age >65 years, creatinine <130 µmol/l, n = 11 | Younger – 2500 U:<br>$C_{max}$ 0.2 ± 0.08 U/ml $t_{½}$ 3.4 ± 1.3 h<br>Younger – 10 000 U:<br>$C_{max}$ 0.98 ± 0.3 U/ml $t_{½}$ 4.1 ± 0.8 h<br>Elderly – 2500 U:<br>$C_{max}$ 0.2 ± 0.05 U/ml $t_{½}$ 3.9 ± 1.2 h<br>Elderly – 10 000 U:<br>$C_{max}$ 0.93 ± 0.2 U/ml $t_{½}$ 4.5 ± 0.6 h |
| Collignon et al. 1995 [27] | 2500 U s.c. single dose | Healthy volunteers, n = 20 | $C_{max}$ 0.22 ± 0.07 U/ml $t_{½}$ 2.81 ± 0.84 h |
| Eriksson et al. 1995 [84] | 5000 U s.c. single dose | Healthy volunteers, n = 12 | $C_{max}$ 0.49 ± 0.13 U/ml $t_{½}$ 2.45 ± 0.66 h |
| Shprecher et al. 2005 [64] | 100 U/kg/12h s.c. for 3 days | Control: >80 ml/min, n = 11<br>RI: 26.1 (16–38) ml/min, n = 11 | Peak anti-Xa on day 3<br>Control: 0.55 ± 0.20 U/ml<br>RI: 0.47 ± 0.25 U/ml |
| Perry et al. 2006 [76] | 5000 U/d s.c. for 4 days | Haemodialysis patients, n = 11 | Post dose 4 results<br>$C_{max}$ 0.31 (0.06–0.55) U/ml<br>$t_{½}$ 3.82 (2.03–9.63) h |
| Stöbe et al. 2006 [66] | 50 U/kg i.v. single dose | I: 101 ± 13 ml/min, n = 8<br>II: 32 ± 14 ml/min, n = 8<br>III: Haemodialysis, n = 8 | I: $C_{max}$ 0.67 ± 0.26 U/ml $t_{½}$ 1.26 ± 0.74 h<br>II: $C_{max}$ 0.86 ± 0.15 U/ml $t_{½}$ 1.83 ± 0.65 h<br>III: $C_{max}$ 0.87 ± 0.16 U/ml $t_{½}$ 1.76 ± 0.61 h |
| Tincani et al. 2006 [67] | 2500 or 5000 U/d s.c. for 6 days | Mild RI: 60–89 ml/min, n = 12<br>Moderate RI: 30–59 ml/min, n = 73<br>Severe RI: <30 ml/min, n = 24 | Values on day 6<br>Mild RI: $C_{max}$ 0.030 ± 0.086 U/ml<br>Moderate RI: $C_{max}$ 0.033 ± 0.075 U/ml<br>Severe RI: $C_{max}$ 0.048 ± 0.084 U/ml<br>Values in general 10x lower than in other studies<br>Values for women 6× higher than for men; however, many confounding factors |
| Cook et al. 2008 [68]<br>Douketis et al. 2008 [69] | 5000 U/d s.c. for median 7 days (IQR 4–12) | ICU patients with severe RI, CrCl 18.9 ± 6.5 ml/min, n = 138 | Range of peak anti-Xa activity 0.29–0.34 U/ml |
| Schmid et al. 2009 [70] | Median 5000 U/d s.c. for median 10 days (IQR 4–13) | Patients on general wards with indication for VTE prophylaxis<br>A: GFR ≥60 ml/min/1.73 $m^2$, n = 18 → 6<br>B: GFR 30–59 ml/min/1.73 $m^2$, n = 15 → 8<br>C: GFR <30 ml/min/1.73 $m^2$, n = 9 → 4 | Values on day 10; adjustment for dose and body weight; median (IQR).<br>A: adjusted peak anti-Xa 3.9 (3.4-4.6) $\times 10^{-3}$ R 1.14 (1.07–1.34)<br>B: adjusted peak anti-Xa 6.1 (4.9-7.0) $\times 10^{-3}$ R 1.09 (0.97–1.40)<br>C: adjusted peak anti-Xa 4.8 (4.2–5.6) $\times 10^{-3}$ R 1.23 (1.01–1.31) |
| *Enoxaparin* | | | |
| Cadroy et al. 1991 [83] | 0.5 mg/kg s.c. single dose | Healthy volunteers, CrCl 105 (88–140) ml/min, n = 12<br>Chronic RI, CrCl 11.4 (5–21) ml/min, n = 12 | Healthy volunteers: $C_{max}$ 0.29 ± 0.06 U/ml $t_{½}$ 2.94 ± 0.91 h<br>Chronic RI: $C_{max}$ 0.35 ± 0.07 U/ml $t_{½}$ 5.12 ± 2.01 h |
| Collignon et al. 1995 [27] | 2000 U or 4000 U s.c. single dose | Healthy volunteers, n = 20 | 2,000 U: $C_{max}$ 0.28 ± 0.06 U/ml $t_{½}$ 3.95 ± 0.65 h<br>4,000 U: $C_{max}$ 0.57 ± 0.14 U/ml $t_{½}$ 4.37 ± 0.47 h |
| Eriksson et al. 1995 [84] | 4000 U s.c. single dose | Healthy volunteers, n = 12 | $C_{max}$ 0.42 ± 0.11 U/ml $t_{½}$ 4.28 ± 1.06 h |
| Brophy et al. 2001 [85] | 1 mg/kg s.c. single dose | Haemodialysis patients, n = 8 | $C_{max}$ 0.69 (0.57–0.77) U/ml $t_{½}$ approx. 8h |
| Collet et al. 2001 [81] | Empirical dose adjustment<br>I: 0.92 ± 0.03 mg/kg/12 h s.c.<br>II: 0.84 ± 0.03 mg/kg/12 h s.c.<br>III: 0.64 ± 0.04 mg/kg/12 h s.c. | I: CrCl >60 ml/min, n = 55<br>II: CrCl >30 and <60 ml/min, n = 28<br>III: CrCl <30 ml/min, n = 28 | Peak anti-Xa before catheterisation on day 3<br>I: 1.01 ± 0.05 U/ml<br>II: 0.95 ± 0.05 U/ml<br>III: 0.95 ± 0.07 U/ml |
| Becker et al. 2002 [87] | 1 mg/kg/12 h s.c. for at least 3 doses (i.e. 2 days) | I: CrCl >80 ml/min, n = 273<br>II: CrCl 40–80 ml/min, n = 149<br>III: CrCl <40 ml/min, n = 11 | Peak anti-Xa after last dose<br>I: 1.29 ± 0.46 U/ml<br>II: 1.53 ± 0.54 U/ml<br>III: 1.53 ± 0.94 U/ml<br>Population: $t_{½}$ 5.0 h |

