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Latest Lessons Learned: Rapid Review of CHEST VTE and CHEST COVID VTE Guidelines

Announcer Intro:
This is CME on ReachMD! This CME activity, titled "*Latest Lessons Learned: Rapid Review of CHEST VTE and CHEST COVID VTE Guidelines",* 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.

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Here's your host Dr Lisa K. Moores, Professor of Medicine at the F. Edward Hébert School of Medicine at the Uniformed Services University of the Health Sciences

Dr. Moores:
Evidence-based medicine is easy, isn't it? We do a systematic review, we pull the data, we perform a metaanalysis and it gives us the golden answer. Actually, on the contrary, healthcare providers today are bombarded with information from multiple sources. It's critical to be able to filter the sound bites into meaningful information that leads to safe, effective patient outcomes and the current global pandemic has only intensified this need with the rapid publication of evidence as we care for these patients. The American College of Chest Physicians strives to be a leader in the development of timely, up-to-date evidence-based guidelines for its members and notably around the prevention, diagnosis, and treatment of venous thromboembolism. Over the past year, CHEST has published two such guidelines, which will be the focus of today's program.

This is ReachMD and I'm Dr. Lisa Moores. I'd like to welcome Dr. Geert-Jan Geersing, who is an Associate Professor and General Practitioner at the University of Utrecht in the Netherlands. He's joining me today to discuss the recently published report titled "*Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guidelines"*an Expert Panel Report." Dr. Geersing, welcome to the program.

Dr. Geersing:
Well, thank you very much, Dr. Moores, I'm really looking forward to this session and really honored to be part of it so hopefully we can provide to best evidence and education which came from our guidelines and help physicians throughout the globe. Thanks for having me.

Dr. Moores:
Thank you.

Also joining us today is Dr. David Jiménez, who works at the Ramón y Cajal Hospital in Madrid, Spain. Dr. Jiménez will highlight the report titled "*Prevention, Diagnosis, and Treatment of VTE in Patients with Coronavirus Disease 2019*", a CHEST Guideline and Expert Panel Report ". Dr. Jiménez, welcome.

Dr. Jiménez:
Thank you very much, Dr. Moores. Thank you for the kind invitation. I'm very happy to be here today to discuss some issues a- around

the very burning topic of antithrombotic therapy in patients with COVID-19.

Dr. Moores:
Thank you, Dr. Jiménez. To start us off, Dr. Geersing, can you tell us a little bit about how your panel chose the clinical questions to update in this most recent guideline?

Dr. Geersing:
Yes of course, because this is indeed a very delicate process, we do not just randomly select PICOs or update them as we feel about it. It's really a process where we look at PICOs that needs an updating because of new trials that have emerged since the last update. For instance there has been new evidence since the previous guidelines on dose reduction in, extended treatments of thromboembolism and also cancer-associated thrombosis. We look at PICOs that were not covered in the previous guideline, but maybe there were in the guideline before the previous one. We felt that maybe we want to address them again see if we can summarize the evidence better, because maybe also newer studies that have been published. One of these examples would be the management of superficial venous thrombosis. And then finally we look at topics that may have not been addressed in previous guidelines altogether and so this is really a discussion where there is an interaction with all the panelists and then we discuss the PICOs that we feel that need to be included in the updated guidelines.

Dr. Moores:
So, Dr. Geersing, staying with this document, spontaneous superficial-vein thrombosis is a common clinical condition that perhaps many providers don't necessarily appreciate. And it often leads to discussion and perhaps debate regarding the optimal management. How did the panel approach this? And how, if at all, did the recommendation differ from prior versions of the guideline?

And then if you have a moment after discussing those, what factors would you highlight for audience that might favor anticoagulant therapy?

Dr. Geersing:
Yeah, so thank you for these questions, Dr. Moores. I think it's indeed important to acknowledge that, it's a common condition that's, particularly doctors how work in general internal medicine or primary care medicine, they see a lot of these type of patients, the incidence is about 1 to 2 per 1,000, so it's more or less the same or maybe even a little bit higher compared to deep-vein thrombosis, and there's a lot of discussion always whether or not you want to treat those patients with anticoagulant treatments. And if you ask this question too, like a primary care doc, he would tell you probably that most of the patients with superficial-vein thrombosis are not treated with anticoagulant treatments. Whereas if you as the same question to a vascular surgeon they would probably get an answer that this doctor would treat most of these patients with anticoagulant treatments. And that's also because it's much less well-studied as compared to our other VTE conditions. But it's also important to acknowledge that indeed, although the clots are smaller, it is a thromboembolic condition and there is always a risk of clot progression to deep-vein thrombosis or pulmonary embolism. And depending on the setting where you work, this risk is probably somewhere around 10%, maybe 20% if you're working in a more setting where more referred patients are seen. But still, this is a substantial risk of getting DVT or pulmonary embolism, in patients with superficial-vein thrombosis.

