Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/how-long-is-too-long-evolving-literature-on-long-term-anticoagulation-therapy-after-vte/13069/

Released: 12/28/2021
Valid until: 12/28/2022
Time needed to complete: 25 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

How Long Is too Long? Evolving Literature on Long-term Anticoagulation Therapy After VTE

Announcer Introduction
This is CME on ReachMD! This CME activity, titled, “How Long Is too Long? Evolving Literature on Long-term Anticoagulation Therapy After VTE,” is brought to you by The American College of Chest Physicians and supported by an educational grant from Janssen Pharmaceuticals, Inc., Administered by Janssen Scientific Affairs, LLC.

Before starting this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Here’s your host Dr. Lisa Baumann Kreuziger Investigator at the Blood Research Institute, Versiti: Associate Professor of Hematology & Oncology at the Medical College of Wisconsin and Medical Director of Antithrombotic Therapy Management Program at Froedtert Health.

Dr. Kreuziger:
Ten million people will experience a venous thromboembolism ever year worldwide and are treated with anticoagulation. Anticoagulation reduces the risk of recurrent thrombosis, but is also associated with the risk of bleeding. So, we ask, how long is too long? Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I’m your host, Dr. Lisa Baumann Kreuziger and I would like to welcome my guests, Dr. Marc Carrier, who is a Professor of Medicine at the University of Ottawa and Dr. Rachel Rosovsky, who is the Director of Thrombosis Research and Hematology at Massachusetts General Hospital and Assistant Professor at Harvard Medical School. Rachel and Marc, thank you for being here, today.

Dr. Rosovsky:
Lisa, it’s great to be here. Thanks for having me.

Dr. Carrier
Thank you for having me.

Dr. Kreuziger:
So, Rachel, we’ll start with you. Which patients would you treat with long-term anticoagulation after a VTE?

Dr. Rosovsky:
So, I think to answer this question, Lisa, we first need to define what the aim of long-term, or extended phase, anticoagulation is after VTE. And it’s really to prevent recurrent VTE over time. So, when I make this decision with my patients, I look at two factors: what is my patient’s risk of developing a new or recurrent blood clot if we were to stop their anticoagulation, versus their risk of bleeding if we continue their anticoagulation. It’s really a balance between those two risks. And to help me determine my patient’s risk of recurrent clot, I use the various classification systems and terminologies that have been developed to describe and group precipitating factors, and the most recent CHEST guidelines, in which, Lisa, you were involved, break these classifications into four categories. So for every patient that I treat, I decide whether their blood clot was: number one – provoked by a major transient risk factor; number two – provoked by a minor transient risk factor; number three – provoked by a persistent risk factor; or number four – I can’t identify any risk factor, which has been termed unprovoked. And then depending on which category my patient is in, will translate into their specific risk of recurrent blood

clot. So, to delve into this a little bit more, my patients with a major transient risk factor are those who had surgery with general anesthesia for more than 30 minutes, a C-section or major trauma. And all have had to occur within three months of when they developed their blood clot. My patients with minor transient risk factors are those that occurred within two months of a clot, and include shorter surgeries, estrogen use, leg injury associated with reduced mobility, or prolonged car or air travel. And then my patients with persistent risk factors are those who have active cancer or antiphospholipid syndrome. And the last, the fourth category, are my patients who have no identifiable risk factors, or are considered unprovoked. And so these categories help me determine and explain to my patients their specific risk of recurrent VTE.

