Dalteparin reduced venous thromboembolic events without increased bleeding in acutely ill medical patients

Leizorovicz A, Cohen AT, Turpie AG, et al. **Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients.** Circulation. 2004;110:874-9.

QUESTION

What is the efficacy and safety of dalteparin for prevention of venous thromboembolic events in acutely ill medical patients?

METHODS

Design: Randomized placebo-controlled trial (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial [PREVENT]).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (patients and monitoring committee).*

Follow-up period: 21 and 90 days.

Setting: 219 study centers in 26 countries.

Patients: 3706 patients ≥ 40 years of age (mean age 69 y, 48% men, based on 3681 patients) who had an acute medical condition (e.g., acute congestive heart failure, respiratory failure not requiring ventilator support, or infection without septic shock) requiring ≥ 4 days of hospitalization and had been immobilized for ≤ 3 days. Except for congestive heart failure and respiratory failure, patients had to have ≥ 1 of the following risk factors for venous thromboembolism (VTE): ≥ 75 years of age, cancer, previous VTE, obesity, varicose veins or chronic venous insufficiency, hormone replacement therapy, history of chronic heart failure or respiratory failure, or the myeloproliferative syndrome.

Intervention: Once-daily subcutaneous injections of dalteparin sodium, 5000 IU (Fragmin, Pharmacia Corp) (n = 1856), or placebo (n = 1850) for 14 days.

Outcomes: VTE at day 21 (composite of objectively confirmed symptomatic deep venous thrombosis [DVT], fatal or symptomatic nonfatal pulmonary embolism, sudden death, and proximal asymptomatic DVT detected by systematic compression ultrasonography). Secondary endpoints included all-cause mortality and major bleeding at 21 days.

Patient follow-up: 81% of patients were included in the primary intention-to-treat analysis at 21 days.

MAIN RESULTS

At 21 days, the dalteparin group had a lower incidence of the primary composite endpoint, proximal asymptomatic DVT, and proximal and symptomatic distal DVT than did the placebo group, but did not differ for all-cause mortality or major bleeding (Table).

CONCLUSION

Dalteparin reduced combined venous thromboembolism and sudden death more than placebo in acutely ill medical patients at 21 days and did not increase bleeding.

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*See Glossary.

Dalteparin vs placebo for prevention of venous thromboembolism in acutely ill medical patients†

Outcomes at 21 d	Dalteparin	Placebo	RRR (95% CI)	NNT (CI)
Composite primary endpoint‡	2.8%	5.0%	45% (20 to 62)	46 (28 to 122)
Proximal asymptomatic DVT	1.8%	3.7%	52% (23 to 69)	34 (33 to 143)
Proximal and symptomatic distal DVT	2.1%	4.4%	51% (27 to 68)	45 (28 to 101)
			RRI (CI)	NNH
All-cause mortality	2.4%	2.3%	1% (–34 to 54)	Not significant
Major bleeding	0.5%	0.2%	2% (–10 to 944)	Not significant

†DVT = deep venous thrombosis. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
‡Composite of symptomatic DVT, fatal or symptomatic nonfatal pulmonary embolism, sudden death, and asymptomatic proximal DVT.

COMMENTARY

Despite evidence that 25% of all venous thromboembolic events in the general population occur after an acute medical illness (1), DVT prophylaxis is underutilized in patients hospitalized for medical illnesses. Patients with New York Heart Association class III or IV heart failure or severe respiratory disease are at increased risk for DVT, as are patients confined to bed with sepsis, stroke, leg weakness, cancer, acute rheumatologic disorders, active inflammatory bowel disease, or previous DVT (2, 3).

The large, well-designed PREVENT study by Leizorovicz and colleagues found that the low-molecular-weight heparin (LMWH) dalteparin reduced VTE in medical patients with risk factors for DVT. Dalteparin joins enoxaparin and low-dose unfractionated heparin (LDUH) as recommended agents for prophylaxis of DVT in medically ill patients at risk for DVT.

PREVENT differed from the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study, which examined the use of enoxaparin, another LMWH, for DVT prophylaxis in medically ill patients (4), thereby making comparisons between the 2 agents difficult. In PREVENT, patients received dalteparin, 5000 IU/d, for a mean 12.6 injections and were evaluated by compression ultrasonography at day 21. In the MEDENOX study, patients received enoxaparin, 40 mg/d, for a mean 7 injections, and most had venography between days 6 and 14. Nevertheless, both LMWH agents were significantly more effective than placebo at preventing DVT.

It is clear from PREVENT, MEDENOX, and studies of LDUH (2) that prophylaxis works and should be used for medically ill patients at risk. It is unclear whether physicians should use LDUH or an LMWH agent. Although LDUH is commonly given at 5000 units twice per day, more data suggest efficacy when it is given 3 times per day (2). The advantage of LDUH is cost; the advantage of LMWH is decreased incidence of heparin-induced thrombocytopenia, as well as 2 fewer injections per day, reducing patient discomfort. Further studies are needed to determine the optimal duration of prophylaxis.

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