[MUSIC PLAYING]

JESSICA BERGER: Today, we're going to talk about VTE treatment, and prevention, and malignancy. This is an important topic in our patient population. This is something that comes up not infrequently both in the inpatient and outpatient services. And we all deal with patients that have this problem. And so it's important to all of us. But we're going to focus on the treatment of VTE in the cancer population today.

The objectives I have is to discuss the incidence, risk factors, and evaluation for VTE in our cancer population. We're going to talk about prevention strategies based on different risk groups. And so we'll talk about hospitalized cancer patients and prophylaxis around the perioperative period, which I feel like are commonly discussed.

We're also going to talk about the ambulatory cancer patient, so the outpatient with cancer who is undergoing chemotherapy. And then, we'll talk about the efficacy and risk factors-- I'm sorry-- efficacy and risks of therapeutic anticoagulation options for patients with cancer, as well as indications for IVC filter replacement. These things have changed dramatically over the recent years. And we've come a long way from heparin bridge to Coumadin.

So first, let's talk about the scope of the problem. VTE is increased significantly in the cancer patient population. Malignancy can increase the risk of thromboembolism by several mechanisms. Part of this is just the [INAUDIBLE] mechanisms. Cancer makes you more susceptible to clot. And that can happen for a number of reasons. There's different cancer pro-coagulants that have been found in the bloodstream. There's increased circulating tissue factor in the bloodstream.

Other structural mechanisms can increase the risk of venous clot-- compression by tumor in the pelvis, comorbidities that these patients have. Patients who have cancer tend to be older. They're more likely to be obese. They may have immobility issues. And then as part of their cancer treatment, they also may be predisposed to clot formation, either by a central line placement or even the drugs that they're on for cancer treatment. And common drugs can be things like high dose steroids. Sometimes, antineoplastic agents such as the antiangiogenesis agents like bevacizumab can increase clot risk, and hormonal agents, things like tamoxifen or megace.

So estimates vary between 4% and 20% for all comers with cancer. And certain cancers are a higher risk than other cancers. So the very high risk category includes things like pancreatic and stomach cancer. Gynecologic cancers fall into the high risk category along with other cancers like long lymphoma, bladder, and testicular cancer. And patients with cancer are at highest risk for blood clots at diagnosis as well as during treatment. And then they can also be at high risk for blood clot at time of recurrence. And this correlates and is related to tumor burden.

You can see in the gynecologic cancer population though risks are high and we're in that high risk category, they vary significantly. And so this is a table that I put together from several different studies reporting venothromboembolic rates. And if you look in the first category, there's both early stage and advanced stage cancers. And you can see that with advanced stage, the risk goes up dramatically.

But you can also differentiate this by histotype. So clear cell cancers are particularly notorious for being thrombogenic cancers. And if you compare in each stage category, clear cell tends to be a higher risk for clot than serous. And if you look at the advanced stage clear cell, that's a very high risk of clot. And your advanced age clear cell patients, nearly half of them are going to have a blood clot at some point in their treatment.

In the post op period, patients that are having an open cancer surgery are at fairly high risk, up to 12%. We have improved this with offering extended prophylaxis to these patients, and so have cut this in less than half, so just under 5%. But then, if you look at our MIS endometrial patient population, these are outpatients that are having minimally invasive hysterectomy at staging. Their risk can be as low as 2% or even less than 1%. And so there's a range of risks in our patient population.

This last category came from a retrospective study that was very simply done but illuminating. It was done in the neoadjuvant ovarian cancer population. And we're going to talk about this in a little bit more detail later. But this is a particularly high risk patient population. And this study divided VTE diagnosis during different stages of treatment. Interestingly, you can see the post-operative period, the period we worry about most and our most aggressive with thromboprophylaxis has the lowest rates, probably for that reason that we intervene here, but have opportunities for intervention at other stages of treatment as well.

So we're just going to briefly talk about how we recognize blood clots, how we evaluate them before we talk about preventing and treating them, just as a quick review. This is a lot of stuff that most of us know. But signs and symptoms of a blood clot can include lower extremity symptoms like leg pain, swelling, warmth. We oftentimes will see lefts more commonly than right blood clots due to the venous anatomy, crossing under the arterial anatomy in the pelvis. This is a site that is at risk for compression of an enlarged uterus, whether that's from tumor, fibroids, pregnancy.

