Effects of Long-Term Low-Molecular-Weight Heparin on Fractures and Bone Density in Non-Pregnant Adults: A Systematic Review With Meta-Analysis

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BACKGROUND: Adults who require long-term anticoagulation with low-molecular-weight heparin (LMWH) such as cancer patients or the elderly may be at increased risk of fractures.

OBJECTIVE: To determine the effects of LMWH therapy of at least 3 months' duration on fractures and bone mineral density (BMD) in non-pregnant adult populations.

METHODS: We systematically reviewed electronic databases (e.g., MEDLINE, EMBASE), conferences and bibliographies until June 2015 and included comparative studies in non-pregnant adult populations that examined the effects of LMWH (≥3 months) on fractures and BMD. We synthesized evidence qualitatively and used random-effects meta-analysis to quantify the effect of LMWH on fractures.

RESULTS: Sixteen articles reporting 14 studies were included: 10 clinical trials (n = 4865 participants) and four observational cohort studies (3 prospective, n = 221; 1 retrospective, n = 30). BMD and fractures were secondary outcomes in the majority of trials, while they were primary outcomes in the majority of observational studies. In participants with venous thromboembolism and underlying cardiovascular disease or cancer (5 RCTs, n = 2280), LMWH for 3–6 months did not increase the relative risk of all fractures at 6–12 months compared to unfractionated heparin, oral vitamin K antagonists or placebo [pooled risk ratio (RR) = 0.58, 95 % CI: 0.23–1.43; I^2 = 12.5 %]. No statistically significant increase in the risk of fractures at 6–12 months was found for cancer patients (RR = 1.08, 95 % CI: 0.31–3.75; I^2 = 4.4 %). Based on the data from two prospective cohort studies (n = 166), LMWH for 3–24 months decreased mean BMD by 2.8–4.8 % (depending on the BMD site) compared to mean BMD decreases of 1.2–2.5 % with oral vitamin K antagonists.

CONCLUSIONS: LMWH for 3–6 months may not increase the risk of fractures, but longer exposure for up to 24 months may adversely affect BMD. Clinicians should consider monitoring BMD in adults on long-term LMWH who are at increased risk of bone loss or fracture.

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INTRODUCTION

Low-molecular-weight heparin (LMWH) is recommended as a first-line agent for the primary and secondary prevention of venous thromboembolism (VTE).[1–7] Extended or long-term therapy with LMWH is indicated in patients who are unable to safely take or tolerate other oral anticoagulants[2,6–11] and in cancer patients, as long-term LMWH has demonstrated superiority for reduction in VTE recurrence and mortality.[12–14]

Studies assessing the safety of long-term LMWH against oral vitamin K antagonists (VKAs) or novel anticoagulants in cancer or other populations were designed to address more common side effects: the risk of bleeding and thrombocytopenia.[15–28] The adverse effects of long-term LMWH on bone in terms of increased risks of fractures (i.e., clinically most important but rare outcomes) and bone loss are less commonly researched and unclear. The effects of LMWH on bone were mainly studied in the pregnant population. Some research has suggested that long-term LMWH prophylaxis in pregnancy for at least 3 months was associated with bone loss and fractures,[29–31] although others have argued that the absolute risk of fracture in this population was small (1–2 %)[32] and that decreases in mean bone mineral density (BMD) of 2–4 % caused by the prophylactic doses of LMWH or unfractionated heparin (UFH) were similar to the bone loss that occurs physiologically during pregnancy.[33,34] Nevertheless, a decrease in BMD of 2–4 % or a small increase in the risk of fracture of up to 2 % would be clinically important for other adult populations such as cancer patients or the elderly who may require long-term LMWH and whose baseline risk of fractures is increased owing to aging or underlying comorbidities.[35–37] Therefore, we reviewed the literature in non-pregnant adult populations to determine the effects of long-term (at least 3 months') use of LMWH on fractures and BMD.

METHODS

Search Strategy and Study Selection

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the conduct and reporting of systematic reviews (online Appendices).[38] We systematically searched electronic databases (MEDLINE, EMBASE, the Cochrane Library and Cochrane Controlled Clinical Trials Register from their inception through June 2015), proceedings from annual meetings and bibliographies (online Appendices 1 and 2). We included English-language clinical trials and observational studies (retrospective and prospective cohort and case-control studies) in non-pregnant adults (age>18 years) that assessed the effects of long-term LMWH treatment (for at least 3 months) on fractures or BMD. We excluded reviews, letters or commentaries (without original data), descriptive (case series/reports) or cross-sectional observational studies, studies that did not report bone outcomes, reported short-term exposure to LMWH or long-term exposure to UFH only or included pregnant participants. One reviewer (OGV) assessed the titles and abstracts of all retrieved citations. Full texts of potentially relevant studies were reviewed by two independent reviewers (OGV, PSS).