When it comes to treatment, I think we as a panel looked at the literature but also at recent Cochrane reports on, on this topic and we discussed that, the best treatment that's been studied in the highest quality trials is, fondaparinux which was studied in the CALISTO trial, compared to placebo. And that trial really showed that indeed for 45 days treatment of fondaparinux really reduced the risk of clot progression, with a lot of high magnitude and actually we, we thought that the evidence for fondaparinux is actually stronger if compared to low-molecular-weight heparin. So, parenteral treatment is probably the first choice of treatment and then fondaparinux would be the first line of treatments. And then we also found that there's a new trial published, the SURPRISE trial, which compared rivaroxaban, with fondaparinux in a non-inferiority trial and this trial showed that rivaroxaban was non-inferior to fondaparinux. But the sample size was not too big so, in terms of quality of evidence I think that fondaparinux trial is a larger trial.

And then finally we indeed looked at risk factors or predictors of clot progression. In the previous guideline, this was really limited to only the length of the clots, looking at 5.0 cm length of clots as indication of a higher risk of clot progression. And we actually extended this a little bit more looking at multiple factors, as compared to only looking at one factor.

So, for instance, the, the location of the clot is important, whether or not it's above the knee or below the knee, closer connection to the saphenofemoral junction is important as well, and also a history or an active cancer or a history of VTE or recent surgery are also predictors that you want to look at as your important predictors for clot progression.

Dr. Moores:
I think that this really highlights one of the wonderful advances in the most recent publication in which your panel was really able to not

only look at the evidence but to focus in on very practical guidance for providers. And as you highlighted, you're able to give them more specific guidance regarding what kind of risk factors need to be considered and importantly what options you might have, particularly for a patient that doesn't want to take parenteral therapy. And this is a really nice advancement from prior iterations of the guideline. And it highlights something that is very important and that is that in many instances, the evidence shows a almost equal balance, right, between risks and benefits that require a conversation with the patient and really leads into my next question.

So, as you mentioned, the prior version really only mentioned one factor and this panel expanded on multiple things that could be taken into consideration. And then what to do with a patient that doesn't want to take parenteral therapy, providing some additional options. Really like the fact that you were able to do that.

Dr. Geersing:
Yeah. Thank you. I think it's really important because this is typically a small clot, so we tend to ignore it. We say that this is just superficial thrombosis so don't bother. But I think really that that's a mistake. It is a thromboembolic disease and indeed luckily most of the clots they disappear without treatment so then just painkillers is enough. But in a subset of the population, clot progression does happen and you should really focus your attention on those types of patients. And indeed, we try to give some guidance on what type of patient when the risk of clot progression is, is higher.

Dr. Moores:
Exactly. And I could not have asked for a better lead-in to my next question. So, as, you know, Dr. Geersing, there are often clinical questions addressed in these guidelines where the benefits and risks may be relatively evenly matched, and shared decision-making becomes paramount. One area in addition to superficial-vein thrombosis that you, as a panel addressed, is choosing the optimal duration of therapy or, or perhaps I should say more precisely determining which patients might benefit from extended therapy. It's that same principal you just mentioned. Who is most likely to benefit? Can you expand on this just a bit four our audience?

Dr. Geersing:
Indeed. I think there are many overlaps, because in the end, with all the thromboembolic conditions that we treat, perhaps also with COVID-19, it all comes back to the question of bleeding risk verus thromboembolic risk. And this is also one of the really difficult questions for patients who have had deep-vein thrombosis or pulmonary embolism and they finished their initial period of treatments, which is three months. We know now for certain you should treat it for three months initially and then the first line of treatment is complete but then the discussion starts because we know that a part of this population, if you stop treatments, they get a recurrent event. And sometimes even really shortly after the treatment is stopped. And this, of course, is really bothering patients. It raises the risk of long term complications from thrombosis like, CTEPH for instance, or in the case of deep-vein thrombosis, post-thrombotic syndrome. So, if possible, you want to prevent those recurrent events from happening and, this indeed comes back to highlighting or focusing the treatment on the group of patients with the highest risk of getting current events. And then the simplest answer would be that if this is really a provoked VT event with a major transient risk factor, most importantly, that's recent surgery, then we know if that's the case it's safe to stop the treatment after the three month periods.

