

In patients with cancer and venous thromboembolism (VTE), enoxaparin was as effective as warfarin for VTE prophylaxis and reduced fatal haemorrhage

Meyer G, Marjanovic Z, Valcke J, et al. *Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study.* *Arch Intern Med* 2002;162:1729–35.

QUESTION: In patients with cancer and venous thromboembolism (VTE), is a fixed dose of subcutaneous low molecular weight (LMW) heparin better than oral warfarin for secondary prophylaxis of VTE?

Design

Randomised {allocation concealed*}†, blinded {outcome assessors and data analysts}†,* controlled trial with primary follow up to 3 months.

Setting

25 centres in France.

Patients

146 patients >18 years of age (mean age 66 y, 55% women) with cancer of any type and deep venous thrombosis and/or pulmonary embolism. Exclusion criteria were previous heparin induced thrombocytopenia, allergy to iodine, pregnancy, fibrinolytic treatment within 3 days, oral anticoagulant use for >5 days, treatment with full dose heparin for this episode of VTE, major pulmonary embolism with shock, life expectancy <3 months, contraindication to anticoagulants, severe hepatic failure, planned major surgery or planned chemotherapy known to induce thrombocytopenia within 3 months. 138 patients (95%) were included in the primary outcome analysis at 3 months.

Intervention

71 patients were allocated to a fixed dose of subcutaneous enoxaparin, 1.5 mg/kg body weight, once daily for 3 months. 75 patients were allocated to oral warfarin sodium, 6–10 mg, subsequently adjusted to achieve an international normalised ratio (INR) of 2.0–3.0 for 3 months.

Main outcome measures

Main outcome was treatment failure (symptomatic and objectively confirmed recurrent VTE and/or major bleeding at 3 mo). Secondary outcomes included major haemorrhage, fatal haemorrhage, mortality, and progression of underlying cancer.

Main results

The study was stopped prematurely because of slow patient accrual. Analysis was by intention to treat. At 3 months, patients in the enoxaparin and warfarin groups did not differ for treatment failure, major haemorrhage, mortality, or progression of underlying cancer (table). Patients in the enoxaparin group had a lower rate of fatal haemorrhage at 3 months (table). At 6 months, the groups did not differ for mortality or cancer progression.

Conclusions

In patients with cancer and venous thromboembolism, subcutaneous enoxaparin and oral warfarin were equally effective for secondary prophylaxis of venous

thromboembolism at 3 months. Patients who received enoxaparin had a lower rate of fatal haemorrhage than those who received warfarin.

*See glossary.

†Information provided by author.

Sources of funding: Aventis and the Délégation à la Recherche Clinique.

For correspondence: Dr G Meyer, Hôpital Européen Georges Pompidou, Paris, France. guy.meyer@hop.egp.ap-hop-paris.fr

Enoxaparin v warfarin for secondary prophylaxis of venous thromboembolism in patients with cancer and venous thromboembolism‡

Outcomes at 3 months	Enoxaparin	Warfarin	RRR (95% CI)	NNT (CI)
Treatment failure§	10%	21%	51% (–10 to 78)	Not significant
Major haemorrhage	7%	16%	56% (–13 to 83)	Not significant
Fatal haemorrhage	0%	8%	100% (35 to 100)	13 (7 to 38)
Mortality	11%	23%	50% (–4.9 to 77)	Not significant
			RRI	NNH
Cancer progression	17%	13%	27% (–40 to 170)	Not significant

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

§Treatment failure = recurrent thromboembolism or major haemorrhage.

COMMENTARY

Stable anticoagulant control is difficult to achieve in patients with cancer and VTE who are receiving warfarin because of hepatic dysfunction secondary to metastatic liver disease or effects of chemotherapy, interactions between warfarin and other cancer related drugs, and erratic absorption because of anorexia or gastrointestinal upset.¹ This explains why such patients show a 6.0 fold increase in major bleeding and a 3.0 fold increase in recurrent VTE compared with patients without cancer.² LMW heparin, while more costly than warfarin, is easy to administer, has predictable pharmacokinetics, and has been reported to be superior to warfarin as secondary prophylaxis in VTE.³

Meyer *et al* showed that fixed dose LMW heparin resulted in fewer fatal haemorrhages at 3 months than warfarin, although all cause mortality and recurrent VTE or major bleeding did not differ. Study weaknesses include the small sample size and the low frequency of fatal bleeding (0 v 6 patients) in the presence of 8 non-evaluable patients in whom bleeding, if it occurred in those receiving heparin, might have reversed the positive result seen here. Also, patient heterogeneity may have masked differential benefits of LMW heparin in particular subgroups.

Clinicians may, on the basis of this study, wish to use LMW heparin in patients with cancer and VTE who are considered to be at high risk of catastrophic bleeding if given warfarin. Larger studies, preferably stratified according to cancer type and stage, are required to define exact circumstances in which LMW heparin, as secondary prophylaxis, is superior to warfarin.

Ian Scott, MBBS, FRACP, MHA,
Princess Alexandra Hospital
Brisbane, Queensland, Australia

- Kuijer PM, Hutten BA, Prins MH, *et al*. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med* 1999;159:457–60.
- Hutten BA, Prins MH, Gent M, *et al*. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 2000;18:3078–83.
- Levine MN, Lee AY. Treatment of venous thromboembolism in cancer patients. *Semin Thromb Hemost* 1999;25:245–9.