Chest symptoms can include dyspnea, pleuritic chest pain, cough, hemoptysis. Patients can have low grade fever, can have tachycardia, tachypnea, hypoxia. But not all patients follow the classic presentation. And so other less common signs that we've seen patients that are post op that have new [AUDIO OUT] with RVR. That can be a sign of a new blood clot or incidental right heart strain seen on an echo for other purposes sometimes can be a sign of a pulmonary embolism.

The evaluation for a DVT or PE has fairly set algorithms. We don't necessarily always formally employ these algorithms when we're making decisions. But I think it's worthwhile going through what they are. This usually starts with determining your pre-test probability. So how worried are you about a clot? And we can do this qualitatively, but there are also quantitative ways to do this with Wells scoring. And I'll show you what the Wells scoring looks like for both DVT and PE.

When evaluating concern for a DVT, you can use the Wells scoring to determine whether your patient falls into a low, moderate, or high risk category. For the low or moderate risk, a D-dimer can then be used to determine which patients need further testing with the Doppler ultrasound versus which ones can just be observed.

D-dimer is a little difficult in the cancer population as well as other populations like the pregnant population, because this can be falsely elevated. And so this is not particularly useful for cancer patients, because it might be elevated just due to the cancer. And that is an indication to not use this. And so we will not infrequently completely skip this step and just go straight to Doppler ultrasound. And then, in the high risk category, going straight to Doppler ultrasound is recommended.

When evaluating for a pulmonary embolus, there is also Wells scoring for this. Again, divides into low, moderate, or high risk. In the low risk category, there is a PERC rule. This is new information for me. I go through what these criteria are, but this is a set of eight criteria where if your patient is low risk on Wells scoring and does not need any of the PERC criteria, you can actually stop there.

If they do meet any of the PERC criteria, you can go to D-dimer testing. Again, this stratifies at the 500 nanogram per milliliter cutoff. If they are above this, then going on to diagnostic testing is recommended. And we've talked about the limitations of D-dimer for the cancer population. Moderate risk, you skip that PERC rule and go right to D-dimer. And high risk, you go straight to diagnostic testing.

So this is the Wells criteria. You get point assignments for [AUDIO OUT] risk criteria. You add up those points. You actually can lose points if you have a likely alternative diagnosis. So you had a recent crush injury to your leg, and that's why it is swollen. And you have muscle damage. Still could consider a clot, but you can lose points for that.

These are the criteria for pulmonary embolism. And there is both the Wells criteria and the modified Wells criteria. The Wells criteria divides into the high, moderate, and low categories. If you use the modified Wells probability, it just divides it at four. So four less is unlikely to be a PE, and four or more, likely. We tend to use the general Wells criteria for the algorithm but can use either.

And these are the criteria for the PERC rule. Again, this is for evaluating a pulmonary embolus in a low risk Wells scoring patient. If they meet any of these criteria, then you need to go on to either D-dimer testing or diagnostic testing.

So when you are thinking about diagnostic testing for a pulmonary embolus, one of the things you have to think about is whether or not your patient requires empiric anticoagulation. And again, this is sometimes the stuff that we don't explicitly line out in our algorithm for working these up. But if your patient has suspicion for a pulmonary embolus and is unstable or has very poor cardiopulmonary reserve, this is a patient you might want to put on empiric anticoagulation while you're doing your workup.

Also, if there's going to be a delay in their testing for some reason. For example, if they have a severe contrast allergy and need to be pre-medicated and are a high risk patient, putting them on anticoagulation for the 13 hours that you're going to have to pre-treat them might be warranted. The gold standard for diagnostic testing for a pulmonary embolus is CT angiography. This is the standard of care. It is highly sensitive and highly specific. It also has the benefit of helping to determine alternate causes of symptoms if they are negative for a PE.

Contraindications to this can include an iodine allergy. Many of these patients can be pre-medicated to overcome this, but some cannot. Patients with renal insufficiency may not be able to tolerate a contrast load. Or if your patient is hemodynamically unstable, you may not be able to proceed with diagnostic testing and have to just treat them empirically.