But it becomes more difficult if you look at unprovoked VT and there is a distinction between unprovoked if there is maybe a minor risk factor, so that's the difficulty, is when we call it unprovoked. But if it's really unprovoked then there is indeed evidence showing that's extended treatments is benefiting the patients. But we do need to know that it's again balancing the risk of thrombosis with bleeding risk, you should look at the individual patients to really discuss if you want to continue with the treatment or not.

At this moment in time, it's really difficult to really highlight the risk factors there. We know some of them from the literature. For instance, we know that male patients have a higher risk of recurrent events. There is some studies being done about D-dimer testing after the treatment has stopped as a predictor for recurrence. So as for now, we, we cannot make really strong recommendations there. So, it, it really comes back to shared decision-making with the patients. And I think it's really interesting for our colleagues to discuss this more often also with other colleagues. Dr. Moores, how to you manage them and do you have like a recommended approach to address this question with your patients?

Dr. Moores:
That's a great question and I would say that probably as, as you have already highlighted here this comes down to perhaps some of the things we know about the patient at the time the event occurred, beyond just the provoking factors, such as whether it was a DVT or a pulmonary embolism some of their comorbidities, the things like gender that you mentioned, but, but also the things at the end of treatment, such as D-dimer and some of the other markers that are being researched. But, hidden in there also is what is the patient most concerned about? Are they more afraid of a recurrent clot? Are they more afraid of bleeding? What is their lifestyle, you know, my background is in military medicine. I have a lot of young, active duty people that want to stay on track in their military career and staying on an anticoagulant is not always consistent with that goal, so they may be more inclined not to continue. I don't have a template and it's

actually what I love this part of caring for patients with venous thromboembolism is seeing the evolution from when I first started my training to now is this is, this is now a patient-focused decision, not a disease-focused decision.

Dr. Geersing:
Exactly. One of the nice things of working in this field is that these are really important questions because we are discussing, lifelong treatments here, so if you have a young patient that would maybe even at least for ten years or fifteen years are on anticoagulant treatment. And we also know a- actually from recent work that's, that's been published in the Annals of Internal Medicine that bleeding risk actually is not something to really ignore on extended treatments. We should also be aware that the evidence that we have on bleeding risk, from the DOACs is only with short-term follow-up so we don't have longer duration of follow-up there. So, I think that could be something that the books have not yet been closed on this topic completely we'll probably come back to the n- new guidelines, after this one, as well and I think indeed we are moving in the direction that we really wanted be more risk-tailored and patient-centered. I think those are the two words we need to look at.

Dr. Moores:
I could not agree more. I want to bring in one other piece of this puzzle and that is for patients that maybe, sort of, on the fence, perhaps, are there options beyond what our historical approach would have been? Which would have been vitamin K antagonist therapy or full dose direct oral anticoagulant? I think you referred to some of the newer studies might suggest that maybe there are some options that they could consider, although we don't have long-term follow-up that might reduce that risk of bleeding, as was highlighted int he recent annals, publication.

Dr. Geersing:
Exactly. So, that's one option I think there will be new evidence coming. One of the important new trials that was published in the interval between the previous update and this update is on the dose reduction for DOACs, in particular. So, we have two DOACs that have been studied in that context. You could reduce rivaroxaban from 20 to 10 mg and the apixaban you could reduce from two times daily 5 to two times daily 2.5 mg. Probably that would also reduce your bleeding risk, although I am not yet that convinced that the evidence is that strong that it actually really does reduce bleeding risk. But probably it's logical to think that if you give a lower dose of a DOACs that you will also reduce the bleeding risk. So, it's really reasonable to, recommend reduce the dose in, in patients who would feel that their bleeding is maybe too high so then that's a possibility. If you really should follow the guidelines, then maybe you should do it after twelve months of treatment but I know some of our colleagues still also reduce the dose earlier.

And then there's also aspirin, but I think that aspirin is not that strong in preventing recurrent events from happening. So, and I also think we sometimes feel that aspirin has a low risk of bleeding, but I think we also know from the field of atrial fibrillation that actually aspirin is not a safe drug in terms of not incurring bleeding risk. So, I think that if you want to consider something, probably your best way to go would be to reduce the dose of the DOACs and then hopefully from there also reduce bleeding risk.

But one of the other things that is important also is to look at modifiable risk factors for bleeding. So it's really important to treat hypertension for instance or make sure renal function is monitored regularly and this, are not combined with all the types of treatment that may increase bleeding risks. So, it's also important to discuss with the patient can do him or herself to reduce bleeding risk. So, no alcohol, no pain killers over the counter, for instance try to monitor renal function, blood pressure. I think those are things you could also look at.