| Authors | Dose | Population | Result |
|---|---|---|---|
| Sanderink et al. 2002 [58] | 40 mg/d s.c. for 4 days | Measured urine CrCl, mean ± SEM | Values shown as mean (% of coefficient of variation) or median (range) |
| | | Healthy volunteers, CrCl 120.7 ± 11. ml/min, n = 12 | Healthy: $C_{max,\ d1}$ 0.386 (26%) U/ml<br>$t_{½,\ d1}$ 5.71 (3.46–14.3) h<br>$C_{max,\ d4}$ 0.421 (26%) U/ml<br>$t_{½,\ d4}$ 6.87 (3.97–13.2) h<br>R 1.11 (15%) |
| | | Mild RI, CrCl 66.4 ± 2.8 ml/min, n = 12 | Mild RI: $C_{max,\ d1}$ 0.486 (31%) U/ml<br>$t_{½,\ d1}$ 5.35 (2.70–8.83) h<br>$C_{max,\ d4}$ 0.562 (29%) U/ml<br>$t_{½,\ d4}$ 9.94 (3.67–20.2) h<br>R 1.16 (11%) |
| | | Moderate RI, CrCl 38.5 ± 1.4 ml/min, n = 12 | Moderate RI: $C_{max,\ d1}$ 0.449 (26%) U/ml<br>$t_{½,\ d1}$ 6.63 (3.41–9.68) h<br>$C_{max,\ d4}$ 0.497 (20%) U/ml<br>$t_{½,\ d4}$ 11.3 (5.53–20.0) h<br>R 1.13 (17%) |
| | | Severe RI, CrCl 19.3 ± 2.0 ml/min, n = 12 | Severe RI: $C_{max,\ d1}$ 0.464 (31%) U/ml<br>$t_{½,\ d1}$ 7.30 (5.27–8.69) h<br>$C_{max,\ d4}$ 0.584 (30%) U/ml<br>$t_{½,\ d4}$ 15.9 (9.66–23.0) h<br>R 1.27 (17%) |
| Chow et al. 2003 [88] | 1 mg/kg/12h s.c. for at least 3 doses | CrCl range 10.8–124 ml/min, n = 18<br>I: CrCl >30 ml/min<br>II: CrCl ≤30 ml/min | Peak anti-Xa after at least 3 dosages<br>I: 0.91 U/ml<br>II: 1.34 U/ml<br>Linear correlation found (R = 0.763, $R^2$ = 0.582, p <0.0005) |
| Collet et al. 2003 [82] Prospective clinical evaluation of Collet et al. 2001 [81] as a subproject | Dose adjustment to renal function<br>Severe RI: 0.70 ± 0.07 mg/kg/12 h<br>Others: 0.90 ± 0.08 mg/kg/12 h<br>All doses s.c. | Severe RI: CrCl ≤30 ml/min, n = 62, a subgroup of other patients that were excluded from other trials (EP), n = 174<br>Others (control, NEP): CrCl >30 ml/min, i.e. CrCl 82.2 ± 33.6 ml/min, n = 341 | Peak anti-Xa<br>Severe RI: 0.85 ± 0.05 U/ml<br>Others, NEP: 0.97 ± 0.02 U/ml |
| Guillet et al. 2003 [86] | 60 U/kg i.v. single dose | Haemodialysis patients, n = 30 | $t_{½}$ approx. 13.9 h |
| Kruse and Lee 2004 [89] | Maintenance dose s.c.<br>Moderate: 0.74 ± 0.03 mg/kg/12 h<br>Severe: 0.50 ± 0.04 mg/kg/12 h | Moderate: CrCl 30–60 ml/min, n = 120<br>Severe: CrCl <30 ml/min, n = 50 | Anti-Xa after 3rd dose<br>Moderate: 0.82 ± 0.18 U/ml<br>Severe: 0.65 ± 0.19 U/ml |
| Bazinet et al. 2005 [91] | Once daily: 1.5 mg/kg/24h s.c.<br>Twice daily: 1.0 mg/kg/12h s.c.<br>Dialysis patients: 75% of dose for 2–3 days | n are given for once and twice daily appl.<br>A: CrCl >50 ml/min, $n_1$ = 38, $n_2$ = 68<br>B: CrCl 30–50 ml/min, $n_1$ = 27, $n_2$ = 27<br>C: CrCl 11–30 ml/min, $n_1$ = 14, $n_2$ = 22<br>D: dialysis patients, $n_1$ = 13, $n_2$ = 5 | Peak anti-Xa on day 2 or 3, mean (95% CI)<br>A: once daily 1.10 (1.00–1.20) U/ml twice daily 1.06 (0.99–1.14) U/ml<br>B: once daily 1.21 (1.09–1.33) U/ml twice daily 1.25 (1.12–1.39) U/ml<br>C: once daily 1.18 (0.92–1.44) U/ml twice daily 1.27 (1.15–1.40) U/ml<br>D: once daily 1.04 (0.79–1.30) U/ml twice daily 1.03 (0.45–1.61) U/ml |
| Brophy et al. 2006 [50] | 1 mg/kg s.c. single dose | Healthy volunteers, n = 8<br>Haemodialysis, n = 8<br>Peritoneal dialysis, n = 8 | Healthy volunteers: $C_{max}$ 0.6 ± 0.1 U/ml<br>Haemodialysis: $C_{max}$ 0.5 ± 0.1 U/ml<br>Peritoneal dialysis: $C_{max}$ 0.7 ± 0.2 U/ml |
| Mahé et al. 2007 [94] | 4000 U/d s.c. for 10 days | Patients aged >75 years<br>A: CrCl 51–80 ml/min, n = 28<br>B: CrCl 41–50 ml/min, n = 26<br>C: CrCl 31–40 ml/min, n = 32<br>D: CrCl 20–30 ml/min, n = 39 | Maximum peak anti-Xa level during day 1–10<br>A: 0.60 ± 0.16 U/ml<br>B: 0.61 ± 0.17 U/ml<br>C: 0.61 ± 0.24 U/ml<br>D: 0.72 ± 0.27 U/ml |
| Mahé et al. 2007 [95] | 4000 U/d s.c. for 8 days | Patients aged >75 years, CrCl 20-50 ml/min (i.e. 33.0 ± 10.2 ml/min), n = 28 | $C_{max}$ day 1: 0.55 ± 0.14 U/ml<br>$C_{max}$ day 8: 0.67 ± 0.23 U/ml<br>R = 1.22 |
| Lachish et al. 2007 [96] | 1 mg/kg/d s.c. for 2–3 days | Patients with CrCl <30 ml/min (i.e. 22.2 ± 6.4 ml/min), n = 19 | Peak anti-Xa<br>day 1: 0.60 ± 0.19 U/ml<br>day 2 or mean of day 2 and day 3: 0.67 ± 0.17 U/ml |

