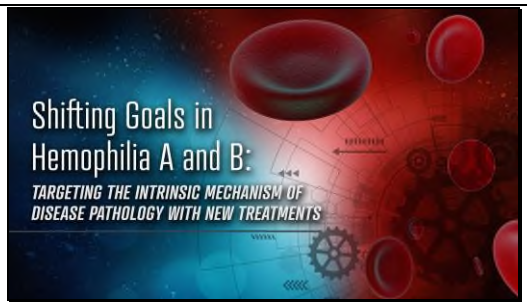
Shifting Goals in Hemophilia A and B: Targeting the Intrinsic Mechanism of Disease Pathology with New Treatments

Hemostasis in Hemophilia: How Improved Disease Knowledge Informs New Treatments

1		My name is Guy Young, and we're going to be discussing some basics of hemophilia, and also some of the new treatment directions that we're going in.
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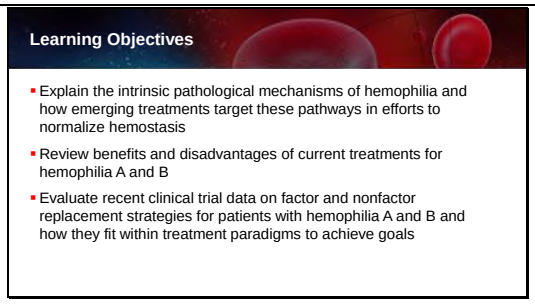
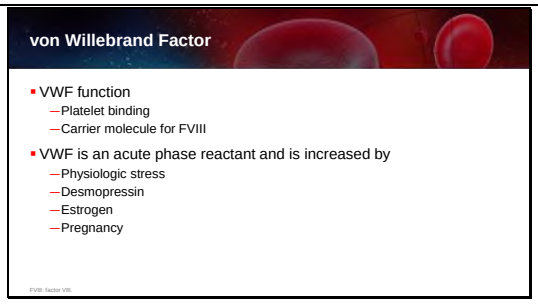
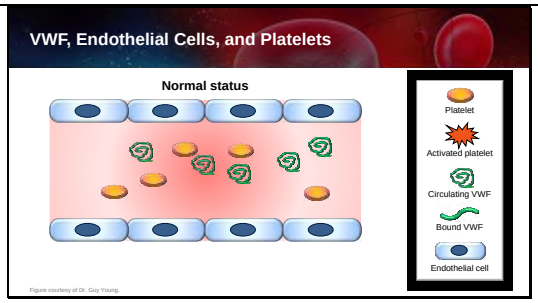
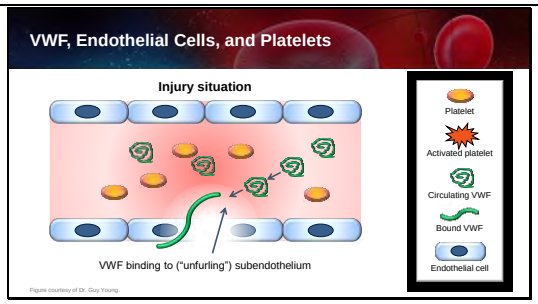
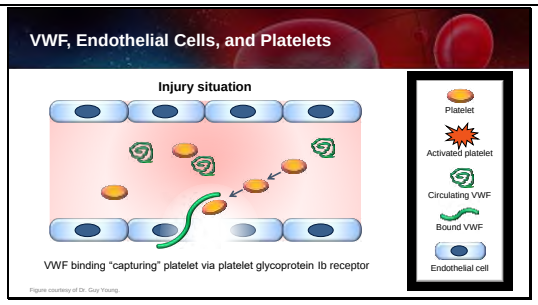
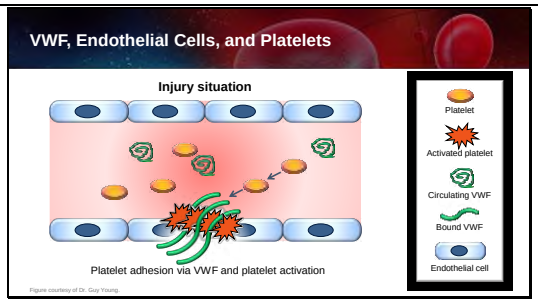
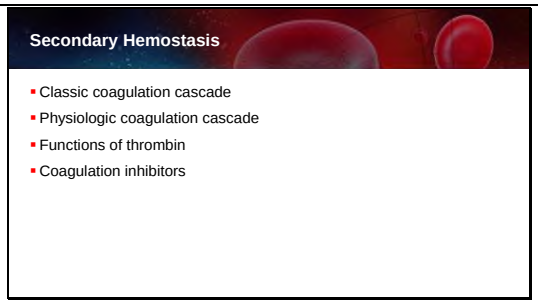
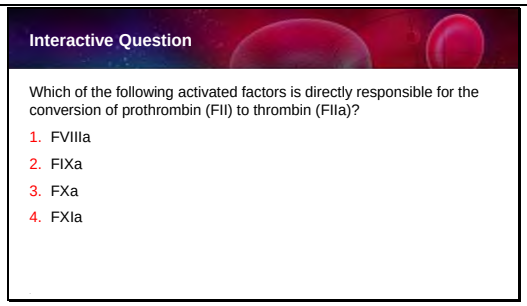
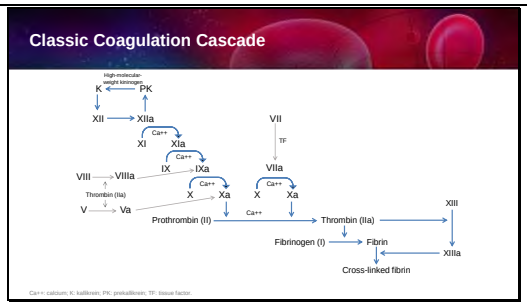
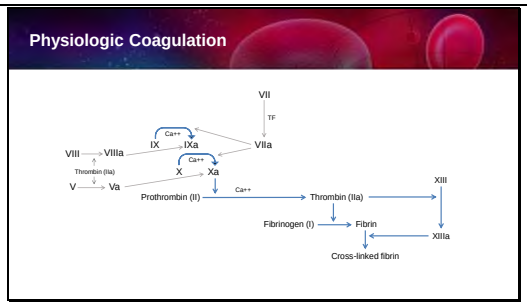
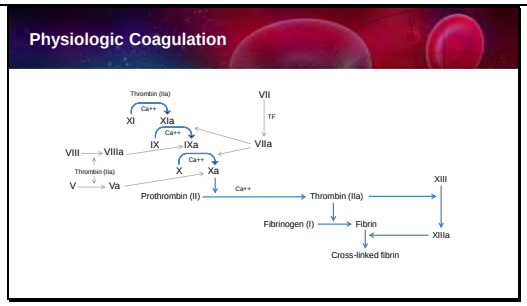
3		So first, we obviously will want to understand the disease knowledge and how that informs new treatment. So here are the learning objectives, specifically: Explain the intrinsic pathological mechanisms of hemophilia and how emerging treatments target these pathways in efforts to normalize hemostasis. Review benefits and disadvantages of current treatments for hemophilia A and B. Evaluate recent clinical trial data on factor and nonfactor replacement strategies for patients with hemophilia A and B and how they fit within treatment paradigms to achieve goals.

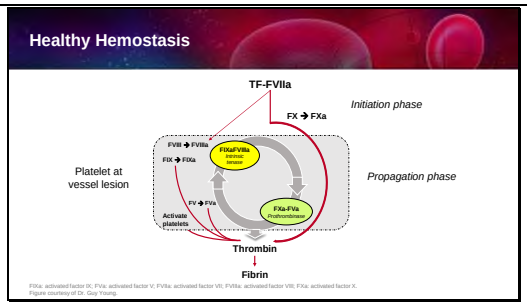
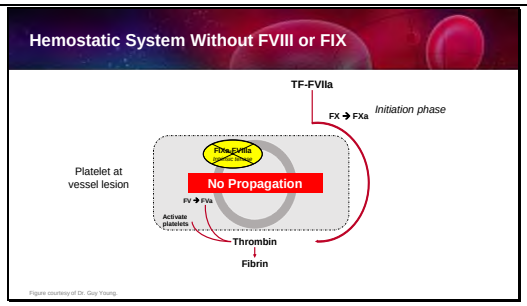
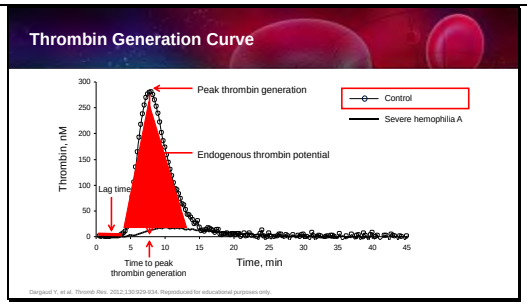
4	**Lecture Outline** ▪ **Hemostasis** —**Primary hemostasis** —**Secondary hemostasis** ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ Novel treatments for hemophilia	This is the basic lecture outline: First, we're going to review hemostasis, just some basics of hemostasis. We'll talk about the mechanism of action of hemophilia medications. We're going to talk about factor therapy, its strengths and weaknesses. And then, discuss novel treatments for hemophilia.
5	**Hemostasis** ▪ Primary hemostasis —Platelets —VWF —Subendothelium ▪ Secondary hemostasis —Coagulation factors —Thrombin generation —Formation of fibrin clot VWF: von Willebrand factor.	So first, hemostasis. We basically break it into 2 parts, although everything is really happening at the same time. Primary hemostasis involves the platelets, the von Willebrand factor, and the subendothelium. Secondary hemostasis is really what we talk about when we talk about the coagulation factors and the formation of a fibrin clot.
6	**Primary Hemostasis** ▪ Subendothelium —Normal collagen —Tissue factor ▪ Platelets —Need adequate number —Need adequate function ▪ VWF —Need normal amount —Need normal function	So what's involved in primary hemostasis? There's basically 3 parts of the body. The subendothelium, the area underneath and supporting the blood vessels. There, we have collagen and tissue factor as important proteins that are involved in the coagulation system. We then have the platelets, as I mentioned, and von Willebrand factor. And for primary hemostasis to be effective, we need an adequate number and function of both of those components.

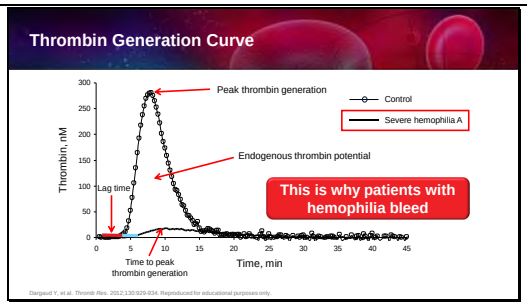
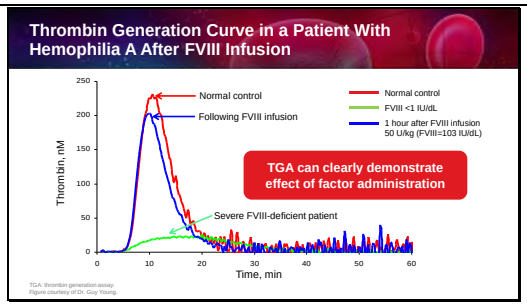
7		Von Willebrand factor has 2 functions, essentially: platelet binding, and it also functions as the carrier protein for FVIII. You should be aware that von Willebrand factor is an acute phase reactant and will be increased by physiologic stress, obviously medications like desmopressin and estrogen, as well as pregnancy. So these conditions can falsely elevate von Willebrand factor levels and can make a patient who might have von Willebrand disease actually have their labs look normal. So keep that in mind as you think about testing for von Willebrand disease.
8		Here is how von Willebrand factor, endothelial cells, and platelets interact. So in a normal status, we've got basically a blood vessel here with endothelial cells at the top and the bottom.
9		When there's a rupture of the blood vessel, we have the von Willebrand factor molecule, which normally circulates in this circular form, so to speak; I made it sort of as a spiral there in this cartoon. But once there's a rupture in the endothelium, it essentially unfurls so that loop because unfurls, von Willebrand factor becomes this long stringlike molecule.
10		And the next thing it does is, besides binding the collagen in the subendothelium where there are receptors for von Willebrand factor, it then actually essentially captures, if you will, the circulating platelets via glycoprotein 1b.