For patients that can't have a CT angiography but are stable, a ventilation-perfusion scan is an alternative. This is generally recommended only for whom a CTA is contraindicated, because it has limited usefulness. The table below shows how you interpret a VQ scan result. This is predicated on having a normal chest X-ray headed into the scan, or you can have false positive or uninterpretable results.

And so then you use your clinical pre-test probability of emboli, either high, intermediate, or low, and compare that to your VQ scan results, which are reported as normal, low probability, intermediate probability, or high probability. A VQ scan can be helpful in a scenario where you have a high clinical probability of emboli, and your VQ scan results are high. So it's good at ruling in what you're already worried about. It is also good at ruling out what you are not that worried about, so if you have a low pre-test probability, and your VQ scan comes back normal or low.

What it is not helpful for is patients for whom you're worried about a PE but don't have a high pre-test probability, and it comes back intermediate. Other testing that can be useful in this situation, venography is the historical standard of care. We don't do that anymore, because it's invasive and difficult. Echocardiography can also be helpful as an adjunct but is pretty limited in its usefulness for diagnostic testing. You can sometimes actually see blood clot on the echo, but that's a pretty big blood clot. And it's pretty proximal and usually can only be seen on a transesophageal echo.

So getting on to our next topic, we're going to talk about pharmacologic prophylaxis, preventing clots in this high risk population. And we'll talk about the hospitalized cancer patient first, then perioperative and extended prophylaxis, and last the ambulatory oncology patient.

I just want to take a minute to review the biologic process that we're talking about. This is the clotting cascade. I know this strikes fear in some people's hearts still. I don't like looking at this, but I think it's useful [AUDIO OUT] review quickly the extrinsic and intrinsic pathways of the clotting cascade and where the drugs work that we use. And I don't know if you guys can see my mouse.

But in the extrinsic pathway, this is the pathway that is best measured by a PT and is mediated by tissue factor. Warfarin works proximally in this pathway on factor VII. Warfarin also works on factor II, prothrombin, factor IX, and factor X. This is our historic gold standard anticoagulant, the vitamin K antagonist. Our newer agents, first heparin. Heparin works by potentiating antithrombin III and working on Xa to inhibit thrombin production. And then our newer oral agents, the Xa inhibitors and the direct thrombin inhibitors, work here. And so you can see that all of these drugs work on the central portion of this clotting cascade here.

And then I just have a list of the different anticoagulants that we use and how they work. And their trade names are also listed there for those of us that are not as familiar with some of the less commonly used ones. We talk [AUDIO OUT] heparin. This works through potentiation of antithrombin III, inhibiting factor Xa and thrombin formation.

The low molecular weight heparins work in a similar fashion. These are drugs like enoxaparin which we use routinely and dalteparin which is Fragmin. Fondaparinux, or Arixtra, we don't use that often. This is a synthetic heparinoid that has a very similar mechanism of action to the heparins and low molecular weight heparins.

Warfarin is our good old fashioned, cheap, used forever vitamin K antagonist. This was discovered at the University of Wisconsin and is named after the Wisconsin Alumni Research Foundation, interestingly. And this inhibits factor II, VII, IX, X, and also protein C and S. The vitamin K antagonists category requires bridging with a heparin due to its delayed onset. It usually takes about five days or so to get a therapeutic anticoagulant effect using this. And so you do need to bridge with either an unfractionated heparin or low molecular weight heparin when using this.

And then our newer agents, the direct oral anticoagulants, or DOACs, these include both the direct factor Xa inhibitors, rivaroxaban which is the Xarelto, apixaban which is Eliquis, and edoxaban which is Savaysa. I don't know how to say that actually. And then the direct thrombin inhibitors, which we don't use nearly as frequently, dabigatran which is Pradaxa is an oral drug. I put argatroban on here. This is actually an IV infusion, but it's also a direct thrombin inhibitor. All right.

So prophylaxis for our hospitalized cancer patients-- we have very good guidelines outlined by numerous organizations. The American Society of Clinical Oncology has very clear guidelines on both prophylaxis and treatment in the cancer populations. I've included those here. Other institutions have guidelines as well, the National Comprehensive Cancer Network and others.

