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Introduction and Overview of AF-Related Strokes CME

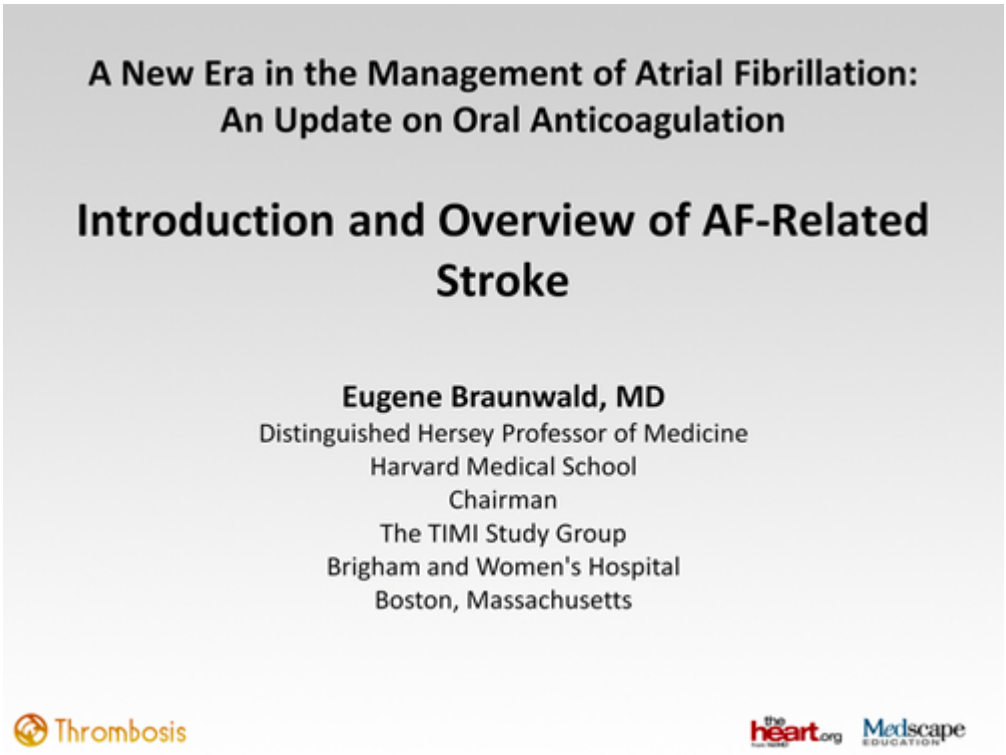
Eugene Braunwald, MD

Posted: 09/27/2011

Download Slides

Slide 1.

Eugene Braunwald, MD: Good afternoon. I am pleased to welcome you to a new era in the management of atrial fibrillation (AF). This should be a very exciting symposium. We are going to hear about at least 6 new drugs and it really represents a change in therapy.

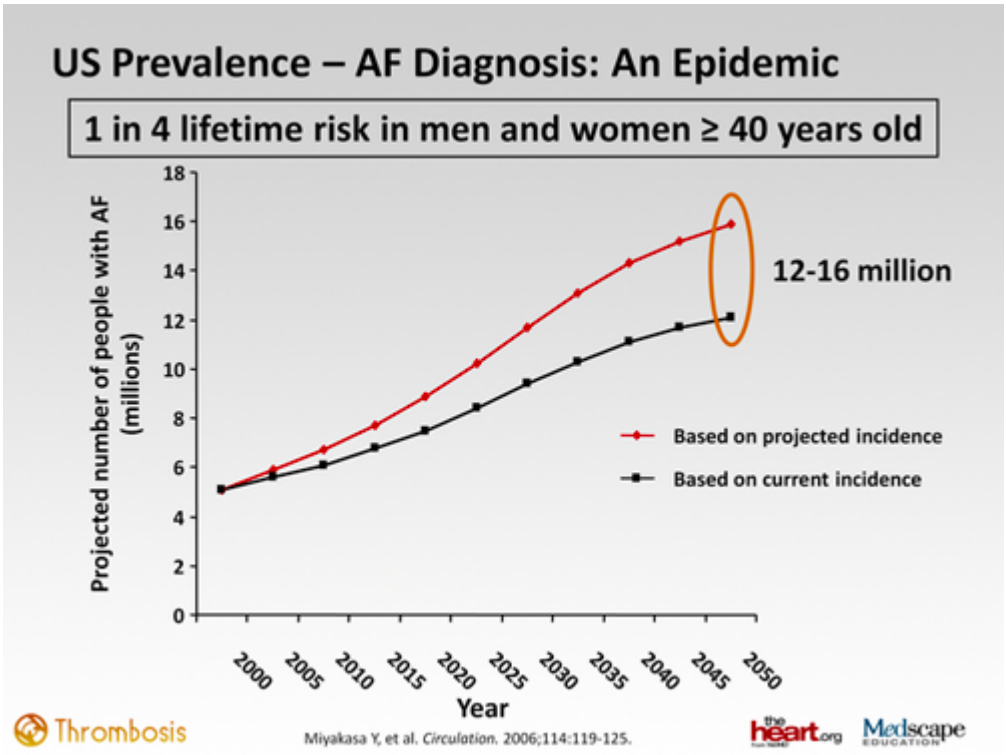


Slide 2.

Dr. Braunwald: I have the pleasure of co-chairing this symposium with Professor Lars Wallentin, who will be the next speaker. I would like to view some background.

Slide 3.

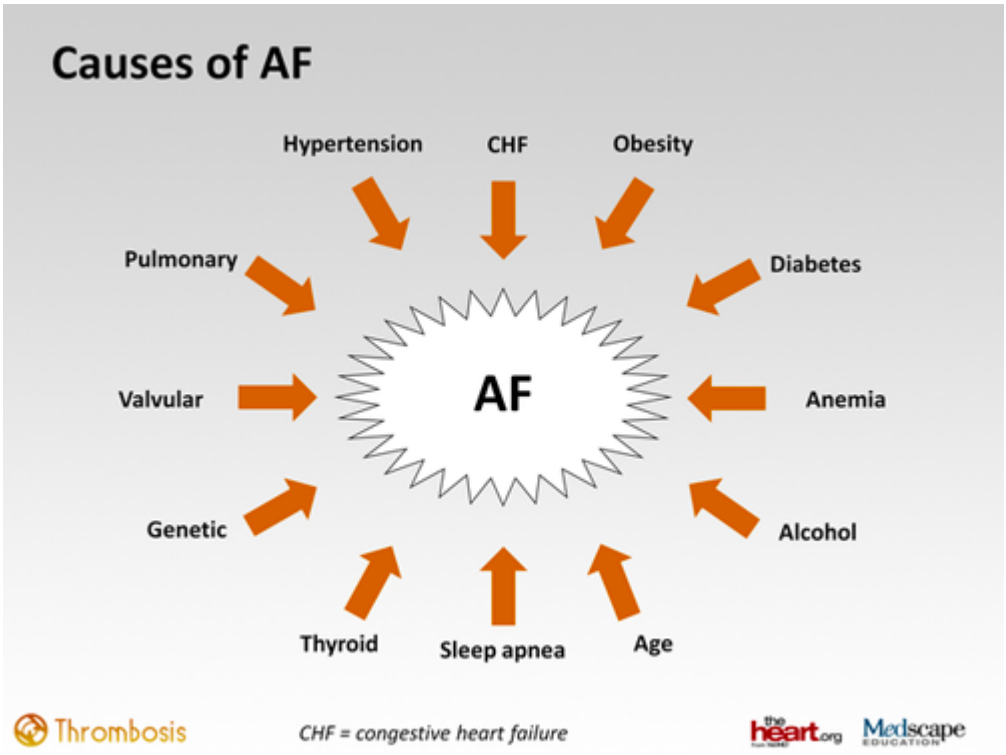
Dr. Braunwald: These are my relevant disclosures.



Slide 4.

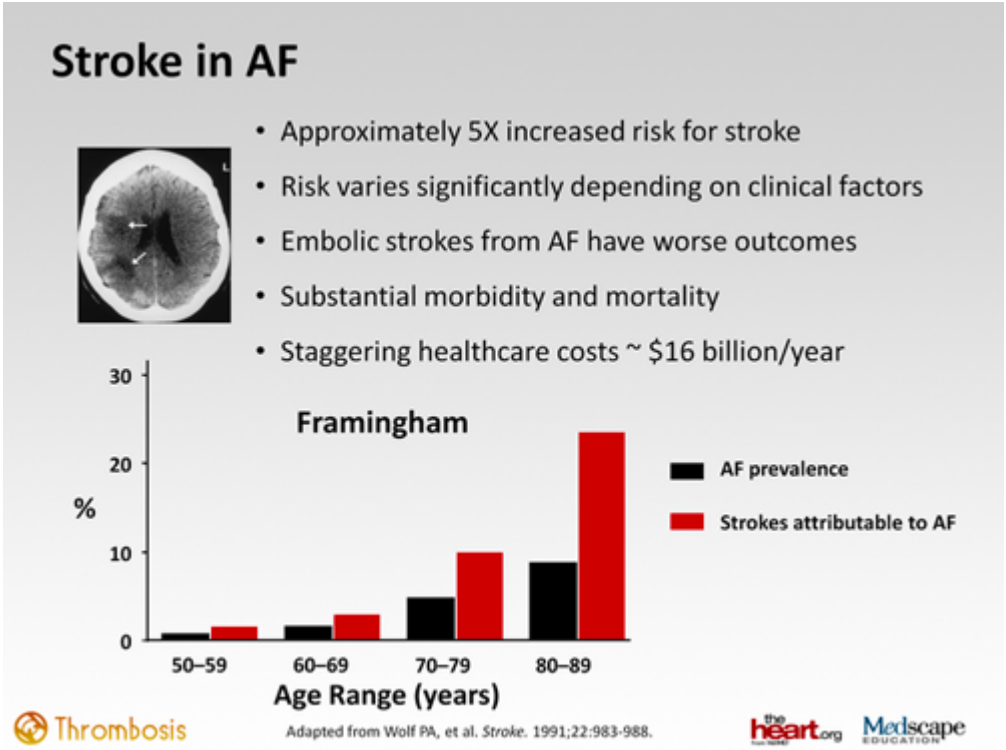
Dr. Braunwald: First, I want to give you an idea of the magnitude of the problem that we are talking about this afternoon. This is the US prevalence. It certainly is an epidemic in the United States. I think if you multiply

everything by 1.5, you get a very good idea of what it is in Europe. So, we expect at the middle of this century to be dealing with a problem in the United States of 12 to 16 million and about 18 to 24 million in Europe. The risk is enormous, 1 in 4 lifetime risk in men and women over the age of 40.



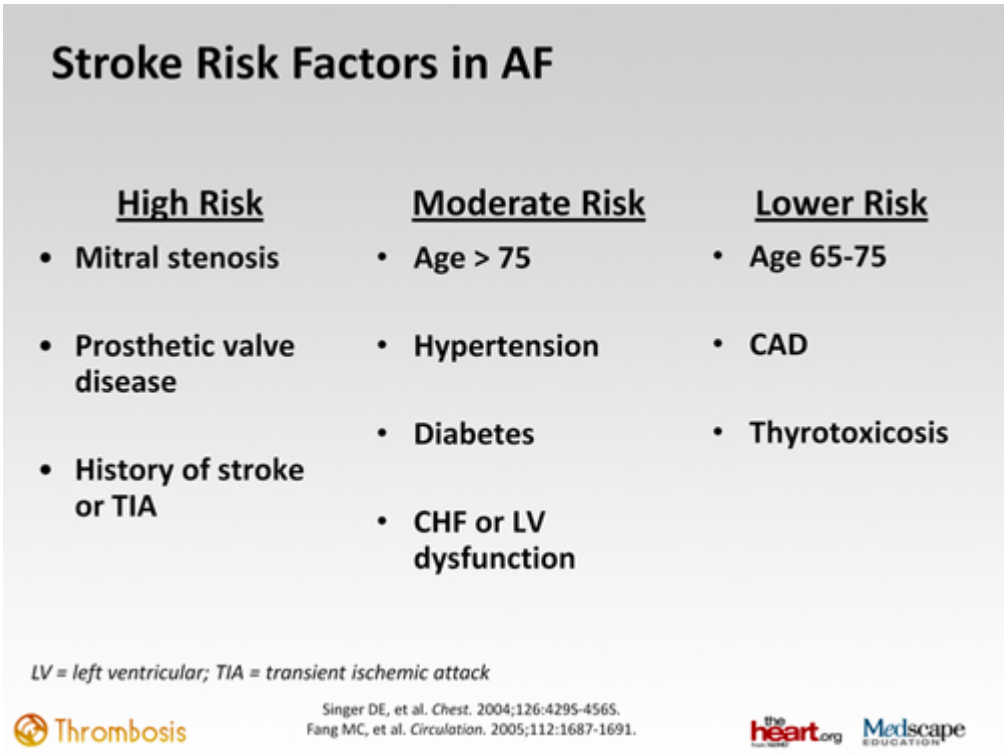
Slide 5.

Dr. Braunwald: There are many causes of AF. You see just a few of them here, beginning at the top left, hypertension, heart failure, obesity, diabetes, anemia, alcohol, age, sleep apnea, hyperthyroidism, genetic abnormalities, obviously valvular heart disease, and pulmonary disease. The incidence of stroke in AF is enormous.



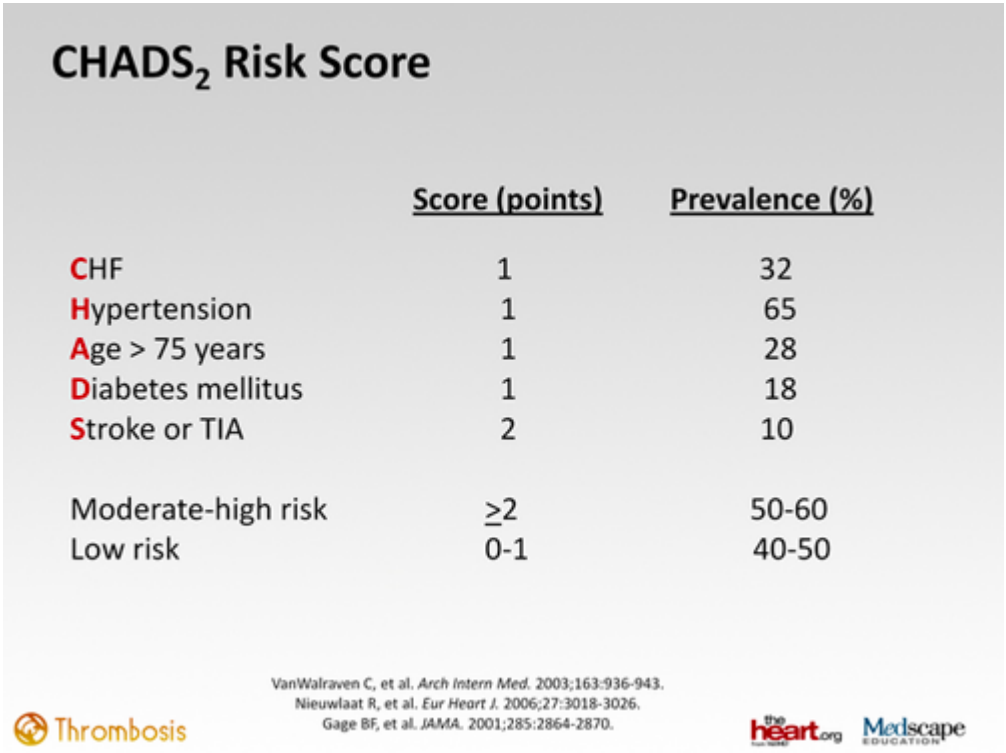
Slide 6.

Dr. Braunwald: On this slide you see Framingham data on the prevalence of AF and you see that almost 10% of the normal population over the age of 80 has AF, about 6% over the age of 70. The strokes attributable to AF are shown in red. You see they range up to 25%.



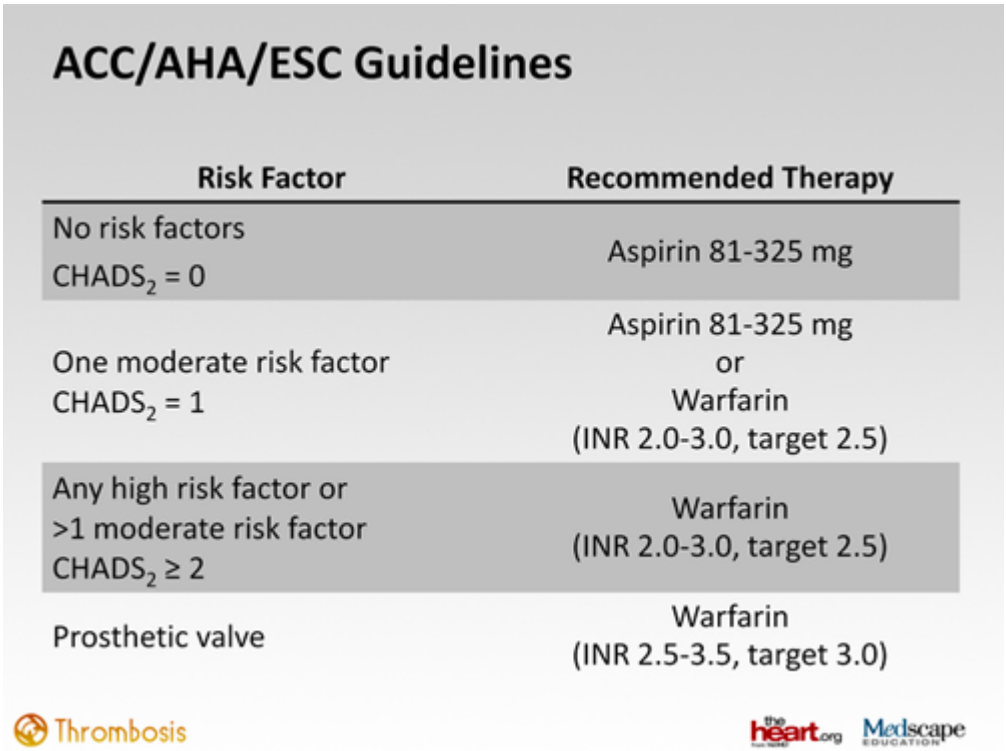
Slide 7.

Dr. Braunwald: The risk factors for stroke in patients who have AF, so these 25%, obviously at highest risk are patients with mitral stenosis, prosthetic valve disease, and history of stroke. At moderate risk are patients over 75; patients with hypertension, diabetes, or heart failure; and at lower risk but still at substantial risk are patients between the ages of 65 and 75, [and those with] coronary artery disease (CAD) and [those with] thyrotoxicosis.



