Extended Out-of-Hospital Low-Molecular-Weight Heparin Prophylaxis against Deep Venous Thrombosis in Patients after Elective Hip Arthroplasty: A Systematic Review

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Purpose: **Evidence-based medicine guidelines based on venographic end points recommend in-hospital prophylaxis with low-molecular-weight heparin (LMWH) in patients having elective hip surgery. Emerging data suggest that out-of-hospital use may offer additional protection; however, uncertainty remains about the risk–benefit ratio. To provide clinicians with a practical pathway for translating clinical research into practice, we systematically reviewed trials comparing extended out-of-hospital LMWH prophylaxis versus placebo.**

Data Sources: **Studies were identified by 1) searching PubMed, MEDLINE, and the Cochrane Library Database for reports published from January 1976 to May 2001; 2) reviewing references from retrieved articles; 3) scanning abstracts from conference proceedings; and 4) contacting pharmaceutical companies and investigators of the original reports.**

Study Selection: **Randomized, controlled trials comparing extended out-of-hospital prophylaxis with LMWH versus placebo in patients having elective hip arthroplasty.**

Data Extraction: **Two reviewers extracted data independently. Reviewers evaluated study quality by using a validated four-item instrument.**

Data Synthesis: **Six of seven original articles met the defined inclusion criteria. The included studies were double-blind trials that used proper randomization procedures. Compared with placebo, extended out-of-hospital prophylaxis decreased the frequency of all episodes of deep venous thrombosis (placebo rate, 150 of 666 patients [22.5%]; relative risk, 0.41 [95% CI, 0.32 to 0.54; $P < 0.001$]), proximal venous thrombosis (placebo rate, 76 of 678 patients [11.2%]; relative risk, 0.31 [CI, 0.20 to 0.47; $P < 0.001$]), and symptomatic venous thromboembolism (placebo rate, 36 of 862 patients [4.2%]; relative risk, 0.36 [CI, 0.20 to 0.67; $P = 0.001$]). Major bleeding was rare, occurring in only one patient in the placebo group.**

Conclusions: **Extended LMWH prophylaxis showed consistent effectiveness and safety in the trials (regardless of study variations in clinical practice and length of hospital stay) for venographic deep venous thrombosis and symptomatic venous thromboembolism. The aggregate findings support the need for extended out-of-hospital prophylaxis in patients undergoing hip arthroplasty surgery.**

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The use of accurate, objective venographic testing to detect deep venous thrombosis in patients who undergo hip arthroplasty has led to randomized trials of various prophylactic regimens against venous thromboembolism (1–23). The need for in-hospital prophylaxis has been firmly established (24, 25) and accepted in clinical practice. Evidence-based medicine guidelines (26) based on venographic end points recommend low-molecular-weight heparin (LMWH) prophylaxis or warfarin prophylaxis for 7 to 10 days in patients who undergo elective hip surgery (25). These guidelines are considered a grade 1A recommendation, which indicates a strong recommendation for a therapy that has a clear benefit; the recommendation is based on randomized clinical trials that do not have important limitations and that can apply to most patients in most circumstances without reservation (26). Recent surveys indicate that more than 90% of patients who have undergone elective hip surgery have received thromboprophylaxis (27, 28).

The results of randomized trials in Europe indicate the need for extended out-of-hospital prophylaxis in patients undergoing hip arthroplasty (29–34). In contrast, on the basis of relatively low rates of symptomatic venous thromboembolism observed in descriptive studies in North America with long-term follow-up, investigators have inferred that extended prophylaxis is not required (35–39). For these reasons, the reports of the Fifth (24) and Sixth (25) American College of Chest Physicians Consensus Conferences stated that extended out-of-hospital prophylaxis by using LMWH may offer additional protection. This is a 2A recommendation because of uncertainty regarding the risk–benefit ratio (24) and cost-effectiveness (25). A grade 2A recommendation indicates unclear benefit based on randomized

clinical trials without important limitations and is an intermediate-strength recommendation (26). A possible interpretation of the North American data (35–39) is that extended prophylaxis is unnecessary for patients in the United States and Canada because of differences in clinical practice, a shorter length of hospital stay, and earlier patient ambulation compared with Europe. A recent epidemiologic study (27) used a linked hospital discharge database provided by the State of California to report the outcomes in 19 586 patients undergoing total-hip arthroplasty and 24 059 patients undergoing knee arthroplasty. Of the patients having elective hip surgery who had symptomatic venous thromboembolism, the median time of the event was postoperative day 17, whereas the median time in patients having knee surgery was postoperative day 7; most patients (>90%) received in-hospital prophylaxis. These findings strongly suggest a need for extended out-of-hospital prophylaxis in patients undergoing total-hip replacement but not for patients undergoing total-knee replacement.

Given the uncertainty about the need for extended prophylaxis, we performed a systematic review to provide clinicians with a practical pathway for translating clinical research into practice.

