Welcome to Management of Elective Surgery in patients with hemophilia. First, Dr. Christopher Ludlam will talk about elective orthopedic surgery in a hemophilia patient from the hematologist’s perspective, in the second presentation, Dr. Adolpho Llinás will speak to us about the same issue from the orthopedist’s perspective, and in the third segment, Dr. Mark Reding will be speaking about surgery in patients with inhibitors.
Glad that I can join you by telephone and give this introduction in which I'm going to review aspects of orthopedic management in hemophilia, both medical, and just a little bit from the orthopedic point of view.
Surgery in Hemophilia

- General surgery in hemophilia can be accomplished with outcomes equivalent to those in individuals with normal hemostasis.

It’s generally assumed that surgery in hemophilia can be safely accomplished these days, but there are very few studies that have actually looked at this objectively.
This is a study that came to my attention recently. It compares abdominal surgery in 55 patients with hemophilia to an equal number of individuals without the congenital bleeding disorder. And what was encouraging was that all patients with hemophilia had good outcome and interestingly enough, blood loss in those with hemophilia was similar to those with normal coagulation, but perhaps it was not surprising that those with hemophilia stayed in hospital a little bit longer because of the need to give them factor 8 infusions.
But what of the outlook for those with hemophilia who require orthopedic surgery?

**Surgery in Hemophilia**

- General surgery in hemophilia can be accomplished with outcomes equivalent to those in individuals with normal hemostasis
- What is outlook for those with hemophilia who require orthopedic surgery?
Let me consider, first of all, the medical status of our patients. Clearly, they’ve got a bleeding disorder, usually hemophilia A or hemophilia B, and what emerged recently is that the severity and frequency of joint bleeds and the need for surgery in hemophilia B appears to be considerably less than the hemophilia A, and I want to come back to tell you a bit more about this in a moment.

Secondly, there’s a potential difficulty for those with mild hemophilia A because what emerged in the last few years is that, in some patients with mild hemophilia, the level of factor A depends on whether you use a 1 stage clotting assay, or a chromogenic assay, to measure the level, and again, I’ll come back to this in a moment.

Clearly, it’s important to know whether your patient currently has an inhibitor and Mark Reding is going to tell you much more about how to manage such patients later. But it’s also important to know that whether the patient has had an inhibitor in the past, because if they have, then there’s an increased chance that this could recur in the post operative period.

(Continued)
You’ll see that I think it’s important to know the viral status of the patient and perhaps this is less important now than it used to be because a number of years ago, having HIV was an absolute contra indication to orthopedic surgery. However, with better management of HIV, it’s now possible to undertake surgery safely in patients who are infected.

The problem before, was that the prosthetic joints were a focus for infection and so, post operative infection in the joint became a problem leading to it loosening and potentially failure of joint which then had to be replaced. As you’ll see, I’ve mentioned that variant Creutzfeldt-Jakob disease is a possible situation that has to be taken into account. Fortunately, this is only in the UK and usually doesn’t affect patients requiring orthopedic surgery, so only causes a difficulty if lymphoid tissue or the central nervous system is operated upon.

It’s important though, from the point of view of hepatitis viruses to make sure that your patient doesn’t have severe liver disease such that they have a coagulopathy. This is uncommon in patients who come to orthopedic surgery in hemophilia because by the time you get the coagulopathy, the liver disease is usually manifest by ascites or other signs of the liver disease.

So these are the main factors that need to be thought about when considering a patient with hemophilia for orthopedic surgery.
This was an interesting study published last year from Italy looking at the number of the arthroplasties that have been undertaken in the country, and as you can see there were 253 for hemophilia A and only 19 for hemophilia B. Now we all know that hemophilia B is much less prevalent, it’s 5 or 6 more less prevalent than hemophilia A, but even taking that into account, the authors of this study concluded that there was about a 3 times increase instance of need for surgery in hemophilia A compared to hemophilia B, and this, perhaps, are caused with some other recent data that’s emerged, suggesting the bleeding incidence in severe hemophilia B may be less than hemophilia A, they bleed, less frequently and therefore, perhaps, have less severe joint damage.

But what’s good to know about this study is the outcome of surgery in hemophilia A and hemophilia B was equivalent.
This relates to the assessment of the factor VIII level in mild hemophilia A. What’s become apparent though, over the last few years is that certain individuals with mild hemophilia A have factor VIII levels when they’re measured by a 1 stage clotting assay, are very different from when they’re measured with 2 stage or a chromogenic assay, and these individuals with discordant factor VIII provoked a lot of interest. The European Association for Hemophilia and Allied Disorders has set up a project that Professor Johannes Oldenburg is leading and is going to include colleagues from the United States.

This slide and the next one, kindly lent by Professor Oldenburg, looks at some of the new patients that give rise to these discordant factor VIII levels. In this slide, which illustrates the mutations that cause a 1 stage clotting assay result to be higher than the chromogenic, these mutations tend to be in the interface between the A1, A2, and A3 domains and it’s so possible that the reason why the discrepancy arises in these individuals is because there’s a more rapid dissociation of the two A2 domains from the rest of the molecule.
This is the reverse situation. These are individuals who have a 1 stage clotting assay that is lower than the chromogenic assay and Professor Oldenburg has plotted these on this molecular diagram and many of the sites are, in fact, related to thrombin cleavage sites in the molecule and for this reason, is why these patients have 1 stage clotting levels that are lower than the chromogenic.

So, it’s important in patients with mild hemophilia before embarking on surgery, to measure the levels of factor VIII by the 1 stage assay and the chromogenic assay and to try to ascertain which you think is the true level and which correlates perhaps best with the phenotype in that particular individual. This is an area of evolution and ongoing work and hopefully, there’ll be more in future about this group of patients particularly relating to the phenotype and genotype to the clinical situation.
I'd like to talk briefly about the orthopedic status of the patient; although I appreciate I am, to some extent, treading on Dr. Llinás' toes, but this is a physician’s view of orthopedics and I already considered the situation in hemophilia B less severe perhaps, than hemophilia A. But then we come on to the indications for surgery and synovectomy is a very good procedure, particularly in young individuals who have recurrent bleeding in to target joints.

Most of my thoughts from now on, will be related to arthroplasty surgery because that’s where I have more experience and the principal indication, I think, for an arthroplasty, is recurrent, uncontrollable joint bleeding or pain. Now, what I think is not appreciated by most hematologists is that the arthritis in hemophilia, when it comes to surgery, is much more severe than the arthritis that is found in non-hemophilic patients.

Not only is the joint topology much more severe, but there’s extensive fibrosis around the joint limiting the joint’s motion and the range of movement, those often associated quite severe muscle atrophy, and furthermore, the bone stock is weak, both from osteoporosis and from cysts. So, technically, the surgery is much harder than that for non-hemophiliacs and furthermore, the problems are compounded in the post-operative period because patients may have difficulty mobilizing with crutches after the surgery because of arthropathy in other joints.

In other words, if they’ve had a knee replacement, when they come to get up on crutches, if they have arthropathy in their elbows, they find it very difficult to get up and hobble around.
Not only is hemophilic arthropathy more severe than in non-hemophilia individuals, but individuals with hemophilia who have an inhibitor, have more severe arthropathy than patients with hemophilia who don’t have an inhibitor and this is being contemplated recently by Professor Morfini from Florence. He looked at patients with inhibitors and saw that they were spending more time off school, had more social disadvantage, more away from university, than non-inhibitor patients and they had a greater need for mobility aids, they needed to go to the hemophilia center more often and furthermore, their X-rays demonstrated more severe arthropathy and the clinic assessment of them demonstrates that they had more severe joint damage than non-inhibitor patients.

And I think all of this will be very relevant to Dr. Reding’s presentation because not only do these patients have more severe joint damage, but it’s harder to achieve hemostasis.
How is orthopedic surgery different in hemophilia?

- Management needs to be individualized
  - Protocol
- Surgery technically more difficult
- Avoid spinal anesthesia
- “Gentle” and graded mobilization
  - Especially if need for partial severance of patella tendon

Having considered some of the background issues, how does the actual practicality of orthopedic surgery in hemophilia differ from those who don’t have hemophilia?