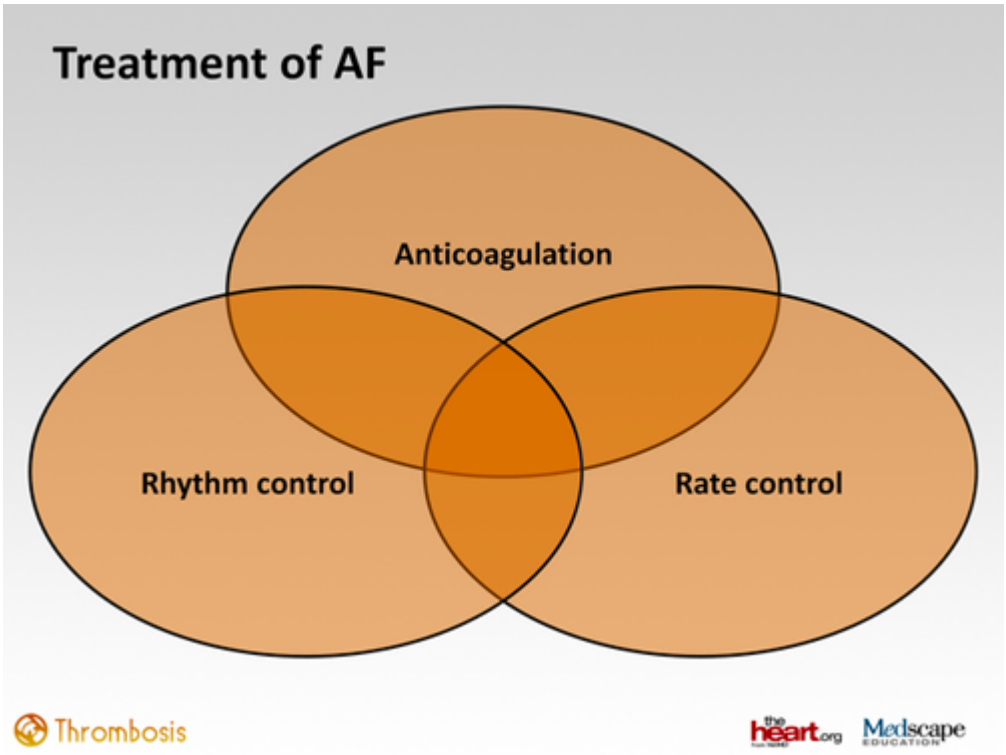
Slide 8.

Dr. Braunwald: There has been conservable interest in determining the risk score, the $CHADS_2$ risk score to help clarify established risks in patients with AF. CHADS is easy to remember. CHADS stands for congestive heart failure, hypertension, age over 75, diabetes, or a previous stroke. In some large series of patients, about 32% had very low risk, just 1 point; 65% had hypertension, 28% were over 75, 18% had diabetes, and 10% had a previous stroke. All you have to do is add these up numerically. Equal or more than 2 CHADS risk scores, the prevalence is about 50% to 60%, and low risk is zero to 1 and 40% to 50%. You will hear reference to $CHADS_2$ risk score throughout this symposium.



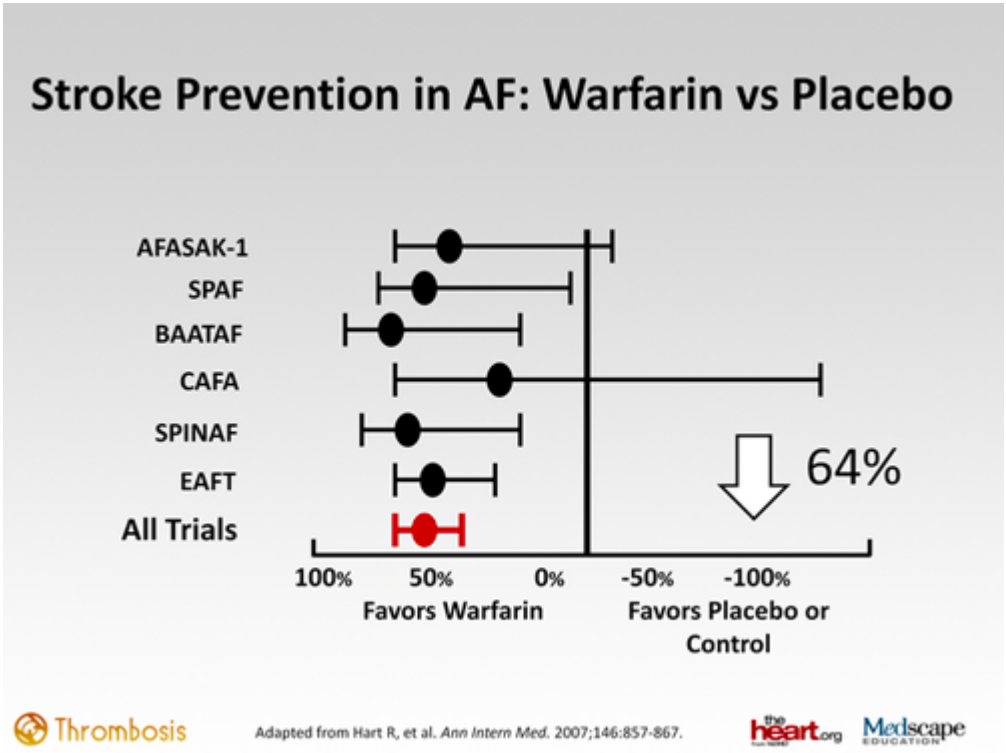
Slide 9.

Dr. Braunwald: The ACC (American College of Cardiology), the AHA (American Heart Association), and the European Society [of Cardiology] (ESC) have guidelines. For patients with no risk factors -- a CHADS score of zero -- the recommended therapy is aspirin, no risk factor -- a CHADS score of 2 --aspirin or warfarin until now, and of 2-3, any high-risk factor or more than 1, would be warfarin, and a prosthetic valve would be warfarin targeted to 2.5 to 3.5.



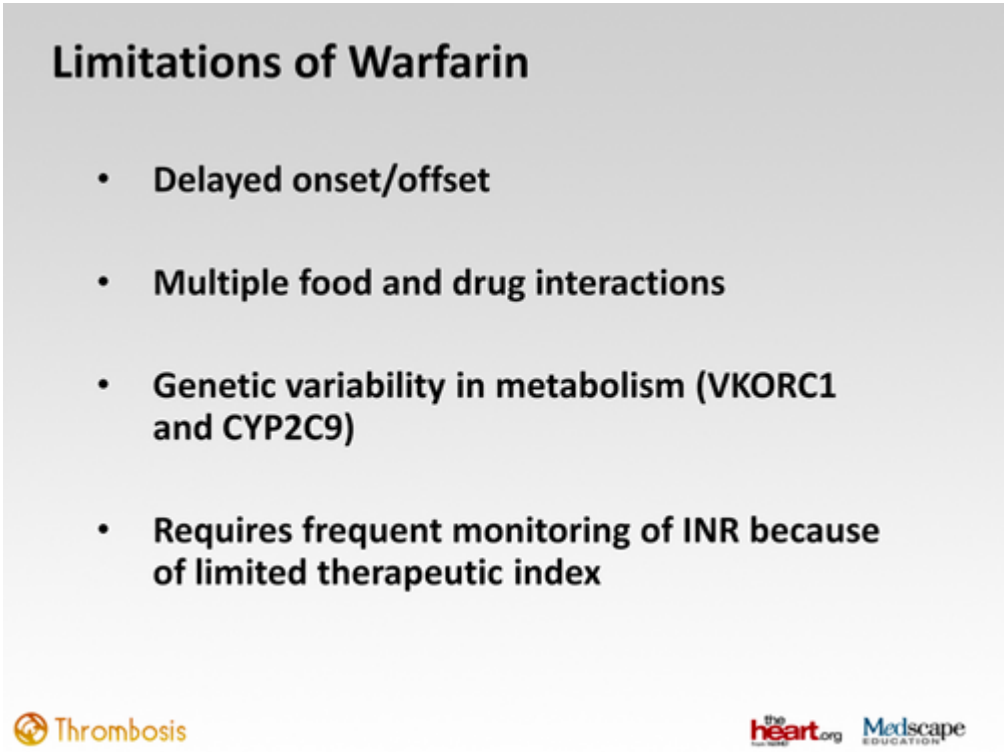
Slide 10.

Dr. Braunwald: These are the current guidelines, and the treatment of AF obviously as we all recognize is threefold. It is rhythm control, rate control, and anticoagulation.



Slide 11.

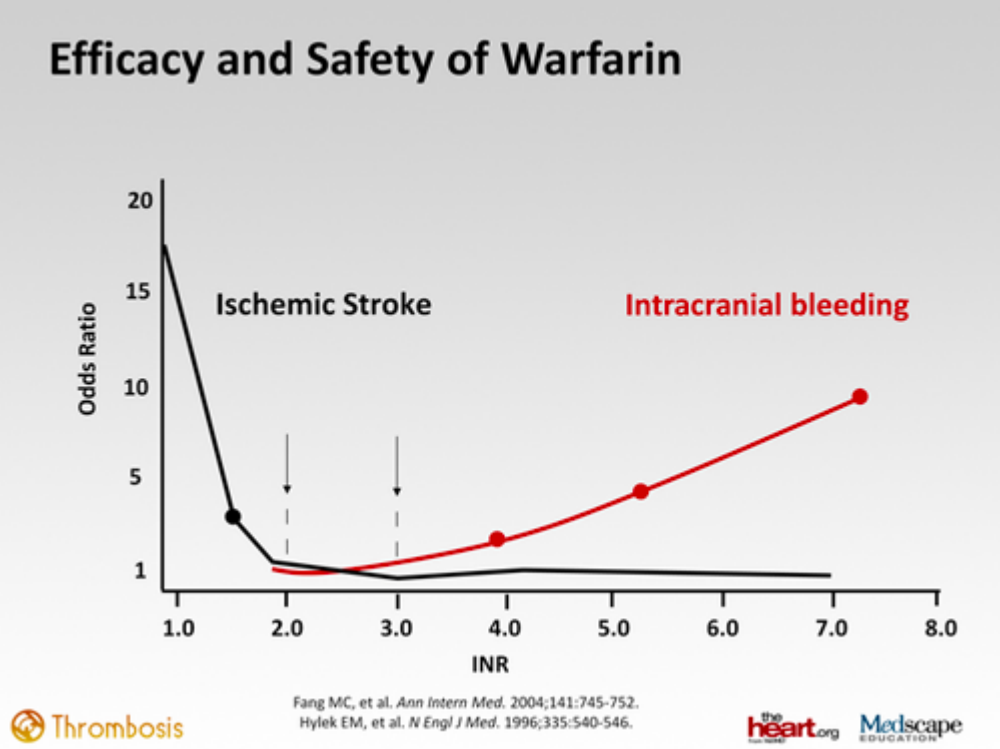
Dr. Braunwald: The new era comes about on a very solid base, a base of 6 trials that studied warfarin against placebo. This is a meta-analysis that showed a 64% reduction of stroke in patients with AF treated with warfarin compared with placebo. A lot of the calculation of sample size for studies of non-inferiority is based on this 64%.



Slide 12.

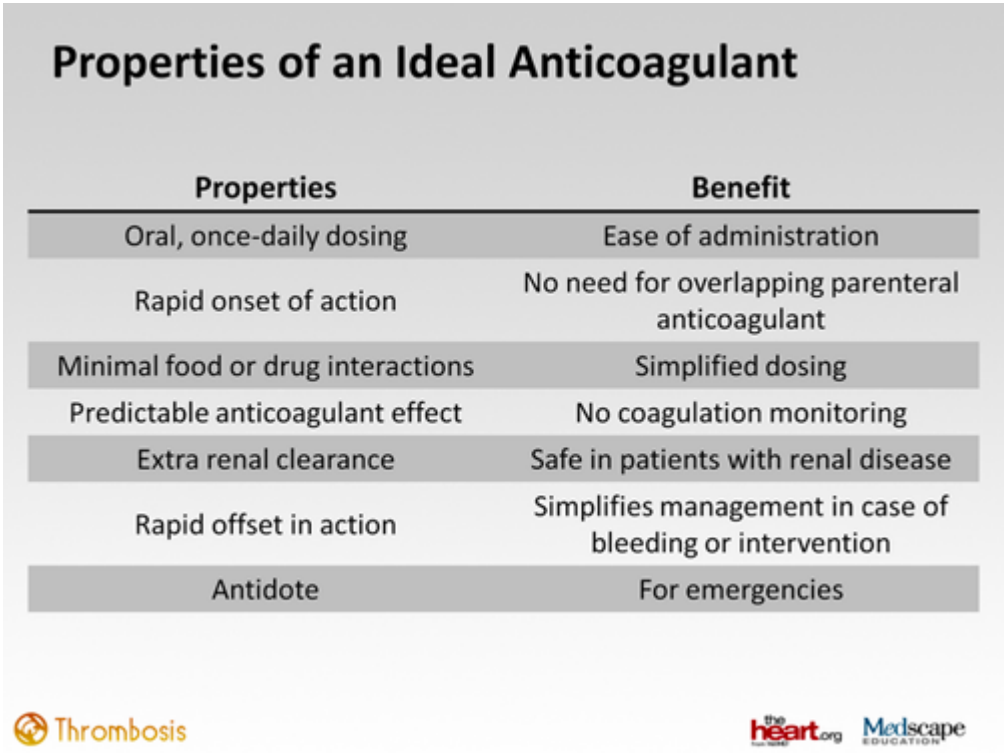
Dr. Braunwald: If warfarin is a useful drug, what are its limitations? There is delayed onset and offset. It takes 2 or 3 days, sometimes 4 days to achieve anticoagulation. If you want to stop the warfarin, it takes an equal

amount of time for the offset. There are multiple food and drug interactions which change the amount of anticoagulation. There is generic variability in metabolism, and now 2 genes have been identified, alleles of which change metabolism. Of course it requires frequent monitoring of the INR (international normalized ratio) [because of the] limited therapeutic index. Maybe in a discussion period we will come back to this.



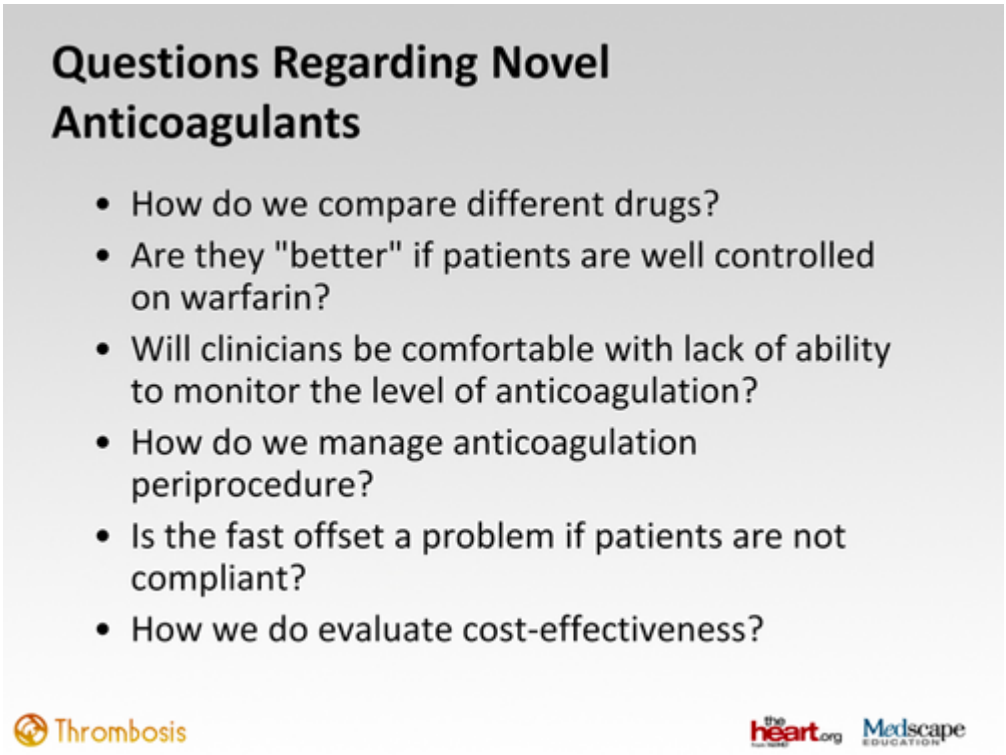
Slide 13.

Dr. Braunwald: This is a classic slide and it shows the odds ratio for ischemic stroke in black and intracranial bleeding is shown in red for various levels of the INR. You can see that this is the ideal zone between the 2 vertical arrows, between an INR of 2 and 3. That is where the stroke risk is lowest and intracranial bleeding risk is lowest. As you depart from being between below 2 [and 3], the incidence of stroke rises and above 3 the incidence of bleeding rises. I think that is why in many of the trials in which warfarin acts as a comparator, I think people tend to look at this INR and how close it came to this optimal 2 to 3.



Slide 14.

Dr. Braunwald: What would be the properties of an ideal anticoagulant? I think as we hear about these new drugs, I think we should keep some of these properties in mind. If possible, you should have all once-daily dosing. The benefit obviously is ease of administration. There should be a rapid onset of action, so there should be no need for overlapping with a parenteral anticoagulant. There should be minimal food or drug interactions so the dosing can be simplified. The anticoagulant effect should be predictable without anticoagulation monitoring required.



Slide 15.

The extra renal clearance is important so that it is safe in patients with renal disease. Many people with AF are elderly and have renal dysfunction. There should be a rapid offset in action. This simplifies the management in case of bleeding. An antidote should be available for emergencies if at all possible.

Supported by independent educational grants from Bayer Healthcare, Daiichi Sankyo, and Boehringer Ingelheim.

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1. Introduction and Overview of AF-Related Strokes [http://www.medscape.org/viewarticle/750177]
2. Development of Oral Direct Thrombin Inhibitors: Lessons From RE-LY [http://www.medscape.org/viewarticle/750178]
3. Development of Oral Factor Xa Inhibitors - Part I: Lessons From ROCKET AF [http://www.medscape.org/viewarticle/750180]
4. Development of Oral Factor Xa Inhibitors - Part II: Lessons From AVERROES and the Design for ARISTOTLE [http://www.medscape.org/viewarticle/750181]
5. Development of Oral Factor Xa Inhibitors - Part III: Design and Rationale for ENGAGE AF-TIMI 48 [http://www.medscape.org/viewarticle/750183]
6. Development of Oral Factor Xa Inhibitors - Part IV: Assessing the Next Wave of Agents [http://www.medscape.org/viewarticle/750184]
7. Panel Discussion and Implications for Patient Care [http://www.medscape.org/viewarticle/750185]

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Development of Oral Direct Thrombin Inhibitors: Lessons From RE-LY CME

Lars Wallentin, MD, PhD

Posted: 09/27/2011

Download Slides

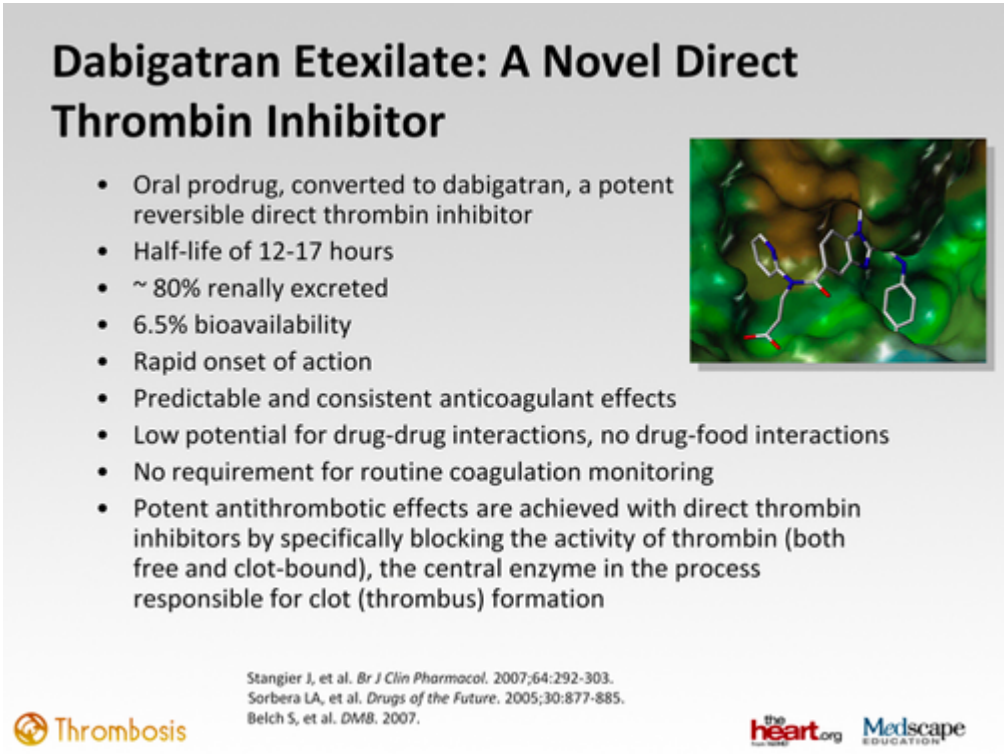
Slide 1.

