Safety and Efficacy of Low Molecular Weight Heparins for Hemodialysis in Patients with End-Stage Renal Failure: A Meta-analysis of Randomized Trials

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Abstract. Low molecular weight heparins (LWMH) are the preferred initial treatment for many thromboembolic disorders but are renally excreted and relatively contraindicated in patients with renal failure because of concerns of increased bleeding risks. The purpose of this study was to evaluate the safety and efficacy of LMWH compared with unfractionated heparin (UFH) for preventing thrombosis of the extracorporeal dialysis circuit. Studies were identified with the use of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and FirstSearch; reference lists were reviewed; and pharmaceutical companies were contacted. Randomized, controlled trials that compared an LMWH with another anticoagulant during hemodialysis in patients with ESRD and reported at least one of bleeding, extracorporeal circuit thrombosis, or anti-Xa levels were chosen. Two reviewers independently extracted data on methodologic quality, study design, clinical outcomes, and anti-Xa levels. Seventeen trials were included in this systematic review, 11 of which were included in the meta-analysis. It was found that LMWH did not significantly affect the number of bleeding events (relative risk, 0.96; 95% confidence interval [CI], 0.27 to 3.43), bleeding assessed by vascular access compression time (weighted mean difference, −0.87; 95% CI, −2.75 to 1.02), or extracorporeal circuit thrombosis (relative risk, 1.15; 95% CI, 0.70 to 1.91) as compared with UFH. LMWH seem to be as safe as UFH in terms of bleeding complications and as effective as UFH in preventing extracorporeal circuit thrombosis. However, inferences from these trials assessing anticoagulation for patients who undergo hemodialysis will continue to be weak until larger, more rigorous randomized trials are conducted.

Low molecular weight heparins (LMWH) are increasingly used for the prevention and treatment of many thromboembolic disorders, because they are as effective and more convenient than unfractionated heparin (UFH) (1). The predictable anticoagulant effect of LMWH eliminates the need for routine laboratory monitoring, allowing many patients with thrombosis to be treated without hospital admission. Other advantages include lower incidences of heparin-induced thrombocytopenia and osteoporosis compared with UFH.

Some important differences exist between LMWH and UFH. Unlike UFH, which inhibits factor Xa and thrombin equally, LMWH have greater activity against factor Xa. The anticoagulant effects of LMWH therefore are monitored by measuring the ability of plasma from patients who are treated with LMWH to inhibit factor Xa; the resultant assay is known as an anti-Xa heparin level. This level reflects the amount of LMWH present in the blood and, by extension, the degree of anticoagulation. Although the minimal therapeutic anti-Xa level has not been established, a conservative therapeutic range measured 4 h after a subcutaneous dose is 0.6 to 1.0 IU/ml for twice-daily administration and 1.0 to 2.0 IU/ml for once-daily dosing (2).

Another important difference is that UFH is cleared through hepatic and renal mechanisms, whereas LMWH are dependent on renal clearance. Patients with renal failure thus are potentially at risk for bleeding as a result of impaired LMWH clearance and prolonged anticoagulant effects. Observational studies report increased bleeding using LMWH in patients with renal insufficiency compared with those without renal impairment (3). Randomized trial data addressing the question of increased bleeding risk are limited because studies that have assessed efficacy and safety of LMWH have either excluded patients with renal failure or failed to specify whether these patients were recruited (4). Subgroup analyses of patients with renal insufficiency in randomized trials that have evaluated enoxaparin for acute coronary syndromes have demonstrated a correlation between creatinine clearance and clearance of anti-Xa activity, such that patients with marked renal impairment had higher trough and peak anti-Xa levels (5) and more major bleeding compared with patients without renal impairment (7.5% *versus* 1.2%; $P = 0.002$) (6).

The degree of renal impairment required before LMWH will bioaccumulate is unknown. A creatinine clearance threshold of

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30 ml/min is frequently used to identify patients who may be at increased risk for bioaccumulation and bleeding, although there is no evidence to support this threshold (7). It is understandable, then, that clinical use of LMWH in patients with renal failure has been inconsistent; when used therapeutically, there is variable reliance on monitoring with anti-Xa levels and variable empiric dose adjustments. The unclear bleeding risk and uncertainty regarding optimal dosing of LMWH in patients with ESRD has resulted in treatment primarily with UFH.

Despite the fact that LMWH are infrequently used for therapeutic anticoagulation in patients who require hemodialysis, they are used to prevent thrombosis of the extracorporeal dialysis circuit. LMWH are not removed from the plasma during hemodialysis (8) or continuous veno-venous hemofiltration (9). Thus, LMWH pose a risk of bioaccumulation and bleeding when used repeatedly for hemodialysis. Randomized controlled trials have evaluated LMWH for preventing thrombosis of the dialysis circuit and are approved for this indication in many countries. No meta-analyses summarizing the effectiveness or bleeding risk of LMWH for this purpose in patients with ESRD have been published.

The objective of this systematic review and meta-analysis was to search, appraise, and summarize the randomized trials that compared an LMWH with UFH during hemodialysis in patients with ESRD to obtain precise estimates of clinically important outcomes, including bleeding rates and thrombosis of the extracorporeal circuit. We also examined anti-Xa levels after LMWH administration to assess the pharmacokinetic properties of LMWH and evaluate whether bioaccumulation occurs with repeated dosing.

Materials and Methods

Study Identification

We sought published and unpublished prospective randomized trials that compared an LMWH with another anticoagulant for preventing thrombosis of the extracorporeal dialysis circuit among patients who were receiving chronic hemodialysis or hemofiltration. We searched three electronic databases: MEDLINE (1966 to March week 2 2004), EMBASE (1980 to 2004 week 13), and the Cochrane Central Register of Controlled Trials (Issue 1, 2004). After consultation with a professional librarian, we developed a keyword and subject heading search strategy limited to clinical trials and/or randomized controlled trials without language restrictions (Appendix A). We searched conference proceedings and papers in the FirstSearch electronic databases (Proceedings and PapersFirst, updated April 9, 2004). We manually reviewed the reference lists of the identified studies, conferred with thromboembolism experts, and contacted pharmaceutical companies for additional studies.

Study Selection

Studies were included when they fulfilled the following inclusion criteria: (*1*) treatment groups were randomly assigned; (*2*) patients were ≥18 yr and had ESRD that required chronic intermittent hemodialysis or hemofiltration; (*3*) an LMWH commercially available in Canada (dalteparin, enoxaparin, nadroparin, or tinzaparin) was compared with a different anticoagulant; (*4*) one of the following outcomes was measured: bleeding, thrombosis of the extracorporeal circuit, or anti-Xa levels. Studies were excluded when patients had underlying hypercoagulability or when anticoagulants or antiplatelet agents were administered in addition to LMWH. Study selection was performed independently in duplicate by two reviewers, with disagreements resolved by consensus.

Study Validity Assessment

Unmasked assessment of study validity was completed independently and in duplicate. We assessed studies for methodologic features including concealed treatment allocation, reporting of groups blinded to treatment, analysis by intention-to-treat, and use of objective outcome assessments. We report the validated quality assessment score proposed by Jadad (10), whereby one point was assigned each for randomization, blinding, and follow-up, with one additional point if the randomization and blinding were appropriate, for a maximum score of five. Studies were categorized as low (≤2) or high (≥3) quality. We also recorded sources of funding. Disagreements were resolved by consensus.