The ASCO Guidelines recommend pharmacologic thromboprophylaxis for hospitalized cancer patients with medical illness or other risk factors. So most hospitalized cancer patients are going to require pharmacologic thromboprophylaxis. This doesn't necessarily extend to every hospitalized cancer patient. Patients being admitted for a minor procedure or a short chemotherapy infusion may not need a pharmacologic agent for prophylaxis.

The preferred agents for this are the heparins, low molecular weight heparins, or fondaparinux. This data is extrapolated from a general medical population at high risk for blood clots and did include cancer patients but was not studied exclusively in cancer patients. And so this data comes from the MAGELLEN trial and the ADOPT trial. These were both randomized controlled trials.

They both compared a DOAC to a low molecular weight heparin. The MAGELLEN trial used rivaroxaban. The ADOPT trial used apixaban. Both trials showed a similar VTE rate when comparing DOACs to low molecular weight heparins. But there was more clinically significant bleeding in the DOAC groups in both of these trials. And for that reason, the low molecular weight heparins--

FEMALE SPEAKER: [INAUDIBLE] Cool. Thank you.

JESSICA BERGER: --have been maintained as the standard of care. They also have shorter half-lives. And so they're more readily reversible for patients that are in a house that might be undergoing procedures or testing that would require holding their anti [AUDIO OUT].

In the perioperative period for a cancer patient, the ASCO Guidelines suggest that patients undergoing major cancer surgery should have pharmacologic thromboprophylaxis starting before their surgery and continuing for seven to 10 days. Mechanical methods can be added and may increase efficacy when used with a pharmacologic agent but should not be used as monotherapy, unless there's a contraindication to a pharmacologic anticoagulant.

Extended post-operative prophylaxis, the prophylaxis extending from the time of surgery to up to four weeks after, should be considered in those patients who are undergoing major abdominal or pelvic surgery with high risk features. In lower risk settings, extended prophylaxis can be offered on a case by case basis. And so it's very clear from these guidelines, and we'll go through the data for these guidelines, that these patients who are at high risk, they warrant pharmacologic prophylaxis. What is not totally clear is what constitutes a major cancer surgery and which of those warrant extended prophylaxis or not.

So these are three of the major trials that were done looking at extended prophylaxis. The ENOXACAN-II trial was randomized, a randomized trial in open abdominal pelvic surgery. They included GI, GU, and GYN cancers. They looked at enoxaparin for seven days followed by placebo compared to enoxaparin for a 21 day period. And they assessed VTE at the completion of the study by venography. Their 30 day VTE rates were lower, so less than half if you got extended prophylaxis. And there was no difference in bleeding complications.

The CANBESURE trial was very similar. It used a different low molecular weight heparin, similar patient population, also assessed VTE by venography. Had slightly lower rates of VTE, but showed a significant reduction with the extended prophylaxis. And also had similar bleeding events. So it doesn't seem to increase harm with regards to bleeding, but does improve the rates of formation.

And then, the FAME trial was another one. This was done in higher risk cancers. They included GI and hepatobiliary cancers. And so their rates are a little bit higher than the other two trials. They used dalteparin in a similar fashion, seven days versus 21 days assessed by venography, and showed again about a 50% risk reduction in VTE formation during that perioperative period. And again, similar bleeding events. So this works really well.

A couple of things to note from this, these trials were all done in patients undergoing a laparotomy. They did not include patients that were going through laparoscopic surgery. And none of these trials evaluated other agents. They all used low molecular weight heparins.

So one of the questions that this raises is, what about those patients that don't seem to be at quite as high of risk as our ovarian cancer debulking patients? All the trials were done in open surgery. Those patients have, from the data we've looked at previously, a greater than 10% risk of perioperative DVT. But we don't have good data in the minimally invasive cancer surgery group. What we have is retrospective data from a couple of different sources.

The first listed here is a retrospective study of 1,400 endometrial cancer patients, all who had laparoscopic or robotic hysterectomy. The VTE rates in this group were less than 1%. Only five of the 1,400 patients had a clot. Now, we can expect these numbers to be a lot lower, because this was in a controlled study. There wasn't routine evaluation for clot. Those patients didn't all get venography like in the previous randomized trials, but overall have very, very low rates of VTE in the post op period.

