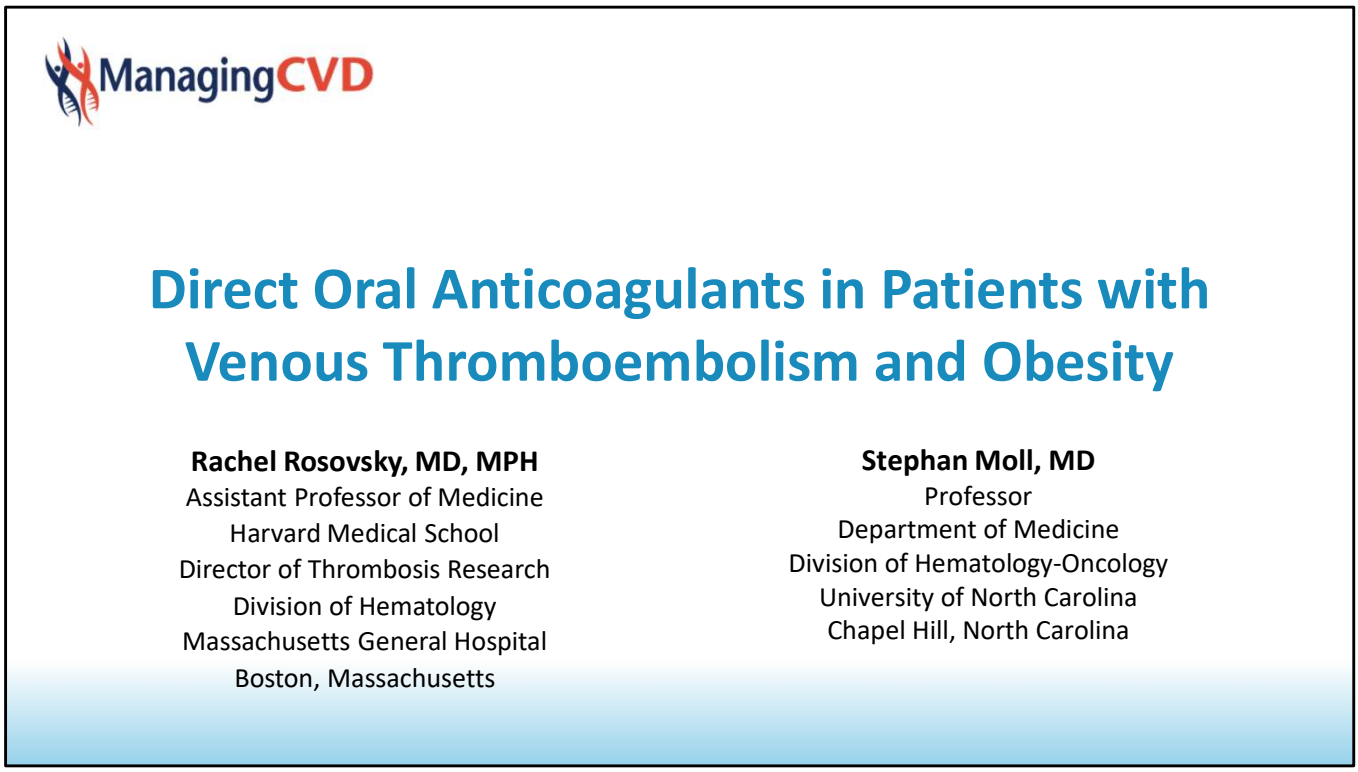


Dr. Rachel Rosovsky: Welcome everyone, to this program on *Direct Oral Anticoagulants in Patients with Venous Thromboembolism and Obesity*. My name is Rachel Rosovsky and I'm a hematologist at the Massachusetts General Hospital and Associate Professor at Harvard Medical School. I am thrilled to be presenting this topic to you with my colleague and friend Stephan Moll, who is a hematologist and Professor of Medicine at the University of North Carolina School of Medicine. Welcome, everyone.

Disclosures

- **Dr. Rachel Rosovsky** has relevant financial relationships related to advisory and consulting activities from Bristol-Myers Squibb Company, Dova Pharmaceuticals Inc., INARI Medical, and Janssen Pharmaceuticals, Inc. She has received research grant(s) from Bristol-Myers Squibb and Janssen.
- **Dr. Stephan Moll** has relevant financial relationships related to consulting from Bristol-Myers Squibb Company and Diagnostica Stago, Inc.

Here are our disclosures.

Agenda

- Scope of the problem
- DOAC and obesity
  - Old guidelines (2016)
  - New guidelines (2021)
  - Bariatric surgery
  - Ongoing challenges and evidence gaps

DOAC = direct oral anticoagulant

For the time we have, we're hoping to share with you briefly the scope of the problem and then really delve into the topic of DOACs (direct oral anticoagulants), VTE (venous thromboembolism), and obesity. We'll review the old guidelines, talk about new guidelines and how they relate to bariatric surgery, and end with some ongoing challenges and evidence gaps.

Beckman M, et al. *Am J Prev Med*. 2010;38(4 Suppl):S495-501.; Wendelboe A, et al. *Throm Haemost*. 2021;121(6):816-825.; Grosse S, et al. *Thrombosis Research.* 2015;137:3-10.

It is estimated from the CDC that each year in the United States, 900,000 men, women, and children will suffer from a VTE every year.

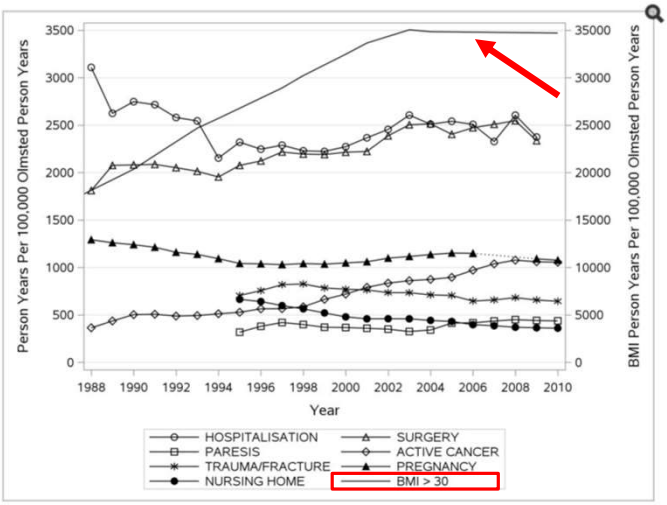
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Estimated Cost of VTE Care $7-10 Billion/Year

VTE = venous thromboembolism
Beckman M, et al. *Am J Prev Med*. 2010;38(4 Suppl):S495-501.; Wendelboe A, et al. *Throm Haemost*. 2021;121(6):816-825.; Grosse S, et al. *Thrombosis Research.* 2015;137:3-10.