Data Extraction and Methodological Quality Assessment

Two reviewers (OGV and CP) extracted data on the number of all reported fractures and absolute or relative changes in BMD as measured by dual-energy X-ray absorptiometry (DXA). At least two reviewers (OGV, CP and PSS) independently assessed the methodological quality of the included studies using previously validated quality assessment checklists (online Appendix 1).[39,40] Disagreements were discussed among the three reviewers and were resolved by consensus (the initial inter-rater agreement was high but was not statistically evaluated using the kappa statistic). Clinical trials were appraised by an 11-item tool developed by the Cochrane Collaboration Back Review Group, and observational studies were appraised by the Newcastle Ottawa Scale-NOS (9 items).[39,40] To evaluate bone outcomes, we *a priori* defined quality criteria specific to osteoporosis research and added six new items to the clinical trial checklist and two new items to the NOS.

Qualitative and Quantitative Syntheses

We qualitatively synthesized the findings of all studies. We combined clinical trials reporting fractures using the Mantel-Haenszel random-effects method of meta-analysis.[41–43] Two *a priori* defined subgroup meta-analyses were performed: one in trials including cancer patients only and one in trials using VKA as comparator. We estimated the pooled relative risk (RR) and pooled risk difference (RD) with the corresponding 95 % confidence intervals (95 % CI). I^2 statistic values were used to quantify statistical heterogeneity beyond chance.[44] As the number of trials was small (>10), a funnel plot was not used to assess publication bias.[41,45] All tests of significance were two-sided with statistical significance defined at $p < 0.05$ for overall effect and < 0.1 for heterogeneity. Meta-analyses were done using R 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS

Search and Study Selection

Of 3098 identified and screened records through searches of electronic databases and bibliographies, 16 articles were included (one was reported as an abstract, [46]; Fig. 1). Eleven citations[46–56] described ten clinical trials. The other five publications were observational cohort studies.[57–61] Two citations described the same study, one presented the results for a shorter 12-month duration,[60] and the second presented the results for a longer 24-month follow-up.[61] Thus, a total of ten clinical trials and four observational studies were included in this review.

Study Characteristics

Of the 10 clinical trials, including 4865 participants, 1 was a cross-over trial,[53] while the rest were parallel-group randomized controlled clinical trials (RCTs) (Table 1). Of the 4 cohort

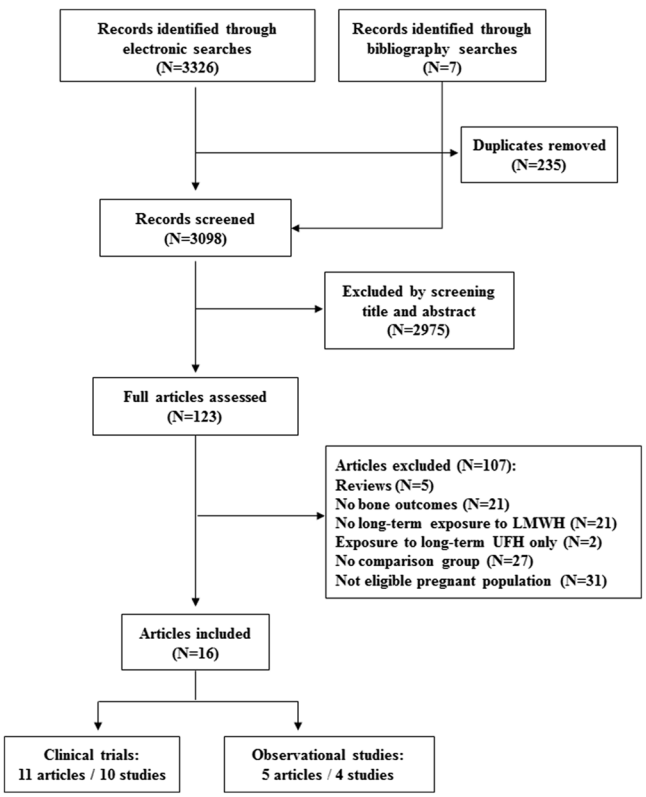

Figure 1. PRISMA flow diagram; n denotes the total number of citations. LMWH denotes low-molecular-weight heparin; UFH denotes unfractionated heparin.