Well, I think it firstly requires a team approach between the hemophilia position, the surgeon, the anesthetist, the post-operative ward, in our case, we’re trying a high dependency unit for a few days. Each of the patients, I think, needs to be considered individually. They’ve got individual difficulties and different clotting abnormalities and so, we draw up a written protocol to make it very clear how the patient should be managed, particularly from the point of view of hemophilia. We hang this protocol at the bottom of the bed so that everyone can see it and follow it.

As I’ve already described, I think the surgery is technically more difficult than in a non-hemophilia patient. We avoid spinal anesthesia because despite giving factor VIII therapy, we’re very concerned that there might be a spinal hematoma. Following surgery, we get patients up, perhaps rather more gently, than a non-hemophiliac and particularly if they’ve had partial severance of the patella tendons, this is sometimes necessary to gain access, fully, to the joint if there’s considerable fibrosis.
How should the clotting factor concentrate be given? I think Dr. Reding’s going to talk a little bit more about this, but briefly, it can be given either as a bolus infusion or continuous infusion. By bolus, for hemophilia A it to be given about 3 times a day for two or three days and then twice daily for 10 or 14 days and initially, the drop level should be about 50%.

This is often a good way to treat patients, particularly if they have severe hemophilia and are used to treating themselves at home. They can treat themselves usually from the second or third post operative day. The disadvantage of bolus infusions, particularly if they’ve been given by the ward staff, is that it is only too easy for a single dose to be missed, particularly evening or overnight and clearly if this happens, the factor VIII level falls and there’s a much increased risk of bleeding.

The alternative is to use continuous infusion. This has been very popular in many units and we find it very useful to have in an orthopedic ward, which is some distance from the hemophilia center. The difficulty is that occasionally, the intravenous cannula becomes displaced from the vein and the infusion is given subcutaneously or occasionally, the pump fails. In both these instances, the factor VIII level clearly falls fairly rapidly, and may result in a bleed.

I think it’s now a generally accepted practice that a fibrinolytic inhibitor should be given to patients during and following orthopedic surgery and there isn’t hard evidence to demonstrate it’s value but the impression is that there’s probably less bleeding.
Fibrin glue, which consists of fibrinogen and thrombin mixture, is used by many surgeons to help secure hemostasis at the operation site. The mixture not only contains thrombin and fibrinogen, which is converted to fibrin, this also contains factor XIII and fibronectin because these co-precipitate in preparation with fibrinogen and hence, when the fibrinogen is converted to fibrin, it’s then cross linked by factor XIII and to make it a much firmer clot.
What are the “medical” complications of orthopedic surgery?

- Post-operative bleeding
  - Factor VIII/IX not given on time!
  - Intravenous cannula displaced
  - Insufficient VIII/IX concentrate administered
  - Development of anti-factor VIII inhibitor
  - Bleeding predisposes to infection
- Infection
- Development of anti-factor VIII inhibitors
- Thrombosis
  - DVT/PE
  - VTE in vWD

DVT = deep vein thrombosis; PE = pulmonary embolism; vWD = von Willebrand disease.

What are the medical complications of orthopedic surgery?

The one that we are clearly all concerned about is post operative bleeding. I’ve listed here a number of the common causes of why this happens, either factor VIII is not given on time or the catheter becomes displaced or maybe the dose of factor VIII or IX has been insufficient. Occasionally, an inhibitor develops and I want to come back and talk a little bit more about that, but it’s very important to try and avoid bleeding because bleeding at the site of surgery predisposes to infection.

This is a terrible complication if infection does occur in an arthroplasty joint because it can be very, very difficult to get rid of and may lead to loosening and we need to replace the joint. The other complication that potentially arises following orthopedic surgery is venous thrombosis, now I’ll come back to this in a moment.
This is a brief clinical scenario of a patient of mine, some years ago, who had a very straightforward operation, arthroscopic removal of a loose body in his knee. He had mild hemophilia, the basal factor VIII level was about 20% and he received continuous infusion of factor VIII for 5 days. All went well, he was discharged after 5 days but returned after 10 days with a large hematoma in the flexor compartment of arm and as you can see, his factor VIII level had fallen to less than 1% and he didn’t respond to factor VIII therapy. We quickly determined that he had an inhibitor, which was, as you can see, much more active against human factor VIII than porcine factor VIII.
And it was this case, along with one or two others that came my way, that led Charlie Hay, who also had an interest in this area, and I to collect together some cases like this of inhibitors that have risen in mild and moderate hemophilia. These were cases we put together from Europe and North America and I'll just summarize the study that we reported.

Twenty-six patients developed these inhibitors, they were all after intensive treatment with factor VIII and this was often given as a result of surgery or trauma. We now think of this as being probably the cause of the degree of immune stimulation or immune perturbation, this probably increased the sensitivity to developing these inhibitors.

But as you can see, interestingly enough, the level of inhibitor against human factor VIII is considerably greater than against porcine and this is similar to the situation in acquired hemophilia where the anti-porcine level is often very much lower than against human. Also, in these patients, the bleeding pattern was very similar to that which you see in acquired hemophilia.

The other interesting thing to note was that these patients often came from families with an inhibitor history. As many of you may know, the particular genotypes, genetic mutations that are associated with a propensity to develop, inhibitors arising in mild and moderate hemophilia are actually not as rare as was previously being thought and in the UK, every year, about a quarter of the new inhibitors arise in such individuals.
One of the other potential problems following surgery is that of venous thromboembolism. In individuals that don’t have hemophilia, there’s about a 40% to 80% chance of getting a deep vein thrombosis (DVT) after a total knee replacement. About 2% to 7% of these people may develop pulmonary embolism and about 5 per 1000 may die from a fatal pulmonary embolism.

But what’s the risk in hemophilia?
Listed here are four studies that have looked at the risk of post operative thromboembolism following orthopedic surgery in hemophilia. In the second column, labeled VTE, you will see the number of clinical diagnoses compared with the number of patients in the study. You can see that in none of these patients, in about 180 operations, was a DVT suspected, but in three of these studies, there were no investigations to ascertain whether there were no clinical DVTs.

But the fourth study, which was by Cedric Hemmons, reported a couple of years ago, he looked with ultrasound for DVT formation in 29 patients and found some small calf DVTs in 3 of them. So there was about a 10% incidence of venous thrombosis in these patients—high risk with total hip replacements.
Because little is known about thromboembolism following orthopedic surgery and to find out what people’s views were and what their practice was, questionnaires have been sent round to a US hemophilia centers by two sets of authors. The first section on this slide are responses from 60 hemophilia centers in the United States. The questionnaires asked is VT prophylaxis necessary and about two thirds of them thought it probably was.

And if you consider it necessary, do you give it to all patients? And about half thought the answer was yes and just under half were a bit more guarded. Those who would give it said that they would give selected prophylaxis, about 80% of them would give it if they fulfilled particular criteria. For example, if the factor VIII level was about 100%, they’d be happy to give prophylaxis.

But what was interesting is the mode of prophylaxis varied quite markedly, compression of stockings were used by third and sequential compression devices by a quarter, but only about 10% used some antithrombotic drugs. In the second study, a questionnaire was retrieved from 19 hemophilia centers and almost half of these reported that they used a low molecular weight heparin or fondaparinux for prophylaxis.

So you can see there’s a wide spectrum of views and practices and I think this reflects ignorance. In fact, this is an appropriate moment to mention an observational study of post operative DVT in patients with hemophilia undergoing orthopedic surgery which Dr. Nigel Key is overseeing from Chapel Hill. This is an observational study and if any of you would like to join it I encourage you to get in touch with Dr. Key to discuss that possibility with him. It is really a major need for us to have better data on these patients and the risk of venous thromboembolism, but orthopedic surgery is relatively uncommon in hemophilia these days, so we need to gather up information on all the patients that we can.
This relates to thrombosis in von Willebrand disease and this is a very different situation. The story goes back to 2002 when Dr. Makris reported 4 cases of venous thromboembolism following treatment with factor VIII and vWF containing concentrates. He noticed that all these cases were associated with markedly elevated factor VIII levels and you can see between 175% and 290%, but interestingly, all 4 patients had risk factors for venous thromboembolism surgery, for example being on the contraceptive pill.

The second report in the same year by Professor Manucci describes 6 symptomatic cases, again with high factor VIII levels and again with risk factors. And what’s clear from these studies is that in patients with von Willebrand disease, there is a possibility for the factor VIII level to become very markedly raised because the concentrates that he used to treat these patients contain factor VIII. Also, in these situations, the patients are often subjected to an acute phase reaction and this elevates the factor VIII level even further.

