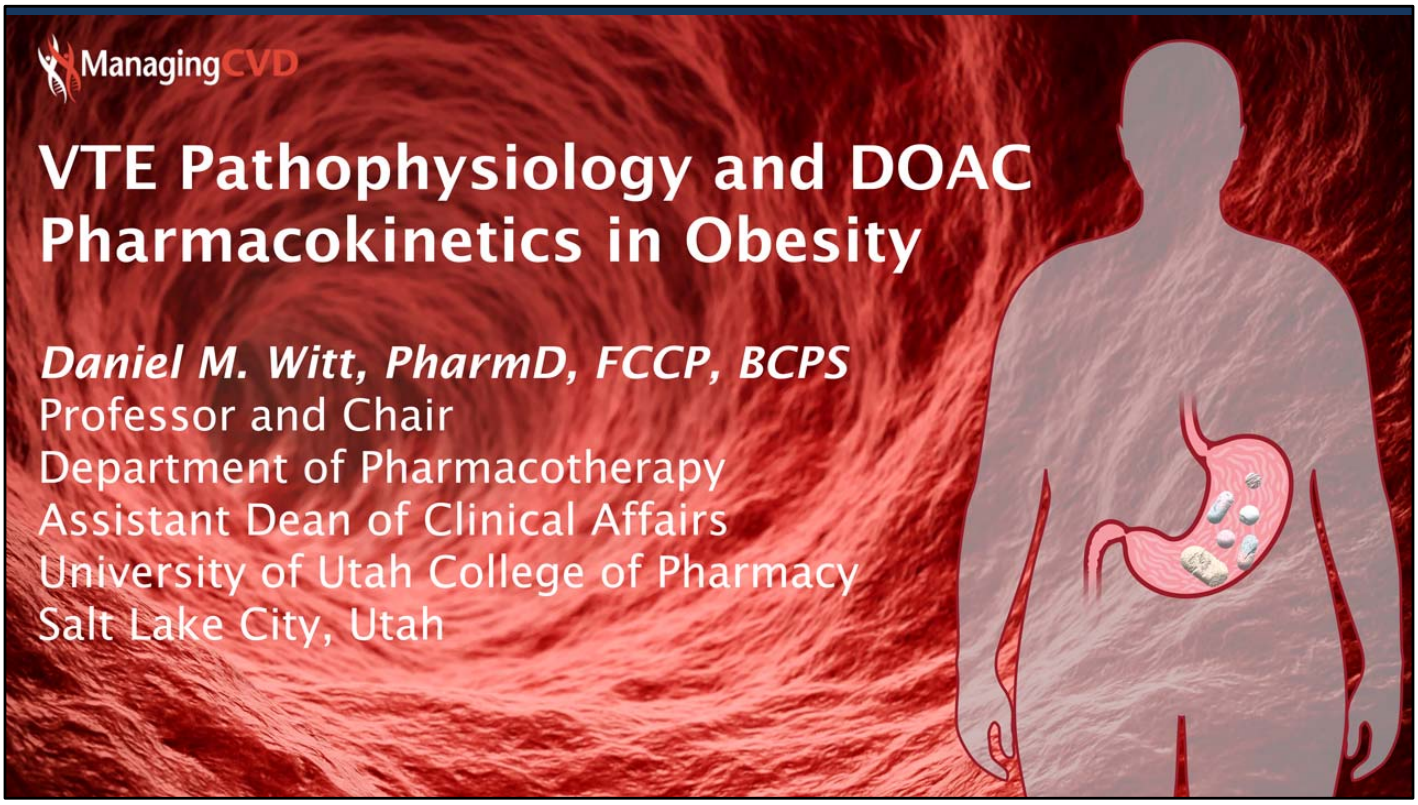
VTE Pathophysiology and DOAC Pharmacokinetics in Obesity



Hi, everyone, my name is Dan Witt. I am the Chair and Professor of Pharmacotherapy at the University of Utah College of Pharmacy. I would like to welcome you today to this activity on managing cardiovascular disease (*ManagingCVD.com*). We'll be discussing today, specifically, venous thromboembolic pathology and direct oral anticoagulant pharmacokinetic considerations in patients with obesity, so let's begin.

Faculty Disclosure

- Dr. Daniel Witt, faculty for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

I don't have any disclosures that are relevant to the content of this particular activity.

Learning Objectives

- Understand the pathophysiologic mechanisms underlying the increased risk of venous thromboembolism associated with obesity
- Describe the potential impact of obesity on DOAC absorption, distribution, metabolism, and excretion

Our learning objectives today are to help you understand better the pathophysiologic mechanisms that underlie the risk of venous thromboembolism that is associated with obesity. We also would like to delve into any pharmacokinetic changes that occur with obesity that might influence the absorption, distribution, metabolism, and excretion of direct oral anticoagulants.