Table 1 Descriptions of the Included Studies and Bone Outcomes

Author, year [ref.]	Study design and duration	Study Participants	LMWH: Type Daily dose Sample (n)	Control: Type Daily dose Sample (n)	Purpose and duration of treatment	Bone outcomes	Changes in BMD	Number of fractures LMWH/control	
Clinical trials									
Monreal 1994[54]	Single center Single blinded RCT 6 months	N = 80 (prior VTE, contraindicated to OA) Mean age: 68 years 50 % female	Dalteparin: 10,000 IU n = 40	UFH: 20,000 IU n = 40	Prophylaxis 3–6 months	BMD fractures (vertebral)	Not reported	1/40	6/40
Bernis 1997[46]	Clinical trial* 24 months	N = 23 (hemodialysis patients, prior VTE)	24 months LMWH‡ n = 13	UFH n = 10	Not reported	BMD	FN BMD, (g/cm^2): LMWH: 0.003 ± 0.2, P > 0.05 UFH: −0.013 ± 0.02, P < 0.05	NA	NA
FRISC II 1999[47]	Multicenter (59 sites) Factorial Open label RCT 3–6 months	N = 2105 (coronary artery disease, prior VTE) Mean age: 67 years 30 % female	Dalteparin: 10,000–15,000 IU n = 1049	Placebo n = 1056	Prophylaxis 3 months	Fractures (all clinical)	NA	No increase in the risk of fractures	
Veiga 2000[56]	Single center Single blinded RCT 12 months	N = 100 (prior VTE, cardiovascular disease or cancer) Mean age: 80 years 60 % female	Enoxaparin: 40 mg n = 50	Acenocoumarol n = 50	Prophylaxis 3–6 months	Fractures (all clinical)	NA	2/50	0/50
Lai 2001[53]	Single center Cross-over trial 20 months	N = 40 (hemodialysis patients, prior VTE) Mean age: 42 years 40 % female	Nadroparin: 10,000-15,000 IU n = 40	UFH: 5000–7500 IU n = 40	Prophylaxis LMWH: 8 months UFH: 12 months	BMD Bone Turnover Markers	NS changes in BMD at FN, trochanter and LS; changes at Ward's (P > 0.05): LMWH: + 0.75 % UFH: −2.4 %	NA	NA
Grassman 2001[48]	Multicenter (4 sites) Double blinded RCT 6 months	N = 118 (coronary artery disease, prior VTE) Mean age: 67 years 30 % female	Certoparin: 80 mg n = 59	Placebo n = 59	Prophylaxis 3 months	BMD	NS changes in BMD	NA	NA
Hull 2007[51] †	Multicenter (22 sites) Open label RCT (Main LITE Broad) 12 months	N = 737 (prior VTE, cardiovascular disease or cancer) Mean age: 54 % >60 years 46 % female	Tinzaparin: 175 IU/kg n = 369	Usual care: short-term UFH and warfarin n = 368	Therapy 3–6 months	Fractures (all clinical)	NA	4/369	7/368
Hull 2006[50] †	Multicenter (22 sites) Open label RCT (Main LITE Cancer) 12 months	N = 200 (prior VTE and cancer, solid tumors and hematologic) Mean age: 69 % >60 years 49 % female	Tinzaparin: 175 IU/kg n = 100	Usual care: short-term UFH and warfarin n = 100	Therapy 3–6 months	Fractures (all clinical)	NA	3/100	5/100
Hull 2009[52]	Multicenter Open label RCT (Home LITE) 22 centers 12 months	N = 480 (first or recurrent VTE) Mean age: 50 % >60 years 42 % female	Tinzaparin: 175 IU/kg n = 240	Usual care: short-term tinzaparin and warfarin n = 240	Therapy 3 months	Fractures (all clinical)	NA	2/240	5/240

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Table 1. (continued)

Author, year [ref.]	Study design and duration	Study Participants	LMWH: Type Daily dose Sample (n)	Control: Type Daily dose Sample (n)	Purpose and duration of treatment	Bone outcomes	Changes in BMD	Number of fractures LMWH/control	
Haas 2012[49]	Multicenter (39 sites) Two double-blinded RCTs (TOPIC-1; TOPIC-2) 6 months	N1 = 352 (disseminated breast cancer-RCT 1) N2 = 546 (non-small-cell lung carcinoma-RCT 2) Mean age: 55 (RCT 1); 60 (RCT 2) % female: 17 (RCT 2)	Certoparin: 3000 IU (RCT 1) n = 174 (RCT 2) n = 273	Placebo (RCT 1) n = 178 (RCT 2) n = 273	Prophylaxis 3 months	Fractures (osteoporotic)	NA	0/174 1/268	0/177 0/264
Serra 2013[55]	Single center Open label RCT 60 months	N = 284 (chronic venous ulcers) Mean age: 69 years 78 % female	Nadroparin: 2850 IU/day n = 142	Compression therapy n = 142	Therapy 12 months	BMD	No osteoporosis in the LMWH group	NA	NA
Observational cohort studies									
Monreal 1991[58]	Prospective cohort 3 months	N = 80 (prior VTE contraindicated OA) Mean age: 67 years 55 % female	Dalteparin: 5,000 IU n = 24	UFH: 10,000 IU n = 28 Coumarin n = 28	Prophylaxis 3 months	BMD and fractures (vertebral)	% Change in LS BMD: −2.4 % (Dalteparin); −3.0 % (UFH); −2.0 % (Coumarin) % change in FN BMD: −2.8 % (Dalteparin); −4.9 % (UFH); −2.1 % (Coumarin)	1/24	3/28 (UFH) 1/28
Rostoker 1995[59]	Prospective cohort 48 months	N = 55 (nephrotic syndrome) Mean age: 48 years 50 % female	Long-term Enoxaparin: 40 mg n = 30	Short-term Enoxaparin 40 mg n = 25	Prophylaxis long term: 6–48 months Short term: <4 months	BMD	BMD remained unchanged in one postmenopausal patient	NA	NA
Warwrzynska 2001[60]	Prospective cohort 12 months	N = 54 (prior VTE) Mean age: 57 years 50 % female	Nadroparin: 15,000 IU n = 15 Enoxaparin: 1 mg/kg n = 15	Acenocoumarol n = 24	Prophylaxis 3–6 months	BMD	% change in LS BMD: Nadroparin: −1.2 % (3 m); Enoxaparin: −3.6 % (6–12 m); Coumarin: −1.2 % (3 m); −1.7 % (6–12 m) % change in FN BMD: Nadroparin: −1.2 % (3 m); Enoxaparin: −3.6 % (6–12 m); Coumarin: −1.2 % (3 m); −1.7 % (6–12 m)	NA	NA
Warwrzynska 2003[61†]	Prospective cohort 24 months	N = 86 (prior VTE) Mean age: 48 years 50 % female	Nadroparin: 15,000 IU n = 15 Enoxaparin: 1 mg/kg n = 42	Acenocoumarol n = 29	Prophylaxis 6–24 months	BMD	% change in LS BMD: Nadroparin: −1.2 %(3 m); Enoxaparin: −4.0 %(12 m); −3.8 %(24 m) Coumarin: −1.7 % (12 m); −2.3 %(24 m) % change in FN BMD: Nadroparin: −1.3 %(3 m); Enoxaparin: −3.1 %(12 m); −4.8 % (24 m) Coumarin: −1.8 % (12 m); −2.5 % (24 m)	NA	NA