Eugene Braunwald, MD: I will ask my co-chairman, Professor Wallentin, who is the director of the Clinical Trials Research Center in Uppsala, Sweden, to talk to us about an antithrombin agent and especially about the RE-LY trial. Professor Wallentin.

Lars Wallentin, MD, PhD: Thank you for the introduction and for the invitation to contribute to this symposium with a review of the development of the only approved oral thrombin inhibitor in this area, the RE-LY trial. I had the privilege to co-chair the RE-LY trial with Dr. Salim Yusuf from Canada. The RE-LY trial was driven by 2 co-principle investigators, Professor Michael Ezekowitz from Philadelphia and Professor Stuart Connolly from Canada. This was really the landmark trial. It was the first trial to really demonstrate that we could accomplish better results with new agents than with warfarin.

Slide 2.

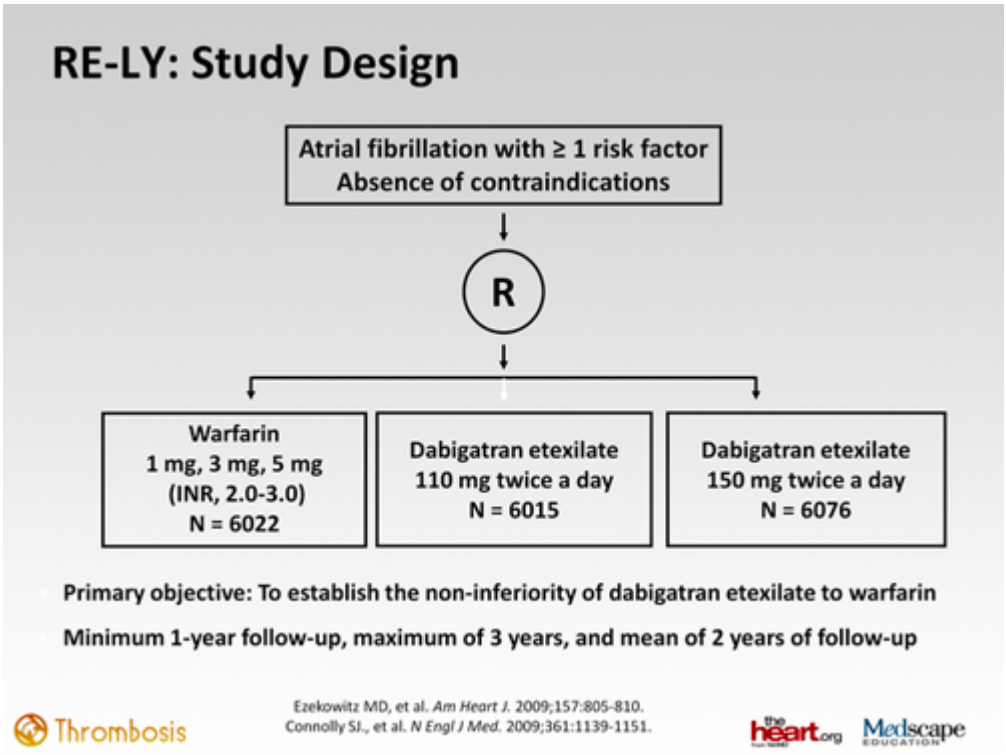
Dr. Wallentin: These are my disclosures. I have been collaborating and I am still collaborating with several companies involved in the development of new antithrombotic agents.



Slide 3.

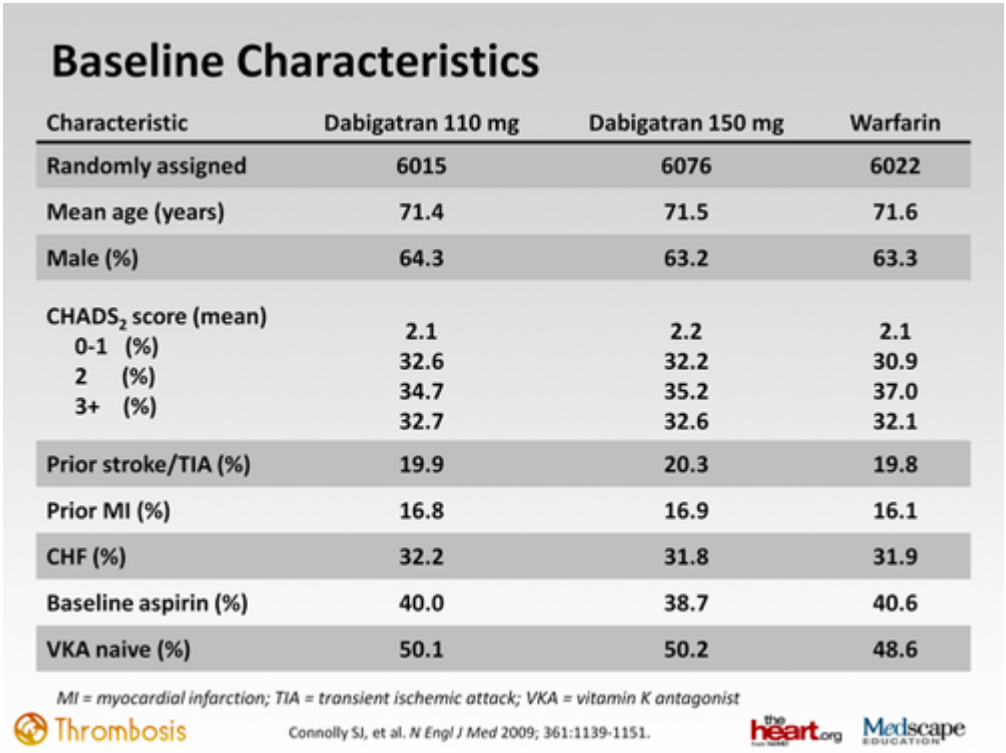
Dr. Wallentin: Dabigatran etexilate is an oral prodrug. It is converted to the active compound and it has a half-life of 12 to 17 hours. It is mainly renally excreted, at least to higher concentration at renal dysfunction. It has a fairly low bioavailability, which was a concern before we saw the [study] results. It has a rapid onset of

action, similar properties [as those of] low-molecular-weight heparin, with a peak level after around 2, 3, or 4 hours. It has a predictable and consistent anticoagulant effect, and there is no need for laboratory monitoring. There are very few drug and food interactions, and it is a really potent agent that is also approved for treatment of prevention of deep venous thrombosis.



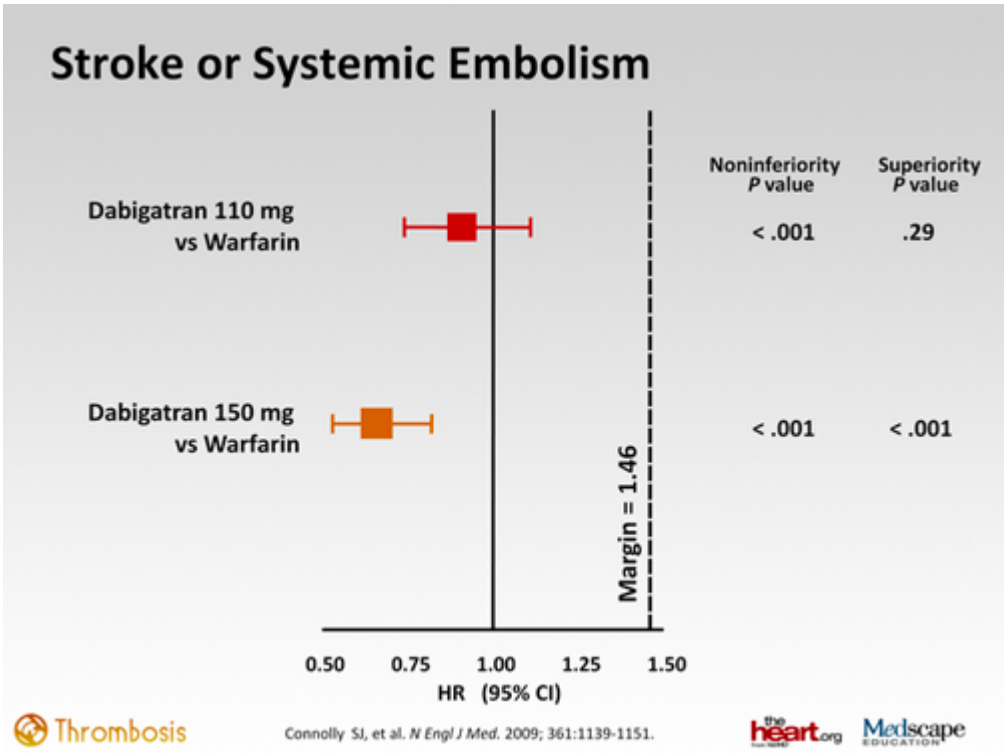
Slide 4.

Dr. Wallentin: The RE-LY design was a prospective randomized trial. The treatment with dabigatran was open label but the 2 dosages were blinded. Warfarin was also given open label with INR (international normalized ratio) control, aiming for an INR between 2 and 3. The primary objective was the same as with many other trials -- to establish the non-inferiority of dabigatran vs warfarin. We had a planned median 2 years follow up.



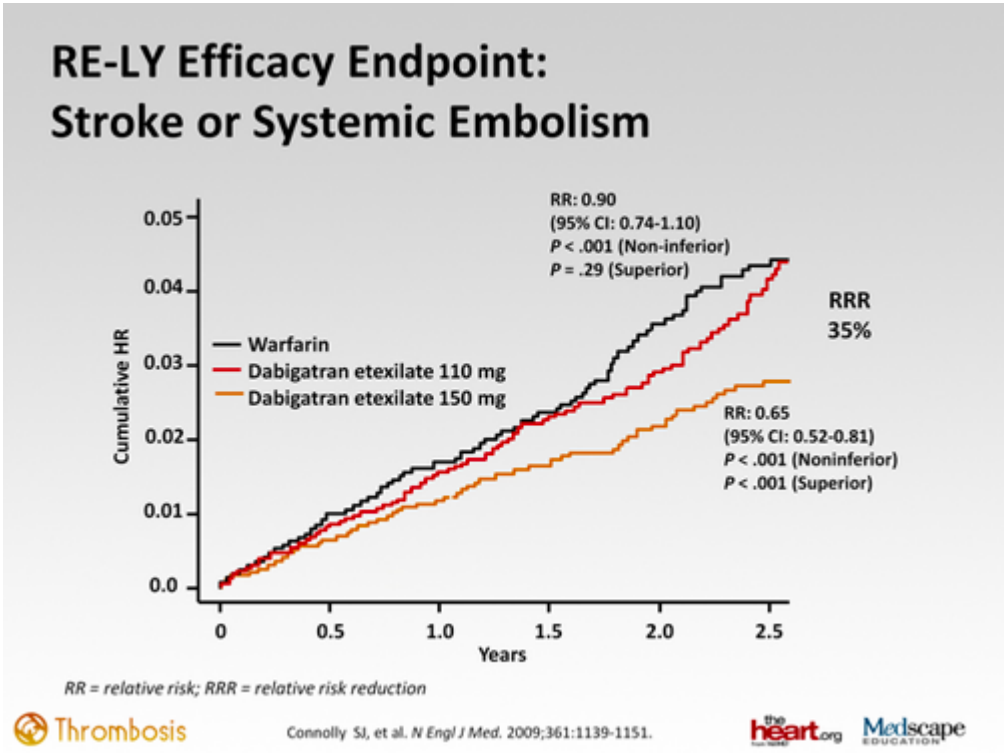
Slide 5.

Dr. Wallentin: The patient population was typical for this type of trial. These are elderly patients, 71 years old, and two thirds were male. We had the distribution of CHADS score about one third in each of these 3 classes, and of course [there were] risk factors like congestive heart failure. We aimed for a population that half of them had not been exposed to warfarin before, and this is also a design that has been taken over by later trials.



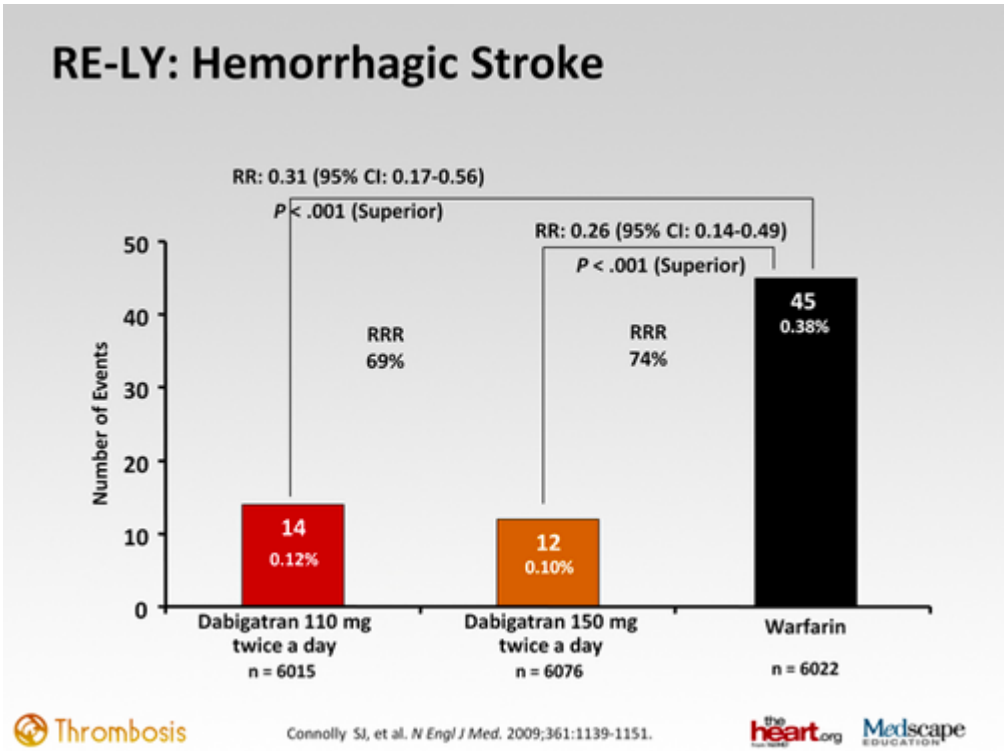
Slide 6.

Dr. Wallentin: The results are well known.



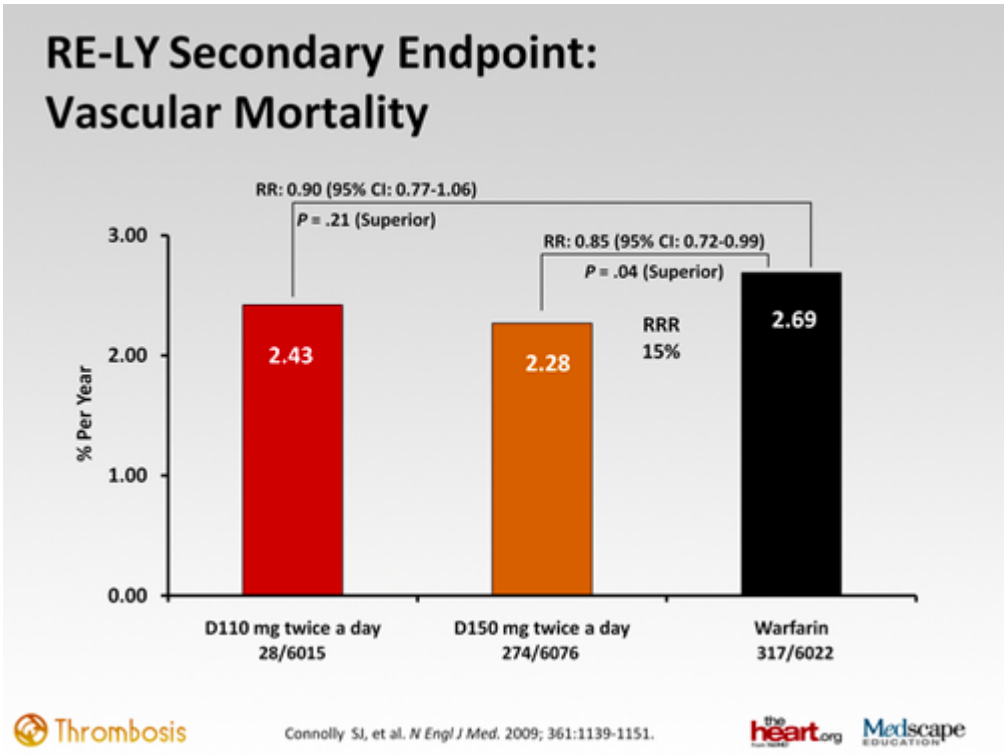
Slide 7.

It was shown that concerning the primary efficacy endpoints of stroke and systemic embolism, there was a reduced event rate with a higher dose, dabigatran 150 mg twice daily. There was non-inferiority with a 110-mg dose. Looking into the point estimate of the hazard ratio (HR) and the confidence interval (CI), it can easily be seen that the dabigatran 110[-mg dose] had a CI crossing the line of unity, but the 150-mg dose was substantially below the line of unity. The dabigatran 150[-mg dose resulted in] a reduction in stroke compared with warfarin. The reduction in stroke was mainly driven by hemorrhagic stroke, but there was also a significant reduction in ischemic stroke.



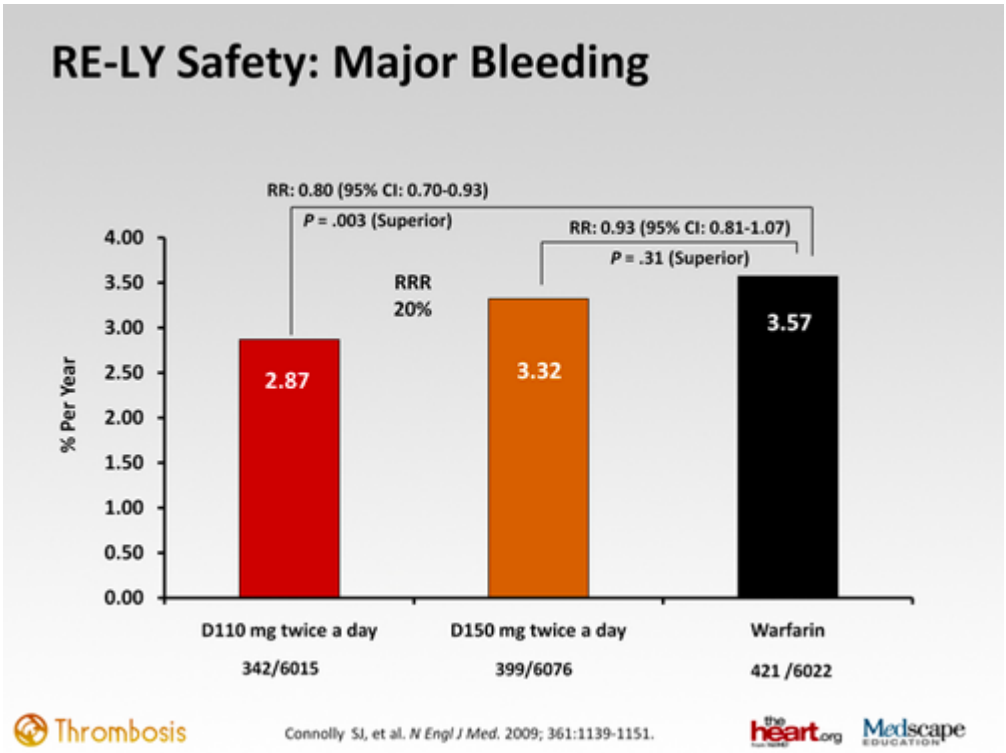
Slide 8.

Dr. Wallentin: This reduction in hemorrhagic stroke was 74%. It is really a dramatic reduction in comparison to warfarin-treated patients. This was the first time that this had been seen with a new anticoagulant.