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Meet Our Patient

Patient Notes

- 56-year-old male who presents with left lower leg swelling and pain x 1 week. Denies trauma. He has a history of DVT 13 years ago. No new risk factors. He denies CP or SOB.
- Weight: (!) 172.8 kg (380 lb 15.3 oz); BMI 49

Labs

- BP: 169/81 mmHg, Pulse: 81 bpm, Temp: 96.6° F, Resp: 18, SpO2: 97%
- Compression ultrasound: Acute appearing DVT of left common femoral vein

I'd like to start off with a patient case to frame what we're going to be talking about in today's activity. We've got a 56-year-old male patient who comes in complaining of left lower leg swelling. This has been going on for about a week. He hasn't had any traumatic episodes. He does have a remote history of a deep vein thrombosis that occurred about 13 years ago, but no new risk factors. Currently, right now he's pretty asymptomatic other than the complaints in his lower leg, he's not having any chest pain or shortness of breath.

You can see his vital signs there, and most importantly, I think is that his blood pressure is a little elevated, but not too far out of line. His respiration rate is good, and also he's got a good O2 saturation, 97%. But importantly, when we weigh this patient, we see that his weight is quite high, 380 lbs, and that calculates out for his height to a BMI of 49. A compression ultrasound revealed that he currently has an acute deep vein thrombosis in his left common femoral vein.

Polling Question #1

What pathophysiologic mechanisms relating to this patient's obesity may have contributed to increased risk for venous thromboembolism?

A. Chronic low-grade inflammation
B. Platelet activation
C. Vascular endothelial dysfunction
D. All of the above

Our question then is what pathophysiologic mechanisms relating to this patient's obesity may have contributed to an increased risk for venous thromboembolism?

A. Chronic low-grade inflammation
B. Platelet activation
C. Vascular endothelial dysfunction
D. All of the above

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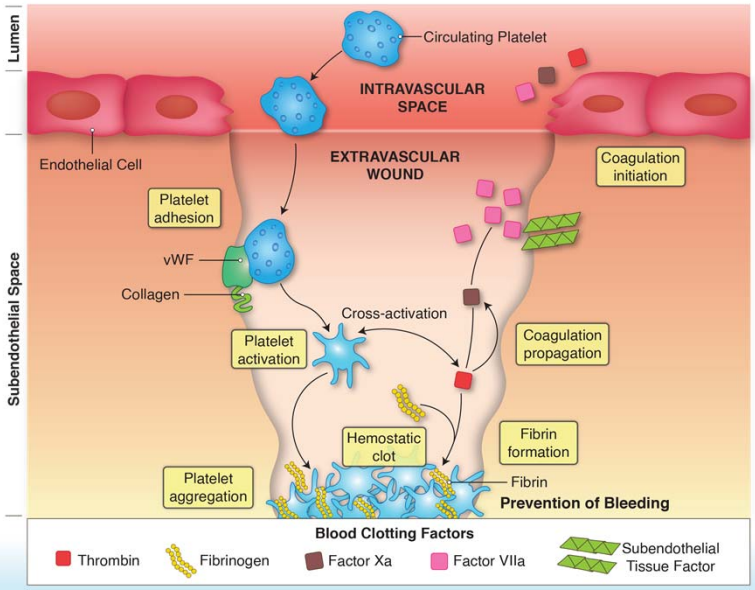
Overview of Hemostasis



Engelmann B, Massberg S. *Nat Rev Immunol.* 2013;13(1):34-45.

Before we dig into the rest of this content, I think it's important for us to just have a very brief overview of the hemostasis process. This is what our bodies have available when we develop bleeding in order to form a blood clot that will then prevent that bleeding from becoming severe, and then allow healing to occur. You've got a cross-sectional view here of a blood vessel and you can see that there's been some disruption to the endothelial cell lining that lines the walls of the blood vessel, and that's exposed the subendothelial spaces beneath that layer. This enables circulating components of the blood, like platelets, red blood cells, clotting factors, to come in contact with these subendothelial layers.

Some key players are von Willebrand factor, as you can see on the top left, collagen, and these interact with receptors on the platelets, to cause those platelets to then become active and begin to stick together or to aggregate. You can see that blood clotting factors also are exposed to something called tissue factor that is exposed in the subendothelial space. This activates the clotting factor process to generate thrombin, and there's also some cross-activation that goes back and forth between thrombin generation and platelet activation. The net result here is that we start to then convert fibrinogen into strands of fibrin which are sticky spider web-like fragments that then begin to form a mesh that traps platelets and red blood cells and white blood cells there to form a stable plug that then prevents bleeding from occurring.

