

Review: low molecular weight heparin reduces recurrent venous thromboembolism better than unfractionated heparin

van Dongen CJ, van den Belt AG, Prins MA, *et al.* Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2004;(4):CD001100.

Clinical impact ratings IM/Ambulatory care ★★★★★☆☆ Internal medicine ★★★★★☆☆ Haematology ★★★★★☆☆

Q In patients with acute venous thromboembolism (VTE), is fixed dose subcutaneous low molecular weight heparin (LMWH) more effective than adjusted dose unfractionated heparin (UFH) for reducing symptomatic recurrent VTE?

METHODS

Data sources: Cochrane Peripheral Vascular Diseases Specialized Register (July 2004), the Cochrane Central Register of Controlled Trials (Issue 3, 2004), LILACS, bibliographies of relevant articles, researchers, and pharmaceutical companies.

Study selection and assessment: randomised controlled trials (RCTs) that compared fixed dose subcutaneous LMWH with adjusted dose UFH (intravenous or subcutaneous) for initial treatment (usually the first 5–14 d) in patients with acute VTE. After selection, each study was assessed for adequacy of concealment of allocation before randomisation.

Outcomes: recurrent symptomatic VTE, major haemorrhage, and all cause mortality.

MAIN RESULTS

22 RCTs (n = 8867) met the selection criteria. Categories of VTE included symptomatic deep venous thrombosis (DVT) of the leg without symptoms of pulmonary embolism (PE) (13 RCTs); PE only (2 RCTs); symptomatic DVT of the leg, with or without symptomatic PE; or asymptomatic DVT of the leg with symptomatic PE or symptomatic DVT or PE (7 RCTs). Preparations of LMWH evaluated included nadroparin, tinzaparin, enoxaparin, dalteparin, CY 222, certoparin, ardeparin, and reviparin. The rates of symptomatic recurrent VTE throughout follow up, major haemorrhage during the initial treatment, and all cause mortality at the end of follow up (3–6 mo) were lower in the LMWH group than in the UFH group (table). Subgroup analysis of patients with proximal DVT also showed that rates of symptomatic recurrent VTE at the end of follow up (relative risk reduction [RRR] 44%, 95% CI 24 to 55), major haemorrhage during the initial treatment (RRR 51%, CI 15 to 72), and all cause mortality at the end of follow up (RRR 37%, CI 15 to 53) were lower in the LMWH group than in the UFH group.

CONCLUSION

In patients with acute venous thromboembolism, fixed dose subcutaneous low molecular weight heparin is more effective than adjusted dose unfractionated heparin for reducing the incidence of

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symptomatic recurrent venous thromboembolism, major haemorrhage, and all cause mortality.

Abstract and commentary also appear in *ACP Journal Club*.

Commentary

Previous meta-analyses comparing fixed dose LMWH with adjusted dose UFH for the treatment of acute VTE showed that LMWH reduces all cause mortality, and found trends for reduction of recurrent VTE and major bleeding.^{1,2} The meta-analysis by van Dongen *et al* used a comprehensive search strategy and included the most recent RCTs (all done after 1990) and thus presents an aggregate of the most current evidence. Furthermore, the large sample size shows that the review had sufficient power to find differences in efficacy. Their analysis confirmed that LMWH confers a survival advantage and significantly reduces the incidence of major bleeding and recurrent VTE.

Limitations include the use of trials that compared LMWH with subcutaneous UFH, which may have contributed to the finding of superiority of LMWH; lack of an analysis examining whether the superiority of LMWH is maintained when limited to trials examining patients treated with LMWH primarily at home; the combining of 8 different LMWH preparations; and the small number of trials examining symptomatic PE. Despite these limitations, the rigorous methodology and consistency of the results with those of previous analyses support the main findings of improved outcomes with LMWH.

Although LMWH has previously been shown to be at least as safe and efficacious as UFH and to allow selected patients with DVT to be treated at home, many patients are still often hospitalised and treated with UFH.³ Potential barriers to home treatment with LMWH are medication cost, inconsistent availability of the medication from area pharmacies, patient education about self injection, and outpatient initiation of oral anti-coagulation.

Given the data showing that LMWH improves outcomes and provides the opportunity to avoid hospitalisation for many patients, it is time to overcome any remaining obstacles and adopt LMWH as the standard of care for appropriately selected patients with VTE.

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Fixed dose subcutaneous low molecular weight heparin (LMWH) v adjusted dose unfractionated heparin (UFH) for acute venous thromboembolism*

Outcomes	Follow up	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
			LMWH	UFH		
Recurrent venous thrombo-embolism	During treatment	15 (6060)	1.4%	2.4%	31% (2 to 51)	100 (100 to ∞)
	3 months	13 (5831)	3.0%	5.0%	30% (11 to 46)	50 (34 to 100)
	6 months	6 (2781)	3.7%	5.7%	31% (3 to 51)	50 (34 to ∞)
	3–6 months	18 (8122)	3.4%	5.4%	31% (15 to 44)	50 (34 to 100)
Major haemorrhage	During treatment	19 (7124)	1.0%	2.0%	42% (16 to 60)	100 (100 to ∞)
All cause mortality	3–6 months	18 (8054)	5.0%	6.0%	23% (7 to 36)	100 (50 to ∞)

*Abbreviations defined in glossary; weighted event rates, RRR, NNT, and CI calculated from data in article using a fixed effect models.