As many as 100,000 people will die of a VTE. That is one person every six minutes.

Incidence of Pulmonary Embolism



BMI = body mass index

Deitelzweig SB, et al. *Am J Hematol.* 2011;86(2):217-220.; Heit J. *Semin Thromb Hemost.* 2002;28 Suppl 3:33-39.

This problem is not going away.

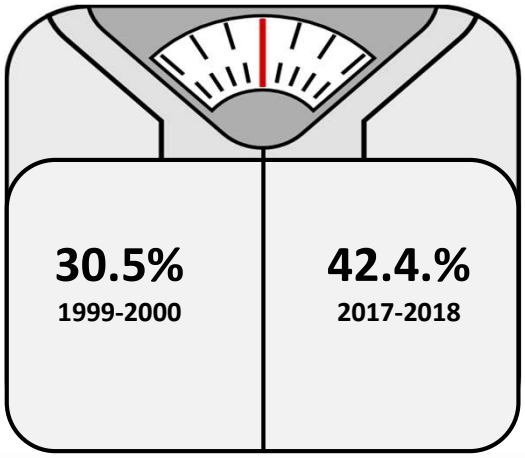
Obesity

Definitions

- Obesity: BMI of 30 kg/m^2 or higher
- Severe Obesity: BMI of 40 kg/m^2 or higher
- Body Mass Index (BMI): A measure of an adult's weight in relation to his or her height, calculated by using the adult's weight in kilograms divided by the square of his or her height in meters

Obesity is defined by weight and BMI. BMI, or body mass index, is a measure of an adult's weight in relation to his or her height, calculated by using the adult's weight in kilograms divided by the square of his or her height in meters. Just a few definitions, obesity is considered a BMI of greater than 30 kg/m^2 and severe obesity is a BMI of greater than 40 kg/m^2.

Obesity in the United States 1999-2018



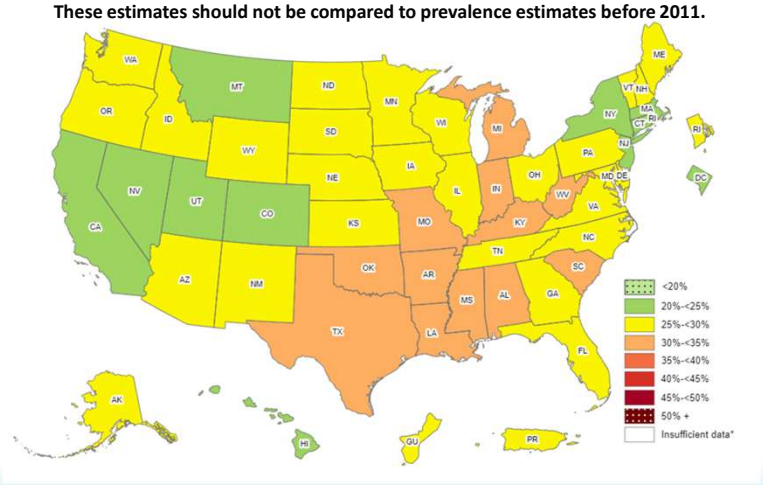
Obesity has increased among adults

National Center for Health Statistics, National Health and Nutrition Examination Survey.
For more information visit: https://www.cdc.gov/nchs/products/databriefs/db360.htm

We know that obesity is a major epidemic in public health problem that has reached crisis proportions.

Prevalence¶ of Self-Reported Obesity Among US Adults by State and Territory, BRFSS, 2011

¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

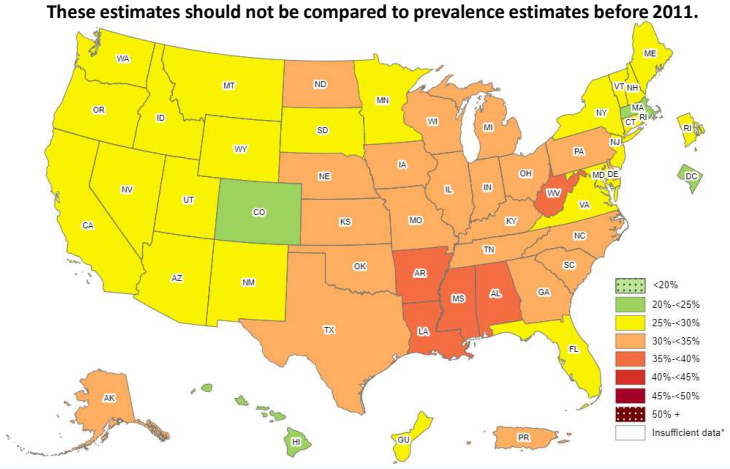


*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

To show you this in a visual way. You can see here the prevalence of self-reported obesity among US adults by state and territory starting in 2011. Where the green is less than 25% of the state is obese. Yellow is between 25% to 30% obese. Orange is 30% to 40% are obese and red which you can't even see. There's no state that has red in 2011 indicates that the prevalence of self-reported obesity is greater than 40%. Watch how the prevalence changes over time, 2011.

Prevalence¶ of Self-Reported Obesity Among US Adults by State and Territory, BRFSS, 2016

¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

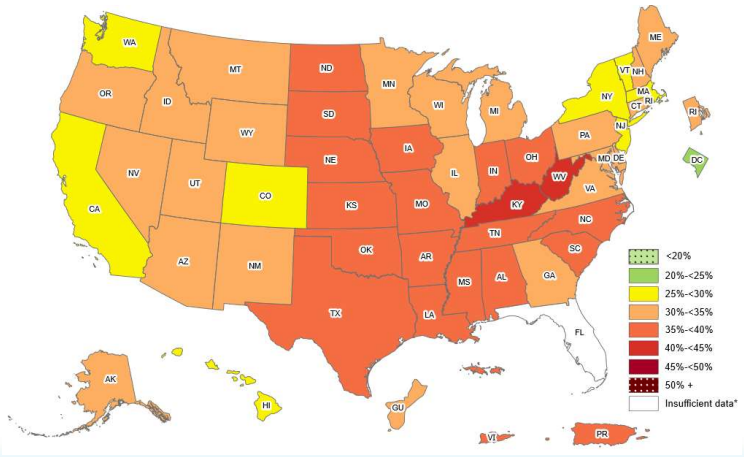


*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

2016

Prevalence¶ of Self-Reported Obesity Among US Adults by State and Territory, BRFSS, 2021

¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

2021. There is only one green state and a handful of yellow states, indicating a significant increase in the prevalence of obesity in every state over time.