Dr. Moores:
I think those are great points to end on and just coming back to the publication you mentioned, I think one thing that practitioners don't always think about is that the bleeding risk tends to stay somewhat similar from year to year, if not go up if they develop more comorbidities whereas the risk of recurrence over time may decrease. And so, that constant reevaluation is also important in this cohort.

Dr. Geersing:
I agree totally. Absolutely.

Dr. Moores:
Thank you very much.

For those of us joining us, this is ReachMD. I'm Dr. Lisa Moores and joining me to talk about CHEST VTE guidelines are Dr. Geert-Jan Geersing and Dr. David Jiménez.

So, I'd like to turn to you now, Dr. Jiménez, and let's discuss the expert panel report regarding VTE in patients with COVID-19.

Dr. Jiménez, your panel was faced with providing guidance to overwhelmed and perhaps frightened providers in the early days of the

pandemic. How did you all approach the development of guidance when there was a lack of high quality evidence?

Dr. Jiménez:
Well, I completely agree that the pandemia was a big challenge for those developing clinical practice guidelines. During the pandemic, ardent guidance was required. But these did not mean that we should apply methodologic shortcuts. Early in 2020, at the beginning of the pandemia, we learned that COVID-19 was associated with a hypercoagulable state. But for identification of the optimal antithrombotic management of COVID-19, we had many, around 20 as more retrospective studies from different regions with different populations, different thromboprophylaxis regimens, and different rates of screening.

Therefore the CHEST panel found very reasonable to start from evidence-based recommendations for non-COVID patients, which, were based in a good number of large trials. For instance, the classical MEDENOX, PREVENT, or THEMIS trials for thromboprophylaxis in acutely ill medical patients who require hospitalization and modify these recommendations if new evidence suggested that patients with COVID-19 were different enough to warrant change. This is why, for instance, it was recommended that all patients admitted to the hospital with COVID-19 should receive thromboprophylaxis without the need of any risk stratification without the need of any score unless contraindicated.

Dr. Moores:
I think that makes complete sense and it's interesting that the approach that the panel took to me anyway, now full conflict of interest here that I was part of that panel, but I love the fact that you highlighted our focus on existing evidence-based guidelines and really using that as the basis to say what needs to change or what does not.

So, continuing on this theme, Dr. Jiménez, were there any other differences between this guideline and prior CHEST guidance? Or perhaps more importantly between the CHEST guidance and other international societies that provided such documentation or guidance to practitioners in the early days of the pandemic?

Dr. Jiménez:
For the first question the answer is yes. There were some important changes as compared to previous non-COVID guidelines. For instance, the 2020 guidelines recommended parenteral anticoagulant thromboprophylaxis for prevention or treatment for confirmed venous thromboembolism over direct oral anticoagulants. And there were a number of reasons for these changes. Number one, to limit staff exposure, and number two, to avoid interactions with other medications that were used for the treatment of coronavirus pneumonia, such as antiinflammatory or antiviral drugs.

And for the second question, I think that guidelines dealing with antithrombotic therapy for COVID-19 patients were quite consistent with the recommendations. First they did not routinely recommended outpatient thromboprophylaxis for those patients with a diagnosis of COVID-19, but who did not require hospitalization. Second, most of these guides recommended standard thromboprophylaxis for COVID-19 patients admitted to the hospital in the ward or in the ICU. However, it is true that from the very beginning, some guides such as the International Society on Thrombosis and Haemostasis, VAS, Europe and Independent Foundation in Angiology/Vascular Medicine, and NICE suggested that intermediate dose thromboprophylaxis, or even therapeutic anticoagulation should be considered. And regarding the duration of thromboprophylaxis, again most of the guides recommended inpatient thromboprophylaxis over extended thromboprophylaxis beyond hospital discharge. But there were some guides such as the Global COVID-19 Thrombosis Collaborative Group, ISTH, and the European Foundation Angiology/Vascular Medicine which suggested extended prophylaxis beyond hospital discharge.

Dr. Moores:
I wanna thank you for that excellent review because I do think that our audience and many front line providers perhaps struggled a little bit with all of the different guidelines and how to make sense of their differing recommendations in some nuanced areas and of course I think we can all say that anecdotally, regardless of the guidelines, many hospitals had more aggressive protocols in place, which I think were understandable in their origin given that we wanted to do whatever we could to save lives in those early days.

On that background, Dr. Jiménez, are there other things that you would like to highlight about this type of rapidly produced guideline in the face of a global pandemic?