So, it’s very important in treating patients with von Willebrand disease that you measure the vWF factor level but also the factor VIII level. I think, in future, we will see increasing amounts of elective surgery undertaken with von Willebrand factor only containing concentrates when these are more universally available.
The prevention of post operative venous thromboembolism in hemophilia depends upon reducing risk factors like weight loss, if that’s possible. Also, mechanical methods can be used, if they are already available, but a lot of physicians will use low molecule heparin or fondaparinex and particularly if the factor VIII level is at a reasonable level.

Clearly, this should not be used for patients with inhibitors. I think low molecule heparin and fondaparinex are absolutely contraindicated in patients who have active inhibitors. Perhaps, when giving the dose of low molecule heparin or fondaparinex, a modest does should be used. In other words, not the full orthopedic does, perhaps the more usual, general surgery post operative prophylactic dose.

And then I think, in patients with von Willebrand disease, it’s important to measure the factor VIII levels after surgery.
Well, let me draw my talk to a conclusion. The first point is, orthopedic surgery, in hemophilia, is more difficult than in individuals with normal hemostasis, and I’m sure Dr. Adolfo Llinás is going to tell you more about the difficulties.

Secondly, patients with a perioperative inhibitor pose two types of difficulties; one is, they’ve got more severe arthropathy and the other is that hemostasis is usually harder to achieve and Dr. Reding is going to tell you more about this.

Thirdly, it’s important to clarify the severity of the hemophilia, and particularly if your patient has mild hemophilia and discrepant factor VIII levels, it’s important to know this. Next, it’s important to monitor, obviously, the factor VIII and factor IX levels following surgery.

Next, I think it’s important to consider the use of passive joint mobilizers initially because that’s where you can get the joints moving very soon after surgery and that’s important to gain as much range of movement as possible as the final outcome.

Next, it’s important to remember venous thromboembolism prophylaxis.

But my final message, the take away message, is that orthopedic surgery in those with hemophilia can have very good outcomes if there’s a careful attention paid to the detail of how the surgery is undertaken and the team works together to ensure a good result. Thank you.
I have a very nice foundation that was laid down by Dr. Ludlam to progress with my presentation. My challenge is to look at the same problem that has been discussed elegantly before, from an orthopedic perspective.
And from the point of view of the orthopedic surgeon, any intra-articular bleeding that happens in a repetitive manner is, in one way or the other, leading to joint degeneration. So, as long as this is going on, as long as there is a joint that has been attacked by repeated bleeding–
A state of synovitis is actually taking place. This is the typical appearance of a target joint, in this case, the right knee, where you can see the increase in volume. At this stage, typically patients have a lot less pain than they used to in the past and there’s a very palpable increase in the amount of sinovial tissue.
From the surgical perspective, there is an inflamed sinovium.
If you approach that joint by translucently before you open the capsule, you can see the typical brick colored sinovium
which is very impressive from the point of view of vascularity and hypertrophy and, on staining, has the appearance of a very biochemically active tissue.
If you go further into the joint, at the microscopic level, at about 400x, you can see the blood vessels that are prevalent in this tissue, which get torn accidentally and randomly by patient movement and produces the repetitive bleeding as well as the deposits of hemosiderin.
At greater magnification, at the intra-cellular level, one can see the intra-cellular deposits of hemosiderin.
Intra-cellular deposits of hemosiderin have been very carefully linked to a very complex biochemical response that generates a proto-oncogene expression, the presence of inflammatory cytokines, and angiogenesis.
Then, angiogenesis, in particular, is of great importance in orthopedics because it usually co-localizes with macrophage presence, and therefore leads to bone resorption, a very well established pathway of joint degeneration that leads to sinovial proliferation. As you can see on this photograph of the inter condylar region, it behaves very much like the sinovial tissue does in rheumatoid arthritis in the way of pannus, in this case, in a very distinctive brick color.
I have the task of talking about synovectomy and the current status of that approach. Dr. Ludlam asked me to mention some reparative procedures that are frequent in elective orthopedic surgery. He also suggested I discuss the status of arthroplasty and its indications and finally, some comments on perioperative management of patients with hemophilia.
So let’s move on to talking about synovectomy very briefly.
This is a paper by Dr. Greene published in 1997 that made very obvious what many of you had already experienced and discussed. That is, once a patient has a target joint, chronic synovitis, increasing the prophylactic level or starting prophylaxis is generally ineffective. About two thirds of the patients will continue to synovitis and continuous bleeding at the end of a year.

So trying to increase a dose or trying to control synovitis with higher doses of concentrate is a very logical approach, but it is ineffective. It is logical but ineffective.
Therefore, there is a strong tendency for hematologists to cling to the patient and to refrain from referring these patients early for some type of percutaneous procedure to control that synovitis. So the flesh is weak but I urge you to look inside you, to feel the force, and to send these patients to your orthopedic surgeon very quickly.
When they are actually referred, they come in different stages. On the extreme left you can see patients that bleed occasionally and those may or may not be eligible yet for synovectomy, but once that joint does not return to normal, between bleeds, then this patient is actually in a state of chronic synovitis and it would be in the second level, depicted in green in your screen, and this is the perfect moment, that’s the sweet spot, that’s when you get the 95+ good results in the series synovectomies that have been reported in the literature.

When you get onto the yellow portion, the grade 3, those patients are going to have mechanical problems down the line, arthritic problems down the line, but still, you can change the pattern of bleeding at that level. And finally, in grade 4, depicted in red, the results are really of low quality, but on occasion, especially in patients that are bleeding in a segment of the joint, that have developed a septum and has a very active portion of the joint, in those cases, you can get away with some good results.
So, from the perspective of the orthopedic surgeon, once you have synovitis, there is one single thought, and that is to deactivate the sinovium. The purpose is to be able to work with physiotherapy in order to gain complete range of motion, complete muscle strength, and complete joint speed, which is one of the hardest targets in terms of rehabilitation.

The final goal is to return the patient to a state where prophylaxis is effective in preventing articular bleeds and/or synovitis.

In other words, to go back to a clinical management of the problem, that is the objective.
So there are several ways or avenues for preventing recurrent hemothrosis, and these avenues can be separated into 2 categories; one is the surgical resection of the sinovium, and two, the induction of sinovial fibrosis.
From a practical aspect, you can do this through a large incision, through the arthroscope, or through a needle percutaneously using different types of chemicals or radioactive isotopes.

**Synovial Deactivation**

**Avenues for Prevention of Recurrent Hemarthrosis**

- Open
- Arthroscopic
- Percutaneous
  - Chemical
  - Radioactive
In one word, open synovectomies are not done, almost anywhere in the world. They are difficult to perform.
You require at least two large incisions in the patient, the hospital stay is lengthy, large amounts of concentrate are required for long times, and the patients stick, they are very difficult to get to move again. So essentially, it was done in the past, it is not done presently, even in developing countries.
This is the perspective of the joint lining, the sinovium from the arthroscope. You can see scars and strands that suggest previous bleeding, the typical discoloration of the tissue and the vulnerability of the sinovial villi that get trapped and bleed continuously. So on arthroscope one can look at the tissue very closely, and can move around the knee or any other joint very efficiently through very small incisions.
Arthroscopic synovectomy is what we would use as a second level intervention. It would not be our number one approach and I will discuss exactly why we don’t do that in a few minutes.

Arthroscopy requires surgical amounts of clotting factor replacement, extensive physiotherapy/loss of ROM, requires hospitalization, and surgical expertise and meticulous execution.
If you want to do the procedure in a percutaneous manner, which is perhaps the number one choice in most countries around the world, you can go the route of using a chemicals like rifampin or oxytetracycline.
Chemical synovectomy has some advantages compared to the radioactive synovectomies that are more commonly performed. It doesn’t require hospitalization, it is minimally invasive, however, it does require 5 to 7 applications of this medication with a one week interval to achieve sinovial deactivation and synovectomy. We dislike that it can be painful, and, as a result, it’s very difficult to get the boys to agree to come a second time.