Data Extraction

Two reviewers independently extracted data on study characteristics and the following outcomes: (*1*) number of patients with bleeding episodes, (*2*) number of hemodialysis sessions complicated by thrombosis, and (*3*) anti-Xa levels. We classified bleeding outcomes as either major or minor. Major bleeding was defined as any clinically overt bleeding that required hospitalization or required transfusion, bleeding into a critical organ or space, or bleeding that caused death. Any other bleeding was classified as minor, including bleeding at vascular access sites. We defined thrombosis of the dialysis circuit as moderate to severe clot formation in the arterial or venous bubble trap, drip chamber, dialyzer, or dialysis lines or thrombosis that required changing of the dialyzer. We abstracted the anti-Xa levels, assay used, and time from LMWH administration. Discrepancies were resolved by consensus. We contacted investigators to clarify data when necessary.

Statistical Analyses

We evaluated agreement between raters for study selection and study validity using a weighted κ statistic. Only studies that compared an LMWH with UFH were included in the meta-analysis. For the clinical outcomes, we calculated the relative risks (RR) and 95% confidence intervals (CI) using Review Manager (RevMan; Version 4.2 for Windows; Oxford, England; The Cochrane Collaboration, 2003). We used a pooled weighted mean difference and 95% CI for analysis of the vascular access compression times. RR and weighted mean differences were pooled using the Mantel-Haenszel method (random effects model). We evaluated statistical heterogeneity of study results using the I^2 statistic, which measures the extent of inconsistency among the studies' results and is interpreted as approximately the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error.

Sensitivity Analysis

Three *a priori* sensitivity analyses were planned, assessing bleeding and extracorporeal thrombosis on the basis of (*1*) studies that achieved therapeutic anti-Xa levels, defined as anti-Xa ≥0.5 IU/ml; (*2*) studies with ≥1 mo follow-up; and (*3*) LMWH type. The first sensitivity analysis was planned because increasing LMWH doses produce increasing anticoagulant effects, and prophylactic-range anticoagulation becomes therapeutic range by increasing the LMWH dose. We anticipated that both prophylactic and therapeutic dose LMWH would be used, which would affect outcome rates. To address

this dose variability, we analyzed outcomes in studies in which UFH was compared with an LMWH dose that resulted in therapeutic-range anticoagulation, as measured by anti-Xa levels. The second analysis was planned because the bleeding risk is low with a single exposure to UFH or LMWH, and any meaningful analysis of bleeding risk would require participants to be exposed to multiple doses over time. Last, differences in techniques used to prepare LMWH result in variable molecular weights and electrostatic charges, resulting in differing pharmacokinetic profiles among products. Although these differences do not affect LMWH use in the general population, they may influence bioaccumulation and, hence, clinical outcomes in patients with renal failure.

Results

Study Identification and Selection

Our search identified 146 published studies (Figure 1). We found no unpublished studies or relevant conference proceedings. One additional study was identified through reference review (11), for a total of 147 potential studies. We excluded 114 studies after title and abstract screening using inclusion and exclusion criteria. Of the 33 remaining studies, 15 did not meet the inclusion criteria after article review: 14 studies were not randomized (12–25), and one study used a historical control UFH arm (26). One study was excluded because all patients had underlying hypercoagulability (27). Thus, we included 17 studies in this systematic review (11,28–43), and 11 of these were included in the meta-analysis comparing LMWH with UFH (11,28–32,35,36,38–40). Interrater agreement for study selection was excellent, with a weighted κ of 0.93 (95% CI, 0.87 to 0.99).

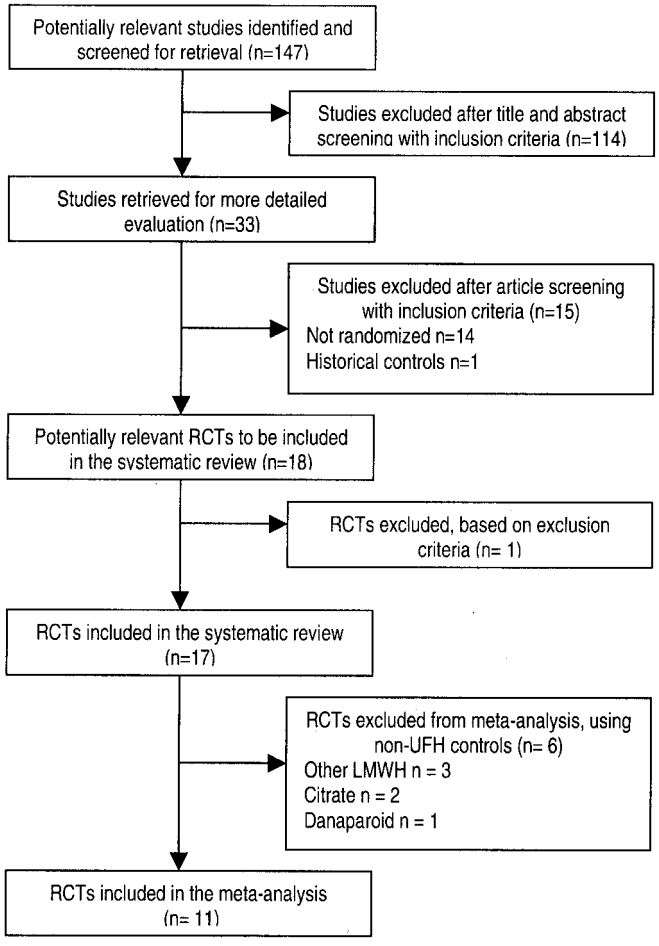

Figure 1. Progression of study selection.

Study Characteristics

The design of the included studies included 10 randomized open trials using a crossover design (11,28,30,32,34–36,38–40), one blinded crossover trial (38), and six open trials using a parallel design (29,31,33,41–43) (Table 1). Studies ranged in size from eight to 149 patients. Three studies included patients who were receiving hemofiltration (29,35,39). Six studies permitted dose adjustments according to bleeding symptoms and/or extracorporeal circuit thrombosis; the mean LMWH dose is reported for these studies (29,34,36,40,41,43). A run-in phase was used in two studies, in which an individualized (optimal) LMWH dose was determined before (43) or after randomization (31). Two studies were dose-finding studies (30,32). In three studies, the patient's hematocrit or duration of hemodialysis determined the initial LMWH dose (31,34,43). One study used therapeutic-dose enoxaparin (1 mg/kg) and subsequently decreased the mean dose to 0.69 mg/kg (slightly above prophylactic range) after frequent minor access site bleeding was noted (36). The remaining studies used LMWH doses in the prophylactic range, administered in fixed or weight-adjusted doses. All studies administered LMWH as a bolus injection, most into the arterial side of the dialyzer; six of the seven dalteparin studies followed the LMWH bolus with an infusion. The comparison anticoagulant was UFH in 11 studies (11,28–33,35,36,39,40), a different LMWH in three studies (38,42,43), citrate in two studies (34,37), and danaparoid in one study (41). UFH was administered in all studies as a bolus followed by continuous infusion, either in fixed or weight-adjusted doses. Fixed-bolus doses of UFH ranged from 1500 to 5000 IU, and weight-adjusted doses ranged from 36 to 62 IU/kg; these doses span the range of prophylactic- to therapeutic-dose anticoagulation.

