Simplifying venous thromboembolism management: a new and safer era

Dr Cohen is a vascular physician and epidemiologist involved in clinical work, designing, managing and analysing clinical trials from phase I to IV. He is the chairman and member of many international steering committees for multicentre trials, and epidemiological and pharmaco-economic studies.

He has participated in cardiovascular clinical trials on anticoagulants, thrombolytic agents, and antiplatelet, antihypertensive and lipid-lowering drugs. He has undertaken numerous meta-analyses, economic analyses and large epidemiological studies.

Dr Cohen has written or co-authored numerous articles and abstracts since 1990; many in the Lancet, New England Journal of Medicine, Annals of Internal Medicine, Archives of Internal Medicine and British Medical Journal. He is also a member of a number of international special-interest societies and serves as an educational supervisor at the Royal College of Physicians.

Dr Cohen is an advisor on the prevention of venous thromboembolism (VTE) to the UK Government Health select committee, the all-party working group on thrombosis, the Department of Health and the National Health Services. He is also an advisor to Lifeblood: the thrombosis charity and is the founder of the European educational charity, the Coalition to Prevent Venous Thromboembolism.

His main interests continue to be in the screening and 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.

During the course of October, Bayer hosted a lecture tour in major centres throughout South Africa on venous thromboembolism (VTE) management. Spanning the interests of a healthcare team approach to the management of VTE, lectures were presented by the eminent vascular physician Dr Cohen and our South African counterparts; haematologist Prof Peter Jacobs and specialist vascular surgeon Dr James Tunnicliffe.

VTE is a ubiquitous condition seen across all specialities. It is the third most common cause of mortality, with 10% of all deaths associated with or caused by VTE. VTE is also the third most common cardiovascular disease, with more than one-third of cases representing recurrent VTE. Deep-vein thrombosis (DVT) and pulmonary embolism (PE) commonly occur in the community, as well as pre- and post-hospitalisation for acute medical illness or surgery. Patients undergoing major orthopaedic surgery are particularly at risk. In the absence of thromboprophylaxis, DVT develops in 40 to 60% of patients undergoing total knee or total hip replacement; and in 10 to 40% of medical and general surgery patients.

In an interview with Dr Cohen, the context of VTE management in resource-limited settings such as sub-Saharan Africa was discussed. ‘The chronic nature of VTE and its complications, such as post-thrombotic syndrome and pulmonary hypertension, place an enormous burden on the healthcare system’, he said.

Data presented in his lecture indicated that post-thrombotic syndrome occurs in 20 to 50% of patients after symptomatic deep-vein thrombosis (DVT). Of pulmonary embolism (PE) patients, 4% will develop pulmonary hypertension, which is difficult to manage. Morbidity at eight years post-VTE is 45% for DVT and 55% for PE.

‘Diagnosis can be difficult and VTE is often missed as a cause of death’, Dr Cohen stated, placing a further morbidity burden on the healthcare system. ‘Diagnosis of DVT requires a comprehensive history and clinical examination.’

Half of DVT cases are asymptomatic, and for diagnosis, Dr Tunnicliffe and Dr Cohen were in agreement that compression ultrasound at two sites is not sufficient. Imaging is also difficult in the obese patient. It is therefore essential to perform a good evaluation.

Dr Cohen advised that the primary-care physician request the radiologist to view intervening segments from the traditional two-point compression. ‘In the UK, it is standard to look from groin into calf and also to look up into the abdomen if nothing presents in the lower limb’, he said.

Furthermore, limitations of current therapies, which are inconvenient and cumbersome, may contribute to suboptimal treatment of VTE and subsequent complications including recurrences. Currently recommended treatments for VTE include unfractionated heparin (UFH), low-molecular weight heparin (LMWH), fondaparinux and vitamin K antagonists (VKAs), usually warfarin. 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 quality of life’, stated Dr Cohen in introducing the new anticoagulant agents that could overcome these considerations. ‘In many countries rivaroxaban is now used for VTE management. The use of one drug to manage blood clots without the need for therapeutic dose monitoring is ideal.’ This furnishes the advantages of improving adherence and reducing overall treatment costs by negating the need for dose...
monitoring.

Trial data in support of rivaroxaban include the EINSTEIN DVT study, which indicated that symptomatic recurrent VTE for the rivaroxaban arm was non-inferior to standard therapy of enoxaparin plus VKA. The EINSTEIN PE trial, the only currently published study of a single-agent approach specifically for the treatment of symptomatic PE, revealed that rivaroxaban was non-inferior to enoxaparin plus VKA for the prevention of symptomatic recurrent VTE.

In the EINSTEIN Extension study, rivaroxaban was significantly superior to placebo with regard to symptomatic recurrent VTE and was associated with a relative risk reduction of 82%. Major bleeding was infrequent and occurred in 0.7% of patients.

Dr Cohen concluded by saying that the novel oral anticoagulants have been shown to be effective and have good safety in the treatment of VTE. Only oral rivaroxaban, given in a dose of 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.

A single-agent approach also allows for the simplifying of complicated guidelines. An example is the American College of Chest Physicians (ACCP) 9th antithrombotic guidelines, consisting of 117 different recommendations.

Dr Tunnicliffe presented a surgeon’s perspective on VTE interventions, initially emphasising that the surgeon does not see VTE early enough and that aggressive early intervention may prevent early PE death. He noted that while anticoagulants will prevent propagation of clot and prevent PE, the existing clot is still a concern. Spontaneous lysis is often incomplete, with residual obstruction resulting in vascular hypertension. ‘Anticoagulation alone is probably insufficient in most cases of proximal DVT’, stated Dr Tunnicliffe, recommending clot removal when anticoagulation proves inadequate. He also noted that the long-term outcomes of anticoagulation in the young were not promising.

A thrombectomy under general anaesthetic entails catheter extraction of the clot through a groin incision. Operative mortality is very low, although there is a risk of groin complications, rethrombosis and very rarely, PE. Cost is a consideration as the hospital stay may exceed 10 days.

Prof Jacobs pondered on the practical realities of VTE. Of primary concern is the pre-emptive avoidance of the first clot. In terms of the initial event, it is essential to ascertain whether the clot was provoked or idiopathic in origin, in order to appropriately intervene. A good family history will often give clues to causation.

Prof Jacobs emphasised the need for simple referral guidelines. He concluded that ‘most underestimate the impact of smoking on the vascular system.’

G Hardy