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Table 1. (continued)

Author, year [ref.]	Study design and duration	Study Participants	LMWH: Type Daily dose Sample (n)	Control: Type Daily dose Sample (n)	Purpose and duration of treatment	Bone outcomes	Changes in BMD	Number of fractures LMWH/control	
Grzegorzewska 2008[57]	Retrospective cohort 24 months	N = 30 (uremic dialysis) Mean age: 65 years (LMWH) and 48 years (no-LMWH) % female: not reported	Nadroparin or enoxaparin n = 14	None n = 16	Prophylaxis 24 months	BMD	LS BMD T-score < −2.5: 4/14 vs. 0/16 FN BMD T-score < −2.5: 6/14 vs. 1/16, differences remained significant ($P < 0.05$) in a multivariable analysis adjusting for age, sex, coffee consumption and drugs	NA	NA

*LMWH = low-molecular-weight heparin; N = total study sample; BMD = bone mineral density; LS = lumbar spine; FN = femoral neck; RCT = randomized controlled trials; UFH = unfractionated heparin; VTE = venous thromboembolism; OA = oral anticoagulants; IU = International Factor Xa Inhibitory Units; NS = not significant ($P > 0.05$); NA = not applicable; m = months; *reported as abstract; ‡same study[50] or the extension of the same study[61]*

studies of 251 participants,[57–61] 3 had a prospective design (221 participants)[58–61] (Table 1).

The majority of the trial participants were older than 60 years, male and had a prior VTE resulting from underlying cardiovascular, renal or malignant diseases. Three studies included cancer patients with solid or hematologic malignancies and with disseminated breast cancer or inoperable non-small-cell lung carcinoma.[49,50,56] Compared to the age and sex of the trial participants, the mean age of the cohort study participants was younger and more heterogeneous (30 to 67 years) with three studies including 50 % or more females (Table 1). Long-term LMWH was compared to long-term UFH in three trials and one cohort study,[46,53,54,58] to VKA in three trials[51,52,56] and two cohort studies,[58,61] to short-term LMWH in one cohort study,[59] compression therapy in one trial,[55] placebo in three trials[47–49] and no treatment in a cohort study.[57] Various preparations of LMWH (dalteparin, enoxaparin, nadroparin, certoparin and tinzaparin) were used for the purpose of prophylaxis (six trials[47–49,53,54,56] and all cohort studies) or therapy (three trials[50–52,55]). The duration of LMWH treatment was between 3 and 24 months in all but one cohort study[59] that compared long- to short-term treatment with LMWH (6–48 months vs. <4 months).

Methodological quality

The overall methodological quality of the included studies was limited (Tables 2 and 3). Two RCTs[47,49] adequately described the generation of the randomization sequence, concealment of the allocation and blinding, and one RCT[47] also adequately addressed incomplete data (Table 2). Most trials did not fulfill the six additional criteria specific to osteoporosis. Calcium and vitamin D dietary intakes, physical activity/immobility/bed rest, prior fractures or history of osteoporosis were not assessed. Timing of BMD or fracture assessment was not different between the groups. One cross-over trial examined BMD as the primary outcome,[53] while in four other RCTs[46,48,54,55] information regarding changes in BMD was limited. In the RCTs,[47,49–52,54,56] fractures were assessed among secondary outcomes, with samples ranging between 80[54] to 883 subjects.[49] Observational studies were small in size (30[57] to 86[61]), but they assessed BMD and/or fractures as primary outcomes (Table 3). All were hospital-based cohort studies, and the majority did not clearly describe loss to follow-up or did not report and adjust for important confounders.