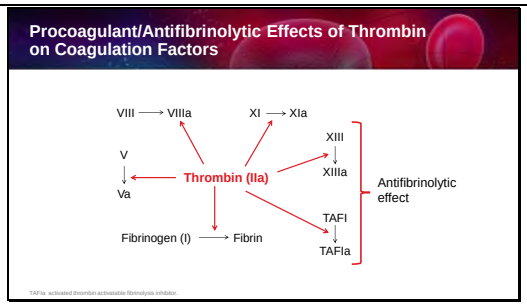
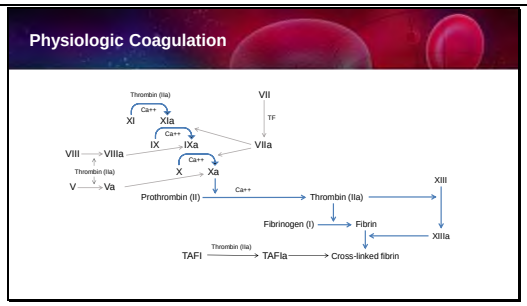
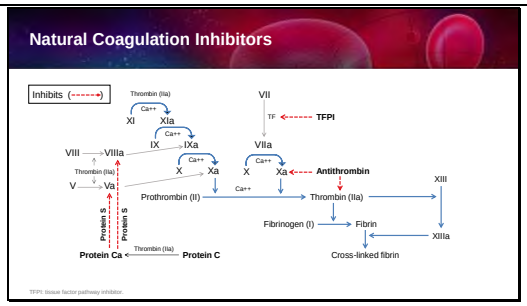
11		And then results in platelet activation. This essentially leads to the first part of hemostasis, which is called platelet adhesion via von Willebrand factor binding and platelet activation. That leads to platelet aggregation, and it is on this surface that the coagulation cascade then has its effect and where thrombin and fibrin get generated later on.
12		In terms of secondary hemostasis, we're going to take a look at the classical coagulation cascade, which is not the physiologic one, but is important when understanding the coagulation tests—the PT and the PTT. We'll then take a look at physiologic coagulation and how it's different. We'll take a look at the functions of thrombin as the key enzyme in the coagulation cascade. And then, of course, we'll review the coagulation inhibitors that are there to keep this reaction from being overly robust and to prevent a thrombosis from happening by ensuring that the thrombus that forms only forms in the area of the tissue injury.
13		Which of the following activated factors is directly responsible for the conversion of prothrombin to thrombin? 1) FVIIIa 2) FIXa 3) FXa 4. FXIa The answer is FXa.

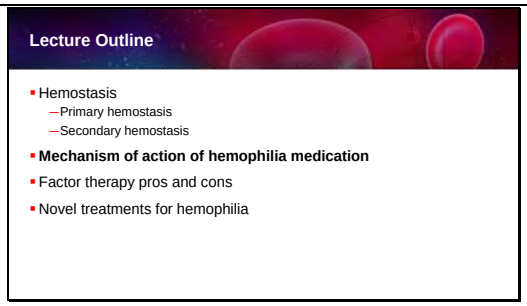
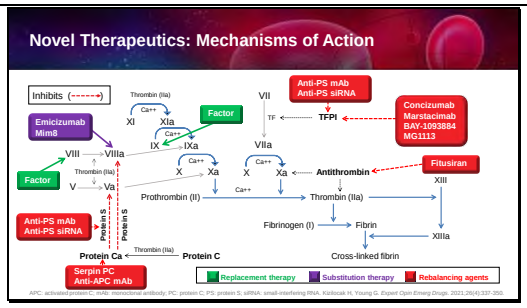
14		So let's take a look at the classical coagulation cascade. In the intrinsic side, which I'm showing you here, it starts with the contact-activating factors, which are kallikrein, prekallikrein, and FXIIa. Now, again, this is not how coagulation typically happens in vivo; unless you have an artificial surface in your body, such as a cardiac valve or catheter, things like that. FXIIa activates FXI, which then activates FIXa. FVIIIa gets involved as cofactor for FIXa to convert X to Xa. FVa is a cofactor for FXa, which converts prothrombin to thrombin. That then converts fibrinogen to fibrin and makes the fibrin clot. Thrombin also activates FXIII—we'll discuss more about that a little bit later. FXIII activated leads to the cross-linking of the fibrin clot and makes the clot more resistant to fibrinolysis. Then we have the extrinsic pathway, FVII, tissue factor. Tissue factor activates VII to VIIa, which activates X to Xa. And then that converts prothrombin to thrombin. Now, again, this is only the classical coagulation cascade. The PTT reaction is essentially the intrinsic part, which I showed you earlier. FFVIII, IX, XI, and XII in the contact factors, the PT is FVII, and the common pathway starting at FX affects both the PT and the PTT.

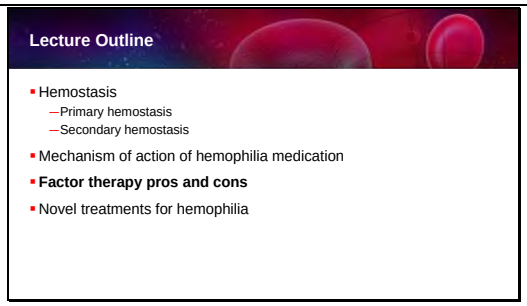
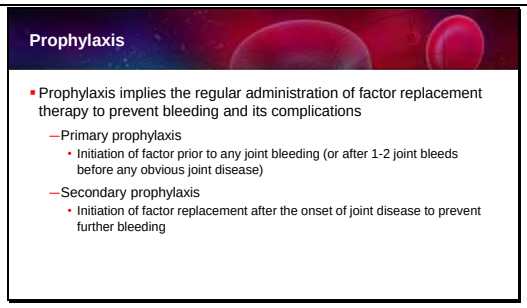
15		What actually happens physiologically? Well, physiologically, I mentioned earlier that when you have a ruptured endothelium, tissue factor sits in the subendothelial space. It activates FVII to VIIa, which converts X to Xa. You then get a conversion of prothrombin to thrombin, but a small amount. And this thrombin mostly is working to activate the cofactors, FVIII and FV. What is not in the class coagulation cascade is the fact that FVIIa actually activates and converts FIX to IXa. This is a key different between the classical coagulation cascade and the physiological coagulation. So keep that in mind. The rest, VIIIa activating as a cofactor for IXa, and Va activating as a cofactor for Xa is highlighted in yellow because, here, we're generating a large amount of FXa. And then that allows a large amount of thrombin to be generated; basically, the thrombin bursts. I'll show you a little bit more about that in the coming slides. The rest is similar to what I showed you before.
16		Also, in stressful situations, you'll notice here I brought in FXIa. So FXI typically is not required for physiological coagulation. However, in conditions of stress, such as surgery or trauma, FXIa, activated by thrombin, can generate more IX to IXa. And this is why maybe where that in FXI deficiency, the bleeding tendency really is only with trauma or with surgery, that on a typical day-to-day basis, patients with FXI deficiency don't actually really bleed excessively. And it's for this reason that you see here.

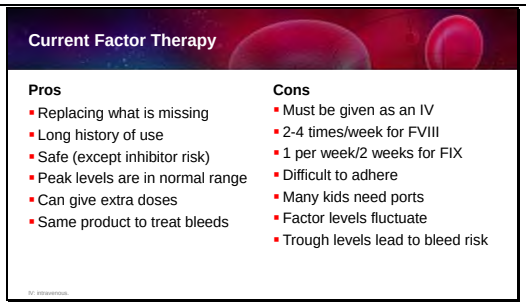
17		Let's take a look at another way to look at this. Again, these are the same reactions I showed you earlier—tissue factor FVIIa, converting X to Xa, and generating a small amount of thrombin. This thrombin, then, activates the platelets, activates FVIII to VIIIa, and FV to Va. In this reaction, the intrinsic tenase, which is FIXa and VIIIa, and the prothrombinase complex Xa and Va, lead to the propagation phase where you generate a large amount of thrombin and convert a large amount of fibrinogen to fibrin. So this is another way of looking at physiologic coagulation.
18		What happens without FVIII or FIX? You have no propagation phase. The initiation phase happens, but you don't have the propagation phase, and so the amount of thrombin generated is a lot less. And that is why hemophilia patients bleed.
19		Another way to look at this is using a thrombin generation device. This is a device that measures thrombin generation over time—basically, a lab-based test. Here we have the control sample and we have these different parameters. So there's a bit of a lag, it takes a few minutes for things to actually unfold. And you might know, if you've ever cut yourself or had some bleeding, you'll know it doesn't stop instantaneously. So these reactions do take some moments and minutes to all develop. You then have a moment of peak thrombin generation, or the amount of thrombin generated that would just peak. You have the time to the peak. And then,

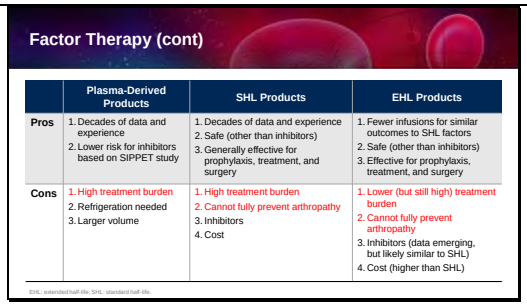
		importantly, this area under the curve, which is called the endogenous thrombin potential, which is the total amount of thrombin generated in this reaction.
20		Now, if you look at the hemophilia patient, you'll notice things are a lot different. There's still the lag time, which may be slightly extended. But the key thing is not your time to peak, but the peak thrombin generation. Here's normal, and here's hemophilia. And of course, the area under the curve, notice it's fairly large here, but in the hemophilia patient, it's almost nonexistent. So essentially, hemophilia is a disease of failure to generate thrombin. And this is why hemophilia patients bleed.
21		If we take a hemophilia patient—again, here you see the normal control in red, the hemophilia patient in green. But if we give them FVIII and give them an FVIII level that is essentially normal, we capitulate the thrombin generation curve really back to normal. So factor replacement does allow for thrombin generation to be formed, if you give the right amount or enough factor. So this is all really in the background of the situation in hemophilia. And really, what I want you to understand is that thrombin is such a key component and thrombin generation is really a key way of measuring the effects.