METHODS

To ensure high methodologic quality, we adhered to the 15 criteria for systematic review outlined by McAlister and colleagues (40, 41). The first 10 criteria assess methodologic rigor, and the last 5 criteria assess the scientific basis of treatment recommendations (40). We also adhered to the QUOROM (Quality of Reporting of Meta-analyses) guidelines (42) for the reporting of meta-analyses of randomized trials. We systematically identified published and unpublished articles for inclusion in this analysis, described variations in study design and execution, evaluated study quality (43), and quantified the relative benefits of extended prophylaxis with LMWH (44). We excluded studies that did not use venography to assess the presence or absence of deep venous thrombosis because previous studies have shown that noninvasive tests, including duplex ultrasonography, are relatively insensitive for detecting thrombosis in patients who have undergone hip replacement (25).

Study Identification

We attempted to identify all published and unpublished randomized trials that compared extended prophylaxis with LMWH versus out-of-hospital placebo in patients undergoing hip arthroplasty. A strategy was developed for locating all studies in the PubMed and MEDLINE databases that were published between January 1976 and May 2001; the search was not restricted to English-language journals. We augmented our MEDLINE search by manually reviewing the reference lists of original articles and review articles. We also reviewed abstracts in conference proceedings and through the Cochrane Library Database and contacted investigators and pharmaceutical companies.

Study Eligibility

Two investigators independently evaluated studies for inclusion in the systematic review, and any disagreements were resolved by discussion between these two investigators. Investigators were not blinded to journal titles, author names, or institutional affiliations. Studies were included if they 1) enrolled patients undergoing elective hip arthroplasty, 2) randomly assigned participants to treatment groups, 3) investigated the extended post–hospital discharge efficacy of once-daily subcutaneous LMWH compared with out-of-hospital placebo for prevention of deep venous thrombosis, 4) objectively documented the presence or absence of all episodes of deep venous thrombosis and proximal venous thrombosis by using bilateral ascending contrast venography, and 5) used objective methods for assessing bleeding complications (29–32, 45, 46). Abstracts that reported full methods and results were eligible for inclusion. *Deep venous thrombosis* was defined as constant intraluminal filling defects in the deep veins; *proximal venous thrombosis* was defined as constant intraluminal filling defects in the popliteal deep veins or in the more proximal deep veins.

Data Extraction

One study investigator collected data on the following study-level factors: 1) the type of LMWH prophylaxis used, 2) whether a high-risk dose, approved by a regulatory affairs authority, was used, 3) the frequency of administration of LMWH, 4) the length of in-hospital stay, 5) the time interval after surgery when venog-

raphy was performed (in days), and 6) venographic findings. For the last factor, we noted new out-of-hospital findings on venography or combined in-hospital and out-of-hospital findings on venography; where both findings were reported, we analyzed new out-of-hospital findings, which were more conservative and more recent.

Two investigators independently extracted data on the major outcomes, which were the frequency of 1) all episodes of deep venous thrombosis, 2) proximal venous thrombosis, 3) symptomatic deep venous thrombosis and pulmonary embolism, and 4) major-bleeding complications. They also recorded data on other variables, including death, minor bleeding, wound hematomas, and thrombocytopenia.

After the two investigators made their respective independent selection of studies for inclusion in the analysis, we compared their selections and calculated the percentage of agreement between them and the κ coefficient (47). Investigator disagreements were resolved by discussion.

Assessment of Study Quality

We assessed the quality and strength of each study by examining four key issues: 1) true randomization by using a random-numbers table or a computer program; 2) the masking of the allocation sequences from the investigators, staff, and patients involved in the study; 3) double-blinding (45); and 4) the proportion of patients with successful (adequate) venography. One investigator extracted these data from the primary studies. When details were not reported, we requested additional information from the authors.

Data Synthesis and Statistical Analysis

For each of the major outcomes, we calculated summary treatment effects as the relative risk and the number needed to treat for benefit (NNT_B) to prevent one thromboembolic event. The relative risk was used as the primary measure of treatment effect. We considered a P value less than 0.05 to be statistically significant for all statistical tests. Analyses were performed by using the metan procedure (48) of Stata software, release 6.0 (Stata Corp., College Station, Texas).

To assess the validity of combining results from individual studies, we used the Mantel–Haenszel test for statistical heterogeneity (49). The outcome values were combined in both fixed-effects and random-effects models to estimate treatment effects on outcomes for all the studies.

The relative risk ratios were consistent among studies for the treatment effect of preventing venographically documented deep venous thrombosis (all episodes and cases of proximal deep venous thrombosis); however, the 95% CIs for the relative risk ratios within studies were relatively wide. Therefore, we combined the data to provide more precise estimates of relative risk and NNT_B. Results for NNT_B were based on random-effects analysis of risk.

Sensitivity Analysis

We performed a sensitivity analysis for each of the three major outcomes. To uncover possible publication bias, we created inverted funnel plots for the major outcomes by plotting odds ratios against the sample size for each study (50). Moreover, to identify any studies that exerted a disproportionate influence on the summary treatment effect, we performed repeated calculations in which the data from each individual study were deleted, one at a time.