Fractures

Fractures were reported in 8 publications,[47,49–52,54,56,58] 7 describing 6 trials of 4320 participants and 1 describing a prospective cohort study of 80 participants[58] (Table 1). We pooled data of the five trials including 2280 participants with VTE and underlying cardiovascular disease and cancer.[49,51,52,54,56] We excluded the FRISC II study (2015 participants) that reported no

Table 2 Methodological Quality of the Ten Included Clinical Trials

Study quality criteria	Monreal 1994[54]	Bernis 1997[46]*	FRISC II 1999[47]	Veiga 2000[56]	Lai 2001[53]	Grassman 2001[48]	Hull 2007[50,51]†	Hull 2009[52]	Haas 2012[49]	Serra 2013[55]
Adequate randomization	Yes	Unclear	Yes	Yes	No	Unclear	Yes	Yes	Yes	Unclear
Concealed allocation	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Prognostic factor balance at baseline for the primary disease	Yes	Unclear	Yes	No	No	Yes	No	No	No	No
Blinding of participants	No	Unclear	Yes	No	Yes	Yes	No	No	Yes	No
Blinding of healthcare providers	Yes	Unclear	Yes	No	No	Yes	No	No	Yes	No
Blinding of outcome assessor	Yes	Unclear	Yes	Yes	No	Unclear	No	No	Yes	No
Co-intervention similar	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Acceptable compliance in both groups	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
Drop-out rate described and acceptable (<10 %)	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Comparable timing of the primary outcome assessment in both groups	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intention to treat analysis	Yes	Unclear	Yes	Yes	No	Unclear	Yes	Yes	No	Yes
Van Tulder internal validity score	**8/11**	**NA**	**10/11**	**8/11**	**4/11**	**5/11**	**6/11**	**6/11**	**8/11**	**4/11**
Additional criterion 1: prognostic factor balance at baseline for osteoporosis	Yes	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear	No	Unclear
Additional criterion 2: contamination, use of heparin in both intervention groups	No	Unclear	No	No	No	No	No	Yes	No	No
Additional criterion 3: comparable timing of bone outcome assessment in both groups	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Additional criterion 4: if fracture was assessed among adverse events, was duration of follow-up to detect a fracture adequate (≥1 year)	No	Unclear	No	Yes	NA	NA	Yes	Yes	No	NA
Additional criterion 5: sample large enough to detect differences between the groups regarding fracture outcome	No	Unclear	Yes	No	No	No	No	No	No	No
Additional criterion 6: bone outcomes assessed as secondary	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

**Study by Bernis et al.[46] was reported as abstract and was rated unclear; †two published articles[50,51] represent the data of the same study.*

increase in the risk of fractures after 6 months of prophylaxis with dalterparin as the corresponding author could not provide the individual group fracture data.[47]

In a 3-month prospective cohort study[58] of 80 participants with recurrent VTE (28 to 91 years), fractures occurred more frequently with UFH (20,000 IU/day) than with dalterparin (10,000 IU/day) or coumarin (Table 1). In RCTs, fractures were more frequent in the control groups than in the LMWH group [UFH: 6/40 (15 %) vs. LMWH: 1/40 (2.5 %)[54]; VKA: 12/658 (1.8 %) vs. LMWH: 8/659 (1.2 %)[51,52,56]]. In the LMWH groups per se, fractures were less frequent in the RCTs that used lower prophylactic doses of certoparin, dalteparin or enoxaparin[49,54,56] than in those that used higher therapeutic doses of tinzaparin[51,52] (4/532 vs. 6/609, 3–6 months of therapy).

Although patient populations were clinically heterogeneous in terms of underlying comorbidities (cardiovascular disease and cancer), the main and subgroup meta-analyses were associated with small statistical heterogeneity (I^2 statistic <13 %).[44] In a random-effects meta-analysis (5 RCTs, 2280 participants), LMWH did not significantly increase the risk of all fractures compared to control [pooled RR: 0.58, 95 % CI: 0.23, 1.43 (P = 0.24); I^2 = 12.5 % (P = 0.33), Fig. 2a]. A subgroup meta-analysis of the three RCTs in 1183 cancer patients[49,50,56] suggested a comparable risk of fractures between the groups as well (pooled RR: 1.08, 95 % CI:0.31, 3.75

Table 3 Methodological Quality of the Four Observational Cohort Studies

Study quality criteria	Monreal 1991[58]	Rostoker 1995[59]	Wawrzynska 2001&2003[60,61]*	Grzegorzewska 2008[57]
Selection				
Representativeness of the exposed cohort	-	-	-	-
Selection of the non-exposed cohort	-	-	-	-
Ascertainment of exposure	*	*	*	*
Demonstration that outcome of interest (i.e., bone outcome) was not present at start of study	*	-	*	-
Comparability				
Comparability of cohorts on the basis of the design or analysis	-	-	-	**
Outcome (i.e., bone outcome)				
Ascertainment of outcome	*	*	*	*
Follow-up long enough for outcomes to occur	*	*	*	*
Adequacy of follow-up of cohorts	*	-	-	*
NOS score	**5/9**	**3/9**	**4/9**	**6/9**
Additional criterion 1: large sample that provides sufficient statistical power to detect differences between the groups regarding fracture outcome	No	No	No	No
Additional criterion 2: bone outcome assessed as secondary	No	Yes	No	No