| Authors | Dose | Population | Result |
|---|---|---|---|
| *Nadroparin* | | | |
| Goudable et al. 1991 [120] | 100 Institut Choay units/kg i.v. single dose (initially defined units by Institut Choay have been replaced by international units, 100 Institut Choay units correspond to 41 U) | A: haemodialysis, n = 7<br>B: CrCl 10–20 ml/min, n = 7<br>C: CrCl 30–50 ml/min, n = 5<br>D: healthy, CrCl 75–200 ml/min, n = 12 | A: $C_{max}$ 2.0 ± 0.4 IC units/ml $t_{½}$ 3.6 ± 0.9 h<br>B: $C_{max}$ 2.3 ± 0.4 IC units/ml $t_{½}$ 4.6 ± 1.5 h<br>C: $C_{max}$ 2.0 ± 0.2 IC units/ml $t_{½}$ 3.0 ± 0.9 h<br>D: $C_{max}$ 1.9 ± 0.2 IC units/ml $t_{½}$ 2.2 ± 0.5 h<br>$C_{max}$ of this study are given as Institut Choay units/ml (1 Institut Choay unit = 0.41 U) |
| Collignon et al. 1995 [27] | 7500 Institut Choay units = 3075 U s.c. single dose | Healthy volunteers, n = 20 | $C_{max}$ 0.32 ± 0.09 U/ml $t_{½}$ 3.74 ± 0.68 h |
| Alhenc-Gelas et al. 1995 [103] | 60 U/kg/d s.c. for 8 days | Patients with nephrotic syndrome, n = 6,<br>all patients with CrCl >30 ml/min, no detailed declaration of renal function | Peak anti-Xa<br>day 1 0.38 ± 0.04 U/ml<br>day 8 0.36 ± 0.10 U/ml |
| Mismetti et al. 1998 [102] | 180 U/kg/d s.c. for 6–10 days | Young healthy, CrCl 114 ± 15 ml/min, n = 12<br><br>Elderly healthy, CrCl 62 ± 6 ml/min, n = 12<br><br>Patients with DVT, CrCl 71 ± 24 ml/min, n = 12 | Young healthy<br>$C_{max}$ day 1 1.34 ± 0.40 U/ml<br>day 10 1.34 ± 0.15 U/ml<br>Elderly healthy<br>$C_{max}$ day 1 1.31 ± 0.29 U/ml<br>day 8 1.63 ± 0.34 U/ml<br>Patients with DVT<br>$C_{max}$ day 1 1.12 ± 0.37 U/ml<br>day 6–9 1.41 ± 0.54 U/ml |
| *Tinzaparin* | | | |
| Eriksson et al. 1995 [84] | 50 U/kg s.c. single dose | Healthy volunteers, n = 12 | $C_{max}$ 0.18 ± 0.04 U/ml $t_{½}$ 2.97 ± 1.01 h |
| Siguret et al. 2000 [108]<br>Pautas et al. 2001 [109] | 175 U/kg/d s.c. for 10 days | n are given for days 2 and 10<br>I: CrCl 20–29 ml/min, $n_2$ = 8, $n_{10}$ = 7<br>II: CrCl 30–39 ml/min, $n_2$ = 9, $n_{10}$ = 8<br>III: CrCl 40–49 ml/min, $n_2$ = 6, $n_{10}$ = 6<br>IV: CrCl ≥ 50 ml/min, $n_2$ = 7, $n_{10}$ = 6 | Peak anti-Xa 5h after injection on days 2 / 10<br>I: d2 0.73 ± 0.16 – d10 0.77 ± 0.19 U/ml<br>II: d2 0.57 ± 0.26 – d10 0.60 ± 0.21 U/ml<br>III: d2 0.72 ± 0.22 – d10 0.79 ± 0.19 U/ml<br>IV: d2 0.65 ± 0.14 – d10 0.71 ± 0.19 U/ml |
| Hainer et al. 2002 [113] | Single dose injection of 75 U/kg i.v. before dialysis 75 U/kg s.c. on off-dialysis day | Patients on chronic haemodialysis, n = 12 | i.v.: $C_{max}$ 1.33 ± 0.32 U/ml, $t_{½}$ 2.31 ± 0.76 h<br>s.c.: $C_{max}$ 0.33 ± 0.08 U/ml, $t_{½}$ 3.89 ± 1.05 h |
| Mahé et al. 2007 [95] | 4500 U/d s.c. for 8 days | Patients aged >75 years, CrCl 20–50 ml/min (i.e. 36.6 ± 12.5 ml/min), n = 27 | $C_{max}$ day 1: 0.44 ± 0.16 U/ml<br>$C_{max}$ day 8: 0.46 ± 0.19 U/ml<br>R = 1.05 |