Trials that met all inclusion criteria except for one—the use of bilateral ascending venography to assess end points at the end of the out-of-hospital study interval—were included in a secondary meta-analysis of symptomatic venous thromboembolism and major bleeding end points.

RESULTS

Study Identification and Selection

Our search strategies identified 206 potentially relevant studies. After an initial scanning of titles and abstracts, we excluded 184 studies: 160 studies did not include patients undergoing hip arthroplasty, 19 were reviews, and 5 had results that were previously reported. The remaining 22 articles were original studies of LMWH used for prophylaxis against deep venous thrombosis in patients undergoing hip arthroplasty; we retained these reports for further evaluation.

We subsequently excluded 15 of these 22 articles because they reported findings for in-hospital prophylaxis only. Thus, a total of 7 studies investigated out-of-hospital extended prophylaxis using LMWH in patients undergoing elective hip arthroplasty. Of these 7 studies,

Table 1. **Characteristics of the Studies Included in the Systematic Review***

Study (Reference)	Year	Time of Randomization	Venograms	Patients	In-Hospital, Out-of-Hospital Prophylaxis	Preoperative or Postoperative Initiation of Therapy	Duration of Prophylaxis		Frequency of Administration	Initial Dose	Subsequent Doses
							In-Hospital	Out-of-Hospital			
			n				*d*				
Bergqvist et al. (29)	1996	At discharge	1								
LMWH group				131	Enoxaparin, enoxaparin	Preoperative	10	19	Once daily	4000 IU	4000 IU
Control group				131	Enoxaparin, placebo	Preoperative	11	18	Once daily	4000 IU	4000 IU
Planes et al. (30)	1996	At discharge	2†								
LMWH group				90	Enoxaparin, enoxaparin	Preoperative	14	21	Once daily	4000 IU	4000 IU
Control group				89	Enoxaparin, placebo	Preoperative	14	21	Once daily	4000 IU	4000 IU
Dahl et al. (31)	1997	At discharge	2†								
LMWH group				117	Ealteparin, dalteparin	Preoperative	7	28	Once daily	5000 IU	5000 IU
Control group				110	Dalteparin, placebo	Preoperative	7	28	Once daily	5000 IU	5000 IU
Lassen et al. (32)	1998	At discharge	1								
LMWH group				140	Dalteparin, dalteparin	Preoperative	7	28	Once daily	5000 IU	5000 IU
Control group				141	Dalteparin, placebo	Preoperative	7	28	Once daily	5000 IU	5000 IU
Hull et al. (45)	2000	Before surgery	2†								
LMWH group				389	Dalteparin, dalteparin	Preoperative, postoperative‡	6	29	Once daily	2500 IU	5000 IU
Control group				180	Warfarin, placebo	Postoperative	6	29	Once daily	5–10 mg	INR 2–3§
Comp et al. (46)	2001	At discharge	1								
LMWH group				224	Enoxaparin, enoxaparin	Postoperative	8	19	Once daily, twice daily‖	30 mg	30–40 mg‖
Control group				211	Enoxaparin, placebo	Postoperative	8	19	Once daily, twice daily‖	30 mg	30–40 mg‖

* INR = international normalized ratio; LMWH = low-molecular-weight heparin.
† The second venogram was used to assess thrombosis end points.
‡ 199 patients were randomly assigned to a preoperative treatment group, and 190 patients were randomly assigned to a postoperative treatment group; the two groups produced similar results and their data have been pooled for this analysis.
§ Warfarin dose was adjusted daily during the in-hospital phase according to a prescriptive protocol that used a predefined warfarin nomogram based on the prothrombin INR findings.
‖ Patients received 30 mg of enoxaparin twice daily during the in-hospital treatment period and 40 mg once daily during the out-of-hospital study interval.

6 met the a priori eligibility criteria outlined in the Methods section (29–32, 45, 46); the remaining study, which did not use venographic deep venous thrombosis as an end point, was included in a secondary analysis (51). The studies were reported from 1996 to 2001. Inter-rater agreement for study eligibility was 95.7% ($\kappa = 0.88$), indicating almost perfect agreement.

Description of Variation in Study Methods

Table 1 shows the design characteristics of the 6 included studies. The number of patients included in these studies ranged from 179 to 569. Two different types of LMWH were evaluated during the out-of-hospital extended prophylaxis interval after in-hospital initiation: Three studies (29, 30, 46) evaluated enoxaparin (Aventis Pharmaceuticals, Inc., Bridgewater, New Jersey), and 3 studies (31, 32, 45) evaluated dalteparin (Pharmacia Corp., Peapack, New Jersey). Five studies (29–32, 46) had a comparator group that received in-hospital LMWH prophylaxis followed by out-of-hospital placebo; the remaining study (45) had a comparator group that received in-hospital warfarin followed by out-of-hospital placebo. Low-molecular-weight heparin prophylaxis was initiated before surgery in four studies (29–32) and after surgery in one study (46). The remaining study included separate randomly assigned