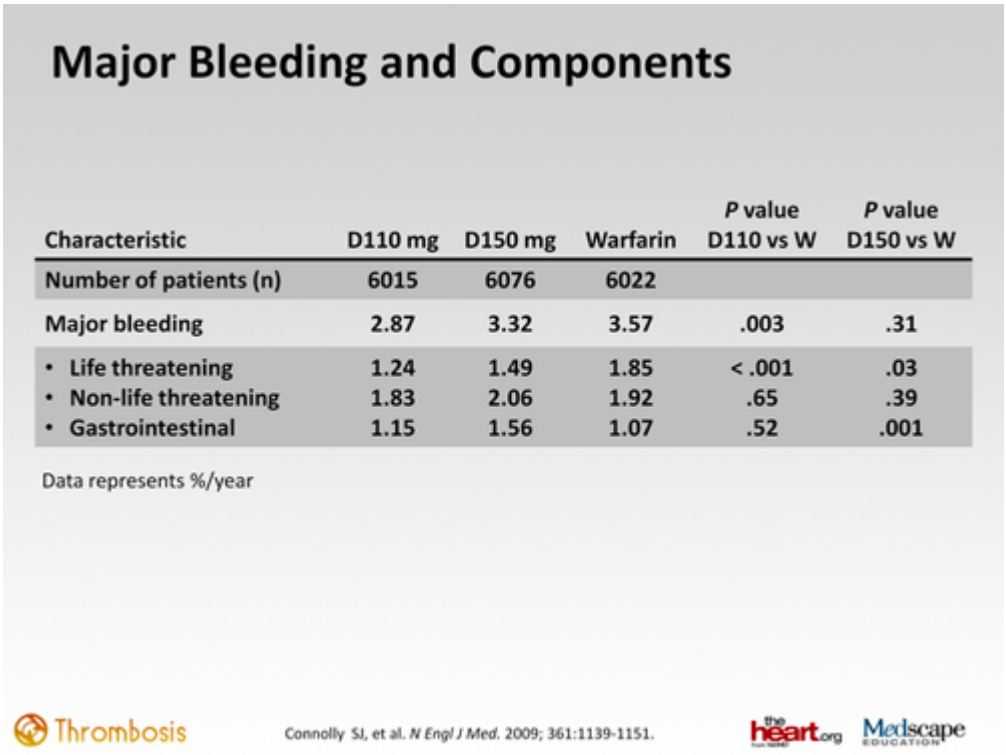
Slide 9.

Dr. Wallentin: Mortality was at the margin of statistical significance, and as you can see, vascular mortality was significantly lower. Therefore there is definitely a strong trend toward reduced mortality with the more effective anticoagulant agent than warfarin.



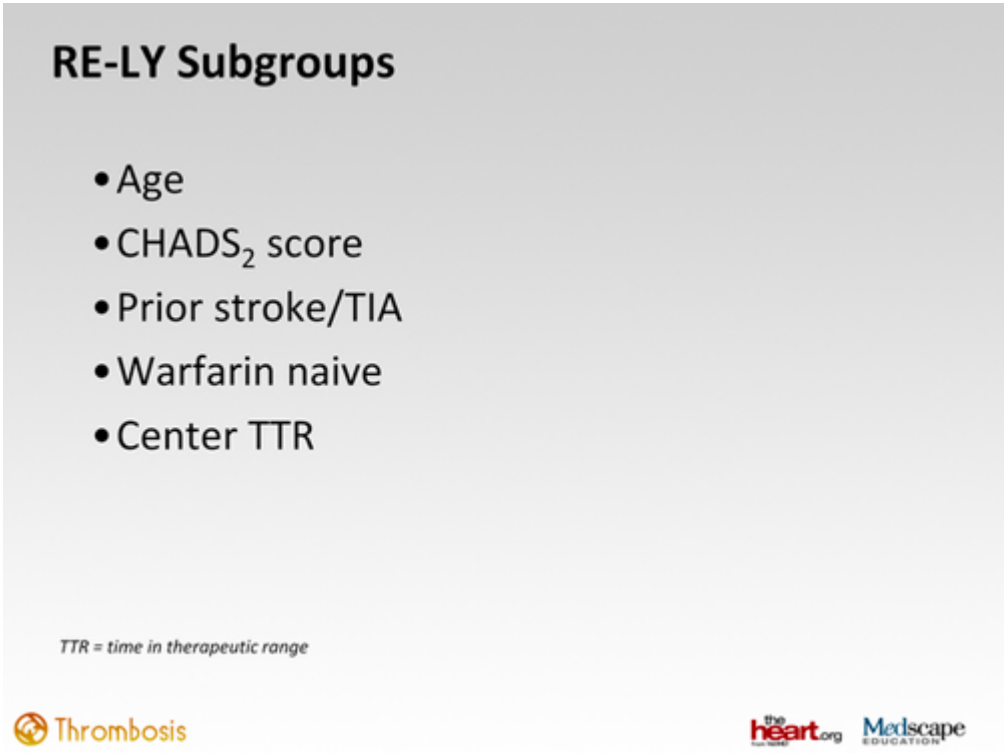
Slide 10.

Dr. Wallentin: Major bleeding was similar at the higher dose, dabigatran 150 [mg]. It was lower with the lower dose. That achieved non-inferiority concerning stroke and embolism. With the lower dose we can have the same effect against stroke with a benefit of [less] bleeding. With a higher dose, we can reduce stroke and we had the same rate of major bleeding.



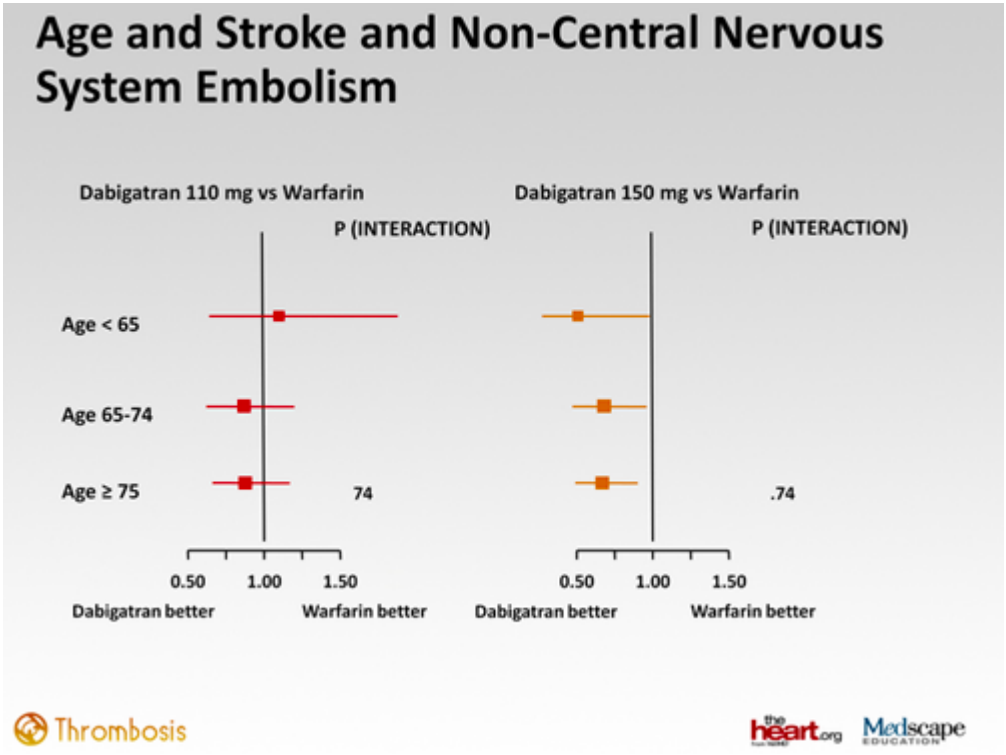
Slide 11.

Dr. Wallentin: Concerning though the major bleeds, the life-threatening bleeds were, [the numbers were] really reduced at both dosages of dabigatran, but there was an increase in gastrointestinal bleeding with a higher dose of dabigatran in comparison with warfarin.



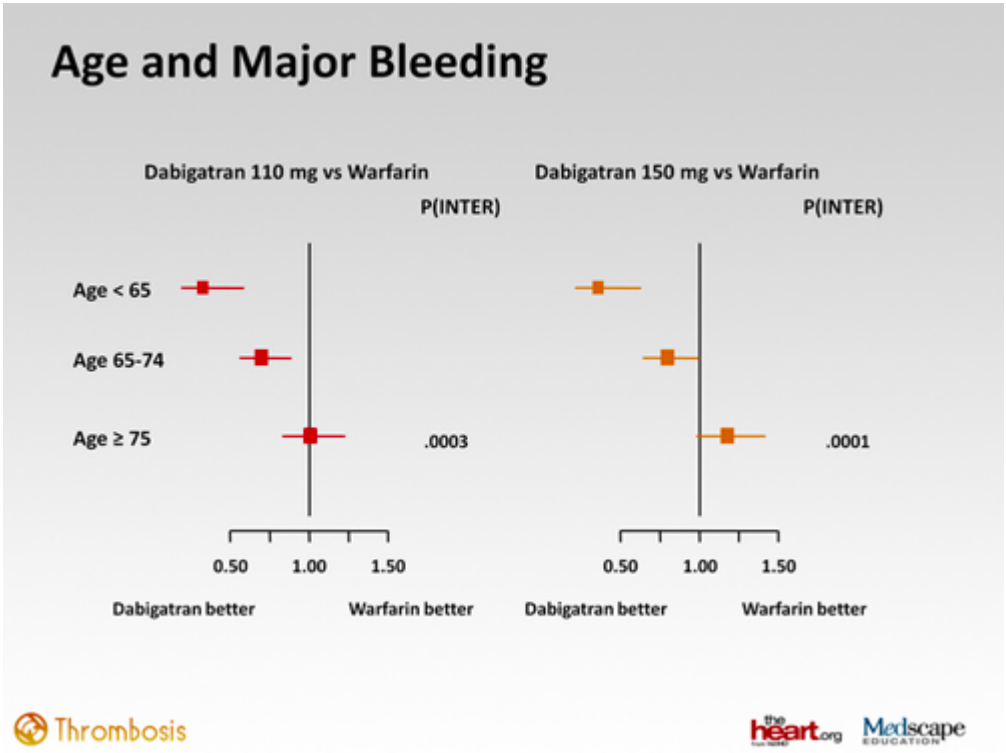
Slide 12.

Dr. Wallentin: The RE-LY trial was presented for the first time in 2009 and we have of course been looking into many different additional questions and subgroups.



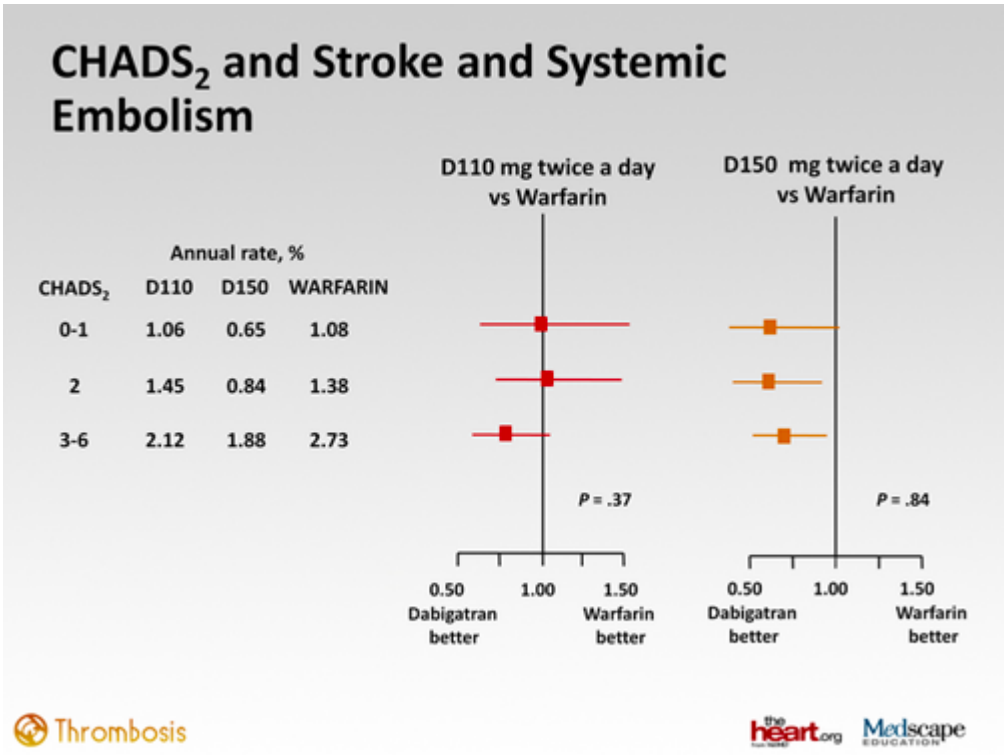
Slide 13.

Dr. Wallentin: We can look into the age issue and it can be seen that the results were consistent in relation to age, reducing stroke in a similar way regardless of age.



Slide 14.

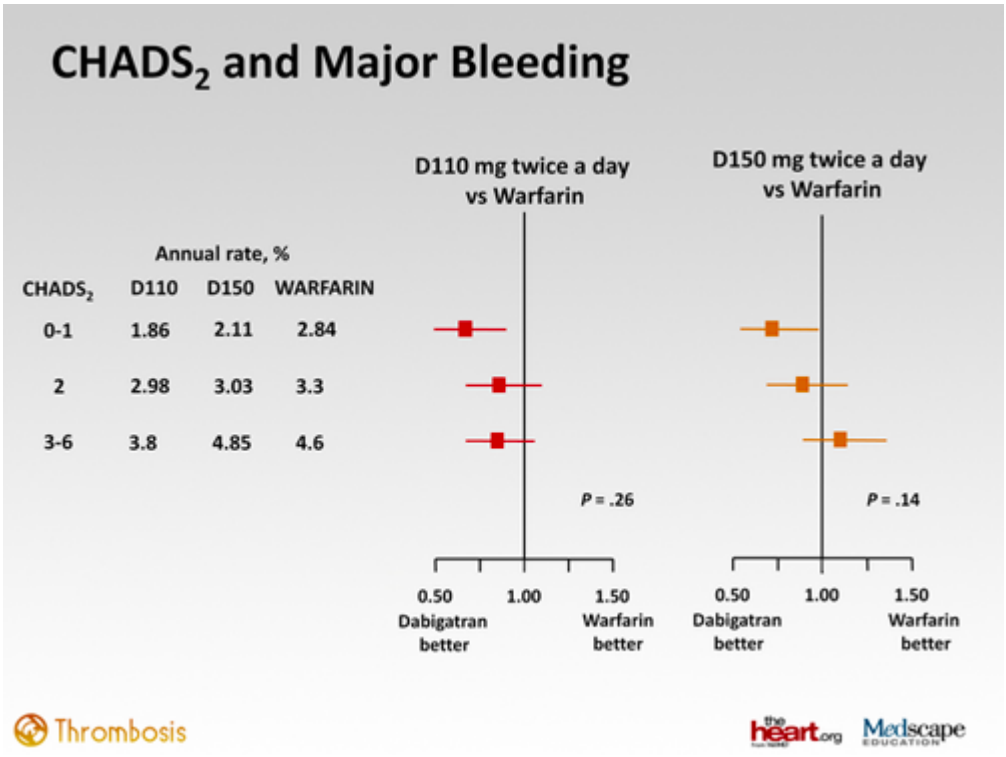
Dr. Wallentin: However, the bleeding of course was related to age. There was an increased bleeding risk in the elderly. Therefore it might be prudent to lower the dose in the elderly who are above 75 years old. There is a new paper on this recently published in *Circulation*, highlighting the relationship between age and bleeding risk with dabigatran and highlighting the need for the lower dose.



Slide 15.

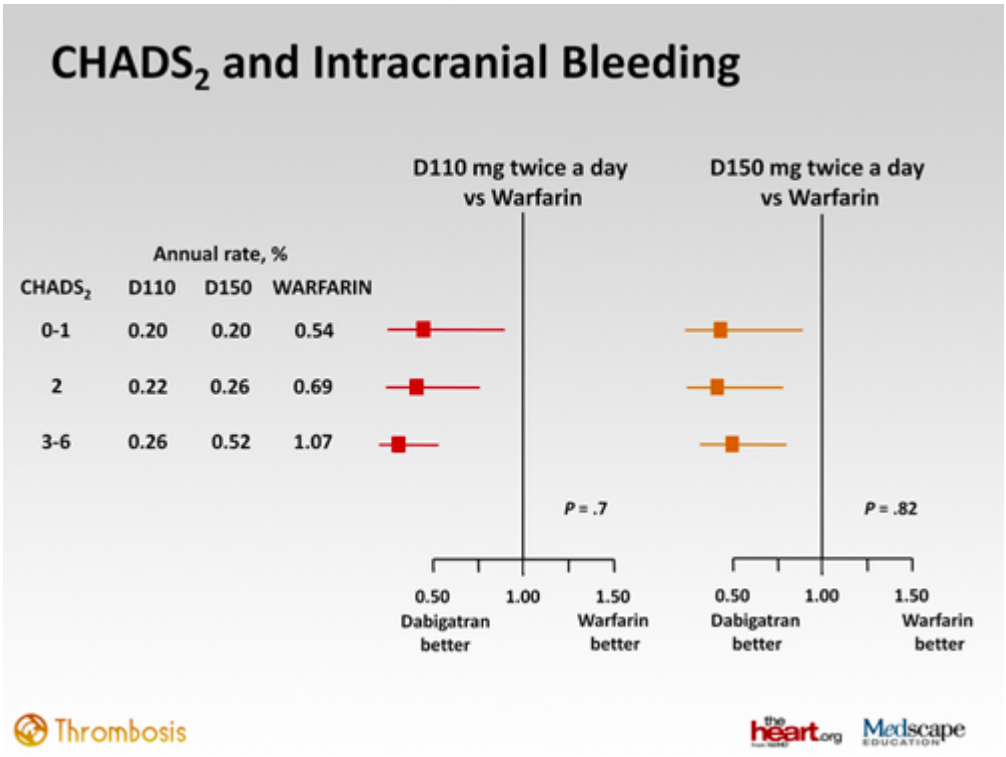
Dr. Wallentin: We have looked into the CHADS risk score and outcomes and the results were very consistent at

all CHADS risk scores. I think this is especially important in relation to the lower-risk population because even patients with low risk for stroke according to the CHADS score have the same benefit, at least the same benefit as patients at higher risk for stroke. Maybe we should consider expanding the indication for the newer oral anticoagulants.



