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

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

QUESTION

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: 3 databases, bibliographies of relevant articles, researchers, and pharmaceutical companies.

Study selection and assessment: Randomized controlled trials (RCTs) that compared fixed-dose subcutaneous LMWH with adjusted-dose UFH for initial treatment (usually the first 5 to 14 d) in patients with acute VTE. Studies were assessed for concealment.

Outcomes: Recurrent symptomatic VTE, major hemorrhage, 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 hemorrhage during the initial treatment, and all-cause mortality at the end of follow-up (3 to 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 hemorrhage 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 symptomatic recurrent venous thromboembolism, major hemorrhage, and all-cause mortality.

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Fixed-dose subcutaneous low-molecular-weight heparin (LMWH) vs 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 thromboembolism	During treatment	15 (6060)	1.4%	2.4%	31% (2 to 51)	100 (100 to ∞)
	3 mo	13 (5831)	3.0%	5.0%	30% (11 to 46)	50 (34 to 100)
	6 mo	6 (2781)	3.7%	5.7%	31% (3 to 51)	50 (34 to ∞)
	3 to 6 mo	18 (8122)	3.4%	5.4%	31% (15 to 44)	50 (34 to 100)
Major hemorrhage	During treatment	19 (7124)	1.0%	2.0%	42% (16 to 60)	100 (100 to ∞)
All-cause mortality	3 to 6 mo	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-effects model.

COMMENTARY

Previous meta-analyses comparing fixed-dose LMWH with adjusted-dose UFH for 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 and colleagues used a comprehensive search strategy and included the most recent RCTs (all done after 1990), thereby presenting an aggregate of the most current evidence. Furthermore, the large sample size shows that the review had sufficient power to find differences in efficacy. The 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 hospitalized and treated with UFH (3).

Given the data showing that LMWH improves outcomes and provides the opportunity to avoid hospitalization 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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