Welcome to The Past, Present and Future of Anticoagulation Therapy.
Your faculty for this activity is Dr. Ann K. Wittkowsky, PharmD. Dr. Wittkowsky is Clinical Professor of Pharmacy at the University of Washington School of Pharmacy and Director of Anticoagulation Services at the University of Washington Medical Center. As a clinician and educator in the field of antithrombotic pharmacotherapy, she has contributed extensively to the care of patients and the education of health care providers regarding antithrombotic pharmacotherapy. She has lectured widely throughout the United States and Canada, maintains an active clinical research program, and is board certified as an anticoagulation care provider. Dr. Wittkowsky serves as an editorial board member for *Pharmacotherapy* and the *Journal of Thrombosis and Thrombolysis*, as a reviewer for numerous medical and scientific journals, and as a member of the board of directors of The Anticoagulation Forum, a multidisciplinary organization of anticoagulation care providers.
Our next faculty is Dr. Edith A. Nutescu, PharmD, FCCP. Dr. Nutescu is Clinical Associate Professor of Pharmacy Practice at the University of Illinois at Chicago College of Pharmacy and Director of the Antithrombosis Center at the University of Illinois at Chicago Medical Center. Dr. Nutescu is also an Affiliate Faculty at the University of Illinois at Chicago, Center for Pharmacoeconomic Research. She earned her PharmD degree with high honors at the University of Illinois at Chicago College of Pharmacy. After graduation, Dr. Nutescu went on to complete an American Society of Health-System Pharmacists (ASHP) – accredited Pharmacy Practice Residency at Lutheran General Hospital – Advocate Health Care and a Primary Care Specialty Residency at the University of Illinois at Chicago Medical Center. As a clinical and educator, Dr. Nutescu has contributed extensively to the care of patients and the education of students and health care providers on topics related to cardiovascular therapeutics. The Antithrombosis Center at the University of Illinois at Chicago Medical Center, which Dr. Nutescu directs, has served as a training site and model for pharmacists and other health care providers throughout the US and various other countries such as Thailand, Hong-Kong, Japan, and Singapore.
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Overview Regarding the Role of Thrombin and Current Antithrombotic Guidelines

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Our first speaker will Dr. Ann Wittkowsky.
Objectives

1. Compare current therapies available for anticoagulant therapy.

2. Assess the role of thrombin in hemostasis.

3. Review current guidelines for use of antithrombotic agents to prevent and treat venous thromboembolism, and to prevent stroke in atrial fibrillation.

Our objectives for this particular session are to make sure that you are feeling very comfortable comparing current therapies that you feel confident about the role of thrombin and hemostasis and we will also be looking at current guidelines for use of antithrombotic agents in both the treatment and prevention of venous and arterial thromboembolism and for the prevention of stroke in atrial fibrillation. So again this is very rudimentary and then more exciting topic is the second one and I know that’s why you are here.
The actions of thrombin include:

1. Conversion of fibrinogen to fibrin
2. Multiple procoagulant activities
3. Multiple antifibrinolytic activities
4. All of the above

Before we get going, I have got some questions for you to answer and there are right and wrong answers and we will get to that at the end but for now, let’s all take a look at this first question. The actions of thrombin include conversion of fibrinogen to fibrin or multiple procoagulant activities or multiple antifibrinolytic activities or finally, number 4 all of the above?
Let’s go on to question#2. This one says that currently available options for the prevention of venous thromboembolism in patients undergoing total hip replacement include either Warfarin, low-molecular weight heparin, fondaparinux or all of the above?
Cancer-associated thrombosis is preferentially treated with:

1. UFH followed by warfarin to INR 2-3
2. LMWH followed by warfarin to INR 2-3
3. LMWH alone
4. Fondaparinux alone

Alright, question#3. Cancer associated thrombosis is preferentially treated with which of the following unfractionated Heparin followed by Warfarin to a goal INR between 2 and 3, low-molecular weight heparin followed by Warfarin to a goal INR between 2 and 3, low-molecular weight heparin alone, or finally fondaparinux alone? Which of those four do you believe is the preferential treatment for cancer associated thrombosis?
Question #4

Patients with atrial fibrillation and diabetes should receive stroke prevention therapy with:

1. ASA 81 mg po daily
2. ASA 325 mg po daily
3. Warfarin to INR 2 - 3
4. 1 and 3

Now finally our last question. Patients with atrial fibrillation and concurrent diabetes should receive stroke prevention with which of the following options first? The answer is Aspirin 81mgs a day, the second is Aspirin 325mgs a day, the third Warfarin to a goal INR between 2 and 3 and the fourth one a combination of both A and C? What makes the most sense to you?
I would like to start off with some visuals to remind you of exactly what we are talking about when we are talking about thromboembolism. These are deep-vein thrombi that have been extracted from the lower extremities. It’s interesting to see the size of these things. I think out in the general community, patients get the feeling from watching television advertising about acute coronary syndrome that clots are tiny little microscopic things that happen inside the coronary arteries but in fact venous thrombi can be enormous, they can extend from the ankle all the way into the groin. And I think this is a very interesting slide to give you a sense of the size, the extent, the width of venous thrombi in the deep-vein system.
Now typically our diagnosis of deep-vein thrombosis is through Duplex Ultrasonography which is actually invented at the University of Washington by the late Dr. Eugene Strandness for whom our vascular lab is named. Now what you would normally be seeing in a normal situation involving a Duplex Ultrasound is blood flow in not a three dimensional view but in a continuous time, this is intended to be a video tape of blood flow and you would be seeing this is leg tissue and so is this and this what ought to be a very black area here is where blood flow should be pulsating through here in blue and red depending on the pulsatile movement. But what you are seeing instead is that there is some blood flow but there is a glob in the way and that glob represents deep-vein thrombosis, it’s interfering with blood flow. So when you are in your hospital and you see the vascular technicians wandering around with the ultrasound machines, this is the kind of tape and image that they are getting from patients who are being diagnosed with deep-vein thrombosis.
In the past, we have always talked about Venography as being the gold standard for diagnosing deep-vein thrombosis and it’s certainly still used in many clinical trials unfortunately exposes patients to contrast material but it’s another really nice way to see the imaging of the extent of deep-vein thrombosis. And what you are seeing here is bone tissue in black and then this represents one of the lower extremity veins and the black material inside this vein is deep-vein thrombosis and you can see its origin here and the fact that this is extending through this venous system.
Now pulmonary embolism is the number 1 complication of deep-vein thrombosis and this is an anatomic specimen showing you saddle emboli throughout the pulmonary arterial system in a patient who has expired from PE but it gives you a great sense of the extent of PE throughout the pulmonary vascular system.
Perhaps as long ago as 5 years ago, it was more common to diagnose PE using the VQ scanning, Ventilation/Perfusion Scanning and patients would be exposed to inhaled radioisotope which would lead to images like this showing you that the inhalation of the radioisotope was able to image the full lung field.
But then when the patient received the radioisotope intravenously, there would be a
mismatch between the two images and what you are seeing here the difference
between the perfusion component and the ventilatory component is indicative of
some kind of vascular abnormality and therefore high probability of pulmonary
embolism. You can see why we used to call this instead of nuclear medicine, we
called it unclear medicine.
These days it’s far more common to diagnose pulmonary embolism through CT angiography. Here is an example of a very clear pulmonary embolism noted by the arrow here and our friends in the CT-scanning department are easily able to visualize pulmonary embolism in this manner, however there are expenses associated with CT scanning that has led to a lot of controversy about where this should fall in the diagnostic approach to pulmonary embolism and where D-dimer falls as well.
And frequently you may find in your own hospital setting if you are working in a very large setting that MRI is more commonly used to diagnose VQ scanning or to diagnose pulmonary embolism. This particular patient has both pulmonary emboli and polycystic kidneys and liver so both of those things are found on this particular image. But it might be interesting for you to know what are the diagnostic techniques that are going on in your healthcare system and is there an algorithm for PE and DVT diagnosis, one day that may be necessary to have in print so that all of your clinicians are doing the same thing but anyway some interesting visuals.
It is less common to use angiography to visualize pulmonary emboli at this point in time again because of exposure to contrast material but this is an interesting image. What you are seeing here is a lung field which ought to be vascularized. We ought to be seeing this type of vascularization throughout the whole lung field but instead, there is a black area down here and that is indicative of loss of vasculature to that area and what that implies is that the vascular component here has been cut off in some way and that is indicative of pulmonary emboli interfering with blood flow to the lung field.
Now, the other situation in which we are concerned about the development of thromboembolic materials not just in the venous system but also in the arterial system and probably the most common reason for patients to be anticoagulated long term is because of atrial fibrillation. In atrial fibrillation, the changes in the integrity of atrial contractions can lead to venous stasis or blood stasis and the development of thrombotic material which is very commonly seen in the left atrial appendage which is a little outcropping or offshoot of the left atrium. This is an anatomic specimen from someone who has expired an old slide from long ago but it clearly shows you the extent of thromboembolic material here that could be the cause of stroke or emboli.
It’s very common to use echocardiography to try and visualize clot in the left atrium. What the people who work in that field call this is they use the term “Smoke”, “Smoke” in the left atrium and here, you are seeing some of that smoke, it’s interfering with what ought to be the empty space of the left atrium and is indicative of thrombotic material.
However, it is often more appropriate to use Transesophageal Echocardiography in order to better visualize the left atrial appendage. And in this particular image, what you see is the left atrium, the left atrial appendage and here is the smoky material right here that is indicative of clot formation. And in the real time videotaping that you would see from this type of image, you could potentially see that thrombotic material flapping in the breeze and you get the sense of the incredible risk of stroke that that represents.
So to move on beyond these lovely visuals as a nice introduction, we will all recall that hemostasis is in fact a balancing act between the coagulation system which is certainly required to stop bleeding when any kind of trauma or wound occurs and the naturally inherent anticoagulant system that protects us from lethal intravascular thrombosis. If you ever think about the fact that you would get a cut, a little paper cut on your hand at work, what keeps you from having total body thrombosis and it is this balancing act that localizes coagulation to the side of injury and prevents systemic clotting in the average normal patient. That can certainly be a very different story in Disseminated Intravascular Coagulation. But for all of us, hopefully, little cuts lead to localized coagulation and it’s the process of hemostasis that keeps that going.
Pathophysiologic clotting is our great concern and the reason that we use antithrombotic therapy and I think many of you are probably familiar with the Virchow's triad which is a model for pathologic clotting. The three components of that model are the fact that endothelial injury like that paper cut can lead to pathologic clotting. Circulatory stasis is another element, the kinds of problems that you might see in a long airplane ride or people who are bed-bound for a long period of time. And the third element of this triad is hypercoagulable conditions. You would classically think of Protein C and S deficiency, antithrombin deficiency as well known hypercoagulable conditions but the more common hypercoagulable states are Factor V Leiden, the prothrombin gene mutation and malignancy as well as antiphospholipid antibody syndrome and a number of other heritable conditions. But this particular model is a good way to think about what causes pathologic clotting and helps us to organize our thoughts around antithrombotic therapy.
Surely you are familiar with the coagulation cascade the intrinsic and extrinsic pathways, the various elements of this cascade and how they are accelerated by pathophysiologic clotting. But the entire cascade finally and eventually comes down to thrombin and I think we can call thrombin really the central core of this process which converts fibrinogen to fibrin and fibrin really is the eventual clot that we can visualize by the variety of diagnostic techniques that we looked at in the first number of slides.
Thrombus formation is not just fibrin strands but a series of red cells and there is a platelet component as well and if you were to look at it in an electron micrograph situation, this is exactly the kind of thing that you would see a mismatch of fibrin, red cells and platelets a higher platelet component in arterial thrombosis, a higher fibrin component in venous thrombosis but all of this plays a role and thrombin really is at the central core of the development of pathologic clotting.
Thrombin is a protease and it is formed as you saw from the image of the clotting cascade by cleavage of prothrombin through the clotting cascade itself and it has many more activities than simply converting fibrinogen to fibrin. Because it is a central mover and shaker in the clotting cascade, it has a number of procoagulant activities and it also has a whole number of antifibrinolytic activities and I leave it for you to read this at your leisure at another time. It is a stimulator of all the negative feedback systems that prevent ongoing coagulation and also maintain hemostasis. So it's going in every direction to maintain hemostasis by having procoagulant, anticoagulant and antifibrinolytic activities a very complex molecule that is doing far more than what I teach my students which is to convert fibrinogen to fibrin to result in stable fibrin clot.
The anticoagulant or antithrombotic agents that we have available to us to date all work somewhere within the clotting cascade and I think all of us are familiar with Warfarin as an indirect inhibitor of the Vitamin K dependant clotting factors II, VII, IX and X. We are certainly familiar with heparin and low-molecular weight heparins as anti-Factor XA and IIa drugs, heparin having a more balanced anti XA, anti IIa pharmacology, low-molecular weight heparins having more anti XA than anti IIa activity. And some of you maybe familiar with fondaparinux or Arixtra which is an indirect XA Inhibitor working via antithrombin. There are also whole slew of drugs known as Direct Thrombin Inhibitors. You are probably familiar with argatroban, lepirudin ximelagatran which never made it to market etc as drugs that more directly inhibit the thrombin molecule. And so our traditional anticoagulants have their impact on the clotting cascade in an indirect manner but the newer direct thrombin inhibitors more directly impact the thrombin molecule itself.
Certainly you are familiar with mechanism of action of warfarin as an inhibitor of the reductase enzyme systems that take oxidized Vitamin K and turn it into reduced Vitamin K and it is this reduced form of Vitamin K that is then able to gamma-carboxylate the precursors to prothrombin and the other Vitamin K dependant clotting factors into inactive clotting factors that can then go on to be activated by the number of things that can stimulate clotting factor production all those Pathophysiologic mechanisms that we talked about earlier.
Now, the differences between unfractionated heparin, low-molecular weight heparin and fondaparinux are all outlined very nicely in this particular diagram. The binding site on the unfractionated heparin molecule and the low-molecular weight heparin molecular is identical to the synthetic binding site that is fondaparinux. It is a 5 carbon chain that interferes with the particular site on antithrombin and therefore inhibits factor XA and factor IIa that’s for unfractionated heparin. Low-molecular weight heparins are shorter molecules, they still have that same binding site on antithrombin but the full chain is shorter than necessary to inhibit most of the molecules of thrombin. So there is more anti-XA than anti-IIA activity for low-molecular weight heparins. Fondaparinux as I mentioned is a synthetic derivative of this 5 carbon molecule and it goes forward binding to the site on antithrombin, inhibits XA but has no ability to inhibit IIa and again, the important point being that this is a synthesized product that is comparable to the active site of both low-molecular weight heparin and unfractionated heparin.
Heparin Manufacturing Process