**Two published articles[60,61] done by the same authors were evaluated together; dash (−) denotes blank cell and no star; NOS = Newcastle Ottawa Scale*

(P = 0.90); I^2 = 4.4 % (P = 0.35), Fig. 2b]. We also found no statistically significant change in the risk of fractures in a subgroup meta-analysis of the three RCTs (1317 participants[51,52,56]) comparing LMWH to VKA [pooled RR: 0.64, 95 % CI: 0.24, 1.71 (P = 0.37), I^2 = 8 % (P = 0.33), Fig. 2c]. The absolute risk difference of fractures was null in all analyses. Pooled risk difference was 0.00 [95 % CI: -0.02, 0.01 (P = 0.62)] in the meta-analysis of all five RCTs and in the subgroup meta-analysis of the RCTs in cancer patients only [95 % CI: −0.004, 0.01 (P = 0.46)]. In the meta-analysis of trials using VKA as control, it was −0.01 [95 % CI: −0.02, 0.01 (P = 0.34)]. The number of included studies was small; thus, it was difficult to make inferences regarding publication bias.

Changes in BMD

BMD was assessed by DXA in 5 clinical trials including 545 participants[46,48,53–55] and in all cohort studies including 251 participants (Table 1). Due to low quality in reporting of BMD data, we did not conduct a meta-analysis. Qualitative synthesis of the results is included below.

Of the five clinical trials that assessed BMD, two trials[48,55] provided statements regarding the absence of bone loss and one RCT[54] did not report the data. The other two trials[46,53] found small or insignificant changes in mean BMD (Table 1). A cross-over trial[53] in 40 stable hemodialysis patients showed no important changes in mean BMD at the lumbar spine, femoral neck or total hip; changes at Ward's triangle of −1.6 % after the first 8 months of UFH and of +0.7 % after another 8 months of LWMH were within the range of test variation (P > 0.05). In a parallel-group clinical trial[46] in 23 hemodialysis patients, UFH for 24 months decreased the mean BMD at the femoral neck (−0.013 g/cm^2, P < 0.05), while LMWH did not have any significant change (0.0003 g/cm^2, P > 0.05).

BMD was assessed as the primary outcome in three of the four cohort studies (Table 1). In contrast to the clinical trials, they found a larger decrease in mean BMD with long-term LMWH treatment. A retrospective cohort study in adult uremic dialysis patients[57] showed that LMWH use was associated with statistically significant decreases in mean BMD at the femoral neck [0.71 ± 0.10 g/cm^2 (LMWH) vs. 0.90 ± 0.12 g/cm^2 (no treatment), P = 0.000]. In a prospective cohort study[58] of 80 participants, a 2.4 % decrease in mean BMD at the lumbar spine and a 2.8 % decrease at the femoral neck were identified after 3 months of prophylaxis with LMWH; the corresponding decreases of 2.0 % and 2.1 % were shown for VKA and 3.0 % and 4.9 % for UFH . Another prospective study of 86 participants[61] reported statistically significant differences in mean BMD between the enoxaparin and coumarin groups (P < 0.005). Twenty-four months of prophylaxis with enoxaparin was associated with a decrease in mean BMD of 3.8 % and 4.8 % at the lumbar spine and femoral neck, respectively, compared to the corresponding 2.3 % and 2.5 % decreases with VKA.

DISCUSSION

This systematic review in adult non-pregnant populations with VTE, cancer and other underlying comorbidities found that long-term LMWH therapy reduced mean BMD from 1.2–2.8 % to 4.8 % after 3 to 24 months of use in two prospective observational studies of VTE prophylaxis with LMWH, while no significant changes were found in five clinical trials. Our meta-analysis did not find an increase in fracture risk with LMWH when compared to controls where the control groups were taking mainly UFH or VKA. Based on the current literature, LMWH does not seem to have a strong detrimental effect on bone. However, the potential for a greater than 3 %

