Low-molecular-weight heparin reduced recurrent VTE in patients with pulmonary embolism and proximal DVT

Hull RD, Raskob GE, Brant RF, et al., for the American-Canadian Thrombosis Study Group. **Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism.** Arch Intern Med. 2000 Jan 24;160:229-36.

QUESTION

In adults with documented pulmonary embolism and proximal deep venous thrombosis (DVT), is low-molecular-weight heparin (LMWH) given subcutaneously without anticoagulant monitoring more effective than unfractionated heparin in preventing recurrent proximal DVT?

DESIGN

Subgroup analysis of a randomized {allocation concealed*}†, blinded (patients and outcome assessors),* controlled trial with 3-month follow-up.

SETTING

15 centers in the United States and Canada.

PATIENTS

200 patients who were ≥ 18 years of age (65% ≥ 60 y of age, 56% women) and had proximal DVT on venography and high-probability findings on perfusion lung scanning. Exclusion criteria were active bleeding or contraindications to anticoagulants; allergy to heparin, bisulfites, or fish; pregnancy; ≥ 2 previously documented episodes of DVT or pulmonary embolism (PE); history of protein C deficiency or heparin-associated thrombocytopenia; severe malignant hypertension; severe hepatic or renal failure; treatment with warfarin sodium, LMWH, or heparinoids in the previous 7 days or with subcutaneous heparin in the previous 12 hours; or current use of intravenous unfractionated heparin (UH). Follow-up was 100%.

INTERVENTION

After stratification according to study center, history of venous thromboembolism (VTE), and presence of risk factors for bleeding, patients were allocated to subcutaneous LMWH (tinzaparin sodium), 175 international factor Xa inhibitory units/kg of body weight per day (n = 97), or to UH (n = 103). UH was given according to a protocol nomogram, with an initial bolus dose of 5000 U.S. Pharmacopeia units and continuous infusion at 40 320 U/d for patients without risk factors for bleeding and 29 760 U/d for patients with risk factors for bleeding, for 5 to 6 days. All patients received warfarin sodium, 10 mg initially with adjustment to maintain an international normalized ratio of 2.0 to 3.0 for 3 months.

MAIN OUTCOME MEASURES

Recurrent VTE, bleeding, and death.

MAIN RESULTS

At 3 months, fewer patients in the LWMH group than in the UH group had recurrent VTE (P = 0.009); the groups had similar rates of bleeding and death (Table).

CONCLUSION

In adults with documented pulmonary embolism and proximal deep venous thrombosis, low-molecular-weight heparin reduced the incidence of recurrent venous thromboembolism and led to similar rates of bleeding and death as did intravenous unfractionated heparin.

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*See Glossary.

†Information provided by author.

Low-molecular-weight heparin (LMWH) vs intravenous unfractionated heparin (UH) in adults with venous thromboembolism‡

Outcomes at 3 mo	LMWH	UH	RRR (95% CI)	NNT (CI)
Recurrent venous thromboembolism	0%	6.8%	100% (43 to 100)	15 (8 to 36)
Major bleeding	1.0%	1.9%	47% (–300 to 930)	Not significant
Minor bleeding	1.0%	2.9%	65% (–143 to 95)	Not significant
Death	6.2%	8.7%	29% (–84 to 73)	Not significant

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

The rising cost of health care has drawn substantial attention from all areas of our society. New technology is believed to be a major source of the cost increase. Therefore, it is noteworthy when a new technology simultaneously improves or maintains the quality of care while reducing the associated cost. The management of VTE by using 1 of several different types of LMWH may be an example of this type of improvement. Although LMWHs are substantially more expensive than UH, they are reported to be cost-effective when used in the ambulatory care setting (1, 2). Consequently, in the current era of managed care, considerable enthusiasm exists for the ambulatory management of VTE. Given the 2 recent reports from Hull and Dolovich and their colleagues, how enthusiastic should we remain?

These 2 studies explore several important issues related to the use of LMWHs for patients with acute VTE. First, Hull and colleagues present results from a subgroup analysis of a larger randomized controlled trial. Their analysis supports the greater efficacy of subcutaneous tinzaparin therapy in reducing recurrent VTE over that of standard UH (3) for hospitalized patients with proximal DVT and an associated PE. In the analysis, they adjusted for a baseline age imbalance; otherwise, groups were comparable. Because most of the patients with proximal DVT had asymptomatic PE (> 85% without PE symptoms), some would presumably be candidates for outpatient management (4). This study affirms and strengthens observations from 2 tinzaparin trials included in the systematic review and meta-analysis by Dolovich and colleagues. A future meta-analysis with inclusion of the subgroups analyzed in the study by Hull and colleagues will need to be done to determine whether a class-specific reduction in recurrent VTE or total mortality, or both, occur.