- Combine 5,000 lbs. intestines, 200 gallons water, 10 gallons chloroform, and 5 gallons toluene. Hold at 90°F for 17 hours.
- Add 30 gallons acetic acid, 35 gallons ammonia, sodium hydroxide to adjust pH, and 235 gallons water. Bring to a boil; then filter.
- Add 200 gallons hot water to filtrate and allow to stand overnight, then skim off the fat.
- Keep pancreatic extract at 100°F for three days, then bring to boil.
- Filter solids and assay for heparin content.

Photo courtesy of Neil Kleiman.

This is a favorite slide of mine that describes where heparin comes from. This is a little scientist in the lab in Chicago where all these pigs are available. And my point is for you to appreciate that heparin is extracted from mammalian sources in a relatively crude way.
Low-molecular weight heparins are prepared from unfractionated heparin using a whole variety of techniques. Some of them are chemical or enzymatic production, there are oxidative techniques, deaminative techniques but the point is that low-molecular weight heparin molecules are extracted from the original heparin source and we need to appreciate that heparin because it comes from a mammalian source, has a potential to be quite variable in the size of the molecules, etc. This is not the cleanly and sophisticated drug development that we see with later products.
The differences between unfractionated heparin and low-molecular weight heparins are outlined here and helpfully this is quite familiar to you. The average molecular weight of the low-molecular weight heparins is of course much smaller, these are smaller extracted molecules and because of that, the bioavailability is particularly when given subcutaneously is much higher than that of unfractionated heparin, the elimination half life is longer and as we have discussed, the anti-XA to anti-IIA ratio is quite a bit higher than it is for unfractionated heparin and that has some implications in terms of pharmacology as well as pharmacokinetics.
The low-molecular weight heparins that have been available in the United States, three of them continue to be, Ardeparin is no longer available in the US. But each of them have some distinguishing characteristics, their average molecular weights are a little bit different, the percent of antithrombin affinity fragments that have a high affinity for antithrombin are a little bit different and their anti-XA to anti-IIA ratios are a little bit different. This may have some impact on efficacy, on safety, on pharmacokinetic parameters but in a general sense, we tend to think of these low-molecular weight heparins as being similar in terms of their therapeutic effects.
There have been very few comparisons of low-molecular weight heparins in clinical practice, one of them is a trial from a couple of years ago that compared both Dalteparin and Tinzaparin for the treatment of acute Venous Thromboembolism and overall rates of major hemorrhage, recurrent thromboembolism and mortality for patients treated with one or another of these drugs was very similar and the authors of this paper concluded that because there are no differences in major endpoints, the choice of agent when one is selecting one low-molecular weight heparin versus another, can be based on practical considerations like price, delivery systems and availability and I would bet that that holds true for all of you. When you think about the low-molecular weight heparin product that is available on your formulary or maybe you have got more than one, you have considered price, delivery systems and availability as the main drivers of what you have selected rather than issues around comparative efficacy and safety.

<table>
<thead>
<tr>
<th>Outcome Events</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
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<tbody>
<tr>
<td></td>
<td>Study Group</td>
<td>Study Group</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Days 1-7</td>
<td>3 (1.2%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Days 8-15</td>
<td>5 (2.0%)</td>
<td>8 (3.1%)</td>
</tr>
<tr>
<td>Days 46-90</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Entire study</td>
<td>9 (3.6%)*</td>
<td>10 (3.9%)*</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>1 (0.4%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Days 1-7</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Days 8-15</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Days 46-90</td>
<td>2 (0.8%)</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>Entire study</td>
<td>12 (4.8%)</td>
<td>14 (5.5%)</td>
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*Four and 3 of the recurrent events in the dalteparin and tinzaparin groups, respectively, were pulmonary embolic.
When it comes to the three commercially available low-molecular weight heparins in the United States, you will find in a general sort of sense that enoxaparin is most commonly found on hospital formularies, Tinzaparin is somewhat rare, Dalteparin less common. The dosing frequency for these drugs is similar although we often use q12 hour dosing for enoxaparin particularly in the treatment of VTE, in obesity and in patients with malignancy. Enoxaparin has an advantage in terms of these pre-filled syringes but Dalteparin now has some pre-filled syringes as well. There are differences in cost, there are differences in FDA approval for treatment of VTE and for treatment of patients on an outpatient basis. These costs here are from a couple of years ago, things maybe very different in your system, they might be very different in mine at this point but my point is for us all to recognize that the choice of one agent over another is not made based on clinical considerations, efficacy and safety considerations but more appropriately made based on practical issues.
The fondaparinux is a very different animal. I mentioned to you that this is a synthesized product. It is the active site of low-molecular weight heparins and of unfractionated heparin, the active component of those drugs so therefore it has a much smaller molecular weight in comparison to not just the low-molecular weight heparins but unfractionated heparin as well. It is synthesized and therefore less likely to be contaminated by pathogens as opposed to the extracted unfractionated heparin from porcine intestinal mucosa. And its composition is quite homogenous because it is a singular chemical entity as opposed to the mishmash glycosaminoglycans that low-molecular weight heparins and unfractionated heparin represent. Its target is that target site on antithrombin which means that it has exclusive anti-XA activity although this is indirect anti-XA activity because it works through antithrombin rather than binding to the XA molecule itself.
Now the direct thrombin inhibitors are the other group of more common antithrombotic agents. Dr. Nutescu will be talking to you about newer antithrombotic agents that are on the horizon. But, we are looking here at the direct thrombin inhibitors and the fact that they are all somewhat different in terms of their pharmacology. If you were to look at the thrombin molecule, this has been described as a molecule that has three distinct sites on the molecule itself, one is a substrate recognition site sometimes referred to as Exosite1 which binds thrombin to fibrinogen and remember that one of the things that thrombin is doing is converting fibrinogen to fibrin but that is not the only thing as you now know but this is the spot where the thrombin molecule binds to fibrinogen. There is an active site on this molecule as well which is responsible for all the enzymatic actions of thrombin and then there appears also to be a heparin binding site linked somehow to this fibrin binding site such that when thrombin is exposed to heparin, its active site is inactive. These different types of direct thrombin inhibitors interfere with these binding sites in different ways. Hirudin, lepirudin, desirudin all of those derivatives tend to bind irreversibly to both the substrate recognition site and the active site and that different type of binding may influence long term adverse effects and efficacy to some extent although that’s not well described. Bivalirudin which we all know so well from the cath lab is a interesting molecule in that it binds irreversibly to the substrate recognition site but reversibly to this catalytic site and there is a binding ligand here that tends to be broken down during the course of the use of the drug so, a very different pharmacology and therefore some different clinical characteristics. And finally argatroban a very small molecule, intravenous molecule as well and Ximelagatran which we were all hoping several years ago was going to replace Warfarin but never made it to market, those are both very small molecules and they bind exclusively and reversibly to the active site on the thrombin molecule. So the point here being that each of these direct thrombin inhibitors has a slightly different pharmacology and that the differences in pharmacology do impact we think clinical and efficacy outcomes.
Comparison of DTIs in HIT

“Selection of DTI should be guided by pt’s clinical status and organ function instead of by efficacy and safety considerations”