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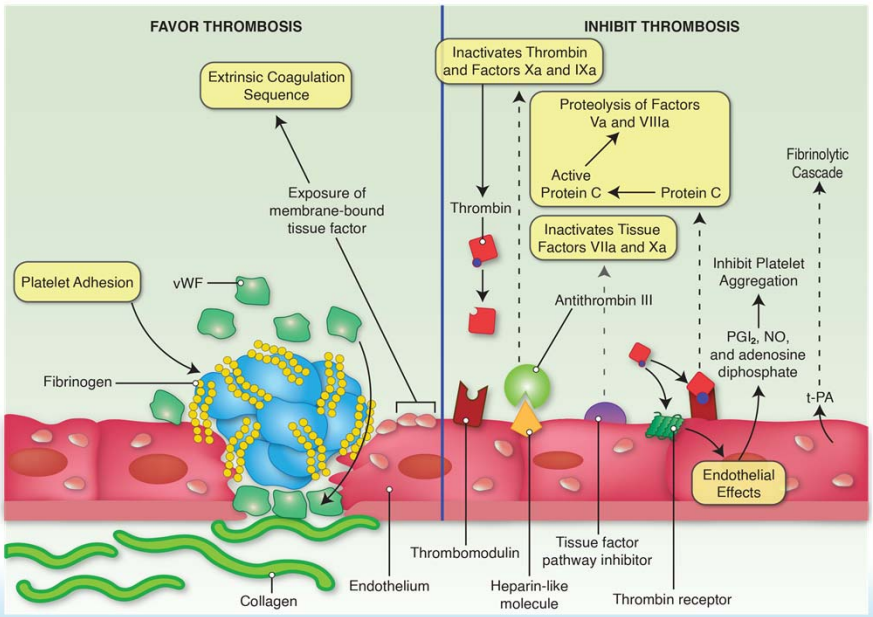
Modulation of Clot Formation



MBBS Medicine. http://medicinembbs.blogspot.com/2011/02/normal-hemostasis.html

You can imagine that if you had a car that only had a gas pedal, it would be very hard to control that car and you would be likely to get out of control, and the same thing is true for the blood clotting process. In addition to those factors that favor thrombosis, which we've just reviewed, and are summarized on the left hand of this diagram here, we've also got some factors that inhibit thrombosis or modulate that process to keep it from getting out of control.

An important thing that I want to point out is that the healthy endothelium that is next to where the clot is forming is very important in this process, and it has substances available, things like antithrombin, tissue factor pathway inhibitor, thrombomodulin, and all of these things then contribute to a braking mechanism on the formation of clotting that keeps that process hopefully highly contained to where the site of injury is and does not start a general thrombosis that could then cause blood flow blockage and ischemia, which would be problematic.

At the far-right hand of this diagram, you can see that healthy endothelium also secretes tissue plasminogen activator, which then initiates the fibrinolytic process, and we'll say a little bit more about that at a later slide, but that helps to dissolve the blood clot when it's no longer needed.

Obesity and VTE

- Obesity produces a low-grade chronic inflammatory state
- This chronic state of inflammation is associated with:
  - Endothelial damage and dysfunction
  - ”Angrier” platelets (increased platelet reactivity)
  - Enhanced coagulability
  - Impaired thrombolysis
- These changes translate into increased risk of VTE

Now, let's focus on why obesity is a risk factor for the development of venous thromboembolism or blood clots that form in the deep veins of venous circulation. At a high level, obesity produces a very low-grade chronic inflammatory state. I'll explain in the next slides why that is important. That state of inflammation then is associated with endothelial damage and dysfunction. Platelets that are "angrier" or more likely to aggregate together and produce thrombosis enhance coagulability so that clotting factor cascade gets ramped up, and then also impairs the ability of the body to break down any clot that's formed. All of these things then translate together into a heightened risk for venous thromboembolism in patients that have obesity.

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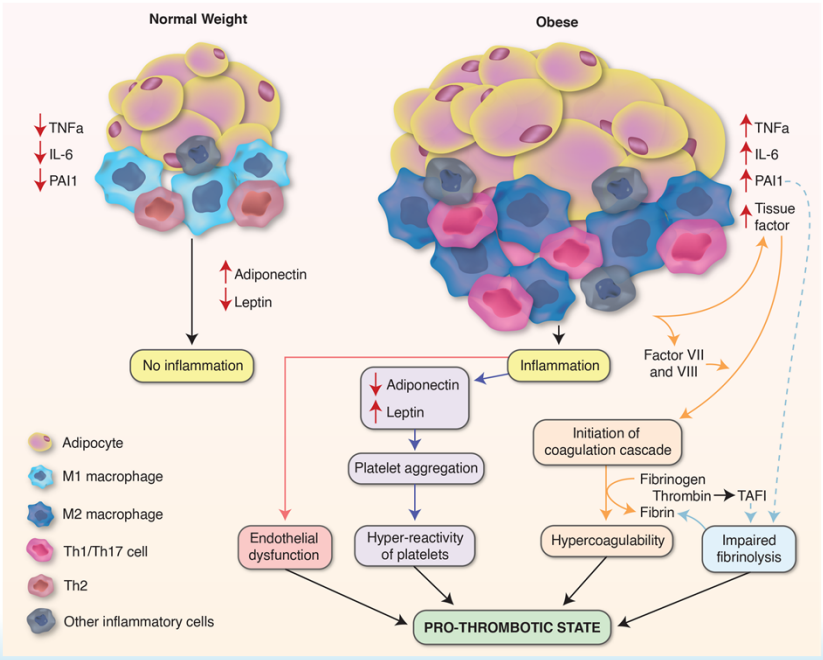

Vilahur G, et al. *Cardiovasc Res*. 2017;113(9):1046-1054.