So for example, if I have a patient who had a major transient risk factor, I explain to them that their cumutalive risk – I explain to them that their cumulative risk of developing a recurrent blood clot, if we stop their anticoagulation, is quite low, less than 3% after five years. For my patients with a minor transient risk factor, the risk of recurrent blood clot, off anticoagulation, is a little bit higher – maybe 3-8%. But in my patients who have suffered an unprovoked or cancer-associated blood clot, their risk can be as high as 30% after five years, so I'm certainly not gonna want to stop anticoagulation in those patients. And in addition to what I just shared, there are specific prediction tools and scoring systems that have been developed to help calculate patients' risk of recurrent VTE. I don't tend to use these scoring systems, as I feel the guidelines are pretty comprehensive. In addition to evaluating my patients' risk of recurrent VTE when considering long-term anticoagulation for them, I also need to evaluate their risk of bleeding, and there are several risk factors associated with bleeding, such as advanced age, prior bleeds, anemia, active cancer, chronic renal or hepatic disease, or if my patient is on an anti-platelet therapy. And similar to the VTE risk prediction scores, there are bleeding scores available, but none of them have been validated in this specific population, for this particular question, and therefore, I don't really use them. As you would expect, the more of these risks my patients have, the higher their risk of bleeding. So if my patient has no risk factors for bleeding, their risk of developing a bleed while on anticoagulation is low, and I tend not to worry about that. However, in my patients who have lots of these bleeding risks, then I do worry, and in those patients, I need to carefully weigh their risk of recurrent VTE if we were to stop their anticoagulation, against their risk of bleeding if we continue their anticoagulation. And importantly, in the patients I keep on long-term anticoagulation, I assess their bleeding risk periodically, annually at the minimum, but also at times of any significant change in their medical condition, to make sure the decision we come up with to continue anticoagulation is still favored. And then finally, a consideration that I always take into account when deciding whether my patients should remain on long-term anticoagulation, is their preference and values. This choice can really only be made through a shared decision-making process, and by engaging in this practice, I am more confident that my patients will be compliant with taking their medication, if, in fact, we decide together that they should remain on long-term anticoagulation.

So putting this all together, what do I do? In my patients with an unprovoked VTE or cancer, I will keep them on long-term anticoagulation unless the bleeding risk is unacceptable. In my patients with ongoing or persistent thrombotic risk factors, I also tend to keep them on long-term anticoagulation. However, in my patients who had a major transient risk factor, in which that risk factor is no longer present, I do not keep them on long-term anticoagulation.

And I think the population that is the most challenging to make this decision with are my patients who had a minor transient risk factor. Those are tough, because this group tends to be more heterogenous in terms of their risk profile, and some of these patients may very well benefit from long-term anticoagulation. Actually, sometimes use those prediction scores with these patients.

Dr. Kreuziger:
Thank you so much for that really great overview of kind of how to balance all of those risk factors that we are looking at when we see our patients.

Can you also then review some of the studies of the therapeutic versus prophylactic dose of anticoagulation after VTE?

Dr. Rosovsky:
Yes. At least I can answer that, the direct oral anticoagulants, or DOACs, have been studied in comparison to vitamin K antagonists in patients with acute VTE and have consistently demonstrated a lower bleeding risk, which is why I use them as first-line therapy in most of my patients. However, DOACs, or really any anticoagulation, are not without risk, and therefore, I have to consider, , that when thinking about long-term anticoagulation for my patients.

Currently, there have been two randomized control trials that have evaluated the use of DOACs for extended or long-term prophylaxis, and in particular, have looked at therapeutic dose versus prophylactic dose. And I share the details of these patients with my patients, so that they can understand why we are considering changing to a lower dose. In both studies, I think it's important to note that physicians had to have equipoise as to whether the patient needed to remain on anticoagulation after being treated for an initial six to twelve months. The first study was called the EINSTEIN CHOICE study, which included over 3,300 patients, of which approximately half had an identifiable cause for their VTEs, but they also had to have an ongoing, persistent VTE risk factor. Those patients were

randomized to receive therapeutic dose rivaroxaban, prophylactic dose rivaroxaban, or 100 milligrams of aspirin. And this study showed that both doses of rivaroxaban exhibited approximately a 70% decrease in symptomatic recurrent fatal or nonfatal TE, as compared to those patients on aspirin. And importantly, I share with my patients that the bleeding rates were low, and there was no statistically significant difference in the rates of major or clinically relevant non-major bleeding, between either doses of rex – between either doses of rivaroxaban and aspirin. The second study, which was called the AMPLIFY-EXTENSION study, enrolled over 2,400 patients, of which 90% had experienced a blood clot without an identifiable risk factor, so unprovoked. And again, after patients completed an initial six to twelve months of therapy, they were then randomized to stay on the therapeutic dose apixaban, decreased to a prophylactic dose of apixaban, and the third arm was placebo. And similar to the EINSTEIN CHOICE study, both doses of apixaban not only resulted in approximately a 70% decrease incidence of symptomatic recurrent VTE or death from any cause as compared to placebo, but also there was no statistically signific difference… But also there was no statistically significant difference in bleeding among any of the arms, and the bleeding rates were low. So I think these trials clearly support the use of prophylactic dose anticoagulation in patients who are treated with an initial, six to twelve months of anticoagulation, and who are felt to warrant extended or long-term anticoagulation, meaning in those patients who have ongoing or persistent risk factors, or ha – or had no identifiable risk factor as the cause of their VTE.