Table 2. **Clinical Characteristics of Patients in the Studies Included in the Systematic Review***

Study (Reference)	Year	Male, Female Patients	Mean Age ± SD	Body Mass Index	Patients Undergoing Cemented, Noncemented Angioplasty†	Patients Receiving General, Regional, or Combined Anaesthesia	Primary Surgery, Revision Surgery	Graduated Pressure Stockings	Patients with Previous Venous Thromboembolism	Patients with Cancer
		n, n	*y*	*kg/m²*	*n, n*	*n, n, n*	*n, n*	← *n/n* →		
Bergqvist et al. (29)	1996									
LMWH group		56, 75	70	26	–‡	–§	131, 0	NR	8/131	0
Out-of-hospital placebo group		57, 74	70	27	–‡	–§	131, 0	NR	12/131	0
Planes et al. (30)	1996									
LMWH group		47, 43	70 ± 9	26 ± 3	NR	NR	78, 12	61/90	2/90	0
Out-of-hospital placebo group		55, 34	68 ± 8	26 ± 3	NR	NR	80, 9	56/89	1/89	0
Dahl et al. (31)	1997									
LMWH group		37, 80	71	NR	93, 117	–‖	108, 9	117/117	10/117	11/117
Out-of-hospital placebo group		29, 81	71	NR	93, 110	–‖	102, 8	110/110	5/110	10/110
Lassen et al. (32)	1998									
LMWH group		66, 74	68	NR	86, 140	52, 88, 0	NR	78/140	10/140	3/140
Out-of-hospital placebo group		62, 79	70	NR	95, 141	54, 87, 0	NR	73/141	5/141	3/141
Hull et al. (45)	2000									
Preoperative LMWH group		106, 93	62 ± 12	29 ± 6	30, 199	142, 91, 27	170, 29	15/199	8/199	28/199
Postoperative LMWH group		87, 103	63 ± 12	29 ± 6	38, 190	150, 77, 30	158, 32	11/190	6/190	20/190
Out-of-hospital placebo group		94, 86	63 ± 12	28 ± 6	31, 180	133, 94, 33	159, 21	16/180	6/180	12/180
Comp et al. (46)	2001									
LMWH group		111, 113	64.4	28.4	NR	56, 168, 0	211, 0	NR	–¶	NR
Out-of-hospital placebo group		106, 105	63.4	28.5	NR	147, 64, 0	243, 1	NR	–¶	NR

* LMWH = low-molecular-weight heparin; NR = not reported.
† Patients with cementing are those in whom the hip arthroplasty involved the setting of the replacement with a cement highly tolerable by the human body. Patients with noncemented procedures did not have the cement as part of the procedure.
‡ Approximately equal numbers of patients having cemented and noncemented surgeries in each treatment group were reported.
§ In 95% of the operations, epidural anesthesia was used.
‖ 225 patients received spinal analgesia, and 2 patients received general anesthesia.
¶ Patients did not have clinical evidence of chronic or acute deep venous thrombosis or thromboembolic events in the past 12 months.

groups for preoperative and postoperative initiation of therapy (45). The specific doses used for the particular LMWH evaluated were those approved by regulatory agencies; all doses were high-risk doses shown effective in patients undergoing elective hip surgery. One study (45) initiated prophylaxis at half the usual high-risk dose; subsequently, on the day after surgery and thereafter, the usual high-risk doses were used. In five studies, the LMWH was administered once daily (29–32, 45); in one study, the prophylaxis was administered twice daily during the in-hospital period and once daily during the out-of-hospital period (46).

Among the studies in our meta-analysis, the in-hospital intervals ranged from 6 to 14 days, and the out-of-hospital intervals ranged from 18 to 29 days (29–32, 45, 46) (**Table 1**). Therefore, the studies evaluated extended prophylaxis through postoperative day 27 to 35.

Three studies obtained two venographic evaluations: an initial venogram at time of hospital discharge, and a second venogram at the end of the extended out-of-hospital study period (postoperative day 35) (30, 31, 45). In two of these studies, randomization occurred at hospital discharge, and some patients were subsequently excluded on the basis of the results of the initial venography. Planes and colleagues (30) excluded all patients with deep venous thrombosis, whereas Dahl and colleagues (31) excluded patients with proximal deep venous thrombosis. Hull and colleagues (45) randomly assigned patients at the time of surgery and reported both the out-of-hospital and cumulative rates of deep venous thrombosis. The remaining three studies (29, 32, 46), which performed venography only once, at the end of the out-of-hospital period, randomly allocated patients at hospital discharge.

All studies reported the incidence of symptomatic venous thromboembolism occurring during the extended out-of-hospital study period and used objective and reproducible methods to identify and confirm all

episodes of deep venous thrombosis, proximal venous thrombosis, and bleeding. Clinical characteristics of the study patients are summarized in **Table 2**.