Obesity and VTE

Prevalence of obesity rising

- More than 650 million adults affected worldwide
- No state or territory had a prevalence of obesity <20%
- Up to **70,000 extremely obese** patients in the US with **VTE** require treatment with anticoagulation

DOACs

- Widely used as first-line treatment and prevention of VTE
- However, uncertainty regarding their efficacy and safety in **patients with obesity**

Moll S, et al. *Res Pract Thromb Haemost*. 2018;3(2):152-155.; Virani SS, et al. *Circulation*. 2021 ;143(8):e254-e743.

We know obesity affects more than 650 million adults worldwide and as I showed you, no state or territory right now has a prevalence of obesity less than 20%.

Now, in terms of anticoagulation, the direct oral anticoagulants are now widely used as first-line treatment for the treatment and prevention of VTE based on several studies that have demonstrated that they are as effective as warfarin for preventing recurrent blood clots, but they all have better safety profiles, meaning less bleeding. However, there is great uncertainty regarding their efficacy and safety in patients with obesity.

In 2016, the International Society of Thrombosis and Haemostasis published a guidance document surrounding the use of DOACs in obese patients with VTE and then updated this guidance in 2021.

Dr. Moll, can you give us a summary of the old 2016 ISTH guidance document on the use of DOACs in obesity and in particular the severe obese patients? Then what is now new in the recent 2021 ISTH guidelines?

Severe Obesity, DVT/PE and DOAC Use

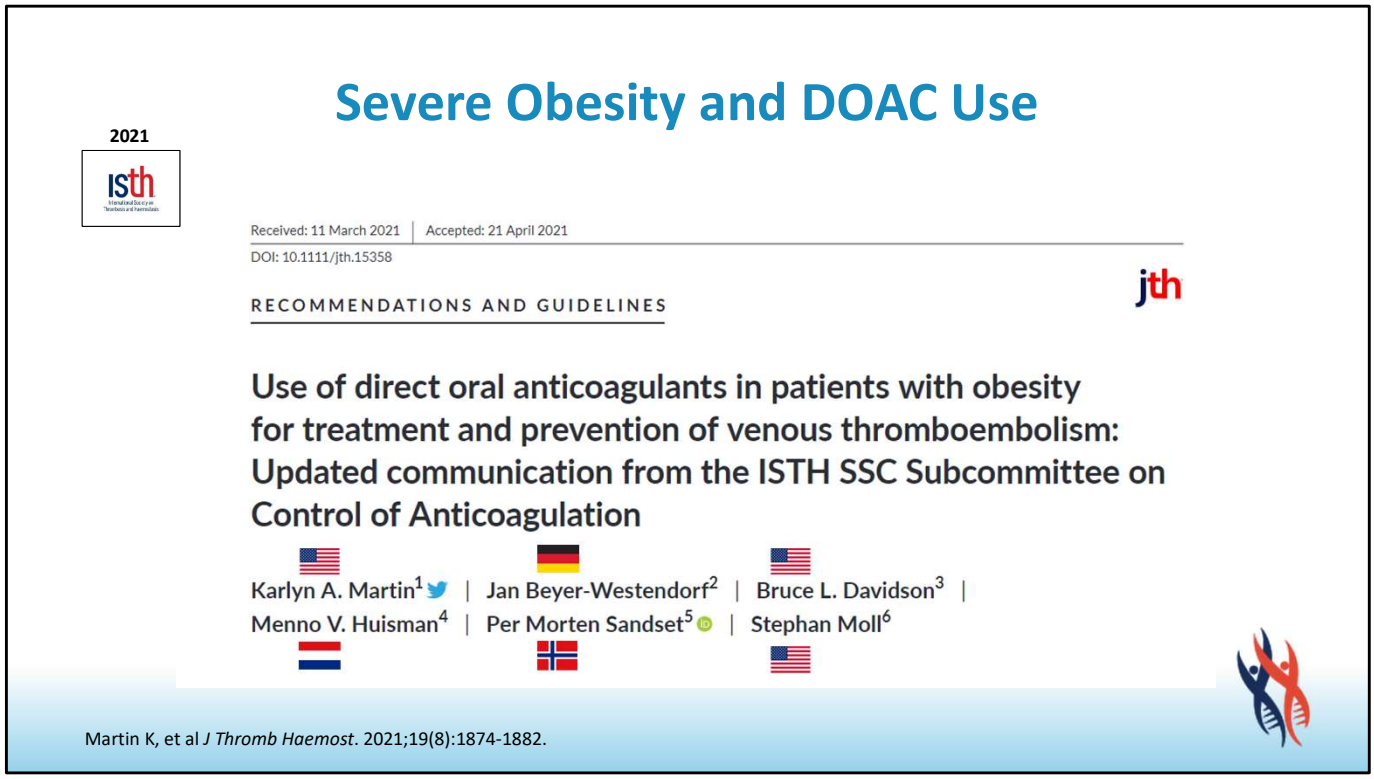
- >120 kg
- BMI >40 kg/m^2

Martin K, et al. *J Thromb Haemost.* 2016;14:1308-1313.; Martin K, et al *J Thromb Haemost*. 2021;19(8):1874-1882.

Dr. Stephan Moll: Would be happy to do that. Thank you for having me on this program. I'll make it simple. I'll talk about the BMI above 40 as severe obesity, which some people call extreme obesity, but often it is also considered a weight of more than 120 kilos. In 2016, a group of mostly hematologists international came together and discussed, what are the data on these very obese patients for the use of DOACs? The clinical trials often patients have been involved that were simply obese i.e BMI above 30, 35. The patients in the trials that were with a BMI of more than 40 were really uncommon or were not reported.

At that time, there were very limited data on the use of the DOACs in the severely obese patients i.e these body weights. Given those limitations, the recommendation in 2016 was to avoid the DOACs in the severely obese patients and use warfarin instead. That was because it was not clear whether the peaks and troughs and area under the curve, i.e the DOAC exposure, how it behaves in the severely obese patients. It was from that time that often people avoided the use of DOACs, at least in the severely obese patients, but sometimes even in the less severe obese patients, i.e the ones with a BMI between 30 and 40.