I also think it's important to note that when patients who are believed to be at a high bleeding risk were excluded from these extension trials. I also think it's important to note that patients who are believed to be at high bleeding risk were excluded from these extension trials, so when I'm considering long-term anticoagulation, even with a prophylactic dose, I always assess my patients' bleeding risk as well. In addition, in order to be enrolled in these extension trials, the physician had to have equipoise as to whether or not long-term anticoagulation was warranted. So in patients where I have no equipoise, such as my patients with recurrent VTE, or high-risk thrombophilia, or cancer, there is no data to support me decreasing to a prophylactic dose. It is unknown if the prophylactic dose in these settings is either safe or effective.

And because both extension studies showed no difference in the bleeding rates in these patients, I think it's a reasonable and preferable to keep them on therapeutic dose anticoagulation. Fortunately, there are a few ongoing trials investigating the safety and efficacy of prophylactic dose in cancer patients, and I look forward to hearing about those results but until then, I keep those patients on full-dose, therapeutic dose anticoagulation and do not decrease them to a prophylactic dose.

Dr. Kreuziger:
So, based on all the data that you just described, what do the current guidelines recommend?

Dr. Rosovsky:
Well, first I want to make a comment about guidelines. So, guidelines are developed by a group of individuals who are experts in the area of discussion. And they take all the data available at the time, and grade its quality based on the type of studies being considered, such as randomized control studies, observation studies, or case series. And obviously, randomized control trials carry a higher certainty of evidence for making recommendations. Then the panel of experts have extensive conversations about what is most important and relevant, and come up with consensus statements that reflect those studies and discussions. So, I find that the guidelines can be incredibly helpful when caring for my patients. It's also important to note that new studies and information are constantly emerging, and therefore, in addition to the guidelines, I need to be aware of new data, and to use the guidelines with the new studies to help guide my patient care. And lastly, I wanna point out the language used by the guidelines. The panel uses the word "recommend" for a strong quality of evidence, and they use the word "suggest" for a weaker quality of evidence. So I think, putting it all together, for the CHEST guidelines, the panel came up with a number of recommendations and suggestions regarding the questions you brought up, Lisa. For patients whose VTE was due to a major, transient risk factor, as we discussed, the panel recommends against offering long-term anticoagulation – and that seems reasonable. Once you remove what caused the blood clot, or the cause is no longer present, the risk of developing a recurrent VTE is low, as long as that risk remains gone. In those patients who develop a VTE due to a minor transient risk factor, the panel suggests, which is based on weaker quality evidence, against offering extended-phased anticoagulation. Again, these are probably the most challenging patients to make this decision with, given the current evidence. However, in patients who had a VTE in the absence of any provoking cause – meaning they had an unprovoked VTE – or in those whose VTE was provoked by a persistent risk factor, the panel recommends that these patients be offered extended-phase, or long-term anticoagulation with a DOAC. Then, in the patients offered extended-phases or long-term anticoagulation, the panel suggests using reduced dose apixaban or reduced dose rivaroxaban over full dose, and that was based on the trials I just mentioned.

And in patients offered extended phase anticoagulation, the panel recommends reduced-dose rivaroxaban or reduced-dose apixaban over aspirin or no therapy, again based on the studies I just reviewed. I also think it's important to note that in any of my patients in whom we've decided to continue extended or long-term anticoagulation therapy, I reassess their risk benefit analysis at periodic intervals – at least annually, or at any times of significant change in their health status – because without reassessment, I have no idea

if my patients are actually following a plan that we have developed

Dr. Kreuziger:
If you are just tuning in, this is CME on ReachMD. I'm Dr. Lisa Baumann Kreuziger and today I'm speaking with Drs. Marc Carrier and Dr. Rachel Rosovsky about long-term anticoagulation after VTE.

We spoke a bit earlier about the clinical trials and guideline recommendations for long-term anticoagulation for VTE, but now let's shift over to some challenging patient populations. Marc, could you help and talk about which patients you would consider continuing therapeutic anticoagulation versus prophylactic dose anticoagulation?

