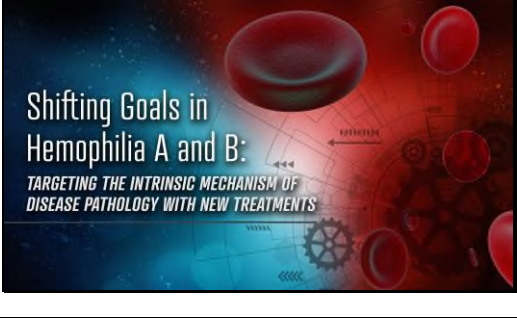



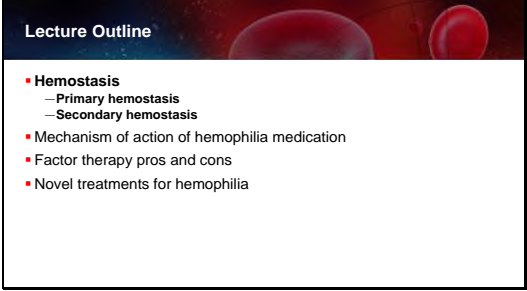
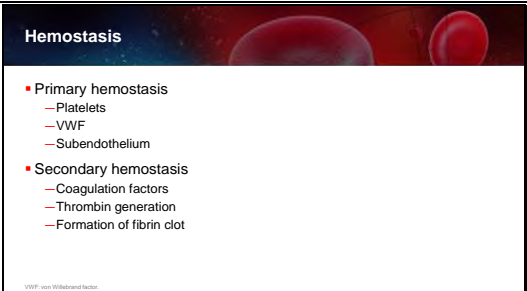
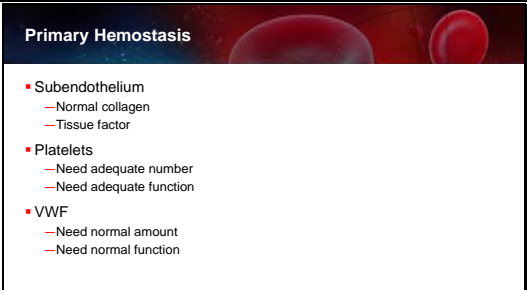
Shifting Goals in Hemophilia A and B: Targeting the Intrinsic Mechanism of Disease Pathology with New Treatments

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1		<p>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.</p>
2		
3	<p>Learning Objectives</p> <ul style="list-style-type: none"> ▪ 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 	<p>So first, we obviously will want to understand the disease knowledge and how that informs new treatment. So here are the learning objectives, specifically:</p> <p>Explain the intrinsic pathological mechanisms of hemophilia and how emerging treatments target these pathways in efforts to normalize hemostasis.</p> <p>Review benefits and disadvantages of current treatments for hemophilia A and B.</p> <p>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.</p>

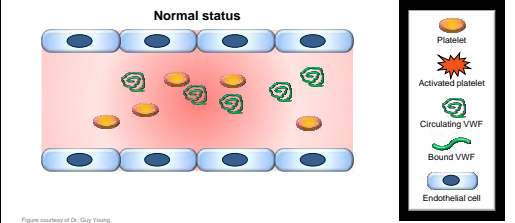
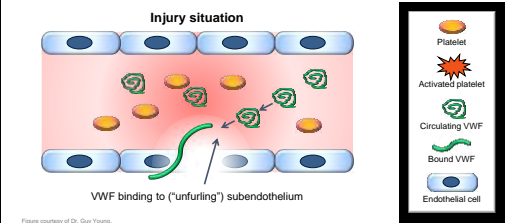
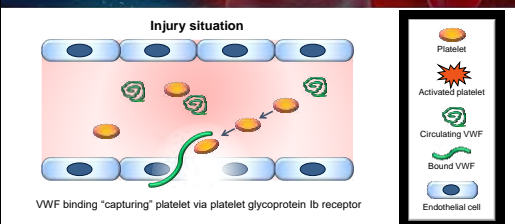
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4	 <p>Lecture Outline</p> <ul style="list-style-type: none"> ▪ Hemostasis <ul style="list-style-type: none"> – Primary hemostasis – Secondary hemostasis ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ Novel treatments for hemophilia 	<p>This is the basic lecture outline:</p> <p>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.</p>
5	 <p>Hemostasis</p> <ul style="list-style-type: none"> ▪ Primary hemostasis <ul style="list-style-type: none"> – Platelets – VWF – Subendothelium ▪ Secondary hemostasis <ul style="list-style-type: none"> – Coagulation factors – Thrombin generation – Formation of fibrin clot <p><small>VWF: von Willebrand factor</small></p>	<p>So first, hemostasis. We basically break it into 2 parts, although everything is really happening at the same time.</p> <p>Primary hemostasis involves the platelets, the von Willebrand factor, and the subendothelium.</p> <p>Secondary hemostasis is really what we talk about when we talk about the coagulation factors and the formation of a fibrin clot.</p>
6	 <p>Primary Hemostasis</p> <ul style="list-style-type: none"> ▪ Subendothelium <ul style="list-style-type: none"> – Normal collagen – Tissue factor ▪ Platelets <ul style="list-style-type: none"> – Need adequate number – Need adequate function ▪ VWF <ul style="list-style-type: none"> – Need normal amount – Need normal function 	<p>So what's involved in primary hemostasis? There's basically 3 parts of the body.</p> <p>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.</p> <p>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.</p>

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7	<p>von Willebrand Factor</p> <ul style="list-style-type: none"> • VWF function <ul style="list-style-type: none"> – Platelet binding – Carrier molecule for FVIII • VWF is an acute phase reactant and is increased by <ul style="list-style-type: none"> – Physiologic stress – Desmopressin – Estrogen – Pregnancy <p><small>Figure courtesy of Dr. Guy Young</small></p>	<p>Von Willebrand factor has 2 functions, essentially: platelet binding, and it also functions as the carrier protein for FVIII.</p> <p>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.</p> <p>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.</p>
8	<p>VWF, Endothelial Cells, and Platelets</p> <p>Normal status</p>  <p><small>Figure courtesy of Dr. Guy Young</small></p>	<p>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.</p>
9	<p>VWF, Endothelial Cells, and Platelets</p> <p>Injury situation</p>  <p>VWF binding to ("unfurling") subendothelium</p> <p><small>Figure courtesy of Dr. Guy Young</small></p>	<p>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.</p>
10	<p>VWF, Endothelial Cells, and Platelets</p> <p>Injury situation</p>  <p>VWF binding "capturing" platelet via platelet glycoprotein 1b receptor</p> <p><small>Figure courtesy of Dr. Guy Young</small></p>	<p>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.</p>

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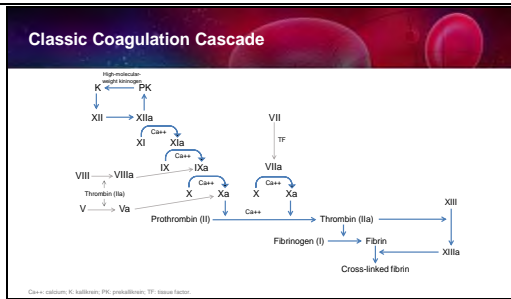
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<p>11</p>	<p>VWF, Endothelial Cells, and Platelets</p> <p>Injury situation</p> <p>Platelet adhesion via VWF and platelet activation</p> <p>Figure courtesy of Dr. Guy Young</p>	<p>And then results in platelet activation. This essentially leads to the 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.</p>
<p>12</p>	<p>Secondary Hemostasis</p> <ul style="list-style-type: none"> ▪ Classic coagulation cascade ▪ Physiologic coagulation cascade ▪ Functions of thrombin ▪ Coagulation inhibitors 	<p>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.</p> <p>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.</p>
<p>13</p>	<p>Interactive Question</p> <p>Which of the following activated factors is directly responsible for the conversion of prothrombin (FII) to thrombin (FIIa)?</p> <ol style="list-style-type: none"> 1. FVIIIa 2. FIXa 3. FXa 4. FXIa 	<p>Which of the following activated factors is directly responsible for the conversion of prothrombin to thrombin?</p> <ol style="list-style-type: none"> 1) FVIIIa 2) FIXa 3) FXa 4. FXIa <p>The answer is FXa.</p>

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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. FVIII, 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.

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<p>15</p>	<p>The diagram illustrates the physiologic coagulation cascade. It starts with Factor VII and Tissue Factor (TF) activating Factor VII to VIIa. Factor VIIa then activates Factor X to Xa. Simultaneously, Factor VIII is activated to VIIIa by Thrombin (IIa). Factor IX is activated to IXa by Thrombin (IIa). Factor Xa, along with VIIIa and IXa, converts Prothrombin (II) to Thrombin (IIa). Thrombin (IIa) then converts Fibrinogen (I) to Fibrin, which is cross-linked by Factor XIIIa. Thrombin (IIa) also activates Factor V to Va and Factor VIII to VIIIa.</p>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>The rest is similar to what I showed you before.</p>
<p>16</p>	<p>This diagram is similar to the one in slide 15 but includes Factor XI and FXIa. Factor XI is activated to XIa by Thrombin (IIa). XIa then activates Factor IX to IXa. The rest of the cascade, including the activation of VII to VIIa, X to Xa, and the conversion of Prothrombin (II) to Thrombin (IIa) and Fibrinogen (I) to Fibrin, remains the same.</p>	<p>Also, in stressful situations, you'll notice here I brought in FXIa. So FXIa 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.</p> <p>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.</p>

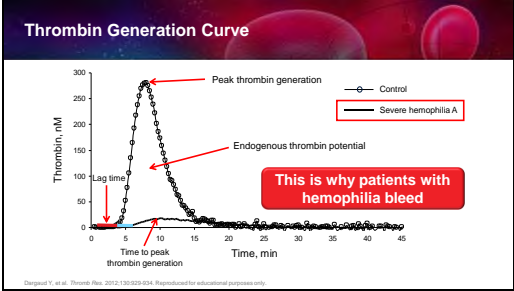
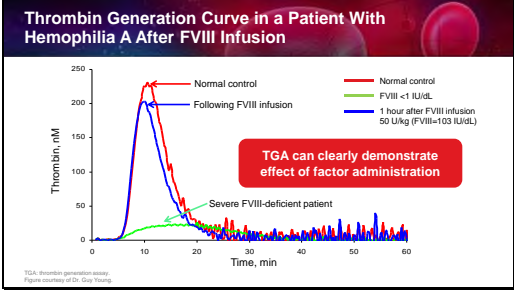
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<p>17</p>	<p>Healthy Hemostasis</p> <p>Platelet at vessel lesion</p> <p>Initiation phase: TF-FVIIa → FX → FXa</p> <p>Propagation phase: FXa + FVIIIa → Prothrombinase (FXa-FVIIIa) → FII → FIIa → Thrombinase (FVa-FXa) → Thrombin</p> <p>Thrombin → Fibrinogen → Fibrin</p> <p>Thrombin also activates platelets and FVIII to FVIIIa.</p>	<p>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.</p> <p>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.</p> <p>So this is another way of looking at physiologic coagulation.</p>
<p>18</p>	<p>Hemostatic System Without FVIII or FIX</p> <p>Platelet at vessel lesion</p> <p>Initiation phase: TF-FVIIa → FX → FXa</p> <p>No Propagation</p> <p>Thrombin → Fibrinogen → Fibrin</p>	<p>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.</p>
<p>19</p>	<p>Thrombin Generation Curve</p> <p>Thrombin, nM</p> <p>Time, min</p> <p>Peak thrombin generation</p> <p>Endogenous thrombin potential</p> <p>Lag time</p> <p>Time to peak thrombin generation</p> <p>Control (red line)</p> <p>Severe hemophilia A (black line)</p>	<p>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.</p> <p>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.</p> <p>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,</p>