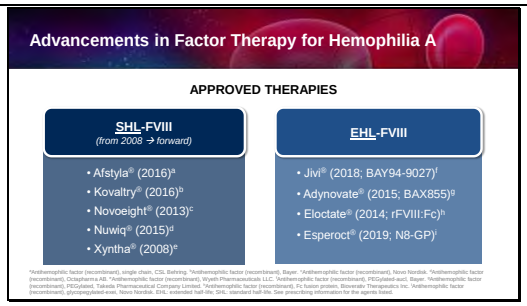
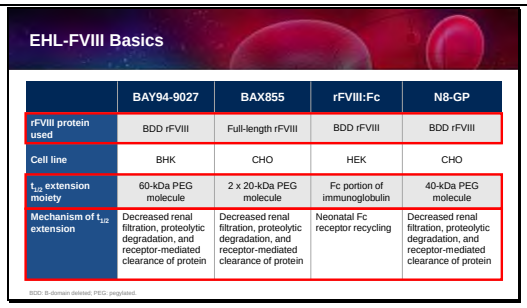
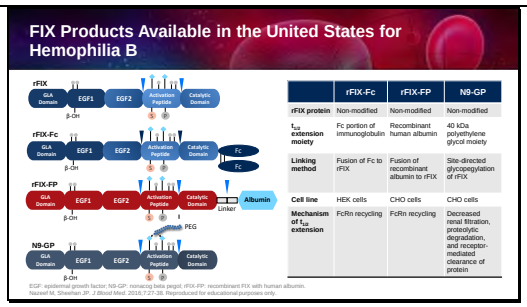
22		Again, thrombin is the key enzyme in the coagulation cascade. It activates FVIII to its activated form, and FV to its activated form. These are the key cofactors in accelerating the formation of more thrombin. So it serves as its own positive feedback look. It also activates FXI in the case of the need for a really large amount of thrombin to be made. Obviously, it converts fibrinogen to fibrin. Also, it converts FXIII to XIIIa. And I didn't mention this protein earlier, thrombin activatable fibrinolysis inhibitor, which is exactly what its name implies. It's activated by thrombin, and it inhibits fibrinolysis. So it activates that. So this is the antifibrinolytic effect of thrombin because both activated FXIII crosslinking fibrin and TAFI inhibit the fibrinolytic pathway and allow for a more stable thrombin clot to form.
23		So back to physiologic coagulation. We now need to look at the inhibitors of coagulation.
24		So the dashed line means inhibitors. We have an inhibitor of the tissue factor pathway, aptly named tissue factor pathway inhibitor. We also have antithrombin, which is also aptly named because it does inhibit thrombin, but it also has a significant effect on FXa. It actually has effects on other coagulation proteins as well, but the key effects of antithrombin are inhibiting thrombin in FXa.

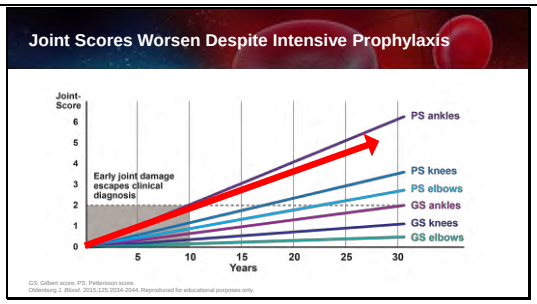
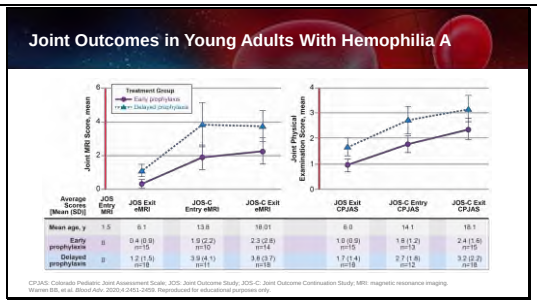
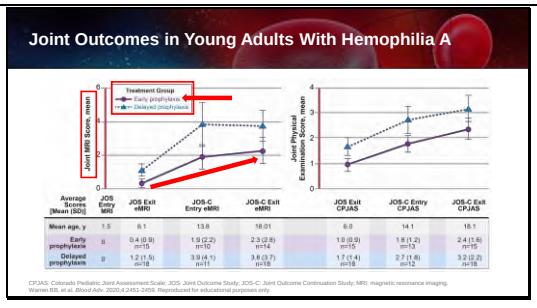
		We have the protein C and protein S system, which are there to inactivate factors Va and factors VIIIa. So these are the key regulators of the coagulation system.
25		
26		So let's take a look at the mechanism of action of hemophilia medication. Again, I'm going to use my clotting cascade here. The green will be replacement therapy; the purple will be what I call substitution therapy; and the red is rebalancing agents. We'll come back to that term later. So of course, factor is replacement therapy. You can replace it at FXIII or FIX, depending on the deficiency the patient has. Substitution therapy: so far we have emicizumab and there's another bispecific antibody being developed that's in clinical trials called Mim8, which is another bispecific antibody that functions like activated FXIII. Then rebalancing agents: we have the fitusiran, which we'll talk about a fair bit, which inhibits antithrombin. We also have inhibitors of tissue factor pathway inhibitor. I list there; the Bayer product is no longer in development, just as an FYI.

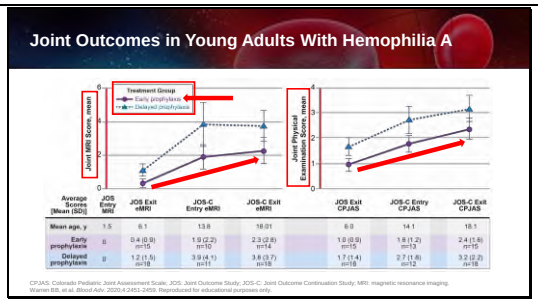
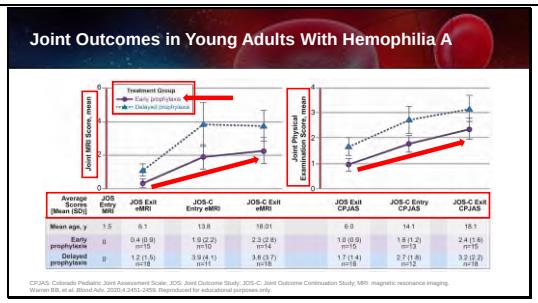
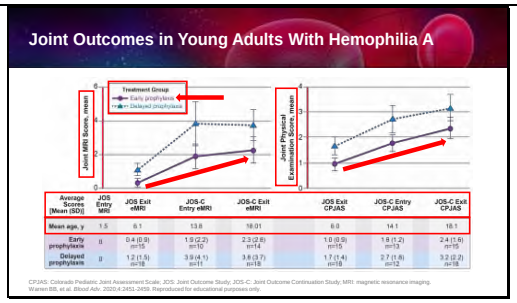
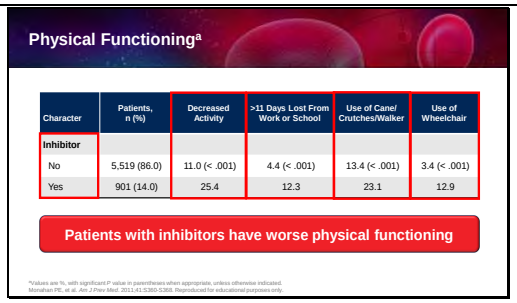
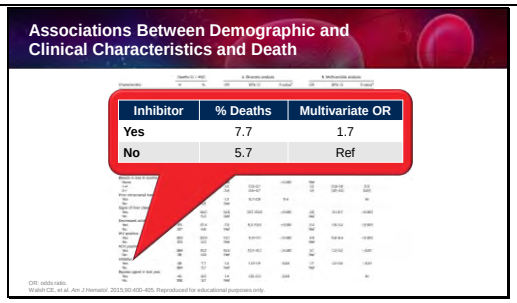
		And then there are molecules aimed at inhibiting activated protein C, particularly serpin PC, which is also in human clinical trials. And there are others that are potentially in development, but not yet in clinical trials to inhibit protein S, which has impacts both on protein S and tissue factor pathway inhibitor.
27		So let's take a look at factor therapy. It's been around for a long time, and we probably still use quite a lot of it for our patients.
28		First, some terms: Prophylaxis implies the regular administration of factor replacement therapy to prevent bleeding and its complications. Although I think that term does apply to the nonfactor therapies as well. Prophylaxis basically being there to prevent bleeding. Primary prophylaxis really means the initiation of factor—or, again, I will say nonfactor therapy at this point as well—prior to any joint bleeding, or at least after 1 to 2 joint bleeds before any obvious joint diseases develop. Secondary prophylaxis would be initiating factor replacement after the onset of joint disease in patients, for example, with target joints. And this is typically only done for patients, in the US anyway, who are, for example, immigrants who didn't have the access to factor therapy or hemophilia

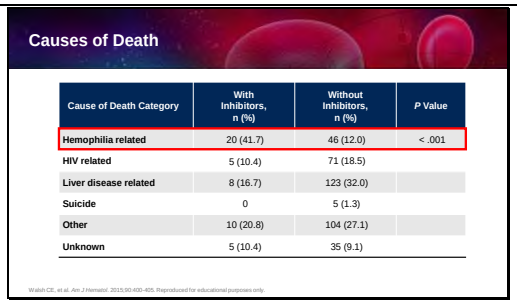
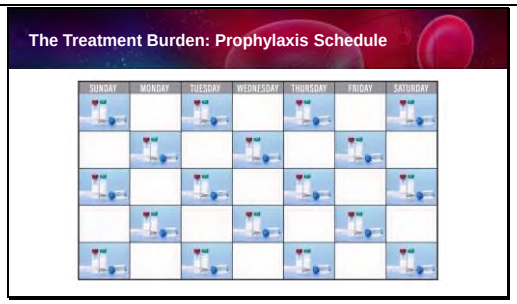
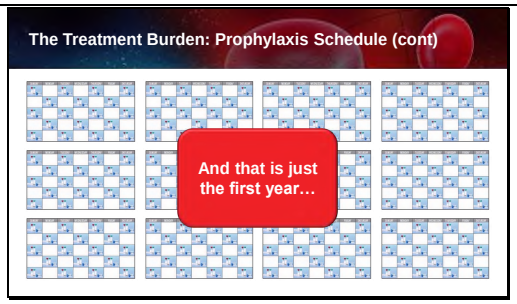
		therapy before and they show up already with joint disease.
29		Let's take a look at the pros and cons of factor therapy, and then we're going to go through some of these in the next slides. First of all, a big advantage is that you're replacing exactly what is missing, which does make a lot of sense for an enzyme deficiency disease; you're replacing the missing protein. We have a long history of use going back decades; in fact, it was 30 years ago that the first recombinant factor therapy was licensed; so, we're at an anniversary year for that. So it's been a long time now, 3 decades, since we've even had recombinant FVIIIs, and even decades longer where we have plasma-derived FVIIIs. They're essentially very safe, other than the risk for inhibitor development, which we know continues to be a complication of factor therapy. But other than that, they really don't have other side effects. You can put peak levels into the normal range. So if you want somebody to have a high level, you can infuse them with the proper dose and they can have a peak level in the normal range, for example, for activities or for surgery, or things like that. There's always the option to give extra doses. So if somebody is dosed every other day, or twice a week, and then they are going to have some sort of activity or procedure, you can just give an extra dose.