Assessment of Study Quality

All studies reported use of objective methods to assess deep venous thrombosis outcomes and proper randomization techniques. All studies had a double-blind design (**Table 3**). The proportion of patients undergoing successful venography is shown in **Table 3**.

Data Synthesis

Statistical tests did not detect heterogeneity in the relative risks among studies for episodes of all and proximal venographically documented deep venous thrombosis; symptomatic, objectively documented deep venous thrombosis or pulmonary embolism; or major bleeding ($P > 0.2$ for each outcome). In addition, heterogeneity was not detected for the secondary outcomes—minor bleeding, wound hematomas, and thrombocytopenia. Heterogeneity for the absolute risk difference was detected for all episodes of deep venous thrombosis and cases of proximal deep venous thrombosis.

Figures 1, **2**, and **3** show the summary treatment effects for the outcomes that were calculated by using the fixed-effects model. The random-effects model produced similar results.

In individual analyses of the six studies (29–31, 45, 46), the relative risk for all episodes of deep venous thrombosis during the out-of-hospital time period was statistically significant in favor of LMWH (**Figure 1**). When all six studies were combined, the frequency of all episodes of deep venous thrombosis in the out-of-hospital placebo group was 150 of 666 patients (22.5%), and the relative risk was 0.41 in favor of LMWH (CI, 0.32 to 0.54; $P < 0.001$) (**Figure 1**). The NNT_B to prevent one event of deep venous thrombosis was 8.2 (CI, 5.7 to 14.6; $P < 0.001$).

In three of six studies (29, 45, 46), the relative risk for proximal deep venous thrombosis during the out-of-hospital period was statistically significant in favor of LMWH (**Figure 2**). When all six studies were combined, the frequency of proximal deep venous thrombosis in the out-of-hospital placebo group was 76 of 678 patients (11.2%), and the relative risk was 0.31 (CI, 0.20 to 0.47; $P < 0.001$) in favor of LMWH (**Figure 2**). The NNT_B to prevent one event of proximal deep venous thrombosis was 14.9 (CI, 9.3 to 38.5; $P = 0.001$).

In one study (29), the relative risk for symptomatic venous thromboembolism during the out-of-hospital time period was statistically significant in favor of LMWH (**Figure 3**). When all six studies were combined, the frequency of symptomatic deep venous thrombosis in the out-of-hospital placebo group was 36 of 862 patients (4.2%), and the relative risk was 0.36 (CI, 0.20 to 0.67; $P = 0.001$) in favor of LMWH. The NNT_B to prevent one event of symptomatic venous thromboembolism was 45.3 (CI, 25.5 to 204.5; $P = 0.012$).

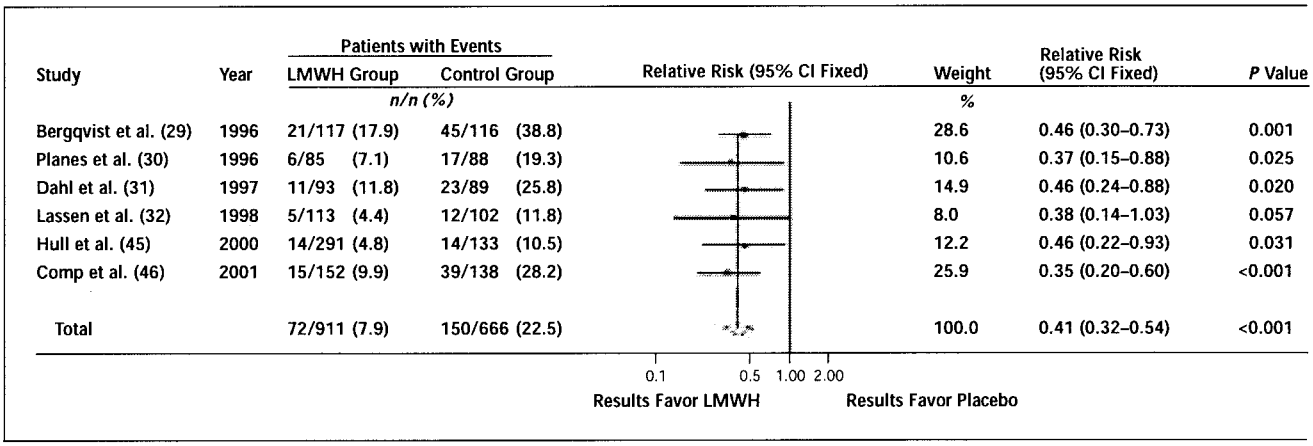
Major bleeding occurred in 1 of 862 patients (0.115% [CI, 0.03% to 0.65%]) in the out-of-hospital placebo group and in none of the patients receiving LMWH.