It requires multiple visits, which is difficult if patients live a long distance away, however, it may be repeated and the logistics and availability are simple.
If you go the route of the radioisotope, which is the one I would recommend to you, and certainly would be the recommendation of the World Federation of Hemophilia, through it’s musculo-skeletal committee, you have a wide spectrum of isotopes that can be used. These are available in different manners throughout the world, so essentially, one uses the isotope that is available in your area.
Radioactive Synoviorthesis

- No hospitalization
- Minimally invasive
- Single dose of concentrate
- Painless
- Single contact
- May be repeated
- Concern with radiation

It requires no hospitalization, it is minimally invasive, it requires a single dose of concentrate which can be a very low dose, it is painless and the longer the half life, the less painful it is. It requires a single contact; patients can come from far away and go back. It can be repeated up to 3 times empirically. There is, however, concern with radiation. It requires extensive discussion with parents, with the patients and with everybody around the hospital.
There’s a strong trend among the people who work in the musculo skeletal area of hemophilia towards agreeing that radioactive isotopes achieve the goal of synovectomy quicker and more reliably than chemical agents. However, the quality of the data is low, as is the case in many aspects of musculo skeletal care with hemophilia.
Also, comparing percutaneous injection of agents that produce sinovial fibrosis, radioactive or not, you can see that there is an ease of application of the radioisotope in comparison to using rifampin or oxytetracycline.
Is radiosynovectomy safe?

This has been a concern around the world, especially here in the US and in Canada. Several years ago, in 2002, Dr. Manco-Johnson published one case of malignancy in a patient that had a synovectomy. Then Dr. Dunn did another study and found 1 patient with a malignancy and there was a large discussion on the subject at the World Federation of Hemophilia (WFH). In 2006 Dr. Claire Infante-Rivard from Canada performed a large cohort study, almost 4000 radioactive isotopes synovectomies of many types of patients, among them, and was able to demonstrate no increased frequency of malignancies in that cohort of patients.

Similar studies have been performed with rheumatoid arthritis in a large number of patients. So, there doesn’t seem to be an increased risk, but this is always a consideration, this is always a concern for everybody.
In the absence of unambiguous data, improve the quality of the informed consent

So our approach is, in the absence of unambiguous data, improve the quality of the informed consent. That’s what we actually do. We tell the patients as much as we know, we ask them to read this monograph, which is monograph number T33, that’s published in English and Spanish in the WFH website, and we download that for the patients, we ask them to read that before they actually sign their consent and we discuss whatever questions they have.

And if patients refuse to go this route, then we go the route of using oxytetracycline, which is our plan B.
I will now move on to discuss very briefly two examples of orthopedic procedures which are often performed in persons with hemophilia.
These are essentially scheduled orthopedic surgeries. There’s a wide spectrum of interventions we can perform to improve the quality of the gait and the comfort to the patient.

<table>
<thead>
<tr>
<th>Orthopedic Surgery in Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flexion contractures</strong></td>
</tr>
<tr>
<td><strong>Hemophilic arthropathy</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Intramuscular hematomas</strong></td>
</tr>
<tr>
<td><strong>Pseudo- tumors</strong></td>
</tr>
</tbody>
</table>

This is one of the most frequent difficulties, the lack of extension of a joint. This is a boy where we had tried everything but still, the joint would not extend. He was in about 35 degrees of flexion deformity. On the slide, you can see him lying prone and that’s his flexion contracture.
In these cases, we approach the knee from the back and we free all the soft tissues, including the posterior capsule, the flexors of the knee, and the posterior cruciate ligament.
It’s a very busy approach, there are numerous vessels and you can see the popliteal artery and vein in the deep portion of the wound. However, once you dissect them out of the way, you get a straight look at the posterior aspect of the joint.
In the lower portion of your screen, you can see the post operative status where the knee which is fully extended. Actually, both of the knees are fully extended.
A second patognomonic musculo skeletal feature of hemophilia is radial head hypertrophy, it only happens in hemophilia. As a consequence, patients loose pronation and supination. It is a disabling condition.
The reason why they lock is because the radial head that is supposed to rotate freely against the ulna, is deformed and it develops impingement.
So we perform a very simple and relatively inexpensive surgery which consists of removing the radial head. As a result, patients recuperate the prono-supination.
It allows patients to access the keyboard or to accomplish a number of tasks and chores that are limited when you have no prono-supination.

On the slide you can see the initially the typical appearance of a hypertrophied radial head and in the post operative appearance of the resected radial head. This procedure is one of the all time favorites of patients who have musculo skeletal conditions related to hemophilia.
Joint arthroplasty is a formidable challenge.
Most patients who undergo joint degeneration are keen about going for a joint replacement. They have the expectation that it will perform perfectly, as often is the case in patients who do not have hemophilia. This high level of expectation is challenging from various points of view. We’ve heard from the previous speaker some of the hematological challenges and I think we’ll hear some more during the next talk.
From the orthopedic perspective, let me just highlight that this type of surgery requires deviation from the standard surgical routine and ingenuity to achieve success. It represents a combination of complexities.
Patients present with severe deformities or unique combination of deformities and contractures or severe bone loss, which make getting back the range of motion or getting the proper alignment or implant fixation, a challenge.

**Idiosyncratic Elements**

- Multiple joint involvement
- Limited range of motion
- Flexion contracture
- Absence of joint space
- Ankylosis
- Poor bone stock
The slide depicts a typical example of a patient who has a large mediolateral diameter of the femur and a narrow anteroposterior dimension, which makes sizing the implant impossible, except with a custom made prosthesis.
Upon exposure, often the cartilage is absent in the three compartments and the joint line is in a state of ankylosis.
On the slide you can appreciate the appearance of a knee joint that has been replaced. The procedure, in essence is a resurfacing of the joint which preserves ligamentous balance and proper alignment.
Dr. Goddard and colleagues from the Royal Free hospital in London just published this paper in the British Journal of Bone and Joint Surgery and it represents one of the largest series in the world. I think it’s a landmark paper in terms of the quality of the results. However, these results are perhaps, only achievable, when you work in a center of excellence in hemophilia.

They operated on 57 patients, during many years, 1983 to 2007, with a mean age of 43 years, which is a very low mean age for an arthroplasty cohort. They had two patients with inhibitors and 28% of their patients were HIV positive.
Their patients did very well during the 9.2 years of average follow-up. I’d like to highlight that 2 of their patients experienced deep vein thrombosis and one of them had pulmonary embolism, both hemophilia B in the early days.
Essentially, their survivorship rate at 10 years is about 77%. This is about 10% lower than the typical outcome for a patient without hemophilia.
There’s a second paper by Dr. Silva and Luck from Orthopedic Hospital in Los Angeles and again, a very large series and another paper of obligatory reference.

- 90 TKA in 68 patients
- 5 year survivorship: 77%
- Late infection: 16%
It reflects what we see in the clinic, which is essentially, a 77% survivorship rate at around 10 years. In this paper, the authors elaborate on an unsolved problem, a late infection rate, which is very high, in their case, about 16%. This rate of late infections was not associated with the presence of HIV. I believe it is related to other factors which we don’t understand fully.
Therefore, an ongoing problem in joint arthroplasty in hemophilia is the development of late infections which may require complex revision surgery. In reference to the etiology of the infections, some of us speculate about the quality of their care, the lack of cleanliness in their techniques of infusion, the quality of their dental care, whether there is some immuno depression associated with the use of concentrates, and many other elements. We don’t know the answer but we do know that on the average they experience a higher infection rate than patients without hemophilia.
In summary, patients with hemophilia who undergo arthroplasty represent a younger age group than those with osteoarthritis. Performing surgery in them involves extraordinary technical and perioperative difficulty and sub-optimal outcomes. However, despite all difficulties, the level of satisfaction in this patient group is high. Perhaps the instruments regularly used to evaluate outcomes in patients with osteoarthritis are not appropriate for patients with hemophilia and we should develop scales specific for hemophilia as we have done for rheumatoid arthritis.
So we do perform these procedures with great care and total joint arthroplasty requires, again, a very strong team approach. Finally I will make some comments about preoperative management.
What happens if the patient continues to ooze after surgery?

We typically schedule surgery on Mondays, to ensure that we will have access to the best human and technical resources the hospital can offer. If the patient does not have proper hemostasis, we stop the rehabilitation process. The hematology team will verify the coagulation screen, including fibrinogen and platelets and we rule out compound coagulopathies.
From the point of view of patients that are on recombinant factor VIIa, we ensure adhesion to processes of administration. Timely administration of rFVIIa is relevant due to the short half life. Fluctuation in the quality of the results of surgery have been associated to fluctuation in the quality of the administration procedures. Most institutions benefit from establishing a team that verifies this process.