Patient Characteristics

Patients who were included in the systematic review were hemodialysis dependent, without characteristics known to increase baseline bleeding risks (including previous bleeding and medications that influence bleeding risk) or thrombosis (Table 2). The duration of follow-up was variable, ranging from assessment after a single dialysis with LMWH (37,41,42) to repeated dialyses and assessments up to 36 mo (39). Losses to follow-up were considerable; of the 645 patients who were included in the systematic review, 562 had complete data and 83 (14.8%) were lost to follow-up. Reasons for loss to follow-up, when specified, included renal transplantation, death, and change to peritoneal dialysis. In studies that recorded mortality, the cause of death was reportedly unrelated to anticoagulant treatment.

Table 1. Study characteristics[a]

Study, Year (Reference)	Patients (*n*); LMWH/UFH (*n/n*)[b]	Frequency and Duration of Dialysis	Type of LMWH	Mean LMWH Dose	Control	Mean Comparison (Control) Dose
Crossover design studies						
Borm et al., 1986 (28)	10	2×/wk 4 h	Dalteparin	(B) 18 IU/kg; (I) 9 IU/kg per h	UFH	(B) 36 IU/kg; (I) 18 IU/kg per h
Anastassiades et al., 1989 (30)	28	2–3×/wk 4–7 h	Dalteparin	(B) 3000 IU, 4000 IU, or 5000 IU; (I) 750 IU/h	UFH	(B) 5000 IU; (I) 1500 IU/h
Anastassiades et al., 1990 (11)	24	2×/wk 4–7 h	Dalteparin	(B) 3000 IU or 4000 IU; (I) 750 IU/h	UFH	(B) 5000 IU; (I) 1500 IU/h
Ryan et al., 1991 (32)	8	2×/wk 5–7 h	Tinzaparin	(B) 1250 IU, 2500 IU, or 5000 IU	UFH	(B) 5000 IU; (I) 1500 IU/h
Janssen et al., 1996 (34)	23	2–3×/wk 4 or 6 h	Nadroparin	(B) 60 IU/kg (Hct <0.3 or HD >4 h) or 80 IU/kg (HD >4 h)	Citrate	(I) 0.68 mmol/min
Moia et al., 1997 (35)	10	NS 3.5 h	Dalteparin	3778 IU; given as 30% B and 70% I	UFH	5833 IU; given as 30% B and 70% I
Saltissi et al., 1999 (36)	36	3×/wk 3–5 h	Enoxaparin	(B) initial 1 mg/kg; titrated 0.69 mg/kg	UFH	(B) 50 IU/kg; (I) 1000 IU/h
Apsner et al., 2001 (37)	18	NS 4 h	Dalteparin	(B) 5094 IU	Citrate	(I) 60 mmol/h
Reach et al., 2001 (38)	15	3×/wk 4 h	Nadroparin	(B) 70 IU/kg	Reviparin	(B) 50, 60, 70, 85, or 100 IU/kg
Stefoni et al., 2002 (39)	54	3×/wk 4 h	Nadroparin	(B) 64.6 IU/kg	UFH	(B) 1500 IU; (I) 1500 ± 500 IU
Lord et al., 2002 (40)	32	3×/wk 3.5–4 h	Tinzaparin	(B) 4318 IU	UFH	(B) 8208 IU (50–75 IU/kg bolus; then I to maintain activated clot time 150–200 s)
Parallel design studies						
Schrader et al., 1988 (29)	70 35/35	NS 4.5–5 h	Dalteparin	(B) 34 IU/kg; (I) 12 IU/kg per h	UFH	(B) 62 IU/kg; (I) 17 IU/kg per h
Nurmohamed et al., 1991 (31)	70 35/35	2–3×/wk 4–6 h	Nadroparin	(B) 80 IU/kg (Hct <0.3) or 100 IU/kg (Hct ≥0.3 or HD >4 h)	UFH	(B) 2500 IU; (I) 600–2200 IU/h
Harenberg et al., 1995 (33)	20 10/10	NS 3–4.5 h	Dalteparin	(B) 1750 IU; (I) 26.4 IU/kg per h	UFH	(B) 2650 IU; (I) 36.6 IU/kg per h
Polkinghorne et al., 2002 (41)	18 5 dalteparin 6 enoxaparin 7 control	3×/wk 4 h	Dalteparin Enoxaparin	(B) 39 IU/kg (B) 0.7 mg/kg	Danaparoid	(B) 35 U/kg
Liu and Wang, 2002 (42)	60 30/30	3×/wk 4 h	Nadroparin	(B) 4100 IU	Other LMWH	(B) 4100 IU
Beijering et al., 2003[c] (43)	149 73 tinzaparin 76 dalteparin	2–3×/wk NS	Tinzaparin	(B) 5024 IU (I) 12 IU/kg per h if HD >4 h	Dalteparin	(B) 5546 IU; (I) 12 IU/kg per h if HD >4 h

[a] LMWH, low molecular weight heparin; UFH, unfractionated heparin; B, bolus; I, infusion; NS, not specified.
[b] No. of patients in each arm (LMWH/UFH) applicable for parallel design trials only.
[c] Designation of control LMWH arbitrary in comparisons of different LMWH.

Table 2. Clinical characteristics of the patients in the studies included in systematic review[a]

Study, Year (Reference)	Mean Age ± SD	Excluded Patients			Duration of Followup	Patients Lost to Follow-up LMWH/ Control, *n/n*
		Other Anticoagulants	Previous Bleeding	Other		
Borm et al., 1986 (28)	58.6	x	—	—	NS	0/0
Schrader et al., 1988 (29)		x		NSAID use	12 mo	5/3
LMWH	54.0 ± 15.2					
control	51.6 ± 17.9					
Anastassiades et al., 1989 (30)	NS	NS	NS	NS	NS	8 (arm NS)
Anastassiades et al., 1990 (11)	NS	NS	NS	NS	8 wk	3 (arm NS)
Nurmohamed et al., 1991 (31)	NS	NS	NS	NS	6 mo	8/5
Ryan et al., 1991 (32)	NS	x	—	—	NS	1 (arm NS)
Harenberg et al., 1995 (33)						
LMWH	53.4 ± 19.9	NS	NS	NS	NS	0/0
control	59.1 ± 15.72					
Janssen et al., 1996 (34)	60.8 ± 3.0	—	x	HIV+, NSAID use, HD <3 mo, age >80	10 wk	2 (arm NS)
Moia et al., 1997 (35)	50 ± 11	NS	NS	NS	NS	0/0
Saltissi et al., 1999 (36)	68.5 (22–85)[b]	x	x	Drugs affecting heparin activity	24 wk	5 (arm NS)
Aspner et al., 2001 (37)	50.2 ± 17	—	—	Liver disease	2 wk	2 (arm NS)
Reach et al., 2001 (38)	66.7 ± 12	x	—	—	8 wk	0/0
Polkinghorne et al., 2002 (41)	NS	x	—	HIT, HD through catheter, vascular access thrombosis <3 mo	4 wk	1 dalteparin 0 enoxaparin 0 control
Liu and Wang, 2002 (42)	44.7 (21–64)	x	x	Liver disease	NS	0/0
Stefoni et al., 2002 (39)	63 ± 7	—	x	Hereditary bleeding disorder, dyslipidemia, MPD, malignant ds, APLA, LA positive	36 mo	7 deaths (arm NS)
Lord et al., 2002 (40)	66.6 ± 14.8	x	x	Plts <150, liver failure, central venous catheter	8 wk	2/0
Beijering et al., 2003 (43)						
tinzaparin	58.5 ± 16.1	x	x	HIT, stroke <6 mo, hypertension, pregnancy	NS	19 tinzaparin
dalteparin	60.1 ± 18.4					12 dalteparin

[a] APLA, antiphospholipid antibody syndrome; HD, hemodialysis; HIT, heparin induced thrombocytopenia; HIV, human immunodeficiency virus; LA, lupus anticoagulant; NS, not specified; NSAID, nonsteroidal anti-inflammatory drug; MPD, myeloproliferative disease; plts, platelet count $\times 10^9$/L.

