Enoxaparin for prophylaxis of venous thromboembolism in hospitalised acute medical patients

A randomised controlled trial has shown that enoxaparin for prophylaxis of venous thromboembolism (VTE) did not reduce the rate of death from any cause at 30 days compared with placebo in hospitalised acute medical patients. However, the study may have been underpowered to assess this endpoint. In addition, it is unlikely that the study population would be representative of an NHS hospitalised general medical population. Both groups also wore elastic stockings with graduated compression; NICE guidance recommends considering mechanical prophylaxis for VTE in medical patients only when pharmacological prophylaxis is contraindicated. Health professionals should continue to follow NICE guidance which recommends routine risk assessment for VTE for general medical in-patients including bleeding risk, and offering pharmacological prophylaxis to people assessed to be at increased risk of venous thromboembolism.

Overview and current advice

It is estimated that 25,000 people die in the UK every year from preventable hospital-acquired venous thromboembolism (VTE). In addition, treatment of non-fatal symptomatic VTE and related long-term morbidities is associated with considerable cost to the health service.1

The NICE clinical guideline on reducing the risk of VTE in patients admitted to hospital recommends that all patients should be assessed on admission to identify those who are at increased risk of VTE. Medical patients are considered to be at increased risk of VTE if they:

- have had or are expected to have significantly reduced mobility for 3 days or more or
- are expected to have ongoing reduced mobility relative to their normal state and have one or more risk factors for VTE such as one or more significant medical comorbidities, age over 60 years, cancer, dehydration, obesity or personal or first-degree family history of VTE.

NICE recommends that, for general medical patients assessed to be at increased risk of VTE, pharmacological prophylaxis with either fondaparinux sodium, low molecular weight heparin or unfractionated heparin (for people with renal failure) should be offered.
Prophylaxis should start as soon as possible after risk assessment has been completed and continue until the person is no longer considered to be at increased risk of VTE.

Before offering pharmacological prophylaxis for VTE, all patients should be assessed for risk of bleeding. Pharmacological prophylaxis should not be offered to patients with any risk factors for bleeding, unless the risk of VTE outweighs the risk of bleeding. Patients’ risk of bleeding and VTE should be reassessed within 24 hours of admission and whenever the clinical situation changes. For medical patients in whom pharmacological VTE prophylaxis is contraindicated, mechanical prophylaxis of VTE with either antiembolism stockings, foot impulse devices or intermittent pneumatic compression devices should be considered.

Other recommendations, particularly around treatment, are made for specific patient groups, such as those with stroke or cancer, and for surgical patients.

See the NICE Evidence topic page on venous thromboembolism for a general overview of the condition. The NICE Pathway: venous thromboembolism brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

The LIFENOX randomised controlled trial evaluated the effect of enoxaparin, a low molecular weight heparin, on the rate of death from any cause in hospitalised, acutely ill medical patients. The study (n=8307) was undertaken in 193 sites in China, India, Korea, Malaysia, Mexico, the Philippines and Tunisia. Participants were at least 40 years of age (mean age 65 years) and had been hospitalised within the previous 48 hours for acute decompensated heart failure, severe systemic infection with at least 1 risk factor for VTE, or active cancer.

Participants were randomised to receive enoxaparin 40 mg or placebo (0.9% saline) once every 24 hours for 6 to 14 days. All wore knee-high elastic stockings with graduated compression. The primary efficacy outcome was the rate of death from any cause between the time of randomisation and day 30. The main safety outcome was the rate of major haemorrhagic events during and up to 48 hours after the treatment period.

The rate of death from any cause at 30 days was 4.9% (205/4171) in the enoxaparin group and 4.8% (199/4136) in the placebo group (risk ratio [RR] 1.0, 95% confidence interval [CI] 0.8 to 1.2, p=0.83). Major bleeding events were reported in 0.4% (16/4171) of patients in the enoxaparin group and 0.3% (11/4136) of patients in the placebo group (RR 1.4, 95% CI 0.7 to 3.1, p=0.35).

This study showed that enoxaparin plus elastic stockings with graduated compression did not reduce the rate of death from any cause at 30 days compared with placebo plus elastic stockings with graduated compression. However, death rates in the placebo group were lower than expected at 4.8% and the study may have been underpowered. It was estimated that with 3944 patients in each group the study would have 90% statistical power to show a 25% reduction with enoxaparin in the relative risk of death from any cause at 30 days, assuming a rate of death of 7% in the placebo group.

The majority of patients in the study had been hospitalised with severe systemic infection (57%) or heart failure (31%) and the incidence of several of the risk factors for VTE listed by NICE appeared low (e.g. previous history of VTE 0.6%, obesity 10.5%). The study authors acknowledged that they did not screen for asymptomatic deep-vein thrombosis and they observed low rates of symptomatic VTE in both groups. They comment that these low rates may be due to less awareness of the disease in the participating countries in which less
frequent diagnostic testing for suspected events was offered, or to the study population being at a lower risk for VTE compared with other studies of pharmacological prophylaxis. For example in the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study the percentage of the study population that had a history of VTE was around 9% and 50% of people were aged over 75 years compared with 0.6% and 25% respectively in LIFENOX. In LIFENOX both groups also wore elastic stockings with graduated compression as mechanical VTE prevention, which also may have reduced the risk of VTE.

Commentary

Commentary provided by Professor Gerard Stansby Professor of Vascular Surgery, Freeman Hospital Newcastle upon Tyne, Co-ordinating Editor Cochrane Peripheral Vascular Diseases Group and Chair of the Guideline Development Group for the NICE Clinical Guideline on Venous thromboembolic diseases

This study from Kakkar and colleagues was a large double-blind, placebo-controlled, randomised trial of the low molecular weight heparin (LMWH) enoxaparin for venous thromboembolism (VTE) prophylaxis in acute medical patients. It is unlikely that the population would be representative of an NHS hospitalised general medical population. The mean age was 65 years and in the NHS the population is likely to be older and have a different spectrum of clinical presentations. Inclusion criteria for the study did not reflect the NICE recommendations on how medical patients should be assessed for VTE risk; in particular the authors did not collect data on mobility status. The overall rate of death was relatively low in both groups and as a result it is likely that the study was underpowered to detect this important end-point. The primary safety outcome was the rate of major bleeding and LMWH was not associated with increased rates of major bleeding but was associated with increased rates of total bleeding.

It should also be noted that in both study groups graduated compression stockings (GCS) were worn and the study did not compare these with LMWH - it was studying the benefit of enoxaparin added to GCS compared to GCS alone. However, in current NICE guidance, the recommendation for general medical patients is to use pharmacological therapy first choice without GCS, which also makes this study less relevant for the NHS.

High risk general medical patients must have VTE prophylaxis and NICE recommends that, for general medical patients assessed to be at increased risk of VTE, pharmacological prophylaxis such as LMWH should be offered. For those in whom pharmacological VTE prophylaxis is contraindicated (e.g. due to bleeding risk), mechanical prophylaxis of VTE should be considered using either GCS or intermittent compression systems. Further work is required as to whether some higher risk subgroups required combined modalities for prophylaxis but this cannot currently be recommended routinely. This study supports that approach.

Study sponsorship

This randomised controlled trial was sponsored by Sanofi.

References

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