Now, that document in 2016 was followed, which was nice to see by a number of studies and sub-analyses trying to answer the question, how do the DOACs really behave in the severely obese patients so that we have some clinical guidance. That prompted this working group to bring out a new guidance document in 2021, which is now one and a half years in circulation.



I want to talk about this statement and how it refers to our severely obese patients. I've listed here the publication in the Journal of Thrombosis and Haemostasis and the authors.

I want to highlight that this was an international working group from Germany, the US, Holland, and Norway. As you see, I'm the senior author on this. I'm well familiar with the background work that went into it and the final recommendations.

Severe Obesity and DOAC Use

TABLE 3 Summary guidance statements

Summary Guidance Statements for use of DOACs in Patients with Obesity
1). Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m^2 or weight 120 kg. For patients with BMI >40 kg/m^2 or weight >120 kg, we recommend that the individual DOACs should be used as follows:
2). For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.
3). For primary prevention of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Drug approval is restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness.
4). We suggest not to use dabigatran, edoxaban, or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m^2 or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.
5). We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.
6). We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

Martin K, et al *J Thromb Haemost*. 2021;19(8):1874-1882.

In the paper, if you pull it from PubMed or wherever you have access to it, there are six points that we recommend, and I will take them a little apart to make them easy to see here on the slides.

Severe Obesity and DOAC Use

KEY TAKEAWAYS

Treatment of VTE

- Up to a BMI 40 kg/m^2 and weight 120 kg: all DOACs reasonable
- >40 kg/m^2 and >120 kg: rivaroxaban and apixaban (less data) are reasonable
- Suggest not to use dabigatran or edoxaban
- Suggest not to regularly obtain peak or trough serum drug levels

Martin K, et al *J Thromb Haemost*. 2021;19(8):1874-1882.

First of all, we are dealing with venous thromboembolism. All of us are hematologists. We did not review the literature on AFib, even though many of us are somewhat familiar with it. We wanted to focus on the use of DOACs in severely obese patients with VTE. Here you see that for the treatment of VTE now, based on the 2021 guidance, the use of all DOACs is reasonable, even in the severely obese patients. Excuse me, up to a BMI of 40, the use of any of the DOACs is reasonable.

However, above the BMI of 40 or a weight of 120 kilos and above, rivaroxaban and apixaban are reasonable to choose.

Then not enough data on the dabigatran or edoxaban, so the guidance group recommended or suggested not to use the dabigatran or edoxaban in the severely obese patients.

Now, the one thing in 2021, I want to highlight in the severely obese patients at that time, there were more data on rivaroxaban than on apixaban. My preference up until 2021 was to use rivaroxaban in the severely obese patients. In the last one and a half years, there have been additional data on apixaban sub-analyses and studies, retrospective studies that have supported the use of apixaban in the severely obese patients.

Now, the guidance group suggests not to use regularly peak or trough level drug levels to determine them. That changed compared to 2016. At this point, it's a regular dose that is to be used in the severely obese patients without checking peak or trough.

Severe Obesity and DOAC Use

KEY TAKEAWAYS

Treatment of VTE

- Up to a BMI 40 kg/m^2 and weight 120 kg: all DOACs reasonable
- >40 kg/m^2 and >120 kg: rivaroxaban and apixaban (less data) are reasonable
- Suggest not to use dabigatran or edoxaban
- Suggest not to regularly obtain peak or trough serum drug levels

VTE Prophylaxis

- Suggest standard VTE prevention dosing of apixaban or rivaroxaban regardless of BMI and weight

Martin K, et al *J Thromb Haemost*. 2021;19(8):1874-1882.

Then some of you may wonder about the use of the DOACs in DVT prophylaxis in the primary DVT prophylaxis and can we use the DOACs in the severely obese patients. The suggestion is that the standard dosing be used for apixaban and rivaroxaban regardless of the BMI and weights. In any of the BMIs and weight groups to use rivaroxaban or apixaban. The insufficient data on dabigatran, edoxaban for DVT prophylaxis in the severely obese patients.

Severe Obesity and DOAC Use

A. PK/PD Summary

	Increasing body weight or BMI on DOAC levels
Apixaban	Lower peak, lower AUC[1] No change in peak levels[2]
Dabigatran	Lower peak levels[3]
Rivaroxaban	No change[4-7] Lower peak levels, no change in trough levels[2,3]

[1] [Wasan SM et al. Thromb Res. 2019 Oct;182:51-55]
[2] [Martin AC et al. Thromb Haemost 2021;121:224-233]
[3] [Piran S et al. Res Pract Thromb Haemost 2018 Aug 29;2(4):684-688]
[4] [Arachchillage D et al. Thromb Res. 2016 Nov;147:32-35]
[5] [Barsam SJ et al. Res Pract Thromb Haemost 2017;1:180-187]
[6] [Speed V et al. J Thromb Haemost. 2020 Sep;18(9):2296-2307]
[7] [Willmann S et al. CPT Pharmacometyrics Syst Pharmacol 2018;7:309-320]

B. Clinical Trial Summary

	Phase 3 DOAC vs VKA		Phase 4 * DOAC vs VKA	
	BMI >35 or BW > 120 kg	BMI > 40	BMI >35 or BW > 120 kg	BMI > 40
Apixaban	no data	no data	Similar outcomes[6]	Similar outcomes[5,6]
Dabigatran	no data	no data	no data	no data
Edoxaban	no data	no data	no data	no data
Rivaroxaban	Similar outcomes[7]	no data	Similar outcomes[5,8-10]	Similar outcomes[5,9]
Pooled DOAC	Similar outcomes[11]	no data	Similar outcomes [12-16]	Similar outcomes[12]

[Martin K et al J Thromb Haemost. 2021 Aug;19(8):1874-1882]

* Includes retrospective and prospective studies and meta-analyses

Martin K, et al *J Thromb Haemost*. 2021;19(8):1874-1882.

For those of you who are interested a little more in the details and this is in the ISTH guidance document, and you can look at that, it really talks about the pharmacokinetic and pharmacodynamic data on these drugs, which are somewhat limited in the severely obese patients.

On the left, you see how the PK data and the PD data behave in apixaban, dabigatran, and rivaroxaban with increase in body weight or increase in BMI. You see comments there like lower peak, lower air under the curve, or no change, lower peak, a variety of different changes in the PK and PD data. It has been somewhat challenging to translate that into clinical efficacy because with the DOACs, we see such a wide variation in serum drug levels, even in normal individuals that it's difficult to really correlate into clinical efficacy unless you look at prospective randomized good clinical trials.