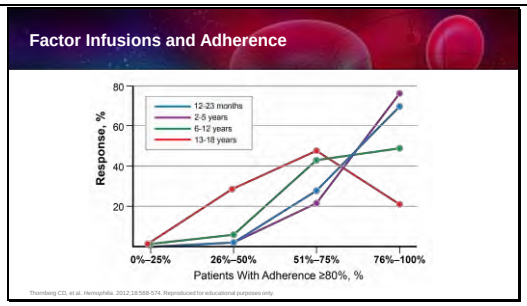
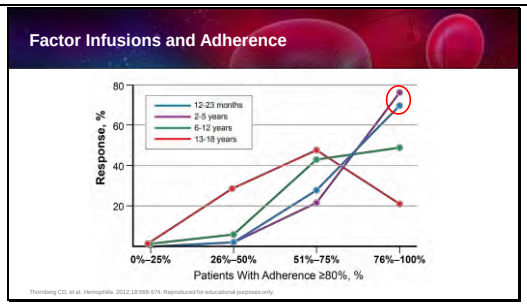
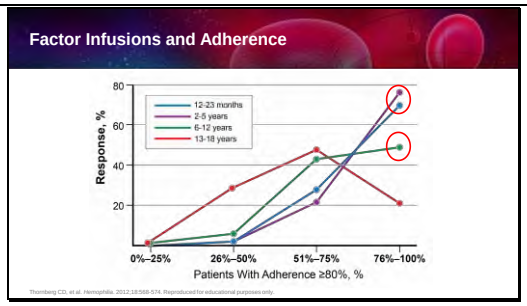
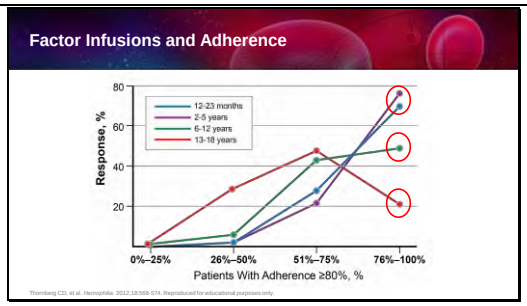
		And you use the same product to treat bleeds when they happen. So that adds to some of the simplicity. However, the down side is, all factor replacement therapies are IV. FVIII typically is 2 to 4 times per week, depending on which product you use. FIX is either once a week or every 2 weeks. For the extended half-life FIXs, probably twice a week for the standard half-life FIXs. Adherence, we know, is notoriously difficult, so we'll take a look at some of that. Children often need ports because it really becomes impossible to access them repeatedly over time, which I'll show you about the treatment burden, which is very high. Factor levels fluctuate. So you have a peak, but then it drops to a trough, and then another peak, and a trough. And the trough levels have increased risk for bleeding.
30		We have plasma-derived products still around. Some people do use these for prevention of inhibitors based on the SIPPET study. However, most people have really moved on to recombinant FVIIIs. We have the standard half-life products and the extended half-life products. So they all have a high treatment burden, which we're going to talk about. And also, for the standard half-life products, probably the EHLs as well, they cannot fully prevent arthropathy, and I'll explain to you what this means in a couple of slides forward from here.

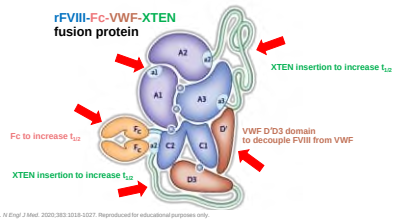
		The EHLs have a lower treatment burden, but there's still a fairly high treatment burden as typically the dosing is twice a week or every 4 days. So it's still multiple infusions a month.
31		Here are just some of the approved therapies. This is the standard half-life list that was approved from 2008 forward. Obviously, we're missing some products here that are more legacy products that are still around, such as Advate and Kogenate (both Antihemophilic Factor [Recombinant]), for example, though Kogenate is now going to be discontinued. And here are the EHL products that are around with their 4 trade names, as you use here. The generics are in parentheses.
32		For the EHLs, again, you have their names listed there. Since we've already said the trade names, it's Jivi, Adynovate, Eloctate, and Esperoct from left to right as you look at the slide. You can see which protein is used. Most of them use B-domain deleted proteins. Three of them are pegylated using different types of PEG moieties. One is an Fc fusion product. And there's a mechanism of half-life extension, one of them utilizing neonatal Fc receptor recycling, and the others essentially decreased renal filtration via the PEG moieties.
33		For recombinant FIX, we've got the standard product, recombinant FIX at the top. Then we have recombinant FIX Fc, known as Alprolix; recombinant FIX function protein, or FP, known as Idelvion; and N9-GP, known as Rebinyn. And you'll see that these 3 extended half-life FIXs use different technologies—one

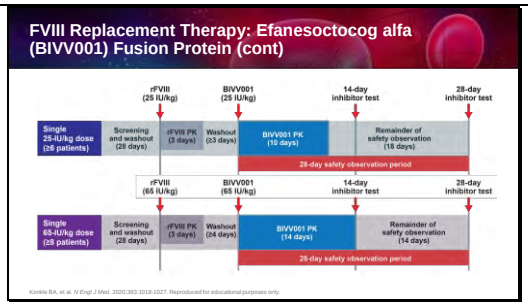
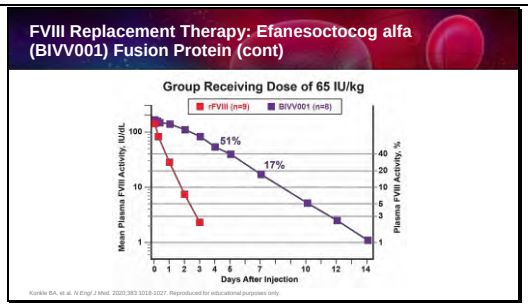
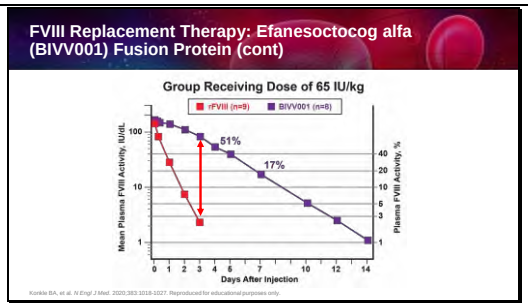
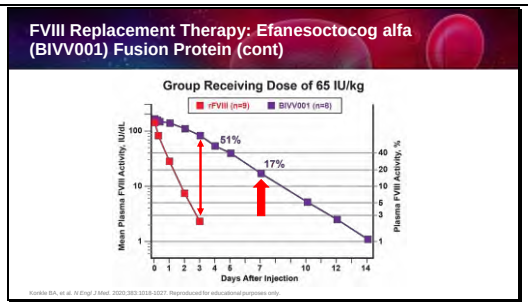
		using Fc fusion, similar to the FVIII Fc fusion; one is a fusion of an albumin to the recombinant FIX; and one is PEGylation.
34		What did I mean earlier when I said that factor products don't necessarily prevent long-term joint disease? This is a study from Germany, which looked at patients in the first 10 years. These are patients who are receiving good, effective prophylaxis. And what they show over a period of decades, highlighted in the box by the actual data they have and then projecting out, is that joint scores get worse over time. PS is the Pettersson score, which is a radiologic score. GS is the Gilbert score, which is an orthopedic score. And you can see that knees, elbows, and ankles do get worse over time, despite of these patients being on intensive prophylaxis.
35		Again, shown really nice here in the Joint Outcomes Study Continuation, the JOSc, you have here also a joint score on the left, MRI score, and then the joint physical exam score. These are a bit different scoring systems than you saw before.
36		And what you see is that patients—even those who started early prophylaxis—have worsening joint MRI scores over time and worsening physical scores.

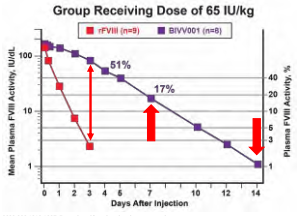
37		And I'll point out to you, as you look here on the bottom at the ages, these are patients who started at the age of one-and-a-half on the Joint Outcomes Study and then entered the Joint Outcome Study Continuation at the age of 13, and exited at 18.
38		So these are young patients and just ending their childhood, starting adult life, and you can see throughout childhood joint disease worsens, even for those who started early prophylaxis.
39		That's what I meant, that factor does not appear to prevent long-term joint disease, at least the iterations of factor that we've had currently. And these patients were all on standard half-life FVIIIs.
40		What about inhibitor patients? We know that they have the worst outcomes. Here's the physical functioning; you can see that on the lower row is the patients with inhibitors. They have more decreased activity, they miss school more, they use assisted devices more, and wheelchairs more often. So we know that historically inhibitor patients suffer worse.
41		We also know they have a higher mortality. This was taken from a CDC study where they have a 1.7-fold higher mortality compared with patients with hemophilia without inhibitors. It's not comparing with the general population; this is comparing inhibitor patients with

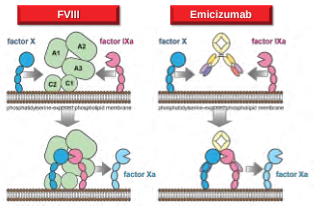
		those without inhibitors. And they have a 70% higher risk of dying.
42		And when they do die, notice here, with inhibitors versus without inhibitors, those with inhibitors, when you see their cause of death, it's much more likely to be hemophilia-related—meaning, bleeding—than those without inhibitors who have other causes of death being more common.
43		What about the treatment burden? So here you see an every-other-day dosing schedule. Not every patient is on this type of dosing schedule, but just to give you a sense of how the treatment burden would be, that's 1 month.
44		And that's 1 year worth of injections. And even with the extended half-life, if it's twice a week or every 4 days, twice a week is 104 infusions a year. Every 4 days is going to be 91/92 infusions a year. So it's still quite a lot of infusions that are required. And this is what I mean by the high treatment burden of factor burden. And that's just the first year. Of course, you have to keep doing this year after year after year. If you let up at any point, bleeding is going to start.

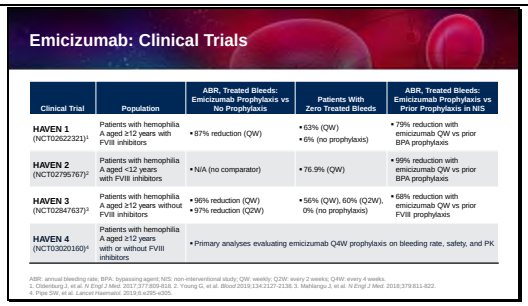
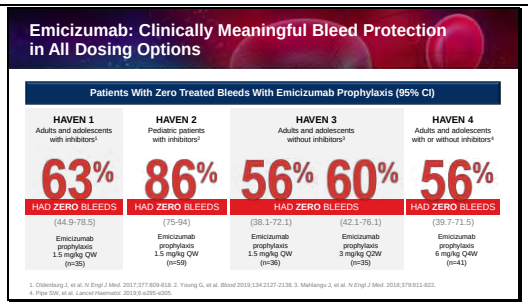
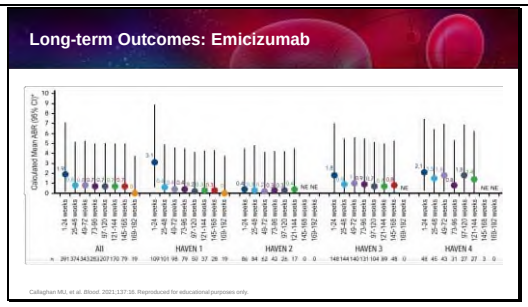
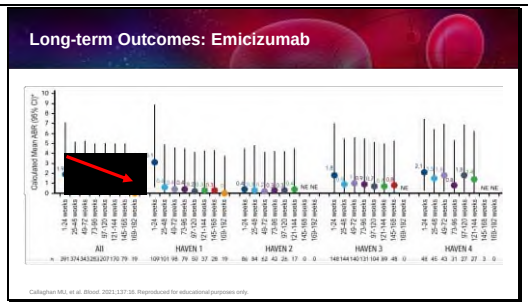
45		There's the extended half-life factor with, for example, a twice-a-week dosing schedule. This would be 104 infusions a year, so it's definitely less than standard half-life factor, but it's still quite a lot of infusions.
46		This leads to poor adherence. And this is a study from my colleague Courtney Thornberg. It's quite old, but it actually still sets the bar for how we evaluate adherence.
47		You can see, for the younger children, in the blue and the purple, adherence is quite high.
48		Once you get to the school years, adherence begins to drop.
49		And in teenagers, it's notoriously poor. Notice, 20% of teenagers reported that they gave most of their infusions.