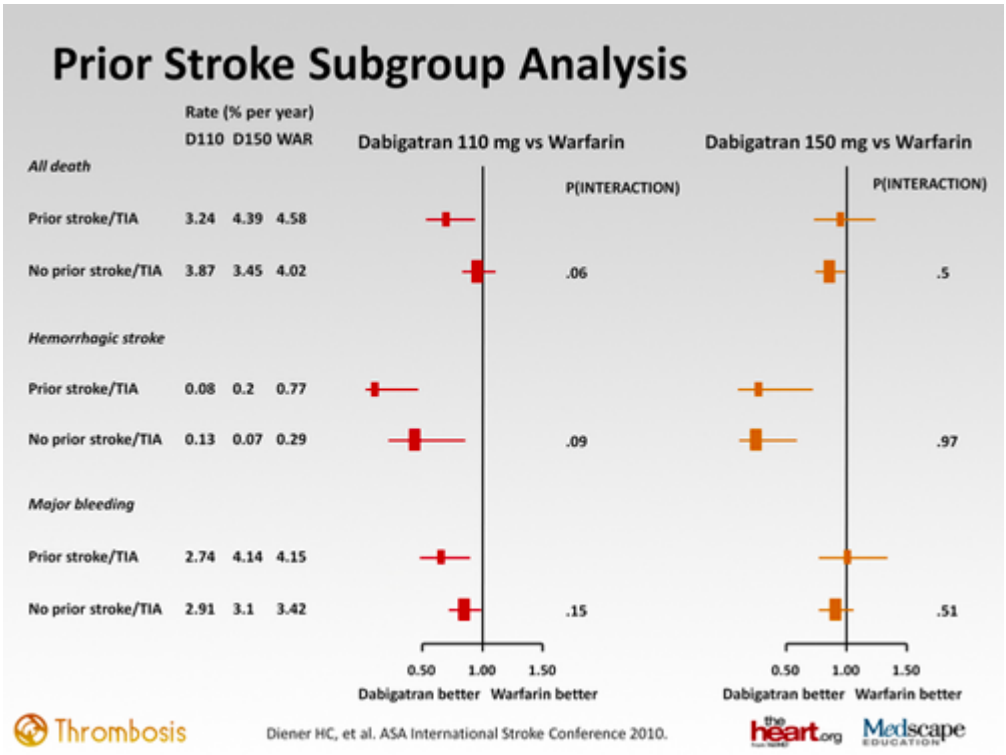
Slide 16.

Dr. Wallentin: The CHADS scores were also related to the risk for bleeding.



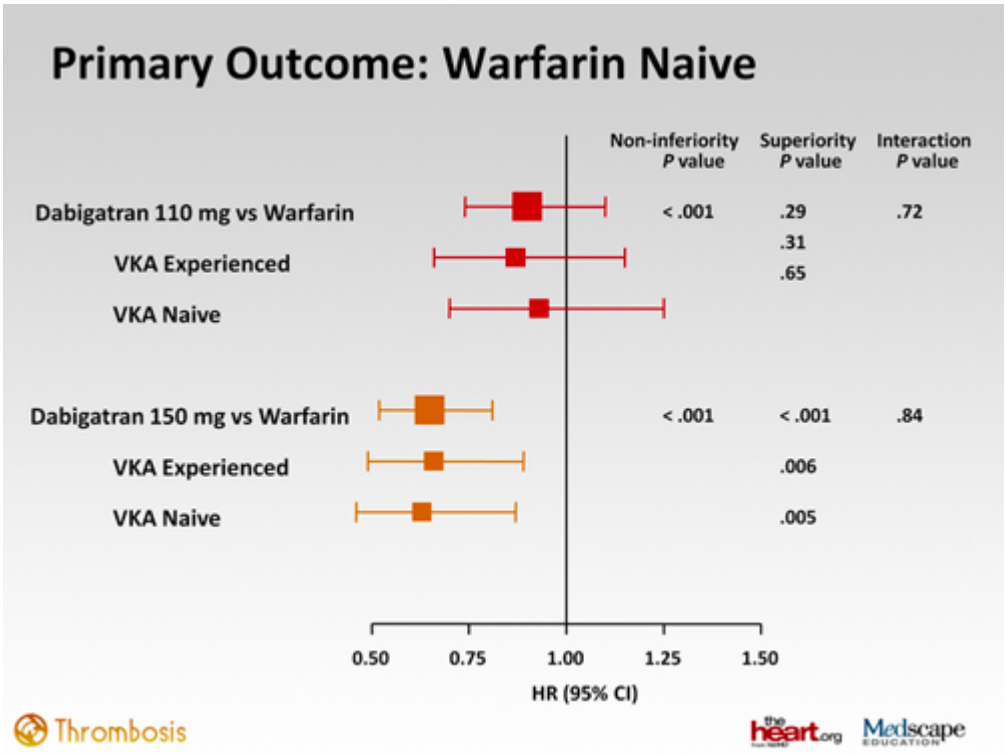
Slide 17.

Dr. Wallentin: Of course elderly patients have higher CHADS scores and therefore [they are] at higher risk for bleeding.



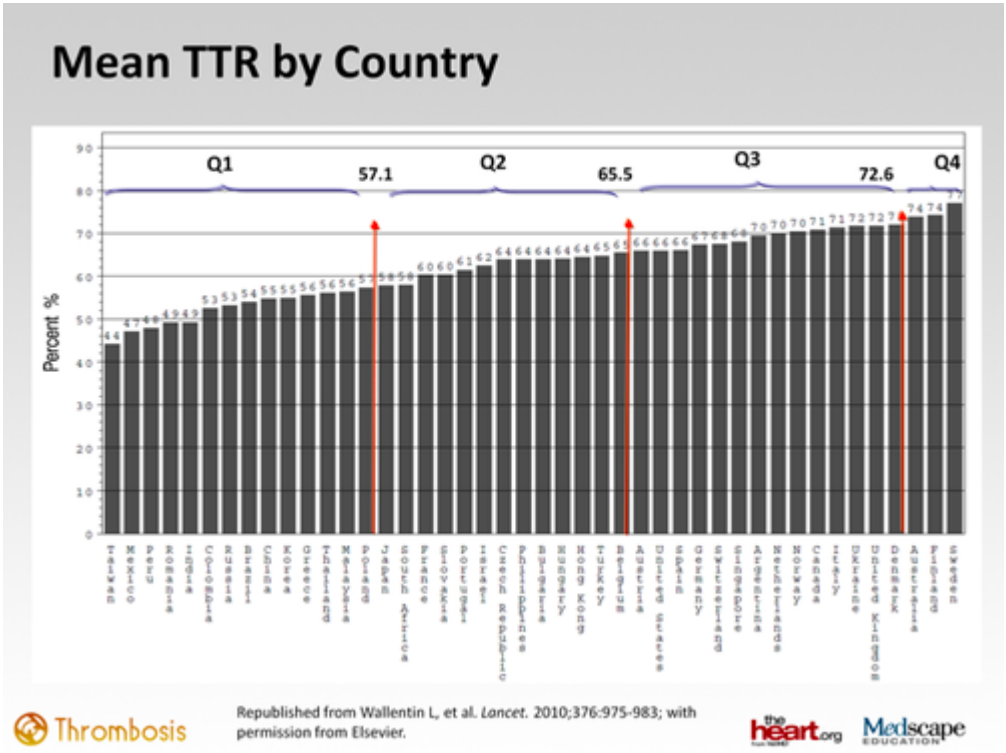
Slide 18.

Still, there is a possibility to consider the lower dose, although the risk for stroke is high, to avoid bleeding.



Slide 19.

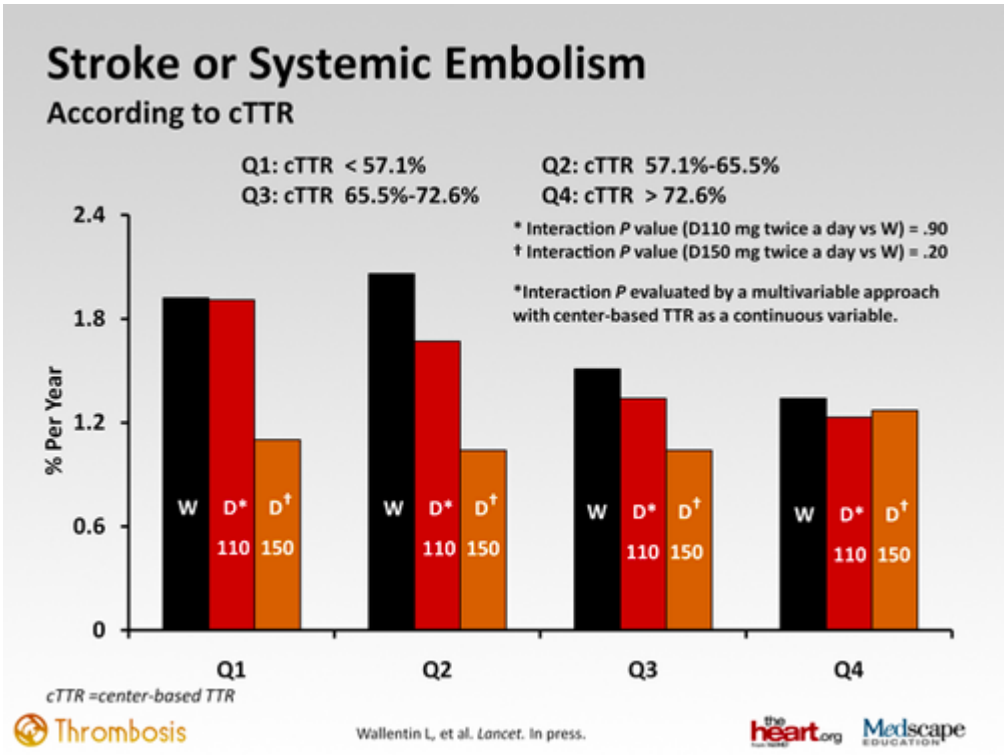
Dr. Wallentin: When we compare the new agents vs warfarin, it is tricky because TTR between 2 and 3 was achieved in the median of 65.5% of patients in the RE-LY trial.



Slide 20.

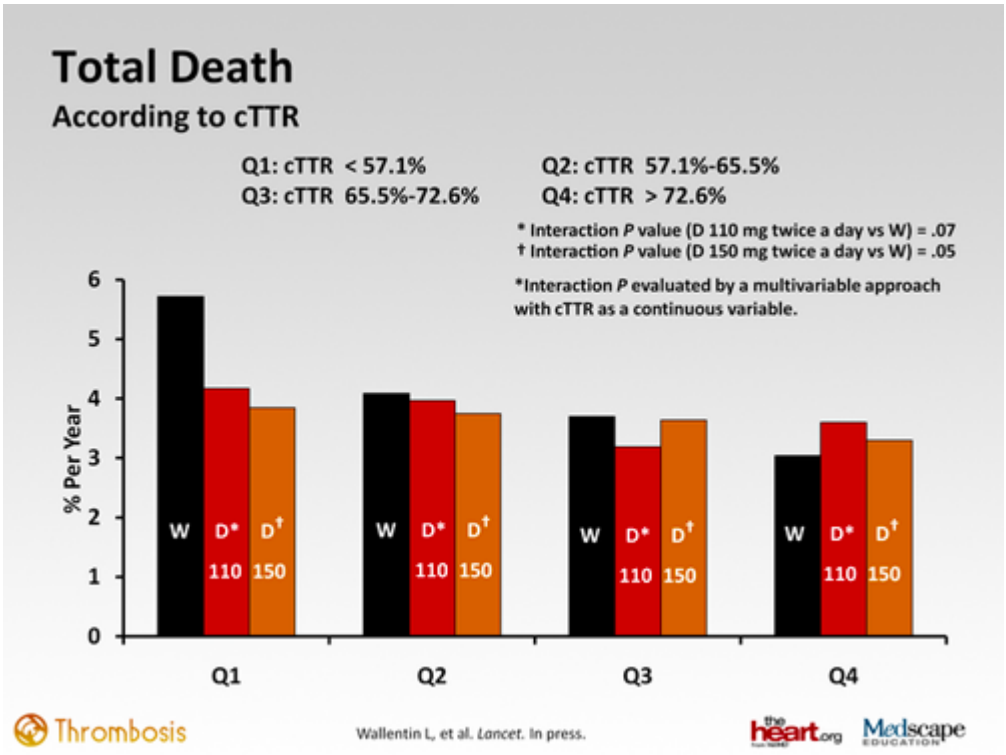
Dr. Wallentin: As you can see, there is a substantial variation among countries and an even larger variation between sites. The best country was Sweden and they had 77% TTR, but the worst as you can see was in Asia and South America, down to 45%.

Is it really appropriate to compare the new agent with a stable anticoagulant effect vs an agent with large variability and [find out] how much of the advantage was dependent on many centers [having] poor INR control.



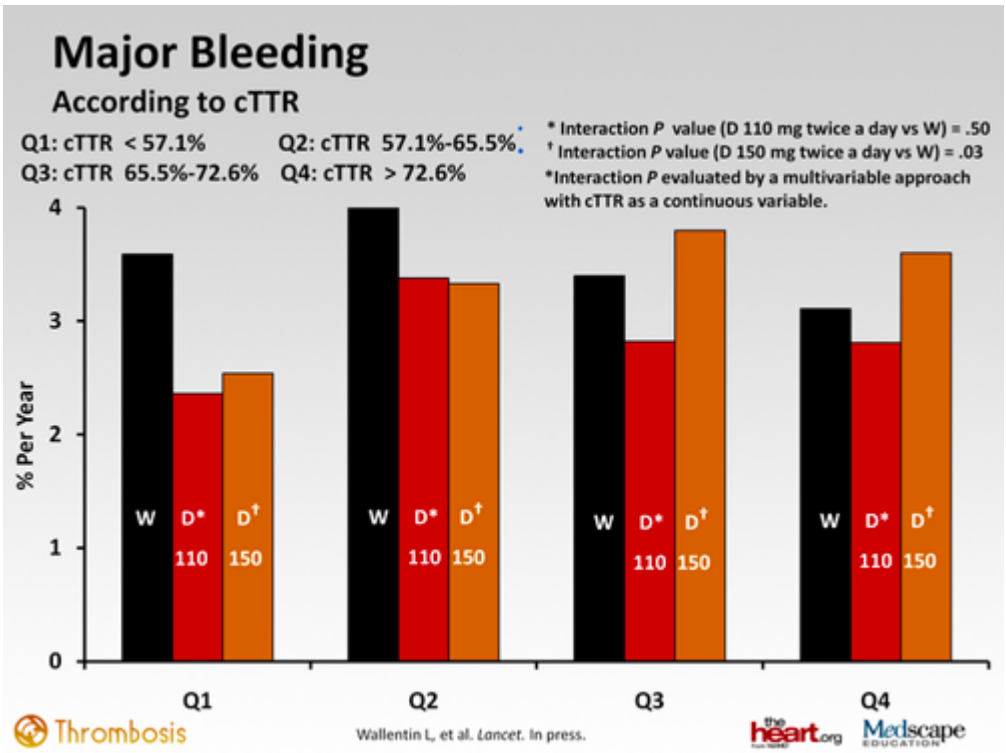
Slide 21.

We developed a method to compare centers' average INR control in the trial. The center's average was used for all its patients in both the dabigatran and warfarin arms. By that, we see that there is a trend to attenuation of the benefit at centers with better INR control, but still this interaction was not significant. So, overall we have an effect regardless of TTR concerning stroke, but there is a trend toward attenuation.



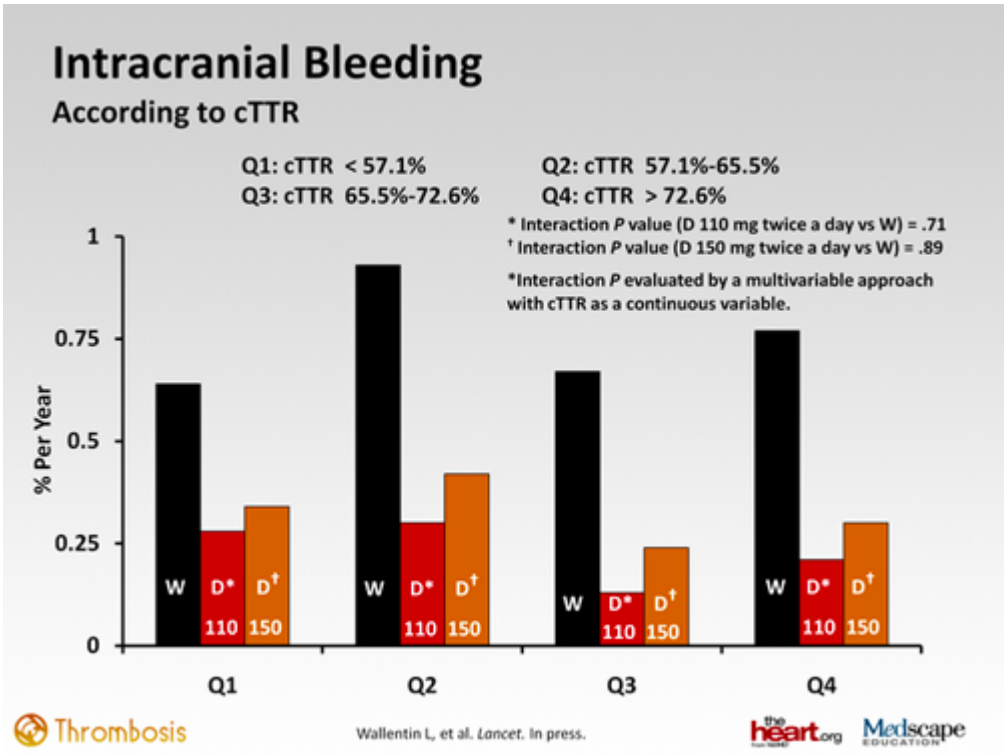
Slide 22.

The same could be seen for mortality, that most of the mortality benefit was obtained in centers with worse INR control and there was not much benefit seen even at the margin of a significant interaction in relation to INR control.



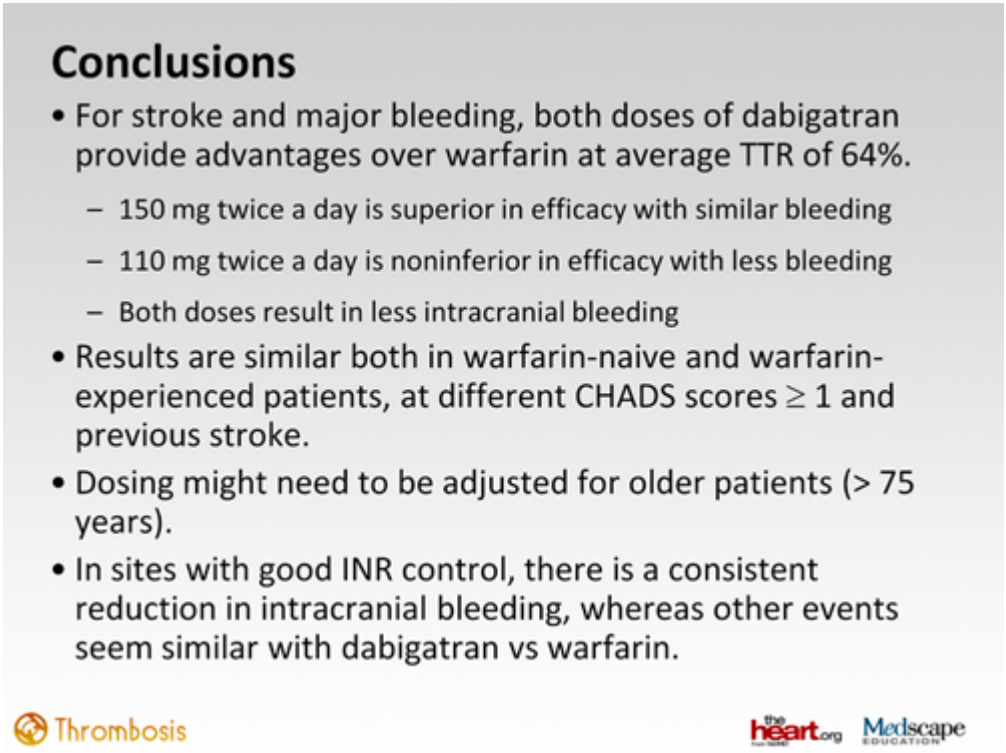
Slide 23.

Dr. Wallentin: Concerning major bleeding, you see the same, that the benefit in bleeding is more at centers with better INR control.



Slide 24.

Dr. Wallentin: I think this is a standard analysis that we should now request from all future trials. You need to show us the results in relation to standards of INR control. We need to have an appropriate comparator. Especially in my country, we have the best INR control in the world. This is always a question from the regulators. What is in it for us? We need to have that answer of what is in it for us.



Slide 25.