Shown pharmacokinetic data base on anti-Xa activity. Values are shown as mean ± standard deviation (SD), or mean (range) if not indicated otherwise. Renal function is expressed as glomerular filtration rate (GFR) or creatinine clearance (CrCl). CI, confidence interval. $C_{max}$, maximum concentration. ICU, intensive care unit. IQR, interquartile range. R, bioaccumulation factor. RI, renal insufficiency. SEM, standard error of the mean. $t_{½}$, apparent elimination half-life time. U, international units. UFH, unfractionated heparin.

## Discussion of specific drugs

Although LMWH have been shown to be clinically comparable [1], they have different pharmacokinetic properties [15, 59] and therefore potentially different pharmacodynamic effects or risks in patients with RI. Unfractionated heparin (UFH) is also briefly mentioned due to its structural and functional analogy. Studies with pharmacokinetic data on LMWH in respect of RI are summarised in table 3. Published or calculated $t_{½}$ of enoxaparin, nadroparin, dalteparin and tinzaparin are shown in relation to GFR in figure 1.

### Unfractionated heparin

Unfractionated heparin (Liquemin®) is predominantly administered continuously i.v. UFH is bound to plasma proteins, which considerably influences the effective dose in acute disorders due to the increase of heparin binding proteins. It is deactivated by the reticuloendothelial system and liver heparinases while being excreted in urine in depolymerised and inactive forms [60, 61]. Because the plasma level of UFH is influenced by so many factors its effect must be monitored by thrombin time, APTT, or anti-Xa activity.

UFH may be used in patients with severe RI using the same monitoring strategy, bearing in mind that patients with severe RI have a higher bleeding risk in general [28]. In unstable situations with imminent intervention or with a high bleeding risk, UFH has the advantages (i) of being stoppable very quickly since it is given continuously i.v., (ii) of being eliminated fairly rapidly due

to the short $t_{½}$, and (iii) of having an effective antagonist (protamine sulphate) [62]. Hence UFH is often preferred in such special clinical situations.