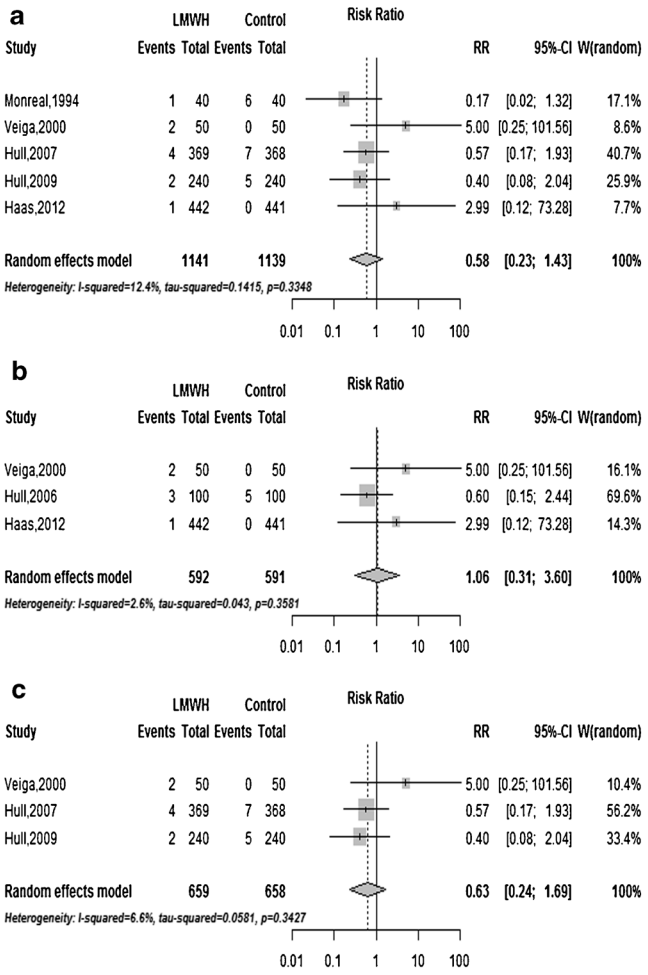

Figure 2. a Forest plot: The effect of long-term low-molecular-weight heparin vs. control on all fractures in non-pregnant participants. LMWH denotes low-molecular-weight heparin. Control: unfractionated heparin, oral vitamin K antagonist or placebo; RR denotes risk ratio; RR < 1 favors LMWH; RR >1 favors control treatment. b Forest plot: Long-term low-molecular-weight heparin vs. control in cancer patients. LMWH denotes low-molecular-weight heparin. Control: oral vitamin K antagonist or placebo; RR denotes risk ratio; RR < 1 favors LMWH; RR >1 favors control treatment. c Forest plot: Long-term low-molecular- weight heparin vs. oral vitamin K antagonists in non-pregnant participants. LMWH denotes low-molecular-weight heparin. Control: oral vitamin K antagonists (i.e., acenocoumarol/warfarin); RR denotes risk ratio; RR < 1 favors LMWH; RR >1 favors control treatment.

decrease in BMD may be clinically important in some adult populations on LMWH as a prior study (the FLEX trial—a trial of alendronate discontinuation) showed that bone loss of greater than 3 % over 2 years was associated with a 1.68-times increased risk of fractures (95 % CI: 1.05–2.72).[62]

Currently, LMWH is not recognized as a major modifying factor for fractures in standardized fracture risk assessment tools such as FRAX or CAROC.[63,64] Using the FRAX 10-year fracture risk assessment tool,[65,66] one can show that if LMWH were to induce a bone loss of 4.8 % over 2 years in a 68-year-old male patient [BMI = 26 kg/cm^2; baseline BMD T-score = −2.0 corresponding to mean BMD (femoral neck) = 0.620 g/cm^2], the 10-year probability of a major osteoporotic fracture would increase by 2.1 % (from baseline 7.9 % to 10 %) and that of a hip fracture by 1.8 % (from 2.2 % to 4.0 %),[67] making the patient potentially eligible for pharmacologic treatment.[63] Thus, it is important for clinicians to make sure adults on long-term LMWH get adequate calcium and vitamin D to minimize bone loss and to consider monitoring BMD in those who are at increased risk of bone loss or fractures.

Strengths and Weaknesses

Our systematic review included a comprehensive search strategy that combined searches of electronic databases, conference proceedings and manual searches of bibliographies.[68,69] This minimized the chance of omitting relevant information regarding the two bone outcomes that were not reported in the abstracts but in the text or tables. We abstracted the fracture and BMD data and conducted quality assessments in duplicate to minimize error due to chance and bias. To reduce the chance of false conclusions, we conducted quantitative and qualitative evidence syntheses.[38] However, the majority of studies included in this review had high risk of bias; thus, the overall level of evidence is limited.

Fractures were collected as secondary outcomes, and their assessment was variable among the studies. The small number of studies, small study populations and short duration of follow-up (up to 1 year) (especially for rare fracture outcomes that occurred in less than 1 % in the VKA and placebo groups) had an impact on the statistical power of our analyses. Also, overall fracture incidence following long-term LMWH treatment may be underestimated. This is because only one trial[54] captured clinical vertebral fractures, as measured by plain radiographs in participants who complained of back pain. Vertebral fractures are the most common type of osteoporotic fractures,[70] but the majority occur asymptomatically and only one-third is clinically recognized.[71]

The lack of an effect of LMWH on BMD was apparent in the clinical trials as opposed to observational cohort studies. However, the observational studies examined bone outcomes as their primary endpoints. Although selection bias and confounding can be better controlled through allocation concealment and randomization in RCTs,[72] the majority of the reviewed trials examined BMD and/or fractures as secondary end points and were adequately powered for their primary efficacy end points. In this review, BMD was the primary outcome in one cross-over trial only.[53] Also, the study populations were similar in terms of their indication for long-term LMWH, but some of these populations such as hemodialysis or cancer patients can have a higher baseline risk of osteoporosis owing to their underlying diseases or treatments.[35–37] Given the various methodological limitations of the cohort studies (selection bias, confounding, small samples, inadequate ascertainment of outcomes), the effect of LMWH on BMD can be distorted in either direction.[72,73] Thus, we qualitatively synthesized the BMD

data to express lack of confidence in the precision and magnitude of bone loss with LMWH.

