Podcast Transcript
VTE: how long should anti-thrombotic treatment be?

Brought to you by:
Prof. Dimitrios Tsakiris, Basel University, Switzerland
Prof. Jerzy Windyga, Institute of Haematology and Transfusion Medicine, Warsaw, Poland

Introduced by:
Tonke de Jong, COR2ED

Please note:
HEMOSTASIS CONNECT podcasts are designed to be heard. If you are able, we encourage you to listen to the audio, which includes emotion and emphasis that is not so easily understood from the words on the page. Transcripts are edited for readability. Please check the corresponding audio before quoting in print.

This podcast is an initiative of COR2ED and developed by HEMOSTASIS CONNECT, a group of international experts working in the field of haemostasis. The podcast is supported by an independent educational grant from Viatris.

The views expressed are the personal opinions of the experts. They do not necessarily represent the views of the experts' institution, or the rest of the HEMOSTASIS CONNECT group.

For expert disclosures on any conflict of interest please visit the COR2ED website.

Tonke de Jong (COR2ED)
Extended anti-coagulation beyond the initial 3 months is indicated for all types of VTE, except in surgery- or trauma-VTE or in patients at high risk of bleeding. Are you up to date on the latest treatment options for VTE and their duration? Listen to find out more!

This is the third podcast episode in a four-part series on thrombosis in various clinical conditions. In this episode we focus on anti-thrombotic treatment for VTE and how long optimal treatment should be.

This podcast is an initiative of COR2ED and supported by an independent educational grant from Viatris.

I'm honoured to introduce to you today's two experts in the field of thrombotic disorders; Professor Dimitrios Tsakiris and Professor Jerzy Windyga We are very excited to listen to your discussion.

Prof. Dimitrios A. Tsakiris
My name is Dimitrios Tsakiris, and I'm a Haematologist specialised in clinical and diagnostic haemostasis at the University of Basel in Switzerland. My colleague, Professor Jerzy Windyga and me are delighted to share with you today a podcast on venous thrombosis and duration

of anticoagulation treatment. We believe that this is important because it can help us choose the right anticoagulant for the right treatment in the right patient.

Let me welcome first our discussion partner, Professor Jerzy Windyga, who is also a specialised haematologist in this field. Good morning Jerzy could you please tell us a few words about your field?

Prof Jerzy Windyga
Thank you, Dimitrios. It's a great pleasure and honour to be with you today. Yes, as you said, I am a Haematologist. I am head of the Department of Haemostasis Disorders and Internal Medicine in the Institute of Haematology and Transfusion Medicine in Warsaw, Poland.

I treat adult patients and we focus in our clinic on patients with benign haematology, including haemostatic problems, of course, other patients with thromboembolic problems.

Prof. Dimitrios A. Tsakiris
Very well, thank you. We will start the discussion, focusing first on pathophysiology issues of thrombotic disease, and then we'll go over to the treatment of this entity. But referring to pathophysiology, I would like to say that angiologists today do not distinguish between deep vein thrombosis and pulmonary embolism. They consider it one entity and the same treatment is taken for both situations.

But going to the triggering mechanisms, what triggers the thrombotic event is always an injury of the vessel wall, a tissue injury on that. This can be mechanical, it can be chemical, it can also be inflammation. We always knew that inflammation can be a trigger for that, but never realised that it could be so important. In the COVID era this condition came very well in the foreground and that is also why the term thromboinflammation was coined because of that.

But let us hear the experience of Professor Windyga on this subject. Is tissue injury alone enough or do we need additional triggers?

Prof Jerzy Windyga
I agree with you that during the COVID era we realised that the pathophysiology of pulmonary embolism or just pulmonary thrombosis, can be different from what we thought before. I believe that venous thromboembolism is a multifactorial disease, of course, and there are many risk factors for development of venous thromboembolism. Of course, we know very well that there are many acquired factors that probably we will discuss in a moment, a little bit more in detail. But there are also, of course, inherited factors like, for instance, inherited thrombophilic defects, but also some other diseases or pathologies that may contribute to the development of venous thromboembolism.