Dr. Wallentin: Overall for stroke and major bleeding, both doses of dabigatran provided advantages over warfarin at an average TTR of 64. The 150[-mg dose] was superior in efficacy with similar bleeds. The 110[-mg dose] was non-inferior in efficacy with less bleeding. Both dosages definitely [result in fewer] intracranial bleeds. The results were similar in warfarin-naive and warfarin-experienced patients at different CHADS scores, and even in patients with a previous stroke. The dosing might need to be adjusted [for older patients]. In sites with good INR control, there was a consistent reduction in intracranial bleeding, while other events were similar at centers with good INR control when you compare dabigatran with warfarin. Thank you for allowing me this quick review.

Supported by independent educational grants from Bayer Healthcare, Daiichi Sankyo, and Boehringer Ingelheim.

This article is part of a CME certified activity. The complete activity is available at: http://www.medscape.org/viewprogram/32165

Contents of *A New Era in the Management of Atrial Fibrillation: An Update on Oral Anticoagulation* [http://www.medscape.org/viewprogram/32165]

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[http://www.medscape.org/viewarticle/750178]

3. Development of Oral Factor Xa Inhibitors - Part I: Lessons From ROCKET AF
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6. Development of Oral Factor Xa Inhibitors - Part IV: Assessing the Next Wave of Agents
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Development of Oral Factor Xa Inhibitors - Part I: Lessons From ROCKET AF CME

Robert M. Califf, MD

Posted: 09/27/2011

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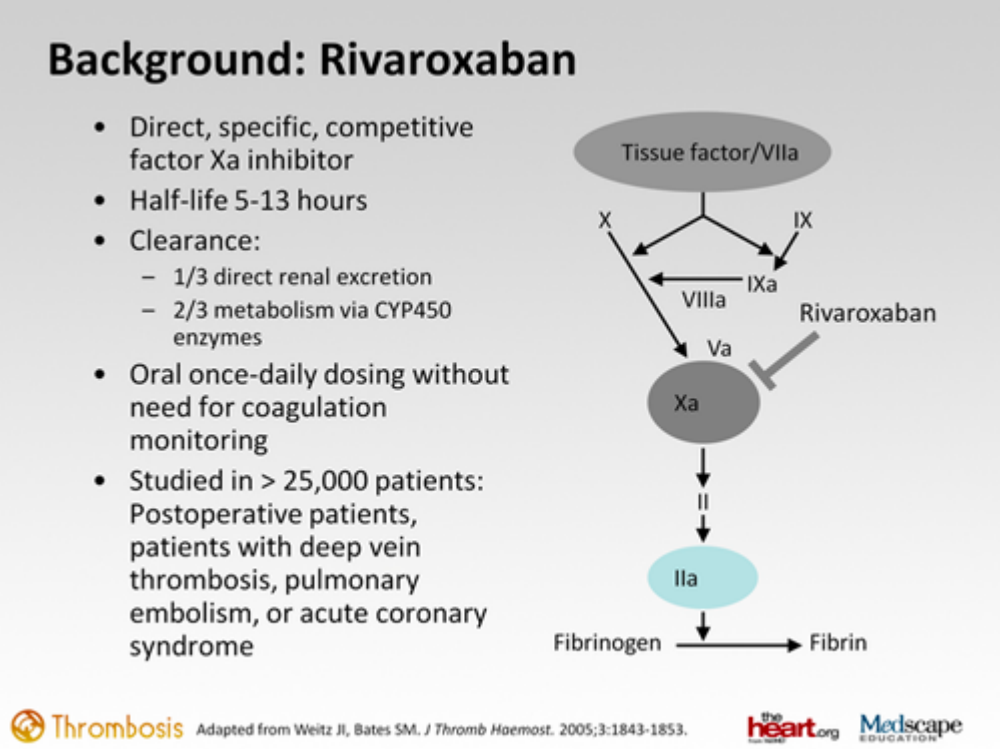
Slide 1.

Lars Wallentin, MD, PhD: By that I leave the floor to our mentor in big clinical trials, Professor Robert Califf from Duke. He will discuss the development of oral factor Xa inhibitors and lessons from the ROCKET AF trial.

Robert M. Califf, MD: Thank you, Lars. It is a pleasure to be here today.

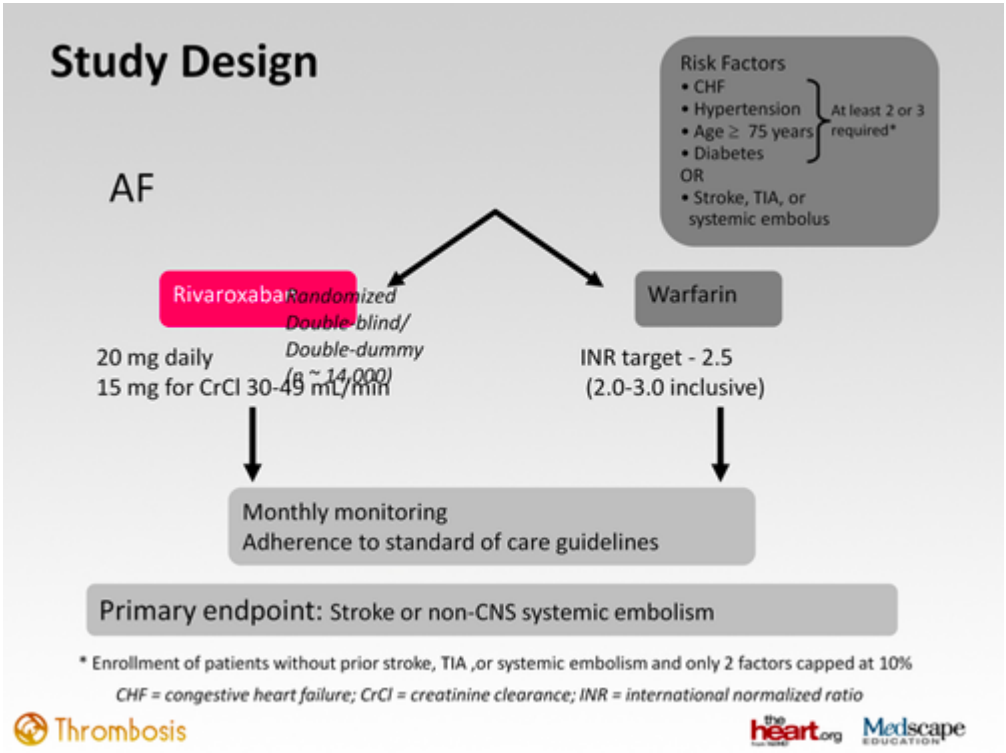
Slide 2.

Dr. Califf: It is my pleasure to talk about the development of [factor] Xa inhibitors, and specifically the ROCKET AF clinical trial. These are my relevant disclosures and I will note that details of interactions with industry can be found on the DCRI (Duke Clinical Research Institute) Website, which I am sure Dr. Alexander will also mention.



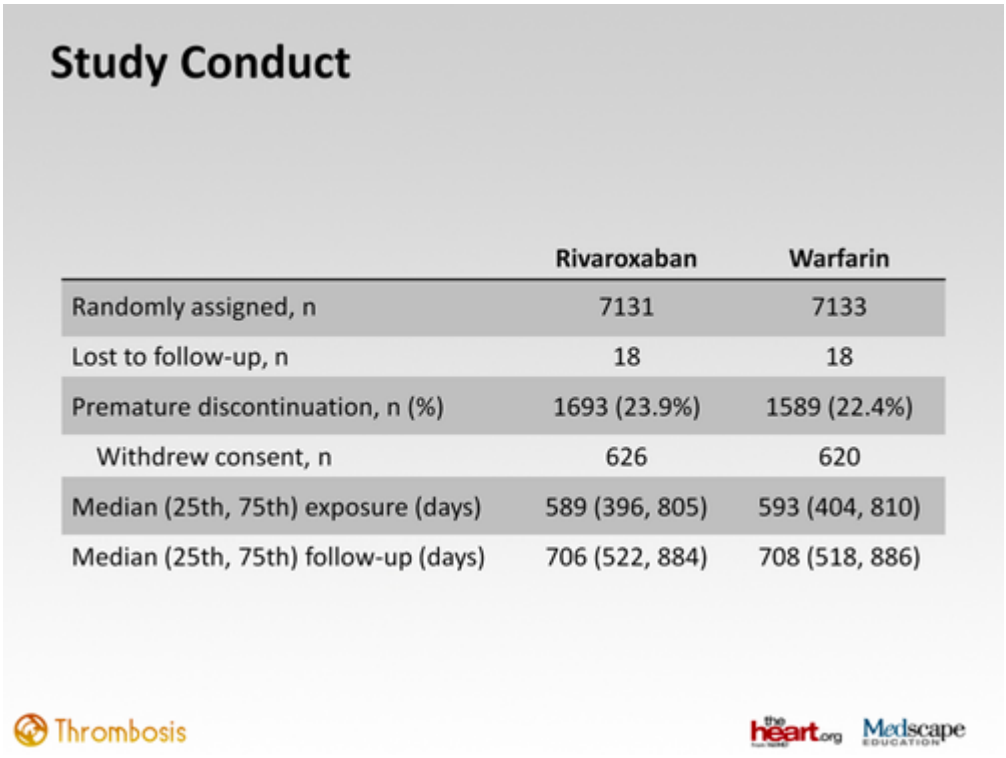
Slide 3.

Dr. Califf: I think you are all aware by now that in addition to the oral direct thrombin inhibitors that Professor Wallentin talked about, for years now a number of us have been working on the area of [factor] Xa inhibition, specifically oral [factor] Xa inhibition. We have had the privilege [to be on the] executive and steering committees working with rivaroxaban, which has a half-life of 5 to 13 hours, has about a third excreted by the kidneys, and importantly two thirds is dealt with by the liver with CYP450 (cytochrome P 450) interactions. It is given orally and was developed as a once-daily dosing regimen in atrial fibrillation (AF). Note that this drug has also been extensively investigated in multiple other populations to round out its total profile. I think you are all familiar with the cascade here and that rivaroxaban is acting a bit upstream compared with direct thrombin inhibitors, which are down lower in the cascade here.



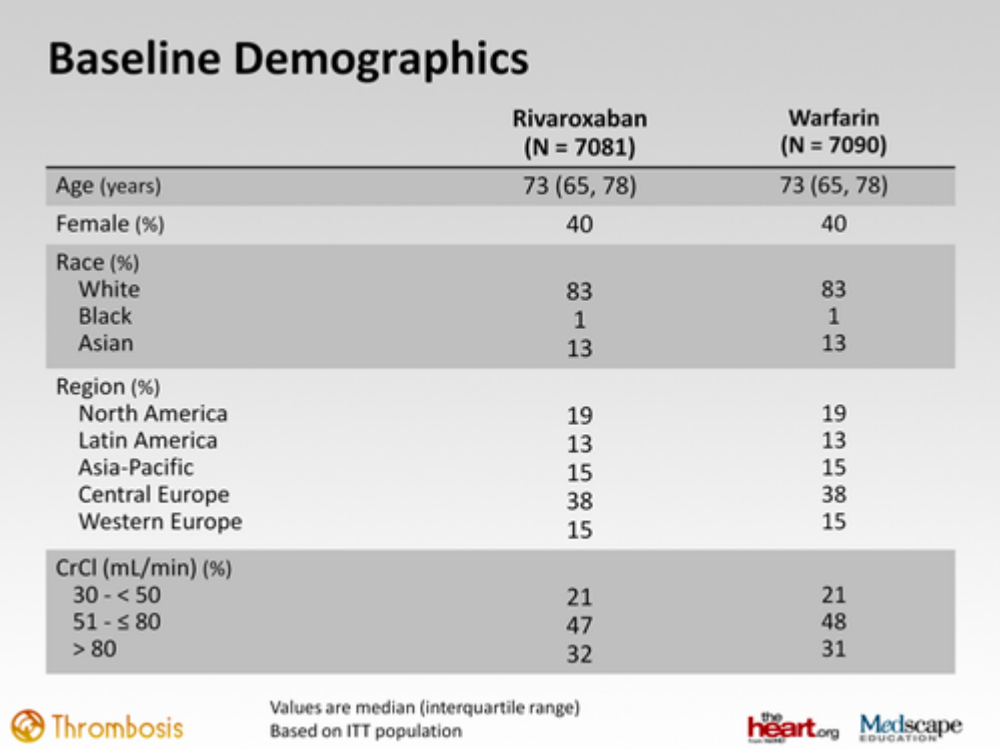
Slide 4.

Dr. Califf: This is a simple schema of the trial that we did. It was intended to include the tweaks of having a higher-risk population with at least 2 of the 3 major $CHADS_2$ risk factors included or a history of stroke, TIA (transient ischemic attack), or a systemic embolus. In the end, we [randomly assigned] 14,000 patients. This was a double-blind, double-dummy study which brought into account many, many issues in terms of the trial administration. That would not have been the case in an open-label trial. The primary endpoint was stroke or non-CNS (central nervous system) systemic embolus, as is standard for this type of trial.



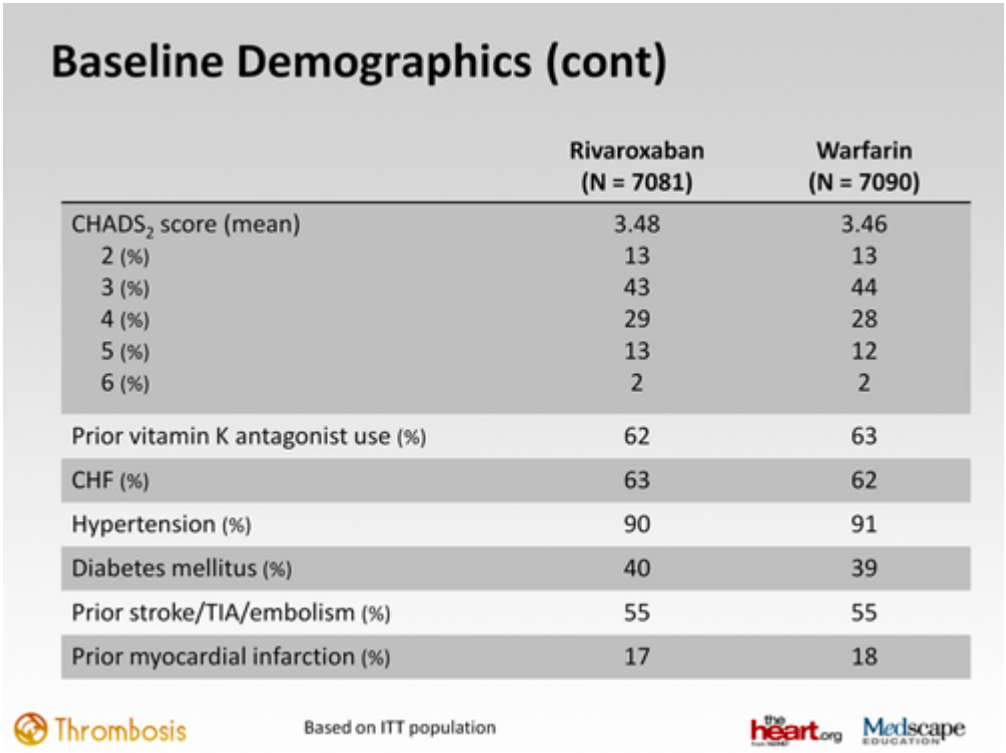
Slide 5.

Dr. Califf: You can see we ended up with just over 7000 participants in each group. Only 18 in each group were lost to follow-up but just over 23% total discontinued in the midst of the trial for a variety of reasons. The median exposure was 589 days with a total follow-up. Importantly, we continued to follow patients who discontinued assigned treatment for the duration of the trial. So, you can see over 700 days of follow-up total.



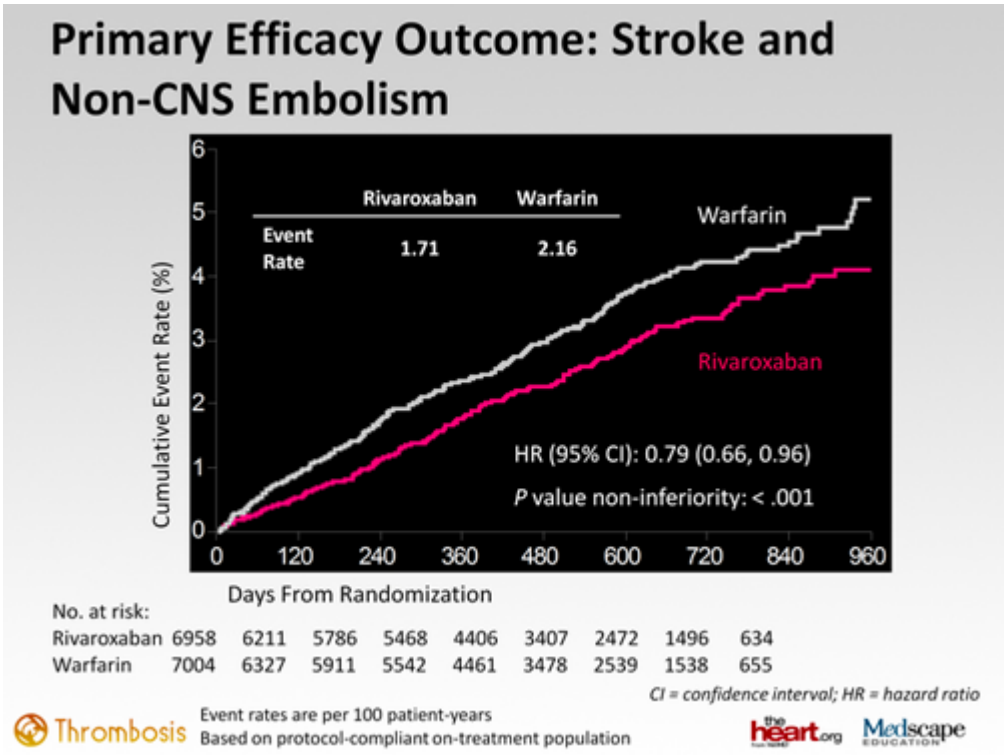
Slide 6.

Dr. Califf: The population was high risk, with a quarter of the patients over the age of 78; 40% were women. You can see we had a large participation of central Europe in this trial. I wish we had time to discuss this in detail, but I think the international variation in the use of warfarin as Lars pointed out is going to be something that merits a lot of attention by the global cardiovascular community. You can see we enrolled a lot of people with impaired creatinine, mostly because of their age and not because of any particular renal dysfunction that we were looking for.



Slide 7.

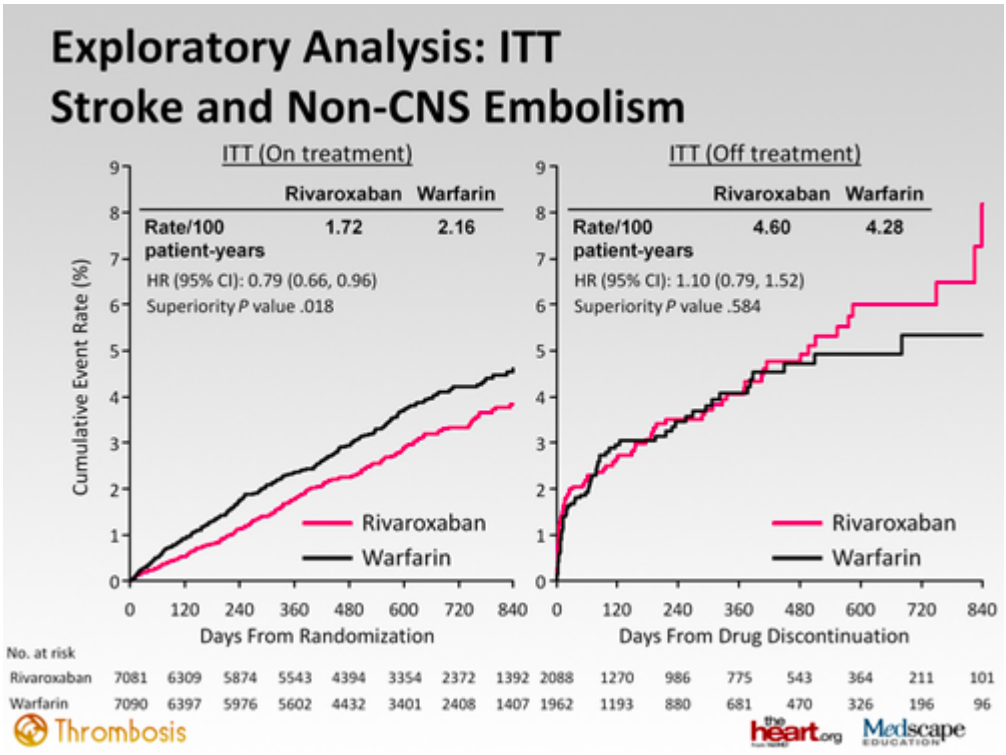
Dr. Califf: Here you see the $CHADS_2$ scores and of note, we did not include patients with CHADS [score of] 1. We were looking for the very high-risk patients, many of whom had multiple comorbidities. You can see that more than 60% had heart failure, 90% had hypertension, 40% had diabetes, and over half had already had a stroke, a TIA, or a systemic embolus. It was a very-high-risk population.