[b] Median age and range.

Study Quality

Among the randomized trials, only one described the sequence generation for the randomization process (43), and one study was reported as double blind and used concealed treatment allocation (38) (Table 3). Consequently, most studies scored 1 or 2 using the Jadad scale, and quality assessment proved to be nondiscriminatory. Eleven studies provided a description of patient withdrawals and dropouts, but most did not indicate or did not conduct analysis using the principal of intention-to-treat. Objective assessments for bleeding were used in four studies (36,39,40,43), and a scale used to assess extracorporeal thrombosis was used in six studies (34,36,40–43). Six studies declared their funding source; three were sponsored by pharmaceutical companies (36,40,43), and three were sponsored by research foundations (33,34,39). The interrater agreement for validity assessment (based on the Jadad score) was good (weighted κ, 0.64; 95% CI, 0 to 1.28).

Clinical Outcomes

Bleeding symptoms or access compression times were reported in 12 studies; 17 assessed extracorporeal thrombosis, and 14 measured anti-Xa levels.

Bleeding

LMWH Compared with UFH. Bleeding events were analyzed in six studies (28,29,31,36,39, 40) (Tables 4 through 6). Most bleeding events were minor, occurring at vascular access sites. One study reported minor bleeding, including epistaxis and subconjunctival bleeding (39); two studies did not specify the site (31,36). Major bleeding was reported in one study in which a patient had access site bleeding after hemodialysis with tinzaparin; however, the patient's activated partial thromboplastin time was elevated and investigators concluded that the patient accidentally received additional UFH (40). Four studies measured the time required to stop bleeding at the vascular access site after hemodialysis (11,36,39,40), and one study measured a bleeding time (35). Arterial compression times were used for the analysis. One study reported bleeding in terms of transfusion requirements (29).

Because the number of major bleeding events was so small, we combined major and minor bleeding events for the statistical analysis (Figure 2). The pooled RR for bleeding with LMWH compared with UFH was 0.96 (95% CI, 0.27 to 3.43; $P = 0.95$). Statistical tests to detect heterogeneity of results among trials were significant ($I^2 = 62.8\%$; $P = 0.03$). Analysis according to the vascular access compression time demonstrated no difference in time required to stop bleeding at the access site with LMWH compared with UFH (pooled weighted mean difference, −0.87; 95% CI, −2.75 to 1.02; $P = 0.37$; Figure 3). In the sensitivity analyses, the pooled RR for bleeding were 0.24 (95% CI, 0.05 to 1.16) for studies that achieved therapeutic anti-Xa levels and 0.81 (95% CI, 0.17 to 3.83) for studies with >1 mo of follow-up (Figure 2). There were an insufficient number of studies to conduct the sensitivity analysis according to the type of LMWH.

LMWH Compared with Other Anticoagulants. Major bleeding was reported in one study that compared tinzaparin with dalteparin (one gastrointestinal bleed and one hemorrhoidal bleed, respectively) with similarly no difference in minor bleeding, which occurred in ~1.5% of hemodialysis sessions with both LMWH (43). A dose-finding study of reviparin demonstrated similar bleeding times with reviparin (85 IU) and nadroparin (6.11 ± 3.20 and 7.33 ± 9.15 min, respectively) (38). In a study that compared enoxaparin and dalteparin with danaparoid, no bleeding episodes were reported (41).

Extracorporeal Thrombosis

LMWH Compared with UFH. Thrombosis that occurred within the dialysis circuit was analyzed in five of 11 possible studies (28,29,32,36,40) (Table 7). Two studies reported units that could not be converted to a proportion of hemodialysis sessions (11,30), and another two reported clotting per number of patients affected (31,33). Two studies had no recorded events, resulting in nonestimable RR (35,39). In the assessable studies, the pooled RR for extracorporeal circuit thrombosis was 1.15 (95% CI, 0.70 to 1.91), favoring UFH (Figure 4). Statistical heterogeneity between studies was significant ($I^2 = 57.3\%$; $P = 0.03$). Sensitivity analyses that were based on therapeutic anti-Xa levels and follow-up time of >1 mo resulted in RR of 1.30 (95% CI, 0.99 to 1.70) and 0.99 (95% CI, 0.56 to 1.77), respectively. The sensitivity analysis according to LMWH type was not performed because of an insufficient number of studies.

LMWH Compared with Other Anticoagulants. Six studies evaluated other anticoagulants (34,37,38,41–43). Two studies that used citrate showed a trend toward lower filter clotting scores with citrate compared with dalteparin (0.31 ± 0.70 *versus* 0.56 ± 0.89) (37) and similar frequencies of clotting of the dialysis circuit with nadroparin compared with citrate (34). In the studies that evaluated other LMWH, no differences were found between tinzaparin and dalteparin (43), reviparin and nadroparin (38), dalteparin and enoxaparin *versus* danaparoid (41), and nadroparin and a domestically manufactured LMWH (42).

Anti-Xa Levels and Risk of Bioaccumulation

The degree of anticoagulation achieved using LMWH, as measured with anti-Xa levels, is shown in Table 8. Three studies did not report the type of heparin assay used (11,40,42); the rest used chromogenic Xa assays. Anti-Xa levels were measured once in 12 studies and on more than one occasion in two studies (29,41). There was no significant difference between anti-Xa levels measured at the fourth week of administration compared with the first week in patients who received dalteparin or enoxaparin (41). Similarly, no evidence of bioaccumulation was shown using dalteparin and UFH over 12 mo, when anti-Xa levels were measured every 3 mo (29).

Discussion

In this meta-analysis, we found that for bleeding events and clotting within the extracorporeal hemodialysis circuit, LMWH seem to be at least as safe and effective as UFH during chronic hemodialysis. No difference was demonstrated in the number

Table 3. Methodologic quality of studies included in the meta-analysis[a]