They actually noted that there was no difference between just mechanical prophylaxis and pharmacologic prophylaxis. And the authors of this trial concluded that mechanical prophylaxis alone might be sufficient for this patient population, which is not what we generally recommend, but I think this highlights that this is a very different cancer population as far as VTE risk goes.

Another retrospective study looked at 588 endometrial or cervix cancer patients who were having minimally invasive surgery. The 30 day VTE rate in this retrospective study was 5%, so again confirming a pretty low risk of VTE events in this patient population. And they concluded that the use of extended prophylaxis isn't supported in this low risk population.

We obviously don't want our patients to get blood clots. So why not just give it to everybody? There's toxicity associated with this. Though there's no difference in the major bleeding risk, which is very important and reassuring, there is other toxicity from asking our patients to do injection thromboprophylaxis for four weeks.

One is financial toxicity. This has improved over the years. Lovenox used to be very expensive for some of our patients depending on their insurance coverages, prohibitively expensive for some. It has an impact on quality of life. And it can add stress to caregivers and patients who are already going through a pretty stressful event dealing with a cancer. And it creates additional home health care needs. And so while we can say this is an easy thing for us to do to prevent an event we never want to have happen, we are adding toxicity to our patients that maybe is not as easily measured.

So extended prophylaxis in cancer patients undergoing minimally invasive surgery should be individualized. It should not be recommended flat out for everybody. And you can base this decision on your individual patient's risk. And things that you would want to consider in making this decision are issues like prior VTE, obesity, immobility, what kind of pulmonary reserve they have if they do throw a clot, and other things that might put them at risk for having a clot. Like, say, for example, a clear cell histology endometrial cancer might be at higher risk than a general endometrial related cancer patient.

And then, the last category I want to talk about is prophylaxis for ambulatory cancer patients. The ASCO Guideline for this says, "routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high risk patients." And so this group of patients that we're talking about are cancer patients, outpatient, who are starting chemotherapy.

And there is a risk scoring system called the Khorana score that's available for stratifying outpatients in this situation, again, keeping in mind this isn't for any cancer patient that walks through your door but cancer patients that are going to be going through and initiating chemotherapy. The criteria that go into this score are the primary site of the tumor. So how high risk is the tumor? And this is divided into very high risk stomach/pancreas, high risk, which is where gynecologic cancers fall into, and then other sites.

And then you get points if you have thrombocytosis at diagnosis, leukocytosis at diagnosis, anemia at diagnosis, or a class 2 morbid obesity. And then below the Khorana point scoring, you can see if you have three or more points, you fall into that high risk category. And you have a generally fairly high risk of VTE greater than 5%. In the independent and phase one validation cohorts that are listed third and fourth over here, the rates are higher than in the derivation and validation cohort for developing this tool.

I want to draw your attention to the intermediate category. These are patients that score one point or two points. In an independent cohort, they actually-- this was the only place they reported this. But they actually reported the differential rates for patients with one point versus two points. And there does seem to be a difference. And so some people will include a score of two in the category of patients that may benefit from outpatient thromboprophylaxis.

And this is the trial or the study that I mentioned earlier that was done out of the University of Michigan for patients undergoing neoadjuvant chemotherapy for ovarian cancer. This was not a complicated trial. This was very simple, but it very telling and actually changed practice in our division after it came out. But what they did was they just-- they took all of their ovarian cancer patients who were going through neoadjuvant chemo, meaning chemo before they had surgery.

These by default are patients that are either already at such an advanced stage that they're not going to benefit or might be harmed by a debulking surgery. They have a large tumor volume. They might be medically infirm or have poor performance status. And so these are already a category of cancer patients that are at high risk.

They took the 125 of these patients that were being treated at their institution and looked at who got blood clots and where in their treatment course they got them. And so right off the bat, at diagnosis, 10% of this patient population already had a thromboembolic event during the neoadjuvant chemotherapy period, so a period of somewhere between six to 12 weeks, depending on how many cycles they got. Another 11.5% were diagnosed with a blood clot during the perioperative period.