<table>
<thead>
<tr>
<th>DRUG</th>
<th>N</th>
<th>Mortality (%)</th>
<th>LOS (Days)</th>
<th>Bleeding (%)</th>
<th>Days to Plt Recovery</th>
<th>Tx aPTT (%)</th>
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</thead>
<tbody>
<tr>
<td>Lepirudin</td>
<td>7</td>
<td>28.5%</td>
<td>11.0</td>
<td>28.5%</td>
<td>5.3</td>
<td>70%</td>
</tr>
<tr>
<td>Argatroban</td>
<td>20</td>
<td>30%</td>
<td>15.1</td>
<td>20%</td>
<td>5.2</td>
<td>65%</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>24</td>
<td>25%</td>
<td>18.7</td>
<td>25%</td>
<td>5.4</td>
<td>74%</td>
</tr>
</tbody>
</table>

P value: NS NS NS NS NS

However in the few comparisons of various direct thrombin inhibitors that have been studied in the main area where we use these drugs which is in HIT, it has been impossible to find differences in mortality, in length of stay, in bleeding complications, in how long it takes platelets to recover or what percent of therapeutic APTTs can be obtained when using these drugs on a intravenous basis. And because of those apparent lack of differences in these hard endpoints, the authors of this particular study said in their abstract that selection of a DTI should be guided by the patient’s clinical status and organ function instead of by efficacy and safety considerations. Each of these direct thrombin inhibitors is a little bit different with respect to its pharmacokinetic characteristics and it is perhaps those issues as well as cost that should be driving our selection of one direct thrombin inhibitor over another just like the situation with low-molecular weight heparins.
All three of these drugs are available in injectable form only, all three of them are monitored using the APTT. You know that there are some differences with respect to thrombin binding but you should also recognize there are some differences with respect to renal clearance, elimination half-life and effect on the INR. In my institution, we have elected to use Bivalirudin as our first line direct thrombin inhibitor for HIT because it is the direct thrombin inhibitor with the shortest half life with only a moderate impact on INR when patients are transitioning to Warfarin and because it has a mixed clearance picture partial renal, partial non-renal clearance, you may have a totally different program in your hospital. We have also found in our situation that Bivalirudin is about half the cost of both argatroban and lepirudin which makes for very nice presentation to our P&T committee. But your situation may be very different than ours and so again the message is the selection of a particular direct thrombin inhibitor ought to be guided by issues other than efficacy and safety just like the low-molecular weight heparins and your answer may be a different one than mine.
Now, we need to recognize as this whole landscape is changing that venous thromboembolism is not only a significant clinical problem but it has been recognized by regulatory agencies and by the federal government as the most common preventable cause of hospital death and when you think about how much effort is going into patients’ safety on a national level, you will see how important this particular clinical problem has become. It's expensive to pre-treat and prevent VTE, estimated cost of $1½ billion a year related to prevention and treatment and managing long term complications like the Post Thrombotic Syndrome and pulmonary hypertension. And there is a reasonable amount of mortality associated with PE about 10% for first episode and that can go up to 20% in patients with recurrent pulmonary embolism.
Adequate thromboprophylaxis is the key to preventing primary DVT/PE, as well as recurrent VTE, post-thrombotic syndrome, and VTE-related mortality.

So it is clear that prophylaxis prevention is really key to preventing a primary event as well as to preventing recurrent thrombosis, the Post Thrombotic Syndrome and any VTE related mortality and because of that, there has been an awful lot of attention recently paid on VTE Prophylaxis.
In the last couple of years, a coalition called the Coalition to Prevent Deep-Vein Thrombosis was formed, it is the blending of all kinds of national organizations that went forward and lobbied Congress to declare March, DVT Awareness Month and you may work in a setting where every March some posters fly up to remind providers and patients as well of the importance of this clinical problem. It's expected that in the winter of 2008, the US surgeon general will issue a call to action around Deep-Vein Thrombosis. This was intended to be a 2007 program but you may recall from reading the news that we have had a little surgeon general problem related to our government, no politics, so I am not going any further than that. But we now have a surgeon general in place and it is expected that DVT call to action will be issued. The point of a program like this is to create public awareness so there would be public awareness campaigns.
While that’s going on, the Center for Medicare Services has developed what's known as the SCIP Project, the Surgical Care Improvement Project and the goal of this program is to reduce surgical complications by 25% by the year 2010. Some of you may work in hospitals where you are collecting data for the SCIP project and are being evaluated next to other benchmarked institutions. But the surgical complications that they are trying to prevent are surgical site infections, cardiac events, post-op pneumonia and finally VTE with a goal of improving the rates of VTE Prophylaxis in surgical patients and reducing the rate of postoperative DVT and PE at 30 days and it would not be a surprise if one day hospitals were compared to one another and because this is a CMS program, that Medicare funding would somehow be linked to your outcomes around VTE Prophylaxis rates and post-op DVT.
Surely all of you are familiar with the 2008 Joint Commission National Patient Safety Goals that have been released. We have until 2009 to reduce the likelihood of patient harm associated with the use of all antithrombotic agents not just traditional heparin and warfarin like we have probably been doing a good job at but also the low-molecular weight heparins, fondaparinux and all the direct thrombin inhibitors and my guess is that in your hospital, pharmacy has if not already will soon be charged with coming up with programs to meet these National Patient Safety Goals. The beauty of a program like this is that it does need to be driven by hospital administration so hopefully you will get support around this but much of the work around meeting these National Patient Safety Goals is falling on pharmacy departments.
In the background, you should be aware that in 2009 it is expected that the Joint Commission and National Quality Forum are going to release VTE performance measures. This is a very different program. This is not about patients’ safety related to drugs, this is about how we manage patients who develop VTE. So there are two of these performance measures aimed at documenting risk and prophylaxis, there are number of them related to VTE treatment including documenting an indication for the implementation of an IVC filter and then all the things that we hopefully are doing already with our antithrombotic drugs overlapping warfarin and heparins appropriately platelet count monitoring for unfractionated heparin, using a nomogram to manage unfractionated heparin and perhaps not so common in many hospitals having appropriate discharge plans for people who have developed VTE which sometimes can mean transition to an ambulatory anticoagulation clinic. And then the last outcome measure among these performance measures is to be able to report the incidence of potentially preventable hospital acquired VTE and once again it will be no surprise if these kinds of data were to become public and you could read about your hospital in comparison to the other hospitals in your city or your state with respect to your rate of hospital-acquired VTE. So know that these performance measures are coming and they are different from the National Patient Safety Goals. Those patient safety goals are organized around drug therapy, the performance measures are around treatment and prevention of a disease state.
When it comes to VTE prevention for surgical patients, the American College of Chest Physicians has done a very nice job of organizing patients according to risk categories low, moderate, high and highest and it's probably quite clear to you that in that highest risk category are patients who undergo orthopedic surgery procedures, patients with major trauma or spinal cord injury and anyone greater than 40 who has a major surgical procedure who has other risk factors.
### VTE Risk without Prophylaxis in Surgical Patients

<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
<th>Highest Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf DVT</td>
<td>2%</td>
<td>10-20%</td>
<td>20-40%</td>
<td>40-80%</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>0.4%</td>
<td>2-4%</td>
<td>4-8%</td>
<td>10-20%</td>
</tr>
<tr>
<td>Clinical PE</td>
<td>0.2%</td>
<td>1-2%</td>
<td>2-4%</td>
<td>4-10%</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>&lt;0.01%</td>
<td>0.1-0.4%</td>
<td>0.4-1%</td>
<td>0.2-5%</td>
</tr>
</tbody>
</table>


Associated with each of these risk categories are some very clear numbers about what the risk is to develop Calf DVT, Proximal DVT, Clinical Pulmonary Embolism or Fatal Pulmonary Embolism, when no prophylaxis is given.
So again, this data comes from enormous analysis of available data by the American College of Chest Physicians and this is the Seventh Consensus Conference, soon to be replaced by the reports from the Eighth Consensus Conference, hopefully in January or February this year. We will see some slight differences in these risk categories, but the concepts are all just really the same. Now, for each of these risk categories there are then recommendations for the appropriate way to prevent VTE in each of these patients and you will notice for the highest risk patients there are many more options than there are for the low risk patients who may simply need early ambulation. It’s entirely possible that the difference between the moderate and high risk patient is where we can differentiate sub-Q Unfractionated Heparin given twice daily versus three times daily, that’s certainly a possibility. We could go on for hours about each of the selections within these categories but I think the main take-home point is to recognize that the work has been done for us already, there are options and the selection of a particular option for an individual patient is dependent on numerous characteristics and then what's available in your hospital is going to be driven by very practical issues including cost.
### Prevention Of DVT After General Surgery

<table>
<thead>
<tr>
<th>Regimen</th>
<th># Trials</th>
<th># Patients</th>
<th>Pts w/DVT</th>
<th>Incidence</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>54</td>
<td>4310</td>
<td>1084</td>
<td>25%</td>
<td>--</td>
</tr>
<tr>
<td>Aspirin</td>
<td>5</td>
<td>372</td>
<td>76</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Elastic Stockings</td>
<td>3</td>
<td>196</td>
<td>28</td>
<td>14%</td>
<td>44%</td>
</tr>
<tr>
<td>LDUH</td>
<td>47</td>
<td>10,339</td>
<td>784</td>
<td>8%</td>
<td>68%</td>
</tr>
<tr>
<td>LMWH</td>
<td>21</td>
<td>9,364</td>
<td>595</td>
<td>6%</td>
<td>76%</td>
</tr>
</tbody>
</table>


It’s quite clear that Unfractionated Heparin and Low-Molecular Weight Heparin are far more efficacious than many of the other options available for preventing Deep-Vein Thrombosis in surgical patients, Elastic Stockings and other mechanical approaches do have their role particularly in patients with high risk of bleeding. And I will point out that Aspirin does not prevent Deep-Vein Thrombosis and in fact there is a guideline in the ACCP Consensus Conference that says specifically do not use Aspirin to prevent Deep-Vein Thrombosis, it does not work.
There are just a couple of things that we need to appreciate about the differences between Low-Molecular Weight Heparins and Unfractionated Heparin when used in DVT prophylaxis. It is quite clear from a number of trials that in orthopedic surgery, in trauma, and in spinal cord injury, Low-Molecular Weight Heparins are in fact superior to Unfractionated Heparin. But in all other kinds of surgical procedures and in the acutely medically ill as well, I think we can pretty much hang on hat on the fact that Low-Molecular Weight Heparins and Low-Dose Unfractionated Heparin are equally effective in preventing DVT. We could have long discussions about each of these categories, but we will just sort of summarize things as this is.
I do want to mention again, Mechanical Prophylaxis because if you were to walk around one of your Intensive Care Units or one of your hospital wards, you might find what we do in our hospital often, which is that instead of being onto the patient, the Sequential Pneumatic Compression Devices are often found on floor, or the counter, or shelf. They can't work unless they are being worn and they are not worn because they are hot and uncomfortable and they get in the way of the nurse. Here, we can see the pump device, but the compression stockings themselves are over here and that’s not a very effective way to prevent Deep-Vein Thrombosis. So in the Seventh ACCP Guidelines, there is actually a statement about being sure to ensure proper use and optimal compliance with mechanical devices, because they can't work unless they are worn.
Now, in the acutely medically ill patient we have lots of work that’s going on to distinguish Unfractionated Heparin from Low-Molecular Weight Heparin, I think it’s become quite clear than in acutely medically ill patients with one or more risk factor for VTE who are confined to bed, who have CHF or respiratory disease that these patients do in fact require DVT prophylaxis and we have a lot of options available to us.
In terms of making a selection, again this is an issue where your cost becomes an important driver of your decision. It is relatively clear that Low-Molecular Weight Heparins given in this kind of setting are associated with a lower risk of minor bleeding complications, a lower risk of Heparin-Induced Thrombocytopenia because in general they are given once a day, they are associated with less nursing time and more patient acceptance. But all of this comes at a price, a higher cost and you may work in a setting where your system is able to look at long-term outcomes and determine that this higher cost of drug itself is saved by prevention of these problems. I work in a setting where the pharmacy budget is separated from all other outcomes and where all we want to do is make sure, we are giving lowest cost drug and so we are more likely to use Unfractionated Heparin in acutely medically ill patients, because the cost is lower and not paying any attention to other long-term outcomes. And do I think that’s appropriate? No, I don’t but that’s the setting of this particular organization and you may work in one similar or different from that. That doesn’t mean that one or the other of these choices is right or wrong, but it is individualized.
Current Guidelines For Anticoagulant Treatment Of DVT/PE