In this diagram, you can see that compared to a normal weight individual, there is just much more inflammatory cell activity just in volume and also in the types of inflammatory cells that are associated with the condition of obesity. Those inflammatory cells then can release different types of cytokines and other inflammatory modulators that translate then into several different things. This is a review somewhat to the slide that we just went over, but endothelial dysfunction is one of those things, differences in platelet reactivity, a heightened sensor as I said before, angrier platelets that are more likely to aggregate together, increased activity of the thrombosis cascade or clotting factors that result in hypercoagulability, and then as I mentioned before, decreased fibrinolysis so any clot that is formed doesn't break down as rapidly. All of those then translate into a prothrombotic state that favors the formation of blood clots. Next, I am going to go over, just briefly, each one of these four different factors that increase clotting risk in venous thromboembolism.

IL-6, Interleukin 6; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin activatable fibrinolysis inhibitor; TNFa, Tumor Necrosis Factor a.

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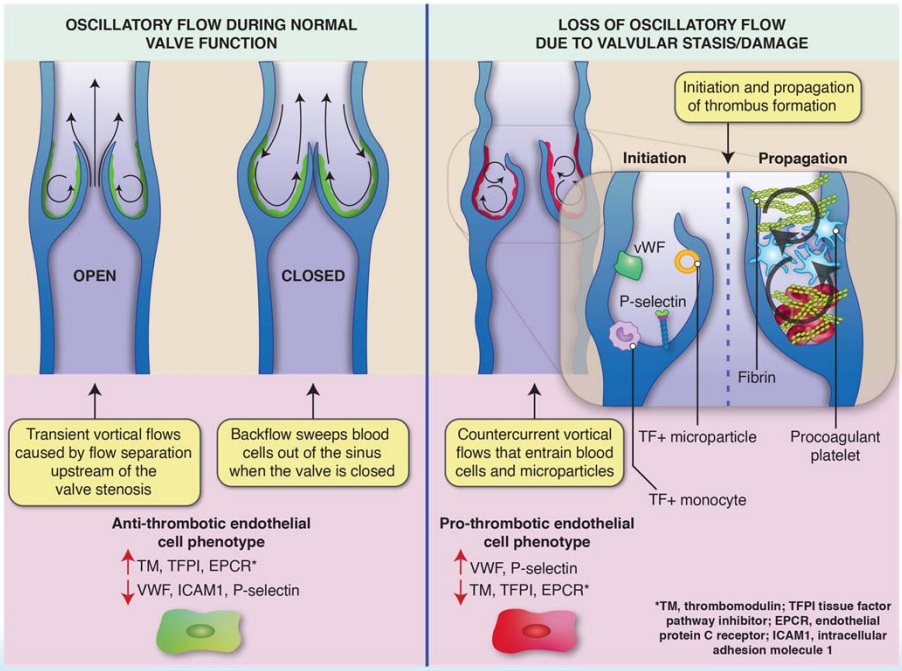
Endothelial Dysfunction



Lin J, et al. *Res Pract Thromb Haemost*. 2021;5(5):e12548.

Let's focus on endothelial dysfunction. On the left side of this diagram, you can see that healthy endothelium plays an important role, and blood flowing through the veins of the lower extremity, there are these one-way valves that help move blood back towards the right side of the heart. As blood flows through those, they then close and you get some sweeping out and clearing out of any blood that might pool in the valve cusps. Healthy endothelium is really important in that process.

In the chronic inflammatory state that is associated with obesity, we get prothrombotic endothelial cell type phenotypes that have many characteristics then that increase the risk of blood clot formation. You can see that depicted in the middle right of the slide. This is important because as blood clots conform in these valve cusps, it caused the valves to then not function as proper, and that further increases the risk for blood clotting.

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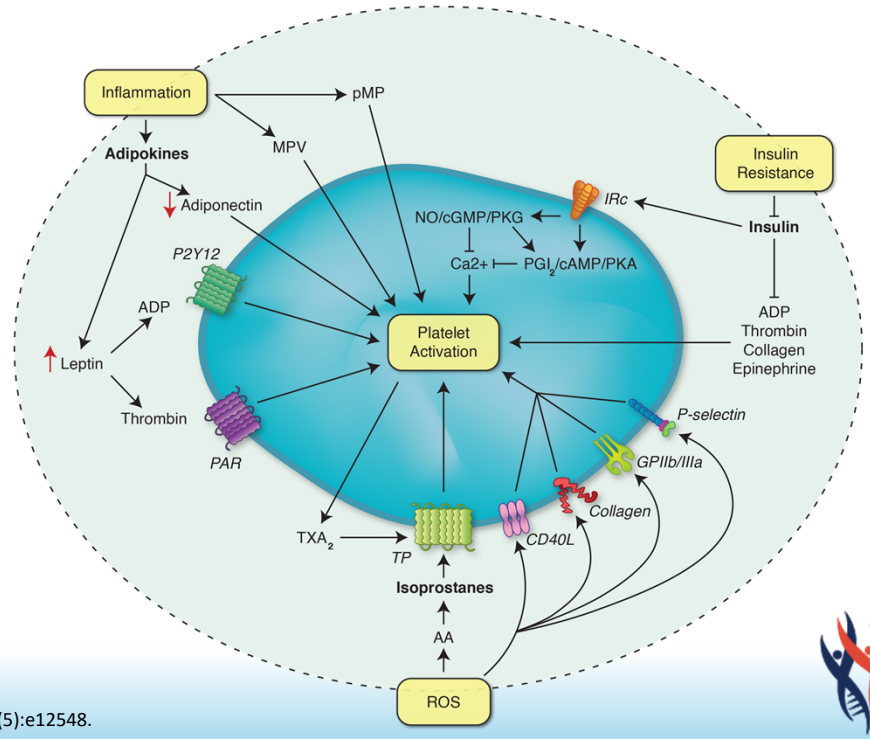
Platelet Hyperreactivity