**In summary:** UFH may be used in patients with severe RI employing the same monitoring strategy as in patients with no RI.

**Certoparin**

There are no data on use of certoparin in patients with RI. There is only one report on critically ill patients showing that patients with generally lower anti-Xa activity have better renal function [63].

**Dalteparin**

Dalteparin (Fragmin® / Kabi 2165) has one of the largest mean molecular weights of the LMWH. Pharmacokinetic studies have shown that this goes together with a smaller anti-Xa : anti-IIa ratio and a clearance less dependent on renal function [15].

**Therapy:** Shprecher et al. [64] reported no significant difference between peak anti-Xa activities after the first administration and after 3 days of therapy comparing patients with normal renal function and patients with mean CrCl of 26 ml/min (range 16–38). The investigated time frame was however short.

**Prophylaxis:** There are several pharmacokinetic studies [65–70] of prophylactically dosed dalteparin (table 3). Tincani et al. have reported surprising results with anti-Xa levels an approximate factor of 10 below levels documented in other studies and measured in our laboratory [67]. A recently published study of dalteparin in ICU patients with severe RI [68, 69] has reported anti-Xa levels in the range of 0.29–0.34 U/ml for a median of 7 days (IQR 4–12). However, peak anti-Xa levels may be lower in ICU patients compared to patients on general wards, since vasopressors may decrease resorption and therefore bioavailability of s.c. administered drugs [71].

**End stage renal disease:** The use of dalteparin as an anticoagulant for haemodialysis has become routine after pharmacokinetic and clinical evaluation [72–75]. It can be used at a prophylactic dose of 5000 U/d s.c. for at least 5 days without clinical signs of accumulation such as bleeding [76]. Schrader et al. have published a case report on the effective and safe treatment of DVT in a patient on peritoneal dialysis with dalteparin administered intraperitoneally [77].

**In summary:** Dalteparin has been shown to be a safe anticoagulant for prophylaxis in patients with severe RI for up to 10 days, although for therapy this has been shown only for 3 days and not for a longer period of time.

**Enoxaparin**

The largest amount of data are available for enoxaparin (Clexane® / Lovenox® / PK 10169).

**Therapy:** Most studies of enoxaparin have involved patients with ACS. ESSENCE and TIMI 11B have shown a general superiority of enoxaparin compared to UFH [78–80]. Although patients with severe RI should have been excluded from these studies, 2% of the patients included had a CrCl ≤30 ml/min. A post-hoc analysis of these patients [7] has shown a trend towards a higher combined end-point (death, myocardial infarction, urgent revascularisation) compared to patients with normal renal function (25.9% vs. 17.0%, p = 0.09) and a significantly higher risk of bleeding (major haemorrhages 6.6% vs. 1.1%, p <0.0001). However, the risk of major or minor bleeding did not differ whether UFH or LMWH was used (p = 0.56 and p = 0.93 respectively); but there has been a clear trend to a higher mortality of patients with UFH compared to LMWH (p = 0.09). A trend towards a higher bleeding risk and worse outcome with UFH compared to LMWH has been found in a registry of patients with non-ST-segment elevation ACS as well [10].

Collet et al. [81] deduced a simple dosing scheme empirically with a reduction in the calculated regular enoxaparin dose to 65% if CrCl was ≤30 ml/min; this scheme is combined with monitoring of anti-Xa activity and adjustment of the maintenance dose after the third injection of enoxaparin to aim peak anti-Xa levels between 0.5 and 1.0 U/ml. A prospective study applying this scheme has shown a comparable bleeding risk and comparable peak anti-Xa levels [82].

Several single-dose [27, 50, 83–86] and multi-dose [37, 58, 87–96] studies have reported data with pharmacokinetic focus in detail. Based on a pharmacokinetic model and data from former studies [35, 90], Hulot et al. proposed a dosing strategy for patients with RI and non ST-segment elevation ACS [93]: first dose 1.0 mg/kg for all patients, followed by 1.0 mg/kg/12h for patients with CrCl ≥50 ml/min, 0.8 mg/kg/12 h for patients with CrCl 30–49 ml/min, or 0.66 mg/kg/12 h for patients with CrCl <30 ml/min, matching rather well doses for patients with severe RI formerly suggested by Collet et al. [81, 82]. Kruse and Lee [89] suggested another algorithm, but this scheme has not yet been validated in a prospective study. Furthermore, the study was criticised for lack of clinical end-points and a risk of under-dosing, particularly in severe RI [97].

**Prophylaxis:** There are several pharmacokinetic studies [58, 83, 94, 95] with prophylactically dosed enoxaparin (table 3). A dose reduction of up to 50% has been suggested even for prophylaxis [1].

**End stage renal disease:** Enoxaparin has been shown to be an effective and safe anticoagulant for haemodialysis and haemofiltration [85, 86, 98, 99]. Enoxaparin has been studied in two single-dose pharmacokinetic studies [50, 100] in patients on peritoneal dialysis. There is a case report of intraperitoneal administration for treatment of VTE in a child on peritoneal dialysis [101].