If patients continue to bleed or start to bleed, we consider a higher dose, a greater frequency of the dose, the use of boosters and keeping the factor levels up for a longer time.
Physiotherapy

- Time of initiation according to regular protocol
- Physiotherapist experienced in the management of hemophilia
- Sedative phase may take longer than usual

In order to achieve good results in any aspect of hemophilia care, a comprehensive team approach is indispensable. In this case, rehabilitation is a critical part of the determinants of a good outcome. Subspecialized physiotherapists are indispensable. Ideally they should know the patient before surgery. In complex cases it is helpful for them to be present during surgery, to develop a collaborative strategy for rehabilitation. A lot of good results from centers not only come from high levels of concentrate use, but also from a lot of team integration, and physiotherapy is a key element in this team.

So we initiate physiotherapy like we would in any other case. Dr. Ludlam was talking earlier about being tender about it, and that’s one of the things experts do, they’re very careful in the way they do it. So there has to be experience. Patients will need a longer sedative phase and a lot of help from the pain clinic in order to recuperate early range of motion.
Physiotherapy

- Sessions should be timed with infusion of coagulation concentrate
- Continuous passive motion may be used
- Spontaneous hemorrhages are common at the end of first postoperative week

The sessions should be timed carefully with the infusion of coagulation concentrate, especially if they’re using substances with short half lives. Some centers continue to use continuous passive motion, however, there is little evidence to suggest that it makes a difference. In particular, it does not contribute to achieving a higher range of motion at the end of the rehabilitation process.

One thing we make sure we do before surgery is to warn patients that there is a good chance that they will have a spontaneous bleed towards the end of the first week post-op. This is something that we see often even if we immobilize the patients during that period.

So, it’s easier to deal with that if they have heard about this possibility before hand.
Dr. James Luck from Orthopedic Hospital always states that arthrofibrosis is what separates the patient with hemophilia from other patients. Based on this observation, that has been substantiated by others, we stress the relevance of an early rehabilitation process in order to protect any attempt to regain range of motion
A joint with arthrofibrosis has a benign appearance when looking at it from the outside. There is minimum increase in volume, if any, and no signs of difficulty other than the rigidity of the joint.
However, arthrofibrosis as the one depicted in the slide is terrible from the inside. It is a very proliferative and aggressive fibrous tissue that blocks all joint motion very quickly. The resulting rigidity and can only be solved partially if you bring the patient back to surgery.
So, in closing, I hope I have transmitted material that is of use to this very sophisticated audience in terms of what is important from the orthopedic perspective with reference to synovectomy, reparative procedures, arthroplasty, and some issues with preoperative management.
I want to leave you with one thought and that is that what I call the Cinderella complex which is prevalent among orthopedic surgeons who are inexperienced with hemophilia care.

They look at the hemophilia patient as a patient that is otherwise normal. If you’re happy, if the hematologist is happy, then this is just a normal patient. You just make him coagulate and leave the rest up, you know, up to me.

The surgeon is perceiving the patient as an easy prey…
The Cinderella Effect

“…You just make him coagulate and leave the rest up to me…”

and it’s often otherwise, it’s pretty much the other way around.
I'll be speaking in the last segment on the topic of Elective Surgery in Patients with Inhibitors. Certainly, the thought of an inhibitor patient needing surgery is a daunting prospect and we have very little in the way of evidence-based guidelines, in fact, we have no evidence based guidelines to go on.

We have a fairly limited clinical experience and there are a number of unanswered questions about how to best manage these patients and I'll try to touch on some of those things today. One of the reasons for this is the lack of a standardized laboratory assay to monitor these patients who are treated with bypassing agents. I'll spend the last portion of my time reviewing some new developments in that area.
So, this is just a list of surgical procedures that we performed at our center over the last several years in hemophilia patients. I've broken them down into routine surgeries, major surgeries, and orthopedic procedures.

The ones that are bulleted and underlined were performed in patients with inhibitors and the point of this slide is just to emphasize that these guys are not immune to the need for surgery, they need the same sorts of procedures that patients without inhibitors have and in fact, the same sorts of procedures that many non hemophilia patients have. So there's no way of getting around this.
In terms of what guides our therapy, we haven’t really even figured this out in the non inhibitor population. This is a paper published about a year and a half ago looking at replacement therapy for invasive procedures in patients with hemophilia, not inhibitor patients, just all patients with hemophilia. This was an extensive literary view, a survey of a number of European treatment centers, identified over 100 papers published in the mid 1960s through 2007 and with the exception of 2 studies in dental surgery, there were no randomized controlled trials of factor replacement therapy were identified.

This is NOT evidence-based medicine!

In terms of what guides our therapy, we haven’t really even figured this out in the non inhibitor population. This is a paper published about a year and a half ago looking at replacement therapy for invasive procedures in patients with hemophilia, not inhibitor patients, just all patients with hemophilia. This was an extensive literary view, a survey of a number of European treatment centers, identified over 100 papers published in the mid 1960s through 2007 and with the exception of 2 studies in dental surgery, there were no randomized controlled trials of factor replacement therapy in any of these papers.

So, this is certainly not evidence-based medicine. And this is in the non-inhibitor population.
So with the rest of my time, I'm going to focus on just on the inhibitor population and the unique challenges that these patients pose to us. There are a number of reasons for that. Certainly, again, clinical experience is limited, there really isn’t any high quality data. The bypassing agents are not completely effective. Literature reports ranging from 75% to 90% efficacy in stopping bleeding episodes and this is not in the surgical setting, this is just in the context of a spontaneous bleed or traumatic bleed. There’s a high degree of variability in response between patients in bleeding episodes and again, there’s no established routine laboratory method of monitoring these bypassing agents. Certainly, risks of thrombosis and cost are other considerations.
These are the two bypassing agents primarily in use today in North America and, I think, most of the rest of the world. FEIBA, which is an activated prothrombin complex concentrate and NovoSeven which is recombinant activated factor VII. We don’t really have any comparative studies looking at these two agents in the surgical setting. The use of these agents, which one you pick and how you do it is generally guided by personal experience, familiarity with the agent.

A lot of it has to do with the patient’s response to the different agents and sometimes product availability and cost are issues that creep in here as well.
There are no evidence based guidelines out there but we have two consensus panel type guidelines and I would like to just briefly review those with you.

One comes to us from the Canadians and one from the UK. So, first the Canadian guidelines; these were published in 2009 and this was a selective literature view looking at orthopedic surgery in inhibitor patients. It was the discussion of a consensus panel of experienced Canadian hemophilia providers and they made a comment in the discussion section of this paper that they didn’t even attempt any sort of formal, systematic review or meta analyses because the data just wasn’t there to be able to do that.
Here is a summary of recommendations and I just want to point out a couple of things. The first point, is that inhibitor patients should not be denied surgery that could enhance their quality of life solely based on the fact that they have inhibitors and I think this is something that's changed in the last few years.

The second point which has been made earlier today by both of the previous speakers is that these procedures really ought to be done only in those centers that have experience doing them and in those centers that have a multi-disciplinary team approach.

In terms of which agent to use, point 4 and point 5 outline these investigators’ thoughts regarding the dosing of recombinant factor VIIa and prothrombin complex concentrates, as you can see, the doses listed there are very standard, essentially what the package inserts say, aggressive therapy in the first 48 hours followed by a tapering schedule over several days.

So point number 6, these guidelines specifically state that antifibrolytic agents are not recommended for routine use although they could be used in selected situations but they don’t really define what those situations are, they do mention duration of therapy, it’s not based on any good data, it’s based on just sort of general experience.

They comment on prophylaxis prior to physiotherapy as has already been touched on and recommend against routine VTE prophylaxis in the inhibitor population.
The second set of guidelines comes from the UK, a paper published at essentially the same time. This one was a consensus panel of 6 experienced hematologists and one orthopedic surgeon from the UK. They reviewed the use of recombinant factor VIIa in elective orthopedic surgery in inhibitor patients.

The aim of this group was to provide a “best practice” protocol from preoperative planning to rehabilitation.

Protocol was formulated based on published reports and personal experience.