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		<p>importantly, this area under the curve, which is called the endogenous thrombin potential, which is the total amount of thrombin generated in this reaction.</p>
<p>20</p>		<p>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.</p> <p>So essentially, hemophilia is a disease of failure to generate thrombin. And this is why hemophilia patients bleed.</p>
<p>21</p>		<p>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.</p> <p>So factor replacement does allow for thrombin generation to be formed, if you give the right amount or enough factor.</p> <p>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.</p>

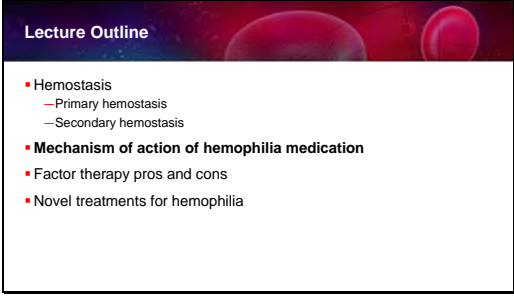
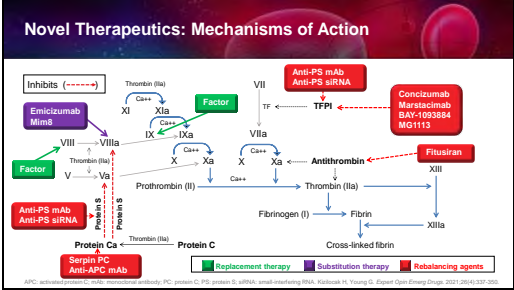
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<p>22</p>	<p>Procoagulant/Antifibrinolytic Effects of Thrombin on Coagulation Factors</p>	<p>Again, thrombin is the key enzyme in the coagulation cascade. It activates FVIII to its activated form, and FV to its activated form. These are the key cofactors in accelerating the formation of more thrombin. So it serves as its own positive feedback loop.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>23</p>	<p>Physiologic Coagulation</p>	<p>So back to physiologic coagulation. We now need to look at the inhibitors of coagulation.</p>
<p>24</p>	<p>Natural Coagulation Inhibitors</p>	<p>So the dashed line means inhibitors. We have an inhibitor of the tissue factor pathway, aptly named tissue factor pathway inhibitor.</p> <p>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.</p>

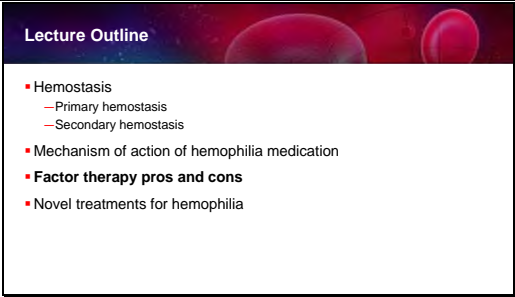
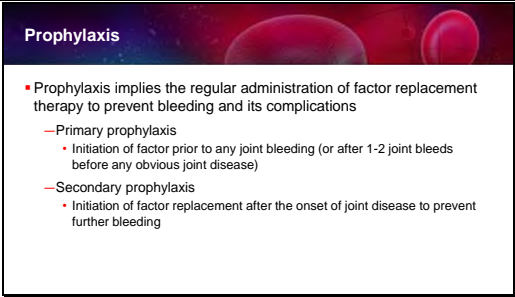
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		<p>We have the protein C and protein S system, which are there to inactivate factors Va and factors VIIIa.</p> <p>So these are the key regulators of the coagulation system.</p>
<p>25</p>	 <p>Lecture Outline</p> <ul style="list-style-type: none"> ▪ Hemostasis <ul style="list-style-type: none"> — Primary hemostasis — Secondary hemostasis ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ Novel treatments for hemophilia 	
<p>26</p>	 <p>Novel Therapeutics: Mechanisms of Action</p> <p>The diagram illustrates the coagulation cascade and the mechanisms of various novel therapeutics. Key components include:</p> <ul style="list-style-type: none"> Inhibitors (purple): Emicizumab, Mim8 (inhibits VIIIa-VIIIa interaction). Factor (green): Replacement therapy for Factor VIII or IX. Rebalancing agents (red): Fitusiran (inhibits Antithrombin), Conicizumab, Marstacimab, BAY-1003884, MG113 (inhibit TFPI). Anti-PS mAb and Anti-PS siRNA (red): Target Protein S. Serpin PC and Anti-APC mAb (red): Target Protein C. <p>The cascade shows the activation of factors VIII, IX, X, XI, XII, XIII, and the conversion of Prothrombin (II) to Thrombin (IIa), which then converts Fibrinogen (I) to Fibrin, leading to cross-linked fibrin.</p>	<p>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.</p> <p>So of course, factor is replacement therapy. You can replace it at FXIII or FIX, depending on the deficiency the patient has.</p> <p>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.</p> <p>Then rebalancing agents: we have the fitusiran, which we'll talk about a fair bit, which inhibits antithrombin.</p> <p>We also have inhibitors of tissue factor pathway inhibitor. I list there; the Bayer product is no longer in development, just as an FYI.</p>

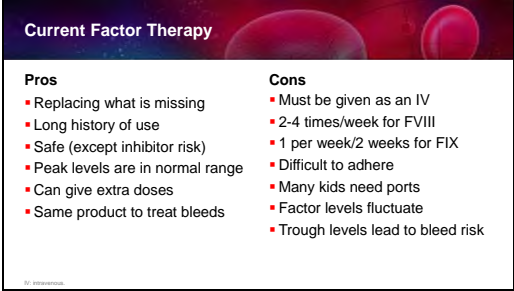
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		<p>And then there are molecules aimed at inhibiting activated protein C, particularly serpin PC, which is also in human clinical trials.</p> <p>And there are others that are potentially in development, but not yet in clinical trials to inhibit protein S, which has impacts both on protein S and tissue factor pathway inhibitor.</p>
27	 <p>Lecture Outline</p> <ul style="list-style-type: none"> ▪ Hemostasis <ul style="list-style-type: none"> – Primary hemostasis – Secondary hemostasis ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ Novel treatments for hemophilia 	<p>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.</p>
28	 <p>Prophylaxis</p> <ul style="list-style-type: none"> ▪ Prophylaxis implies the regular administration of factor replacement therapy to prevent bleeding and its complications <ul style="list-style-type: none"> – Primary prophylaxis <ul style="list-style-type: none"> ▪ Initiation of factor prior to any joint bleeding (or after 1-2 joint bleeds before any obvious joint disease) – Secondary prophylaxis <ul style="list-style-type: none"> ▪ Initiation of factor replacement after the onset of joint disease to prevent further bleeding 	<p>First, some terms:</p> <p>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.</p> <p>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.</p> <p>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</p>

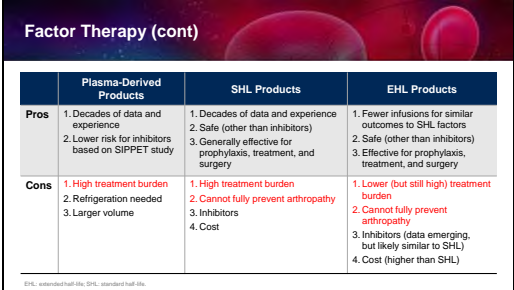
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		<p>therapy before and they show up already with joint disease.</p>		
<p>29</p>	 <p>Current Factor Therapy</p> <table border="0"> <tr> <td> <p>Pros</p> <ul style="list-style-type: none"> ▪ Replacing what is missing ▪ Long history of use ▪ Safe (except inhibitor risk) ▪ Peak levels are in normal range ▪ Can give extra doses ▪ Same product to treat bleeds </td> <td> <p>Cons</p> <ul style="list-style-type: none"> ▪ Must be given as an IV ▪ 2-4 times/week for FVIII ▪ 1 per week/2 weeks for FIX ▪ Difficult to adhere ▪ Many kids need ports ▪ Factor levels fluctuate ▪ Trough levels lead to bleed risk </td> </tr> </table>	<p>Pros</p> <ul style="list-style-type: none"> ▪ Replacing what is missing ▪ Long history of use ▪ Safe (except inhibitor risk) ▪ Peak levels are in normal range ▪ Can give extra doses ▪ Same product to treat bleeds 	<p>Cons</p> <ul style="list-style-type: none"> ▪ Must be given as an IV ▪ 2-4 times/week for FVIII ▪ 1 per week/2 weeks for FIX ▪ Difficult to adhere ▪ Many kids need ports ▪ Factor levels fluctuate ▪ Trough levels lead to bleed risk 	<p>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.</p> <p>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.</p> <p>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 FVIII, and even decades longer where we have plasma-derived FVIII.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>Pros</p> <ul style="list-style-type: none"> ▪ Replacing what is missing ▪ Long history of use ▪ Safe (except inhibitor risk) ▪ Peak levels are in normal range ▪ Can give extra doses ▪ Same product to treat bleeds 	<p>Cons</p> <ul style="list-style-type: none"> ▪ Must be given as an IV ▪ 2-4 times/week for FVIII ▪ 1 per week/2 weeks for FIX ▪ Difficult to adhere ▪ Many kids need ports ▪ Factor levels fluctuate ▪ Trough levels lead to bleed risk 			