Around the time of debulking another 5% were diagnosed. This is a smaller time period, also a time period where we routinely offer thromboprophylaxis, and so expectedly would be lower than the other groups. Although, I would point out that this is the one time during treatment where we are pretty aggressive about thromboprophylaxis. And then in the adjuvant setting after surgery, this is now a patient population that has been hopefully optimally cytoreduced or cytoreduced and has a much lower disease burden. We still see another 10% get blood clots during this time period.

And if you add this all up, the approximately six months of time that these patients are going through their cancer treatment, more than a third of them developed a blood clot. I think this represents a very high risk patient population that we treat. When this came out, and we reviewed this data, our division did decide to start offering pharmacologic thromboprophylaxis to neoadjuvant chemotherapy patients with ovarian cancer. And this will hopefully be a quality improvement project in the future, so we can see what those efforts-- how they impacted patients.

I would just also point out that this was-- we're doing this irrespective of Khorana scoring. So the Khorana score of two or higher is useful, but a lot of the patients that fall into this neoadjuvant group that are at high risk don't actually have a Khorana score of two or higher. A lot of them don't. So I think using all of the data that we have available to make this decision is important.

So the trials that support temporal prophylaxis in the outpatient setting, I have a couple for low molecular weight heparin, and then I have a couple for DOACs. So that the two low molecular weight trials are PROTECHT and SAVE-ONCO. These were unselected risk categories of cancer patients that had metastatic advanced cancer that were initiating chemo.

So PROTECHT did include a fair amount of ovarian cancer patients and used nadroparin as its low molecular weight heparin versus placebo for up to four months during treatment. The VTE risk was significantly reduced and had similar bleeding side effects. SAVE-ONCO only had one ovarian cancer patient and included 3,200 patients. Used semuloparin as its low molecular weight heparin versus placebo. Also had a significant reduction in VTE events without increase in major bleeding. And so using a low molecular weight heparin would be a reasonable choice in this patient population.

There's also some evidence for the use of the direct oral anticoagulants. The AVERT trial, this included 25% GYN cancers and 574 patients total. This was risk stratified. So these patients all had a Khorana score of two or higher and were initiating chemo. AVERT used apixaban versus placebo. It had a significant reduction in VTE events but did have more major bleeding events.

And then the Cassini trial had 841 patients also risk stratified. So they used a Khorana score of two or higher. Used rivaroxaban versus placebo and had a significant reduction in VTE, again, with slightly more major bleeding. Although, this was not statistically significant. And so for our patients that were putting on this in our division, we will oftentimes recommend a low molecular weight heparin. But I think [INAUDIBLE] a reasonable alternative if the patient is adverse to an injection medication or there's cost prohibition. Just needs to know that there might be a slight increase in bleeding events. All right.

So then, we're going to move on to the treatment of VTE in the cancer population. This is divided into initial and then long term anticoagulation. We think about anticoagulation in that regard because of the way it was prescribed historically with heparin bridge to warfarin. And so for initial anticoagulation, the ASCO Guidelines recommend low molecular weight heparin unfractionated heparin, fondaparinux, or rivaroxaban.

Low molecular weight heparin [AUDIO OUT] to unfractionated heparin for the first five to seven days of parenteral treatment. And this is based off of a Cochrane meta-analysis comparing trials that used low molecular weight heparins compared to unfractionated heparins. The outcome they looked at was three months mortality. And the difference was not statistically significantly different between the two groups.

But if you look at the plot here, you can see it favored the low molecular weight heparin group. The confidence interval on the risk ratio does cross 1. So it was not statistically significant but was compelling enough for ASCO to recommend the use of low molecular weight heparin rather than unfractionated heparin. Reasons that you might want to use unfractionated heparin instead of low molecular weight would be a patient with renal insufficiency who dosing is going to be difficult, or a patient who is high risk for bleeding, or anticoagulation turned off for procedures.