Dr. Carrier:
It's a, it's a wonderful question, Lisa, because, , some patient population may have different risk/benefit ratio regarding their risk of recurrence and their underlying risk of bleeding and therefore clinicians, , need to take that into consideration. And one of the things I often think about dosing is in the obesity. And as you're probably aware, in 2016 the International Society of Thrombosis Hemostasis really recommended not to use direct oral anticoagulants in patients with a body mass index over 40 or a weight over 120 kg. And at the time i- I think it was probably reasonable because very few patients with obesity, , were included in the trials assessing DOACs to vitamin k for different indications. But I think since then there's been several PK and PD studies and large observational studies that have provided very reassuring data to clinicians and, and therefore the ISTH in 2021 revised their guidance a- and suggested that the tr- for the treatment of VTE, , an atrial fibrillation, , direct oral anticoagulant can be used regardless of high BMI and weight. And for the treatment of VTE specifically, , they recommended rivaroxaban and apixaban. There's fewer data with apixaban than rivaroxaban but enough to reassure, , panel members.

However, it's important to keep in mind that when we think about secondary prevention or dose reduction versus a prevention of recurrent VTE, there's really not a whole lot of data to guide, , clinicians, , for dosing requirements in obese patients. So, after the initial 6 months of therapy, it's really unknown what to look for. Prespecified analysis from EINSTEIN CHOICE for example, that Rachel alluded to showed similar rates of the primary outcome measure which was recurrent VTE in patients with a body mass index over 30 and another prespecified subgroup analysis from AMPLIFY-EXT also showed similar reassuring data when we looked at the risk of recurrent VTE in patients with weight over 60 kg. However, you know, there's really not a whole lot of data to guide clinical practice. So, personally right now I tend to feel more comfortable continuing on with the therapeutic dosing in that patient population.

Another thing that I often have reflection on is, patients with thrombophilias. There's also insufficient evidence to provide guidance to clinicians regarding DOAC dose reduction with certain types of thrombophilias. These patients have persistent minor risk factors and, some thrombophilias may be more potent than others. So, if we think for example about protein S, protein C antithrombin deficiency, they may have a different risk/benefit ratio compared to the more frequent, less potent ones like prothrombin gene defect, for example of Factor V Leiden.

If you look at the EINSTEIN CHOICE and the EINSTEIN-Extension trials, if you pool them together, there's only 173 patients that had some form of inherited thrombophilia that have received rivaroxaban and 102 that received placebo or aspirin. And the risk of recurrent VTE were 1.7 and 7.0, respectively. So, it looks like direct oral anticoagulant is still very effective in that patient population. But again, you have a look at the event rate stratified based on the rivaroxaban dosing in these particular trials, these were not reported and therefore we don't really know. Furthermore, as I mentioned before that the rate of recurrent VTE probably defers from one inherited thrombophilia to another, it's controversial in the literature, right? We don't know if certain thrombophilia would be good predictors of recurrent VTE. And, and we know for sure that some very common low potency thrombophilias are not good predictors of recurrent VTE. So, usually I feel comfortable dose-reducing direct oral anticoagulants for patients with Factor V Leiden prothrombin gene defect, for example. However, for a more potent thrombophilia, like what protein S and C that maybe associated with a high risk of recurrent, then I think it's really a case-by-case discussion about dose reduction, especially for those that are low risk of bleeding, I tend to continue on therapeutic dosing.

Dr. Kreuziger:
That's fantastic. And especially giving some, some guidance to our, listeners about what our personal practices are, as well.

So, another high-risk group that we often encounter are patients with cancer. So, what dose of anticoagulation would you continue for patients with cancer in VTE?

Dr. Carrier:
Well, that's really a million-dollar question. It's really difficult to extrapolate the data that has assessed dosing for standard prevention for recurrent VTE from the trials that Rachel discussed to the cancer population. Patients with cancer are at higher risk of having recurrent VTE and at higher risk of having bleeding complications. So, it's really hard to extrapolate plus, not a whole lot of these patients were

included in EINSTEIN CHOICE and they were actually excluded from some of these trials, like AMPLIFY-EXT and EINSTEIN-Extension, and therefore it's really hard to figure out if they would benefit from dose reduction or need to continue therapeutic dosing of DOAC verse secondary prevention.

When, when you think about it, there's only really four pieces of information that can help clinicians. There's two single arm studies that assessed low molecular weight heparin, dalteparin or tinzaparin for a total duration of 12 months. These studies are called Daltacan and Ti-CAT and again it's single arms, right? So, no controls. So, in these studies, the risk of major bleeding between months 7 and 12, so beyond the initial 6 months, was the primary outcome measure for these studies. And what we've found is that the risk of major bleeding in this second 6-month period was relatively low and comparable to the rates reported during the first 6 months of therapy. And therefore, indirect evidence that it's probably safe to continue anticoagulation with low-molecular-weight heparin at those dosing up to 12 months. When they looked at the risk of recurrent VTE, it was still elevated beyond the initial 6 months, that there's some benefit to continue anticoagulation in that patient population.