Consensus protocol for the use of recombinant activated factor VII [eptacog alfa (activated); NovoSeven®] in elective orthopaedic surgery in hemophilic patients with inhibitors


A very similar set of recommendations comes from this paper. Again I’ll just point out a couple of things. Point number 1, the same point that we’ve already made, we should only be doing this in places that know what they’re doing and have a multidisciplinary team approach. They make the point of doing this early in the week with hematologists readily available to help out the surgeons.

These guidelines actually do recommend administration of antifibrinolytic agents. Well, point number 4 here, this is the difference between the two guidelines and then point 5 outlines their approach to dosing of recombinant factor VIIa. The only difference I’ll point out is that they do recommend initial preoperative dose that’s a bit larger than the standard dose with subsequent doses looking very similar between the two guidelines.

They don’t specifically, in this document, address the use of prothrombin complex concentrates other than to state in point 6 that the use of PCC is recommended with equal weight to recombinant factor VIIa in other guidelines that they had previously published.
Bolus infusion or continuous infusion?

- Bolus infusion is standard for individual bleeding events in patients with and without inhibitors
- Continuous infusion of FVIII / FIX concentrates in the perioperative setting is routinely done in many centers
- Continuous infusion of bypassing agents:
  - aPCC – no published data
  - rFVIIa – small amount of published data
- Only one randomized, comparative study of bolus vs. continuous infusion . . .

So turning away from the guidelines. We don’t have evidence based guidelines; we’ve got some consensus guidelines to go on.

Let’s talk now about some of the unanswered questions and I think this is probably the one that gets the ball rolling. So, bolus infusion versus continuous infusion; we all know that bolus infusion is standard for individual bleeding events in patient both, with and without inhibitors.

The continuous infusion of factor VIII and factor IX concentrates is certainly, routinely done in many centers in North America, in our center we do it that way in the operative setting, but when it comes to the bypassing agents, we don’t have nearly the same degree of experience. In fact, as far as I’m aware, there is no published data regarding the use of continuous infusion for prothrombin complex concentrates and when it comes to recombinant factor VIIa, we do have a small amount of published data.
There is one randomized study that is summarized here. This was published in 2007 and they looked here at 24 patients, 12 in each arm, bolus infusion versus continuous infusion, treated with recombinant factor VIIa.

You can see the dosing outline there, fairly standard in terms of the bolus infusion and the continuous infusion dosing there is quite similar to other reports in the literature.
And this slide reviews the outcomes, the results and conclusions where there really wasn’t any huge difference. So if you look at effectiveness of hemostasis, essentially the same in both groups, the mean total dose of recombinant factor VIIa, looking similar but slightly higher than the continuous infusion group, duration of therapy, number of patients needed to be treated for an extended period of time, very similar in both groups.

And so, the conclusions were that recombinant factor VIIa certainly can be administered either by bolus or continuous infusion with comparable efficacy and safety, although the optimal and minimal doses to achieve hemostasis are unknown and wasn’t really addresses in the study and they couldn’t really conclude there was any clear advantage to one route of administration over the other.

And as far as I am aware, this is really the only study published to-date comparing the continuous versus bolus infusion of a bypassing agent.

<table>
<thead>
<tr>
<th></th>
<th>Bolus infusion</th>
<th>Continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Hemostasis</td>
<td>8 / 11</td>
<td>9 / 12</td>
</tr>
<tr>
<td>Mean total dose, days 0–3</td>
<td>237.5 mg</td>
<td>292.2 mg</td>
</tr>
<tr>
<td>Median duration of therapy</td>
<td>10 days</td>
<td>9 days</td>
</tr>
<tr>
<td>Number treated &gt;10 days</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

- rFVIIa can be administered by either bolus or continuous infusion with comparable efficacy and safety
- Optimal and minimal doses unknown
- No clear advantage of one route over the other at the doses used in this study
So, this is one of several unanswered questions. The other questions are which agent do we use, what's the optimal dose, the dosing interval, how do we taper, how long do we treat. These questions linger, I think, in large part because we have yet to develop a reliable and widely available standard laboratory assay with which to correlate the clinical outcomes in these patients, and so, I want to review some more recent work in this area that may be shedding a ray of hope in this regard.
This is a table that basically lists the available assays, there are a number of them have been reported in the literature but I really want to focus your attention on the first two.

The thrombogram or thrombin generation testing is a test that measures thrombin generation in plasma and the second test listed there is the thromboelastogram or TEG, really measures changes in mechanical properties of clot formation using cold blood, and I want to spend the rest of the time reviewing these two tests in more detail.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Measures</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombogram (TGT)</td>
<td>Thrombin generation</td>
<td>Plasma</td>
</tr>
<tr>
<td>Thromboelastogram (TEG and roTEG)</td>
<td>Changes in mechanical properties of clot</td>
<td>Whole blood</td>
</tr>
<tr>
<td>Platelet contractile force</td>
<td>Platelet contractile force and clot elastic modulus</td>
<td>Whole blood</td>
</tr>
<tr>
<td>Clot signature analyzer</td>
<td>Platelet function and plasma clotting parameters under flow</td>
<td>Whole blood</td>
</tr>
<tr>
<td>Modified ACT</td>
<td>Clotting time of whole blood</td>
<td>Whole blood</td>
</tr>
</tbody>
</table>

ACT = activated clotting time.  
The first one, the thrombogram is again, measurement of thrombin generation in plasma, reagents that you add to the sample contain phospholipin tissue factor and a fluorogenic thrombin substrate. The test measures what's called the endogenous thrombin potential (ETP) corresponds to the area under the curve.
The TEG is a slightly different test. TEG’s have been around for a long, long time, as many of you know, but haven’t found their way into hemophilia until more recently.

The concept here is that you have a metal cup into which you place whole blood. Suspended in the blood is a metal pin which attached to a torsion wire which is attached to a sensor on a computer and the idea here is that the cup starts to rotate back and forth. As a clot forms in the cup, there is physical connection between the sidewall of the cup and the metal pin suspended within the blood and when the clot starts to attach those two together, the pin starts to rotate back and forth. The result of that is transmitted through the torsion wire and what you get is a printout which you can see in the bottom panel there. The next slide shows a little bit bigger example. So this is really a visual depiction of the formation of a clot in that cup.
The variety of things that you can look at in terms of understanding what’s going on, the ones I’d like to draw your attention to are what we call the R time, which is the time from the beginning of the test until clot starts to form.

So the first instant that the pin suspended in the cup starts to move back and forth, that means there’s been some attachment between it and the sidewall. That’s when the clot starts to form and, I just want to point out, that this is essentially the endpoint of the standard coagulation assays, the INR and the PTT. So these other tests don’t really give us any idea about what’s happening after this point.

The second thing to draw your attention to is the angle. This is essentially the speed with which clot is generated or propagated within the cup and then the maximum amplitudes is the third thing that is the height of the curve and this really represents reflection of clot strength.
And so, just some examples here; this is a normal TEG tracing.
For comparison, here’s a patient with severe hemophilia. So what we characteristically see in these patients is a severely delayed clot initiation, very slow generation or propagation of the clot and overall clot that’s very weak in strength.
If you treat patients with bypassing agents and look at TEGs before and after, you can find tracings that look like this. Here’s an example of a patient who clinically responds well to recombinant factor VIIa, you can see the baseline TEG tracing on the top panel; the bottom panel showing essentially normalization of the TEG profile after infusion of a larger dose of recombinant factor VIIa.

In fact, the maximum amplitude in this patient is actually greater than normal, so this could perhaps suggest that this patient might have a little too much hemostasis going on.
Similarly, if you look at prothrombin complex concentrates, this is an example of another patient who clinically responds well to PCCs. The baseline tracing shown above looking very similar to the previous example and then after infusion of a standard dose of prothrombin complex concentrate. We see that in this example, the TEG looks much more normal, although there still is a delayed time for initiation of clotting so that R time is still significantly abnormal in this patient.
Variability Is a Major Problem

- More than 100 papers published in the last 5 years on the topic of thrombin generation assays in hemophilia
- Several studies have shown promising *in vitro* and *ex vivo* results

*But...*

- Large intra- and inter-patient variability and lack of standardization continue to hinder broad clinical implementation of bypassing agent monitoring assays

*However...*

- Perhaps these assays could be useful for tailoring individual patient treatment...