**In summary:** Enoxaparin has been studied in patients with severe RI. Dose reductions are recommended, but excessive reduction of the enoxaparin dose has been shown to increase the risk of thromboembolic complications.

**Nadroparin**

Limited data are available for nadroparin (Fraxiparine® / Fraxiforte® / CY 216) in patients with RI (table 3).

**Therapy:** Mismetti et al. have reported a significant increase in peak anti-Xa activity in subjects with only very mild RI [102].

**Prophylaxis:** Alhenc-Gelas et al. [103] investigated VTE prophylaxis with nadroparin in 6 patients with nephrotic syndrome. However, renal function was not clearly specified and only declared to be >30 ml/min.

**End stage renal disease:** Several studies have shown that nadroparin is a safe and effective replacement for UFH during haemodialysis [104–107].

**In summary:** Limited data on nadroparin have shown bioaccumulation even in patients with mild RI.

**Tinzaparin**

Tinzaparin (Logiparin® / Innohep® / LHN-1) is known to have the largest molecular weight of all LMWH and therefore to be structurally closest to UFH.

**Therapy:** Tinzaparin has been safely used for up to 10 days in a single-injection-per-day therapeutic regime (175 U/kg/24 h s.c.) without bioaccumulation in patients with severe RI (CrCl 20–29 ml/min, n = 8) [108, 109]. It was also used in patients with CrCl of 51.2 ± 22.9 ml/min for up to 30 days, with bleeding episodes occurring in only 1.5% [110], a figure comparable with the bleeding risk in patients without RI [28].

**Prophylaxis:** Mahé et al. have reported no significant bioaccumulation after 8 days of tinzaparin in 27 patients with CrCl 36.6 ± 12.5 ml/min [95].

**End stage renal disease:** Tinzaparin has been safely used for haemodialysis even for long-term use [111, 112]. A detailed pharmacokinetic profile after i.v. and s.c. single dose injections was measured by Hainer et al. in haemodialysis patients [113].

**In summary:** Available limited data has shown that tinzaparin does not significantly accumulate in severe RI. We postulate that this is related to its larger mean molecular weight compared to other LMWH.

## Current guidelines

**Product monographs**

Official Swiss product monographs give warnings and/or dosing suggestions for most LMWH involving patients with severe RI [61]. A GFR of 30 ml/min/1.73 $m^2$ has been shown to be a typical cut-off level. Only nadroparin is at the moment formally contraindicated in these patients not on haemodialysis [61]. At present there is no Swiss product monograph for tinzaparin.

**Proposed strategies**

On the basis of growing evidence, various dosing strategies have been proposed for LMWH in patients with RI [1, 2, 22, 114]:

a) Use empirically reduced doses of LMWH according to predefined guidelines.

b) Monitor anti-Xa activity and adjust the LMWH dose according to a predefined target range.

c) Combination of a) and b)

d) Replace LMWH with UFH.

However, each LMWH has its own pharmacokinetic profile, a factor to be borne in mind in choosing the best dosing strategy for a particular LMWH. The best strategy for one LMWH may not be the best for another.

## ACCP guidelines 2008

The American College of Chest Physicians (ACCP) commented on the use of LMWH in patients with RI in their recently updated guidelines on anticoagulation [1–4, 115]. We discuss some quotations in order to emphasise, specify or modify important points on the basis of the current literature discussed in the present review.

**General considerations:**

– "Appropriate dosing of LMWH in patients with severe renal insufficiency is uncertain." [reference 1, page 148S, right column, line 27]
"The data on accumulation with LMWHs other than enoxaparin are limited." [reference 1, page 148S, right column, line 53]
*Comment:* There are more clinical and pharmacokinetic data on the use of enoxaparin in severe RI than of any other LMWH (table 3),

including a prospective evaluation of a dosing scheme [82]. However, there are growing data on the use of dalteparin and tinzaparin for patients with severe RI as well, indicating that there is less bioaccumulation with these drugs (table 3, fig. 1). Both drugs may therefore be advantageous alternatives for patients with severe RI. Further studies are needed, most importantly prospective trials at a therapeutic dose and with clinical end-points. There are not enough data at present on certoparin and nadroparin to allow their use in patients with severe RI other than in trials.