There's also a post-hoc analysis from Hokusai-VTE Cancer, the trial that compared edoxaban to, dalteparin, there's a post-hoc analysis assessing the event rates from major bleeding and VTE beyond the initial 6 months of therapy and the results are again suggesting that therapeutic dosing of edoxaban in that trial was 60 mg unless you made the, the different criteria for dose reduction or dalteparin are probably safe and effective in up to 12 months.

And then finally, more recently, the second randomization of the SELECT-D trial. So, remember this is the trial that has compared dalteparin to rivaroxaban for the acute treatment of cancer associated thrombosis. Well, after the initially 6 months they had a second randomization where they randomized patients with an index PE or residual venous obstruction after 6 months to rivaroxaban or placebo and followed patients over time. And what they've shown is that the risk of recurrent was much lower in those that received rivaroxaban. There was no major bleeding and similar number of clinically relevant non-major bleeding between the two groups. So, somewhat reassuring data., but it's important to, for that particular second randomization, it's very modest sample size, only 92 or 94 patients were included. It was stopped early because it was difficult to, recruit patients in that trial.

So, you know, all that to say that we do have data that suggests that continuing therapeutic anticoagulation low molecular weight heparin or direct oral anticoagulant seems to be safe and effective in that patient population.

Dr. Carrier:
So, do we have any data supportive of decreasing the dose of the direct oral anticoagulant in the setting of, , secondary prevention for cancer associated thrombosis? We don't have a whole lot. But there's two randomized control trials that are ongoing. The EVE trial, which is based in the United States and the API-CAT trial, based in France are two trials that are randomizing patients with cancer associated thrombosis. They completed 6 months of and then they still have cancer or ongoing treatment so they need to continue anticoagulation for secondary prevention. They're randomized to apixaban 2.5 mg po b.i.d.or 5 mg po b- b.i.d. and then followed for up to 12 months. So, this really will give clinicians an idea if we can dose reduce DOACs in that setting. So, for the time being, I tend to continue on with therapeutic dosing.

Dr. Kreuziger:
Thank you very much.

So, as we wrap up our discussion, let me ask each of you to share some key take-aways or final thoughts for our listeners. So, let's start with Rachel.

Dr. Rosovsky:
I think when thinking about long-term anticoagulation, providers need to assess their patients for both recurrent risk of clot, as well as their risk of bleeding, to really help determine which patient is appropriate for long-term anticoagulation. I think when thinking about long-term anticoagulation, providers need to assess their patients for both recurrent risk of clot, as well as risk of bleeding, to really help determine which patients are appropriate for long-term anticoagulation. I think it's also important to include patients in that decision and have a shared decision-making process. And then lastly, it's important to reassess these risks periodically, to ensure that the decisions you've come up with, whether it's to continue anticoagulation, is still favored, and that patients are actually following a plan that you and they have come up with.

Dr. Kreuziger:
And Marc, any follow-up final thoughts from you?

Dr. Carrier:
I completely agree with Rachel. And regarding dosing, as it was mentioned based on clinical practice guidelines, most patients would benefit from a reduced dose of a direct oral anticoagulant long-term for secondary prevention of recurrent VTE. However, in some

challenging patient population, obesity, thrombophilia, cancer, they may have a different risk/benefit ratio and a case-by-case discussion including patients' preferences is probably desirable.

Dr. Kreuziger:
Marc and Rachel, thank you so much for those important summaries of the literature and the current guidelines. We see these patients every day in clinic and your opinion about managing of these current situations and challenging patient populations have been very helpful. I'd also like to point out there's multiple upcoming studies that we should watch out for that may impact, the guideline recommendations, as well.

So, I'd like to thank my guests, Dr. Rachel Rosovsky and Dr. Marc Carrier for speaking with me and our ReachMD audience. I'm Dr. Lisa Baumann Kreuziger, thanks for listening.

Announcer Close
This activity was part of a 3-part series brought to you by The American College of Chest Physicians and supported by an educational grant from Janssen Pharmaceuticals, Inc., Administered by Janssen Scientific Affairs, LLC. To receive your free CME credit or to view other activities in this series, go to reachmd.com/cme. This is CME on ReachMD. Be part of the knowledge.