Study, Year (Reference)	Randomization Sequence Described	Double Blinding,[b] Blinded Groups[c]	Description of Withdrawals and Dropouts[d]	Objective Outcome Measurements[e]			Intention-to-Treat Analysis	Quality Assessment; Jadad Score
				Bleeding Symptoms	Bleeding Time	Dialysis Circuit Thrombosis		
Borm et al., 1986 (28)	No	No, OA	No	NS	NE	NS	NA	Low; 1
Schrader et al., 1988 (29)	No	No —	Yes	NS	NE, no. of packed red blood cells transfused	NS	Unclear	Low; 2
Anastassiades et al., 1989 (30)	No	No —	Yes	NE	NE	Yes, visual inspect q1h during HD	No	Low; 2
Anastassiades et al., 1990 (11)	No	No —	Yes	NE	Yes	Yes, clot frequency measured q1h	No	Low; 2
Nurmohamed et al., 1991 (31)	No	No —	Yes	NS	NE	Yes, visual inspect at 4, 13, and 26 wks	No	Low; 2
Ryan et al., 1991 (32)	No	No —	Yes	NE	NE	Yes, visual inspect q1h during HD	Yes	Low; 2
Harenberg et al., 1995 (33)	No	No —	No	NE	NE	Yes, visual inspect before and after HD	NA	Low; 1
Janssen et al., 1996 (34)	No	No —	Yes	NE	Yes	Yes, 3-point scale at end of HD	Unclear	Low; 2
Moia et al., 1997 (35)	No	No —	No	NS	Yes	NS	NA	Low; 1
Saltissi et al., 1999 (36)	No	No —	Yes	Yes, rated severity	Yes	Yes, 10-point scale at end of HD	Unclear	Low; 2
Apsner et al., 2001 (37)	No	No —	Yes	NE	Yes	Yes, filter clotting score	Yes	Low; 2
Reach et al., 2001 (38)	No	Yes, P, I, HCP, OA	No	NE	Yes	Yes, visual inspect q1h during HD	NA	Low; 2
Polkinghorne et al., 2002 (41)	No	No —	Yes	NS	NE	Yes, 4-point scale at end of HD	No	Low; 2
Liu and Wang, 2002 (42)	No	No —	No	NE	Yes	Yes, 2-point scale at end of HD	NA	Low; 1
Stefoni et al., 2002 (39)	No	No —	NS	Yes, major/ minor	Yes	Yes, visual inspect during HD	NA	Low; 1
Lord et al., 2002 (40)	No	No —	Yes	Yes, survey with each HD	Yes	Yes, 4-point scale during & end of HD	Yes	Low; 2
Beijering et al., 2003 (43)	Y, opaque envelopes	No, P, HCP	Yes	Yes, major/ minor	NE	Yes, 4-point score at end of HD	Yes	High; 4

[a] P, patients; I, investigators; HCP, health care providers; OA, outcome assessors; —, not indicated. NA, not applicable; NE, not evaluated; NS, not specified.
[b] Allocation concealment with respect to investigators; considered unclear if not reported.
[c] Study considered double blind if reported as such; blinded groups include P, I, HCP, and OA.
[d] Studies with no withdrawals/dropouts must explicitly state as such, otherwise considered not reported and given a score of 0 on Jadad scale.
[e] Study considered to have objective outcome measurement if a scale/score was used to measure extent of bleeding and/or degree of clotting in extracorporeal circuit.

Table 4. Summary of meta-analysis for bleeding events with LMWH compared with UFH

Study, Year (Reference)	Patients LMWH/UFH (*n/n*)	Bleeding in LMWH Group (Patients)	Bleeding in UFH Group (Patients)	Relative Risk (95% CI)	Notes
Studies using objective outcome assessment					
Saltissi et al., 1999[a] (36)	36/36	12	6	2.00 (0.84–4.75)	Overall no. of events before (1 mg/kg) and after (0.69 mg/kg) dose adjustment LMWH bleeding 1 severe, 11 moderate UFH bleeding 0 severe, 6 moderate
Lord et al., 2002 (40)	32/32	3	8	0.38 (0.11–1.29)	LMWH bleeding (1 major access, 2 minor access); UFH (8 minor access)
Stefoni et al., 2002 (39)	54/54	0	7	0.07 (0.00–1.14)	UFH bleeding (0 major; 2 epistaxis, 5 subconjunctival hemorrhage)
Studies with method of outcome assessment not specified					
Borm et al., 1986 (28)	10/10	2	1	2.00 (0.21–18.69)	No major bleeding; all noted bleeding events were hematomas at bleeding site
Nurmohamed et al., 1991 (31)	35/35	3	0	7.00 (0.37–130.69)	No major bleeding reported 3 withdrawals due to bleeding (unclear which arm) LMWH bleeding (3 minor access)
Schrader et al., 1988 (29)	35/35	0	0	Not estimable	No reported bleeding events throughout study
Summary	202/202	20	22	0.96 (0.27, 3.43) $P = 0.95$	

[a] Bleeding occurring during dialysis used for analysis. Data obtained from authors show that 33 patients received LMWH and UFH; statistical analysis done by intention-to-treat (36 patients).

Table 5. Summary of meta-analysis for vascular access compression time with LMWH compared with UFH[a]

Study, Year (Reference)	Mean Compression Time, SD (min)		*P* Value	Weighted Mean Difference (95% CI)
	LMWH	UFH		
Anastassiades et al., 1990 (11)	(A) 12.46 ± 2.19 (V) 8.45 ± 1.04	(A) 13.44 ± 2.54 (V) 11.12 ± 1.39	<0.05 NS	−0.98 (−2.32 to 0.36)
Moia et al., 1997 (35)	9.5[b]	17.25[b]	<0.05	—
Saltissi et al., 1999 (36)				
1 mg/kg	(A) 6.47 ± 2.73 (V) 6.30 ± 2.45			0.95 (−0.21 to 2.11)
		(A) 5.52 ± 2.25	—	
0.69 mg/kg	(A) 6.50 ± 2.77 (V) 6.33 ± 2.68	(V) 5.45 ± 2.37		0.98 (−0.19 to 2.15)
Stefoni et al., 2002 (39)	7 ± 3	13 ± 7	<0.01	−6.00 (−8.03 to −3.97)
Lord et al., 2002 (40)	9.5 ± 3.0	9.5 ± 1.8	—	0.00 (−1.21 to 1.21)
Summary				−0.87 (−2.75 to 1.02) $P = 0.37$

[a] A, arterial; V, venous; HD, hemodialysis.
[b] Bleeding time, median.

Table 6. Summary of meta-analysis for transfusion requirements with LMWH compared with UFH

Study, Year (Reference)	LMWH	UFH	*P* Value	Notes
Schrader et al., 1988 (29)	1 unit/37 HD (2.71%) (19 pts; 76 units)	1 unit/26 HD (3.85%) (16 pts; 88 units)	<0.05	Transfusion if Hg <6.5 g/dl