In the six trials, 21 of 862 patients (2.44% [CI, 1.51% to 3.70%]) receiving out-of-hospital placebo and 29 of 1091 patients (2.66% [CI, 1.79% to 3.80%]) receiving LMWH experienced minor bleeding; 3 of 862 patients (0.34% [CI, 0.07% to 1.01%]) receiving out-of-hospital placebo and 5 of 1091 patients (0.46% [CI, 0.15% to 1.07%]) receiving LMWH had thrombocytopenia. Among trials reporting wound hematoma (29, 30, 31, 45), 8 of 510 patients (1.57% [CI, 0.68% to

Table 3. **Methodologic Quality of Studies Included in the Systematic Review**

Study (Reference)	Year	Randomized Allocation Sequence Generated	Randomized Allocation Sequence Masked	Double-Blinded	Patients Undergoing Successful Venography, *n/n (%)*
Bergqvist et al. (29)	1996	Yes	Yes	Yes	233/262 (88.9)
Planes et al. (30)	1996	Yes	Yes	Yes	173/179 (96.7)
Dahl et al. (31)	1997	Yes	Yes	Yes	218/265 (82.3)
Lassen et al. (32)	1998	Yes	Yes	Yes	215/281 (76.5)
Hull et al. (45)	2000	Yes	Yes	Yes	454/569 (79.8)
Comp et al. (46)	2001	Yes	Yes	Yes	290/435 (66.6)

Figure 1. **Relative risk for all deep venous thrombosis during the out-of-hospital time interval.**



Summary and individual-study results are shown. LMWH = low-molecular-weight heparin.

3.06%]) receiving out-of-hospital placebo and 12 of 727 patients (1.65% [CI, 0.86% to 2.87%]) receiving LMWH had wound hematomas.

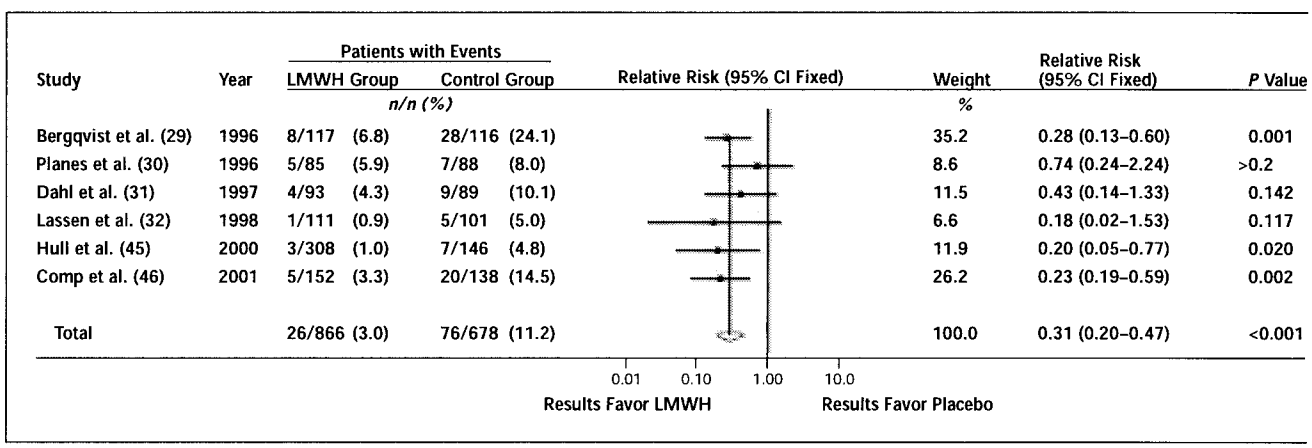
Mortality was low among the LMWH and out-of-hospital placebo groups; 3 of 862 patients (0.34% [CI, 0.072% to 1.01%]) receiving out-of-hospital placebo and 1 of 1091 patients (0.09% [CI, 0.002% to 0.51%]) receiving LMWH died. Two of the deaths in the placebo group were attributed to pulmonary embolism.

Sensitivity Analysis

One study (45) reported cumulative and out-of-hospital frequencies for venographic deep venous thrombosis. An additional study (31) reported partial cumulative and out-of-hospital frequencies for venographic deep venous thrombosis. For both studies, we analyzed the out-of-hospital deep venous thrombosis frequency alone; however, inclusion of the cumulative or partial cumulative findings from these two studies strengthened our findings and inferences.