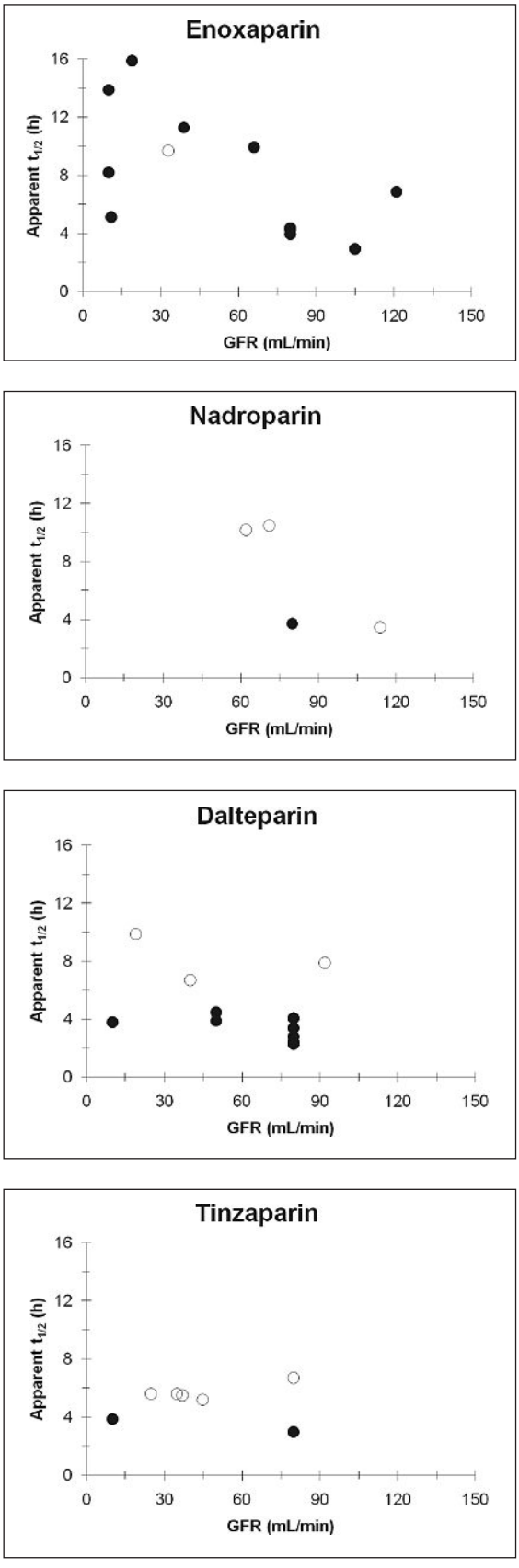


**Figure 1**

**Apparent elimination half-life times $t_{½}$ of s.c. injected LMWH in relation to renal function:** enoxaparin [27, 58, 83–86, 95], nadroparin [27, 102], dalteparin [27, 65, 70, 76, 84], and tinzaparin [84, 95, 108, 113]. Filled symbols represent published data, open symbols represent calculated $t_{½}$ from published bioaccumulation data using equation 6. Dialysis patients are shown with a glomerular filtration rate (GFR) of 10 ml/min. Healthy volunteers without declaration of renal function in the original study are shown with a GFR of 80 ml/min. Renal function is not shown in detail for elderly subjects in Simoneau et al. [65]. It can be determined as in the range of 30–60 ml/min based on data in this publication. These data are shown with a GFR of 50 ml/min in this figure.

– "In the setting of severe renal insufficiency where therapeutic anticoagulation is required, use of UFH avoids the problems associated with impaired clearance of LMWH preparations." [reference 1, page 149S, left column, line 51]
*Comment:* This strategy truly avoids potential problems of bioaccumulation of LMWH. However, it may avoid the best possible therapy as well. A registry study has shown that the risk of fatal pulmonary embolism exceeds the risk of fatal bleeding in therapeutically anticoagulated patients with severe RI [9]. Moreover, LMWH use has been associated with a significantly lower rate of fatal PE when compared with UFH, even in patients with severe RI. There is a risk of underdosage at the start of UFH, especially in acutely ill patients, due to increased plasma levels of heparin-binding proteins. LMWH have been shown to be more effective and safer than UFH in general [1, 3, 10, 115] and, with limited data, even in patients with severe RI [7, 9, 10, 24].
– "Although there is no specific CrCl threshold at which the risk for accumulation becomes clinically significant, a CrCl of about 30 ml/min is a reasonable cutoff value based on the available literature." [reference 1, page 149S, left column, line 54]
*Comment:* This cut-off level may be lower for certain LMWH such as tinzaparin.
– "If LMWH is chosen, anti-Xa monitoring and/or dose reduction should be done to ensure that there is no accumulation." [reference 1, page 149S, right column, line 2]
*Comment:* LMWH should not be used in patients with severe RI without the possibility of monitoring anti-Xa activity.

**Therapy:**
– "In patients with severe renal insufficiency (CrCl <30 ml/min) who require therapeutic anticoagulation, we suggest the use of UFH instead of LMWH (Grade 2C). If LMWH is used in patients with severe renal insufficiency (CrCl <30 ml/min) who require therapeutic anticoagulation, we suggest using 50% of the recommended dose (Grade 2C)." [reference 1, page 149S, right column, line 34]
*Comment:* These suggestions have a low grade of evidence and may change in time. In particular, a dose reduction by 50% in patients with severe RI may under-dose enoxaparin, as has been shown [89, 97]. Under-dosage may lead to loss of efficacy with a worse clinical outcome [35, 36]. Reduction of the mainte-

nance dose to 65% [81, 82, 93] may be preferable for enoxaparin. Monitoring of LMWH with anti-Xa activity is recommended.