In addition, control treatments in the studies were not consistent and included UFH, VKA or placebo. Previous research has suggested that UFH and VKA increase the risk of bone loss and fractures. For example, animal models suggest that UFH adversely affects bone metabolism as it accelerates bone resorption and suppresses bone formation.[74,75] Warfarin use was also shown to increase both bone loss and risk of vertebral fractures in some studies in women.[76,77] The potential adverse effects of LMWH on bone may be portrayed to be less when the comparator group has an increased likelihood for developing such adverse events. In light of our findings of a statistically nonsignificant increase in the risk of fractures between the groups [LMWH vs. control (UFH, VKA or placebo): RR = 0.58, 95 % CI: 0.23–1.43; LMWH vs. VKA: RR = 0.64, 95%CI: 0.24–1.71], one interpretation could be that long-term LMWH treatment poses a similar risk of fractures as UFH or VKA—a conclusion that needs further confirmation in large well-designed prospective studies.

Some animal studies have suggested a dose-dependent effect of LMWH on bone,[78,79] but this relationship has not been fully explored or confirmed in humans. Qualitative analysis of the data suggests a slight trend towards dose-dependent effects of LMWH on bone. In the prophylactic-dose LMWH groups (using certoparin, dalteparin or enoxaparin), 0.75 % of participants had fractures compared to 0.99 % in the higher therapeutic-dosing groups (using tinzaparin). However, both the numbers of fractures and sizes of the RCTs are small, and the observed difference could be due to chance alone. More importantly, patients requiring larger therapeutic doses are likely at different baseline risks for fractures compared to those who only require prophylactic doses. Also, it remains unclear whether various preparations of LMWH exert different effects on bone. Some authors suggest that the preparations of LMWH can be considered a family of closely related drugs (i.e., class effect) despite their *in vitro* differences.[80] Our analysis also suggests that the amount of LMWH may be more important than the LMWH preparation. Consequently, future studies need to explore whether there is a threshold effect with LMWH when it comes to the dose and duration of LMWH treatment.

Evidence from Other Studies

Few studies have systematically examined the risk of fractures with long-term LMWH therapy in non-pregnant adults.[31] To our knowledge, three reviews systematically evaluated bone complications of long-term LMWH treatment in pregnant participants prone to VTE.[29–31] Ensom et al.[29] reviewed 40 studies associated with long-term LMWH use in over 700 pregnant women and found two cases of osteoporotic vertebral fractures. Greer et al.[30] identified 64 eligible studies in 2777 pregnancies comparing long-term LMWH against control treatments and found one study reporting one vertebral fracture (rate: 0.04 %) in a woman treated with high-dose LMWH (15,000 IU/day) for 9 months. The authors warned about other cases of osteoporotic fractures in this population and urged further research concerning LMWH-induced osteoporosis. Lefkou et al.,[31] who qualitatively synthesized the literature in pregnant women and one study in non-pregnant adults, recommended against supplementation with calcium until the effects of long-term LMWH on bone are examined for different doses and in other non-pregnant populations. Lastly, a few studies have examined the effects of novel anticoagulants on bone. For example, in vitro studies found that rivaroxaban, an oral factor-Xa inhibitor, reduced osteoblast function in a similar way as enoxaparin, while this effect was not shown for fondaparinux, a parenteral factor Xa inhibitor.[1,81]

Future Studies

The lack of solid evidence on the long-term effects of LMWH on bone in non-pregnant adults suggests a need for future prospective studies. Not only is this patient population heterogeneous, but it is also susceptible to osteoporosis and fractures.[35–37] For instance, breast cancer and prostate cancer patients face an increased risk of secondary osteoporosis resulting from the use of aromatase inhibitors and androgen deprivation therapy.[37] As we extend the anticoagulation armamentarium to include novel agents, future studies should assess the effects of these therapies on bone as some were shown to adversely affect bone.[81] Also, future phase IV or post-marketing surveillance studies should examine this potential but uncommon drug side effect. One way to improve the detection of asymptomatic (morphometric) vertebral fractures can be to use lateral spine X-rays or vertebral fracture assessment (VFA) by DXA to detect subclinical vertebral fractures.

CONCLUSION

Our systematic review and meta-analysis showed that the use of LMWH for 3–6 months did not increase the risk of fractures compared to UFH or VKA, but longer exposure for up to 24 months was associated with a decrease in BMD. These findings should be interpreted with caution because the current evidence is limited. Future well-designed studies should corroborate whether there are negative effects of long-term LMWH treatment on BMD and fractures in non-pregnant adults. While awaiting better evidence, clinicians should consider monitoring BMD and optimizing vitamin D and calcium intakes in adults on long-term LMWH who are at increased risk of bone loss or fractures.

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