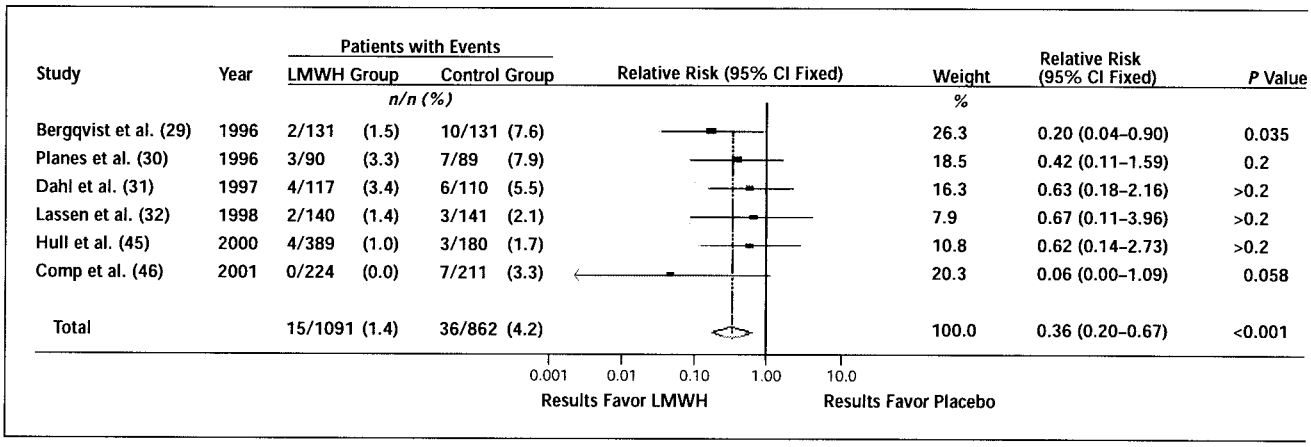
Inverted funnel plots of study odds ratios versus study sample size were generally symmetric in appearance for all episodes of deep venous thrombosis, cases of proximal deep venous thrombosis, and cases of symptomatic venous thrombosis; thus, we found no indication of publication bias. Deleting individual studies one

Figure 2. **Relative risk for proximal deep venous thrombosis during the out-of-hospital time interval.**



Summary and individual-study results are shown. LMWH = low-molecular-weight heparin.

Figure 3. **Relative risk for symptomatic venous thromboembolism during the out-of-hospital time interval.**



Summary and individual-study results are shown. LMWH = low-molecular-weight heparin.

at a time did not disproportionately influence the summary relative risks observed for all episodes of deep venous thrombosis (range of relative risks, 0.40 to 0.44), cases of proximal venous thrombosis (range of relative risks, 0.27 to 0.34), and cases of symptomatic venous thromboembolism (range of relative risks, 0.31 to 0.44).

Adequate adherence to the use of LMWH prophylaxis was achieved in each study included in our systematic review. The one study not included in our analysis (51) used symptomatic end points only and did not use ascending contrast venography to search for deep venous thrombosis. This study (51) was underpowered, reported data on a mixed group of patients undergoing hip or knee replacement, and had poor adherence for the use of LMWH prophylaxis (52). Findings were not altered when we included this study (51) in a secondary analysis of symptomatic venous-thromboembolic and major-bleeding end points. When this trial was included, the overall placebo rate was 41 of 1093 patients (3.8%), and the relative risk for symptomatic venous thromboembolism was 0.39 in favor of LMWH (CI, 0.225 to 0.677; $P = 0.001$).

Because there was no indication of heterogeneity among studies and the number of studies was small, we did not perform additional analyses of between-study differences.

Discussion

Extended prophylaxis with LMWH versus out-of-hospital placebo showed consistent effectiveness (**Figures 1** to **3**) and safety among the trials. Extended LMWH prophylaxis was effective and safe regardless of variations in clinical practice and length of hospital stay. The results of trials from North America (45, 46) have been consistent with findings in trials conducted in Europe (29–32). The aggregate findings support the need for extended out-of-hospital prophylaxis in patients undergoing hip arthroplasty.

Symptomatic, objectively documented deep venous thrombosis was found less frequently in the extended LMWH group. This observation is consistent with the findings obtained by screening with venography. The clinically important and statistically significant reduction in symptomatic venous thromboembolism resolves the uncertainty about the risk–benefit (24) of using extended prophylaxis. The risk–benefit findings based on the outcome of symptomatic venous thromboembolism clearly favors extended prophylaxis. No major bleeding occurred in patients receiving extended out-of-hospital prophylaxis in any of the 6 trials. Nevertheless, clinicians should be prudent in selecting patients for extended prophylaxis because of the potential risk for bleeding.

The optimal duration of extended prophylaxis remains uncertain. The intervals of extended out-of-hospital prophylaxis that were evaluated in the randomized clinical trials by using venographic end points ranged from 19 to 28 days. This interval is in harmony, however, with the findings by White and colleagues (27) and Dahl and colleagues (53), who found that patients with venographically confirmed symptomatic deep venous

thrombosis after hip surgery in whom prophylaxis was stopped at hospital discharge were readmitted, on average, 17 and 27 days after surgery, respectively. Thus, in all patients undergoing elective hip surgery, 19 to 28 days would seem a reasonable duration for use of extended LMWH prophylaxis. It is uncertain whether all patients undergoing elective hip surgery require continued thromboprophylaxis after hospital discharge. The current data suggest that all patients are eligible candidates for extended prophylaxis because hip arthroplasty is a dominant high-risk factor (25) for postoperative venous thromboembolism. A recent epidemiologic study (54), however, has shown that independent predictors of rehospitalization for symptomatic venous thromboembolism after total-hip arthroplasty included age older than 85 years, female sex, history of venous thromboembolism, and body mass index of 25 kg/m^2 or greater. Further research is warranted to determine whether thromboprophylaxis should be extended to all patients undergoing surgery or to selected high-risk patients only.