Tinzaparin has been used for 10 days at a therapeutic dose even in patients with CrCl 20–29 ml/min without significant bioaccumulation [108]. Data for other LMWH at a therapeutic dose are still too scant to allow recommendations.

– **Venous thromboembolism:** "In patients with acute DVT and severe renal failure, we suggest UFH over LMWH (Grade 2C)." [reference 3, page 455S, right column, line 27]

"In patients with acute PE [= pulmonary embolism] and severe renal failure, we suggest UFH over LMWH (Grade 2C)." [reference 3, page 458S, left column, line 23]

*Comment:* Both are suggestions with a low grade of evidence. New data and recommendations in other parts of these guidelines [1] discussed above indicate that these suggestions will change in future.

**Prophylaxis:**

– "We recommend that renal function be considered when making decisions about the use and/or dose of LMWH, fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients, patients with diabetes mellitus, and those at high risk of bleeding (Grade 1A). Depending on the circumstances, we recommend one of the following options in this situation: avoiding the use of an anticoagulant that bioaccumulates in the presence of renal impairment, using a lower dose of the agent, or monitoring the drug level or its anticoagulant effect (Grade 1B)." [reference 2, page 382S, right column, line 6]

– "The current recommendation for prophylactic-dose enoxaparin in patients with a CrCl <30 ml/min is 50% of the usual dose (i.e. 30mg once daily). No specific recommendations have been made for other LMWH preparations." [reference 1, page 149S, right column, line 25]

*Comment:* Underdosage may be a problem with this dose reduction for enoxaparin, as discussed above. Furthermore, the standard prophylactic dose for enoxaparin is 40 mg/d in Europe, in contrast to obviously 60 (2x30) mg/d in the USA. We would not suggest using enoxaparin 20 mg/d for medical patients.

Evidence of dalteparin and tinzaparin at a prophylactic dose seems to be strong enough to suggest using them without dose adjustments in patients with severe RI, if precautions are followed as outlined in the next chapter.

## Summary and conclusion

Therapy and prophylaxis of thromboembolic events intrinsically involve both the risk of bleeding [28] and the risk of thromboembolic complications [35, 36]. Patients with severe RI have a higher risk of both [7, 10]. Renal function decreases with age or may be impaired due to disease. About a quarter of in-house medical patients of a tertiary care hospital have at least moderate RI; about 10% have severe RI [23].

Despite the warnings in many product monographs there is increasing knowledge of the degree of bioaccumulation of LMWH in patients with severe RI. Various LMWH exhibit specific molecular and structural attributes due to different production processes [116]. Various pharmacokinetic and pharmacodynamic properties have been documented [15, 27, 117] (see table 3 and fig. 1). Dosing strategies in patients with RI may vary depending on which LMWH is used. Bleeding risk, predictable course of the disease, imminent regular or emergency interventions and concomitant drugs influencing the coagulation system must be considered.

### Suggested approach to anticoagulation of a patient with RI

Due to the lack of data, no simple dosing suggestion can be given for all LMWH. However, in the light of all the information discussed in this review, we suggest the following approach for the use of LMWH in patients with (severe) RI:

– Evaluate the patient's renal function when starting anticoagulation. Not all patients are in steady state at admission. Reevaluate renal function over time. Evaluate the patient's bleeding risk on the basis of history, clinical status, use of concomitant drugs, imminent interventions, and – where appropriate – coagulation tests.
– Prefer LMWH to UFH on the grounds of better efficacy, safety and convenience.
– However, prefer i.v. UFH to s.c. LMWH if a patient (i) is unstable, (ii) may need emergency intervention, or (iii) has an increased bleeding risk, on the grounds that i.v. UFH can be stopped quickly, has a short $t_{½}$, and can be antagonised.
– Use only LMWH that have known pharmacokinetic and clinical data for patients with RI, such as, currently, enoxaparin, dalteparin or tinzaparin. Use dosing schemes accordingly.
– Choose therapeutic schemes with injections of LMWH twice daily instead of once daily, to avoid high peak anti-Xa levels. There are scant data on once-daily dosing schemes for most LMWH.

– Avoid underdosing due to excessive concern regarding bleeding complications.
– Monitor LMWH with peak anti-Xa levels in patients with severe RI regularly, and adjust dose to be in target range. Adjust frequency of anti-Xa activity monitoring depending on renal function, clinical development and your experience with the specific drug.
– Do not use LMWH in patients with severe RI if there is no opportunity to measure anti-Xa levels.
– Adjust your future anticoagulation strategy for patients with severe RI in the light of new evidence.

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## Appendix

**Search strategy**

We used the following search strategy in PubMed to obtain a complete set of literature on LMWH in patients with RI. This search was done repeatedly, on the last occasion in March 2009, returning 489 articles.

#1 Search kidney failure
#2 Search renal insufficiency
#3 Search kidney disease
#4 Search low molecular weight heparin
#5 Search certoparin
#6 Search nadroparin
#7 Search dalteparin
#8 Search enoxaparin
#9 Search tinzaparin
#10 Search lmwh
#11 Search fondaparinux
#12 Search unfractionated heparin
#13 Search ufh
#14 Search (#1 or #2 or #3) and (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)

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