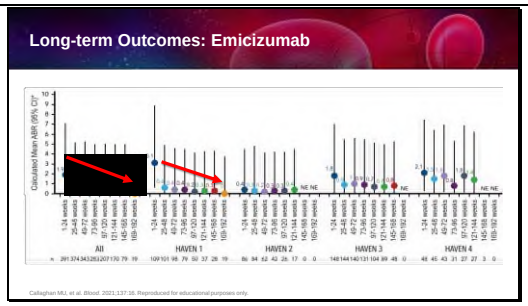
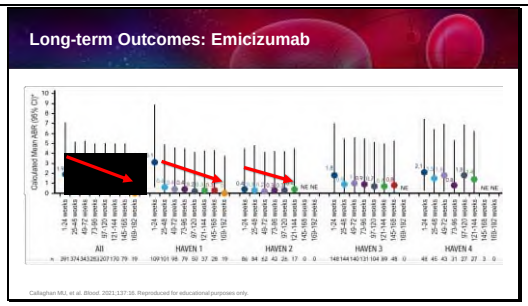
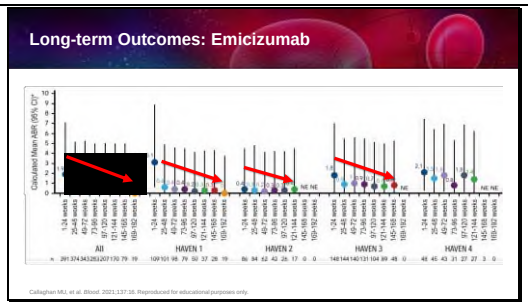
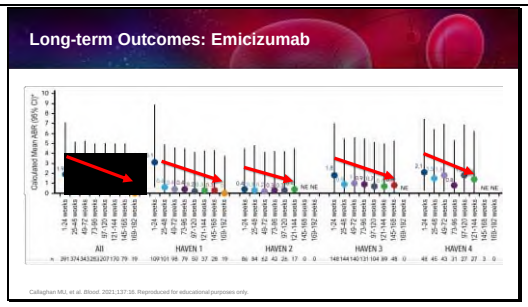
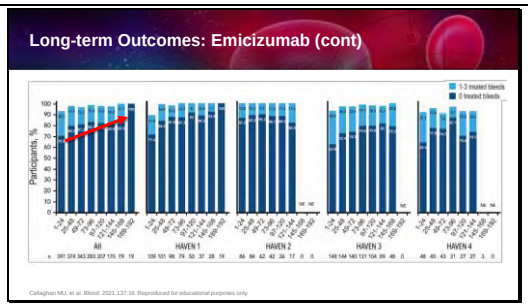
50	**Lecture Outline** ▪ Hemostasis —Primary hemostasis —Secondary hemostasis ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ **Novel treatments for hemophilia** —**Improving factor therapy** —Non-factor therapy • Bispecific antibodies —Rebalancing agents	So if we move to novel treatments for hemophilia therapy, we're going to take a look at, first, improving upon factor therapy, and then looking at nonfactor therapy and rebalancing agents.
51	**Improving Factor Therapy** Efanesoctocog alfa (BIVV001) is a novel experimental FVIII concentrate which aims: ▪ To reduce the treatment burden by offering a weekly infusion schedule ▪ Increase the trough levels	In terms of improving factor therapy, there was a molecule we'd been calling BIVV001. It now has a generic name, efanesoctocog alfa; we're calling it EFA for short. This is a novel, experimental FVIII concentrate which aims to both reduce the treatment burden by offering a weekly infusion schedule, and, at the same time, allow higher trough levels; and, in fact, higher factor levels throughout the entire week.
52	**FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein**  Konkle BA, et al. N Engl J Med. 2020;383:1018-1027. Reproduced for educational purposes only.	What is this molecule? It starts as a base of FVIII Fc, the molecule I showed you earlier. So in the purple/blue color is the FVIII molecule itself with the A1, A2, A3, C1, and C2 domains linked to an Fc fusion protein. What this molecule adds is 2 parts: One is, in the brown, the VWF D'D3 domain. What this does is it blocks the binding site for von Willebrand factor. So this molecule cannot bind to von Willebrand factor. We feel that this is the reason why the EHLs we currently have on the market can only have a half-life that's about 1.5 times longer than FVIII because that's the half-life of von Willebrand factor. So as von Willebrand factors clear, those molecules get cleared as well. By adding this blocking site using the VWF D'D3 domain, this FVIII molecule cannot bind von Willebrand factor.

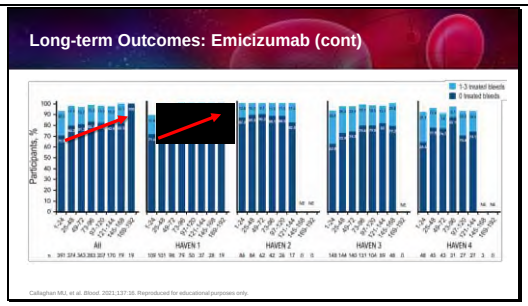
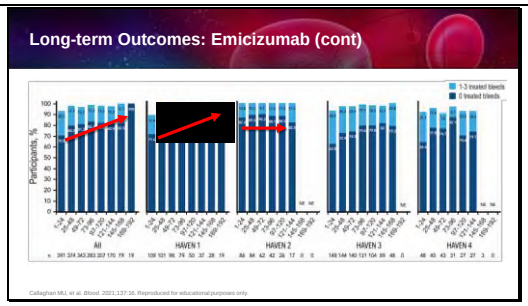
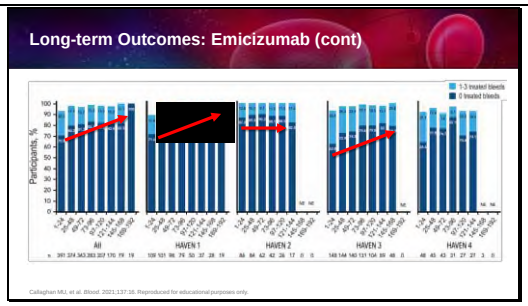
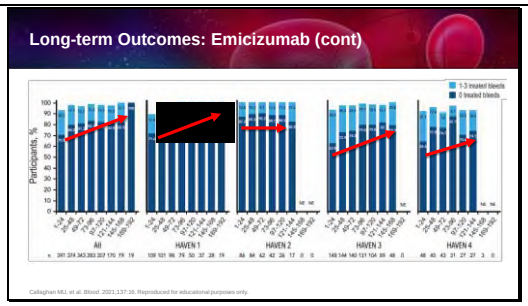
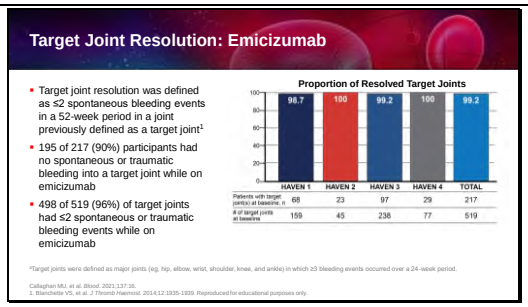
		And then, in addition, you see 2 XTEN sequences, which are added. These are essentially amino acid sequences that function like PEG, making the molecule less able to be filtered by the kidneys. So all of these 3 enhancements have led to an enhanced half-life.
53		There was a phase 1 study that is now published in *The New England Journal of Medicine*. And I'll just show you the data here.
54		You've got a standard half-life recombinant factor in red; and you've got the BIVV001 in purple. And what we're showing is the mean factor level over time.
55		So let's point out day 3. Standard half-life FVIII is down around 2%; notice it's a log scale. Whereas the BIVV001 is still close to 80% at that point.
56		If we go to day 7, the trough level is 17%. Of course, you would have nothing left out of the recombinant FVIII, but even an extended half-life factor you'd have virtually nothing left at this point.

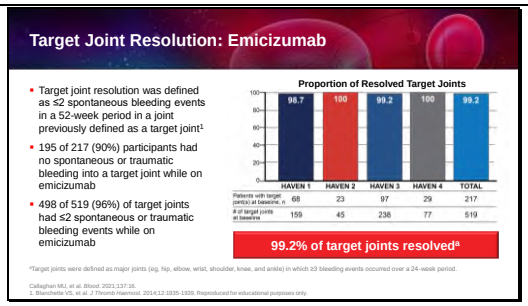
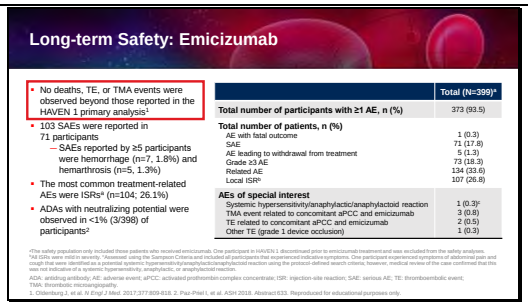
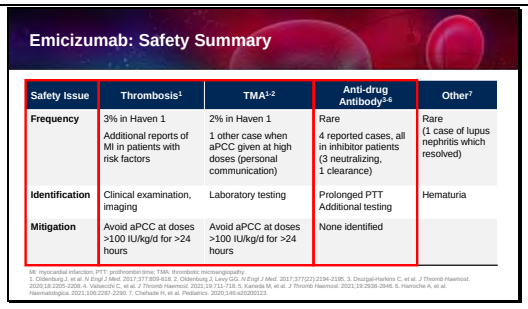
57	**FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein (cont)**  Konkle BA, et al. *N Engl J Med*. 2020;383:1018-1027. Reproduced for educational purposes only.	And even going out to 2 weeks, there's still a 1% level that can be measured out 2 weeks with this molecule. Phase 3 data was recently presented, which was very positive in terms of both the PK, but also, importantly, the bleed rates. I expect that you will see that published soon. Additional data will be presented at upcoming meetings as well.
58	**Other Future FVIII Therapies: Factor-Based** **Hemophilia A Factor Products in Development** Product / MOA / Comments **BIVV 001** — EHL 2.0 — Much longer $t_{1/2}$ than current EHL; May reduce treatment burden and improve outcomes; Phase 3 clinical trials underway ~~**OCTA 101**~~ — ~~SC FVIII~~ — ~~Potential for SC delivery; Reduce treatment burden; Phase 1 clinical trials are underway~~ ~~**SIG 001**~~ — ~~Implanted spheres~~ — ~~May provide several years worth of "therapeutic" levels; Phase 1 clinical trials are underway~~ **RANI pill** — Oral FVIII — Uses robotic pill to "inject" factor into intestinal wall; Preclinical	What about other FVIII therapies? I have OCTA 101 and SIG 001; I won't spend time talking about these. One of them was a subcutaneous FVIII; notice I've crossed it out. One of them was implanted spheres. Both of these have led to an increased number of inhibitor patients unexpectedly in previously treated patients, and these have been discontinued. So BIVV001 is there at the top. There is still a possibility of having oral factor using a robotic pill, but this is still in animal studies. And so, not sure when this will get to human trials.
59	**Lecture Outline** ▪ Hemostasis —Primary hemostasis —Secondary hemostasis ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ **Novel treatments for hemophilia** —Improving factor therapy —**Non-factor therapy** • **Bispecific antibodies** —Rebalancing agents	Let's take a look at novel treatments that are not factor therapy.