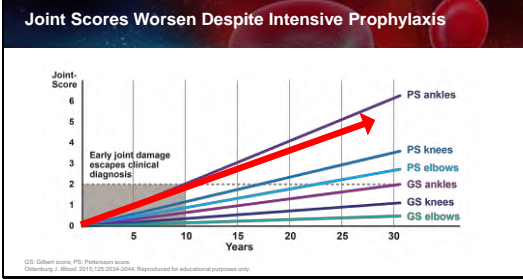
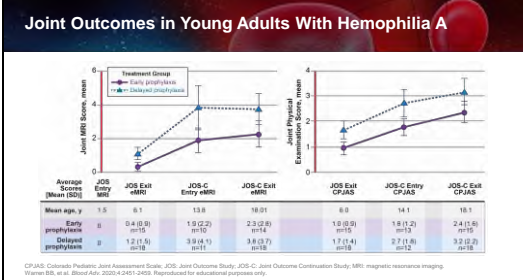
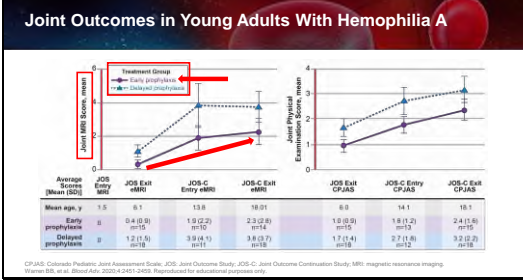
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		<p>And you use the same product to treat bleeds when they happen. So that adds to some of the simplicity.</p> <p>However, the down side is, all factor replacement therapies are IV. FVIII typically is 2 to 4 times per week, depending on which product you use.</p> <p>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.</p> <p>Adherence, we know, is notoriously difficult, so we'll take a look at some of that.</p> <p>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.</p> <p>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.</p>												
30	 <table border="1"> <thead> <tr> <th></th> <th>Plasma-Derived Products</th> <th>SHL Products</th> <th>EHL Products</th> </tr> </thead> <tbody> <tr> <td>Pros</td> <td> <ol style="list-style-type: none"> Decades of data and experience Lower risk for inhibitors based on SIPPET study </td> <td> <ol style="list-style-type: none"> Decades of data and experience Safe (other than inhibitors) Generally effective for prophylaxis, treatment, and surgery </td> <td> <ol style="list-style-type: none"> Fewer infusions for similar outcomes to SHL factors Safe (other than inhibitors) Effective for prophylaxis, treatment, and surgery </td> </tr> <tr> <td>Cons</td> <td> <ol style="list-style-type: none"> High treatment burden Refrigeration needed Larger volume </td> <td> <ol style="list-style-type: none"> High treatment burden Cannot fully prevent arthropathy Inhibitors Cost </td> <td> <ol style="list-style-type: none"> Lower (but still high) treatment burden Cannot fully prevent arthropathy Inhibitors (data emerging, but likely similar to SHL) Cost (higher than SHL) </td> </tr> </tbody> </table>		Plasma-Derived Products	SHL Products	EHL Products	Pros	<ol style="list-style-type: none"> Decades of data and experience Lower risk for inhibitors based on SIPPET study 	<ol style="list-style-type: none"> Decades of data and experience Safe (other than inhibitors) Generally effective for prophylaxis, treatment, and surgery 	<ol style="list-style-type: none"> Fewer infusions for similar outcomes to SHL factors Safe (other than inhibitors) Effective for prophylaxis, treatment, and surgery 	Cons	<ol style="list-style-type: none"> High treatment burden Refrigeration needed Larger volume 	<ol style="list-style-type: none"> High treatment burden Cannot fully prevent arthropathy Inhibitors Cost 	<ol style="list-style-type: none"> Lower (but still high) treatment burden Cannot fully prevent arthropathy Inhibitors (data emerging, but likely similar to SHL) Cost (higher than SHL) 	<p>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.</p> <p>We have the standard half-life products and the extended half-life products.</p> <p>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.</p>
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		<p>using Fc fusion, similar to the FVIII Fc fusion; one is a fusion of an albumin to the recombinant FIX; and one is PEGylation.</p>																													
<p>34</p>	 <p>Joint Scores Worsen Despite Intensive Prophylaxis</p> <p>Joint Score (0-6) vs. Years (0-30). Lines represent PS ankles, PS knees, PS elbows, GS ankles, GS knees, and GS elbows. A red arrow points to the PS ankles line. A box highlights the first 10 years with the text 'Early joint damage escapes clinical diagnosis'.</p>	<p>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.</p> <p>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 Petterson 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.</p>																													
<p>35</p>	 <p>Joint Outcomes in Young Adults With Hemophilia A</p> <p>Joint MRI Score (mean) and Examination Score (mean) vs. Time Points (Entry, Entry eMRI, Exit eMRI). Lines represent Early prophylaxis (solid) and Delayed prophylaxis (dashed).</p> <table border="1"> <thead> <tr> <th>Average Score (Mean [SD])</th> <th>JOS Entry eMRI</th> <th>JOS-C Entry eMRI</th> <th>JOS-C Exit eMRI</th> <th>JOS Exit CPJAS</th> <th>JOS-C Entry CPJAS</th> <th>JOS-C Exit CPJAS</th> </tr> </thead> <tbody> <tr> <td>Mean age, y</td> <td>7.5</td> <td>8.7</td> <td>13.8</td> <td>19.01</td> <td>8.8</td> <td>14.1</td> <td>18.1</td> </tr> <tr> <td>Early prophylaxis</td> <td>0.4 (0.9) n=15</td> <td>1.9 (2.2) n=12</td> <td>2.3 (2.6) n=14</td> <td>1.9 (0.9) n=12</td> <td>1.9 (1.2) n=12</td> <td>2.4 (1.6) n=15</td> </tr> <tr> <td>Delayed prophylaxis</td> <td>1.2 (1.5) n=13</td> <td>3.0 (4.7) n=11</td> <td>3.8 (3.7) n=8</td> <td>1.7 (1.4) n=12</td> <td>2.7 (1.6) n=12</td> <td>3.2 (2.9) n=8</td> </tr> </tbody> </table>	Average Score (Mean [SD])	JOS Entry eMRI	JOS-C Entry eMRI	JOS-C Exit eMRI	JOS Exit CPJAS	JOS-C Entry CPJAS	JOS-C Exit CPJAS	Mean age, y	7.5	8.7	13.8	19.01	8.8	14.1	18.1	Early prophylaxis	0.4 (0.9) n=15	1.9 (2.2) n=12	2.3 (2.6) n=14	1.9 (0.9) n=12	1.9 (1.2) n=12	2.4 (1.6) n=15	Delayed prophylaxis	1.2 (1.5) n=13	3.0 (4.7) n=11	3.8 (3.7) n=8	1.7 (1.4) n=12	2.7 (1.6) n=12	3.2 (2.9) n=8	<p>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.</p>
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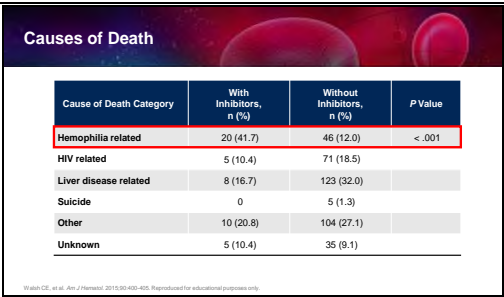
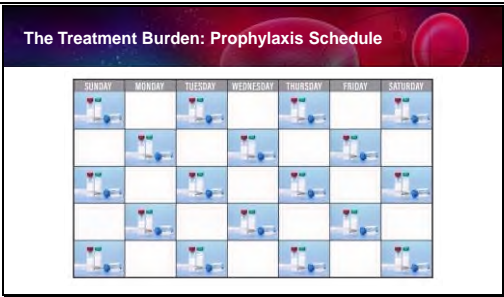
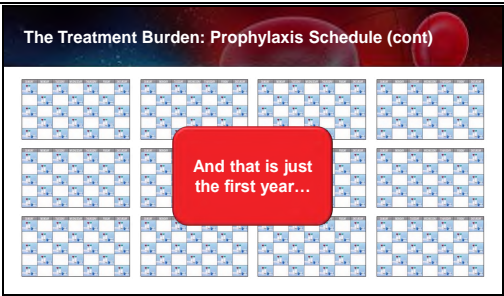
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<p>37</p>		<p>And I'll point out to you, as you look here on the bottom at the ages, these are patients who started at the age of one-and-a-half on the Joint Outcomes Study and then entered the Joint Outcome Study Continuation at the age of 13, and exited at 18.</p>																								
<p>38</p>		<p>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.</p>																								
<p>39</p>		<p>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 FVIIIIs.</p>																								
<p>40</p>	<table border="1"> <thead> <tr> <th>Character</th> <th>Patients, n (%)</th> <th>Decreased Activity</th> <th>>11 Days Lost From Work or School</th> <th>Use of Cane/Crutches/Walker</th> <th>Use of Wheelchair</th> </tr> </thead> <tbody> <tr> <td>Inhibitor</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No</td> <td>5,519 (86.0)</td> <td>11.0 (<.001)</td> <td>4.4 (<.001)</td> <td>13.4 (<.001)</td> <td>3.4 (<.001)</td> </tr> <tr> <td>Yes</td> <td>901 (14.0)</td> <td>25.4</td> <td>12.3</td> <td>23.1</td> <td>12.9</td> </tr> </tbody> </table> <p>Patients with inhibitors have worse physical functioning</p>	Character	Patients, n (%)	Decreased Activity	>11 Days Lost From Work or School	Use of Cane/Crutches/Walker	Use of Wheelchair	Inhibitor						No	5,519 (86.0)	11.0 (<.001)	4.4 (<.001)	13.4 (<.001)	3.4 (<.001)	Yes	901 (14.0)	25.4	12.3	23.1	12.9	<p>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.</p>
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		<p>those without inhibitors. And they have a 70% higher risk of dying.</p>																												
<p>42</p>	 <p>Causes of Death</p> <table border="1"> <thead> <tr> <th>Cause of Death Category</th> <th>With Inhibitors, n (%)</th> <th>Without Inhibitors, n (%)</th> <th>P Value</th> </tr> </thead> <tbody> <tr> <td>Hemophilia related</td> <td>20 (41.7)</td> <td>46 (12.0)</td> <td>< .001</td> </tr> <tr> <td>HIV related</td> <td>5 (10.4)</td> <td>71 (18.5)</td> <td></td> </tr> <tr> <td>Liver disease related</td> <td>8 (16.7)</td> <td>123 (32.0)</td> <td></td> </tr> <tr> <td>Suicide</td> <td>0</td> <td>5 (1.3)</td> <td></td> </tr> <tr> <td>Other</td> <td>10 (20.8)</td> <td>104 (27.1)</td> <td></td> </tr> <tr> <td>Unknown</td> <td>5 (10.4)</td> <td>35 (9.1)</td> <td></td> </tr> </tbody> </table> <p><small>Wahle CE, et al. Am J Hematol. 2012;93:400-405. Reproduced for educational purposes only.</small></p>	Cause of Death Category	With Inhibitors, n (%)	Without Inhibitors, n (%)	P Value	Hemophilia related	20 (41.7)	46 (12.0)	< .001	HIV related	5 (10.4)	71 (18.5)		Liver disease related	8 (16.7)	123 (32.0)		Suicide	0	5 (1.3)		Other	10 (20.8)	104 (27.1)		Unknown	5 (10.4)	35 (9.1)		<p>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.</p>
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<p>43</p>	 <p>The Treatment Burden: Prophylaxis Schedule</p> <p>A calendar grid showing a prophylaxis schedule. The days of the week are listed at the top: SUNDAY, MONDAY, TUESDAY, WEDNESDAY, THURSDAY, FRIDAY, SATURDAY. The grid shows alternating days with a blue icon representing a treatment session.</p>	<p>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.</p>																												
<p>44</p>	 <p>The Treatment Burden: Prophylaxis Schedule (cont)</p> <p>A grid of 12 small calendar icons representing 12 months. A red callout box in the center says: "And that is just the first year..."</p>	<p>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.</p> <p>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.</p>																												

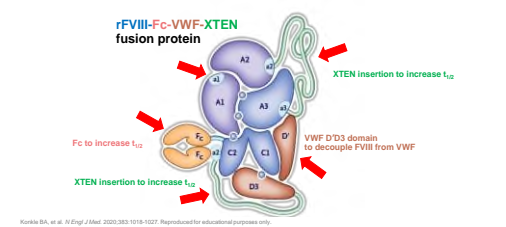
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45	<p>Prophylaxis Schedule With EHL FVIII</p>	<p>There's the extended half-life factor with, for example, a twice-a-week dosing schedule. This would be 104 infusions a year, so it's definitely less than standard half-life factor, but it's still quite a lot of infusions.</p>																									
46	<p>Factor Infusions and Adherence</p> <table border="1"> <caption>Approximate data for Figure 46</caption> <thead> <tr> <th>Adherence Category</th> <th>12-23 months</th> <th>2-5 years</th> <th>6-12 years</th> <th>13-18 years</th> </tr> </thead> <tbody> <tr> <td>0%-25%</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>26%-50%</td> <td>5</td> <td>5</td> <td>10</td> <td>30</td> </tr> <tr> <td>51%-75%</td> <td>20</td> <td>25</td> <td>45</td> <td>50</td> </tr> <tr> <td>76%-100%</td> <td>75</td> <td>70</td> <td>50</td> <td>20</td> </tr> </tbody> </table>	Adherence Category	12-23 months	2-5 years	6-12 years	13-18 years	0%-25%	0	0	0	0	26%-50%	5	5	10	30	51%-75%	20	25	45	50	76%-100%	75	70	50	20	<p>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.</p>
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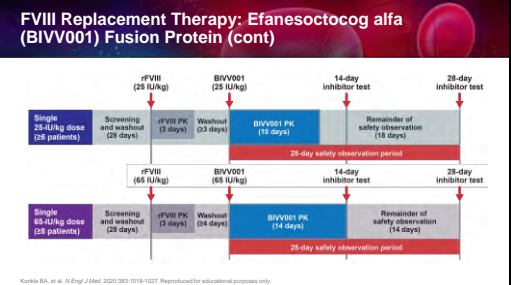
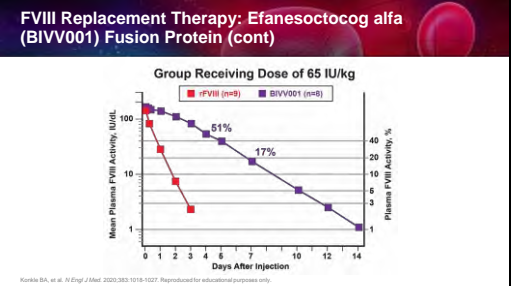
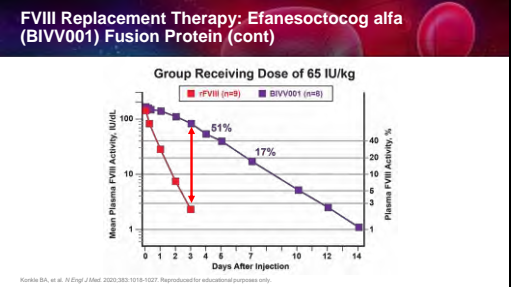
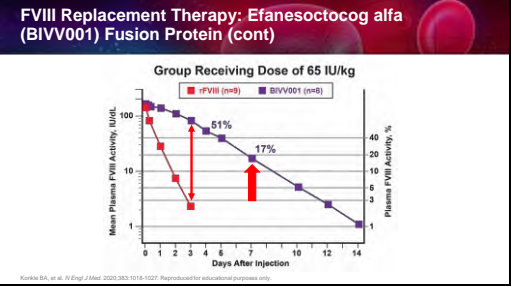
Shifting Goals in Hemophilia A and B: Targeting the Intrinsic Mechanism of Disease Pathology with New Treatments