For long term anticoagulation, ASCO recommends at least six months of treatment with a low molecular weight heparin, edoxaban, or rivaroxaban. I imagine apixaban will be added to this. And we'll talk about the data that came out recently for this. But these are preferred over vitamin K antagonists because of documented improved efficacy. There does seem to be an increase in major bleeding with the DOACs. This is particularly observed in patients that have GI cancers and possibly other genitourinary malignancies or tumors that have a high submucosal tumor burden.

So when we are looking at the trials for agent selection, we're going to go back to the CLOT trial, which compared low molecular weight heparin to the vitamin K antagonists. This was the turning point where we recognized that warfarin wasn't the best choice in cancer patients. The CLOT trial was a randomized controlled trial.

It included 672 patients with cancer who had an acute venothrombolic event. They used dalteparin compared to a low molecular weight heparin followed by warfarin. And patients were followed for six months. The recurrent VTE risk was 9% in the low molecular weight heparin group versus 17%. This represented about a 50% reduction in risk and no change in bleeding events or mortality.

The Cochrane review on this is a meta-analysis of eight randomized controlled trials. There's 2,300 cancer patients that were evaluated comparing low molecular weight heparin to warfarin. Showed similar benefit, a nearly 50% risk reduction with no change in survival and no difference in bleeding. And this is what set the stage as low molecular weight heparin as the standard of care for VTE treatment in the cancer population.

This makes some sense. Warfarin is a drug that is highly dependent on diet, and our cancer population is a population of people who are going through chemotherapy, have intermittent nausea, might have trouble eating due to tumor burden if they have intermittent obstructions or carcinoma ileus. And so you can see quite easily why vitamin K might be hard to maintain-- sorry-- a vitamin K antagonist might be hard to maintain a therapeutic INR in this patient population.

The direct oral anticoagulants have been evaluated. And we'll talk about three studies that looked at this compared to low molecular weight heparin. The general consensus from these trials is that they seem to be comparable in efficacy, but there might be an increased risk of bleeding. The bleeding events seem to be limited to patients with GI cancers but are still something worth noting.

So edoxaban was studied in a non-inferiority RTC with over 1,000 patients with cancer and an acute VTE. They used dalteparin versus a low molecular weight heparin followed by edoxaban. So they did bridge to the DOAC. The recurrent VTE risk was not significantly lower but was numerically lower. And then, edoxaban had more bleeding events.

In select-D, they used rivaroxaban. And this was compared to the low molecular weight heparin dalteparin and included over 400 patients. Again, we had a significant reduction in-- or we had a significant reduction in VTE risk with the DOAC but did have more bleeding events. Most of these were non-major.

And then CARVAGGIO, this was just recently published. And this used apixaban. And so I expect that apixaban will be added to the list that ASCO provides in the future. But apixaban compared to dalteparin, again, similar VTE risk. Seems to work just as well as low molecular weight heparin is due. And in this trial, the major bleeding events were not different.

So overall, it looks like DOACs or low molecular weight heparins are appropriate for treatment of our cancer patients. But the potential risk for increased bleeding has to be discussed and should be considered if you have a patient with, say, a transmural bowel involvement or other mucosal tumor with high tumor burden.

These patients should be treated for at least six months, assuming that there's no contraindication or intolerance. This can be extended through the completion of their cancer treatment. And you should consider extending anybody beyond the six month period who has continued active cancer, because they're going to have that continued increased risk with tumor burden. Also, those that have had a recurrent thromboembolus either during or after anticoagulation therapy should be considered for lifelong treatment.

And then I want to talk briefly just about IVC filter placement, because this has changed over recent years. We used to utilize these much more commonly for patients with blood clots. Currently, the indications for an IVC filter placement include really only patients that have an absolute contraindication to anticoagulation in the setting of a hemodynamically significant pulmonary embolus.

And then it also includes patients who have progression of thrombus despite optimal anticoagulant therapy. So this doesn't mean the patient who progressed through one agent. It means the patient that progressed through multiple agents with following dosing levels and anti-Xa levels and things like that.

No longer are they recommended for patients who need a temporary break from their anticoagulation. So this is our surgery patients. And the reason for this is that they have increasingly been associated with adverse outcomes, not just from procedural related adverse outcomes but from increased clot risk over the long term. And they also shouldn't be used for primary prevention of pulmonary embolism in a patient with a DVT with large clot burden.