Lin J, et al. *Res Pract Thromb Haemost*. 2021;5(5):e12548.

Let's focus on platelet hyperreactivity. Three key areas that I want to highlight with this slide is and we've talked about the inflammation that occurs with obesity, but that causes alterations in the secretion of different adipokines, namely, increase in leptin secretion. You can see there that that causes interaction with different receptors on the platelet surface that increase the activation of platelets and make them more likely then to participate in blood clot formation.

On the right top, you can see the insulin resistance. Normally, insulin actually has some properties that decrease the reactivity of platelets, and with obesity and the state of insulin resistance that can be associated with that condition, that removes this blocking mechanism and that also results in platelet activation. Then the formation of reactive oxygen species can also cause interactions through the arachidonic acid cascade with various receptors on the platelet, all of these things translating into platelets that are more likely to aggregate together and recruit other platelets to get involved with the clot formation process.

AA, arachidonic acid; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; IRc, Insulin receptor; MPV, mean platelet volume; NO, nitric oxide; ROS, reactive oxygen species; pMP, platelet-derived microparticles; TP, thromboxane receptor; PK, proten kinase; PGI2, prostacyclin; TXA2, thromboxane A2

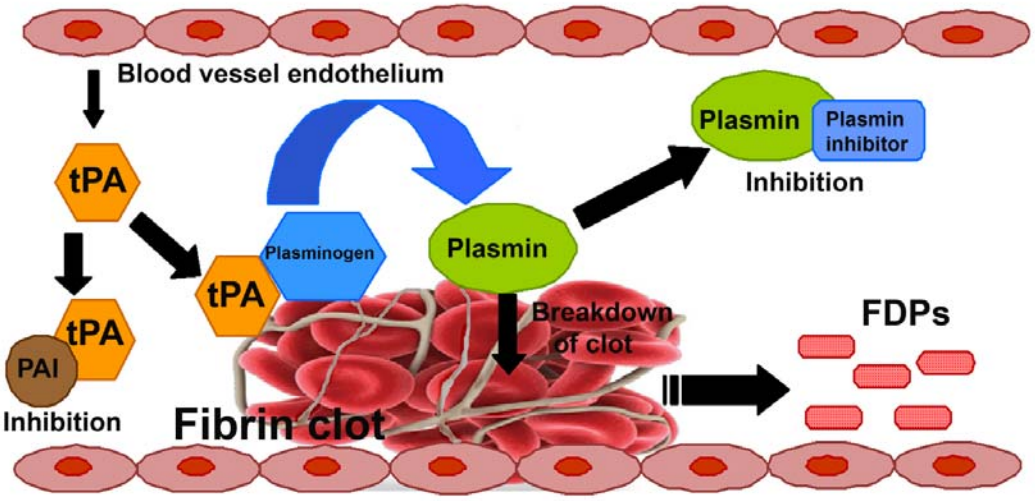
Hypercoagulability

- Obesity is characterized by increases in several molecules involved in clot formation, including:
  - Tissue factor
  - Fibrinogen
  - von Willebrand factor
  - Factors VII and VIII

In terms of hypercoagulability, there are several different molecules within the coagulation cascade that are increased or altered in obesity. An important one is tissue factor. Tissue factor can be considered the fuse that really lights the coagulation cascade and gets it going. Increased tissue factor concentrations can also increase the potential for clot formation. Fibrinogen is the precursor of those fibrin strands that are used to form the stable clot. If there's more fibrinogen around, there's more potential for fibrin to be formed. Von Willebrand factor is what attracts the platelets, so that is another factor that increases platelet activity. Then Factor VII and Factor VIII are important components of the clotting factor cascade that get increased, thus increasing the potential that we're going to get fibrin clot formation and increased risk for pathologic clot in the lower extremities.

VTE Pathophysiology and DOAC Pharmacokinetics in Obesity

Fibrinolytic Process



Kolev K (Ed.) (2014). *Fibrinolysis and Thrombolysis*. IntechOpen. https://doi.org/10.5772/57039

This slide gives a depiction of the fibrinolytic process. As we discussed before, healthy endothelium releases tissue plasminogen activator or TPA on this slide. It converts plasminogen into plasmin, and plasmin is what helps to break down those fibrin strands and help dissolve the blood clot. Plasminogen activator inhibitor depicted in the bottom left of this diagram in the brown, PAI, that is an important inhibitor of tissue plasminogen activator. In obesity, we get a dramatic upregulation of the activity of plasminogen activator inhibitor, which then decreases the action of TPA, thus making it more difficult for a clot that is formed to break down. The net result of that is just increased clot burden and greater potential for clot formation.

