NEW INSIGHTS INTO THE DEFINITIVE MANAGEMENT OF VENOUS THROMBOEMBOLISM

Summary of the Presentations from the Daiichi Sankyo Symposium, ESC Congress 2013, Amsterdam, the Netherlands

Chairperson

Valentin Fuster[1]

Speakers

Ajay K. Kakkar,[2] Gregory Y. H. Lip,[3] Ander Cohen,[4] Harry R. Büller[5]

1. Director of Mount Sinai Heart at the Mount Sinai Medical Center, Chicago, USA
2. Professor of Surgery, University College London, UK
3. Professor of Cardiovascular Medicine, University of Birmingham, UK
4. Honorary Consultant Vascular Physician, Kings College Hospital, London, UK
5. Professor of Internal Medicine, Academic Medical Center, University of Amsterdam, the Netherlands

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INTRODUCTION

This educational symposium, supported by an unrestricted educational grant from Daiichi Sankyo, was given at the European Society of Cardiology (ESC) Congress, held between 31st August and 4th September 2013 in Amsterdam, the Netherlands. This meeting highlighted the global burden of venous thromboembolism (VTE), and discussed the available therapies, both new and old.

Understanding the Burden of VTE

Prof Ajay K. Kakkar

Prof Ajay Kakkar began by discussing the high incidence of VTE. Population data from the USA and Europe indicate annual incidence rates of 120–180 per 100,000 adults.[1-3] This constitutes a significant burden of disease which has a large impact on public health. Pulmonary embolism (PE) is the third leading cause of cardiovascular death after myocardial infarction and stroke.[4]

Much research has focused on hospitalised populations as they are at a high risk of VTE. Medical patients have a 10–15% increased risk of thrombosis and patients undergoing major orthopaedic surgery have a 40–60% risk of thromboembolism.[5] However, one study found that only half of hospitalised patients at high risk for VTE were receiving thromboprophylaxis.[6] Prof Kakkar presented data showing that more than 12% of patients presenting with PE have died 3 months after diagnosis.[7] In addition, data from the Computerised Registry of Patients with Thromboembolism (RIETE) shows that despite receiving treatment, 17% of medical ward patients (6% of surgical patients) have died 3 months after presenting.[8] Medical patients were also more likely to have major and fatal bleeds than surgical patients during long-term anticoagulation therapy.

Recurrent thrombosis occurs in over 20% of patients despite receiving early anticoagulation measures for their first thrombotic event.[9] The highest risk of recurrence (≥10%) is seen in patients who present with an initial idiopathic VTE.[10]

Studies suggest that extending treatment with anticoagulants for 6–12 months is associated with a lower risk of recurrent thromboembolism.[11] In patients presenting with idiopathic thromboembolism, the risk of recurrence is renewed when anticoagulants are ceased; however, if maintained on anticoagulant medication long-term, there is a heightened risk of major bleeding.[11]

Another risk identified was the development of long-term complications such as post-thrombotic syndrome, which occurs in 5–40% of patients.[9] Post-thrombotic syndrome is characterised by ulceration, induration and pigmentation in the lower limbs as a result of destruction of the venous valvular architecture and development of venous hypertension. A recent study showed that the frequency of post-thrombotic syndrome was greater in patients whose anticoagulation was suboptimal in the 6 months following presentation.[12] Chronic thromboembolic pulmonary hypertension occurs in 3–4% of patients within 2 years of presentation with a PE, and is an extremely debilitating illness.[13]

Prof Kakkar concluded that there is a substantial economic burden associated with VTE in terms of its acute presentation, management, long-term complications of disease, and associated morbidity and mortality.[14–16]

Anticoagulant Profiles: What You Need To Know

Prof Gregory Y. H. Lip

Prof Gregory Lip discussed the targets of the classic anticoagulant medications, heparin and vitamin K antagonists. Heparin targets various stages of the coagulation pathway – initiation, amplification and thrombin activity.[17] Vitamin K antagonists, like warfarin, target vitamin K-dependent coagulation factors II, VII, IX and X.[17]

The target international normalised ratio (INR) for patients receiving warfarin is 2–3. Above this level, there is a substantially increased risk of serious bleeding, while below 2 there is an increased risk of stroke.[18,19] A balancing act is therefore required in in order to minimise risk and maximise benefit to the patient. The quality of anticoagulation control is determined by the time in the therapeutic range (TTR), which is time spent within an INR of 2–3.

Limitations associated with vitamin K antagonists include variability in response between individuals, risk of haemorrhage (particularly intracranial bleeds), a narrow therapeutic window, multiple food and drug interactions and slow onset and offset of action.

Studies of patients with atrial fibrillation (AF) receiving warfarin showed that those who had at least 70% TTR had a substantially reduced risk of stroke, haemorrhage and thromboembolism.[20,21] Patients who were suboptimally treated fared worse than patients who were untreated. The key message identified by Prof Lip was that the quality of anticoagulation control, as measured by TTR, should be considered at an individual level in order to improve outcomes. These data demonstrate that vitamin K antagonists such as warfarin are limited by the need for good quality INR control.