For me, as a haematologist, of course, some diseases are particularly interesting, like for instance, paroxysmal nocturnal haemoglobinuria or myeloproliferative neoplasms. I mentioned these two groups of disorders because there is something very characteristic about them. Namely, anticoagulants are normally not sufficient to prevent venous thromboembolism or just thromboembolism in patients with paroxysmal nocturnal

haemoglobinuria (PNH) or a patient with myeloproliferative neoplasms, which means that pathophysiology of VTE, understanding pathophysiology in a given patient with some concomitant disorders is extremely important to adjust therapy and tailor therapy to a given patient.

Prof. Dimitrios A. Tsakiris
Very well. You just mentioned a couple of acquired defects which can lead to a thrombotic event. Thrombosis in nature is not very rare. I mean it has been estimated that we have an incidence, an average incidence of one case per thousand per year. If you take younger patients, below 30 years, these can be ten times less. But if you take also older people, this can be ten times higher.

We know that age alone is a triggering risk factor because we see in the epidemiological studies that above the 55th year of age, the incidence rises dramatically.

Now concerning the heritable thrombophilia, do you see, let's say, an importance in this situation, in this genetic background as a cause for thrombotic disease? Because in nature, in evolution, heritable thrombophilia has been a survival advantage on that but later on it turns out to be deleterious. What is your opinion on that?

Prof Jerzy Windyga
This very interesting point, but I agree with you as far as I remember some publications on this topic. Factor V Leiden developed because it was the sort of protection of women during delivery. I mean, the amount of blood loss during delivery is decreased in women with factor V Leiden and thanks to that this inherited thrombophilic defect is so common in our population, I mean at least in white race. So I would say that of course inherited thrombophilia plays an important role as one of many factors that contribute to the index episode or the first episode of venous thromboembolism.

Of course, when it comes to recurrent VTE, then the situation is much more complex and it seems that thrombophilic defects are not so important or they do not contribute that much to the risk of recurrent VTE, but definitely it depends on the defect we are talking about. Factor V Leiden, prothrombin gene mutations are probably of less importance in terms of recurrent VTE. However, protein C, protein S, or particular antithrombin deficiency, I believe these defects play important roles also in VTE recurrence.

Prof. Dimitrios A. Tsakiris
Very well. This leads us very smoothly to our next subject on treatment of thrombotic disease. If we have a patient who has a thrombosis, then it is inevitable and undisputable that we should anticoagulate him. But do we need the so called prognostic or risk scores that have been occasionally published in the literature? My personal experience is that although there are some scores which have been also prospectively tested, I can mention two of them, the Vienna prognostic score and the Dutch score, they use very common item score factors to identify the risk. But at the end, my experience is that nobody uses them directly because thrombotic treatment is decided upon direct clinical characteristics. What do you think on that?

Prof Jerzy Windyga
I agree. I am aware, of course, of discourse and as far as I know they are not recommended in international guidelines to be used in daily practice because they have not been validated sufficiently in clinical trials.

We generally, in our centre, in our hospital, we decide on the duration of therapy, taking into account acquired inherited factors that play a role in the occurrence of index episode and of course the risk of recurrent VTE episodes. But we always take into account, also, the risk of bleeding complications because we know very well that anticoagulants unfortunately are still associated with increased risk of bleeding complications. And it is probably the most important and critical is to weigh the benefit of prolonging anticoagulation versus risk of bleeding complications in a given patient.

Prof. Dimitrios A. Tsakiris
Now, this is correct. Traditionally, we used to treat these patients for a short period of time, three months or six months, depending on the treating centre. But studies have made us aware that the risk for recurrent thrombosis remains high for life and concerning idiopathic or not provoked, unprovoked thrombotic events, the current guidelines propose that they should be treated for life, except if there are contraindications such as high bleeding risk.

How do you see this development? Some treaters still have, let's say, psychological hindrance to accept that. They don't give young patients, for example, an anticoagulation for life just because they had a thrombotic event. How do you handle that in your centre?

Prof Jerzy Windyga
Yeah, this very interesting. I think that our approach changed significantly once direct oral anticoagulants arrived and we started to use these drugs because they simplified our management of people with VTE. I believe that DOACs carry less risk of bleeding complications. At the same time, they are very convenient for the patient, mostly because the patients don't have to monitor INR during therapy, which is necessary of course, when it comes to vitamin K antagonists.

