Product News

Simplifying venous thromboembolism management: A new and safer era

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Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), commonly occurs both in patients in the community and during and following hospitalisation for surgery or acute medical illness.

Patients undergoing major orthopaedic surgery have a particularly high risk. In the absence of thromboprophylaxis, DVT develops in 40–60% of patients undergoing total knee replacement (TKR) or total hip replacement (THR) and in 10–40% of medical and general surgery patients.

Diagnosis can be difficult and VTE is likely to be missed as a cause of death because of the lack of routine post-mortem examinations, resulting in an underestimation of the true incidence. The chronic nature of VTE and its complications, such as post-thrombotic syndrome and pulmonary hypertension, generate a considerable healthcare burden.

Numerous risk factors are associated with VTE and these are generally cumulative. Intrinsic risk factors include gender, age and malignancy, whereas extrinsic risk factors include recent surgery or trauma. In all cases, risk is higher if anticoagulants are discontinued earlier.

Management encompasses primary prevention and treatment (including secondary prevention); given the availability of effective VTE prophylaxis and treatment, the current use of anticoagulant therapy is suboptimal.

Currently recommended treatments for VTE include unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and vitamin K antagonists (VKAs), usually warfarin. However, despite their recommendation by current guidelines, current therapies have numerous limitations. For example, UFH, LMWH and fondaparinux require parenteral administration, while the oral VKAs have a slow onset of action, require regular coagulation monitoring and have numerous drug and food interactions. These limitations make the management of patients with VTE difficult, and they negatively affect patients' quality of life. As a consequence, research has focused on new anticoagulant agents that could overcome these limitations. In many countries rivaroxaban is now used for VTE management.

The EINSTEIN programme comprised three phase III randomised trials of rivaroxaban, in DVT, PE and the extended therapy study in both DVT and PE. All three have been completed and the last study, the EINSTEIN PE study, was published in 2012. In the EINSTEIN DVT study, a total of 3 449 patients underwent randomisation and the results showed the primary efficacy outcome of symptomatic recurrent VTE for the rivaroxaban arm was non-inferior to standard therapy of enoxaparin plus VKA (36 events [2.1%] vs. 51 events [3.0%] respectively; p<0.001 for non-inferiority with a one-sided test).

In addition, net clinical benefit in terms of VTE plus major bleeding favoured rivaroxaban, (rivaroxaban 2.9% of patients vs. enoxaparin/VKA 4.2% of patients; p=0.03). A low rate of bleeding was seen with less major bleeding in the rivaroxaban arm. The EINSTEIN PE trial of rivaroxaban is the only currently published study of a single-agent approach specifically for the treatment of symptomatic PE. In this study, rivaroxaban was non-inferior to enoxaparin/VKA for the prevention of symptomatic recurrent VTE (p=0.003 for non-inferiority) and reduced major bleeding by 50%.

The EINSTEIN Extension study, had an intention-to-treat population that comprised 1 196 patients (rivaroxaban, n=602; placebo, n=594). Of these patients, 34.1% had completed the EINSTEIN DVT study and 19.1% had completed the EINSTEIN PE study. In this study, rivaroxaban was significantly superior to placebo with respect to the primary efficacy outcome of symptomatic recurrent VTE (1.3% vs. 7.1%; p<0.001) and was associated with a relative risk reduction of 82%. Major bleeding was infrequent and occurred in 0.7%.

The novel oral anticoagulants (NOACs) have been shown to be effective and have good safety in the treatment of VTE. Only one NOAC, oral rivaroxaban, given 15 mg twice daily for three weeks for acute therapy followed by 20 mg once daily provides a simple, single-drug approach for short-term treatment and continued prevention of VTE.

References available on request

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Dr Cohen is a vascular physician and epidemiologist involved in clinical work, designing, managing, and analysing clinical trials from phase I to IV. His main interest lies in the screening and the prevention of vascular disease. He specialises in the primary and secondary prevention of cardiovascular disease, prevention of stroke and coronary artery disease, and prophylaxis and treatment of venous thromboembolism (VTE).

He is the Chairman and member of many international steering committees for multicentre trials, epidemiological and pharmaco-economic studies. He has written or co-authored over 250 papers and abstracts since 1990, many in *The Lancet, New England Journal of Medicine, Annals and Archives of Internal Medicine* and *BMJ*. He has over 30 publications in the *Lancet* and *New England Journal of Medicine*.