So, one of the problems with using these sorts of tests in clinical practices is there’s tremendous variability from patient to patient and from lab to lab. In the last 5 years, over a 100 papers have been published on the topic of thrombin generation assays in hemophilia and there are several studies that have shown some encouraging, both in vitro and ex vivo results but we continue to struggle with a large intra and inter patient variability, lack of standardization, lack of wide availability of these assays and these are only the things that have really hindered the broad clinical implementation of these assays in our practice.

However, I think there may be some beginnings, at least, of some encouraging results seen in the literature and certainly with our own experience in our center that perhaps these assays although they may no be suitable for widespread use across the board in a standardized way, we may be able to use these assays to tailor individual treatment plans.

I’d like to spend the last few slides just reviewing a couple of papers in the literature that have done this and then a brief example at the end of an example from our own center.
This is a paper that was pre-published online just a couple of months ago. What they did in this study is to prospectively evaluate both, the biological and the clinical efficacy of bypassing agents using thrombin generation testing. They have 6 patients with severe hemophilia A and high titer inhibitors who are in need of some surgical procedure. The goal of this was to really tailor the treatment around the time of the procedure based on the results of in vitro spiking experiments in which they used varying concentrations of the two bypassing agents available to see which agent and which dose gave maximum correction or normalization of the thrombin generation test.

Once that was determined, the second step was an ex vivo confirmation step in which the dose that was identified from the in vitro experiments was given to the patient and they did thrombin generation testing before and after to verify that indeed, ex vivo that we do see maximum correction of the thrombin generation test. Based on that, these patients went on to have the surgical procedure and then they assessed the hemostatic efficacy of the agent selected.
The second slide shows the results, the 6 patients are listed there. The second column really goes through the clinical history and as I was pointing out earlier, there is variable response to these agents from patient to patient. Patient 1, for example, was known to have a poor response to prothrombin complex concentrate and a fairly weak but better response to recombinant factor VIIa.

Patients 2 and 3 were known to respond well to prothrombin complex concentrates and so on. You can see for yourself that there’s variability. The third column shows the bypassing agent that was selected and the dose that was selected and this is based on the results of the in vitro testing. If you look there at the drug that ranked best in the in vitro testing, it correlates with the clinical history.

The second step, which is the ex vivo confirmation is reflected in the next to last column which is labeled ETP. This measures, again, after giving the dose of the bypassing agent identified as optimal from the in vitro experiments, the ability of that drug and that dose to correct the endogenous thrombin potential. And you can see that 4 of the 6 patients had normalization of that profile and if you look at the last column and look at surgical outcomes, when these patients are treated, what they found in vitro and ex vivo was reflected in what they saw clinically.

So, the two patients that had poor correction of their endogenous thrombin potential actually, one had such lousy response they decided not to even use the bypassing agent for the surgery. The other patient, unfortunately, had excessive bleeding and actually died of hemorrhage following surgery. The other 4 patients who had at least encouraging in vitro and ex vivo results went on to have good surgical outcomes.
The second paper, this was actually published 4 years ago by Guy Young’s group. A similar approach, so they had 3 patients that had advanced joint disease and very frequent bleeding and they were really struggling in trying to understand how to better treat these patients and so they looked at the TEG as a way to try to understand how to dose these bypassing agents better in these patients to try to improve their clinical outcome.

You can see the patients were young men with, two with hemophilia A and 1 with hemophilia B.
This is patient 1. This patient was known to really not respond very well to recombinant factor VII but to have a pretty decent response to prothrombin complex concentrate. The table here shows the results of the 3 TEG parameters that I reviewed earlier, the R time, the angle and the maximum amplitude. The normal ranges are shown across the top row.

At baseline, the patient essentially had no thrombin generation as measured by this assay. Following a dose of recombinant factor VIIa, there really wasn’t any response and that’s reflected in the third row. Fifteen minutes after a dose of prothrombin complex concentrate, you can see that the TEG parameters listed corrected to essentially normal. Four hours later, repeat testing showed that there was still better than baseline but the normalization of the TEG profile in this patient was being lost, particularly with regard to the R time and the angle.

They next went on to give this patient a dose of factor VIIa following the dose of prothrombin complex concentrate. What you can see there in the last row, is that the TEG parameters corrected even better and so this patient went on to have a new treatment regimen which consisted of prothrombin complex concentrate followed by recombinant factor VIIa if the bleed was initially unresponsive. After doing this for some length of time, they reported that this patient had more rapid resolution of his bleeding events, fewer hospitalizations and significantly improved quality of life.

So this is an example of using the TEG as a way to tailor the therapy to treat this patient’s bleeding episodes.

Results and Clinical Outcome – Patient 1

- No response to rFVIIa 200 mcg/kg
- Good response to aPCC 75 U/kg
- Better response to rFVIIa given 4 hrs after aPCC

<table>
<thead>
<tr>
<th></th>
<th>R (min)</th>
<th>Anglc (dgr)</th>
<th>MA (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4–8</td>
<td>47–74</td>
<td>55–73</td>
</tr>
<tr>
<td>Patient baseline</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15 min post rFVIIa</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15 min post aPCC</td>
<td>12.4</td>
<td>48.7</td>
<td>65.4</td>
</tr>
<tr>
<td>4 hours post aPCC</td>
<td>34.5</td>
<td>32.7</td>
<td>65.3</td>
</tr>
<tr>
<td>15 min post rFVIIa</td>
<td>10.3</td>
<td>53.7</td>
<td>64.2</td>
</tr>
</tbody>
</table>

New treatment regimen of aPCC followed by rFVIIa (if bleed unresponsive) resulted in more rapid resolution of bleeds, fewer hospitalizations, improved quality of life.
The second two patients, briefly represented in this slide, both of these guys were known to respond well to rVIIa and to prothrombin complex concentrates but they were using excessive amounts of factor. So they used the TEG studies to try to tailor the dose, try to find the dosing interval, dosing amount and dosing interval that resulted in maximum normalization of the TEG parameters. With that, they developed a modified treatment schedule and for both of these patients, they were able to demonstrate significant reduction in the factor utilization, fewer hospitalizations and shorter length of stay.

So, again, another example of how we might be able to use these thrombin generation assays to tailor our treatment approach to individual patients.
Lastly, I will just share with you an example from our center where we do essentially the same thing. This is a 28 year old we’ve known for a long time. He has severe hemophilia A, high titer inhibitor, he’d failed in the intolerance previously and clinically, this patient really had variable success to both, prothrombin complex concentrates and recombinant factor VIIa. Looking back through his charts and talking with him, it was very difficult to get a clear sense of what agent seemed to work best for him in various situations.

He underwent 2 knee replacements. The first was done in April 2005 on the left side. The photo that I’m showing here was taken just before the March 2007 right knee replacement. Both of those procedures were done using immuno absorption to first remove his antibody to allow us to use factor VIII, at least in the initial preoperative period and, again, the reason that we did that is because that he is poor in variable response to the bypassing agents.

Both of those surgeries, although initially successful from a hemostatic standpoint, were complicated by delayed post operative bleeding and we ultimately ended up going to sequential therapy with prothrombin complex concentrate and recombinant factor VIIa in both of the knee replacements in order to achieve hemostasis.
Then he shows up with this x-ray.

His right hip is totally shot. This x-ray was taken about a year and a half ago. He’s really exhausted all other approaches and so he really was felt to need a hip replacement.
And the problem is the columns that we use to absorb out the antibodies were no longer available in the US so we couldn’t go with the approach that we went with the knee replacements. Because of his variable response to the bypassing agents I was really struggling to figure out how we were going to treat him in the perioperative period. So we looked at his TEG profile and we spent some time doing a variety of things with different doses of the two bypassing agents and basically, trying to identify what route of administration of which product and what dose would result in the maximum correction of his TEG.

And from that we essentially settled on a specific regimen using recombinant factor VIIa. We took him to surgery, he had almost no blood loss and really a completely uncomplicated post operative course. He went on to post op day 7 with no complications and extremely satisfied with the outcome.
Here are his TEG tracings, the black line is his baseline which is typical of the previous examples that I showed you. What we found in this particular patient is that with just standard doses of recombinant factor VIIa, we didn’t get complete correction until he’d had several doses in a row and so the green tracing shows what it looks like after just one dose and after two additional doses given two hours apart of the standard 90 mcgs per kilo amount. We found that was what it took to get the TEG to look as normal as possible. So our strategy for surgery was to give him an initial dose of 180 mcgs per kilo followed by 90 mcgs per kilo every 2 hours. We didn’t start the surgery until he’d had the third dose administered. So we took him to surgery with what we felt was the best hemostasis we could achieve, at least based on what the TEG showed us. Fortunately, the surgery was very successful.