**INITIAL THERAPY**

- **Drug:** LWMH, IV UFH, or SQ adjusted dose UFH
- **Intensity:** Reagent-specific aPTT range (UFH)
- **Duration:** 4-5 days overlapping with warfarin AND until INR > 2

**LONG-TERM THERAPY**

- **Drug:** Warfarin (LMWH or SQ UFH if contraindicated)
- **Intensity:** INR 2.0-3.0
- **Duration:** 3-6 months


Now, we would be talking a lot about DVT Prophylaxis. I have just got some final comments about DVT treatment, I think it’s quite clear that there are a lot of options for the treatment of DVT that we can use a Low-Molecular Weight Heparin, IV Unfractionated Heparin, even sub-Q adjusted-dose Unfractionated Heparin. When we were using those Unfractionated Heparin products, we are monitoring according to an APTT, which is hopefully reagent specific and we are remembering to overlap with Warfarin for a minimum of 4 to 5 days and until the INR is greater than 2 that’s just given something that we need to pay attention to. For long-term therapy we are using Oral Anti-Coagulation and in some settings continuing with a Heparin or Low-Molecular Weight Heparin product if we are talking about cancer associated thrombosis or some contraindication to Warfarin. Typical goal of INR for treatment of VTE is 2 to 3 and the typical duration of therapy is three months although that can be extended to 6 in some situations and longer in patients with hypercoagulability or a history of recurrent thrombosis.
Why Warfarin and Heparin Need to Overlap When Treating VTE

1. Pharmacokinetics: 4-5 days for warfarin to reach steady state
2. Pharmacodynamics: 4-5 days for f II to be depleted
3. Physiology: relative hypercoagulable state when protein C is initially depleted
4. Clinical: higher rate of recurrent VTE without appropriate overlap

Why do we need to do this overlap thing, that 4 or 5 days in overlap? When the INR is 2 on day 2, why do we need to keep the Heparin going? Well, there are four very clear reasons. One is pharmacokinetic in nature, you know very well that the elimination half-life of Warfarin is like say 4 to 5 days and it takes that long to reach steady state of Warfarin. You also know that the clotting factors that Warfarin is impacting have their own elimination half-lives and it takes 4 or 5 days for factor 2 or thrombin to be depleted, so we have got to have a bridge or overlap to deal with that problem. It is also clear that when one starts Warfarin, it is not only factors 2, 7, 9, and 10 that are being depleted but also protein C, a naturally occurring anticoagulant and a relative hypercoagulable condition can be developed, when protein C, which has a very short elimination half-life is initially depleted. This is likely to manifest in patients with protein C deficiency and you probably don’t know who they are. But this is yet another reason for the overlap of Heparin and Warfarin. And then clinically, we also know that there is a higher rate of recurrent VTE, when patients do not receive that appropriate overlap, so again it’s critical to have a program or a system in place that meets this particular goal.
Now, when it comes to Cancer Associated Thrombosis, our treatment options are quite a bit different than they were in the past because of quite a bit of work that has helped us to understand that many patients with malignancy who develop thrombosis fail oral anticoagulation. And so these days, when we talk about thrombosis and malignancy, what we talk about is an initial phase of treatment with a Low-Molecular Weight Heparin. A sub-acute phase of treatment that typically is 3 to 6 months long, continuing Low-Molecular Weight Heparin instead of transitioning to Warfarin and then a chronic phase that could be either Warfarin or a Low-Molecular Weight Heparin because the presence of malignancy continues to represent a hypercoagulant condition. This is a big change in clinical practice, it’s supported by the ACCP guidelines, it is also supported by the guidelines from the National Cancer of Care Network “NCCN” and it is something that many more cancer associated institutions have caught on to, but not necessarily outlying hospital. So you should be aware that the new guidelines for the treatment of Cancer-Associated Thrombosis are to continue a Low-Molecular Weight Heparin exclusively for at least the first 3 to 6 months and then reevaluate at that time. The transition to Warfarin does not happen until after 3 to 6 months and again that’s because of much better clinical outcomes with long-term Low-Molecular Weight Heparins in these patients.
Our last topic is just a couple of comments about Atrial Fibrillation and as I mentioned earlier, this is the setting in which Warfarin is used on a long-term basis, more frequently than any other clinical indication. The annualized risk of stroke for what we refer to as permanent or persistent afib is exactly the same as it is for Paroxysmal Atrial Fibrillation. So if a patient is in and out of afib or in it all the time, the annualized risk of stroke is still the same and all these patients should be anticoagulated. The outlier is patients with Lone Atrial Fibrillation who are less than 65 years of age, who have no prior history of TIA or Stroke and no underlying risk factors for stroke or frankly for Atrial Fibrillation. This maybe people who develop afib in association with alcohol with thyrotoxicosis or some acute situation. Their annualized risk of stroke is quite a bit lower and in many cases these patients revert back to normal sinus rhythm without difficult and do not require long-term stroke prevention.

<table>
<thead>
<tr>
<th>Annualized Risk of Stroke</th>
<th></th>
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<tbody>
<tr>
<td>Permanent/Persistent AF</td>
<td>3.2%</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>3.3%</td>
</tr>
<tr>
<td>Lone AF</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

- Age < 65
- No prior hx TIA or stroke
- No HTN or DM
- No CHF or LV dysfunction

Aspirin reduced the risk of ischemic stroke by 2%–38% versus control. The aggregate relative risk reduction in ischemic stroke was 22%.

We have got lots of data from many, many years ago that helped us to understand that Aspirin does reduce the risk of stroke by a range of 2% to 38% and the average relative risk reduction of about 22%.
But we also know that although Aspirin can work, it is certainly no more and certainly not more effective than Warfarin. Warfarin on an average basis reduces the relative risk of stroke by about 68%, we have got all kinds of clinical trials that have substantiated that and we have got years and years and years of clinical guidelines from all kinds of organization that have helped us to understand that Warfarin really is our preferred approach to stroke prevention and Atrial Fibrillation.
The current recommendations from the chest guidelines, American College of Chest Physicians note that for any patient with a risk factor for stroke that the choice of therapy is long-term oral anticoagulation. However, if you are encountering a patient who is 65 to 70 years of age and does not have any risk factors for stroke, including the history of TIA, Diabetes, history of Hypertension or any left ventricular dysfunction you might select Aspirin in those patients. You would probably, preferentially choose Warfarin, but Aspirin is an option if you have a patient with some potential bleeding risk factor etc for treatment with Warfarin or who was unable to comply with their regimentation that Warfarin requires. And for patients who are 65 years of age or less with no other risk factors for stroke then Aspirin is considered the preferred approach. These are well established guidelines and again, we could go on for hours about where they come from, but we leave it as a kind of a summary.
It is important to recognize that as we are all aging, so are those around us and that means that not only as the elderly population in the United States increasing dramatically, but the expected number of patients with Atrial Fibrillation is also growing quite dramatically. These data are from 2001, which established that by 2050, we ought to be looking at 5 million patients in the United States with Atrial Fibrillation. There are new data based on new population studies of how our population is expanding and that number is now 15 million. So if you are a person who is working in cardiology, you have got a long career ahead of you dealing with Atrial Fibrillation and if you are a pharmaceutical company, you have got a long life of looking for new options for stroke prevention in patients with afib.
Summary

1. Summarize current therapies available for anticoagulant therapy.
2. Assess the role of thrombin in hemostasis.
3. Review current guidelines for use of antithrombotic agents to prevent and treat venous thromboembolism, and to prevent stroke in atrial fibrillation.

So to summarize here, we have had an opportunity to look at current therapies available for antithrombotic therapy. I hope you have got a sense now of the real world of thrombin in hemostasis. And we have had a chance to look at a lot of our guidelines.
Question #1

The actions of thrombin include:

1. Conversion of fibrinogen to fibrin
2. Multiple procoagulant activities
3. Multiple antifibrinolytic activities
4. All of the above

So I would like to stop here and just transition over to those 4 self-assessment questions. Looks to those one of time before we move onto our next speaker. This time we will show you the right answers. Answer this now if you would please. What is the action of Thrombin? Conversion of fibrinogen to fibrin, multiple procoagulant activities, multiple antifibrinolytic activities or all of the above,

Alright, we are ready to look at the answers then. There we go, so 50% of you now realize that all of these things are involved. Okay I didn’t do very well in my teaching today. You are hungry, you want that boxed lunch.
Question #1

The actions of thrombin include:

1. Conversion of fibrinogen to fibrin
2. Multiple procoagulant activities
3. Multiple antifibrinolytic activities
4. All of the above

Alright, we are ready to look at the answers then. There we go, so 50% of you now realize that all of these things are involved.
Currently available options for prevention of venous thromboembolism in patients undergoing total hip replacement include:

1. Warfarin
2. Low Molecular Weight Heparin
3. Fondaparinux
4. All of the Above

Alright, question #2 currently available options for prevention of VTE and patients undergoing hip replacement include, which of the following: Warfarin, Low-Molecular Weight Heparin, Fondaparinux, all of the above, what's the right answer?
Currently available options for prevention of venous thromboembolism in patients undergoing total hip replacement include:

1. Warfarin
2. Low Molecular Weight Heparin
3. Fondaparinux
4. All of the Above

For VTE prevention and hip replacement, alright, well let’s take a look at our answers so. Here we go, so 75% of you are aware that all of these are potential options for VTE prevention.
Alright our third question, Cancer-Associated Thrombosis maybe I hit the winner on this one? What is the preferred strategy for treatment of Cancer-Associated Thrombosis? Is it Unfractionated Heparin followed by Warfarin, Low-Molecular Weight Heparin immediately followed by Warfarin, Low-Molecular Weight Heparin alone or Fondaparinux alone?
Okay, so let me tell you, the answer is Low-Molecular Weight Heparin alone for that first 3 to 6 months and then a transition to Warfarin or continuation of Low-Molecular Weight Heparin after that. That’s the new guidance for treatment of Cancer-Associated Thrombosis.
Patients with atrial fibrillation and diabetes should receive stroke prevention therapy with:

1. ASA 81 mg po daily
2. ASA 325 mg po daily
3. Warfarin to INR 2 - 3
4. A and C

Last question #4, if a patient has Atrial Fibrillation and Diabetes, which is a risk factor for stroke in afib, what's the most appropriate strategy for preventing stroke in those patients; low-dose Aspirin, regular-dose Aspirin, Warfarin to an INR of 2 to 3 or Aspirin plus Warfarin, patient has diabetes and afib?
Patients with atrial fibrillation and diabetes should receive stroke prevention therapy with:

1. ASA 81 mg po daily
2. ASA 325 mg po daily
3. Warfarin to INR 2 - 3
4. A and C

The answer is in fact number 3, Warfarin alone, very good.
Alright, well I would like to thank you very much for your attention.
Indeed I think, what we are seeing now are exciting times in anticoagulant antithrombotic therapy as you will see in the next segment of our program we have quite a few compounds that are entering advanced phase 3 development or are in fact in advanced phase 3 development. So that is going to be the focus of my talk today and by way of disclosure let me tell you that obviously, the compounds we are going to be reviewing none of them are FDA-approved as of this stage and of course all of the proposed indications at this point are investigational.
Learning Objectives

• Compare pharmacokinetic and pharmacodynamic characteristics of investigational agents that might replace traditional anticoagulants.

• Evaluate the current status of investigational antithrombotic agents.

So as far as the objectives of my presentation we are going to be looking at pharmacokinetic and pharmacodynamic differences of the current agents that might compete or perhaps have a chance of replacing some of the traditional agents and then secondly, we are going to be looking at currently available clinical data of the various agents and really today, I am going to be focusing on for the most part of phase-3 data where that is available and phase-2 data I am going to be presenting selectively only to highlight certain dose selections for the phase-3 process.
Thromboembolism: A Systemic Disease

Arterial
- Coronary artery disease
  - UA, NSTEMI, STEMI, angina
- Cerebrovascular disease
  - TIA, ischemic stroke
- Peripheral arterial disease
  - Claudication

Atrial
- Atrial fibrillation
  - Stroke

Venous
- Deep vein thrombosis
- Pulmonary embolism


So thromboembolism of course, we all recognize that is a systemic disease and we have a fairly large number of indications both on the arterial side and on the venous side requiring anticoagulant and antithrombotic therapy. So when we look at the multitude of indications requiring anticoagulant, antithrombotic therapy, we also recognize this tremendous unmet clinical need for new compounds that perhaps are less complex to use, not only from a patient’s perspective, but also from a provider’s perspective, right. So although, we have made very nice progress on adding new compounds, the majority of course on the injectable side we will be limited to coming up with compounds that are fairly easy to use and not very tedious to use from a dosing and monitoring perspective.
So again, thromboembolism is a problem of course in United States but also in other parts of the world. This slide indicates some recent numbers just comparing US numbers with European numbers as you see here there are numbers of patients in millions, so of course Myocardial Infarction is up there close to 8 million cases, ischemic stroke if we just focus on US data, slightly over 5 million and then venous thrombosis of course, where a lot of the long-term usage would be for patients especially if they have recurrent events, fairly a large numbers again were now over 500,000 cases or close to 600,000 per year in US.
Of course, the mortality is also linked to thromboembolism and when we look at the mortality rate focusing in numbers, US-based numbers, you see here, the numbers here are in hundreds of thousands. Again, stroke is a leading cause of deaths so again, fairly high number of patients in coronary heart disease and of course, Venous Thromboembolism again, this is more up-to-date data that now indicates that we have over 200,000 cases obviously where mortality obviously is due to this particular disease.
Incidence of Atrial Fibrillation Will Increase with the Growth of Elderly Population

Now, Dr Wittkowsky showed you this data, but we are looking here now at a publication from circulation published a bit more recently and so the estimated numbers for Atrial fibrillation seen here are closer to 15-16 million. So again what I am trying to highlight here is that with the aging population of course, indications like A-fib or the number of patients go up and so we are going to be seeing even higher need for compounds that can be safely and easily used for long-term chronic type indications.

AF = atrial fibrillation.
Clinical Development of New Anticoagulants

- Primary prevention of VTE
- Treatment of VTE
- Secondary prevention of VTE
- Prevention of stroke in AF
- Short- and long-term treatment in ACS

So with that, then, what are some of the areas where some of the new anticoagulants are being developed in? So there are some major indications that are currently being evaluated; one of them being primary prevention or primary prophylaxis of Venous Thrombosis. And as you recall historically, a lot of the compounds initially get evaluated in orthopedic surgery patients because we know that in orthopedic surgery, the risk of Venous Thrombosis is very high without any prophylaxis so we are looking at rates as high as 60% to 80%, and so this is kind of a good area to start to evaluate some of these new compounds. And once orthopedic data is in, we are seeing branching out into other prophylactic indications such as the medically ill population obviously. So that’s a bit of a lower risk, but then the number of patients of course that will qualify would be much larger. Treatments of Venous Thrombosis; of course, this is acute treatment of both Deep Vein Thrombosis and Pulmonary Embolism, secondary prevention of VTE so this would be a longer-term indication then as Dr. Wittkowsky suggested beyond the acute phase period. So we are looking at both short and longer-term indications, stroke prevention in Atrial Fibrillation. And then, interestingly, some of these compounds are also being evaluated both for short and long-term treatment in acute coronary syndromes. So again, if you look at the landscape now, in ACS, although we have longer-term our mainly anti-platelet agents, but interestingly now, some of these inhibitors, direct factor inhibitors are being considered for some of these longer-term indications in ACS.
Oral Direct Factor Xa and IIa Inhibitors: The Next Step in Anticoagulant Evolution

<table>
<thead>
<tr>
<th>Class</th>
<th>Target</th>
<th>Route</th>
<th>1930s</th>
<th>1940s</th>
<th>1980s</th>
<th>1990s</th>
<th>Direct Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATIII + Xa + IIa (1:1 ratio)</td>
<td>Parenteral</td>
<td>Heparin</td>
<td>VKAs</td>
<td>LMWH</td>
<td>Direct Thrombin Inhibitors</td>
<td>Indirect Xa Inhibitors</td>
</tr>
<tr>
<td></td>
<td>II, VII, IX, X (Protein C, S)</td>
<td>Oral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Oral</td>
<td>FXa; FIIa</td>
</tr>
</tbody>
</table>

- Parenteral administration
- Narrow therapeutic window
- Unpredictable pharmacology
- Need for routine monitoring
- Increased bleeding risk
- Drug and food interactions
- Parenteral administration
- Risk of HIT
- Requires switch to warfarin for chronic treatment – need for dual therapies
- Potential for thrombin rebound after discontinuation
- Current use limited to cardiovascular disease
- Requires switch to warfarin for chronic treatment – need for dual therapies

VKA = vitamin K antagonist; LMWH = low-molecular-weight heparin.

So this is again just a snapshot of again how we have evolved historically with the various anticoagulant agents in the United States. So, of course, as you recall, Heparin first became available in the late 1930s, early 1940s; then of course, this was followed by Vitamin K antagonists Warfarin mainly in the United States in the mid 1940s; then the low-molecular-weight heparins came along about 40-50 years after regular heparin. And this clearly were a significant improvement over traditional heparin, again lot easier to use, better side-effect profile, however, were still limited by a subcutaneous route of administration. And the direct thrombin inhibitors, Ann has done a tremendous job of viewing the agents and where they fit in currently, but again what we have currently, our intravenous compounds. And the last addition to the class of anticoagulants are the Indirect Factor Xa inhibitors, also known as Pentasaccharides, looking at the structure of the compounds of this class currently, we have one agent on the market that is Fondaparinux and of course, that is also a subcutaneous agent. So what the big need is obviously for all agents that again would aid in not only acute but also longer-term indications. And the two targets that are again in most advanced phases where we see compounds being developed are Factor Xa inhibitors and Factor IIa inhibitors.
Goals of NEW Anticoagulants

- Broad therapeutic window
  - Low inter- and intra-patient variability
  - No need for routine monitoring
- No need for anticoagulant switch (parenteral to oral)
  - Use as single agent in acute and chronic indications and in both the hospital and home settings
- Oral administration
  - Once vs. twice daily
- No drug or diet interactions
- Safe

So what are the goals then that are being targeted for some of these new anticoagulant agents. So ideally, what we would like to see as we are comparing these with the traditional compounds like Warfarin especially, when we think of all compounds or even agents like regular heparin, we would like to see a broader therapeutic window, of course, with low inter or interpassionary ability. So ideally, we would want to be able to give a single dose without huge variations or huge margin between safety and efficacy and of course, the good predictability of those responses that would allow us to give these agents without routine anticoagulant monitoring. Also, what is being proposed and looked at with some of these compounds is the fact that perhaps we could use them without a need from a parenteral-to-oral switch. So we could see patients coming in with an acute clot burden perhaps and initiating one of these new oral compounds without that initial transitioning in period with a subcutaneous or intravenous agent. Of course, all administration and again, the less complex regimen once a day would be preferred versus twice a day, but as you’d see in the data, we have both once-a-day and twice-a-day regimens being evaluated. Of course, we want clean compounds from a drug-and-diet interaction profile perspective. Safety is a huge issue based on the lessons that we have learned with some of the previous compounds like ximelagatran that have not been approved in the US due to safety concerns. And of course, as a pharmacist, what I would like to add is that we want all of these obviously and at the lowest possible cost. Now, of course, this may not be what the companies that are developing these agents are thinking, but of course, that’s going to be the big battle out there having all of these close to these ideal characteristics, but also something that is affordable.
So again, this shows you this idea of again searching for an agent that has a broader therapeutic window and if we think of Warfarin of course, we all recall the narrow safety-to-efficacy margin, and this is really why with agents like Warfarin, we have to do routine INR monthly and constantly change the appropriate dose so that we avoid huge fluctuations due to this narrow therapeutic window. So we would like to see something that would allow us or give us a little bit more cushion between the efficacy and safety margin.
So Dr. Wittkowski has covered with you the mechanism of various anticoagulant agents and again, this is another cartoon depicting, again this is the basic scheme of the coagulation cascade. Now, really, what I would like you to take away from this is that what we are seeing now with the new landscape of all anticoagulants is really we are moving towards a very highly targeted mechanism of action on the clotting cascades. So, of course, when you look at traditional heparin, the Vitamin K antagonists, we see the various targets on the cascade that these agents affect. We have seen again a nice discussion on the Indirect Factor Xa inhibitor Fondaparinux, this still requires a cofactor to exert its effect. But then really, the new compounds what we are looking at are the Direct Factor Xa inhibitors and Direct Thrombin inhibitors that would target Factor Xa and Thrombin directly.
New Anticoagulants