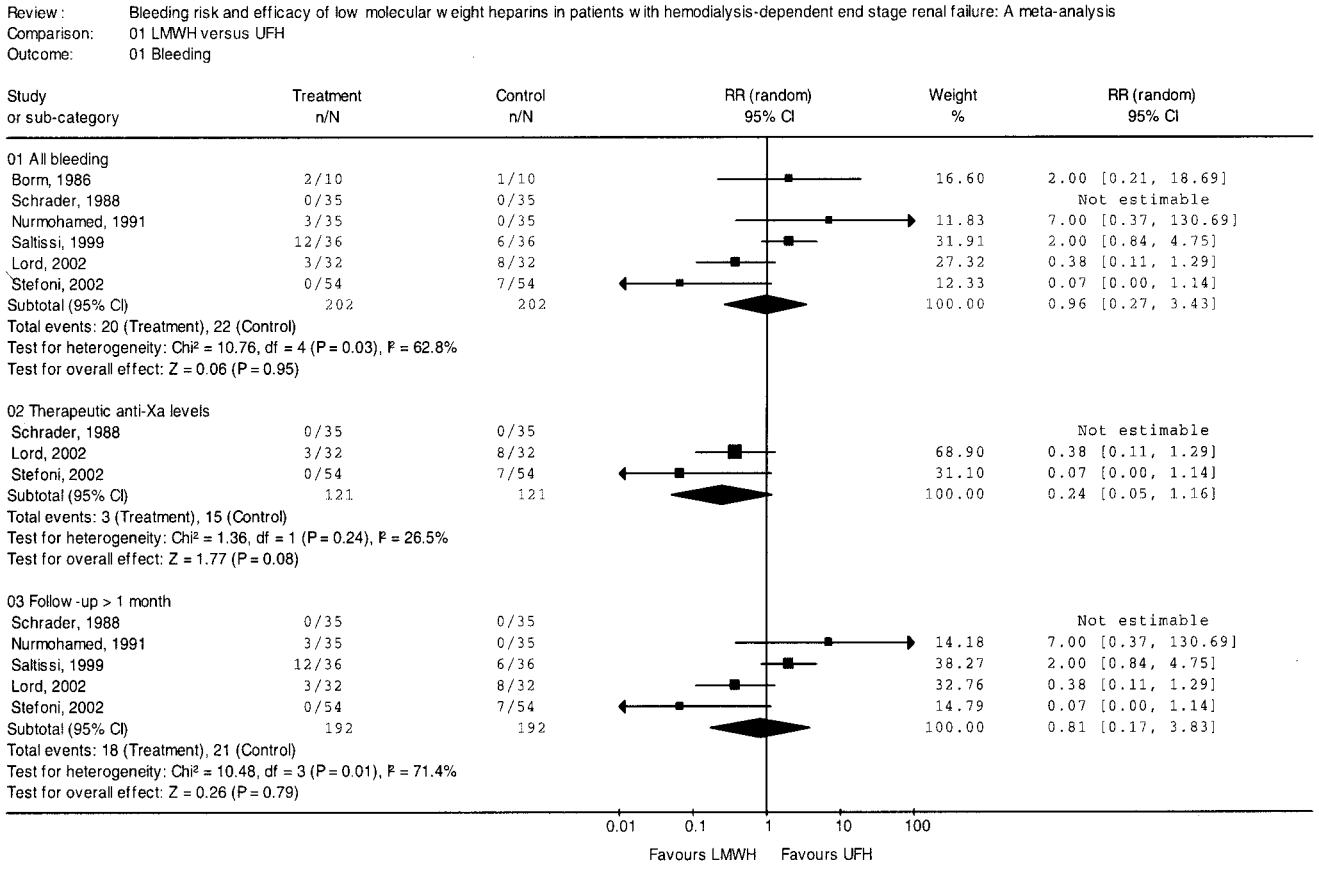

Figure 2. Individual study and summary relative risks for bleeding.

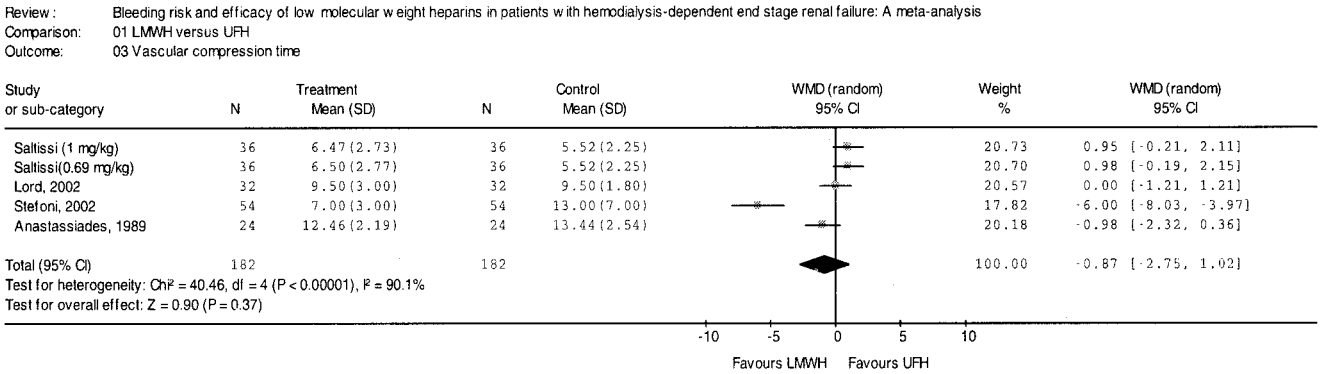

Figure 3. Individual study and summary weighted mean differences for bleeding assessed as vascular access compression time.

of bleeding events or in vascular access compression times. However, these conclusions must be interpreted in light of the statistical heterogeneity and the wide CI of our findings.

The heterogeneity of results that we observed likely reflects the variability in LMWH doses. Previous studies that evaluated UFH in hemodialysis have demonstrated that anti-Xa levels

Table 7. Summary of meta-analysis for extracorporeal circuit thrombosis[a]

Study, Year (Reference)	Total (*n*), LMWH/ UFH (*n*/*n*)	Circuit Thrombosis in LMWH Group (*n*)	Circuit Thrombosis in UFH Group (*n*)	Relative Risk (95% CI)
Studies assessing no. of HD sessions with thrombosis				
Borm et al., 1986 (28)	20			
	10/10	4	4	1.00 (0.34–2.93)
Schrader et al., 1988 (29)	10,242			
	5045/5197	80	69	1.19 (0.87–1.64)
Ryan et al., 1991 (32)	UFH 8			
1250 IU	8	8	0	17.00 (1.14–252.54)
2500 IU	8	1	0	3.00 (0.14–64.26)
5000 IU	7	1	0	3.38 (0.16–71.67)
Saltissi et al., 1999[b] (36)	2252			
	1111/1141	17	35	0.50 (0.28–0.89)
Lord et al., 2002[c] (40)	760	32	21	1.54 (0.90–2.62)
	378/382			
Summary	6567/6754	143	129	1.15 (0.70–1.91)
				$P = 0.58$
Studies assessing no. of patients with extracorporeal thrombosis				
Nurmohamed et al., 1991 (31)	70			
week 4	27/30	0/26 (0%)	1/29 (3%)	—
week 13		1/27 (4%)	0/30 (0%)	
week 26		2/27 (7%)	0/30 (0%)	
Harenberg et al., 1995 (33)	20			—
	10/10	1 (1%)	1 (1%)	
Studies in which no. of HD sessions unknown				
Anastassiades et al., 1989 (30)	NS	0	0	—
Moia et al., 1997 (35)	NS	0	0	—
Stefoni et al., 2002 (39)	NS	0	0	—
Studies reporting unique units[d]				
Anastassiades et al., 1990 (11) (clot frequency)	NS	0.20	0.15	$P < 0.02$

[a] NS, not stated.
[b] Clotting of dialyzer used in meta-analysis, with grade ≥5 (out of 10) defining clotting.
[c] Clotting of dialyzer used in meta-analysis, with scale ≥2 (out of 4) defining clotting.
[d] Clot frequency: number of hourly observations with clotting/duration of HD; filter score: 0 (no sign of clotting) to 4 (complete occlusion).

>0.5 IU/ml provide sufficient anticoagulation to prevent clotting of the extracorporeal circuit and occur with a UFH 5000 IU bolus and infusion of 1500 IU/h (44). Consequently, the optimal UFH dose was compared with potentially suboptimal doses of LMWH; use of subtherapeutic LMWH doses might both decrease bleeding and increase circuit thrombosis. This is illustrated by one dose-finding study in which a single dose of tinzaparin 1250 IU resulted in all dialyses complicated by thrombosis but only one dialysis that required additional UFH when tinzaparin doses of 2500 and 5000 IU were used (32). Another study found that circuit clotting occurred more frequently with LMWH compared with UFH in the early phase of the study; 26 of 32 patients required dose adjustments, with 20 of these patients requiring increased LMWH doses (40). As a corollary, higher doses of LMWH are expected to increase bleeding risk, and in a study of therapeutic-dose enoxaparin, frequent minor bleeding was noted, which decreased after dose reduction (36).