So this is, again, another example of using thrombin generation assays to try to tailor individual treatment for specific patients.
In summary, again, as the other speakers have presented, these procedures can be safely performed in hemophilia patients, even those with inhibitors but we really don’t have good data to guide in an evidence based way. So we’re still feeling our way through this, the protocols that are out there are based largely on clinical experience and opinion and some anecdotal experience. I think we just need to be very diligent about continuing to collect these patients and talk with each other and try to come up with the best protocols available based on our experience.

The thrombin generation assays available may, in fact, be useful, although I think right now, we’re still at the stage of being unable to apply these in a broad way but perhaps we can use them in an individual way to tailor our treatments with specific patients. Regardless of how we do this, I’ll just reiterate for the third time, as the other speakers have, that doing this really does require an experienced center and a multi-disciplinary team approach with physicians, both from orthopedics and hematology. We need the help of our lab colleagues if we’re going to do these assays, we need nursing support, physiotherapists and so on.

So, this is something that can be done but does require a great deal of expertise and certainly, a great deal of teamwork and coordination.
Panel Discussion
Dr. Reding-

For the patient that I showed, the third example, because of his inhibitor status, we elected not to use pharmacologic VT prophylaxis, we just gave him mechanical prophylaxis.
Dr. Reding-

So the question is in non-inhibitor patients. In our center we use continuous infusion of both, factor VIII and factor IX and so, we generally check levels after the initial bolus to make sure they’re going into surgery with a decent level. We’ll check the level when they come out of surgery in the recovery room. We often find the levels are a bit lower because there’s been some consumption during the case itself and if things look good, then we’ll just check the level daily.

We do use the factor level although certainly, a normal PTT would be a surrogate for a normal factor level. We generally try to keep the level between 80% and 100% for the first 3 to 5 days, kind of depending on how things are going, depending on the nature of the surgery and then taper from there. That’s probably a bit more aggressive than it absolutely necessary but again, there aren’t any good evidence based guidelines to guide our therapy there.
Dr. Reding-

Certainly with the von Willebrand patients, regardless of the subtype, we do pay close attention to both the von Willebrand factor levels and the factor VIII levels. It’s been our experience, certainly in the last couple of years, that these patients, similar to the ones that Dr. Ludlam described, do really experience very significant elevations in their factor levels. We often find that we have to give much less factor post operatively than we had anticipated because the levels go up very high and they stay high for a number of days following surgery.

We fortunately have not seen any thrombotic events although we don’t specifically look for them, we don’t do screening ultrasounds, and so there may be some distilled DVTs that we miss because we don’t look for them.
Dr. Reding-

The majority of our patients have chronic hepatitis C and they have varying degrees of liver dysfunction. Some of these patients don’t have normal platelet counts at baseline although you have to clearly account that’s pretty decent, at least 80 or 100 thousand to have the parameters look normal.

So it may be that some of the variability is due to those sorts of things, but really, there’s a lot more to it than that, and I don’t think we really understand what it is. Even from lab to lab, if you take the same sample and run it in my lab and somebody else’s lab, the results aren’t always the same.

So, this is very much in it’s infancy in terms of us understanding what’s going on. I’m not sure we have the best tests in use right now, there may be other tests that we need to develop to try to sort this out.
Dr. Reding-
In our center, we haven’t routinely given pharmacologic VTE prophylaxis even in the non inhibitor patients. When we’ve done it, we tended to use low-molecular-weight heparin because that’s the standard, our approach has been when we’ve done it, to use whatever standard protocol would be in place for the procedure in a non-hemophilia patient.

The point is well taken. Maybe that the use of unfractionated heparin would be safer.

Dr. Llinás-
One of the attractive issues of, fondaparinux with the exception of the longer half life is the fact that it has no anti IIa activity and it gives the surgeon a drier wound and this has been an issue in orthopedics for many years. So that’s one attractive issue because patients with hemophilia, by nature, already have very soupy, very wet wounds
Dr. Llinás-

This is one of the big questions in joint arthroplasty and it's been very difficult to demonstrate the association between laminar air flow and the diminution of the infection rate. We use laminar air flow in joint arthroplasties, especially in hip surgery, knees pose a very difficult challenge because the wound in the knee is exposed to the air. The flow hits the wound straight on and there's discussion as to whether it actually increases the risk of infection in knees and then there's the issue of whether it's vertical laminar air flow or horizontal laminar air flow and it's a very complex issue from a research point of view.

The short answer to your question is we do use laminar air flow in all of our joint arthroplasties, I think it's a very important surrogate variable in your infection rates, but it is very difficult to demonstrate evidence based.
Dr. Reding-

That is a huge concern for us. The way that we address that is to notify the lab ahead of time that we're going to be sending a TEG down and to have it set up. We have one of our nurse coordinators actually go up to the floor and retrieve the sample and transport it to the lab directly and to try to avoid that variable. It's far from perfect, but those are the sorts of things that we try to do to try to make it as uniform as possible from patient to patient.
Dr. Llinás-

We stagger them one week and by doing so, we save about two weeks worth of concentrate. We don’t do them simultaneously because we are concerned about erratic behavior of the patient in the immediate post-op, whereas when you started that patient for a week, you’ve already mapped out that behavior and you can emulate what you did the week before and you can still save about two thirds of your cost in concentrate.

So I think staggering them one week is an intermediate approach, you get the best of both worlds.
Dr. Reding-
That's actually a good point. We haven't yet done that, but certainly, from the perspectives that you outlined, I think that would make some sense.

Dr. Llinás-
We do do it and some groups actually do it routinely. In my experience, the ones that do it more, in a more resolute way are the ones that work with the liver transplant and they have a liver transplant going on at the same time and they have this culture of using anti-fibrinolytics or the patients that have cardiac surgery. So we always go to surgery with our anesthesiologists who are in the liver transplant program, they are very close to coagulation in contrast to all of the other anesthesiologists who don’t have that clear idea.

So, yes we do and I think you have a point, that’s exactly the reason why we believe they bleed at that point. We also do tell the patients, you know, if you bleed, please don’t be disappointed, because they get so disappointed when they bleed one week out. They’re all really progressing and they bleed in a different manner because the capsule is open, so when they bleed, they bleed into the thigh, the calf, all over the place, it’s a different type of bleed and it’s very disabling, it takes about two weeks to go away.
Dr. Reding-

I would say that, in general, we’re certainly much more comfortable using antifibrinolytic agents when we’re treating patients with recombinant factor VII. We generally don’t do it when we have a patient receiving prothrombin complex concentrates because of the perception, at least, that agents more thrombogenic.

This is certainly not evidence based. I think the practice varies widely, even within centers, we don’t do it the same every single time, so we probably can be more diligent in that regard.
Dr. Reding-
We’ve used topical antifibrinolytic agents to treat wounds that were oozy, post op wounds that are oozing a little more than we’d like them to. We’ve had pretty good success with that, actually. It’s certainly not sort of, common place or widespread

Would you comment on the use of topical tranexamic acid during surgery on patients with hemophilia?
Dr. Llinás-

Yes, we are careful to instruct mothers to bring them back to us because the question is when we should bring them to the orthopedic surgeon. When a joint bleeds and it doesn’t return to normal between bleeds, that is a definition that parents can actually understand. So when we see a boy that is bleeding and you examine the joint and it is actually inflamed or puffy and you can feel the thickness of the sinovium, you specifically inquire about whether this joint goes to normal between bleeds. If the answer is no, then that is a candidate for radioactive synovectomy in our institution.

We do repeat the synovectomies up to 3 times. It is empirical but you can see, in more of the series that this has been done, you get a very good effect if the patient is at an early stage when you do it once. The patients who are in stage 3 for example, or in those patients where the thickness of the sinovium is large, would require a repetition. The reason for that is that many of the isotopes can only remove 3 to 5 mm of sinovium at a time and sometimes, the villi are a centimeter or more in length.

If we are not successful the third time, then that’s our indication for a arthroscopy and we would do an arthroscopic synovectomy and then the chances of being successful are, you know, the collective chance of those 3 interventions plus the arthroscopy are very, very high.