Slide 8.

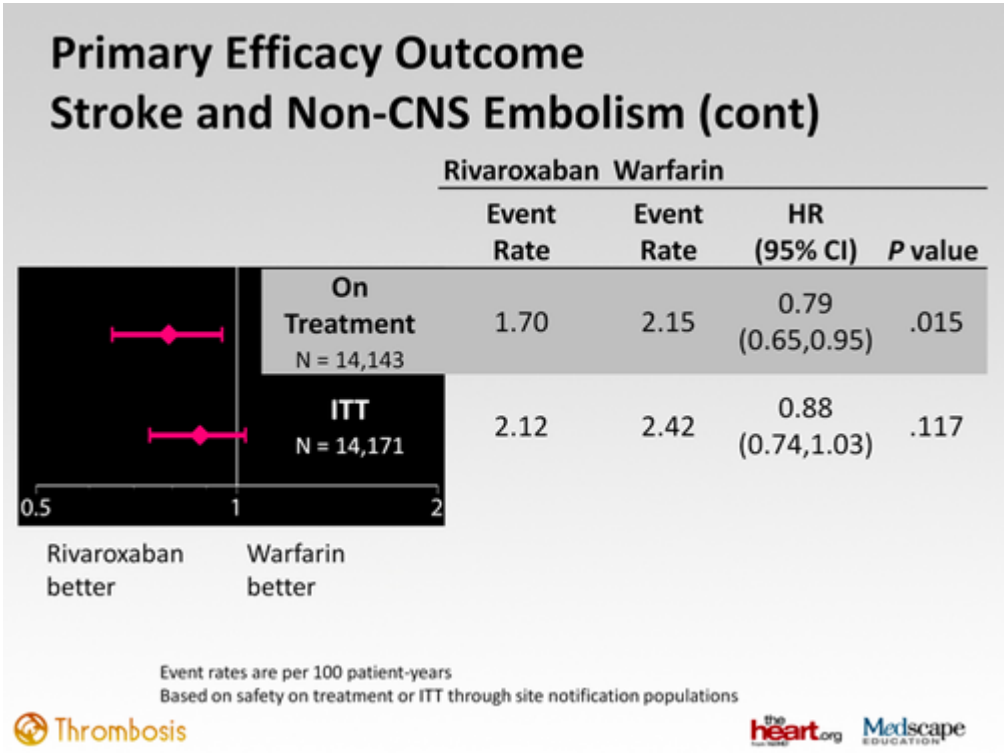
Dr. Califf: The primary results were presented last year and the paper just came out in the *New England*

Journal [of Medicine] this month. Importantly, the primary analysis was done as an intended non-inferiority trial, so the primary analysis was done for the period of time on treatment. You can see here a nice result for non-inferiority, highly significant.



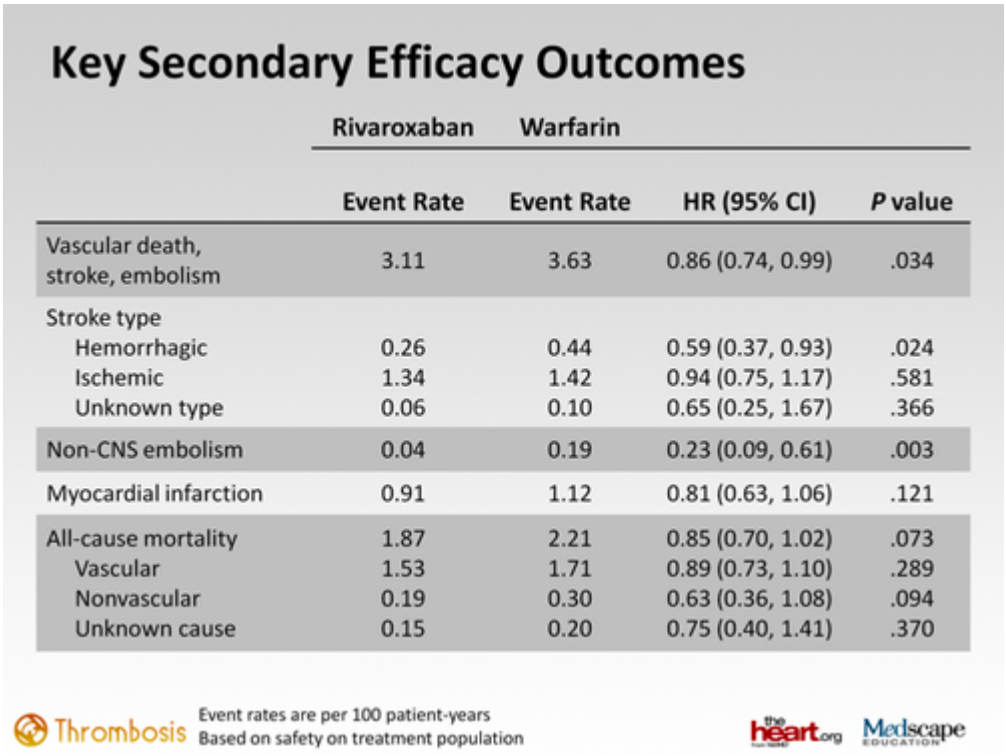
Slide 9.

Dr. Califf: However, when we look at the trial as a whole, including all patients [randomly assigned] for all time of treatment, you can see what you might expect from a trial of a drug given for acute [anticoagulation], even given orally. In the lower left hand side here you see that on treatment is this nice effect that was seen in the primary analysis, but of course when people discontinued treatment there was no difference between those who had been assigned to warfarin and those who had been assigned to rivaroxaban. As is noted in our paper, at the time of discontinuation, at the end of the trial, when the patients were switched from rivaroxaban to warfarin, there was an excess of events during that period of transition that merits a lot more discussion. I am sure we will get into it during the panel discussion.



Slide 10.

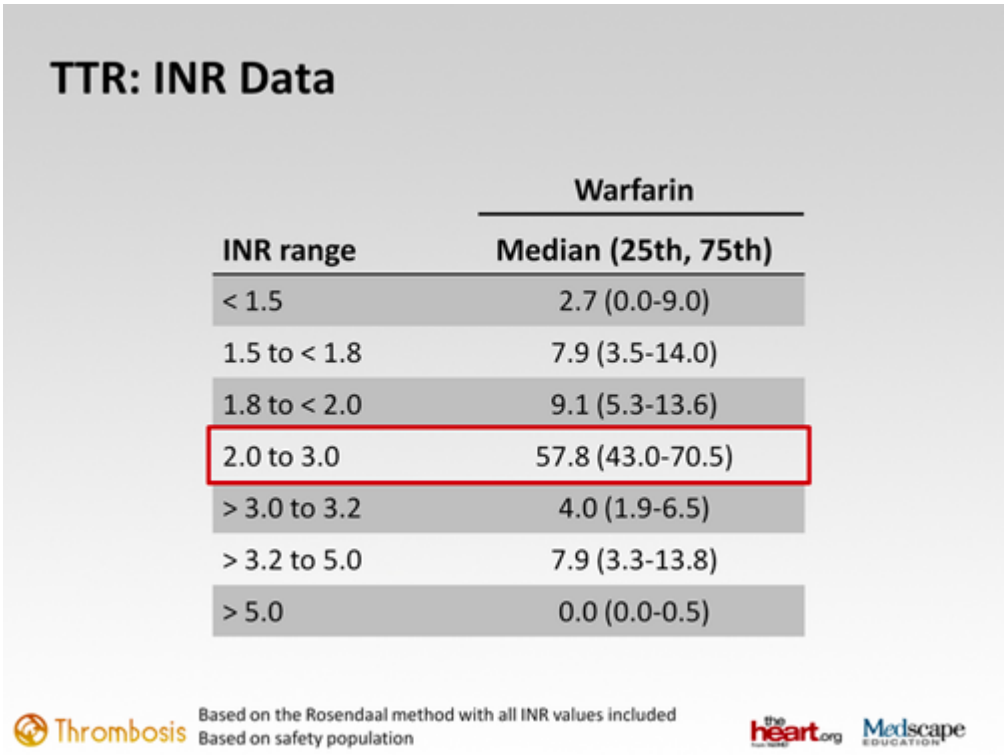
Dr. Califf: An overview of the trial results would look like this. The on-treatment analysis showed that while patients were taking assigned treatment, there was a very nice reduction in the primary endpoint. By overall intention-to-treat (ITT) [analysis], you can see a trend in the right direction but not reaching statistical significance.



Slide 11.

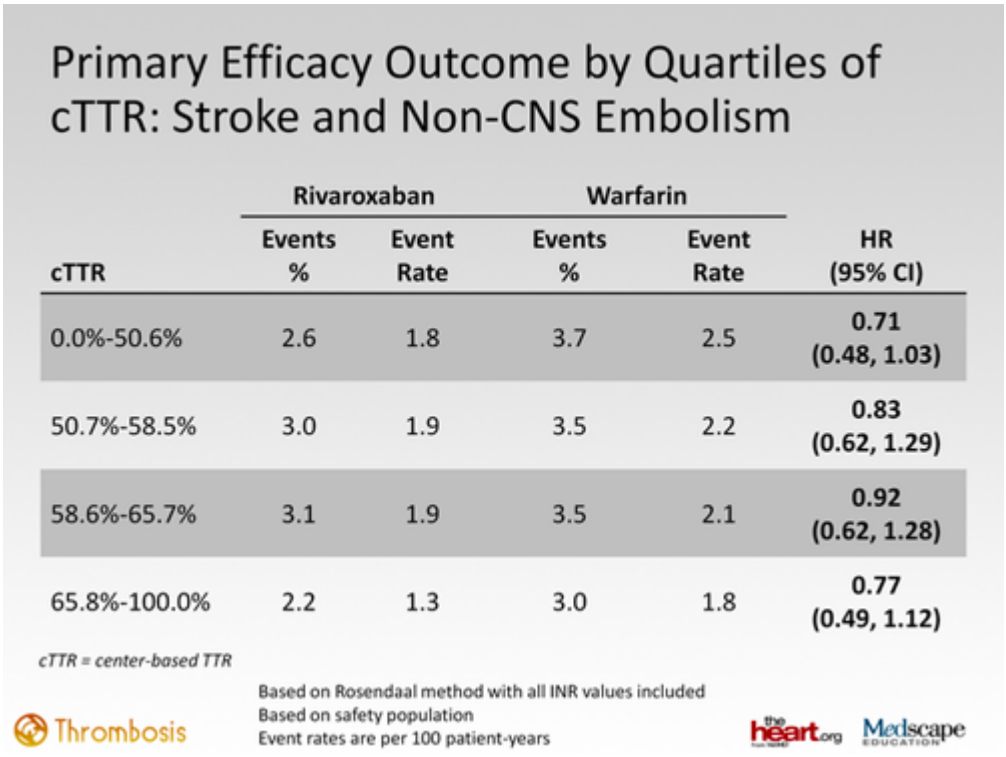
Dr. Califf: If we then look at key secondary endpoints, interestingly as was shown with dabigatran, the most

important point to make here is that there was a reduction in hemorrhagic stroke. In addition, the myocardial infarction trend was in the right direction and the all-cause mortality trend was also in the right direction. It was not statistically significant, but the reduction in hemorrhagic stroke was significant, and there was a reduction in death from bleeding.



Slide 12.

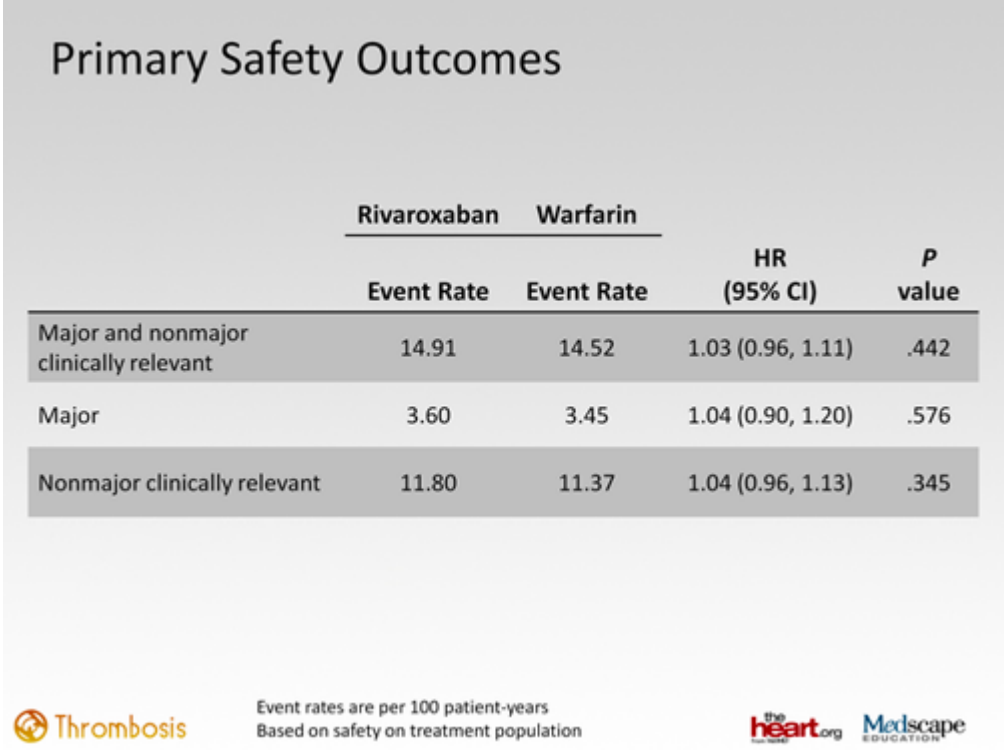
Dr. Califf: As Professor Wallentin has said, it is important to look at the time in therapeutic range (TTR). Our TTR was lower than in the RE-LY trial. You can see the mean TTR was 57.8.



Slide 13.

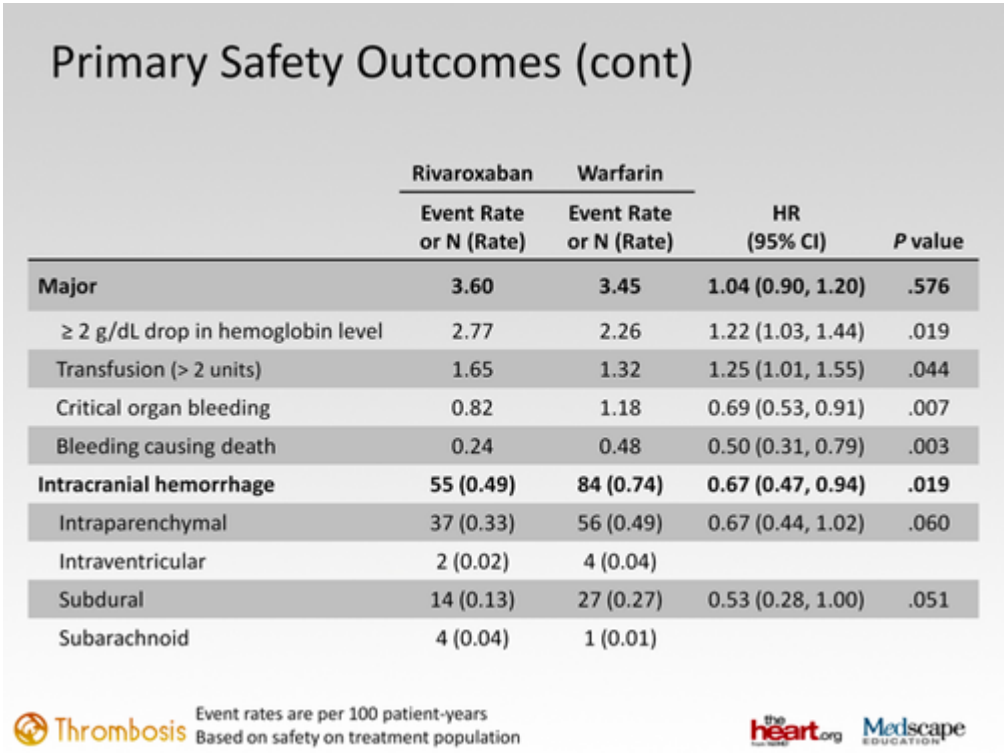
Dr. Califf: When we looked at the outcomes by quartile of TTR, interestingly we could not find that there was a relationship between benefit of the drug or the difference between warfarin and rivaroxaban in the quartile of range. You will notice that because our overall distribution was lower, the fourth quartile encompasses a fairly large range, 66% to 100%.

A lot of analyses have been completed but have not yet been presented publically, so I am not going to show them at this meeting, and also because of the limitation of time. I am sure we will have a good discussion during the discussion period about this issue.



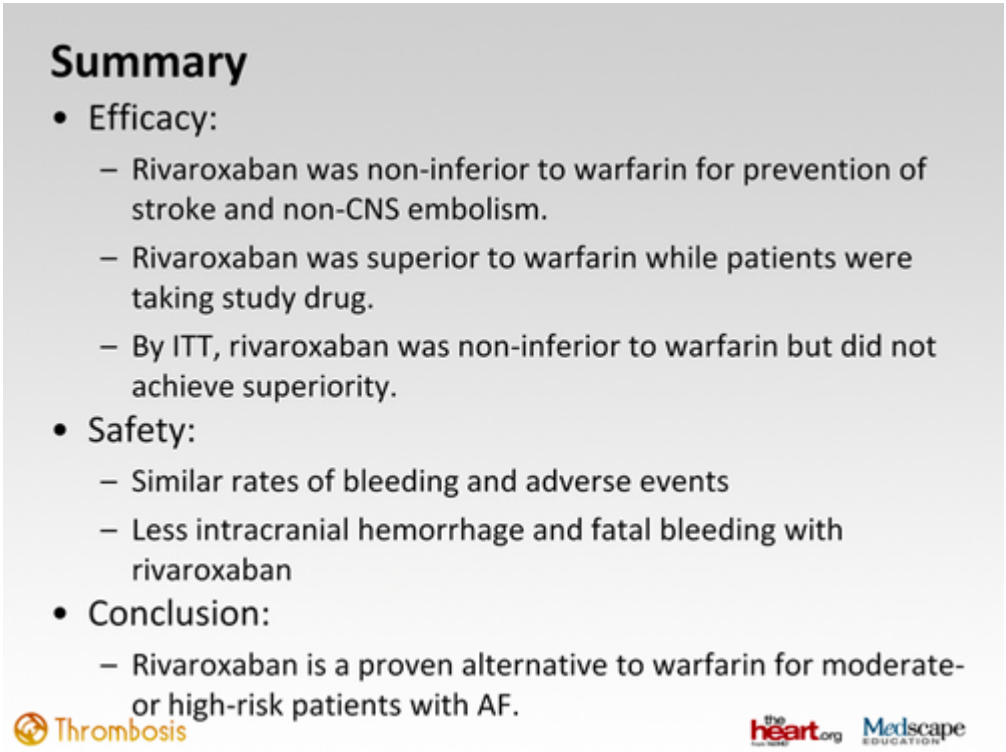
Slide 14.