The authors of a recent, interrupted double-blind randomized trial (51) of extended prophylaxis with LMWH in patients undergoing elective hip or knee surgery that used clinical end points for deep venous thrombosis and pulmonary embolism concluded that extended use of LMWH is not clinically important for most patients who undergo elective hip or knee surgery. The authors of an accompanying editorial disagreed with this inference and noted that 1) the amount of prophylaxis used may have been inadequate because of a lack of patient adherence and 2) the inclusion of patients undergoing knee surgery might have confounded the data (52).

The findings of randomized and nonrandomized trials (35–39) that have evaluated the frequencies of out-of-hospital symptomatic venous thromboembolism have been used to support the inference that extended out-of-hospital prophylaxis is unnecessary. These trials lacked statistical power, were not designed to specifically address this question, or also included patients undergoing knee arthroplasty, which has a different epidemiologic pattern (the median time for having symptomatic venous thrombosis is day 7) (27). The findings of a recent trial (39) that specifically evaluated the frequency of symptomatic venous thromboembolism support the aggregate findings of our review. In this trial of 1516 patients, the researchers found a clinically and statistically significant difference between the frequencies of in-hospital venous thromboembolism during prophylaxis (4 of 1516 patients [0.3%]) and out-of-hospital venous thromboembolism after prophylaxis was stopped (51 of 1516 patients [3.4%]) ($P < 0.001$).

Several studies (55–60) support the need for prolonged prophylaxis. For example, in the Norwegian Arthroplasty Register (55) of 39 543 patients undergoing hip arthroplasty, patients in the first 60 days after elective total-hip replacement had a significantly higher mortality rate than the general population; these results are consistent with the findings of other studies (56, 57). Moreover, the mortality rate among patients in the Norwegian Arthroplasty Register continued to be higher at 90 days after surgery. Other studies, such as the National Confidential Enquiry into Perioperative Deaths in the United Kingdom (60), have shown that vascular complications, including pulmonary embolism, are the dominant cause of death after elective hip arthroplasty (56–59).

In our meta-analysis, sensitivity analysis demonstrated that the results for the major outcomes of all episodes of deep venous thrombosis, cases of proximal deep venous thrombosis, and cases of symptomatic venous thromboembolism were robust. Removal of individual studies did not alter our findings. In all cases, the extended prophylaxis advantage was not lost for any of the three major outcomes when a single study was removed from the meta-analysis.

Although the number of studies was small, the funnel plots for the major outcomes were roughly symmetrical. Therefore, assuming that individual study results should be evenly distributed around the summary treatment effect, the plots gave no indication of publication bias. In our secondary analysis, wherein an additional study (51) that did not use venographic end points was included, the findings of the meta-analysis for the end points of symptomatic venous thromboembolism and major bleeding were not altered.

Low-molecular-weight heparins differ because of the different methods of preparation (61–63). The strong homogeneity of the findings suggest that the once-daily high-risk prophylactic regimens used for the LMWHs under study are effective and safe for extended out-of-hospital use. The LMWH regimens evaluated for extended out-of-hospital prophylaxis were effective for

in-hospital prophylaxis using a high-risk regimen (the actual dose used was specific to the particular LMWH being evaluated). Each study used a regimen of extended out-of-hospital prophylaxis that consisted of a high-risk dose administered subcutaneously once per day. A recent study reported that patients or a family member can self-administer LMWH subcutaneously as effectively and safely as a visiting home nurse (64). Thus, the cited literature suggests that out-of-hospital administration of LMWH regimens is practical and cost-effective (65). It is also possible that oral anticoagulants may be effective for extended out-of-hospital prophylaxis; however, the effectiveness and safety of oral anticoagulants in this context have not been established by a randomized trial.

Among the studies in our review, the reported mean length of in-hospital stay varied from 6 to 14 days; the length of in-hospital stay did not affect the need for extended prophylaxis. Cumulative findings, when reported, strengthen the findings of this systematic review, showing more striking clinical and statistical significance in favor of extended LMWH use. The absolute frequencies of deep venous thrombosis reported in each study varied considerably according to the reporting interval, which ranged from a combined in-hospital and out-of-hospital time interval to an out-of-hospital only time interval.

The NNT_B provides a useful public health overview (66, 67). Only 24 to 28 patients required out-of-hospital LMWH prophylaxis to prevent one new episode of out-of-hospital proximal venous thrombosis compared with out-of-hospital placebo in patients having elective hip arthroplasty in the United States and Canada (45). The cost-effectiveness of extended prophylaxis for approximately 1 month is beyond the scope of this review and should be addressed separately. The findings of individual trials and our meta-analysis, together with epidemiologic and pathophysiologic data, support the important benefit of extended out-of-hospital prophylaxis. We conclude that extended out-of-hospital prophylaxis with LMWH should be considered in patients undergoing elective hip arthroplasty.

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