On the other hand, the safety margin is much wider now and thanks to that we can prolong therapy. I also believe that you mentioned unprovoked VTE, I fully agree. Also, those VTEs that are associated with some moderate risk factors, I believe that at least some patients may benefit from prolonged anticoagulation.

And finally, also patients who have persistent big risk factors of VTE. They should be treated, frankly speaking, indefinitely or lifelong even. I mean, of course, patients with cancer, but also patients, for instance, with antiphospholipid antibody syndrome or of course, patients who have already recurrent venous thromboembolism. In those patients I would definitely go in today's direction of lifelong therapy because I believe the benefit for the patient is clear. Of course, we always, we always look at the risk of bleeding.

Prof. Dimitrios A. Tsakiris
This is interesting, you touched a sensitive subject. If you have a patient and give him anticoagulation, then we know that the recurrence risk diminishes by time, and after four or

five years, the risk for a recurrent thrombosis is the same as the risk of bleeding due to the anticoagulant. So the patient has to decide or you as a treater, you have to decide, shall I leave with the risk of bleeding or for the rest of my life, or with the risk of a thrombotic event for the rest of my life? What do you do here?

Prof Jerzy Windyga
Dimitrios, this is a very important part of our discussion, I believe. First of all, I'd like to mention that it is extremely important to discuss with the patient what is her or his will. I mean, from my practice, most of my patients are very much afraid of recurrent deep vein thrombosis or pulmonary embolism, definitely, and they prefer to be treated. But that is correct, in some patients, even though the risk of bleeding is not that high, the patients are afraid also of bleeding complications. And in those patients, of course, we can find a solution, I believe, at least in some of them, because DOACs at least in some of them, we can use lower doses of anticoagulation. And thanks to that, we believe that we diminish the risk of bleeding complications and at the same time we still protect our patients against venous thromboembolism.

Of course, in some patients it is not a good solution. I mean, those patients who have very high risk of recurrent VTE. However, in many patients, I deeply believe this is a solution that can be used and will be welcomed by the patients.

Prof. Dimitrios A. Tsakiris
Very well. That is very important to mention. It is indeed an advantage that DOACs allow us to use a reduced dosing modal because, as you mentioned, it offers equal efficacy with less risk for bleeding in that case.

Now, my second question about the antiphospholipid syndrome that you mentioned. We have been handling antiphospholipid syndrome as a situation which needs a long-term anticoagulation, but what about when the laboratory finding disappears? After some years, five, six years, ten years, you do not find any antiphospholipid antibodies anymore. Sometimes it's not very often, but it can happen. Then we used to stop anticoagulation when we see that this negative finding persists. Is that correct? Or do we do something? What is your experience? Because if you see the newest modern guidelines, then everybody says treat them for life.

Prof Jerzy Windyga
Yeah, that's correct. That's correct. This is a very interesting issue. You know, in those patients who have very high titres of anti-cardiolipin, anti B2GP1 antibodies, and at the same time for instance, I mean for instance lupus anticoagulant, which is probably the most important antiphospholipid antibody in terms of risk of thromboembolic episodes. I have never seen, frankly speaking, the disappearance of high titres of those antibodies.

But you are absolutely correct. I have many patients in whom we diagnose antiphospholipid syndrome based on their lab results and of course the occurrence of thromboembolic episode, and with time the antibodies disappeared. In most cases, the baseline antibodies, antiphospholipid antibodies, levels were relatively, I would say, they were elevated. However, they were rather mildly elevated or moderately elevated. And in those patients,

frankly speaking, we don't know what is the best approach. If I see disappearance of antiphospholipid antibodies, definitely I wouldn't give up with anticoagulation immediately. I would rather prefer to test the patient for the second time, maybe even for a third time. Of course, discuss with the patient what is the meaning of such finding and if a disappearance of antiphospholipid antibodies persists, then of course I would suggest to think about discontinuation of anticoagulation.

But definitely this is my view. This is my, let's say experience, this is based on my experience, but I am afraid we don't have enough data and evidence to support this approach, in any case, that I described, yes .

Prof. Dimitrios A. Tsakiris
Thank you for that clarification. Now let's take a focus on other patient groups, the elderly and the pregnant women.