Dr. Jiménez:
Absolutely. Regarding differences in clinical practice guidelines, I think that the main reason was lack of evidence at the beginning of the pandemia. But we know that for COVID-19, scientific evidence is rapidly evolving. Therefore, I think that we should be ready to update guidelines as soon as new evidence appears. This is the so-called living guides. For instance, in the last month, there were two new randomized, controlled trials that were published in major journals regarding the efficacy and safety of therapeutic anticoagulation for non-critically ill patients hospitalized with COVID-19, the HEP-COVID trial and the RAPID trial. And in addition, I think that we should

have in mind that guidelines support but not replace clinical judgment, particularly in the COVID arena, where evidence is not that strong. Therefore, I think it is very important to adapt the recommendations to particular characteristics of individual patients.

Dr. Moores:
I think that's a very important point and, and, and certainly one that as a young provider, I did not understand and as a evidence-based geek, if you want to call me that, I kept thinking that the evidence would give the answer. And you realize that there is so much more that goes into decision-making, I guess perhaps that's the best job security that we have.

I think you gave me an excellent lead-in to my final question for both of you, which is to think about sharing with our listeners what your plans are for updating your guidance moving forward?

So, let's start and go back to Dr. Geersing.

Dr. Geersing:
Yeah, so what Dr. Jiménez also pointed out that we are actually a living guideline, task force. So, we stay together we will remain searching in the literature and if needed there will be updated recommendations, if that's warranted by the panelists. And of course, it will be a full guideline update at the five year mark, as well, but it's important to realize that this is like a living process where writing the guideline and publishing it isn't the end of the story, actually it's the beginning of the story of how we will remain active as a living group of panelists. And I think maybe you will be interested to know areas where we may expect new evidence from coming if that's maybe important to discuss as well.

I think as, as I mentioned earlier the books have not yet been completely closed about the real indication or identifications, so to say, of the, the patients at risk of recurrent VTE. So, I would expect that this is a topic that will be in the literature for a longer period of time and maybe they will be updated guidelines coming from that and, and going back to the discussion about thromboembolic risk of bleeding risk. I think also an area where there is still a lot of uncertainty is the, the treatment of like, sub massive pulmonary embolism where, we may want to look at reduced dose of thrombolytics, for instance, and also maybe more invasive procedure like catheter, directed thrombus removal. I think as for now in the guideline we are pointing out that it's not a big indication but maybe we want to fine tune that area a little bit more in, in future guidelines.

Dr. Moores:
I'm sure that many of our listeners ears perked up with that. That is obviously something of interest to everybody. Many of us are facing pressure, perhaps, if that's the best term from some of our colleagues to try these therapies but as a guideline panel, as you've already highlighted very eloquently, we need to look at the evidence and there are some ongoing trials that may help us with those questions.

Dr. Jiménez, is your panel currently working on an update given the publication of those two trials you just mentioned, but several others really since, the beginning of 2021?

Dr. Jiménez:
Yes, the panel is currently working on an update after systematic review of the evidence, the panel has reached consensus for each of the questions and is actually drafting the new recommendations. And we expect they will be published soon.

For the new guides we expect some new recommendations since at least for non-critically ill COVID-19 patients who require hospitalization, we have four randomized, controlled trials published in major peer review journals, the multi-platform trial in the New England Journal of Medicine, the ACTION trial in the Lancet, the HEP-COVID trial in JAMA Internal Medicine and the RAPID trial in British Medical Journal. So, we might expect some new recommendations for these particular group of patients. And we have some other studies and results, for other scenarios, such as for extended thromboprophylaxis, the results of the Michelle trial were recently presented in the European Society of Cardiology Annual Meeting and would be published very soon.

Dr. Moores:
Excellent. I'm sure that many of our audiences are very excited about both of these updates, perhaps the COVID guidance just because we're clearly not about of this yet.

But I think that's a great way to finish up. And we will definitely look forward to the updates when they are available.

I wanna thank my guests, Dr. Geert-Jan Geersing and Dr. David Jiménez for helping us better understand the development and application of evidence-based guidelines in the management of patients with venous thromboembolisms. Doctors, friends, it was great speaking with you, today.

Dr. Geersing:
Absolutely agree Dr. Moores and Dr. Jiménez. It was a pleasure to be in this session and I hope our colleagues, learned from it.

Looking forward to meeting again also in person during future conferences.

Dr. Moores:
Absolutely.

Dr. Jiménez:
A great pleasure also from my side. Thank you.

Announcer Close:
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