Second, the systematic review by Dolovich and colleagues has shown that 5 different LMWHs are at least equivalent to UH in preventing recurrent VTE. For each LMWH included, the point estimate of total mortality reduction favors LMWH but is not significant

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Review: Low-molecular-weight heparin reduces death but not recurrent VTE events, bleeding, or thrombocytopenia in VTE

Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. **A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism. Examining some unanswered questions regarding location of treatment, product type, and dosing frequency.** Arch Intern Med. 2000 Jan 24;160:181-8.

QUESTIONS

In adults with venous thromboembolism (VTE), is low-molecular-weight heparin (LMWH) more effective than unfractionated heparin (UH)? Does the setting (outpatient or inpatient) and regimen influence effectiveness?

DATA SOURCES

Studies were identified by searching MEDLINE (1986 to 1996), HEALTH (1975 to 1996), and the Cochrane Library and reviewing the reference lists of review articles, files of local thromboembolism experts, and abstracts from recent meetings.

STUDY SELECTION

2 reviewers independently selected studies that were randomized controlled trials; involved adults with confirmed VTE; compared intravenous UH with subcutaneous LMWH; and evaluated the outcomes of recurrent VTE, bleeding, death, or thrombocytopenia. Exclusion criteria were publication language other than English or French, inability to extract data, no patient follow-up beyond initial administration of heparin therapy, or comparison of subcutaneous UH with LMWH. Disagreement was resolved by consensus.

DATA EXTRACTION

Data were extracted on setting; LMWH regimen; duration of treatment and follow-up; and event rates for recurrent VTE, major bleeding, and total mortality. 2 reviewers independently assessed the quality of study methods; discrepancies were resolved by review of the original study.

MAIN RESULTS

13 studies involving 4447 patients (mean age range 57 to 67 y, 44% to 61% men) met the inclusion criteria. 883 of these patients had pulmonary embolism (PE). Treatment duration ranged from 5 to 10 days, and follow-up ranged from 2 to 20 months. Fewer patients who received LMWH died than did those who received UH (10 studies, P = 0.03) (Table). Groups did not differ for rates of recurrent VTE, PE, bleeding, or thrombocytopenia. A trend existed toward fewer patients with major bleeding in the LWMH group than in the UH group (relative risk reduction 37%, 95% CI –5% to 63%). 3 studies examined outpatient therapy; inpatient LWMH therapy was associated with a 60% (CI 24% to 70%) relative risk reduction in major bleeding, whereas outpatient LWMH therapy led to a nonsignificant relative risk increase of 18% (CI –44% to 149%). Subgroup analysis of once-daily and twice-daily LWMH showed no differences between LWMH and UH or between the 2 schedules. Differences among the 5 LMWH products were not tested in meta-analyses because the number of studies for each product was too small.

CONCLUSIONS

In adults with venous thromboembolism (VTE), low-molecular weight heparin (LMWH) reduced death and led to rates of bleeding, recurrent VTE, and thrombocytopenia similar to those of intravenous unfractionated heparin (UH). For inpatients, LMWH produced fewer major bleeding events than did UH, whereas bleeding rates were similar for both treatments in outpatients.

Source of funding: No external funding.

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Low-molecular-weight heparin (LMWH) vs intravenous unfractionated heparin (UH) in recurrent venous thromboembolism*

Outcome at 3 to 6 mo	Number of studies	Weighted event rates LMWH	Weighted event rates UH	RRR (95% CI)	NNT (CI)
Death	10	5.0%	6.5%	24% (2 to 41)	64 (38 to 768)

*Abbreviations defined in Glossary; NNT, CI, and weighted event rates calculated from data in article.

COMMENTARY

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until the data are pooled across LMWH class. The LMWHs are not directly compared to determine relative efficacy or safety. The reason for a mortality reduction without a similar reduction in recurrent VTE remains unclear.

Third, the study by Hull and colleagues supports the observation by Dolovich and colleagues that once-daily dosing is equivalent to twice-daily dosing for reducing recurrent VTE and total mortality. This characteristic of treatment will probably improve patient compliance in the outpatient setting.

Finally, the systematic review reported by Dolovich and colleagues should generate some caution with respect to the implementation of an outpatient VTE program. Although not statistically significant, the risk for major bleeding seemed to be higher in studies done in the "ambulatory" setting. In each of the 3 outpatient trials, < 50% of the included patients were managed entirely in the outpatient setting. In these studies, insufficient data existed to determine whether the risk for major bleeding differed between those primarily treated as outpatients and those initially treated in the hospital. Furthermore, when this approach is used outside a trial setting, bleeding complications will probably be higher than those currently reported. Close monitoring and careful patient selection that mirror the trial setting must be incorporated into an outpatient VTE treatment program.

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