The SAMe-TT_2R_2 score uses clinical risk factors to predict those patients who would benefit from warfarin.[22] It takes into account sex (S, one point), age (A, one point), medical history (Me, one point), treatment – especially interacting medicines such as amiodarone (T, one point), tobacco use in the previous two years (T, two points) and race (R, two points). The maximum score is 8, and patients scoring 0–1 are most likely to benefit from warfarin since they are also more likely to have ≥70% TTR, indicating good quality anticoagulation control. Patients with a score above 2 are at risk of suboptimal anticoagulant control.

Prof Lip then discussed novel oral anticoagulants (NOACs). The four main NOACs available are the direct thrombin inhibitor dabigatran and the Factor X inhibitors apixaban, edoxaban and rivaroxaban. (Edoxaban is currently available only in Japan). These target various stages of the coagulation pathway.[17]

There are relevant pharmacokinetic differences between the NOACs. Dabigatran has the lowest bioavailability (3–7%), while only 27% of apixaban is excreted renally, compared to 80% of dabigatran, 50% of edoxaban and 35% of rivaroxaban.[23] The half-lives of dabigatran, edoxaban and apixaban are approximately 10 to 12 hours, whereas for rivaroxaban it is 5–9 hours in the young, and longer in the elderly. The half-life of dabigatran is markedly increased in patients with chronic kidney disease, therefore renal function must be observed closely in these patients.[23]

Prof Lip presented data from his research group concerning the change in renal function in a cohort of patients with AF who were receiving anticoagulants.[24] A low glomerular filtration rate was associated with increased frequency of thrombotic/vascular events, bleeding and mortality. Renal function declined in approximately one in five patients over the follow-up period, highlighting the need for regular checking of renal function.

Prof Lip concluded that older vitamin K antagonists are subject to diet, drug and alcohol interactions, and as such their administration needs to be monitored to maintain an INR of 2–3. NOACs such as direct thrombin inhibitors and factor Xa inhibitors are less subject to food and drug interactions, and therefore require less monitoring.

At the Crossroads: Deciding Factors for Optimising VTE Treatment

Dr Ander Cohen

Dr Ander Cohen compared the design of phase III acute VTE studies; RE-COVER (dabigatran), EINSTEIN (rivaroxaban), AMPLIFY (apixaban) and Hokusai-VTE (edoxaban).[25–30] All studies were double-blind, except the EINSTEIN study that evaluated quality of life. EINSTEIN evaluated DVT and PE separately while the other studies evaluated combined VTE. There were variations in study duration and in the use of a heparin bridge.

The RE-COVER I and II studies evaluated dabigatran in comparison to warfarin. In RECOVER-I the level of recurrent VTE was 2.4% for dabigatran-treated patients and 2.1% for warfarin-treated patients. Major bleeding was observed in 1.6% versus 1.9% of dabigatran-treated patients versus warfarin-treated patients. RECOVER-II had very similar results.[29,30] RE-MEDY was an extension study of dabigatran that monitored recurrent VTE (1.8% in dabigatran-treated patients versus 1.3% in warfarin-treated patients) and major bleeding (0.9% in the dabigatran group versus 1.8% in the warfarin group).[31] The RE-SONATE study evaluated dabigatran versus placebo and demonstrated an 80–90% reduction in recurrent VTE with dabigatran treatment, with a small (0.3%) increase in major bleeding.[31]

The EINSTEIN-DVT study demonstrated recurrence rates of 2.1% versus 3.0% and major bleeding of 0.8% versus 1.2% in rivaroxaban versus conventional therapy.[26] In the EINSTEIN-PE study, rivaroxaban led to an approximately 50% reduction in major bleeding.[27] The EINSTEIN extension study demonstrated an 82% reduction in recurrence in those treated with rivaroxaban versus conventional therapy and major bleed rates of 0.7% (rivaroxaban) versus 0.1% (conventional).[26]

The AMPLIFY study showed non-inferiority for apixaban in VTE (both DVT and PE) with a reduction in major and clinically relevant non-major bleeding.[28] The AMPLIFY extension study compared 2.5 mg or 5 mg apixaban twice-daily to placebo.[28] The risk of recurrence was reduced by 80% in the apixaban groups, with no significant difference in major bleeding.

While there were similarities in the studies, there were also some differences, including variations in dosage and side-effect profile. Overall, NOACs show similar efficacy to warfarin but are safer and easier to administer. Dr Cohen commented that there are still a number of areas that require further study. There is limited information on the use of NOACs in cancer patients, and it is unknown whether the dose of NOACs can be lowered, in particular for secondary embolism prevention. It is also necessary to define which patients are the most suitable candidates for NOACs. Patients with poor INR control on warfarin would be candidates, however only if poor INR control was not due to poor compliance.