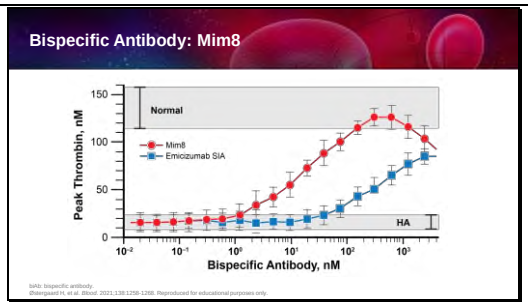
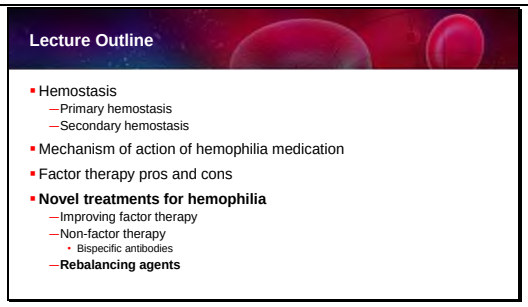
60	**Non-factor Therapy** ▪ Medications that improve hemostasis without replacing the missing factor ▪ They are also designed to reduce the treatment burden – All are designed to be given subcutaneously and at relatively infrequent intervals	We'll start with nonfactor therapies that are bispecific antibodies. Again, in terms of nonfactor therapy, these are medications that are designed to improve hemostasis without replacing the missing factor. And by virtue of that, they can be designed to be given subcutaneously, and even at relatively infrequent intervals. So they really are there to address the difficult treatment burden I mentioned earlier.
61	**Emicizumab: FVIII Mimetic** ▪ Humanized bispecific antibody ▪ Exerts FVIII-mimetic activity ▪ Not affected by FVIII inhibitors ▪ Good subcutaneous absorption ▪ Long $t_{1/2}$ (4-5 weeks) 	Emicizumab: We've heard about this molecule. It is now licensed and available throughout the United States for patients with hemophilia A. It's important to understand that this is an FVIII mimetic drug, so it's only going to work in patients with hemophilia A. Its mechanism of action, you can see on the right. It's a bispecific antibody. One arm binds FX. The other arm of the antibody binds FIXa. And it essentially substitutes for the function of activated FVIII by bringing FX an FIXa to proper alignment, and then generating FXa from that. It has a long half-life, as you can see, about 30 days. It's not affected by FVIII inhibitors, so it can be used in patients with and without inhibitors. And as I mentioned, it's given subcutaneously.

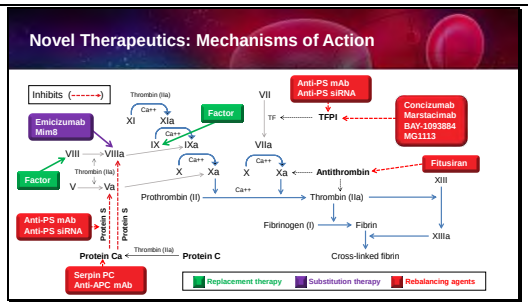
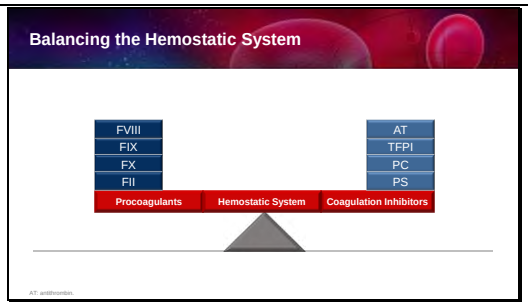
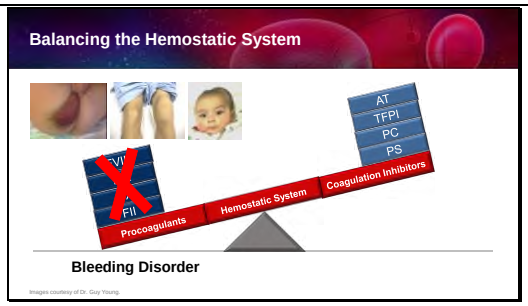
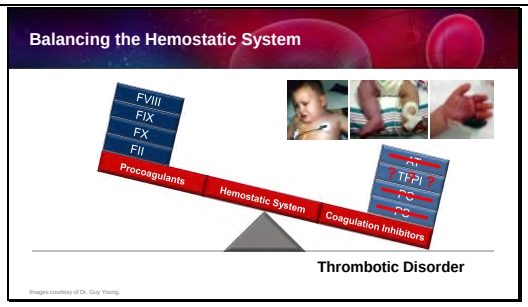
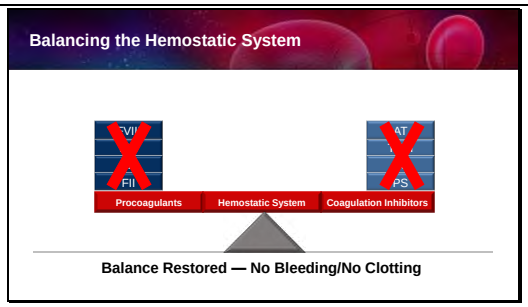
62		So there was a series of pivotal trials called the HAVEN trials—HAVEN 1, 2, 3, and 4—that assessed this medication in adolescents and adults with inhibitors in HAVEN 1; children with inhibitors in HAVEN 2; adolescents and adults without inhibitors in HAVEN 3; and then an every-4-week dosing schedule in HAVEN 4. I'm not going to go through the whole table. These studies have been extensively presented. They've all been published now, going back as much as 5 years. And so, certainly you can go and have a look at those.
63		Now, if we take a look at their bleeding rates, the percentage of patients with zero bleeds, you'll notice that across the studies it's over 50%. In fact, close too 60% for the adolescent and adult trials, HAVEN 1, 3, and 4, and actually over 80% for HAVEN 2. So the percentage of patients with zero bleeds in these trials was really quite high.
64		If we look at long-term outcomes—this paper's a little more recent, published a year ago – you can see the bleed rates over time. So as patients stayed on the trial, this shows you 24-week increments over time as patients continued to stay on emicizumab.
65		And what you notice is that the bleed rates in the emicizumab group goes down. That's all the trials together.

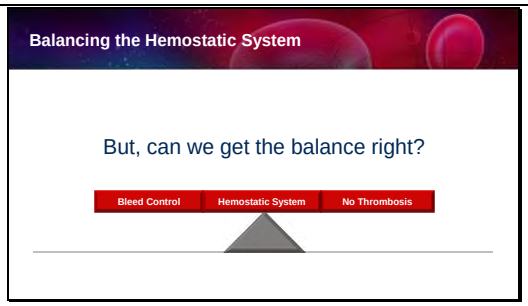
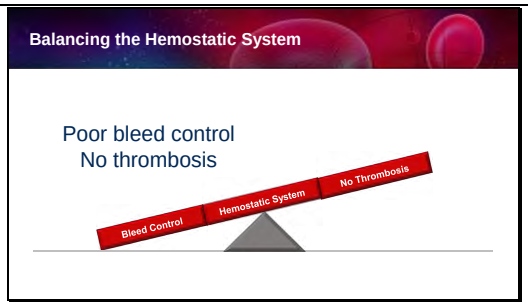
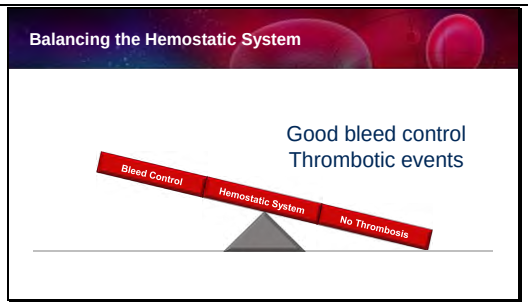
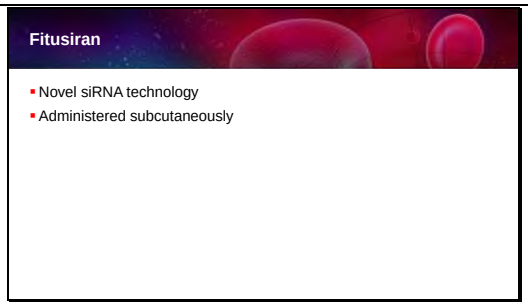
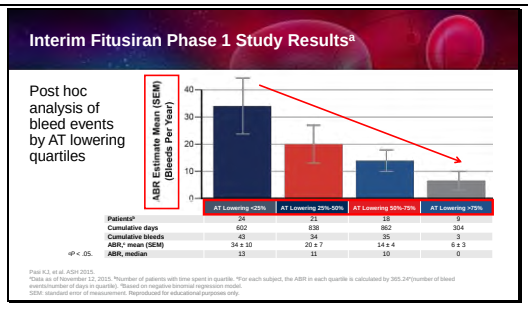
66		Specifically, here's HAVEN 1.
67		HAVEN 2, we started with a very low bleed rate to start with, so it's going to be hard to improve upon that.
68		But in HAVEN 3, you see the bleed rate going down.
69		HAVEN 4 was a smaller study, so you see a little bit up and down which is just statistical noise.
70		If we look at the percentage of patients with zero bleeds, again, overall, that increases.

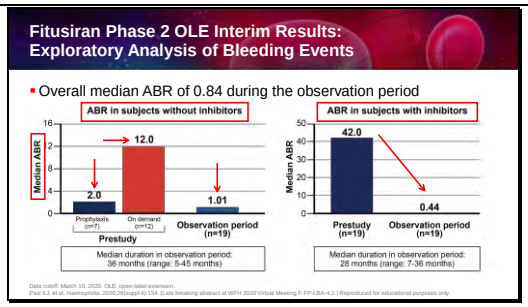
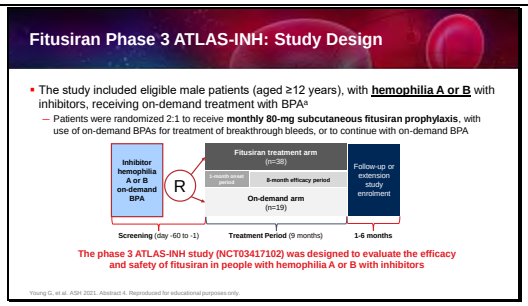
71		And again, HAVEN 1.
72		HAVEN 2 was already quite high.
73		HAVEN 3 is increasing.
74		HAVEN 4 is a little bit up and down.
75		Importantly, target joint resolution. If you look across the trials, over 99% of target joints in these trials resolved.