Of course, there's extenuating circumstances. So there's no rule that can be followed every single time. If you have a patient with an urgent need to interrupt anticoagulation in the setting of an acute clot that was hemodynamically significant or the patient has exceedingly poor cardiopulmonary reserve, that may be a patient for whom a temporary filter is indicated. But we're putting these in a lot less frequently than we used to. We used to put in temporary filters for patients undergoing surgery fairly regularly.

It's now few and far between that we need to place one of these filters. If you do need to place one, you should utilize your multidisciplinary team. Sometimes, vascular or hematology can be helpful in risk stratifying these patients, or the center for perioperative care can be helpful. And generally, you want to use a retrievable filter. And you want to use it for the shortest duration of time possible.

So whereas, we used to put these in maybe the week before surgery and then they came out six to eight weeks after surgery, now they're put in immediately before surgery, the day of surgery, and taken out as soon as the patient can be reinitiated on anticoagulation, so sometimes even during the same hospitalization for their surgery or a few weeks later.

And then lastly, I just want to talk quickly about the direct oral anticoagulant reversal agents. One of the problems that has come up with increased use of the DOACs is that sometimes our patients come in on these, get admitted to the hospital. And they either need to go through an urgent procedure or they come in with life threatening bleeding. And they're on these agents where as when they were on warfarin, we could easily reverse that with FFP or vitamin K. We could use protamine if we needed to reverse heparin or even partially reverse Lovenox if it was really urgent.

It's harder to know what to do with these direct oral anticoagulants. And so there are reversal agents for these, but they are difficult to use and can be very expensive. And so one of the things that can be used to help partially reverse the DOAC's prothrombin complex concentrate. There's a couple of commercially available products, but they have clotting factors in them. Some of them have four clotting factors. Some have three. There's different products but generally are the vitamin K dependent clotting factors.

For the factor Xa inhibitors, apixaban and rivaroxaban, there's a reversal agent called adexicant-- let's see-- andexanet. It's complicated to use. You have to know what dose your patient's on, when they last took it. And you can see in this graph how you differentiate who needs what dose. There's low dose and high dose. And the dosing schemes are listed above.

This is incredibly expensive. If you look at the amount of drug you would need for either of these protocols, it works out to be about $30,000 to $60,000. I have never used these reversal agents. I'm not even sure, actually, if they're readily available at Magee or not. They are available within our system. And they carry a significant risk of inducing clots when you use them. So you can have venous or arterial clotting events, heart attack, or stroke when you're using them. And so shouldn't be used without the help of an expert consultant, either from hematology and perhaps from the blood bank.

There's also a reversal agent for the thrombin inhibitors, idarucizumab. And this is not nearly as expensive as the factor Xa inhibitor reversal agents. So these exist. We generally, if we have a patient come in on a DOAC, manage the bleeding conservatively, transfuse through it, and wait for these to wear off, which usually takes a couple of days.

So in conclusion, there are cancer patients that are at high risk of VTE, but there is a wide range of risk categories within our gynecologic cancer population ranging from the minimally invasive outpatient [INAUDIBLE] for endometrial cancer, which has a very low risk of clotting, all the way up to our ovarian cancer patient population going through neoadjuvant chemo who has more than a third chance of having a clot at some point during their treatment. And the prevention strategies that we utilize should be individualized by risk. And we should be thoughtful about who we're offering what to and what the consequences of offering that or not offering that are.

So for the hospitalized patient, most of them are going to benefit from a low molecular weight heparin. That's the agent of choice. Perioperatively, low molecular weight heparins or heparins for a short versus extended course, using your judgment. It's left up in the air according to the guidelines. And then, the ambulatory cancer patient, only the very highest risk patients are going to be offered outpatient thromboprophylaxis. And a low molecular weight heparin appears to be the agent of choice for this. Although, a DOAC can be considered with perhaps a slightly increased risk of bleeding.

As far as treatment, either a low molecular weight heparin or a direct oral anticoagulant are appropriate. And treatment should be for six months through active cancer treatment and then lifelong for patients with clots during untreatable recurrence, or progressive cancer, or with a second clot, acknowledging that the DOACs may have a slightly higher risk of bleeding.