How these DOACs behave in the phase three and phase four clinical trials, we've listed here in the table B on the right hand side. Again, you have apixaban, dabigatran, edoxaban, rivaroxaban listed in the different rows. In the phase three, i.e the randomized comparison trials of the DOACs versus vitamin K in the severely obese patients, BMI above 40, you see in red that there are no prospective data specifically for this patient population on any of the DOACs, which is a limitation and has given this hesitancy initially to use the DOACs in the severely obese patients. Now, there are data in the less severe patients, BMI 35, 40, and you see them that with rivaroxaban, you have similar outcomes. The other ones are listed as no data. Then if you look at the phase four clinical trials, which are the post-FDA approval studies, typically retrospective or claims database data, you see that for the severely obese patients, BMI above 40, for apixaban, there's similar outcomes between warfarin and apixaban and with rivaroxaban, similar outcomes as well in DVT NPE. This has led to the recommendation that even in the severely obese patients, it is reasonable to use of apixaban and rivaroxaban.

Dr. Moll: As Dr. Rosovsky, Rachel, you said earlier, from a safety point of view, often the DOACs do have an advantage over warfarin, thus similar efficacy and sometimes better safety. There are no data on dabigatran and edoxaban in the severely obese patients.

With that, I think we can maybe turn to a clinical question. Rachel, let's just be practical. We are both hematologists. We see patients with DVT/PE. Imagine you have, a patient who's, let's say 64 years old, has a newly diagnosed unprovoked, DVT or PE, proximal DVT, needs treatment, weighs 135 kilos, and the body mass index is 44.6, so severely obese. Creatinine is normal. Platelets are normal. You're not concerned about bleeding, but severely obese. What anticoagulant would you use and what is your thought process?

Dr. Rosovsky: I think as you have just shown us, there's no good evidence that supports the use of direct oral anticoagulants and in particular rivaroxaban and apixaban in obese patients. For this patient with a BMI over 40, which as you said would be considered severe obesity, I would feel entirely comfortable prescribing either rivaroxaban or apixaban. As you suggested, even though the 2021 guidelines noted that there was less supportive data with use of apixaban, since that publication, there's been additional data that have shown that looking at the efficacy and safety of both rivaroxaban and apixaban in patients with obesity, and in fact, there's been over 15 studies, many of them single center retrospective, some of them multi-center and a few observational. There's actually been three systematic reviews in meta-analyses.
I think there is now as much data for apixaban as there is for rivaroxaban, and therefore I would use either one. I would use the FDA-approved doses. For rivaroxaban, that would be 15 milligrams twice a day for 21 days, and then 20 milligrams daily after that. It's important as you know, to tell patients to take rivaroxaban with food. Then, as I said, I would feel entirely comfortable prescribing the apixaban based on what you just shared. That would be 10 milligrams twice a day for the first seven days and then five milligrams twice a day thereafter.

I just want to point out the importance of knowing the correct dose. Both you and I are hematologists and we prescribe these drugs all the time, but I think if you're a healthcare provider and you're not someone that prescribes these a lot or routinely, I would encourage people to confirm the dose because we know patients that are put on incorrect doses have higher rates of complications such as recurrent clots and bleeds. As you shared already, there's not enough data for dabigatran or edoxaban and therefore I would not feel comfortable using either one of those drugs in this situation.

Dr. Moll: Rachel, would you see any role to do a peak or trough level in this patient with a BMI or 44 or so where you want to use a DOAC?

Dr. Rosovsky: I think in line with the guidance documents you just mentioned, for this patient with the BMI of 44, I would not check peak or trough levels, and I would feel entirely comfortable not doing that. What about you?

Dr. Moll: Yes, I would feel the same. A question that comes up not infrequently is what about at six months based on the Einstein Choice trial or the Amplify extension trials where patients with DVT/PE after six months were lowered in their dose to the more prophylactic dose, and those were found to be effective in both those studies in the population studied, which had limited numbers of severely obese patients, if any. We don't know that for sure. What would you do in the more severely obese patient, the BMI above 40? Would you lower the dose at six months?

Dr. Rosovsky: I would say just take a step back in terms of how long this person needs to be treated with anticoagulation because you mentioned this was an unprovoked blood clot. I think if she has low bleeding risk, this is someone that I absolutely would recommend long-term anticoagulation that's based on a number of studies that have shown patients with unprovoked VTE who stop their anticoagulant are at a very high risk of recurrent clots. Some studies up to 25% at five years, others up to 50% over 10 years. I absolutely would do long-term. Just as you mentioned, there's two trials, one with rivaroxaban and one with apixaban that have demonstrated that after that 6-12 months of therapeutic anticoagulation, it is both safe and effective to decrease these drugs to a prophylactic dose. However, I don't think there is enough data in the obese population to practice this, and I would therefore not decrease the dose at the six-month mark in this patient.

That decision is in line with the ISTH guidance from 2021 that you just shared with us, and that states that it is not possible to provide evidence-based guidance on DOAC dose reduction following the initial six months of full dose treatment owing to insufficient data. There's just no dedicated data or analyses specifically looking at dose reduction for patients with severe obesity. I also think it's important to point out that in those two studies where patients were randomized to stay on therapeutic dose, decreased to a prophylactic dose. In both trials, as you know, there was a third arm. In the rivaroxaban trial, the third arm was aspirin, and in the apixaban trial, the third arm was a placebo. There was no statistically significant difference in major bleeding rates. To me, that is reassuring to keep my obese patients on the therapeutic dose long-term if it's indicated. Stephan, what do you think?

Dr. Moll: I have the same clinical approach. In the severely obese patients BMI above 40, I would not lower the dose at six months. In the patients with a BMI between 30 and 40, I might consider it, but I wouldn't rush into it either.

Dr. Rosovsky: I would do the same. I think BMI between 30 to 40, it also depends if they have other risk factors. If they have more than just obesity as a risk factor, I'd be more inclined to keep them on the higher dose.

Dr. Moll: Let's imagine the patient who is really at the extreme body weight end, whether BMI of 61 who had an acute DVT or PE. Would you feel comfortable using a DOAC in that patient and would your consideration of peak or trough level testing change where that's really extreme body weight?

Dr. Rosovsky: I would say, and I think we might differ here, in patients who are extremely obese, i.e., BMI greater than 60, I think the issue with the ISTH guidance, which I think is great. They don't state an upper limit for which DOACs should not be considered. Although somewhat arbitrary, I would have some reservations in a BMI greater than 60. This is not based on any evidence-based data. I know there are several more limitations with warfarin. It's really a conversation I would have with a patient. I would say my first choice, I think with the BMI over 60 in this particular patient, would probably be warfarin. If the patient were really averse to that, I would consider either rivaroxaban or apixaban, but unlike the patient with the BMI of 44, if I were going to prescribe rivaroxaban or apixaban, I would absolutely check plasma DOAC levels and specifically I would check trough levels.