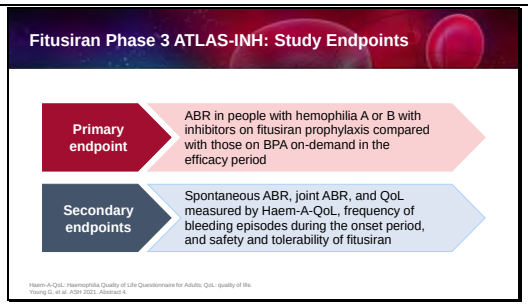
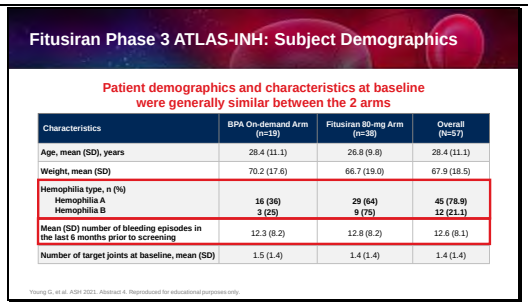
76		So, almost every single patient who was on these trials, who entered with a target joint, which was over 200 patients overall, with 500 target joints, virtually all of those resolved. That's an important outcome.
77		And then, in terms of long-term safety, there were no additional deaths, thromboembolic events, or thrombotic microangiopathy beyond those reported in the original HAVEN 1 study in this long-term safety analysis. So the mitigation strategies that had been put into place, and the boxed warning about not mixing this product with aPCC—if aPCC is to be used to treat bleeding, it needs to be used for short duration and at relatively lower doses. And therefore, since that has been adhered to, we haven't seen more of those safety events that we saw in HAVEN 1.
78		I do want to point out some safety issues with emicizumab in general. Again, here we have the frequency, the identification, and the mitigation strategies. So thrombosis and TMA—again, the mitigation is to basically avoid using aPCC at doses of more than 100 IU/kg for more than 24 hours. That's what's in the boxed warning. So that's your mitigation. You can use aPCC to treat bleeds if you need to, but at lower doses. Obviously, thrombosis is identified by clinical examination and imaging, and TMA by laboratory testing. Antidrug antibodies—these are very rare. There've been 4 reported cases overall: 3 neutralizing, 1 a clearance antibody. In

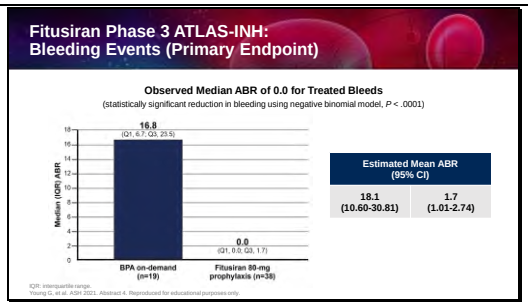
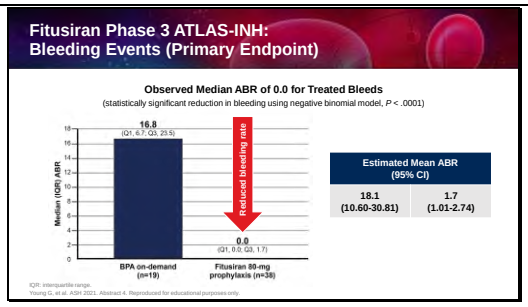
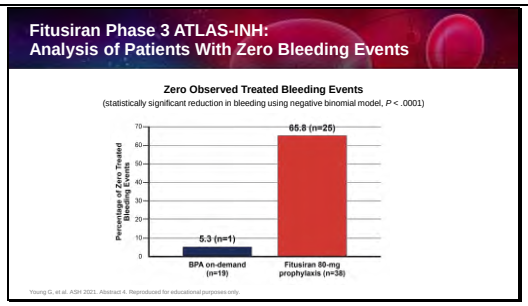
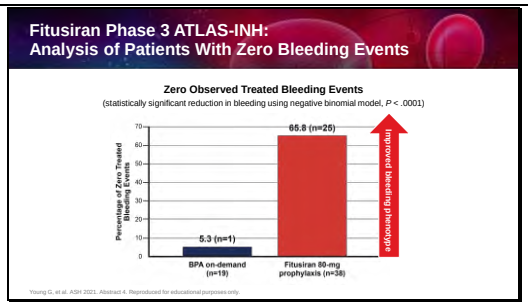
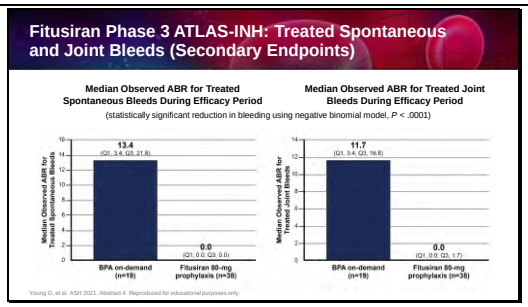
		other words, these are cases that actually had a clinical impact. You can identify these by showing a patient with a prolonged PTT. With emicizumab, if it's functioning, patients have a normal PTT. There's been no mitigation identified for these. And then there was 1 rare case of lupus nephritis that was shown, that was presented.
79		Then there's another bispecific antibody called Mim8. Here, you see, looking at thrombin generation on the Y axis. This is comparing with an emicizumab analogue. And essentially what this is showing is that at lower concentrations, you get higher peak thrombins with Mim8. And in fact, you can get into normal peak thrombin with this molecule. This is taken from animal studies. So this molecule is now in clinical development. Both phase 1 studies are going on; phase 3 study's been initiated. So this is something to keep an eye out for. There were some data presented just a couple weeks ago at ISTH on the first human trials.
80		So let's take a look at rebalancing agents.

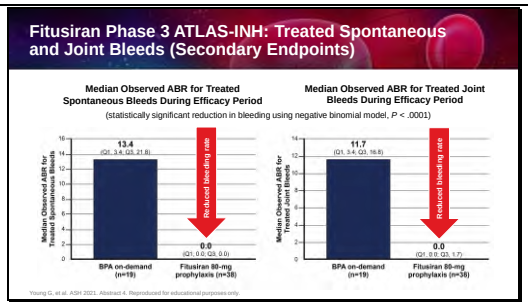
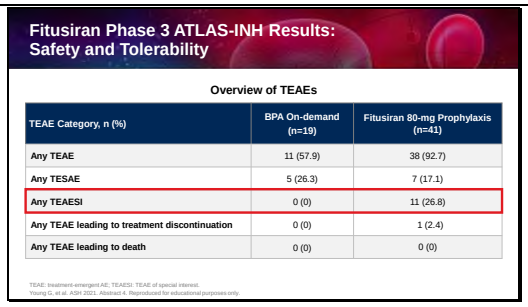
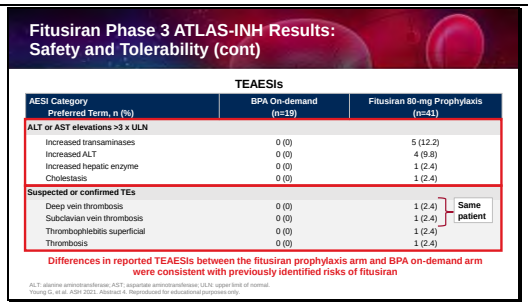
81		Again, this is the coagulation cascade. So we're going to talk about fitusiran; mostly fitusiran. A little bit on serpin PC, and the TFPI inhibitors. But for time's sake, we'll focus just on fitusiran.
82		First, what does rebalancing mean? The hemostatic system is in a balance. I just put in 4 coagulant factors on the left, and coagulation inhibitors on the right. And typically, that's our balanced hemostatic system.
83		If we're missing a protein on the left side, we have a bleeding disorder.
84		If we're missing a protein on the right side, we have a thrombotic disorder.
85		But if we take 1 protein out of each side, is that some way that we can rebalance the coagulation system? Balance restored, no bleeding or clotting.

86		But can we get the balance, right?
87		We may not get the balance right and have poor bleed control, although no risk for thrombosis.
88		Or, we may have good bleed control, but potential for thrombotic events. So we really need to figure out how to get this balance exactly right.
89		Let's talk about fitusiran. This is a novel, small interfering RNA technology. It is administered subcutaneously. And what it does is it inhibits the production of antithrombins. So it induces an antithrombin deficiency in the patient who receives this molecule.
90		This is illustrated here. Here, we have from the phase 1 study the ABR estimate on the Y axis by the percent lowering of antithrombin in these quartiles at the bottom. So with a little bit of antithrombin lowering, less than 25%, you don't really get bleed control. But as you lower the antithrombin more and more, you can see

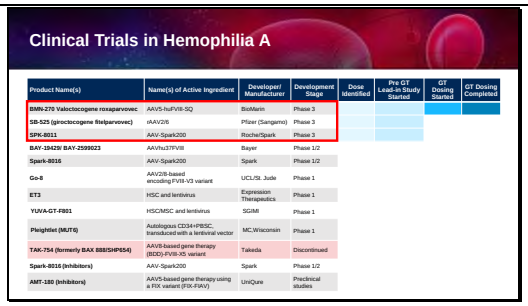
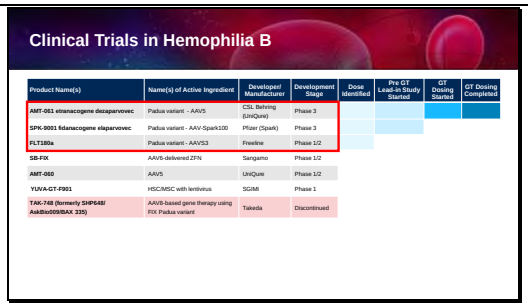
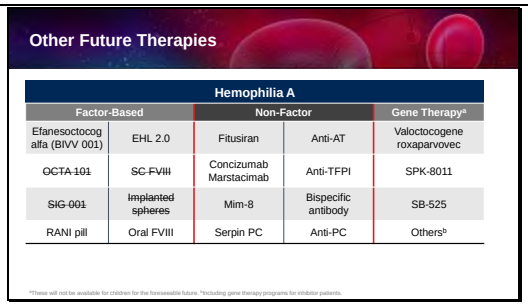
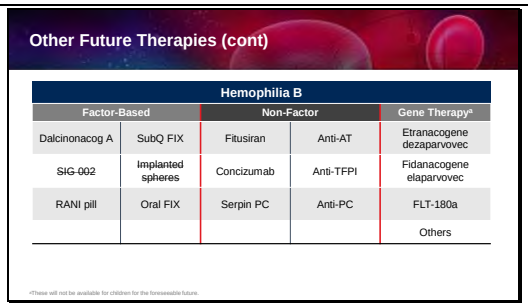
		as you move to the right, you have greater than 75% antithrombin lowering. You actually end up with fewer bleeding events.
91		This is a phase 2 ongoing extension study. Open-label extension is what OLE stands for. Looking here at patients without inhibitors, the ABR on the Y axis with patients who are on prophylaxis with whatever factor product they're on, they have low bleed rates. Those who are on demand have a higher bleed rate. Those on fitusiran had a very low bleed rate, similar to that of prophylaxis. If we look at inhibitor patients, we really do see a dramatic reduction in the ABR in these patients over time, from an ABR of 42 down to less than 1. So this is the phase 2 ongoing extension study.
92		Recently, the phase 3 studies have been presented. There are 3 of them: The ATLAS-INH, which is the inhibitor study for patients older than 12. There's also the ATLAS-A/B study, which is for patients without inhibitors. That was presented at ASH as a late-breaker abstract. This was presented at ASH as a plenary abstract. And then just recently at ISTH, we had the ATLAS-PPX, or prophylaxis study, which compared patients coming in on prophylaxis. So in other words, this study is inhibitor patients and we're comparing fitusiran to on-demand treatment. The A/B study that