Our results are strengthened by similar findings in the sensitivity analyses. In the analysis that was based on therapeutic anti-Xa levels, higher (therapeutic) anti-Xa levels should be associated with an increased anticoagulant effect and, therefore, an increased bleeding risk. However, the RR of bleeding seemed to be lower when only studies that achieved therapeutic anti-Xa levels were analyzed (RR, 0.24 *versus* 0.96 in the primary analysis). This may be due to the methods by which bleeding outcomes were assessed, because studies that used objective outcome assessments (39,40) demonstrated decreased bleeding risks with LMWH compared with studies that did not report their method of outcome assessment (28,31). The

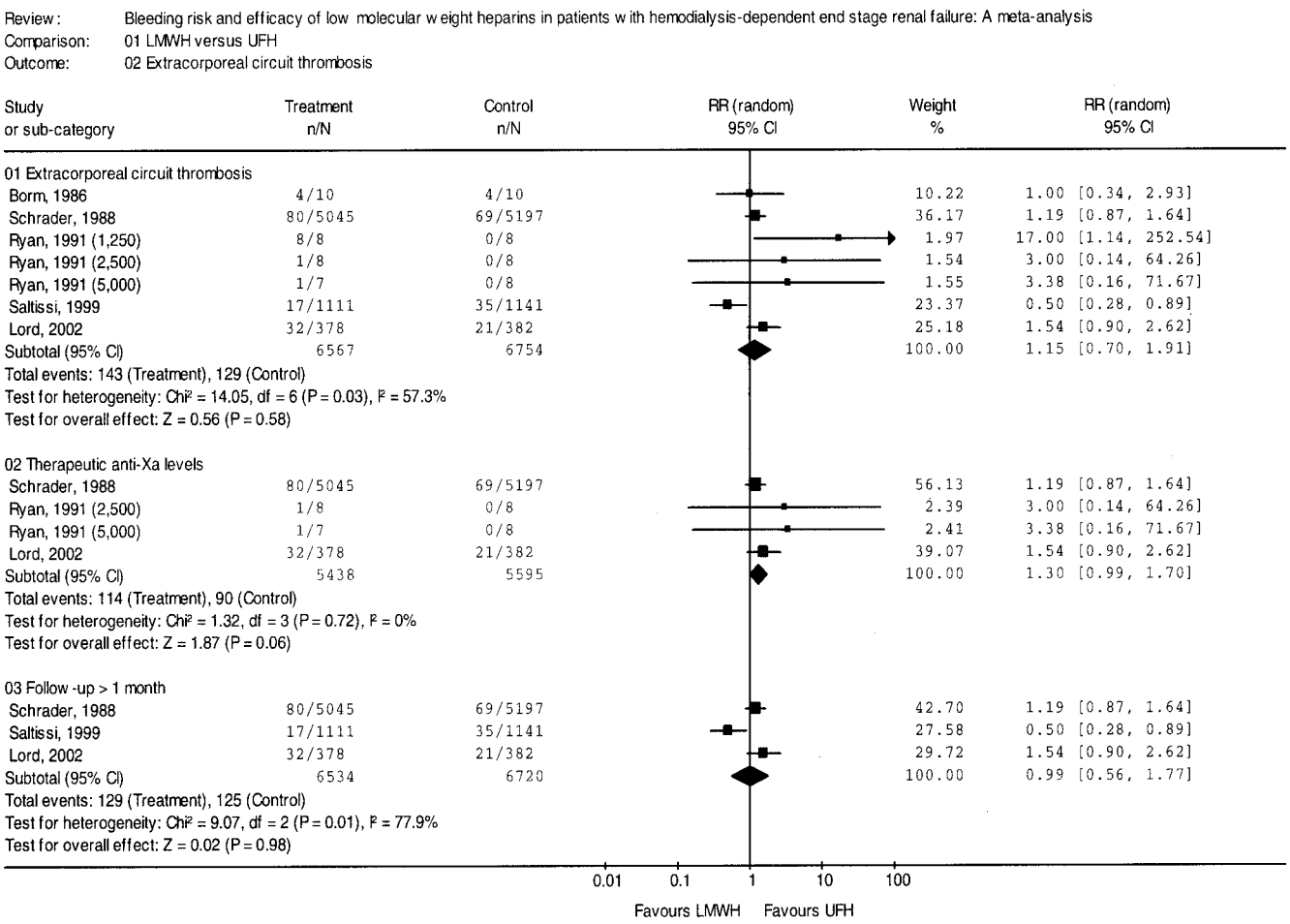

Figure 4. Individual study and summary relative risks for extracorporeal circuit thrombosis.

sensitivity analysis of studies with >1 mo follow-up was also suggestive of a lower rate of bleeding compared with the primary analysis done for bleeding.

Although proposed, the evidence that LMWH cause less microvascular bleeding than UFH has been demonstrated only in animal models and has not been confirmed in humans (45). In randomized trials comparing enoxaparin with UFH for acute coronary syndromes, major bleeding rates with enoxaparin and with UFH in patients with renal insufficiency were not significantly different (7.5 and 5.8%, respectively; $P = 0.56$) (6). This was also seen in a retrospective cohort study in which therapeutic-dose enoxaparin that was administered to patients with glomerular filtration rates <60 ml/min was associated with a major bleeding rate of 20.7 per 1000 patient-days, similar to that observed with UFH (26.3 per 1000 patient-days) (46). The results of our meta-analysis support previous individual findings in which the bleeding risk of LMWH seems at least equivalent to UFH when used in the setting of hemodialysis. It is important that this not be interpreted that LMWH may be used to treat thrombosis in patients with renal insufficiency, because LMWH were not evaluated for that indication in this meta-analysis. Intravenous doses of LMWH resulting in short-term therapeutic anticoagulation for the prevention of dialysis circuit thrombosis are lower than the subcutaneous doses administered for therapeutic anticoagulation. The low rates of major bleeding observed in these randomized trials, compared with studies of therapeutic anticoagulation for acute thrombosis, likely reflect the relatively low doses and intermittent administration of LMWH used.

Another important consideration is the inability to reverse completely the anticoagulant effects of LMWH using protamine sulfate, as compared with UFH (47). Patients with increased bleeding risks were excluded from many of the trials included in this analysis. Therefore, our conclusions should be taken in light of the patient population studied. Patients who are perceived to be at increased risk of bleeding may be unsuitable candidates for LMWH.