I would also acknowledge that the DOAC drug levels do not have good or proven correlation to clinical efficacy and safety. If the trough level were too low, I would not adjust the DOAC level to a non FDA-approved dose as there's really no guidance for that or evidence for that. If I did check it and it was not within range, I would just change to another agent, likely warfarin. I'm interested. I think you probably have a little bit different opinion. What do you think?

Dr. Moll: The guidance document from the ISTH could not comment on a cutoff of weight where you get more concerned, or you think about different management because we just don't have the data. It was left open on purpose. That's really left up to each individual physician then to consider. I would tend to use a DOAC even in the severely obese patient, but I would definitely get a trough level. I never do a peak level because that fluctuates from patient to patient at what time that is reached, but I would get a trough level. My hope would be that the trough level is in the expected range and lets me sleep easier. If the level is lower than expected, then I'm more nervous and I don't quite know what I would do with it. You said you would switch then to a different anticoagulant, and that's perfectly appropriate. That's an individual decision than what I would do but I would not say, "Oh, let's use a higher dose of DOAC."

Dr. Rosovsky: Yes, absolutely.

Dr. Moll: That, I don't think has much behind it, and then risk for bleeding may also come in. It's a very individual decision that's severely obese patients.

Dr. Rosovsky: I think so too. I think so. I think you're right. There's no right answer here, and I also think it's really a conversation you need to have with your patient and really do a shared decision-making and really outline the challenges and limitations. Also, you got to take into consideration the side effects of other drugs and all the limitations with warfarin.

Dr. Moll: Rachel, let's talk about DVT prophylaxis dosing with the DOACs. The patient with a BMI of 44.6 didn't have a clot, but is heavy, needs DVT prophylaxis after hip or knee replacement or some other intervention. Would you use a DOAC and what dose would you use?

Dr. Rosovsky: I think for a BMI of 44 for a prophylaxis to prevent VTE, I would feel entirely comfortable using, again, rivaroxaban or apixaban at the standard prophylactic dose. For rivaroxaban, that would be 10 milligrams a day, and for apixaban that would be 2.5 milligrams twice a day.

Dr. Moll: Got it. Would that be different for you if the BMI was, let's say again, above 61 or so?

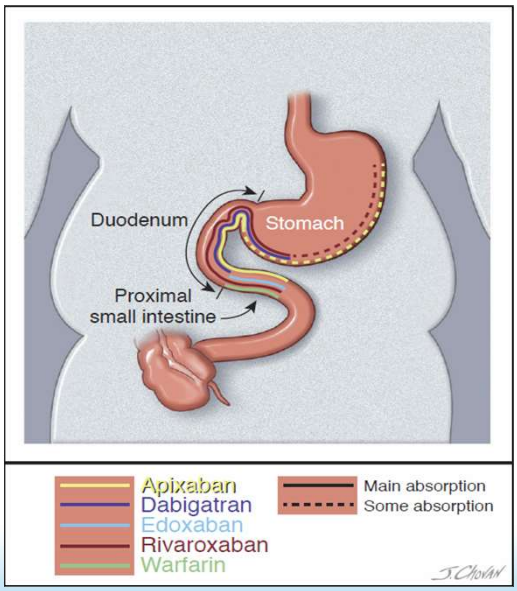
Dr. Rosovsky: I think that's a completely different story. Again, I would feel uncomfortable with just the prophylactic dose with the BMI greater than 60. In that patient, I would probably do lovenox (enoxaparin sodium) 40 milligrams twice a day or I would consider fondaparinux, but I would feel a little bit uncomfortable. Again, completely arbitrary. I just don't know of evidence surrounding that and I don't think there is a lot of evidence surrounding that, and so I would feel pretty uncomfortable. How about you?

Dr. Moll: I think I would see very similar, and I say I think. We've talked about this BMI above 60 or so. Sometimes I'm even more nervous about using the DOACs at a BMI of 55 or so. That's still a pretty extreme body weight. We just have more experience with enoxaparin, let's say 40 BID, which we use at my institution once a BMI is above 40. I have to say, even with that, sometimes I wonder how well does it get absorbed in the severely obese patients. You mentioned fondaparinux and the typical dose is 2.5 milligram once daily, and we don't have a adjustment for body weight. I also do wonder is should you increase that to maybe five milligrams in the severely obese patient? The treatment is difficult or the treatment decision is difficult. The DOAC uses a standard dosing with a BMI between, let's say, 40 and 50, these severely obese patients. I'm okay with that. Once you get towards the BMI of 55 and above, I probably would be more comfortable with the more established and enoxaparin at the higher dose of 40 milligram twice daily.

Dr. Rosovsky: Similar to me. I would say again, the fondaparinux at 2.5, again, you got to look at other risk factors, and if patients have significantly more risk factors than that, I might consider doing that. That's our standard, the 40 twice a day with a BMI over 40.

That was a great discussion on using DOACs in obese patients. I'm wondering now if we can turn towards the patients who are undergoing bariatric surgery. Stephan, what did the 2021 ISTH guidance say about use of DOACs after bariatric surgery? Can you share that with us?

Bariatric Surgery and DOAC Use

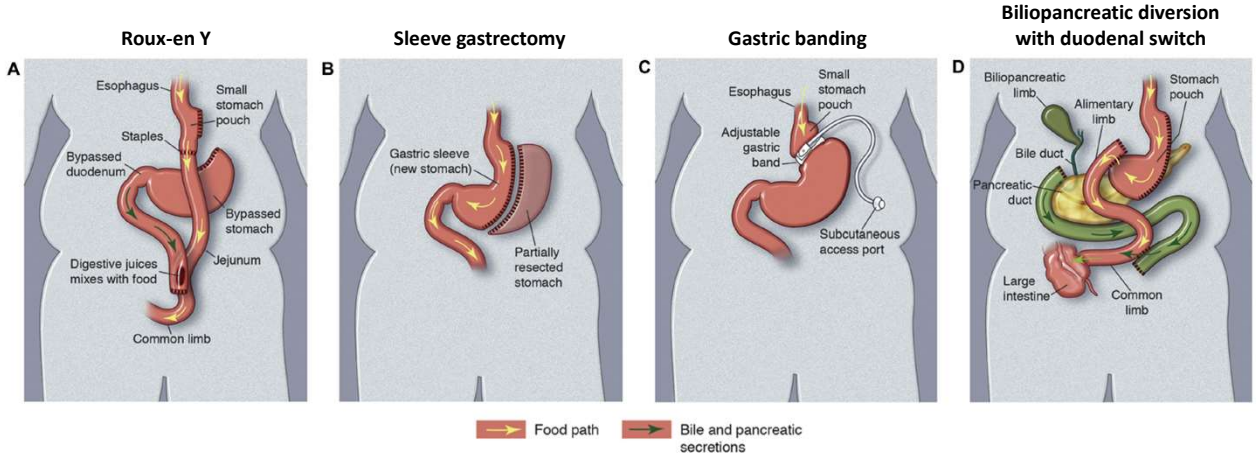


Martin KA, et al. *Am J Med*. 2017;130(5):517-524.