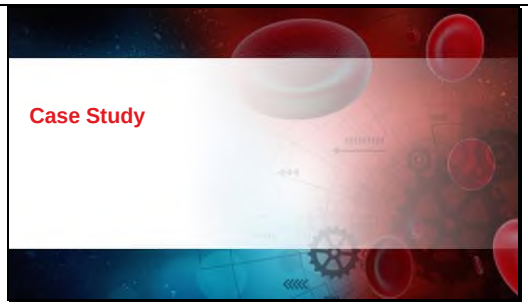
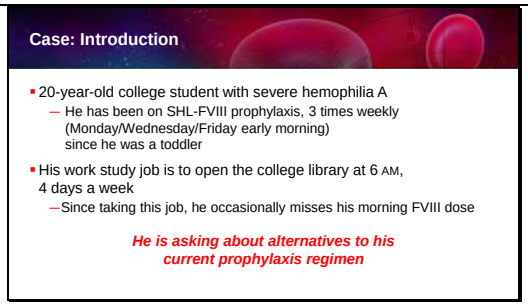
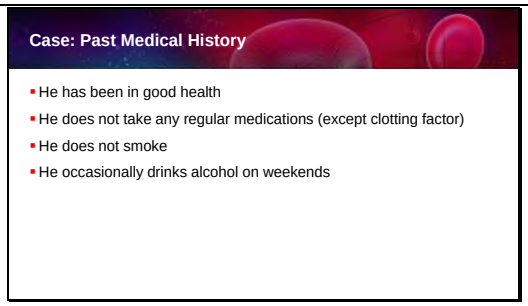
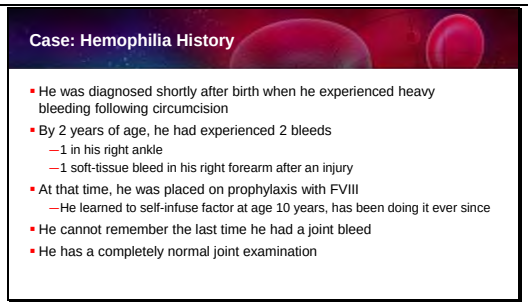
		I don't have time to show you is comparing fitusiran also to on-demand treatment, but in patients without inhibitors. And the prophylaxis study took patients with and without inhibitors who were on prophylaxis and compared them with fitusiran. I will only have time to show you this study. I will say that the other 2 studies—the A/B study and the prophylaxis study, are showing similar results. So here, we have patients randomized to either fitusiran or continued on-demand treatment. Again, these are patients with inhibitors, hemophilia A or B.
93		The main endpoint was ABR. And then there's a number of secondary endpoints.
94		The patients were mostly hemophilia A patients, but you see 20% had hemophilia B. So that's the typical ratio, usually, even though with hemophilia B we see fewer inhibitors. You can see that these patients had high bleed rates. This is in the 6 months prior to screening; so really you can just double that for the ABR more or less of 25. Most of them have target joints.

95		So here are the key data. The bypassing agent on demand arm is in blue. They had an ABR of 17 median. And on fitusiran, the median ABR was zero.
96		The means, on the left, the means went from 18 down to 1.7.
97		If we look here at the percentage of patients with zero bleeds, you had 1 patient out of the 19, 5% on the on-demand arm during the main phase of the trial, which was 9 months.
98		And in the fitusiran arm, it was nearly two-thirds of the patients, 66%, that had zero bleeding events. Obviously, a very dramatic and important difference.
99		If we take a look at spontaneous bleeds or treated bleeds, we again see the same reductions.

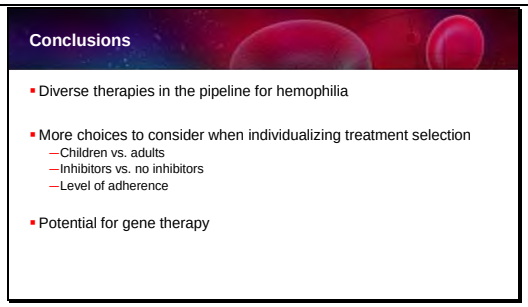
100		When comparing bypassing agent on demand to fitusiran—again, zero median ABR for both spontaneous bleeds and for treated joint bleeds, which is what's on the right.
101		There were some adverse events; in particular, 11 treatment-emergent adverse events of special interest in the fitusiran group.
102		And these comprised mostly ALT elevations, as you see at the top. Now, none of these led to discontinuation of the study drug. Most of these resolved over time, or basically remained stable at ranges that were not concerning. So these patients continued despite the AST/ALT elevations. Again, they were not very significantly elevated. And then there were 2 patients with deep vein thrombosis. It looks like 4, but those 3, the bracket actually should be a little bit lower. The first 3 are the same patient, just with different names for their clot—deep vein thrombosis, subclavian vein thrombosis, a superficial form of phlebitis. The other patient had a suspected thrombotic event called a spinal vessel thrombosis that wasn't really quite confirmed. But those are the adverse events of special interest.

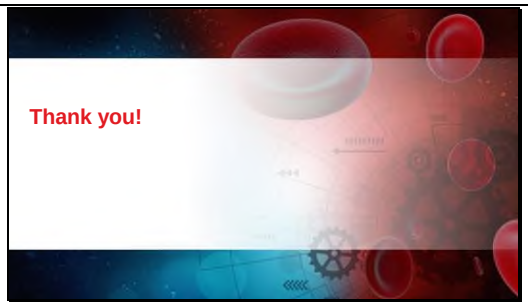
103	**Other Rebalancing Agents** ▪ Inhibitors of coagulation inhibitors —Inhibitors of TFPI —Inhibitors of APC and PC —Inhibitors of PS ▪ Administered subcutaneously —Some are daily —Some are weekly —Some are monthly	I don't have time to get into these other molecules. There are clinical data available for some of these.
104	**Molecules in Development** MOA / Molecule / Development Stage / Comments Anti-TFPI: BAY1093884 (Bayer) — Program discontinued — 3 thrombotic events led to discontinuation Anti-TFPI: MG1113 (Green Cross) — Phase 1 — Single ascending dose phase 1 study has started Anti-TFPI: Marstacimab (Pfizer) — Phase 3 — Weekly subcutaneous dosing; phase 3 just started Anti-TFPI: Concizumab (Novo Nordisk) — Phase 3 — Daily subcutaneous dosing; Plan for a weekly dosing study; 3 TEs in phase 3 led to pause in study; Mitigation strategy developed and study will resume soon Anti-APC: Serpin PC (Apcintex) — Phase 1 — Phase 1 study has started Anti-APC: Anti-APC mAb — Preclinical — Last data from ASH 2016 abstract; unclear if this program is ongoing Anti-PS: PS siRNA — Preclinical Anti-PS: Anti-PS mAb — Preclinical — Data only available from a *Blood* paper in 2018; unclear if this program is continuing	I'll just show you a table here. We've got the anti-TFPI molecules. First of all, the Bayer molecule is no longer in development due to thrombotic events. We've got the Pfizer product, marstacimab, which is in phase 3. Concizumab is also in phase 3. They did have some thrombotic events, which led to a pause in the study and a mitigation strategy that was developed. And the study actually has resumed; it says it will resume soon, but it has resumed now for a while. The serpin PC molecules is in phase 1 and soon to start phase 3. I'm not aware of what's happening with those other 2 at the bottom, the anti-APC monoclonal antibody or those molecules against protein S. So that's really the summary of these molecules.
105	**Gene Therapy** ▪ 1-time infusion with the goal to provide a "therapeutic" factor level permanently (aspirational goal)	Lastly, just briefly, gene therapy. It's a 1-time infusion with the goal to provide what we're calling therapeutic factor level and hopefully permanently. So the aspirational goal is that this will be permanent.

106		There are a number of clinical trials with FVIII. There are 3 that are in phase 3—valoctocogene roxaparvovec; giroctocogene fitelparvovec; and the SPK molecule. And then there are others that you can see that are at earlier stages, some of which are continuing their development.
107		For hemophilia B, there are 3 that are in phase 3. One is etranacogene dezaparvovec, which is originally developed by uniQure by now under CSL Behring. Fidanacogene elaparvovec, which is the molecule from SPK. And then the molecule from Freeline known as FLT180a. But it's got a name, too, now, verbrinacogene setparvovec. I know it's hard to remember and say those names. Those are the ones that are furthest along in development, although there are some others, as you see there, that are a bit further behind. I won't really have time to get into these.
108		Other future therapies—again, here we have the hemophilia A, we already mentioned those. For hemophilia A, also, nonfactor therapies. We've mentioned fitusiran. Concizumab and marstacimab, anti-TFPIs. Briefly mentioned Mim8. Serpin PC. And then, the gene therapies you see on the right side.
109		For hemophilia B, there's also those implanted spheres, but I don't think that's moving forward. I'm not sure what happened with this molecule dalcinonacog alfa, a subQ FIX. I know that that company is no longer in existence. So I guess that molecule is potentially up for grabs if somebody wants to work on that. And then the RANI pill, again, this is a robotic pill that is not yet in human trials.

		For hemophilia B nonfactor therapies, again, we mentioned fitusiran, concizumab, and marstacimab, as well as serpin PC and then the gene therapy molecules.
110		A case study for you here with a 20-year-old college student with severe hemophilia A.
111		He'd been on a standard half-life prophylactic molecule 3 times a week since he was a very young child, a toddler. His work/study job is to open the college library early in the morning and it's really tough for him to get his doses early in the day, so he's not been very adherent. He's asking about alternatives to his current prophylaxis regimen.
112		He's otherwise in good health. Doesn't take other medications. Doesn't smoke. Drinks occasional alcohol.
113		He was diagnosed shortly after birth when he had significant bleeding from a circumcision. And again, he's had a typical kind of course. I won't read every line here for time's sake. He hasn't really had joint bleeds, and he's been pretty good at doing all of his infusions. So he's been, generally

		speaking, quite adherent. It's just that this 6 AM job is making things very challenging.
114	**Case: Hemophilia History (cont)** ▪ As a child he was active but never participated in sports ▪ He is now becoming more active —He goes to the campus gym where he is working out regularly —He is also playing soccer with friends on the weekends ***He is interested in a more convenient dosing schedule, but is concerned about having bleeds***	He's also now becoming more active. And so, he's interested in a more convenient dosing schedule, but is concerned about having bleeds because he's managed to avoid them really quite well.
115	**Case: What Treatment Would You Consider?** ▪ BIVV001 (investigational) – 1x a week dosage	So what molecule might you choose for him? Well, BIV001 is not available yet, but that's once a week, so he could dose that on the weekends, for example, and not worry about it interfering with work. It does give him high levels throughout the week so it should help him, even with his activity.
116	**Case: What Treatment Would You Consider?** ▪ BIVV001 (investigational) – 1x a week dosage ▪ Subcutaneous therapy options	On the other hand, he might want a different type of therapy, like a subcutaneous therapy that can be given, let's say, every 2 weeks, every 4 weeks, or even every month, or less. And so, there are some subcutaneous options that are available now in the form of emicizumab. There are also other subcutaneous options that will become a possibility for him in the future.
117	**Case: What Treatment Would You Consider?** ▪ BIVV001 (investigational) – 1x a week dosage ▪ Subcutaneous therapy options ▪ Importance of shared decision-making and assessing preference —High bleed protection focus —Low treatment burden focus —Combination of both factors	So I think the key point here is to really know your patients well. Ask them what their values are, what is important for them? Is it important for them to have really high bleed protection? Is it important for them to have really low treatment burden? Is it some combination of both where they would be happy with an improved treatment burden, but also at the same time want to make sure they're protected for being involved in activities.

		Those are the questions you need to ask. And then understanding the molecules that are available and those that will become available in the not-too-distant future so you can make the best choice for your patient.
118		So to summarize, I'll just say that there are many therapies coming forward for hemophilia. In the past, we were basically choosing what type of factor therapy because that's all we had. And there was not a lot to choose between until we got the extended half-life FVIIIs. And then there were some different options you had there. But now we also have emicizumab. In the future, we'll also have efanesoctocog alfa. In the too distant future as well, concizumab, fitusiran, and marstacimab. So pretty soon, you're going to have lots of options for your patients with hemophilia A and B. Are they children? Are they adults? Do they have inhibitors? Do they not have inhibitors? Are they adherent? Are they not adherent? There are lots of questions you'll be needing to ask them so that you can make the best choice for them. And let's not forget gene therapy. For those who are older than 18, that could become an option as well, a possibility of having a single infusion that can protect them from bleeding and not have to infuse any sort of product for perhaps years. And maybe even permanently; although again, I'm not sure that we have that yet because we need to see those data moving forward.

119		With that, I'm going to stop and that'll be the end of our discussion. Thank you.