A new era in anticoagulation

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For half a century, heparins and vitamin K antagonists (VKAs) were the gold standards in the treatment of venous thromboembolism (VTE). The novel oral anticoagulants (NOACs) provided a new therapy option that was as effective as warfarin but with added safety and convenience.

The new oral fixed dose agents are easy to administer, without the need for regular coagulation monitoring as required with vitamin K antagonists such as warfarin. They are associated with a significantly reduced risk of intracranial haemorrhage, and their rapid onset of action and short half-lives means they have established safety and efficacy in the prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE).

Indeed, the arrival of the NOACs ushered in a new era in antithrombotic therapy and in doing so, transformed traditional hospital anticoagulation services.

At the Irish Anticoagulation Forum 2015, which took place recently at the RCPI in Dublin, health professionals discussed their experience of the newer agents and shared information and knowledge on what they had learned during their everyday clinical practice. National and international speakers presented their experience and views at the event, which aimed to provide the most up-to-date medical education across the various disciplines involved in the care of patients at risk of thrombotic disorders.

Chairing the meeting was Professor Sean Murphy, consultant physician in general medicine, medicine for the older person and stroke, from the Mater Hospital in Dublin, who told the audience that data has shown the use of warfarin is on the decrease, as the use of NOACs continues to rise.

He outlined a 2014 US study that highlighted the difficulties of using warfarin properly, with just 55-60 per cent of patients being kept within the therapeutic range.

A workshop entitled “Anticoagulation in VTE – Real Life Irish Data and Optimal Treatment Duration” took place on the day and this was hosted by Dr Mike Watts, Consultant Physician, and Dr Denis O’Keeffe, Consultant Haematologist, who together run the anticoagulation clinic at Mid-Western Regional Hospital (MWRH) in Limerick.

They presented their own observational data from MWRH on the ambulatory management of venous thromboembolism (VTE), and discussed the evidence on optimal duration of anticoagulation for patients.

Ownership and the multidisciplinary team

Dr O’Keeffe began by giving the audience an overview of how the anticoagulation clinic operates at the hospital.
He asserted that one of the key issues with optimal anticoagulation treatment is that of “ownership” – often falling between various departments, a successful anticoagulation service requires leadership and organisation, as well as trained staff, he said, adding that it is not something that can be looked after by junior doctors.

“The service needs a consultant to manage it, run it, and oversee it, in order to provide the best service you can. That is true from the moment the (deep vein thrombosis) DVT is diagnosed to the moment that anticoagulation is stopped or is decided to continue.”

Dr O’Keeffe discussed the importance of the multidisciplinary anticoagulation team, explaining that this was previously “the warfarin team”. Unskilling of the various members of the team has taken place, including the nursing staff, in order for them to be sufficiently knowledgeable of the new raft of oral anticoagulants, he said.

“We have used the skills and experience of the team, particularly of Jane Conway our clinical nurse specialist, to evolve the service into an anticoagulation service,” he said.

Dr O’Keeffe said that any such service should have a specific DVT/anticoagulation nurse who looks after patients from the outset and manages their anticoagulation.

He added that a consultant radiologist should be available to assess scans if required.

Protocol
Dr O’Keeffe then explained the particular protocol they follow at MWRH.

Assessing whether a VTE is provoked or unprovoked by the identification of a transient risk factor such as surgery, fracture, oral contraceptive pill, pregnancy, injury, etc., is the initial step. If the VTE is provoked, then three months anticoagulation is given as “standard”, with all patients receiving a NOAC, he said, adding that the evidence shows no benefit for prolonged anticoagulation in this instance.

“Our experience has told us that if a patient has a provoked VTE, they only need three months treatment; there is no justification for a patient with a VTE caused by a true transient risk factor to be on treatment longer than three months. This is about two-thirds of your DVT patients and they are the perfect population for the NOACs,” he asserted.

He outlined a prospective study carried out at their clinic of new patients with provoked DVT who received rivaroxaban for three months between November 2013 and December 2014, with this data then matched to a comparable historical group treated with VKA in the unit. It was seen that 37.5 per cent of patients on VKA spent less than 60 per cent of time in the therapeutic range and in addition patients on warfarin required a significantly higher number of outpatient visits than those on rivaroxaban, with an average of 14.58 visits versus 2.92.

“There were more visits, and poor control for a significant number of patients over three months, so by the time they become stable they are coming off treatment anyway. The NOACs are perfect for this group of patients as it is simple and you can discharge them straight away.”

The study also showed that the costs were comparable over three months – it was estimated that the cost per patient was €260.68 for VKA compared with €273.30 for rivaroxaban; this does not include the patient cost and time, added Dr O’Keeffe.

“The bottom line is that patients should be on direct oral anticoagulants – it is safer, it is cheaper, and it is far easier for the patient. This should be the standard of care for provoked DVTs.”

After three months, patients are reassessed within the clinic and if all transient risk factors have been resolved, anticoagulation is stopped.

Unprovoked VTEs are “trickier” to manage, continued Dr O’Keeffe, explaining that the recurrence rate at three years is roughly 20 per cent for males and 10 per cent for females. These patients are generally treated with low molecular weight heparin or warfarin, but if control is poor they are switched to a NOAC.

“With a true unprovoked VTE, you have to consider long-term anticoagulation,” he said. Patients with unprovoked VTEs are also assessed after three months, and additional factors such as their bleeding risk, lifestyle, patient preference, whether it is minor or extensive DVT or PE, and their compliance, are taken into account.

The evidence shows that with an unprovoked extensive VTE, there is “strong justification” for long term anticoagulation, according to Dr O’Keeffe. In terms of tests to predict the recurrence of VTE, he explained that studies have shown that looking at the residual thrombosis was unhelpful and the same was found of thrombophilia testing.

He told the audience that MWRH took part in the international DODS (D-Dimer Optimal Duration Study) trial, the results of which were published in the Annals of Internal Medicine at the beginning of this year. This study examined whether D-dimer testing could be used in order to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy.

It was determined that D-dimer should not be done in high risk group, as it has a poor negative predictive value. It also showed that for men the reduction in recurrence risk was not enough falling from 20 to 10 per cent. For women, however, the risk drops to just four per cent. Hence, the D-dimer is used for women but not men in MWRH, Dr O’Keeffe explained.

Continuation
The haematologist then discussed evidence in relation to the continuation of NOAC therapy. He told the audience that the EINSTEIN extend study illustrated that an additional six 12-months of rivoroxaban therapy dramatically reduced the risk of a recurrent DVT but there was still a risk of major bleeding of 0.7 per cent per year.

“This is less than warfarin, but there is still a significant rate of major bleeding. Yes the direct oral anticoagulants are a possible choice, the bleeding risk is less, but it is still significantly more than placebo and so doesn’t take away the need to make a decision on long-term anticoagulation,” he stated, adding that a study with dabigatran had similar results.

Dr O’Keeffe highlighted the importance of the stepwise process used in the anticoagulation clinic at MWRH and again asserted that this should be the standard of care for patients in need of anticoagulation.

Dr Watts added that VTE is the third most frequent cardiovascular disease, and a potentially lethal, chronic disability that is often preventable. He reiterated Dr O’Keeffe’s point that as an orphan illness, its management has been historically poor.

The new era of anticoagulation has, in his opinion, brought easier access to tests and better drugs with emerging competition.