Considering the elderly, we know that an old person should not bleed more than a young person just because of the anticoagulant. But in the clinical studies they seem to bleed more often. But this is because of comorbidities or comedication that they have. Do we need to give elderly people less anticoagulation than indicated by the guidelines or not? Because some treaters, because of fear, they reduce the intensity. What is your experience on that?

Prof Jerzy Windyga
No, I would rather, you know, follow the product characteristics. I mean, I wouldn't reduce the dose only because of age. We know very well that, you know, the biological age of people is different. You know what I mean? That in some patients, even those who are really elderly, there are very few concomitant diseases, they are fit patients. They do not complain that much. They are in very good biological shape. And in those patients, I would definitely stick to recommended normal doses, let's say.

The reduction I would consider, of course, in those patients you already mentioned. So with some concomitant diseases that definitely lead to increase risk of bleeding complications.

Prof. Dimitrios A. Tsakiris
Yes. Very well, then we could shortly touch the issue of pregnancy and thrombosis, because this could be the subject of a podcast by itself. But let me say, in pregnancy, we have only one choice and that is heparins, which we could give. If we have a thrombotic event in pregnancy, do we treat it also beyond the three-month period that is indicated as long as pregnancy is still active? Or do you stop it during pregnancy if the three-month period is complete?

Prof Jerzy Windyga
Okay. There's another very important issue. Definitely. I wouldn't stop during pregnancy if the event occurred during pregnancy and the three-month period ended during pregnancy. I would continue anticoagulation. I would definitely continue also after delivery, at least for six weeks after delivery because of the higher risk of thromboembolism, also recurrence of thromboembolic episodes in the period, in the six-week period, after delivery.

On top of that, frankly speaking, in young patients definitely I would think about, you know, looking for thrombophilic defects because we believe that the reason of VTE in a very young patient should be explored and we should at least try to find the reason of this episode. Therefore, I would recommend also thrombophilia testing in such patients because it can be very important also for the future of this young woman to decide not only with respect to subsequent pregnancies but also with respect to some drugs. You know what I mean of course, oestrogens and some other oral contraceptives and so on, whether she can use those drugs safely or not. So that is my approach and that is our approach.

Prof. Dimitrios A. Tsakiris
Very well. Thank you Jerzy. It's very interesting but we are running out of time. We have to close slowly the discussion here. And let me give three takeaway messages concerning duration of anticoagulation.

Now extended anticoagulation beyond initial three months is indicated for all types of thrombotic events except surgery or trauma VTE, that is the provoked ones and except in cases of high risk for bleeding.

Now, as you said, DOACs are suitable for extended treatment and they can be used in reduced dose after the initial six months, which is a very helpful issue in the context of personalised medicine that we are handling with.

And the third message, which we didn't really discuss, is that aspirin alone can be used instead in, let's say, special cases as an exception if DOACs are not applicable.

Now, would you like to add to these key takeaway messages Jerzy?

Prof Jerzy Windyga
Yeah, maybe one or two things, Dimitrios. So the first with respect to aspirin, of course, it also has a role in the VTE based on the evidence we know or we got it over the last years. However, of course, it is a minor role only for some very special patients, as you mentioned in your conclusions.

The second thing I would like to stress again is the role of decision taken by the doctor and the patient with respect to duration of anticoagulation, I believe this is very important.

And finally, I would also mention the importance of clinical monitoring of the patient who receives indefinite anticoagulation because, of course, the situation can change over time. And because of that, we not only can, but we sometimes should change our approach and either stop the anticoagulation or maybe we should make some changes in the drugs or in other aspects of anticoagulation therapy.

Prof. Dimitrios A. Tsakiris
Thank you again for these interesting points and for sharing your experience with us. Thank you listeners, for being with us today. We hope that we can have you again next time dealing with perioperative haemostasis. Thank you.

Tonke de Jong
Thank you so much for this episode. We've learned a lot from your discussion on how long anti-thrombotic treatment should be and its impact on different patient categories.

If you liked this episode and want to find out more on thrombosis in various clinical conditions, then look on the haematology medical conversation podcast under the account of COR2ED Medical education for the other episodes on monitoring anti coagulation, thrombosis and cancer and peri-operative thrombo-prophylaxis. Also don't forget to rate this episode, or inform your colleagues about it. Thank you for listening and see you next time.