Hemostasis in Hemophilia: How Improved Disease Knowledge Informs New Treatments

50	<p>Lecture Outline</p> <ul style="list-style-type: none"> ▪ Hemostasis <ul style="list-style-type: none"> – Primary hemostasis – Secondary hemostasis ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ Novel treatments for hemophilia <ul style="list-style-type: none"> – Improving factor therapy – Non-factor therapy <ul style="list-style-type: none"> • Bispecific antibodies – Rebalancing agents 	<p>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.</p>
51	<p>Improving Factor Therapy</p> <p>Efanesoctocog alfa (BIVV001) is a novel experimental FVIII concentrate which aims:</p> <ul style="list-style-type: none"> ▪ To reduce the treatment burden by offering a weekly infusion schedule ▪ Increase the trough levels 	<p>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.</p> <p>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.</p>
52	<p>FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein</p>  <p><small>Konkle BA, et al. N Engl J Med. 2020;383:1018-1027. Reproduced for educational purposes only.</small></p>	<p>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:</p> <p>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.</p> <p>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.</p> <p>By adding this blocking site using the VWF D'D3 domain, this FVIII molecule cannot bind von Willebrand factor.</p>

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		<p>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.</p> <p>So all of these 3 enhancements have led to an enhanced half-life.</p>
53	<p>FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein (cont)</p>  <p><small>Korkeila SA, et al. N Engl J Med. 2020;383:1016-1027. Reproduced for educational purposes only.</small></p>	<p>There was a phase 1 study that is now published in <i>The New England Journal of Medicine</i>. And I'll just show you the data here.</p>
54	<p>FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein (cont)</p>  <p><small>Korkeila SA, et al. N Engl J Med. 2020;383:1016-1027. Reproduced for educational purposes only.</small></p>	<p>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.</p>
55	<p>FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein (cont)</p>  <p><small>Korkeila SA, et al. N Engl J Med. 2020;383:1016-1027. Reproduced for educational purposes only.</small></p>	<p>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.</p>
56	<p>FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein (cont)</p>  <p><small>Korkeila SA, et al. N Engl J Med. 2020;383:1016-1027. Reproduced for educational purposes only.</small></p>	<p>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.</p>

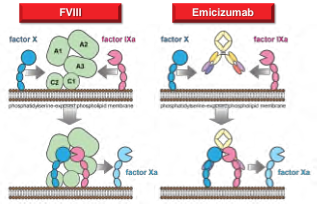
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<p>57</p>	<p>FVIII Replacement Therapy: Efanesoctocog alfa (BIVV001) Fusion Protein (cont)</p> <p>Group Receiving Dose of 65 IU/kg</p> <p>Mean Plasma FVIII Activity, IU/dL (Left Y-axis, 1 to 100)</p> <p>Plasma FVIII Activity, % (Right Y-axis, 1 to 40)</p> <p>Days After Injection (X-axis, 0 to 14)</p> <p>Legend: rFVIII (n=9) [Red squares], BIVV001 (n=8) [Purple squares]</p> <p>Annotations: 51% (at day 7), 17% (at day 14)</p> <p><small>Konkle HA, et al. J Thromb Haemostasis. 2020;20(10):1919-1927. Reproduced for educational purposes only.</small></p>	<p>And even going out to 2 weeks, there's still a 1% level that can be measured out 2 weeks with this molecule.</p> <p>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.</p>																		
<p>58</p>	<p>Other Future FVIII Therapies: Factor-Based</p> <table border="1"> <thead> <tr> <th colspan="3">Hemophilia A Factor Products in Development</th> </tr> <tr> <th>Product</th> <th>MOA</th> <th>Comments</th> </tr> </thead> <tbody> <tr> <td>BIVV 001</td> <td>EHL 2.0</td> <td>Much longer $t_{1/2}$ than current EHL May reduce treatment burden and improve outcomes Phase 3 clinical trials underway</td> </tr> <tr> <td>OCTA 101</td> <td>SC-FVIII</td> <td>Potential for SC-delivery Reduce treatment burden Phase 1 clinical trials are underway</td> </tr> <tr> <td>SIG 001</td> <td>Implanted spheres</td> <td>May provide several years worth of "therapeutic" levels Phase 1 clinical trials are underway</td> </tr> <tr> <td>RANI pill</td> <td>Oral FVIII</td> <td>Uses robotic pill to "inject" factor into intestinal wall Preclinical</td> </tr> </tbody> </table>	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	<p>What about other FVIII therapies?</p> <p>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.</p> <p>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.</p>
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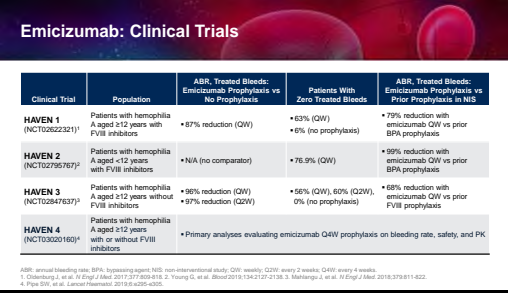
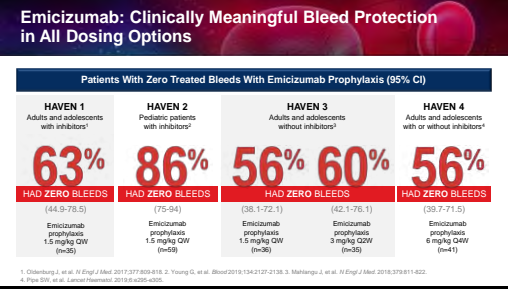
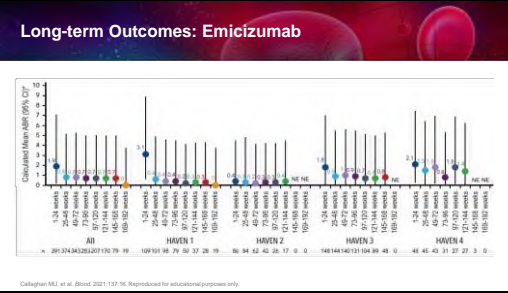
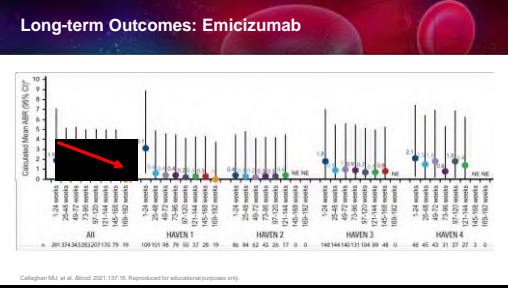
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<p>60</p>	<p>Non-factor Therapy</p> <ul style="list-style-type: none"> Medications that improve hemostasis without replacing the missing factor They are also designed to reduce the treatment burden <ul style="list-style-type: none"> All are designed to be given subcutaneously and at relatively infrequent intervals 	<p>We'll start with nonfactor therapies that are bispecific antibodies.</p> <p>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.</p> <p>So they really are there to address the difficult treatment burden I mentioned earlier.</p>
<p>61</p>	<p>Emicizumab: FVIII Mimetic</p> <ul style="list-style-type: none"> Humanized bispecific antibody Exerts FVIII-mimetic activity Not affected by FVIII inhibitors Good subcutaneous absorption Long $t_{1/2}$ (4-5 weeks)  <p><small>Chen H, et al. N Engl J Med. 2015;373:2530-2541.</small></p>	<p>Emicizumab: We've heard about this molecule. It is now licensed and available throughout the United States for patients with hemophilia A.</p> <p>It's important to understand that this is an FVIII mimetic drug, so it's only going to work in patients with hemophilia A.</p> <p>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 and FIXa to proper alignment, and then generating FXa from that.</p> <p>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.</p>