There are several limitations to this meta-analysis. First, analyzing all LMWH assumes a class effect, whereas LMWH may behave differently in patients with renal insufficiency. Studies have shown decreased clearance of enoxaparin in patients with renal failure compared with patients without renal failure (5). Other studies that have used tinzaparin have not observed bioaccumulation even at low levels of calculated creatinine clearance (48). Thus, combining LMWH may result in an overall estimate that, although useful, does not reflect the true risk of an individual LMWH. Although we planned *a priori* to estimate outcomes associated with each type of

Table 8. Measured anti-Xa levels[a]

Study, Year (Reference)	LMWH Dose	Time Repeat Levels	Anti-Xa Level (IU/mL), (SD) Time from LMWH Administration (h)							
			0	1	2	3	4	5	24	48
Dalteparin										
weight-adjusted										
Borm et al., 1986 (28)	(B) 18 IU/kg; (I) 9 IU/kg per h	—	0.007	0.21 ± 0.11	0.23 ± 0.09	0.27 ± 0.10	0.36 ± 0.21	—	—	—
Schrader et al., 1988 (29)	(B) 34 IU/kg; (I) 12 IU/kg per h	Start	—	—	0.58	—	—	—	—	—
		3 mo			0.66					
		6 mo			0.65					
		9 mo			0.63					
		12 mo			0.61					
Polkinghorne et al., 2002 (41)	(B) 39 IU/kg	Wk 1	0.004 ± 0.004	0.58 ± 0.072	0.42 ± 0.054	0.29 ± 0.045	0.20 ± 0.045	—	0.01 ± 0.008	<0.01
		Wk 4	<0.01	0.70 ± 0.102	0.49 ± 0.064	0.34 ± 0.033	0.26 ± 0.038	—	<0.01	0.01 ± 0.009
fixed dose										
Harenberg et al., 1995 (33)	(B) 1750 IU; (I) 26.4 IU/kg per h		—	—	0.496 ± 0.146	—	—	—	—	—
Moia et al., 1997 (35)	3778 IU total	(B) 1750 IU; (I) 2028 IU/h	0.015 ± 0.008	—	—	0.64[b] ± 0.32	—	—	—	—
Anastassiades et al., 1989 (30)	(B) 3000 IU; (I) 750 IU/h		—	0.82	—	—	—	—	—	—
Anastassiades et al., 1990 (11)	(B) 3500 IU; (I) 750 IU/h		—	0.87	—	—	—	—	—	—
Anastassiades et al., 1989 (30)	(B) 4000 IU; (I) 750 IU/h		—	0.92	—	—	—	—	—	—
Anastassiades et al., 1989 (30)	(B) 5000 IU; (I) 750 IU/h		—	1.00	—	—	—	—	—	—
Beijering et al., 2003 (43)	(B) 5546 IU; (I) 12 IU/kg per h		0.12 ± 0.4	—	0.63 ± 0.4	—	0.44 ± 0.3	—	—	
Enoxaparin										
Polkinghorne et al., 2002 (41)	(B) 0.7 mg/kg	Wk 1	0.05 ± 0.031	0.75 ± 0.046	0.61 ± 0.045	0.46 ± 0.022	0.38 ± 0.023	—	0.08 ± 0.01	0.04 ± 0.015
		Wk 4	0.03 ± 0.009	0.70 ± 0.053	0.57 ± 0.047	0.48 ± 0.042	0.40 ± 0.055	—	0.10 ± 0.018	0.05 ± 0.008
Nadroparin weight-adjusted										
Stefoni et al., 2002 (39)	(B) 64.6 IU/kg		—	—	1.10	0.99	0.60 ± 0.06	—	0	—
Janssen et al., 1996 (34)	(B) 70 IU/kg		—	—	0.75	—	—	—	—	—
Reach et al., 2001 (38)	(B) 70 IU/kg		—	—	0.78	—	0.65	—	—	—
fixed dose										
Liu and Wang, 2002 (42)	(B) 4100 IU		0	—	0.627 ± 0.065	—	0.508 ± 0.063	—	—	—
Tinzaparin										
Ryan et al., 1991 (32)	(B) 1250 IU		—	0.31	0.24	0.20	0.09	—	—	—
Ryan et al., 1991 (32)	(B) 2500 IU		—	0.55	0.4	0.28	0.22	0.15	—	—
Lord et al., 2002[c] (40)	(B) 4318 IU		0.06 ± 0.05	—	0.77 ± 0.20	—	0.59 ± 0.26	—	—	0.03 ± 0.02
Ryan et al., 1991 (32)	(B) 5000 IU		—	0.95	0.80	0.70	0.57	0.50	—	—
Beijering et al., 2003 (43)	(B) 5024 IU		0.12 ± 0.3	—	0.61 ± 0.4	—	0.41 ± 0.3	—	—	—

[a] NS, not specified.
[b] Measured at 3.5 hours.
[c] Subgroup of 10 patients.

LWMH, the small number of studies did not permit a formal analysis of effects. The small number of assessable patients and the infrequent outcome events also precluded a precise estimate of bleeding risk for either LMWH or UFH. However, both the primary analysis and the sensitivity analyses produced similar results, suggesting no identifiable differences in the bleeding rates for LMWH or UFH. Moreover, apparent equivalence in bleeding risk was found in two previous meta-analyses that compared LMWH and UFH for treatment of venous thromboembolism (49,50).

Future trials to examine LMWH in patients with renal failure should compare one or more LMWH with UFH. More direct comparisons of different LMWH are also needed. For addressing issues of bias, random allocation should be concealed. Patients, investigators, and outcome assessors should be blinded, because lack of blinding may be associated with overestimation of the treatment effect and may modify the reported bleeding rates. Anti-Xa levels should be measured to document the level of anticoagulation. An objective, systematic method of outcome assessment should be incorporated in future trials. Sample size calculations and sufficient numbers of patients to detect plausible treatment effects are required, and analysis should be intention-to-treat.

Overall, this meta-analysis identified no difference in bleeding events or thrombosis of the extracorporeal circuit when LMWH was compared with UFH in patients who were receiving chronic hemodialysis and are not at risk for bleeding or were receiving other antithrombotic agents. However, recommendations about anticoagulation for chronic renal failure patients who undergo dialysis will continue to be weak until larger, more rigorous randomized trials are conducted in this field.

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Appendix A. Search strategy example using MEDLINE

Database: Ovid MEDLINE(R) <1966 to March Week 2 2004> Search Strategy:

1	exp Heparin, Low-Molecular-Weight/ (4542)
2	low molecular weight heparin.mp. (3361)
3	(dalteparin or dalteparine or tedelparin or fragmin or fragmine or kabi 2165 or K2165 or fr 860).mp. [mp=title, abstract, name of substance, mesh subject heading] (721)
4	(enoxaparin or enoxaparine or lovenox or clexane or klexane or pk 10169 or emt 996 or emt 967).mp. [mp=title, abstract, name of substance, mesh subject heading] (1251)
5	(nadroparin or nadroparine or fraxiparin or fraxiparine or seleparine or tedegliparine or cy 216).mp. [mp=title, abstract, name of substance, mesh subject heading] (464)
6	(tinzaparin or tinzaparine or innohep or logiparin or logiparine or Ihn1).mp. [mp=title, abstract, name of substance, mesh subject heading] (159)
7	1 or 2 or 3 or 4 or 5 or 6 (5740)
8	exp Renal Dialysis/ (59630)
9	(hemodialy$ or haemodialy$).mp. [mp=title, abstract, name of substance, mesh subject heading] (34969)
10	renal dialysis.mp. (47366)
11	8 or 9 or 10 (65843)
12	7 and 11 (210)
13	limit 12 to (clinical trial or controlled clinical trial or randomized controlled trial) (72)
14	random$.mp. (318547)
15	13 or 14 (318595)
16	12 and 15 (73)
17	from 16 keep 1–73 (73)

Keywords used in the search strategy were low molecular weight heparin(s), dalteparin(e), Fragmin(e), tedelparin, kabi 2165, K2165, enoxaparin(e), Lovenox, Clexane, Klexane, PK-10169, emt 996, emt 967, nadroparin(e), Fraxiparin(e), seleparine, tedegliparine, Cy 216, tinzaparin(e), Innohep, logiparin(e) OR Ihn1, combined with AND renal dialysis, h(a)emodialysis, AND random$.