Venous thromboembolism: prevention with rivaroxaban in people with acute medical illness

A large randomised controlled trial in people who were admitted to hospital for acute medical illness found that oral rivaroxaban was noninferior to subcutaneous enoxaparin on a composite outcome of venous thromboembolism (VTE) and death related to VTE at 10 days. Extended prophylaxis with 35 days of rivaroxaban was statistically significantly superior to 10 days of enoxaparin, but more people in the rivaroxaban group had clinically relevant bleeding. This use of rivaroxaban is outside its licensed indication. Since the manufacturer is not pursuing a licence in this indication, NICE is not now developing a technology appraisal of rivaroxaban for the prevention of VTE in people hospitalised for acute medical conditions.

Overview and current advice

Medical patients admitted to hospital are considered to be at increased risk of venous thromboembolism (VTE) if they have had, or are expected to have, significantly reduced mobility for 3 days or more, or if they are expected to have ongoing reduced mobility relative to their normal state and have one or more risk factors for VTE such as age over 60 years, cancer, dehydration and obesity. The NICE clinical guideline on reducing the risk of VTE in patients admitted to hospital 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 used. Prophylaxis should start as soon as possible after risk assessment has been completed and continued until the person is no longer considered to be at increased risk of VTE.

There is some evidence that, in acutely ill medical patients, the risk of VTE persists after discharge from hospital. However, randomised controlled trials (RCTs) have not supported the routine use of extended prophylaxis in such people. In EXCLAIM, extended treatment with enoxaparin 40 mg daily (for 28 days after open-label treatment for 10 days) reduced VTE incidence compared with placebo, but it also increased the risk of bleeding. Furthermore, its benefits were restricted only to certain patients. ADOPT compared the new oral anticoagulant apixaban 2.5 mg twice daily for 30 days with subcutaneous enoxaparin 40 mg daily for 6 to 14 days. There was no statistically significant difference
between these on the 30-day composite outcome of VTE and death related to VTE. However, apixaban was associated with significantly more bleeding events than enoxaparin².

Three new oral anticoagulants are currently available in the UK (apixiban, dabigatran and rivaroxaban). All are licensed for preventing VTE after hip or knee replacement surgery, and for preventing stroke and systemic embolism in adults who have non-valvular atrial fibrillation and one or more risk factors. In addition, rivaroxaban is also licensed for treating deep vein thrombosis (DVT) and pulmonary embolism (PE), and preventing recurrent DVT and PE in adults. However, none are currently licensed for preventing VTE in patients with acute medical illness. Since the manufacturer of rivaroxaban is not pursuing a licence for this indication, the NICE technology appraisal on rivaroxaban for the prevention of VTE in people hospitalised with acute medical conditions was terminated in June 2012.

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

MAGELLAN was a multinational, double-blind RCT that compared extended thromboprophylaxis using oral rivaroxaban with subcutaneous enoxaparin for a standard period in 8101 people aged 40 years or more (median 71 years) who were admitted to hospital for an acute medical illness⁴. Patients were randomised to receive subcutaneous enoxaparin 40 mg once daily for 10±4 days and oral placebo for 35±4 days, or subcutaneous placebo for 10±4 days and oral rivaroxaban10 mg once daily for 35±4 days⁴.

The two primary outcomes were a composite of asymptomatic proximal deep vein thrombosis (DVT), symptomatic proximal or distal DVT, symptomatic non-fatal pulmonary embolus (PE) or death related to VTE from either day 1 to day 10 or from day 1 to day 35. The study was designed to assess for noninferiority at day 10 and for superiority at day 35⁴.

At day 10, rivaroxaban was noninferior to enoxaparin on the primary outcome in the per-protocol population (relative risk [RR] with rivaroxaban 0.97; 95% confidence interval [CI] 0.71 to 1.31; p=0.003 for noninferiority). The primary outcome was reported in 2.7% of people in both the rivaroxaban group (78 of 2938) and in the enoxaparin group (82 of 2993). At day 35, extended prophylaxis with rivaroxaban was statistically significantly superior to 10 days of enoxaparin on the primary outcome in the modified intention-to-treat population (RR 0.77; 95% CI 0.62 to 0.96; p=0.02; rivaroxaban 4.4%, 131 of 2967; enoxaparin 5.7%, 175 of 3057).

Between days 1 to 10, statistically significantly more people in the rivaroxaban group (2.8%; 111 of 3997; 5 had fatal bleeding) than in the enoxaparin group (1.2%; 49 of 4001; 1 had fatal bleeding) had clinically relevant bleeding (RR 2.3; 95% CI 1.63 to 3.17; p<0.001). Extended prophylaxis with rivaroxaban was also associated with statistically significantly more clinically relevant bleeding by day 35 (4.1%; 164 of 3997; 7 had fatal bleeding) than 10 days of enoxaparin (1.7%; 67 of 4001; 1 had fatal bleeding; RR 2.5; 95% CI 1.85 to 3.25; p<0.001). The prespecified analysis of net clinical benefit or harm did not show a benefit with rivaroxaban at either day 10 or day 35.

Commentary

Commentary provided by Dr Will Lester, MBChB BSc MRCP FRCPath PhD, Haematology Consultant Queen Elizabeth Hospital and Birmingham Women’s Hospital and Honorary Senior Clinical Lecturer in the School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham
In contrast to the results of trials in patients after elective hip and knee replacement surgery\textsuperscript{5,6}, in acutely ill medical patients there is only equivalent efficacy and increased bleeding risk for VTE prophylaxis with oral direct inhibitors of factor Xa (rivaroxaban, apixaban) compared with prophylactic enoxaparin\textsuperscript{2,4}. In the MAGELLAN study, although at day 35 extended prophylaxis with rivaroxaban reduced VTE or death related to VTE compared with 10 days of enoxaparin, when the authors considered the net clinical benefit balanced against harm, they did not find a benefit with rivaroxaban. The authors suggest that acutely ill medical patients are older with greater comorbidity and bleeding risk than patients enrolled into trials of elective orthopaedic surgery. The MAGELLAN trial control arm does not quite reflect standard practice; many medical patients will not receive 10 (or even 6) days of pharmacological prophylaxis because treatment will stop at discharge. In addition, ultrasonography at day 10 may also have led to treatment of asymptomatic VTE and, therefore, altered the natural history of the disease. For example, patients in the enoxaparin arm who were found to have asymptomatic VTE at day 10 may have otherwise presented clinically later on. This could reduce any apparent advantage of extended prophylaxis as these patients are excluded from further analysis.

A further limitation of this study is that the primary outcome included asymptomatic proximal DVT detected by ultrasonography, which is not routine practice. This contributed to about a quarter of patients who were randomised to each group not being included in the analysis of the primary outcome, in many cases because they did not undergo ultrasonography or because their ultrasonograms could not be properly assessed.

Those with responsibilities for reviewing local policies will need to consider these results alongside the terminated NICE technology appraisal of rivaroxaban for this indication, the issues involved with off-label prescribing, the inconvenience of injectables for both patients and staff, and the non-reversibility of the newer agents. On the basis of current evidence extended thromboprophylaxis for medical inpatients has not been demonstrated to be beneficial; further trials are required to identify the patients at highest risk of VTE where a clear net clinical benefit can be demonstrated.

Study sponsorship

This study was sponsored by Bayer HealthCare Pharmaceuticals and Janssen Research and Development.

References

About this Medicines Evidence Commentary

Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

Visit Evidence Search

Copyright © 2013 National Institute for Health and Care Excellence. All Rights Reserved.