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<p>62</p>	 <p>Emicizumab: Clinical Trials</p> <table border="1"> <thead> <tr> <th>Clinical Trial</th> <th>Population</th> <th>ABR, Treated Bleeds: Emicizumab Prophylaxis vs No Prophylaxis</th> <th>Patients With Zero Treated Bleeds</th> <th>ABR, Treated Bleeds: Emicizumab Prophylaxis vs Prior Prophylaxis in NIS¹</th> </tr> </thead> <tbody> <tr> <td>HAVEN 1 (NCT02623211)¹</td> <td>Patients with hemophilia A aged ≥12 years with FVIII inhibitors</td> <td>• 87% reduction (QW)</td> <td>• 63% (QW) • 6% (no prophylaxis)</td> <td>• 79% reduction with emicizumab QW vs prior BPA prophylaxis</td> </tr> <tr> <td>HAVEN 2 (NCT02795767)²</td> <td>Patients with hemophilia A aged <12 years with FVIII inhibitors</td> <td>• N/A (no comparator)</td> <td>• 76.9% (QW)</td> <td>• 99% reduction with emicizumab QW vs prior BPA prophylaxis</td> </tr> <tr> <td>HAVEN 3 (NCT02476373)³</td> <td>Patients with hemophilia A aged ≥12 years without FVIII inhibitors</td> <td>• 96% reduction (QW) • 37% reduction (Q2W)</td> <td>• 56% (QW), 60% (Q2W), 0% (no prophylaxis)</td> <td>• 68% reduction with emicizumab QW vs prior FVIII prophylaxis</td> </tr> <tr> <td>HAVEN 4 (NCT03020160)⁴</td> <td>Patients with hemophilia A aged ≥12 years with or without FVIII inhibitors</td> <td>• Primary analyses evaluating emicizumab Q4W prophylaxis on bleeding rate, safety, and PK</td> <td></td> <td></td> </tr> </tbody> </table> <p><small>ABR, annual bleeding rate; BPA, bypassing agent; NIS, non-inhibitor NIS; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks. 1. Oldenburg J, et al. N Engl J Med. 2017;377:800-816. 2. Young G, et al. Blood. 2019;134:2127-2136. 3. Makergo J, et al. N Engl J Med. 2018;379:811-822. 4. Pfaeffli W, et al. Lancet Haematol. 2019;6:e258-265.</small></p>	Clinical Trial	Population	ABR, Treated Bleeds: Emicizumab Prophylaxis vs No Prophylaxis	Patients With Zero Treated Bleeds	ABR, Treated Bleeds: Emicizumab Prophylaxis vs Prior Prophylaxis in NIS ¹	HAVEN 1 (NCT02623211) ¹	Patients with hemophilia A aged ≥12 years with FVIII inhibitors	• 87% reduction (QW)	• 63% (QW) • 6% (no prophylaxis)	• 79% reduction with emicizumab QW vs prior BPA prophylaxis	HAVEN 2 (NCT02795767) ²	Patients with hemophilia A aged <12 years with FVIII inhibitors	• N/A (no comparator)	• 76.9% (QW)	• 99% reduction with emicizumab QW vs prior BPA prophylaxis	HAVEN 3 (NCT02476373) ³	Patients with hemophilia A aged ≥12 years without FVIII inhibitors	• 96% reduction (QW) • 37% reduction (Q2W)	• 56% (QW), 60% (Q2W), 0% (no prophylaxis)	• 68% reduction with emicizumab QW vs prior FVIII prophylaxis	HAVEN 4 (NCT03020160) ⁴	Patients with hemophilia A aged ≥12 years with or without FVIII inhibitors	• Primary analyses evaluating emicizumab Q4W prophylaxis on bleeding rate, safety, and PK			<p>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.</p> <p>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.</p>
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<p>63</p>	 <p>Emicizumab: Clinically Meaningful Bleed Protection in All Dosing Options</p> <p>Patients With Zero Treated Bleeds With Emicizumab Prophylaxis (95% CI)</p> <table border="1"> <thead> <tr> <th>HAVER 1</th> <th>HAVER 2</th> <th>HAVER 3</th> <th>HAVER 4</th> </tr> </thead> <tbody> <tr> <td>Adults and adolescents with inhibitors¹</td> <td>Pediatric patients with inhibitors²</td> <td>Adults and adolescents without inhibitors³</td> <td>Adults and adolescents with or without inhibitors⁴</td> </tr> <tr> <td>63%</td> <td>86%</td> <td>56%</td> <td>60%</td> </tr> <tr> <td>HAD ZERO BLEEDS</td> <td>HAD ZERO BLEEDS</td> <td>HAD ZERO BLEEDS</td> <td>HAD ZERO BLEEDS</td> </tr> <tr> <td>(44.9-78.5)</td> <td>(75-94)</td> <td>(38.1-72.1)</td> <td>(42.1-76.1)</td> </tr> <tr> <td>Emicizumab prophylaxis, 1.5 mg/kg QW (n=36)</td> <td>Emicizumab prophylaxis, 1.5 mg/kg QW (n=69)</td> <td>Emicizumab prophylaxis, 1.5 mg/kg QW (n=36)</td> <td>Emicizumab prophylaxis, 6 mg/kg Q4W (n=41)</td> </tr> </tbody> </table> <p><small>1. Oldenburg J, et al. N Engl J Med. 2017;377:800-816. 2. Young G, et al. Blood. 2019;134:2127-2136. 3. Makergo J, et al. N Engl J Med. 2018;379:811-822. 4. Pfaeffli W, et al. Lancet Haematol. 2019;6:e258-265.</small></p>	HAVER 1	HAVER 2	HAVER 3	HAVER 4	Adults and adolescents with inhibitors ¹	Pediatric patients with inhibitors ²	Adults and adolescents without inhibitors ³	Adults and adolescents with or without inhibitors ⁴	63%	86%	56%	60%	HAD ZERO BLEEDS	HAD ZERO BLEEDS	HAD ZERO BLEEDS	HAD ZERO BLEEDS	(44.9-78.5)	(75-94)	(38.1-72.1)	(42.1-76.1)	Emicizumab prophylaxis, 1.5 mg/kg QW (n=36)	Emicizumab prophylaxis, 1.5 mg/kg QW (n=69)	Emicizumab prophylaxis, 1.5 mg/kg QW (n=36)	Emicizumab prophylaxis, 6 mg/kg Q4W (n=41)	<p>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 to 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.</p>	
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<p>64</p>	 <p>Long-term Outcomes: Emicizumab</p> <p>Calculated Mean ABR (95% CI)*</p> <p>ALL HAVEN 1 HAVEN 2 HAVEN 3 HAVEN 4</p> <p><small>Calaghan MJ, et al. Blood. 2021;137:16. Reproduced for educational purposes only.</small></p>	<p>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.</p>																									
<p>65</p>	 <p>Long-term Outcomes: Emicizumab</p> <p>Calculated Mean ABR (95% CI)*</p> <p>ALL HAVEN 1 HAVEN 2 HAVEN 3 HAVEN 4</p> <p><small>Calaghan MJ, et al. Blood. 2021;137:16. Reproduced for educational purposes only.</small></p>	<p>And what you notice is that the bleed rates in the emicizumab group goes down. That's all the trials together.</p>																									

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<p>66</p>	<p>Long-term Outcomes: Efficizumab</p> <p>Forest plot showing bleed rates (Culicetus Mean ABR (95% CI)) for various studies across HAVEN 1, HAVEN 2, HAVEN 3, and HAVEN 4. The y-axis ranges from 0 to 10. A red arrow points to the HAVEN 1 study, which shows a significantly lower bleed rate compared to the control group.</p>	<p>Specifically, here's HAVEN 1.</p>
<p>67</p>	<p>Long-term Outcomes: Efficizumab</p> <p>Forest plot showing bleed rates (Culicetus Mean ABR (95% CI)) for various studies across HAVEN 1, HAVEN 2, HAVEN 3, and HAVEN 4. A red arrow points to the HAVEN 2 study, which shows a very low bleed rate.</p>	<p>HAVEN 2, we started with a very low bleed rate to start with, so it's going to be hard to improve upon that.</p>
<p>68</p>	<p>Long-term Outcomes: Efficizumab</p> <p>Forest plot showing bleed rates (Culicetus Mean ABR (95% CI)) for various studies across HAVEN 1, HAVEN 2, HAVEN 3, and HAVEN 4. A red arrow points to the HAVEN 3 study, which shows a lower bleed rate compared to the control group.</p>	<p>But in HAVEN 3, you see the bleed rate going down.</p>
<p>69</p>	<p>Long-term Outcomes: Efficizumab</p> <p>Forest plot showing bleed rates (Culicetus Mean ABR (95% CI)) for various studies across HAVEN 1, HAVEN 2, HAVEN 3, and HAVEN 4. A red arrow points to the HAVEN 4 study, which shows a bleed rate similar to the control group.</p>	<p>HAVEN 4 was a smaller study, so you see a little bit up and down which is just statistical noise.</p>
<p>70</p>	<p>Long-term Outcomes: Efficizumab (cont)</p> <p>Stacked bar chart showing the percentage of participants with 0 bleeds (blue) and 1-3 bleeds (light blue) across various studies. The percentage of participants with 0 bleeds increases from left to right.</p>	<p>If we look at the percentage of patients with zero bleeds, again, overall, that increases.</p>