**ORAL**
- TTP889
- Rivaroxaban
- Apixaban
- LYS17717
- YM150
- DU-176b
- PRT-054021
- Ximelagatran
- Dabigatran

**PARENTERAL**
- TFPI (tifacogin)
- APC (drotrecogin alfa)
- sTM (ART-123)
- Fondaparinux
- Idraparinux
- TX-9065a
- Otamixaban

So again, going back to the cascade then, this is what is going on, on the parenteral side. There are some agents being developed against some that would block again the tissue factor, factor VIIa, a point in the cascade, and of course, activated protein C ART123, again see the steps here. As far as Indirect Factor Xa inhibitors Idraparinux is a subcutaneous agent that is given once a week. This is in advanced Phase III development. And the interesting news about this compound, if you follow the development of this compound, we have some Phase III data and even some recent data that has been presented at ISTH in Geneva in July looking at a nonreversible formulation of Idraparinux, and of course, that is a fairly huge concern because this is an agent that has a tremendously long half life, thus we are being able to give it once a week. But those studies used a formulation that did not have an anti-dose or no reversibility. So obviously, these issues raise all kinds of red flags, but the nice thing is that now they came up with a version that is reversible. They isolated a substance from egg white called biotin and they came up with a formulation called Biotinylated Idraparinux and so then, you could reverse it in an instance and so that is now being evaluated. I am not going to be focusing on injectable agents today, but again, I think it's interesting to note this and follow the development of this particular compound because in the near future, we will have data coming out with Idraparinux. Another point here, then looking at Direct Factor Xa inhibitors on the injectable side, we have the DX 9065A compound and otamixaban. Otamixaban is an interesting compound. It's very, very short half life and this is in advanced Phase II study so Phase II B study is mainly looking at acute coronary syndrome indications. Now, in the oral side, as you see, there is a quite a bit of activity. Ximelagatran, of course, is the one but never made it to the market. And the follow-up compound now that is developed by a different company but again is in advanced Phase III is dabigatran. As far as Direct Xa inhibitors, you see the various compounds that are being evaluated, but the two that are most advanced are Rivaroxaban and Apixaban. Now, let me highlight the fact that there are also some Factor IX inhibitors that are being considered and in fact, there are fewer more in pipe but very early phases. And so what we are seeing now in the field is this big debate of what is the best approach. Is it better to hit the thrombin molecule directly or is it better to go up higher in the cascade. For instance, hit factor X or perhaps even higher like Factor IX. And the big argument is that if you go higher in the cascade, initially, you still have some residual thrombin left off in the sockets and so this residual thrombin can exert its activity such as wound healing activities, some of the beneficial activities of thrombin, until obviously, we move down the cascade and obviously we reach the thrombin inhibitory effect of the various anticoagulants. Whereas with a direct thrombin inhibitor, you hit the molecule directly and so perhaps, we see or hear these theoretical concerns or perhaps more bleeding or maybe oozy--weepy wounds. So this is all theoretical, a lot of speculation, we don’t have outcomes-based data at this point to substantiate any of these, but it is a very interesting scientific argument. And so of course, I think that this question can only be answered once we have the Phase III data in, but it's interesting to pay attention on how this is evolving.
So let me begin then my discussion with the two Factor Xa inhibitors, Rivaroxaban and Apixaban, and then the second half, I am going to be talking about dabigatran. So to compare these agents then, of course, they are both very small molecular weight compounds. Again, you see the molecular weight there. They are both targeting Factor Xa and again both of these are direct inhibitors of Factor Xa so they do not require a cofactor. Interestingly, neither of these are a prodrug so they do not have to be converted to the active compound. So this is a major difference from these two agents when we compare them to the direct thrombin inhibitors dabigatran. So dabigatran, as you see, is a double prodrug. So that is actually, similarly if you recall ximelagatran was a prodrug and so dabigatran is a double prodrug. Now, another major difference between these two and the IIa inhibitor dabigatran is the cytochrome P450 metabolism. Both of these compounds are metabolized to the P450 enzyme system minimally. And so, of course, this is, to us as pharmacist, this is somewhat of a concern because although we see minimal here and what we are hearing so far from the companies developing these products is that apparently, we should not expect or would not expect significant drug interactions. Of course, we’ve got burned many, many times with this and so at this point, I am not ready to buy any of these arguments until we have all of those big culprits that we know that get metabolized through this pathway studied against these various compounds. So I think we still have to learn a little bit more by looking at individual level drug interactions. So that’s a difference when we look at the IIa inhibitor there again, that particular compound is not metabolized through this pathway. Now, time to peak, this is very interesting to note, please note very short time-to-peak concentration. So again, this is intriguing because this raises the possibility of giving a tablet formulation and not needing a subcutaneous injection or an intravenous injection even when somebody comes in with a DVT or PE, right. Half life again, you see a little bit shorter with Rivaroxaban than with Apixaban. And so when you look at this half life and you kind of think how does half life is compared with low-molecular-weight heparins, right. Low-molecular-weight heparin’s half life is around three to five hours depending on the compound that you are looking at. So with these agents then, it is feasible to consider of course once-a-day dosing and again, we are going to be seeing either once-a-day, twice-a-day so various dosing regimens are being evaluated. Now, excretion is very important so you see that Rivaroxaban is really excreted to about 65%; and then again, Apixaban, about 25%. So, of course, renal dosing would have to be addressed with these compounds as well so the hope is that we will get hopefully some guidance from the manufactures in area on how to dose or at least some cautions about the use of these compounds in these Asian populations.
So this is just a cartoon of the crystal structure of the Factor Xa Rivaroxaban complex. As you see here, this small molecule, the five sugar moieties and again the binding into the socket, so again, this is what we are looking at with this particular compound.
Now, one question that comes up a lot in practice is whether we have any biological markers or laboratory markers that we can use to measure or call back to the anticoagulant effect of these new compounds. Of course, we recognize the fact that with these new compounds, we see a much more predictable dose response than what we see with traditional agents like Warfarin. Well, of course, we do not follow linear kinetics and we do not see linear dose response. But we can all think of cases in practice where a patient comes in and swears that they were taking the medication but they have a major event, right. Now, we just may want to know what the anticoagulant level is. Or a patient comes in with a major bleeding complication and we wonder well, are there differences in drug levels in this particular patient and where is the concentration, so are there any tools we could use. So this comes up a lot and so again, we are interested to see whether there is anything we could use to measure drug effect. And so with this particular compound, Rivaroxaban, at this point, it appears that we get pretty good coalition of drug concentration so what you see here is plasma concentration of Rivaroxaban, Prothrombin Time and again see our coalition factor here. So again, a Prothrombin Time may seem a reasonable tool. Some of the other markers do not get as good of a coalition.
So with that, let’s look at the Phase II and III program for this particular compound. You see that they have a very ambitious target enrollment, around 40,000 patients. Some of the major indications for Rivaroxaban currently being evaluated are in the area of orthopedic surgery so this is again one of the major indications as I mentioned. And this is known as the RECORD program, I mean the EINSTEIN program for DVT and PE treatment and then on the arterial side, stroke prevention in Atrial fibrillation the ROCKET program and then the ATLAS program in acute coronary syndromes.
So let’s look at some Phase II data of Rivaroxaban in orthopedic surgery for Venous Thrombosis prevention. And the three fairly large studies have been published today, these are known as the ODIXa studies, so one is a KNEE study that used a twice-a-day dosing regimen and then we have two hip studies, one that evaluated the compound again in a b.i.d. fashion and the other hip study in a once a day fashion. So what you see here is the rivaroxaban dosing, so of course these were all dose ranging studies to find the best dose moving on to the Phase III program. So again the various dosing regimens, again same here in the ODIXa-HIP study and then this was the one study so again slightly higher dose is given once a day. The comparator agents was enoxaparin as this considered now standard of therapy low-molecular-weight heparin obviously in orthopedic surgery for VTE prevention. In the knee study, as expected the higher dosing regimen was picked at 30 mg twice a day because this is the only approved dosing regimen in the United States, now in European countries, the 40 mg once a day regimen is used in knee replacement as well, but not in United States. And then the 40 mg once a day regimen of course is an alternative in the US for hips, we have either this or we have the once a day dosing regimen, so that is appropriate. Well the duration of the three studies, again these are fairly short duration studies about five to nine days post surgery. This is the follow up for the end points and then you see the total enrollments, so again overall over 2200 patients enrolled in the three studies. What I am going to be showing you results wise actually, I am going to be showing you the knee study, which I think is pretty significant because it compares the agent against the 30 b.i.d. enoxaparin and then the once a day dosing regimen in hips, because the once a day dosing is the one that moved into Phase III development.
So this is the ODIXa-Knee trial and what you see here on the left-hand side is venous thromboembolic events. These are the various Rivaroxaban doses and then this is enoxaparin 30 mg twice a day and the end point is incidence of DVT or all-cause mortality. And overall again you know you see the numbers here, so it appears to perform at least as well as enoxaparin again with you know some numeric rates a bit lower, but of course the numbers in each particular group are fairly low, so we are looking at this as an overall response. On the safety side again, this is enoxaparin and then of course we are seeing you know as we are going up of course, we see a dose response, bleeding goes up, so again you know what we are looking at something around this dosing regimen.
So looking at the ODIXa-HIP once a day study, this is the efficacy data, again remember this is once a day so various dosing regimens, this is enoxaparin once a day and so what we see overall is a trend toward lower event rates with rivaroxaban with the once a day regimen.
And then this is the same study looking at safety, major bleeding rates with rivaroxaban and enoxaparin and again enoxaparin about 2% of course as I mentioned we see a dose response, but when you pull it all together and when you are looking at the lower end, again are fairly comparable.
So based on what we have learned from Phase II studies, the dose that we expect for Phase III studies is the 10 mg once a day dosing regimen and just to better, I think put this in perspective what you see here is the total daily dose of rivaroxaban in milligram, this is enoxaparin, this is looking at venous thromboembolic events and these are the little blue dots and then also the little red figure here is looking at major bleeding. So of course what we see here for efficacy as dose of rivaroxaban goes up of course, we see a response, inefficacy events go down but we are paying a tradeoff on the bleeding side, so bleeding goes up. So the happy medium that was fixed here at least in a company’s perspective is the 10 mg once a day dose again, so balancing efficacy and safety and then when we compare this with the 40 once a day regimen of the low-molecular heparin again, these are the numbers that we have seen again based on dose ranging studies.
So of course then we also have to address the issue of whether we see an appropriate anti-thrombotic effect out to 24 hours given the half-life of these compounds and what you see here is time versus anti-Xa factor, Xa inhibition with various doses of rivaroxaban and if we just focus on the 10 mg dosing regimen that was picked for Phase III again then you see the response here, so again bottom line is that these results based on this study provided the foundation for selecting the once daily dosing regimen, so all of these regimens they are most rated appropriate Xa inhibition out to at least 24 hours.
So this brings us to the Phase III Orthopedic Surgery Trials, four notch trials are, well four notch trials have been planned, three of these have been completed and one of these is still ongoing. So we have two hip trials RECORD 1 and RECORD 2 that have been completed. Two knee trials RECORD 3 that has been completed and presented and RECORD 4 that is still ongoing. Now none of these Phase III trials of 40 rivaroxaban have been published as of yet, okay. So the dosing then you know for trials is consistent 10 mg orally once a day. For the hip trials as you might expect enoxaparin 40 mg once a day. For the knee trials, one trial picked the European dosing regimen, so this would be appropriate for Europe. For us in the US really, what we need to see is how this compares with the enoxaparin 30 mg twice a day. Now the duration for knees of course is shorter duration because if you look at the current consensus guidelines, we typically treat knee patients for about 7 to 10 up to 14 days, but ACCP currently recommends 7 to 10 days. In hips, of course we know that we see two peaks of events after surgery, one early and one late, and so current guidelines recommend one month of prophylaxis post surgery. So this is why we are pushing out treatment for about 35 days. Now RECORD 2 in my opinion is kind of a little bit of cheating, because enoxaparin was given for 14 days, rivaroxaban was pushed out for 35 days, however RECORD 1 gets around this, because both of them have been given for the same amount of time and we are comparing them against the same enoxaparin dosing regimen. Fairly ambitious program again you see the target enrollment, you see the follow-up point and then the primary endpoint is the similar for 12 venous thromboembolic events that includes DVTPE or death, of course this includes symptomatic and asymptomatic events as documented by the venography.
So what I can share with you today are the results of the RECORD 3 Trial, RECORD 3 was presented at ISTH meeting in July of this year in Geneva. And so again remember that this is the study that compared enoxaparin 40 mg once a day versus rivaroxaban 10 once a day and this is the knee study. And here what we see is a lower event rate, about a 50% risk reduction in favor of rivaroxaban and one important thing to note here that this is a superiority study and what we see with some of the IIa Inhibitors like some of the dabigatran, some of those studies were designed as non-inferiority studies, so again that’s kind of you know a major difference in those trials.
As far as bleeding outcomes, safety is very similar, major bleeding about the same, non-major bleeding about the same and an overall bleeding around 5% in both groups, so safety you know looks very promising and with some hope as far as efficacy. So this is RECORD 3 in the total knee arthroplasty, of course as I said we really have to see the results of RECORD 4 in order to make a conclusion for this particular indication in the United States because remember there we are looking at the higher enoxaparin dosing regimen.
Rivaroxaban in Orthopedic Surgery

