

# Review: Extended-duration prophylaxis with heparin prevents deep venous thrombosis in hip or knee replacement

Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet*. 2001 Jul 7;358:9-15.

## QUESTION

In patients who have received total hip or knee replacement, what is the effectiveness of extended-duration prophylaxis with warfarin or heparin for preventing venous thromboembolism (VTE)?

## DATA SOURCES

Studies were identified by searching MEDLINE and EMBASE/Excerpta Medica (1980 to July 2000). Bibliographies of relevant articles were reviewed, and manufacturers of low-molecular-weight heparin (LMWH) were contacted for information on unpublished trials.

## STUDY SELECTION

Studies were selected if they were randomized controlled trials (RCTs) comparing extended-duration prophylaxis consisting of LMWH or unfractionated heparin or warfarin (treatment group) with placebo or no treatment (control group), patients had had elective total hip or total knee replacement, and objective methods were used to confirm the diagnosis of symptomatic VTE.

## DATA EXTRACTION

2 reviewers independently extracted data on sample size, key components of the intervention, study quality, and outcomes. Outcomes included symptomatic VTE (deep venous thrombosis [DVT] and pulmonary embolism), symptomless DVT, bleeding (major and minor), and all-cause mortality.

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## MAIN RESULTS

9 RCTs met the selection criteria: 7 RCTs included only patients receiving total hip replacement, and 2 RCTs included patients receiving both total hip and knee replacements. The LMWH preparations assessed included ardeparin, dalteparin, enoxaparin, and nadroparin. One study used fixed-dose unfractionated heparin. The rates of symptomatic VTE, symptomatic DVT, and symptomless DVT were lower in the treatment group than in the control group {all  $P$  values  $< 0.05$ }\* (Table). The incidence of minor bleeding was greater in the treatment group than in the control group [ $P = 0.039$ ]\*

(Table). The groups did not differ for pulmonary embolism, major bleeding, or all-cause mortality (Table).

## CONCLUSIONS

In patients who have received total hip or knee replacement, extended-duration prophylaxis with heparin is more effective than placebo or no treatment for preventing deep venous thrombosis. The preventive effect is associated with increased minor bleeding.

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\* $P$  values calculated from data in article.

## Heparin vs placebo or no treatment (control) for extended prophylactic prevention of thromboembolism after total hip or knee replacement†

Outcomes at 4 to 6 wk	Weighted event rates		RRR (95% CI)	NNT (CI)
	Heparin	Control		
Symptomatic venous thromboembolism	1.9%	3.3%	61% (38 to 76)	71 (45 to 178)
Deep venous thrombosis	1.5%	2.7%	58% (31 to 75)	87 (52 to 256)
Pulmonary embolism	0.4%	0.6%	57% (-5 to 82)	Not significant
Major bleeding	0.2%	0.3%	38% (-74 to 78)	Not significant
All-cause mortality	0.2%	0.3%	32% (-85 to 75)	Not significant
			RRI (CI)	NNH (CI)
Minor bleeding	3.6%	2.5%	53% (8 to 118)	95 (49 to 1865)

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

## COMMENTARY

VTE prophylaxis given for 7 to 14 days after total hip or knee replacement is highly effective (1). However, venographic evidence exists that asymptomatic DVT is frequently present at the time of discharge and that patients can develop new asymptomatic DVT in subsequent weeks (2). This well-done systematic review by Eikelboom and colleagues provides convincing evidence that extended-duration prophylaxis prevents about 2 symptomatic VTE events per 100 patients. 2 explanations exist for the low benefit of extended-duration prophylaxis: First, asymptomatic postoperative DVT appears to be effectively managed with only 7 to 14 days of prophylaxis. The incidence of subsequent symptomatic VTE is  $< 5\%$  (2). Second, in 5 of the 9 selected studies, all eligible patients had venography, ultrasonography, or impedance plethysmography at the time of discharge. Patients found to have DVT were excluded, making the risk for subsequent symptomatic VTE smaller and limiting the potential for finding benefit from extended-duration prophylaxis.

Are there certain patient subgroups particularly at risk for VTE after in-hospital prophylaxis? Screening duplex ultrasonography at discharge has not been found to be a useful strategy because of its low sensitivity

in asymptomatic patients (1, 2), and routine venography at discharge is not acceptable because of its invasive nature and high cost. Additional research is needed to answer this question. At this time, prophylaxis after total hip or knee replacement should be continued for at least 7 to 10 days, even if the patient is discharged from the hospital sooner, because shorter durations of prophylaxis have not been evaluated. Although extended-duration prophylaxis with LMWH is safe and effective, its cost-effectiveness for routine use has not been proved. Until we have further information, extended-duration prophylaxis should be reserved for patients with risk factors for VTE in addition to surgery.

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## References

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