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<p>71</p>	<p>Long-term Outcomes: Emicizumab (cont)</p> <p><small>Colquhoun MJ, et al. Blood 2021;137:16. Reproduced for educational purposes only.</small></p>	<p>And again, HAVEN 1.</p>																								
<p>72</p>	<p>Long-term Outcomes: Emicizumab (cont)</p> <p><small>Colquhoun MJ, et al. Blood 2021;137:16. Reproduced for educational purposes only.</small></p>	<p>HAVEN 2 was already quite high.</p>																								
<p>73</p>	<p>Long-term Outcomes: Emicizumab (cont)</p> <p><small>Colquhoun MJ, et al. Blood 2021;137:16. Reproduced for educational purposes only.</small></p>	<p>HAVEN 3 is increasing.</p>																								
<p>74</p>	<p>Long-term Outcomes: Emicizumab (cont)</p> <p><small>Colquhoun MJ, et al. Blood 2021;137:16. Reproduced for educational purposes only.</small></p>	<p>HAVEN 4 is a little bit up and down.</p>																								
<p>75</p>	<p>Target Joint Resolution: Emicizumab</p> <ul style="list-style-type: none"> Target joint resolution was defined as ≤ 2 spontaneous bleeding events in a 52-week period in a joint previously defined as a target joint¹ 195 of 217 (90%) participants had no spontaneous or traumatic bleeding into a target joint while on emicizumab 498 of 519 (96%) of target joints had ≤ 2 spontaneous or traumatic bleeding events while on emicizumab <p><small>*Target joints were defined as major joints (eg, hip, elbow, wrist, shoulder, knee, and ankle) in which ≥ 3 bleeding events occurred over a 24-week period. Colquhoun MJ, et al. Blood 2021;137:16. 1. Borchers YE, et al. J Thromb Haemost 2014;14:1030-1039. Reproduced for educational purposes only.</small></p> <table border="1"> <thead> <tr> <th>Trial</th> <th>Patients with target joints at baseline, n</th> <th># of target joints at baseline</th> <th>Proportion Resolved (%)</th> </tr> </thead> <tbody> <tr> <td>HAVEN 1</td> <td>68</td> <td>159</td> <td>96.7</td> </tr> <tr> <td>HAVEN 2</td> <td>23</td> <td>45</td> <td>100</td> </tr> <tr> <td>HAVEN 3</td> <td>97</td> <td>236</td> <td>99.2</td> </tr> <tr> <td>HAVEN 4</td> <td>29</td> <td>77</td> <td>100</td> </tr> <tr> <td>TOTAL</td> <td>217</td> <td>519</td> <td>99.2</td> </tr> </tbody> </table>	Trial	Patients with target joints at baseline, n	# of target joints at baseline	Proportion Resolved (%)	HAVEN 1	68	159	96.7	HAVEN 2	23	45	100	HAVEN 3	97	236	99.2	HAVEN 4	29	77	100	TOTAL	217	519	99.2	<p>Importantly, target joint resolution. If you look across the trials, over 99% of target joints in these trials resolved.</p>
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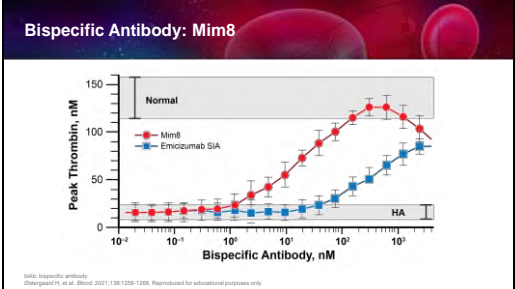
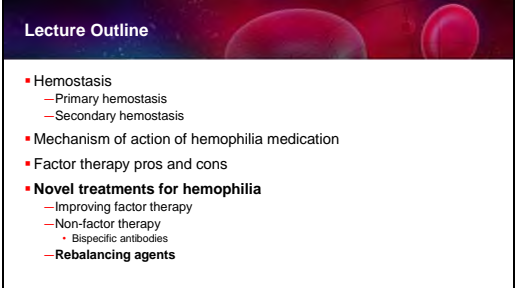
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<p>76</p>	<p>Target Joint Resolution: Emicizumab</p> <p>Proportion of Resolved Target Joints</p> <ul style="list-style-type: none"> Target joint resolution was defined as ≥2 spontaneous bleeding events in a 52-week period in a joint previously defined as a target joint¹ 195 of 217 (90%) participants had no spontaneous or traumatic bleeding into a target joint while on emicizumab 498 of 519 (96%) of target joints had ≥2 spontaneous or traumatic bleeding events while on emicizumab <p>99.2% of target joints resolved²</p> <p><small>*Target joints were defined as major joints (eg, hip, elbow, wrist, shoulder, knee, and ankle) in which ≥3 bleeding events occurred over a 24-week period. ¹Callaghan MJ, et al. Blood. 2021;137:16. ²Reissman DE, et al. J Thromb Haemost. 2014;14(12):2228-2235. Reprinted with editorial permission only.</small></p>	<p>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.</p>																						
<p>77</p>	<p>Long-term Safety: Emicizumab</p> <ul style="list-style-type: none"> No deaths, TE, or TMA events were observed beyond those reported in the HAVEN 1 primary analysis¹ 103 SAEs were reported in 71 participants <ul style="list-style-type: none"> SAEs reported by ≥5 participants were hemorrhage (n=7, 1.8%) and hemarthrosis (n=5, 1.3%) The most common treatment-related AEs were ISRs² (n=104, 26.1%) ADAs with neutralizing potential were observed in <1% (3/398) of participants³ <table border="1"> <thead> <tr> <th>Total number of participants with ≥1 AE, n (%)</th> <th>Total (N=399)⁴</th> </tr> </thead> <tbody> <tr> <td>AE with fatal outcome</td> <td>1 (0.3)</td> </tr> <tr> <td>SAEs</td> <td>71 (17.8)</td> </tr> <tr> <td>AE leading to withdrawal from treatment</td> <td>5 (1.3)</td> </tr> <tr> <td>Grade 3 SAE</td> <td>73 (18.3)</td> </tr> <tr> <td>Related AE</td> <td>134 (33.6)</td> </tr> <tr> <td>Local ISRs</td> <td>107 (26.8)</td> </tr> </tbody> </table> <p>AEs of special interest</p> <table border="1"> <tbody> <tr> <td>Systemic hypersensitivity/anaphylactoid/anaphylactoid reaction</td> <td>1 (0.3)⁵</td> </tr> <tr> <td>TMA event related to concomitant aPCC and emicizumab</td> <td>3 (0.8)</td> </tr> <tr> <td>TE related to concomitant aPCC and emicizumab</td> <td>2 (0.5)</td> </tr> <tr> <td>Other TE (grade 1 device occlusion)</td> <td>1 (0.3)</td> </tr> </tbody> </table> <p><small>¹The safety population only included those patients who received emicizumab. One participant in HAVEN 1 discontinued prior to emicizumab treatment and was excluded from the safety analysis. ²AEs were either bleeding, hemorrhage, or bruising. Hemorrhage, bruising, and bruising of participants that were spontaneous or related to emicizumab treatment. One participant reported a spontaneous bruise and one participant was treated with a systemic systemic hypersensitivity/anaphylactoid/anaphylactoid reaction using the protocol-defined search criteria. However, medical review of the case confirmed that this was not evidence of a systemic hypersensitivity, anaphylactoid, or anaphylactoid reaction. ³ADA: anti-drug antibody; AE: adverse event; aPCC: activated prothrombin complex concentrate; ISRs: injection site reaction; SAE: serious AE; TE: thromboembolic event. ⁴Thrombotic microangiopathy. ⁵Chen Y, et al. N Engl J Med. 2017;377(26):2512-2521. Pao Peck, et al. JOP. 2019;40(10):1000-1005. Reprinted with editorial permission only.</small></p>	Total number of participants with ≥1 AE, n (%)	Total (N=399) ⁴	AE with fatal outcome	1 (0.3)	SAEs	71 (17.8)	AE leading to withdrawal from treatment	5 (1.3)	Grade 3 SAE	73 (18.3)	Related AE	134 (33.6)	Local ISRs	107 (26.8)	Systemic hypersensitivity/anaphylactoid/anaphylactoid reaction	1 (0.3) ⁵	TMA event related to concomitant aPCC and emicizumab	3 (0.8)	TE related to concomitant aPCC and emicizumab	2 (0.5)	Other TE (grade 1 device occlusion)	1 (0.3)	<p>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.</p> <p>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.</p>
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<p>78</p>	<p>Emicizumab: Safety Summary</p> <table border="1"> <thead> <tr> <th>Safety Issue</th> <th>Thrombosis¹</th> <th>TMA^{1,2}</th> <th>Anti-drug Antibody^{3,4}</th> <th>Other⁷</th> </tr> </thead> <tbody> <tr> <td>Frequency</td> <td>3% in Haven 1 Additional reports of MI in patients with risk factors</td> <td>2% in Haven 1 1 other case when aPCC given at high doses (personal communication)</td> <td>Rare 4 reported cases, all in inhibitor patients (3 neutralizing, 1 clearance)</td> <td>Rare (1 case of lupus nephritis which resolved)</td> </tr> <tr> <td>Identification</td> <td>Clinical examination, imaging</td> <td>Laboratory testing</td> <td>Prolonged PTT Additional testing</td> <td>Hematuria</td> </tr> <tr> <td>Mitigation</td> <td>Avoid aPCC at doses >100 IU/kg/d for >24 hours</td> <td>Avoid aPCC at doses >100 IU/kg/d for >24 hours</td> <td>None identified</td> <td></td> </tr> </tbody> </table> <p><small>¹Myocardial infarction; PTT: prothrombin time; TMA: thrombotic microangiopathy. ²Chen Y, et al. N Engl J Med. 2017;377(26):2512-2521. Chelvanayagam S, et al. N Engl J Med. 2017;377(22):2194-2202. 3. Druggals-Holten C, et al. J Thromb Haemost. 2020;20(10):2028-2036. 4. Wessendorf, et al. J Thromb Haemost. 2011;11(11):2118-2124. 5. Reissman DE, et al. J Thromb Haemost. 2017;17(12):2496-2504. 6. Reissman DE, et al. J Thromb Haemost. 2017;17(12):2496-2504. 7. Reissman DE, et al. J Thromb Haemost. 2017;17(12):2496-2504.</small></p>	Safety Issue	Thrombosis ¹	TMA ^{1,2}	Anti-drug Antibody ^{3,4}	Other ⁷	Frequency	3% in Haven 1 Additional reports of MI in patients with risk factors	2% in Haven 1 1 other case when aPCC given at high doses (personal communication)	Rare 4 reported cases, all in inhibitor patients (3 neutralizing, 1 clearance)	Rare (1 case of lupus nephritis which resolved)	Identification	Clinical examination, imaging	Laboratory testing	Prolonged PTT Additional testing	Hematuria	Mitigation	Avoid aPCC at doses >100 IU/kg/d for >24 hours	Avoid aPCC at doses >100 IU/kg/d for >24 hours	None identified		<p>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.</p> <p>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.</p> <p>Obviously, thrombosis is identified by clinical examination and imaging, and TMA by laboratory testing.</p> <p>Antidrug antibodies—these are very rare. There've been 4 reported cases overall: 3 neutralizing, 1 a clearance antibody. In</p>		
Safety Issue	Thrombosis ¹	TMA ^{1,2}	Anti-drug Antibody ^{3,4}	Other ⁷																				
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		<p>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.</p> <p>And then there was 1 rare case of lupus nephritis that was shown, that was presented.</p>
79	 <p>Bispecific Antibody: Mim8</p> <p>Peak Thrombin, nM</p> <p>Bispecific Antibody, nM</p> <p>Normal</p> <p>Mim8</p> <p>Emicizumab SIA</p> <p>HA</p> <p><small>©2019 Cytospecific antibodies. All rights reserved. Reproduced for educational purposes only.</small></p>	<p>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.</p> <p>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.</p> <p>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.</p>
80	 <p>Lecture Outline</p> <ul style="list-style-type: none"> ▪ Hemostasis <ul style="list-style-type: none"> - Primary hemostasis - Secondary hemostasis ▪ Mechanism of action of hemophilia medication ▪ Factor therapy pros and cons ▪ Novel treatments for hemophilia <ul style="list-style-type: none"> - Improving factor therapy - Non-factor therapy <ul style="list-style-type: none"> ▪ Bispecific antibodies ▪ Rebalancing agents 	<p>So let's take a look at rebalancing agents.</p>




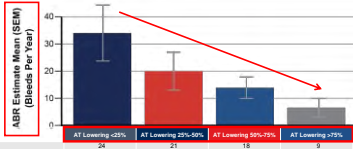
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<p>81</p>	<p>Novel Therapeutics: Mechanisms of Action</p>	<p>Again, this is the coagulation cascade. So we're going to talk about fitusiran; mostly fitusiran. A little bit on serpin PC, and the TFPI inhibitors. But for time's sake, we'll focus just on fitusiran.</p>
<p>82</p>	<p>Balancing the Hemostatic System</p>	<p>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.</p>
<p>83</p>	<p>Balancing the Hemostatic System</p> <p>Bleeding Disorder</p>	<p>If we're missing a protein on the left side, we have a bleeding disorder.</p>
<p>84</p>	<p>Balancing the Hemostatic System</p> <p>Thrombotic Disorder</p>	<p>If we're missing a protein on the right side, we have a thrombotic disorder.</p>
<p>85</p>	<p>Balancing the Hemostatic System</p> <p>Balance Restored — No Bleeding/No Clotting</p>	<p>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.</p>

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86	<p>Balancing the Hemostatic System</p> <p>But, can we get the balance right?</p> 	But can we get the balance, right?																														
87	<p>Balancing the Hemostatic System</p> <p>Poor bleed control No thrombosis</p> 	We may not get the balance right and have poor bleed control, although no risk for thrombosis.																														
88	<p>Balancing the Hemostatic System</p> <p>Good bleed control Thrombotic events</p> 	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	<p>Fitusiran</p> <ul style="list-style-type: none"> Novel siRNA technology Administered subcutaneously 	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	<p>Interim Fitusiran Phase 1 Study Results^a</p> <p>Post hoc analysis of bleed events by AT lowering quartiles</p>  <table border="1" data-bbox="383 1724 773 1776"> <thead> <tr> <th></th> <th>AT Lowering <25%</th> <th>AT Lowering 25%-50%</th> <th>AT Lowering 50%-75%</th> <th>AT Lowering >75%</th> </tr> </thead> <tbody> <tr> <td>Patients*</td> <td>54</td> <td>51</td> <td>51</td> <td>54</td> </tr> <tr> <td>Cumulative days</td> <td>602</td> <td>638</td> <td>662</td> <td>304</td> </tr> <tr> <td>Cumulative bleeds</td> <td>43</td> <td>34</td> <td>26</td> <td>9</td> </tr> <tr> <td>ABR* mean (SEM)</td> <td>34 ± 10</td> <td>20 ± 7</td> <td>14 ± 4</td> <td>6 ± 3</td> </tr> <tr> <td>ABR_{50%} median</td> <td>12</td> <td>11</td> <td>10</td> <td>0</td> </tr> </tbody> </table> <p><small>Fitusiran, et al. ASH 2015. *Data as of November 12, 2015. *Number of patients with time spent in quartile. *For each subject, the ABR in each quartile is calculated by 365.24/(number of bleed events) × (days in quartile). †Based on separate logistic regression models. SEM, standard error of mean; SEM, standard error of mean. Reproduced for educational purposes only.</small></p>		AT Lowering <25%	AT Lowering 25%-50%	AT Lowering 50%-75%	AT Lowering >75%	Patients*	54	51	51	54	Cumulative days	602	638	662	304	Cumulative bleeds	43	34	26	9	ABR* mean (SEM)	34 ± 10	20 ± 7	14 ± 4	6 ± 3	ABR _{50%} median	12	11	10	0	<p>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.</p> <p>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</p>
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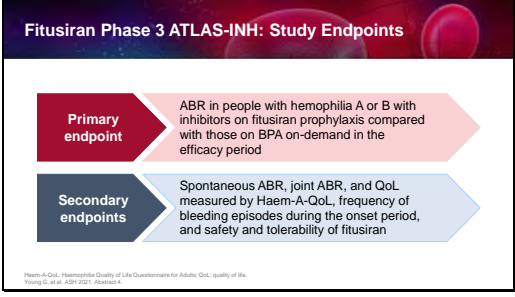
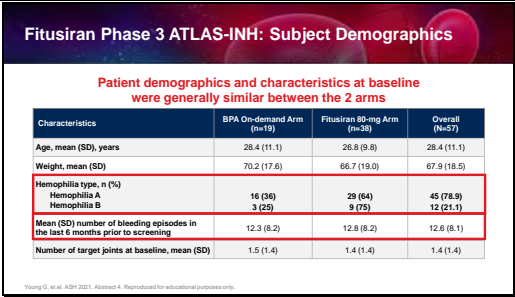
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		<p>as you move to the right, you have greater than 75% antithrombin lowering. You actually end up with fewer bleeding events.</p>																					
<p>91</p>	<p>Fitusiran Phase 2 OLE Interim Results: Exploratory Analysis of Bleeding Events</p> <ul style="list-style-type: none"> Overall median ABR of 0.84 during the observation period <p>ABR in subjects without inhibitors</p> <table border="1"> <tr><th>Treatment</th><th>n</th><th>Median ABR</th></tr> <tr><td>Prophylaxis</td><td>7</td><td>2.0</td></tr> <tr><td>On demand</td><td>12</td><td>12.0</td></tr> <tr><td>Observation period</td><td>19</td><td>1.01</td></tr> </table> <p>Median duration in observation period: 36 months (range: 5-45 months)</p> <p>ABR in subjects with inhibitors</p> <table border="1"> <tr><th>Period</th><th>n</th><th>Median ABR</th></tr> <tr><td>Prestudy</td><td>19</td><td>42.0</td></tr> <tr><td>Observation period</td><td>19</td><td>0.44</td></tr> </table> <p>Median duration in observation period: 28 months (range: 7-36 months)</p>	Treatment	n	Median ABR	Prophylaxis	7	2.0	On demand	12	12.0	Observation period	19	1.01	Period	n	Median ABR	Prestudy	19	42.0	Observation period	19	0.44	<p>This is a phase 2 ongoing extension study. Open-label extension is what OLE stands for.</p> <p>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.</p> <p>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.</p> <p>So this is the phase 2 ongoing extension study.</p>
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<p>92</p>	<p>Fitusiran Phase 3 ATLAS-INH: Study Design</p> <ul style="list-style-type: none"> The study included eligible male patients (aged ≥ 12 years), with hemophilia A or B with inhibitors, receiving on-demand treatment with BPA^a <ul style="list-style-type: none"> Patients were randomized 2:1 to receive monthly 80-mg subcutaneous fitusiran prophylaxis, with use of on-demand BPAs for treatment of breakthrough bleeds, or to continue with on-demand BPA <p>The phase 3 ATLAS-INH study (NCT03417102) was designed to evaluate the efficacy and safety of fitusiran in people with hemophilia A or B with inhibitors</p>	<p>Recently, the phase 3 studies have been presented. There are 3 of them:</p> <p>The ATLAS-INH, which is the inhibitor study for patients older than 12.</p> <p>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.</p> <p>And then just recently at ISTH, we had the ATLAS-PPX, or prophylaxis study, which compared patients coming in on prophylaxis.</p> <p>So in other words, this study is inhibitor patients and we're comparing fitusiran to on-demand treatment. The A/B study that</p>																					