• Phase II trials
  – Trend toward lower event rates with rivaroxaban (both bid and qd dosing) vs. enoxaparin
  – Similar major bleeding rates
  – 10 mg qd dosing of rivaroxaban selected for phase III trials

• Phase III trials
  – RECORD 3 (TKR): Rivaroxaban 10 mg qd provides superior efficacy & similar safety vs. enoxaparin 40 mg qd
  – RECORD 4 trial in TKR is ongoing
  – RECORD 1 and 2 trials in THR are completed

VTE = venous thromboembolism; TKR = total knee replacement; THR = total hip replacement.

Now what can we conclude based on what we know so far, the Phase II trials show trends toward lower event rates with rivaroxaban both b.i.d., once a day versus enoxaparin similar major bleeding rates and this is the dose that move forward. RECORD 3 we have reviewed, but we are awaiting RECORD 4 anxiously for the knee indication. Now RECORD 1 and 2 have been completed and the data is being presented at the American Society of Hematology on Monday, December 10. So I cannot present that data to you today, but the abstracts are available on the ASH website. And what I can tell you just as a bottom line that the results hold up to what we have seen in RECORD 3. So efficacy appears better and safety is about the same. And so this is out now to a month in orthopedic surgery. Now the actual numbers, we will have to go and get from the abstract, so we now have three very large Phase III trials that consistently show superiority over standard therapy with low-molecular-weight heparin.
So let’s switch gears now and talk about treatment of venous thrombosis, acute VTE. And this is a Phase II Dose Ranging Study that was presented by Dr. Bueller back in 2006. This is known as the EINSTEIN-DVT Study. Slightly over a 500 patients with symptomatic proximal DVT were randomized to one of three doses of rivaroxaban and then the comparator here was a low-molecular-weight heparin transitioned over to vitamin-K antagonist at a range INR of 2-3. You see again patients were objectively evaluated at day 84 and then followed out to slightly a low over 3 months.
So what have we learned from this Phase II dose ranging study then for treatment of DVT? Looking at the efficacy, again you see the endpoint defined here, the three doses and this is the traditional therapy with heparin low-molecular heparin to vitamin-k antagonist, so again fairly similar numbers compared to the combination. And then again when we look at safety, again the numbers compare fairly nicely with the traditional treatment approach.
So based on this then what we have learned, this is the Phase III program the EINSTEIN program for VTE treatment. I am actually pleased to see that they are doing a separate DVT and a separate acute PE study as we know with some of the low-molecular-weight heparins a lot of the early PE data was lumped in together with DVT studies. So now we will have a clearly DVT and PE and then also there is some extension study that would be looking for secondary prevention, so this would be long-term therapy. Rivaroxaban dosing, let me highlight the fact here that they picked a more aggressive approach for the first three weeks of therapy, so note the fact that there is no injectable, no IV heparin, no subcutaneous low-molecular-weight heparin or pentasaccharide 15 mg twice a day for three weeks and then after that the dose is dropped to 20 mg once a day up to 12 months and then obviously the extension just as six months and beyond is just 20 once a day regimen. Now why did they pick a higher dosing regimen for the first three weeks? Well if you go back to ximelagatran and you think about the lessons that we learned with that compound, it appeared that when we started the product as again you know the oral compound without an injectable, we had an early peak in recurrent events. And also if you think about VTE, typically we see the highest rate of events in the first month of therapy, a highest rate of recurrent events. So this is why a more aggressive dose was picked for the first few weeks and then of course the dose is dropped beyond. Comparator dosing is enoxaparin, the traditional twice a dosing regimen and then Vitamin K antagonist. In these two studies and then here of course, this is a placebo study because you know we are looking at six months and beyond. This is the follow-up and of course the primary endpoint with a standard composite endpoint. I cannot show you any Phase III data for VTE because those studies are ongoing.
This is what’s going on in AFIB the ROCKET Program, again this is very large ambitious Phase III program looking at around 14,000 patients. Now here the difference is that this is designed as a non-inferiority study and here we are comparing rivaroxaban once a day to adjust the dose warfarin and this is the primary endpoint and again this is ongoing.
ATLAS ACS: Rivaroxaban Phase II Trial in Acute Coronary Syndromes

- Randomized, double-blind, placebo-controlled, parallel-group, dose-escalation and dose-confirmation study in patients with ACS
  - Unstable angina, or
  - Non-ST-elevation myocardial infarction, or
  - ST-elevation myocardial infarction
- Rivaroxaban in combination with aspirin or aspirin plus thienopyridine

ATLAS in ACS again this is looking at these particular clinical scenarios and we are looking at rivaroxaban in combination with aspirin or aspirin plus a thienopyridine.
Apixaban

- Follow-up to razaxaban (development halted due to bleeding concerns)
- Phase II study for VTE prevention after TKR: completed
  - Double-blind; dose-ranging; three od and three bid apixaban doses; comparator enoxaparin and warfarin; target enrolment
    - n=1202
- Phase II pilot study for VTE prevention in patients with advanced metastatic cancer: ongoing
- October 2006 – Phase III program initiated
  - NCT00371683: A Phase III Randomized, Double-Blind Active-Controlled (enoxaparin), Parallel-Group, Multi-Center Study to Evaluate the Safety and Efficacy of Oral Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery
    - n=3056

Second compound of this class Apixaban this is a follow up to razaxaban. The development of razaxaban was stopped due to bleeding concerns, so this is a follow up compound that appears to have a better safety profile. We have some Phase III and Phase II data for VTE prevention in orthopedic surgery that’s completed, so we have learned a little bit about dosing regimen to move forward in Phase III trials. Also there is Phase II study ongoing interestingly in patients with advanced metastatic cancer. And then a Phase III Program has already been initiated for orthopedic surgery and you see the target enrollment at the bottom of the slide.
**Apixaban**

- The Botticelli-DVT study for treatment of acute symptomatic DVT: ongoing
  - Efficacy and safety of apixaban 5 mg bid, 10 mg bid and 20 mg od; comparators LMWH or fondaparinux followed by VKA
- Phase II study in patients with recent UA or MI: ongoing
  - Placebo-controlled; double-blind; target enrolment n=1800
- AF Study

There is also activity in the DVT treatment arena that both the Botticelli study is off the ground and so here we are looking at two b.i.d. dosing regimens and one once a day dosing regimen and again comparing it to traditional therapy. Phase II Study also ongoing in ACS and also an AFIB study planned.
Dr. Wittkowsky talked about the direct thrombin inhibitors that are currently being used and available on the market. So I am not going to get into the discussion of historical development of these agents. What I would like to show you is what are some of the small molecule compounds again that would be available as a tablet formulation and are in Phase III, so that compound is dabigatran and I would just like to highlight AZD0837 that is a follow-up compound to ximelagatran that you could barely see here and so this is now in Phase II development.
So dabigatran, let’s talk a little bit about dabigatran again a direct factor IIa inhibitor, this is a double pro-drug, you see the structure of the molecule here, the molecular weight. Interesting fact, it has a very low bioavailability and so thus it requires fairly high doses and the absorption of the compound is dependent on the presence of an acidic environment.
Dabigatran Etexilate

- Double pro-drug; MW 628
- Low bioavailability
  - Requires high doses
- Absorption is dependent on an acid environment
  - Tartaric-acid containing capsules
- Absorption reduced 20-25% by PPIs
- Effect on coagulation markers
  - Minimal effect on INR
  - aPTT prolonged but not dose dependent
  - ECT prolongation is concentration dependent

So the way this is formulated is in a capsule that contains tartaric acid. But you could see how this could be an issue in patients that may take agents that may affect this acidic environment, right. So for instance Proton Pump Inhibitors have been reported to decrease absorption of the compound by 20% to 25%. So this is going to be something that we will have to authorize, because you can think of the number of patients that are on a Proton Pump Inhibitor, right. So of course education and great care would be needed. Again question on affect on coagulation markers at least what we know so far is that there has been a mild affect on INR, APTT is prolonged, but not dose dependent and we see a concentration-dependent prolongation of ecarin clotting time. So this maybe an option you know to peak at drug concentrations or looking at the correlation of such that again we have to recognize the fact that this is not something that is available on a routine basis, okay.
Further features of dabigatran, again we talked about the low bioavailability, it comes as a capsule, I mentioned affect previously that is non-metabolized P-450 enzyme system. So this potentially could be an advantage over the Factor Xa inhibitors that go via that pathway, time to peak fairly quick, so again although it has a longer half-life. In some of the Xa inhibitors, we see a very rapid time to peak, so again here we could entertain the idea of perhaps no injectables so it’s going to be interesting to see what they are going to be doing in their acute VTE studies. Renal secretion though is fairly significant about 80%, so renal dosing will have to be addressed. Now liver toxicity, at this point I am not sure we can conclude anything on this, I am going to be showing you some short-term data, but of course the jury is still out and we really have to wait for longer term data based on the lessons we have learned today from previous compounds.