Obesity and Virchow's Triad

Hypercoagulability	Increased von Willebrand factor Increased fibrinogen Increased PAI-1 Increased thrombin-antithrombin levels Increased platelet reactivity Increased procoagulant microparticles Increase tissue factor expression
Stasis	? Increased due to larger vein size ? Impaired function of venous valves ? Increased due to local venous pressure
Vessel wall damage	Endothelial dysfunction due to chronic low-level inflammation

Adapted from Hunt B. *Semin Thromb Hemost.* 2018;44:632-639

A really helpful construct to think about the increased risk for blood clotting is something called Virchow's Triad. What this hypothesizes is that there are three sides of a triangle here; hypercoagulability of blood, stasis of blood, and then damage to blood vessel walls. If any of those components, and especially if more than one of those components are involved, that increases the risk for pathologic blood clot formation. You can see that with obesity, we hit on almost all of those elements of Virchow's Triad. We've just been over in pretty good detail, the top one there, the hypercoagulability, all the different derangements that we just talked about, and down at the bottom, blood vessel wall damage as well. That is something that is associated with obesity and the inflammation that goes on during that condition.

In terms of stasis of blood, although this is a little less well characterized than some of the other ones, it could be that the blood is more static because of the larger vein size that is associated with obese individuals. It could be that there is impaired function of those venous valves, as was demonstrated in the slide that we looked at just a moment ago, and there could be increased pressure within the veins making it harder for the blood to get back up towards the heart. When that blood pools in the lower extremities, that increases the risk for blood clot formation. It's important to realize that nearly all of the elements of Virchow's Triad are impaired in obesity.

Obesity and VTE Risk

- Pro-inflammatory and pro-thrombotic environment makes obesity an independent risk factor for VTE; **by two- to six-fold**
- Presence of other risk factors for VTE increases risk even more:
  - Hospitalization
  - Pregnancy
  - Combined estrogen-progestin hormonal contraceptive use
  - Immobility
  - Others
- Many of the obesity-related changes that increase VTE risk are reversible with weight loss

This translates to an almost two- to six-fold increase in risk for venous thromboembolism in individuals with obesity. That's important because that combines with other risk factors, like if an individual is hospitalized, patients who are pregnant, patients who are taking combined estrogen-progestin hormonal contraceptives, those who are immobile for whatever reason, a plaster cast, hospitalization, those types of things. There are many other types of risk factors, all of these things combined together with risk factors to increase the risk for venous thromboembolism in patients with obesity. I think it's important for us to recognize that many of these obesity-related changes can be reversible with weight loss. That's something that I think can be an important educational point as we're working with our patients who have suffered venous thromboembolism, if obesity is among the risk factors.

Obesity: Impact on Drug Absorption, Distribution, Metabolism, and Excretion (ADME)

- Obesity has significant impact on organs/organ functions involved in ADME of drugs
- Before the DOACs, anticoagulants were dosed according to either laboratory testing (warfarin, unfractionated heparin) or by weight (low molecular weight heparin)
- Fixed-dose DOACs present a clinical challenge as dosing is not based on weight or labs

Now, I want to shift gears just a little bit and talk about the impact that obesity might have on the pharmacokinetics of direct oral anticoagulants. Direct oral anticoagulants are newer drugs. The standard drug was warfarin and different types of heparin, that these newer drugs, the direct oral anticoagulants, which I'm going to refer to from here on out as DOACs, just so it's a little easier to say. Obesity can have a significant impact on different pharmacokinetic parameters.

What do I mean when I talk about pharmacokinetics? These are things like how drugs are absorbed, distributed throughout the body, metabolized or broken down, and then excreted from the body, so ADME. Now, with the older drugs that we used to use, like warfarin, and especially unfractionated heparin, we actually would use a blood test to monitor the effects of these drugs. When you are given a dose of warfarin, you could tell if you are given the right dose because you would order a blood test and see if it was in the right range, same thing with heparin, or with the newer low-molecular-weight heparins, you would actually then base them on the patient's weight. These two things made us a little less leery about using these types of drugs inpatients at different weights, and especially those at the extremes of weight, very low weight or very heavy. Along came to fixed-dose DOAC drugs and this threw a little bit of a wrench into the status quo because now we've got a fixed dose of drug, but potentially differences in the way that these drugs are handled in the body, and that makes them a little bit more clinically challenging to use, or at least we didn't have a lot of information about how these drugs might perform in patients at the extremes of the weight spectrum.