Dr. Moll: Yes, I will. Rachel, before I do that, I want to show this slide here from a publication, which shows where the anticoagulants are absorbed, and it lists the different anticoagulants. Keep in mind that any of the anticoagulants absorbed in the proximal small intestine, rivaroxaban even in the distal stomach, but everything else in the duodenum and the small intestine very proximally. Anything that changes the anatomy of the distal stomach, particularly the small intestine, will lead to some disturbance of absorption of the anticoagulants. It's true for warfarin as well.

Obviously, this is only true for the oral anticoagulants, but even warfarin, after bariatric surgery, it's very difficult. The transit time of the drugs is different, the meal size is different, the acidity is different, and then the absorptive surface is different. Keep that in mind.

Bariatric Surgery and DOAC Use



Martin KA, et al. *Am J Med*. 2017;130(5):517-524.

This is true probably for any of the gastric bypass surgeries, and it depends on the center, which one is done mostly, and also the time practices change. There's the Roux-en-Y, which is depicted here on the left, the sleeve gastrectomy, the gastric banding, and then a more complex, but it all disturbs the anatomy of the upper intestine.

Therefore, absorption of the DOACs and warfarin may be different. Now, the one thing that's interesting to keep in mind is, number one, rivaroxaban is also absorbed in the distal stomach, so that may be most sensitive to the disturbances after bariatric surgery. The second thing to keep in mind is that apixaban is to some degree also absorbed in the more distal small intestine, so apixaban may be the preferred DOAC in patients after bariatric surgery. I have to say, when I looked into this and tried to find a group information about where these drugs are absorbed, it's really difficult to find solid data on that to come to a really solid conclusion.

Bariatric Surgery and DOAC Use

TABLE 2 Expected impact of bariatric surgery procedures on absorption of DOACs

DOAC	Site of Absorption in Gastrointestinal Tract	Surgical Intervention and Anticipated Effect on Absorption		
		Gastric Banding	Partial /Sleeve Gastrectomy	RYGB
Apixaban	Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Lower stomach and proximal small intestine	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Proximal small intestine, dependent on acidic environment	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Largely stomach, some small intestine, but absorption reduced when released distal to stomach	Possibly reduced	Possibly reduced	Possibly reduced

Abbreviations: DOAC-direct oral anticoagulant; RYGB-Roux-en-Y gastric bypass.

Martin KA, et al. *Am J Med*. 2017;130(5):517-524.

We've listed here in the publication on bariatric surgery in the DOAC use, number one, where the site of absorption is based on the limited published data, and then on the right-hand side in greenish, what do you expect is the anticipated effect of the surgical intervention. Look at apixaban in the first line. Gastric banding unlikely affects the apixaban because the small intestine is not affected and with the others possibly reduced absorption.

If somebody has had a bariatric surgery, my preference is if I use a DOAC, apixaban, and not rivaroxaban, dabigatran, edoxaban again, in the severely obese patients after these surgeries has no data that I would even consider them.

Bariatric Surgery and DOAC Use

KEY TAKEAWAYS

Bariatric surgery

- In the acute post-operative phase: **parenteral anticoagulant**
- After ≥4 weeks, a switch to warfarin or a DOAC may be considered
- If a DOAC is used: suggest trough level testing

Martin K, et al *J Thromb Haemost*. 2021;19(8):1874-1882.

The ISTH document from 2021 has the following comments on bariatric surgery. In the acute post-operative phase, for the first, at least four weeks, use a parenteral anticoagulant. The purpose is if this patient who had a DVT or PE in the past needs full-dose anticoagulation after surgery, you don't know how it's absorbed, and therefore, let's use a parenteral anticoagulant, fondaparinux or enoxaparin or edoxaban for that matter that we know the patient is absorbing it from the sub Q tissues.

Then, once the patient is four or more weeks after the bariatric surgery, and that could be 8 weeks, 12 weeks, once the patient is more adjusted to the different meal size, has recovered from the surgery, it's reasonable to consider switching to either warfarin or a DOAC for that matter.

If a DOAC is used, we don't know how well it's absorbed. Therefore, the committee has suggested to do trough level testing, again, not peak but trough level, to make sure it's roughly in the expected range. Then the same applies that we discussed earlier.

If the level is below the expected range, and we do not take reference to that in the guidance document, if it's below the expected range, then we wonder, what does that really mean, and what do we do now? Do we switch to warfarin or do we switch back to parenteral anticoagulant, or does it just make us uneasy? I would not empirically increase the DOAC to a non-traditional dose.

Dr. Rosovsky: First of all, Stephan, it's great to have this material out there because this question comes up a lot. Just having this guidance document has been so, so helpful, so thank you to you and the group. What anticoagulant would you use in the following patient? Let's say this is a 43-year-old male, BMI of 49 is going to be undergoing gastric banding in four weeks, and he's currently on full-dose anticoagulation long-term with either rivaroxaban or apixaban. For a history of an unprovoked VTE, what anticoagulant would you use after the surgery?