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**Dabigatran Etexilate**

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Dabigatran VTE Prevention: BISTROII - THR/TKR (Phase II)

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* P < 0.05 VS ENOX

Quickly, let me show you some Phase II data that has led up to Phase III evaluation. This is from the BISTRO II studies looking at hip replacement and knee replacement. You see that various dabigatran doses evaluated, mainly twice a day and then once a day dosing regimen comparator here was enoxaparin 40 once a day, the number of patients. When you look at overall venous thromboembolic events, these are the doses that have the low start that feared better than enoxaparin. These are proximal events and major bleeding and no significant difference. Now dose of dabigatran here was initiated 1 to 4 hours post-op and given for 6 to 10 days, of course enoxaparin, this is the package insert approved regimen that’s used for hip replacement of course we know the issue with this dose in knees.
This is your development program for primary DVT prevention, 3 large studies have been completed, renovate, remodel, remobilize, again this is all in orthopedic surgery. I am going to come back to the rest in a little bit.
### Study Design: Phase III Orthopedic Trials

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<td><strong>Test Therapies</strong></td>
<td>D 150 and 220 mg</td>
<td>D 150 and 220 mg</td>
<td>D 150 and 220 mg</td>
</tr>
<tr>
<td><strong>1st Dose</strong></td>
<td>6 to 12 h post-op</td>
<td>1 to 4 h post-op</td>
<td>1 to 4 h post-op</td>
</tr>
<tr>
<td><strong>Reference Therapy</strong></td>
<td>E 30 mg bd*</td>
<td>E 40 mg od†</td>
<td>E 40 mg od†</td>
</tr>
<tr>
<td><strong>Treatment Duration</strong></td>
<td>12 to 15 days</td>
<td>6 to 10 days</td>
<td>28 to 35 days</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Total VTE + all-cause mortality</td>
<td>Total VTE + all-cause mortality</td>
<td>Total VTE + all-cause mortality</td>
</tr>
<tr>
<td><strong>Non-inferiority margin</strong></td>
<td>9.2 %</td>
<td>9.2%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

*Commenced 12-24 h post surgery; †Commenced evening before surgery.


These are the 3 studies again all completed, two published, one presented, so I am going to be able to share the data with you. We have two knee studies, one hip study. These are the doses, so two different dosing regimens were evaluated all in a once a day fashion. First dose, interestingly in remodel and renovate were given fairly close to surgery and then in remobilize they decided to push the dose out 6 to 12 hours post-op. Reference therapy, remodel, renovate enoxaparin once a day, but of course for knees, here this is the appropriate study for us in US is enoxaparin 30 mg twice a day. Treatment duration, these two are shorter term studies, this renovate in hips goes out to a month. Primary endpoint, standard and then again remember that these were decided as non-inferiority studies with the defined non-inferiority margins. This just shows you the baseline characteristics and basically they are very similar, so I am not going to get into this, that’s there for your reference of course. The big difference though here is, in remobilize the time to first dose that was for some reason delayed in this study.
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RE-MOBILIZE TKR</th>
<th>RE-MODEL TKR</th>
<th>RE-NOVATE THR</th>
</tr>
</thead>
</table>
| **Patient
Characteristics** |                 |              |               |
| Age (mean) – years | 66              | 68           | 64            |
| Females – %       | 58              | 66           | 56            |
| Weight (mean) – kg | 88              | 83           | 79            |
| **Study Drug
Administration** |                 |              |               |
| Time to first oral dose* (mean) – h | 9.5          | 3.5          | 3.4           |
| Treatment duration (median) – days | 13            | 8            | 33            |

*From completion of surgery

So looking at the results and the efficacy data in the three studies, two different dabigatran dosing regimens, enoxaparin, renovate and remodel have both met their primary endpoint the non-inferiority criteria. See the enoxaparin numbers and of course the numbers here are little bit better with the higher dosing regimen. And then remobilize, interestingly with enoxaparin 2.2, events rate compares to 3.4 and 3% with dabigatran. So remobilize actually has not met its primary endpoint, it met its secondary endpoints, but in this one the non-inferiority again they did not meet the criteria of being non-inferior compared to enoxaparin 30 mg twice a day.
## Results: Major VTE and VTE-Related Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Dabigatran 150 mg</th>
<th>Dabigatran 220 mg</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (THR)</td>
<td>4.3% (38/888)</td>
<td>3.1% (28/909)</td>
<td>3.9% (36/917)</td>
</tr>
<tr>
<td>RE-MODEL (TKR)</td>
<td>3.8% (10/527)</td>
<td>2.6% (13/506)</td>
<td>3.5% (18/511)</td>
</tr>
<tr>
<td>RE-MOBILIZE (TKR)</td>
<td>3.0% (20/656)</td>
<td>3.4% (21/618)</td>
<td>2.2% (15/668)</td>
</tr>
<tr>
<td>Pooled</td>
<td>3.8% (78/2071)</td>
<td>3.0% (62/2033)</td>
<td>3.3% (69/2096)</td>
</tr>
<tr>
<td>Absolute risk difference</td>
<td>0.5</td>
<td>-0.2</td>
<td>[-0.6 to 1.6] [-1.3 to 0.9]</td>
</tr>
</tbody>
</table>

Now what they have done then is actually a meta-analysis pulling all the data together from the three studies and this was a pre-specified analysis, so this was actually planned to be done. And when you see all the data pulled together from the three studies then again then the numbers look similar and so here we meet the non-inferiority criteria compared to enoxaparin.
Results: Major VTE and VTE-Related Mortality

<table>
<thead>
<tr>
<th>Population</th>
<th>Dabigatran dose</th>
<th>Risk difference*, % ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MODEL TKR</td>
<td>150 mg</td>
<td>-5</td>
</tr>
<tr>
<td></td>
<td>220 mg</td>
<td>-4</td>
</tr>
<tr>
<td>RE-MOBILIZE TKR</td>
<td>150 mg</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>220 mg</td>
<td>0</td>
</tr>
<tr>
<td>All Studies‡</td>
<td>150 mg</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>220 mg</td>
<td>-1</td>
</tr>
</tbody>
</table>

This is the same thing again meta-analysis, but clearly we see the outlier here, so this is the study that did not meet its primary endpoint, the two that did and then pulled data with the two different dosing regimens. So of course it appears that the higher dosing regimen fears a bit better than the 150 once a day.
Safety: Major Bleeding Events

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th></th>
<th>Enoxaparin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg</td>
<td>2737</td>
<td>220 mg</td>
<td>2682</td>
<td>2716</td>
</tr>
<tr>
<td>Major Bleeding Event – n (%)</td>
<td>29 (1.1)</td>
<td>38 (1.4)</td>
<td>39 (1.4)</td>
<td></td>
</tr>
</tbody>
</table>

- All bleeding events adjudicated by the same independent adjudication committee in all three studies
- Results consistent across all three studies with no statistically significant differences for any of the bleeding outcomes

Safety of course, there is concern, so we have to look at this, this worked out so basically both the 150 or 220 dosing regimen feared comparably well with enoxaparin, so no major concerns there.
Hepatic safety, currently we have then data all through about a month, this is based on renovate and you see again percentage of patients with ALTs over 3 times the upper limit of normal, this is enoxaparin and this is what we see with dabigatran and this is pulled data. So far again, it appears that we have no reasons for concern, but again I would say that at this point, let’s wait and see what the longer term data is going to show.
If you recall, with ximelagatran, we also had some issues with heightened cardiovascular complications in the orthopedic surgery trials, so this is also something that they looked at with dabigatran. And when we look at treatment of emergent ACS events and post treatment ACS events, none of these appear to be an issue as compared to the low-molecular-weight heparin.
## Summary of Individual Components Contributing to the Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 220mg</th>
<th>Dabigatran 150mg</th>
<th>Enoxaparin 30mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>857</td>
<td>871</td>
<td>868</td>
</tr>
<tr>
<td>Treated and operated</td>
<td>857</td>
<td>871</td>
<td>868</td>
</tr>
<tr>
<td>FAS</td>
<td>604</td>
<td>649</td>
<td>643</td>
</tr>
<tr>
<td>Total VTE and all cause mortality</td>
<td>188 (31.1)</td>
<td>219 (33.7)</td>
<td>163 (25.3)</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>174 (28.8)</td>
<td>212 (32.7)</td>
<td>153 (23.8)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>7 (1.2)</td>
<td>6 (0.9)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>6 (1.0)</td>
<td>0</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Death, VTE cannot be ruled out</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death not associated with VTE</td>
<td>0</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Need reference

The point I would like to make here is that really the difference in that trial was mainly due to asymptomatic deep vein thrombosis. So again if you look at enoxaparin about 24% and then of course about 33% and 29% with the two different doses of dabigatran, so not as much symptomatic, asymptomatic but of course you know venography was part of this.
So again why perhaps we see some differences in remobilize again, we see a different of course a higher dosing regimen of enoxaparin and then the delay in dabigatran dosing initiation. We talked about asymptomatic events driving the primary endpoint and another thing we have to remember that although in the US this is the appropriate enoxaparin regimen in knees, really we do not have had that comparator data at least to my knowledge that looks at 40 once a day versus 30 b.i.d. in a head-to-head study for this particular indication. So really, you know honestly I think we are all anxiously awaiting for RECORD 4 and see how this is going to play out.
So this is then what’s going on for the other indications, they are looking at venous thrombosis treatment, acute DVT and PE resolve and recover remedy. This is secondary VTE prevention and a fairly large spec program known as RELY and so I don’t have a lot of data on the VTE treatment design, so these studies are ongoing and so at this point, I cannot present any data.
So of course now the big controversy as I said is which one is better and of course it’s going to be a question of who makes it to the market first, but then of course how the efficacy data is going to shake out, convenience some of the pharmokinetic, pharmodynamic factors that we have reviewed and so at this point, I think the jury is still out on what perhaps the better target is going to be.
Now for us as practitioners, what is the impact of all of this on anticoagulant clinics and anticoagulant management services? I maybe too much of an optimist, but you know what I keep reminding myself is that low-molecular-weight heparins have been around since the early 1990s, we are in 2007 and we are still using bulk loads of heparin, so I really think that this is going to be a tremendous improvement over what we have and I think this is good news for practitioners for patients for industry for everybody, but I don’t think that we will wake up one day and you know everything that’s traditional is going to go away. I think it is going to be a gradual process. And I think it is for the better you know if we have efficacy safety data convenience is better than yes, absolutely we are all for it, but you know remember that not all in-patients are being evaluated, we still have the high risk some of the controversial indications, thrombophilic states, cancer patients mechanical heart valves, so initially I think it is going to be a transitioning phase and so it is going to be a gradual process.
Thank you.

And we then thank you very much for your attention.