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		<p>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.</p> <p>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.</p> <p>So here, we have patients randomized to either fitusiran or continued on-demand treatment. Again, these are patients with inhibitors, hemophilia A or B.</p>																																
93		<p>The main endpoint was ABR. And then there's a number of secondary endpoints.</p>																																
94	 <table border="1" data-bbox="321 1304 768 1461"> <thead> <tr> <th>Characteristic</th> <th>BPA On-demand Arm (n=19)</th> <th>Fitusiran 80-mg Arm (n=38)</th> <th>Overall (N=57)</th> </tr> </thead> <tbody> <tr> <td>Age, mean (SD), years</td> <td>28.4 (11.1)</td> <td>26.8 (9.8)</td> <td>28.4 (11.1)</td> </tr> <tr> <td>Weight, mean (SD)</td> <td>70.2 (17.6)</td> <td>66.7 (19.0)</td> <td>67.9 (18.5)</td> </tr> <tr> <td>Hemophilia type, n (%)</td> <td></td> <td></td> <td></td> </tr> <tr> <td> Hemophilia A</td> <td>16 (36)</td> <td>29 (64)</td> <td>45 (78.9)</td> </tr> <tr> <td> Hemophilia B</td> <td>3 (25)</td> <td>9 (75)</td> <td>12 (21.1)</td> </tr> <tr> <td>Mean (SD) number of bleeding episodes in the last 6 months prior to screening</td> <td>12.3 (8.2)</td> <td>12.8 (8.2)</td> <td>12.6 (8.1)</td> </tr> <tr> <td>Number of target joints at baseline, mean (SD)</td> <td>1.5 (1.4)</td> <td>1.4 (1.4)</td> <td>1.4 (1.4)</td> </tr> </tbody> </table>	Characteristic	BPA On-demand Arm (n=19)	Fitusiran 80-mg Arm (n=38)	Overall (N=57)	Age, mean (SD), years	28.4 (11.1)	26.8 (9.8)	28.4 (11.1)	Weight, mean (SD)	70.2 (17.6)	66.7 (19.0)	67.9 (18.5)	Hemophilia type, n (%)				Hemophilia A	16 (36)	29 (64)	45 (78.9)	Hemophilia B	3 (25)	9 (75)	12 (21.1)	Mean (SD) number of bleeding episodes in the last 6 months prior to screening	12.3 (8.2)	12.8 (8.2)	12.6 (8.1)	Number of target joints at baseline, mean (SD)	1.5 (1.4)	1.4 (1.4)	1.4 (1.4)	<p>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.</p> <p>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.</p> <p>Most of them have target joints.</p>
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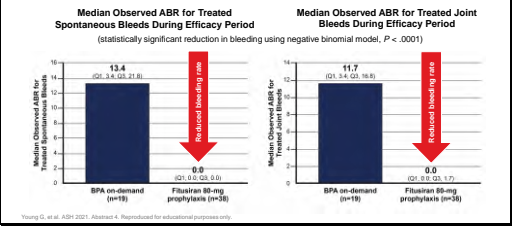
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<p>95</p>	<p>Fitusiran Phase 3 ATLAS-INH: Bleeding Events (Primary Endpoint)</p> <p>Observed Median ABR of 0.0 for Treated Bleeds (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p> <p>ICR: Interquartile range. Young D, et al. ASH 2021. Abstract 4. Reproduced for educational purposes only.</p>	<p>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.</p>
<p>96</p>	<p>Fitusiran Phase 3 ATLAS-INH: Bleeding Events (Primary Endpoint)</p> <p>Observed Median ABR of 0.0 for Treated Bleeds (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p> <p>ICR: Interquartile range. Young D, et al. ASH 2021. Abstract 4. Reproduced for educational purposes only.</p>	<p>The means, on the left, the means went from 18 down to 1.7.</p>
<p>97</p>	<p>Fitusiran Phase 3 ATLAS-INH: Analysis of Patients With Zero Bleeding Events</p> <p>Zero Observed Treated Bleeding Events (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p> <p>Young D, et al. ASH 2021. Abstract 4. Reproduced for educational purposes only.</p>	<p>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.</p>
<p>98</p>	<p>Fitusiran Phase 3 ATLAS-INH: Analysis of Patients With Zero Bleeding Events</p> <p>Zero Observed Treated Bleeding Events (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p> <p>Young D, et al. ASH 2021. Abstract 4. Reproduced for educational purposes only.</p>	<p>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.</p>
<p>99</p>	<p>Fitusiran Phase 3 ATLAS-INH: Treated Spontaneous and Joint Bleeds (Secondary Endpoints)</p> <p>Median Observed ABR for Treated Spontaneous Bleeds During Efficacy Period (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p> <p>Median Observed ABR for Treated Joint Bleeds During Efficacy Period (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p> <p>Young D, et al. ASH 2021. Abstract 4. Reproduced for educational purposes only.</p>	<p>If we take a look at spontaneous bleeds or treated bleeds, we again see the same reductions.</p>