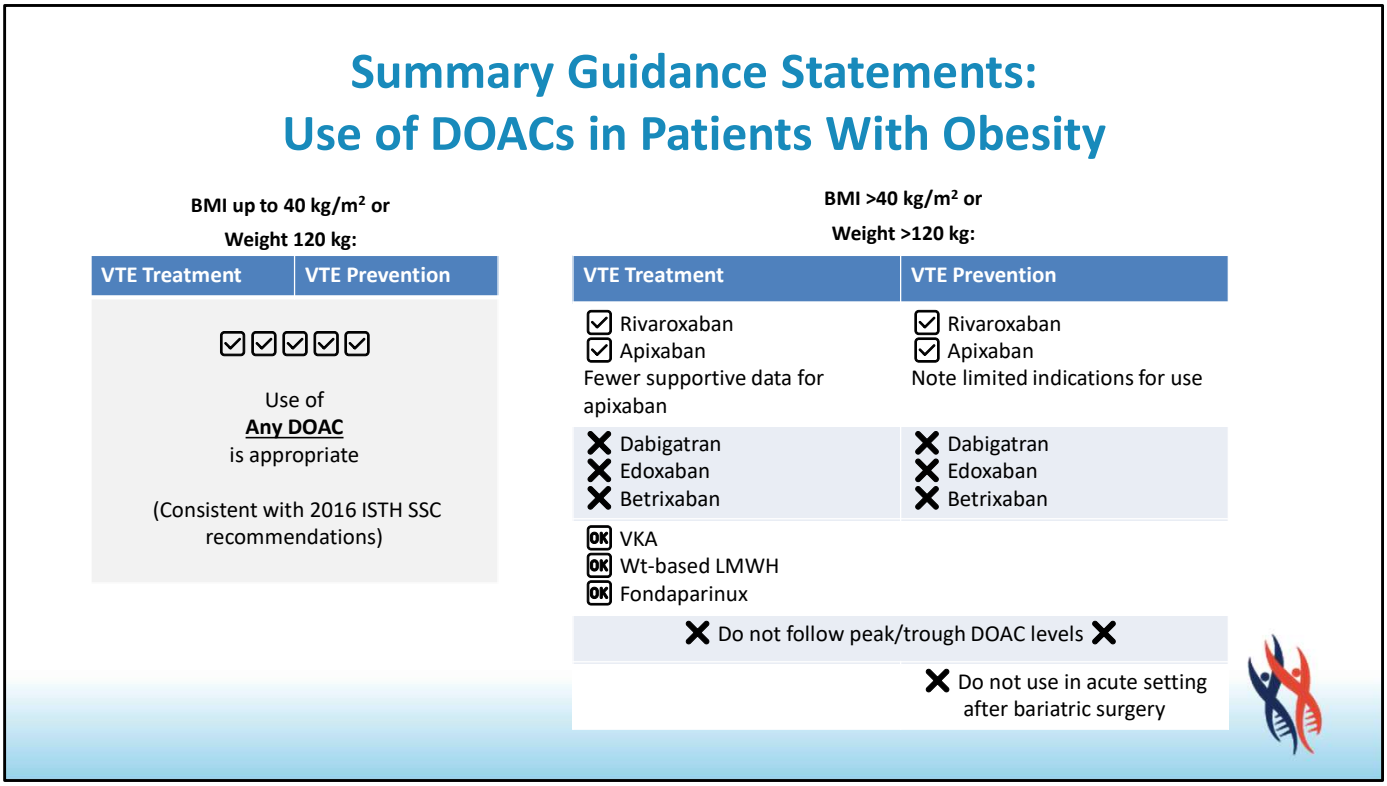
Dr. Moll: This patient needs a full-dose anticoagulation, so I would use, based on the guidance document which I fully stand behind to use a parenteral anticoagulant for the first few weeks and then just rethink it at four or six or eight weeks or so. My preference is, and I don't have data for that to use fondaparinux because it's once daily, but people are often more familiar with enoxaparin. To use that twice daily at the appropriate dose would be what I would do, and then after a few weeks, it's reasonable to consider a switch to a DOAC.

My preference would be to use apixaban because of the absorption even further down in the small intestine. I would use the traditional long-term dose, which in this case would be the 5-milligram BID, and I would do a trough level to make sure it's in the expected range.

Rachel, one thing if I may point out, I sometimes see patients who are on a DOAC for DVT or PE in the past and they did not volunteer that they had bariatric surgery in the past, or let's say they need to be started on an anticoagulant because they have a DVT/PE and they had bariatric surgery eight years ago and they don't think about it.

I tend to ask the patient, have you had bariatric surgery quickly done? Then I now got to be careful with the DOACs and consider what we just discussed.

Dr. Rosovsky: Yes, that's a really, really good point. I think as hematologist or anybody, any medical professional taking care of somebody with a VTE asking that background information is really important because a lot of times, if it's been a while though, people are not going to share all that information or they may not remember to.



Dr. Rosovsky: Well, this has been an incredible discussion with you, Stephan. Just to summarize the guidance statements of the use of DOACs in patients with obesity, as you've shared in patients with the BMI up to 40, or weight up to 120, really using any DOAC is appropriate. I think for BMI greater than 40 or weight greater than 120kg, you have shared really great information that there's good data with rivaroxaban and apixaban for the treatment.

There's also great data looking at rivaroxaban apixaban for prevention. I think we've both talked about how there's just not enough data with dabigatran, edoxaban or betrixaban in either those situations, VTE treatment or prevention. Then we also shared that it is completely appropriate to think of alternatives if necessary, Vitamin K antagonist, weight-based lumbar white heparin, and fondaparinux. Although the guidance documents do not recommend checking peak and trough levels, we both talked about how we would check trough levels at certain BMI levels.

You're probably comfortable above the 50/60, a probably same way above 50, I would probably check. We also both talked about how we would check trough levels in patients after bariatric surgery. Then I think it's very clear that these direct oral anticoagulants in particular rivaroxaban, apixaban, should not be used in the acute setting after bariatric surgery. It's entirely reasonable to think about their use after four weeks. Again, either one of those, and again, in checking trough levels.

I would say although the 2021 updated guidance has removed obesity as a limitation to their use, some healthcare providers are still avoiding DOACs altogether in patients with any level of obesity. I think there's still huge evidence gaps regarding the treatment of severe obesity as we've discussed. I mean, we had differing opinions about the BMI greater than 60. I think there is still some gaps and challenges about thinking about the role of peak and trough levels.

I think we both agreed we would check trough levels in some of these patients. The use of DOACs after bariatric surgery, which you also elegantly laid out for us. Then the appropriateness of DOAC dose reduction, I think we have very limited data on that for the secondary VTE prevention. I still think there's a lot of challenges and gaps.

I'm hoping that the information that Stephan and I shared with you today will help providers feel more comfortable using direct oral anticoagulants in obese patients with VTE. I think both of these problems are healthcare crisis and the problems are going to continue as I showed with you earlier. I think having these drugs to use will be very helpful for our patients for many, many reasons. I'd like to thank Stephan for joining us. This has been a great discussion, and again, I really do hope that it educates providers and gives providers some confidence in using these drugs. Thank you very much.

Dr. Moll: Thank you very much.