Areas of uncertainty regarding NOACs include their use in severe PE and DVT patients, as some clinicians advocate longer use of low molecular weight heparin. Dr Cohen noted that all the reported studies included patients with moderately severe PE, however there is a need to know more about the co-medications, the role of p-glycoprotein, and the impact of inducers and inhibitors and Cyp3A/4. There is a need for more information regarding fragile patients; those who are elderly, of low body weight or with renal impairment.

Dr Cohen suggested that the use of NOACs represents an opportunity to simplify therapy and streamline the transition from hospital to home, saving money and improving patient quality of life. Challenges of NOAC therapy include collecting follow-up information on these unmonitored therapies, and the lack of monitoring tests for these drugs. Another challenge is that unlike for warfarin, there are no specific

antidotes. However, a phase II study of the Portola antidote is currently ongoing, which may prove effective in reversing the pharmacodynamic effects of Xa inhibitors.

Dr Cohen concluded that there is a need for more information on NOAC use in patients with severe VTE, cancer, low- and high-weight patients, patients with renal impairment and on the effect of comedications and optimal dosing schedules.

Recent Clinical Trial Data: Future Opportunities for VTE Prophylaxis and Treatment

Prof Harry Büller

Prof Harry Büller presented the results of the global Hokusai-VTE study.[25] This study aimed to evaluate the use of edoxaban versus warfarin in patients with VTE. The inclusion of more patients with extensive VTE as they may not have been represented adequately in previous studies, distinguishes Hokusai-VTE from previous NOAC trials. Patients were treated with initial parenteral heparin, followed by three months of edoxaban (60 mg) treatment, after which it was continued at the treating physician's discretion. All patients were followed for 12 months.

The primary efficacy outcome was symptomatic recurrent VTE, comprising deep vein thrombosis (DVT), non-fatal PE and fatal PE. There were multiple secondary outcomes: recurrent VTE in the on-treatment period; recurrence of DVT and PE separately; severe PE with right ventricular dysfunction; and TTR quartiles. The primary safety outcome was a composite of major or clinically relevant non-major bleeding in the treatment period.

Prof Büller highlighted that 40% of patients in the study had a qualifying diagnosis of PE. A high proportion of patients had more extensive disease; in 42% of DVT patients the thrombus extended into the femoral or iliac vein, while 45% of PE patients had extensive disease. Thirty percent of patients with PE had right ventricular dysfunction defined by NT-pro B type natriuretic peptide (NT-pro BNP) of 500 pg/mL.

The rate of VTE recurrence was 3.2% in the edoxaban group and 3.5% in the warfarin group, which confirmed non-inferiority of the NOAC ($p<0.001$). This was valid both for patients with DVT and those with PE. In patients with PE and elevated NT-pro BNP, the recurrence rate for VTE in the warfarin group was 6.2%, while those treated with edoxaban had a recurrence rate of 3.3%; equivalent to an almost 50% risk reduction.

Edoxaban therapy was associated with significantly improved safety; 8.5% of patients treated with edoxaban had a major or clinically relevant non-major event compared with 10.4% of warfarin patients (hazard ratio [HR] 0.81, $p<0.004$). There were also fewer fatal and non-fatal bleeds in patients treated with edoxaban.

Prof Büller noted that there was a higher proportion of patients with more severe disease in the Hokusai-VTE study compared to other studies of NOACs. In the EINSTEIN-PE study, in which 25% of patients had more severe disease, the HR for patients treated with rivaroxaban was 1.12.[27] In the Hokusai-VTE study, the HR was 0.73, and in those patients with more severe PE, the HR was 0.52.

In the Hokusai-VTE study, the rate of VTE in patients with >70% TTR was 3.7% in the warfarin group and 2.5% in the edoxaban group, demonstrating non-inferiority of edoxaban and showing that patients treated with warfarin were receiving an optimal treatment regimen, since outside of the clinical trial setting, Prof Lip noted that the TTR for warfarin patients is usually 40–50%.

The 60 mg dose of oral factor Xa inhibitor edoxaban was chosen for investigation. However, in certain situations (such as moderate renal impairment, low body weight, concomitant use of p-glycoprotein inhibitors) this dose should be reduced to 30 mg in order to prevent patients from overexposure and bleedings. Edoxaban 30 mg was shown to be comparable in efficacy to the 60 mg dose. In addition, there were almost 40% fewer cases of clinically relevant bleeding in patients treated with edoxoban 30 mg compared to those treated with warfarin. Thus the dose adaption to 30 mg was shown to be effective and safe in patients treated for VTE.

Prof Büller concluded that low molecular weight heparin plus edoxaban was non-inferior to low molecular weight heparin plus warfarin therapy, and demonstrated a significant reduction of VTE in patients with right ventricular dysfunction.

Panel Discussion

The main presentations were followed by a panel discussion with chair Prof Valentin Fuster and the four speakers. Prof Kakkar commented that cardiologists will be key in providing education about NOACs and VTE. Dr Cohen considered it unlikely that there would be head-to-head comparisons of NOACs, and that differentiation between individual therapies would not be of value. He emphasised the importance of the positive results from NOACs in general over those for individual treatments, advocating that this should be the take-home message from the symposium.

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