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<p>100</p>	<p>Fitusiran Phase 3 ATLAS-INH: Treated Spontaneous and Joint Bleeds (Secondary Endpoints)</p>  <p>Median Observed ABR for Treated Spontaneous Bleeds During Efficacy Period (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p> <p>Median Observed ABR for Treated Joint Bleeds During Efficacy Period (statistically significant reduction in bleeding using negative binomial model, $P < .0001$)</p>	<p>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.</p>																																	
<p>101</p>	<p>Fitusiran Phase 3 ATLAS-INH Results: Safety and Tolerability</p> <p>Overview of TEAEs</p> <table border="1" data-bbox="305 653 781 810"> <thead> <tr> <th>TEAE Category, n (%)</th> <th>BPA On-demand (n=19)</th> <th>Fitusiran 80-mg Prophylaxis (n=47)</th> </tr> </thead> <tbody> <tr> <td>Any TEAE</td> <td>11 (57.9)</td> <td>38 (92.7)</td> </tr> <tr> <td>Any TESA</td> <td>5 (26.3)</td> <td>7 (17.1)</td> </tr> <tr> <td>Any TEAE SI</td> <td>0 (0)</td> <td>11 (26.8)</td> </tr> <tr> <td>Any TEAE leading to treatment discontinuation</td> <td>0 (0)</td> <td>1 (2.4)</td> </tr> <tr> <td>Any TEAE leading to death</td> <td>0 (0)</td> <td>0 (0)</td> </tr> </tbody> </table> <p>TEAE, treatment-emergent adverse event; TESA, TEAE of special interest.</p>	TEAE Category, n (%)	BPA On-demand (n=19)	Fitusiran 80-mg Prophylaxis (n=47)	Any TEAE	11 (57.9)	38 (92.7)	Any TESA	5 (26.3)	7 (17.1)	Any TEAE SI	0 (0)	11 (26.8)	Any TEAE leading to treatment discontinuation	0 (0)	1 (2.4)	Any TEAE leading to death	0 (0)	0 (0)	<p>There were some adverse events; in particular, 11 treatment-emergent adverse events of special interest in the fitusiran group.</p>															
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<p>102</p>	<p>Fitusiran Phase 3 ATLAS-INH Results: Safety and Tolerability (cont)</p> <p>TEAE SIs</p> <table border="1" data-bbox="305 951 781 1125"> <thead> <tr> <th>AESI Category Preferred Term, n (%)</th> <th>BPA On-demand (n=19)</th> <th>Fitusiran 80-mg Prophylaxis (n=47)</th> </tr> </thead> <tbody> <tr> <td colspan="3">ALT or AST elevations $\geq 3 \times$ ULN</td> </tr> <tr> <td>Increased transaminases</td> <td>0 (0)</td> <td>5 (12.2)</td> </tr> <tr> <td>Increased ALT</td> <td>0 (0)</td> <td>4 (9.8)</td> </tr> <tr> <td>Increased hepatic enzyme</td> <td>0 (0)</td> <td>1 (2.4)</td> </tr> <tr> <td>Cholestasis</td> <td>0 (0)</td> <td>1 (2.4)</td> </tr> <tr> <td colspan="3">Suspected or confirmed TEAEs</td> </tr> <tr> <td>Deep vein thrombosis</td> <td>0 (0)</td> <td>1 (2.4)</td> </tr> <tr> <td>Subclavian vein thrombosis</td> <td>0 (0)</td> <td>1 (2.4)</td> </tr> <tr> <td>Thrombophlebitis superficial</td> <td>0 (0)</td> <td>1 (2.4)</td> </tr> <tr> <td>Thrombosis</td> <td>0 (0)</td> <td>1 (2.4)</td> </tr> </tbody> </table> <p>Differences in reported TEAE SIs between the fitusiran prophylaxis arm and BPA on-demand arm were consistent with previously identified risks of fitusiran.</p> <p>ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.</p>	AESI Category Preferred Term, n (%)	BPA On-demand (n=19)	Fitusiran 80-mg Prophylaxis (n=47)	ALT or AST elevations $\geq 3 \times$ ULN			Increased transaminases	0 (0)	5 (12.2)	Increased ALT	0 (0)	4 (9.8)	Increased hepatic enzyme	0 (0)	1 (2.4)	Cholestasis	0 (0)	1 (2.4)	Suspected or confirmed TEAEs			Deep vein thrombosis	0 (0)	1 (2.4)	Subclavian vein thrombosis	0 (0)	1 (2.4)	Thrombophlebitis superficial	0 (0)	1 (2.4)	Thrombosis	0 (0)	1 (2.4)	<p>And these comprised mostly ALT elevations, as you see at the top.</p> <p>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.</p> <p>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.</p> <p>The other patient had a suspected thrombotic event called a spinal vessel thrombosis that wasn't really quite confirmed.</p> <p>But those are the adverse events of special interest.</p>
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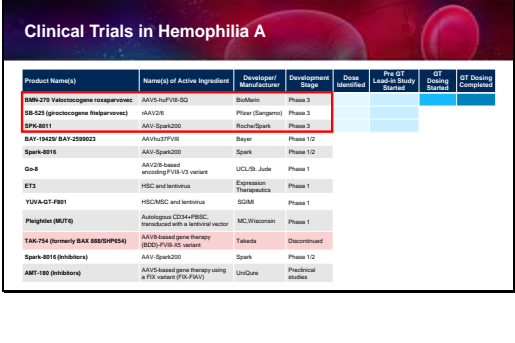
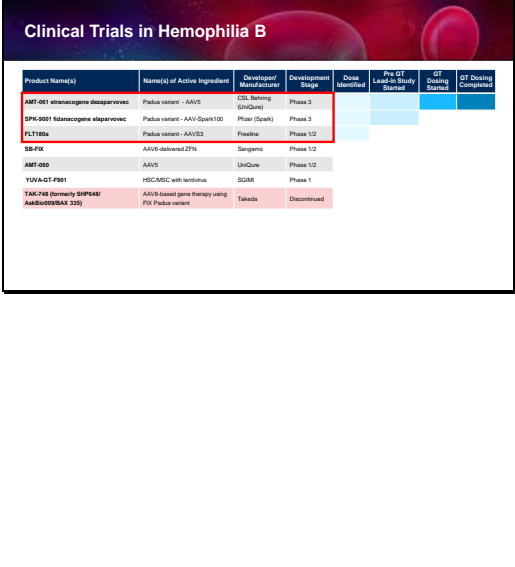
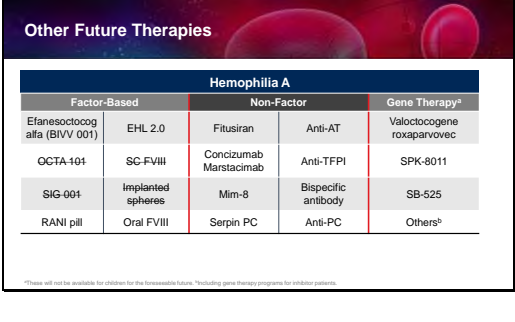
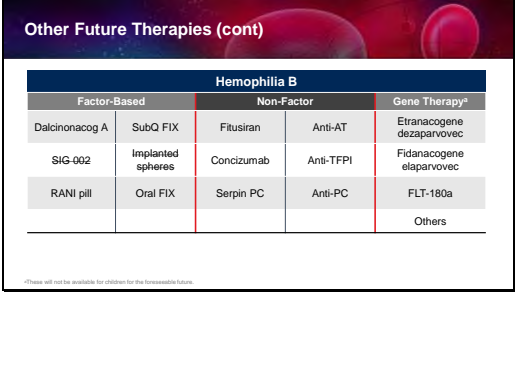
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103	<p>Other Rebalancing Agents</p> <ul style="list-style-type: none"> ▪ Inhibitors of coagulation inhibitors <ul style="list-style-type: none"> – Inhibitors of TFPI – Inhibitors of APC and PC – Inhibitors of PS ▪ Administered subcutaneously <ul style="list-style-type: none"> – Some are daily – Some are weekly – Some are monthly 	<p>I don't have time to get into these other molecules. There are clinical data available for some of these.</p>																																
104	<p>Molecules in Development</p> <table border="1"> <thead> <tr> <th>MOA</th> <th>Molecule</th> <th>Development Stage</th> <th>Comments</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Anti-TFPI</td> <td>BAY1093884 (Bayer)</td> <td>Program discontinued</td> <td>3 thrombotic events led to discontinuation</td> </tr> <tr> <td>MG1113 (Green Cross)</td> <td>Phase 1</td> <td>Single ascending dose phase 1 study has started</td> </tr> <tr> <td>Marstacimab (Pfizer)</td> <td>Phase 3</td> <td>Weekly subcutaneous dosing; phase 3 just started</td> </tr> <tr> <td rowspan="2">Anti-APC</td> <td>Concizumab (Novo Nordisk)</td> <td>Phase 3</td> <td>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</td> </tr> <tr> <td>Serpin PC (Apcointex)</td> <td>Phase 1</td> <td>Phase 1 study has started</td> </tr> <tr> <td>Anti-APC</td> <td>Anti-APC mAb</td> <td>Preclinical</td> <td>Last data from ASH 2016 abstract; unclear if this program is ongoing</td> </tr> <tr> <td rowspan="2">Anti-PS</td> <td>PS siRNA</td> <td>Preclinical</td> <td>Data only available from a Blood paper in 2018;</td> </tr> <tr> <td>Anti-PS mAb</td> <td>Preclinical</td> <td>unclear if this program is continuing</td> </tr> </tbody> </table>	MOA	Molecule	Development Stage	Comments	Anti-TFPI	BAY1093884 (Bayer)	Program discontinued	3 thrombotic events led to discontinuation	MG1113 (Green Cross)	Phase 1	Single ascending dose phase 1 study has started	Marstacimab (Pfizer)	Phase 3	Weekly subcutaneous dosing; phase 3 just started	Anti-APC	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	Serpin PC (Apcointex)	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	Data only available from a Blood paper in 2018;	Anti-PS mAb	Preclinical	unclear if this program is continuing	<p>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.</p> <p>We've got the Pfizer product, marstacimab, which is in phase 3.</p> <p>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.</p> <p>The serpin PC molecules is in phase 1 and soon to start phase 3.</p> <p>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.</p> <p>So that's really the summary of these molecules.</p>
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105	<p>Gene Therapy</p> <ul style="list-style-type: none"> ▪ 1-time infusion with the goal to provide a "therapeutic" factor level permanently (aspirational goal) 	<p>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.</p>																																

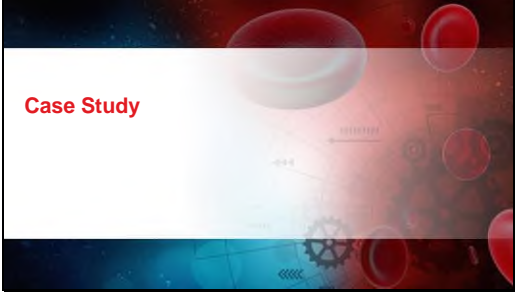
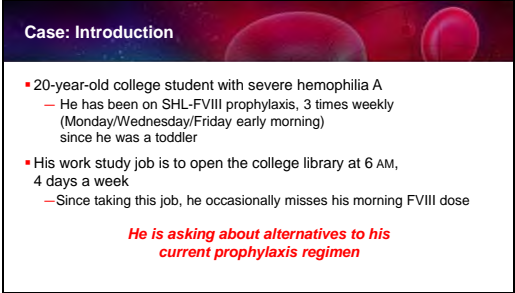
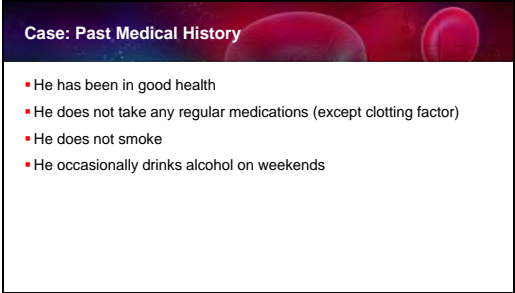
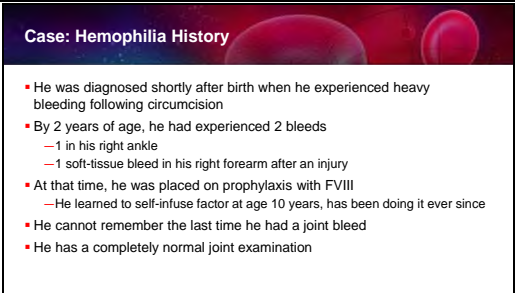
Shifting Goals in Hemophilia A and B: Targeting the Intrinsic Mechanism of Disease Pathology with New Treatments

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		<p>For hemophilia B nonfactor therapies, again, we mentioned fitusiran, concizumab, and marstacimab, as well as serpin PC and then the gene therapy molecules.</p>
110	 <p>Case Study</p>	<p>A case study for you here with a 20-year-old college student with severe hemophilia A.</p>
111	 <p>Case: Introduction</p> <ul style="list-style-type: none"> ▪ 20-year-old college student with severe hemophilia A <ul style="list-style-type: none"> – He has been on SHL-FVIII prophylaxis, 3 times weekly (Monday/Wednesday/Friday early morning) since he was a toddler ▪ His work study job is to open the college library at 6 AM, 4 days a week <ul style="list-style-type: none"> – Since taking this job, he occasionally misses his morning FVIII dose <p><i>He is asking about alternatives to his current prophylaxis regimen</i></p>	<p>He'd been on a standard half-life prophylactic molecule 3 times a week since he was a very young child, a toddler.</p> <p>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.</p> <p>He's asking about alternatives to his current prophylaxis regimen.</p>
112	 <p>Case: Past Medical History</p> <ul style="list-style-type: none"> ▪ He has been in good health ▪ He does not take any regular medications (except clotting factor) ▪ He does not smoke ▪ He occasionally drinks alcohol on weekends 	<p>He's otherwise in good health. Doesn't take other medications. Doesn't smoke. Drinks occasional alcohol.</p>
113	 <p>Case: Hemophilia History</p> <ul style="list-style-type: none"> ▪ He was diagnosed shortly after birth when he experienced heavy bleeding following circumcision ▪ By 2 years of age, he had experienced 2 bleeds <ul style="list-style-type: none"> – 1 in his right ankle – 1 soft-tissue bleed in his right forearm after an injury ▪ At that time, he was placed on prophylaxis with FVIII <ul style="list-style-type: none"> – He learned to self-infuse factor at age 10 years, has been doing it ever since ▪ He cannot remember the last time he had a joint bleed ▪ He has a completely normal joint examination 	<p>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.</p> <p>He hasn't really had joint bleeds, and he's been pretty good at doing all of his infusions. So he's been, generally</p>

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		speaking, quite adherent. It's just that this 6 AM job is making things very challenging.
114	<p>Case: Hemophilia History (cont)</p> <ul style="list-style-type: none"> ▪ As a child he was active but never participated in sports ▪ He is now becoming more active <ul style="list-style-type: none"> — He goes to the campus gym where he is working out regularly — He is also playing soccer with friends on the weekends <p><i>He is interested in a more convenient dosing schedule, but is concerned about having bleeds</i></p>	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	<p>Case: What Treatment Would You Consider?</p> <ul style="list-style-type: none"> ▪ 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	<p>Case: What Treatment Would You Consider?</p> <ul style="list-style-type: none"> ▪ 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	<p>Case: What Treatment Would You Consider?</p> <ul style="list-style-type: none"> ▪ BIVV001 (investigational) – 1x a week dosage ▪ Subcutaneous therapy options ▪ Importance of shared decision-making and assessing preference <ul style="list-style-type: none"> — 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.

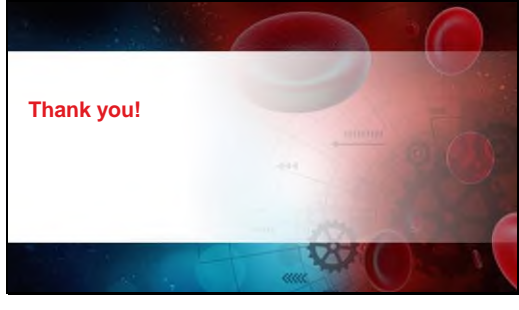
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		<p>Those are the questions you need to ask. And then understanding the molecules that are available and those that will become available in the not-too-distant future so you can make the best choice for your patient.</p>
118	 <p>Conclusions</p> <ul style="list-style-type: none">▪ Diverse therapies in the pipeline for hemophilia▪ More choices to consider when individualizing treatment selection<ul style="list-style-type: none">— Children vs. adults— Inhibitors vs. no inhibitors— Level of adherence▪ Potential for gene therapy	<p>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 FVIII. And then there were some different options you had there.</p> <p>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.</p> <p>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.</p> <p>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.</p>

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