Obesity-related Changes in ADME

Pharmacokinetic Parameter	Effect of Obesity
Absorption	Not altered with oral drugs
Distribution	V_d increased; weight-adjusted V_d may decrease for some drugs V_d will be markedly increased in obesity for highly lipophilic drugs
Metabolism	Drug clearance increases somewhat proportionally with body weight CYP 3A4 activity may decrease
Excretion	Increases in V_d and/or decreases in clearance can prolong half-life

Some of the obesity-related changes that we can expect with ADME is absorption doesn't tend to really be affected. With distribution though, you can imagine that a drug that is lipophilic or that dissolves well in fat, if there's just a greater burden of adipose tissue in an obese individual, it just means that there's more drug that could then disperse, and to fill up that space, and that might then result in lower levels of the drug actually in the blood. There can also be some differences in volume of distribution if we adjust things based on weight.

The important thing to remember here is that the volume of distribution is generally going to increase for lipophilic drugs in obese individuals. The clearance of drug from the body, their metabolism in liver, or other types of breakdown of drugs sometimes increases proportionately with body weight, and an important metabolizing agent for the DOACs is CYP 3A4, and that activity might actually decrease. It's hard to predict what the actual net effect of this is going to be in an obese individual, and I'll go over that in just a second. As far as excretion is concerned, either elimination in the urine or in the bile, we can get increases or decreases in clearance. We might see prolonged half-lives, or we can actually see decreases in half-lives. Again, the uncertainty of how an individual patient is going to respond to a DOAC with the fixed-dose gives us some cause for concern.

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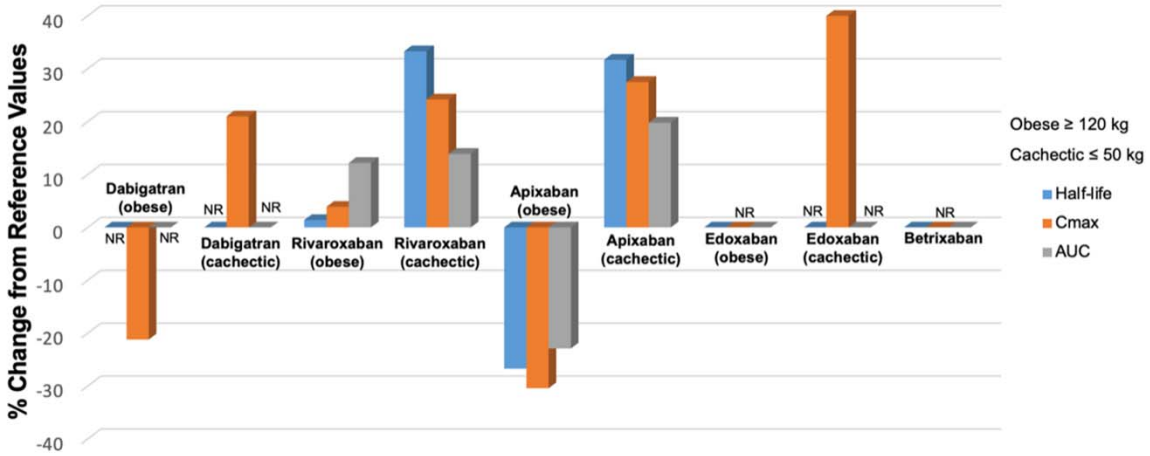
DOAC Drug Exposure and Clearance in Obesity



Chen A, et al. *J Am Heart Assoc.* 2020;9:e017559.

In this slide, it's actually focused on both low-weight individuals and obese individuals, but we're going to focus in on the obese individuals. Starting at the left hand of the slide, you can see that in obese individuals, dabigatran, the maximum concentration in the plasma has actually decreased in the obese state, whereas with rivaroxaban, we see the opposite effect. We actually see some increases in the exposure to drug for a patient. Then with the apixaban, we see the opposite. Again, decreases in some of these pharmacokinetic parameters, indicating that maybe we're not achieving the levels of drugs that we would in a normal weight individual. With edoxaban, we just don't have a whole lot of information. The key takeaway point from this slide is that it's hard to know what the net effect is going to be in any individual obese patient, and that's why I think we're a little nervous when we were using a fixed dose of drug.

VTE Pathophysiology and DOAC Pharmacokinetics in Obesity

DOACs: Pharmacokinetic Parameters

Medication	Absorption	Distribution	Metabolism	Excretion
Dabigatran	3%-7%	Vd: 50-70 L; 35% PPB	Hepatic	Urine (80%)
Rivaroxaban	10 mg: 80%-100%; 20 mg: 66%	Vd: 50 L; 92-95% PPB	Hepatic	Urine (66%) and feces
Apixaban	50%	Vd: 21 L; 87% PPB	Hepatic	Urine (27%) and feces
Edoxaban	62%	Vd: 107 L; 55% PPB	Hepatic	Urine (50%) and feces

Abbreviations: PPB, plasma protein bound; Vd, volume of distribution.

- Apixaban: lowest Vd and renal elimination
- Rivaroxaban: highest protein binding
- Based on PK alterations seen in high BW/BMI patients, DOACs with low Vd, high protein binding, and limited renal elimination are least likely to be affected by weight

Sebaaly J, Kelley D. *Ann Pharmacother*. 2020;54(11):1144-1158.

Pharmacokinetic principles would lead us to believe then that in high body weight individuals, probably the profile that we're looking for is a DOAC that has a low volume of distribution, high protein binding, and limited renal elimination. Those things might then confer some favorable properties to help us to conclude that we're not going to see much difference between obese individuals and normal-weight individuals.

If you look at the table at the top of the slide there, you can see that apixaban is the drug that has the volume of distribution and renal elimination, whereas rivaroxaban has the highest protein binding. Maybe those are drugs that if we're going to use in obese individuals might have the most favorable pharmacokinetic profile.

Unanswered Questions

- Do alterations in DOAC pharmacokinetic parameters associated with obesity translate into clinically relevant changes in VTE outcomes?
- Are DOACs narrow therapeutic index drugs similar to warfarin and unfractionated heparin?
  - There is evidence to suggest a much wider therapeutic index with DOACs
    - Comparable outcomes to dose-adjusted warfarin with fixed DOAC dosing
    - Use of higher DOAC doses at the initiation of VTE
    - Use of lower DOAC doses for VTE maintenance treatment
- Does the “obesity paradox” apply to DOAC use in obese patients?
  - Obesity in older subjects or in patients with several chronic diseases may be protective and associated with decreased mortality

All right, as we begin to wrap up the presentation for today, let's focus on some unanswered questions. We've talked about alterations in DOAC pharmacokinetic parameters. The real question is, are these associated with different outcomes in obese individuals compared to normal-weight individuals? Unfortunately, in the clinical trials for these drugs, there were not many patients at the extremes of body weight, including high-weight individuals that were included. So, we really don't know if we're going to see any differences in the outcomes. Although emerging evidence would lead us to believe that there appears to be not big changes in the outcomes associated with extremes in weight.

Now, the prior drugs that we've used, historically warfarin and heparin, are associated with a narrow therapeutic index. What I mean by that is the difference between a drug that would produce toxicity or increased bleeding risk, and the dose of drug that would produce the desired therapeutic effect is small. We're used to that paradigm of anticoagulants associated with the narrow therapeutic index. There's evidence to suggest that with the DOACs, we may not be dealing with a narrow therapeutic index drug. For instance, we know that from the clinical trials using a fixed dose of these medications produce similar clinical outcomes, or in some cases, better clinical outcomes, than using closely monitored warfarin therapy. That's one line of evidence to indicate that they may not have the same type of narrow therapeutic index that warfarin does.

A second line of evidence is when we initiate therapy for venous thromboembolism treatment with these drugs, we actually start out with much higher doses of the drugs. In the case of apixaban, we actually give double the dose. Now that just wouldn't happen with warfarin. If you gave double the dose of warfarin to a patient, you would likely very much increase the risk for bleeding, but that doesn't seem to be the case with the DOACs. That's another line of evidence to suggest a wider therapeutic index.

Also, as we've treated patients with venous thromboembolic disease, after three to six months, we can actually half the dose of the DOAC, and not seem to really influence how well it does at preventing further risk for blood clotting. All of these things might indicate that with DOACs, we have a much wider therapeutic index, meaning that some of the changes that we actually observe in the absorption, distribution, metabolism, and excretion of these drugs with obesity may not translate into meaningful differences in how well they're actually going to perform clinically.

Finally, there's a thing known as the obesity paradox. What that means is that obesity in some subjects with several chronic diseases has actually been associated with decreased mortality. That's unknown why that actually is, but there's some theory behind that. It also seems to apply to the use of DOACs in obese patients, meaning that we were very worried that we'd see different outcomes with obese patients. The pharmacoepidemiologic data that we've had heretofore is indicating that obese patients might actually do better than patients that are normal weight.

Back to Our Patient

Patient Notes

- 56-year-old male with history of DVT now with new DVT of left common femoral vein
- Clinically stable
- Weight: (!) 172.8 kg (380 lb 15.3 oz); BMI 49

To wrap up, let's go back to our patient case. Remember, we had a 56-year-old man that was presenting with an acute DVT in his left common femoral vein, and he was quite obese.

Polling Question #2

What pathophysiologic mechanisms relating to this patient's obesity may have contributed to increased risk for venous thromboembolism?

A. Chronic low-grade inflammation
B. Platelet activation
C. Vascular endothelial dysfunction
D. All of the above

Now that you've gone through this activity, let's ask the same question.

What pathophysiologic mechanisms relating to his obesity may have contributed to his increased risk for having this blood clot?

A. Chronic low-grade inflammation
B. Platelet activation
C. Vascular endothelial dysfunction
D. All of the above?

Answer A is correct because adipose tissue from obese individuals is associated with changes to various inflammatory cells that induce a systemic inflammatory response (increase in cytokine release). Answer B is also correct because the increased cytokine release results in impaired endothelial function. Answer C is also correct because obesity is associated with increased levels of tissue factor and certain clotting factors and impairment of fibrinolysis (mediated through increased levels of PAI-1). The net result of these changes is a prothrombotic state. Because answers A, B, and C are all correct, the best answer to this question is answer D (all of the above).

Hopefully, through participating in this activity, you're feeling much more confident with your answer. Thank you for taking the time to participate in this activity today.

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