Dr. Califf: We looked at the primary safety outcomes. You can see no difference in the totality of major and nonmajor clinically relevant bleeding. What we did see was a very nice reduction in intracranial hemorrhage, as I have already pointed out, and a reduction in bleeding causing death.



Slide 15.

Dr. Califf: We also saw an increase in hemoglobin drop and the use of transfusion. As Dr. Wallentin pointed out, compared with warfarin, we saw a similar increase in gastrointestinal bleeding as the major difference in nonlethal bleeding in favor of warfarin.



Slide 16.

Dr. Califf: In summary, for efficacy rivaroxaban was not inferior to warfarin for prevention of stroke and non-CNS embolism. It was superior while patients were taking study drug, but by ITT rivaroxaban was not inferior to

warfarin but did not achieve superiority. With regard to safety, there were similar rates of bleeding and adverse events, but clearly less intracranial hemorrhage and fatal bleeding with rivaroxaban. We concluded that rivaroxaban is a proven alternative to warfarin for moderate- to high-risk patients with AF. Thank you.

Supported by independent educational grants from Bayer Healthcare, Daiichi Sankyo, and Boehringer Ingelheim.

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Development of Oral Factor Xa Inhibitors - Part II: Lessons From AVERROES and the Design for ARISTOTLE CME

John H. Alexander, MD, MHS

Posted: 09/27/2011

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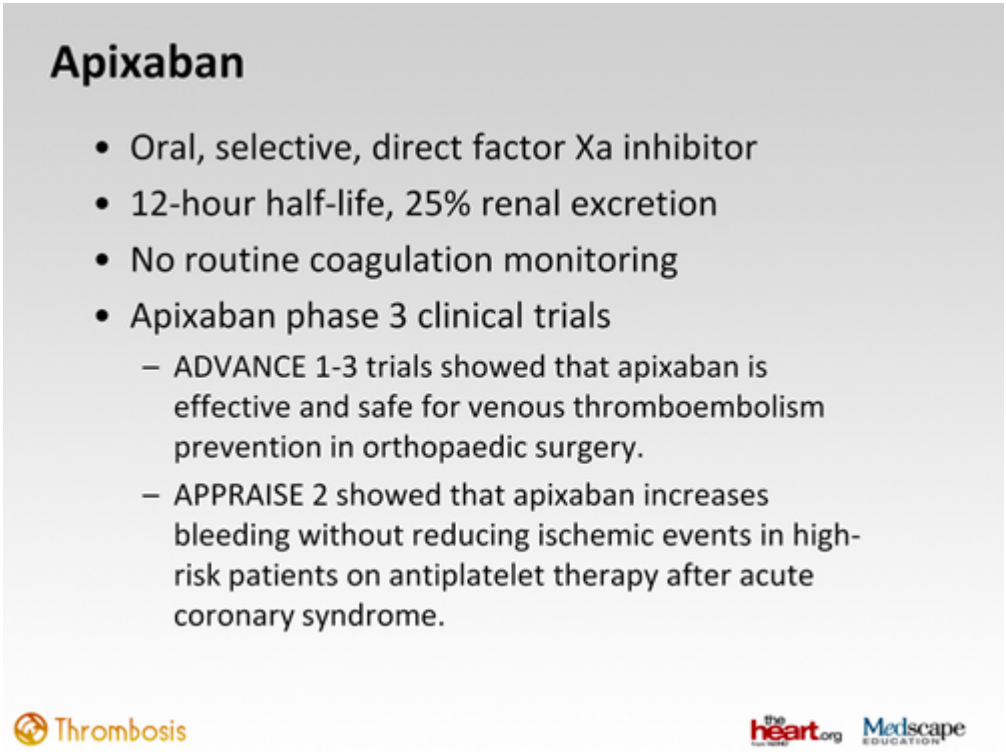
Slide 1.

Eugene Braunwald, MD: It is now my pleasure to introduce Dr. Alexander, also from the Duke Clinical Research Institute, who is going to talk about lessons from AVERROES and the design of ARISTOTLE.

John H. Alexander, MD, MHS: Dr. Braunwald and Dr. Wallentin, thank you very much for this invitation to discuss some of the programs in atrial fibrillation (AF) with another oral factor X inhibitor, apixaban. I am going to go over the highlights of the results of the AVERROES trial, which have already been presented and published, and then I am going to talk about some of the key elements of the design of the ARISTOTLE trial, which will be presented tomorrow by Dr. Chris Granger.

Slide 2.

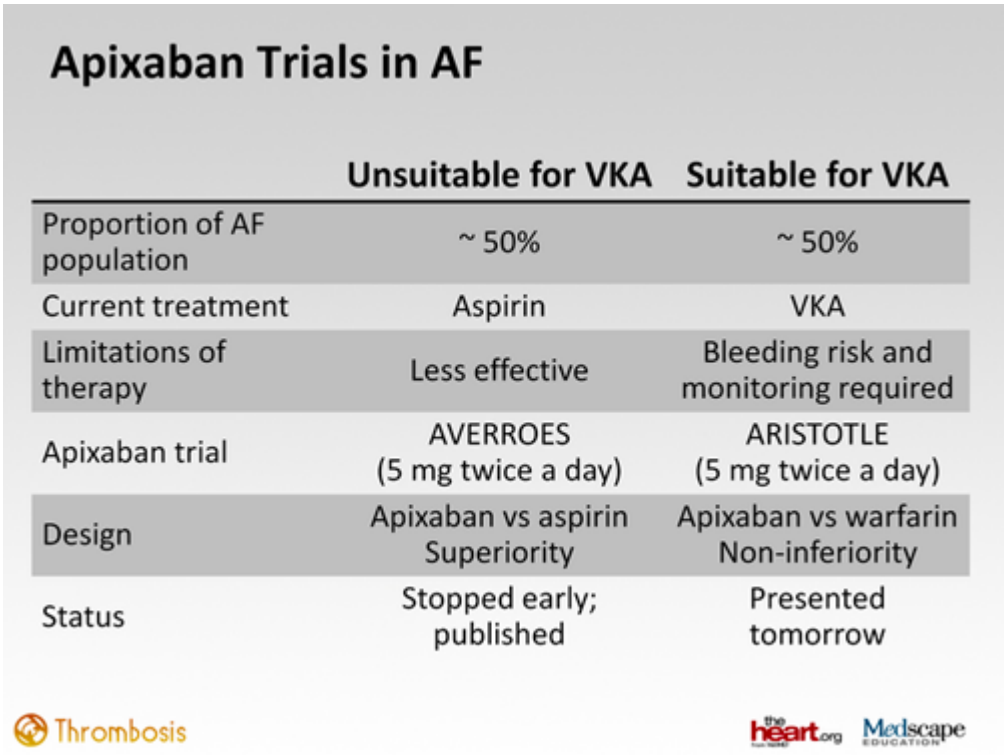
Dr. Alexander: These are my disclosures. Both AVERROES and ARISTOTLE are co-sponsored by Bristol-Myers Squibb and Pfizer. As Dr. Califf mentioned, my disclosures and many DCI (Duke Clinical Institute) faculties' disclosures are available on the DCI website.



Slide 3.

Dr. Alexander: Apixaban is an oral selective direct factor X inhibitor that targets factor X at the same point in the coagulation cascade as rivaroxaban. It has a 12-hour half-life quite similar to rivaroxaban and approximately

25% renal excretion. Like all of these drugs, no routine coagulation monitoring is required.



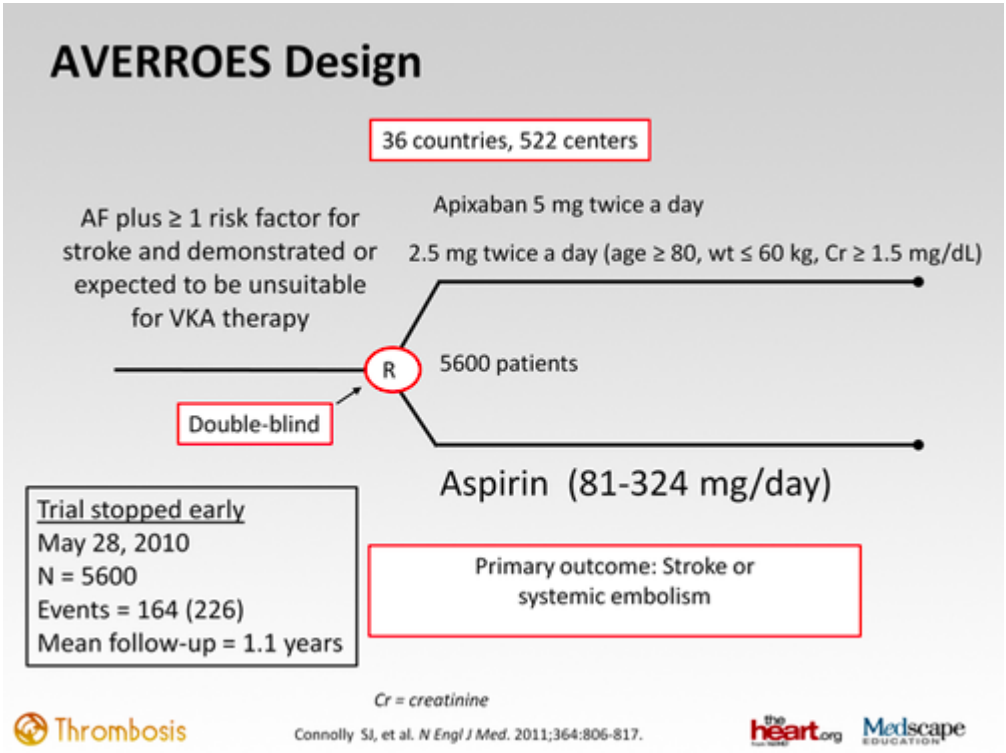
Slide 4.

Dr. Alexander: Apixaban has been studied in phase 3 clinical trials in the ADVANCE program in venous thromboembolism prophylaxis in patients undergoing orthopaedic surgery and [has been] shown at a dose of 2.5 mg twice a day to be safe and effective compared with enoxaparin in that setting. It has also been studied in patients [after] acute coronary syndrome at a dose of 5 mg twice a day. We recently presented and published those results showing that high-risk patients at least do not derive benefit and do have an increased risk for bleeding [if there is] a background of antiplatelet therapy.

The apixaban program has 2 trials in patients with AF. You have just heard about the 2 trials in the populations of patients who are candidates for warfarin, but because of all the known limitations of warfarin, about half of patients who have an indication for warfarin never receive it.

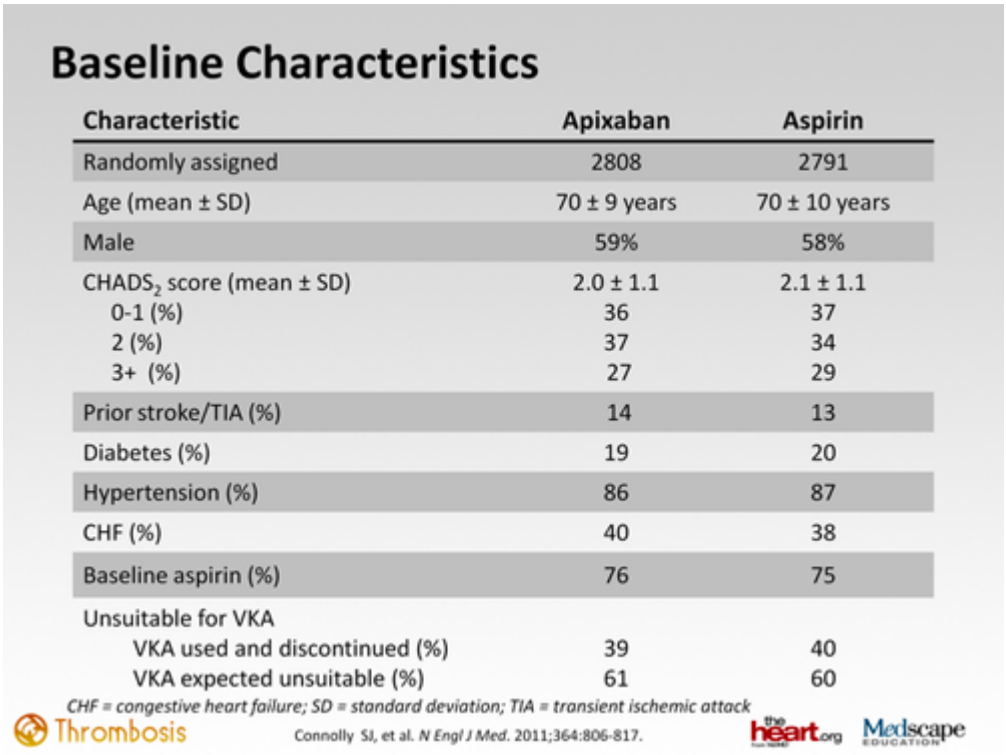
The AVERROES trial studied patients who are unsuitable for vitamin K antagonists (VKA), again making up about 50% of the population. The current treatment in that group is aspirin, which is known to be less effective than warfarin. The AVERROES trial studied 5 mg twice a day of apixaban. This dose was chosen primarily from phase 2 studies in venous thromboembolism prophylaxis. The design is a superiority trial of an apixaban vs aspirin. This trial was stopped early because of efficacy, and as I said it has been presented and published.

The other trial is ARISTOTLE, which like RE-LY and ROCKET is studying patients who are candidates for VKAs. The limitations here are the limitations of warfarin, which are bleeding risk and the monitoring required. ARISTOTLE is also studying 5 mg twice a day of apixaban. It is designed primarily as a non-inferiority trial vs blinded warfarin and [data from] this trial will be presented tomorrow.



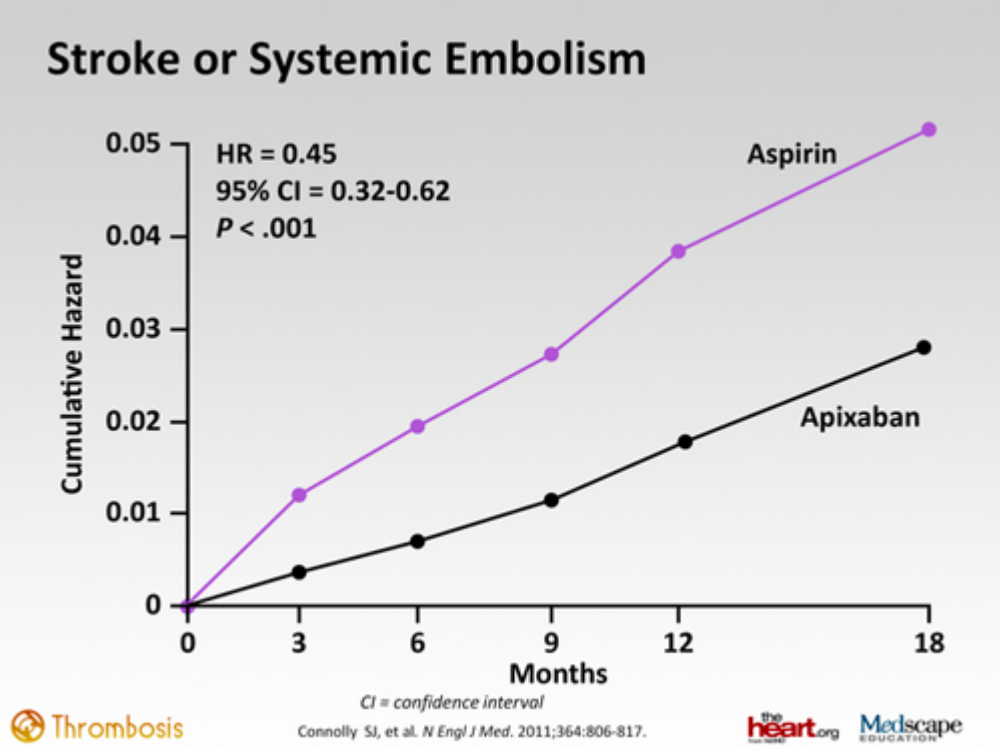
Slide 5.

Dr. Alexander: This is a schematic of the design of the AVERROES trial. AVERROES enrolled patients with AF plus at least 1 additional risk factor for stroke. As Dr. Braunwald showed, these patients have an indication for warfarin but about half of our patients with this indication don't receive it. That is the population targeted by AVERROES. They enrolled 5600 patients and [randomly assigned] them in a double-blind fashion to apixaban 5 mg twice a day or aspirin 81-324 mg/day in 36 countries at 522 centers. The primary outcome was stroke or systemic embolism. The trial was stopped early in May of last year after they had enrolled the entire cohort but before completion of follow-up with 164 or roughly 70% of their planned total events and a mean follow-up of 1.1 years.



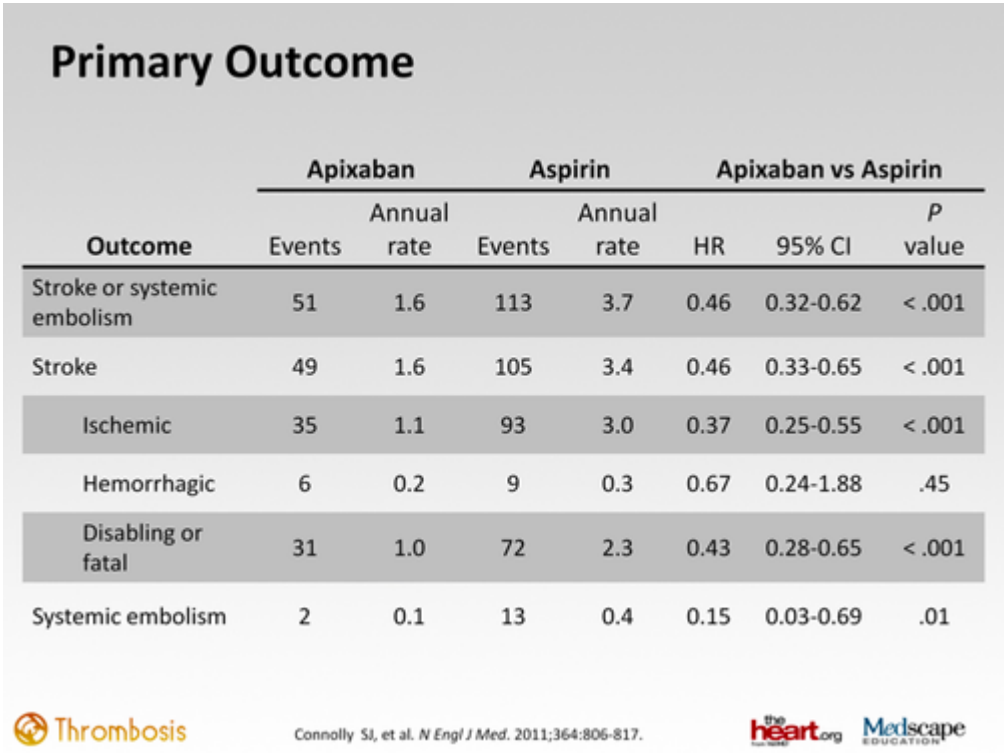
Slide 6.

Dr. Alexander: This is a schematic of the baseline characteristics. The average age was 70 years; 60% were male. You can see that the average CHADS score was 2, similar to the RE-LY population but lower risk than the ROCKET population. Over a quarter of patients had a CHADS score of 3 and again these are patients who are not deemed to be candidates for VKA therapy. Almost 20% had diabetes. More than 80% had hypertension; 40% had heart failure. The majority, 75% of patients, were taking aspirin at the time of enrollment and in most of these patients VKA therapy was deemed to be unacceptable, but about 40% of the patients had tried it previously and had to discontinue it.



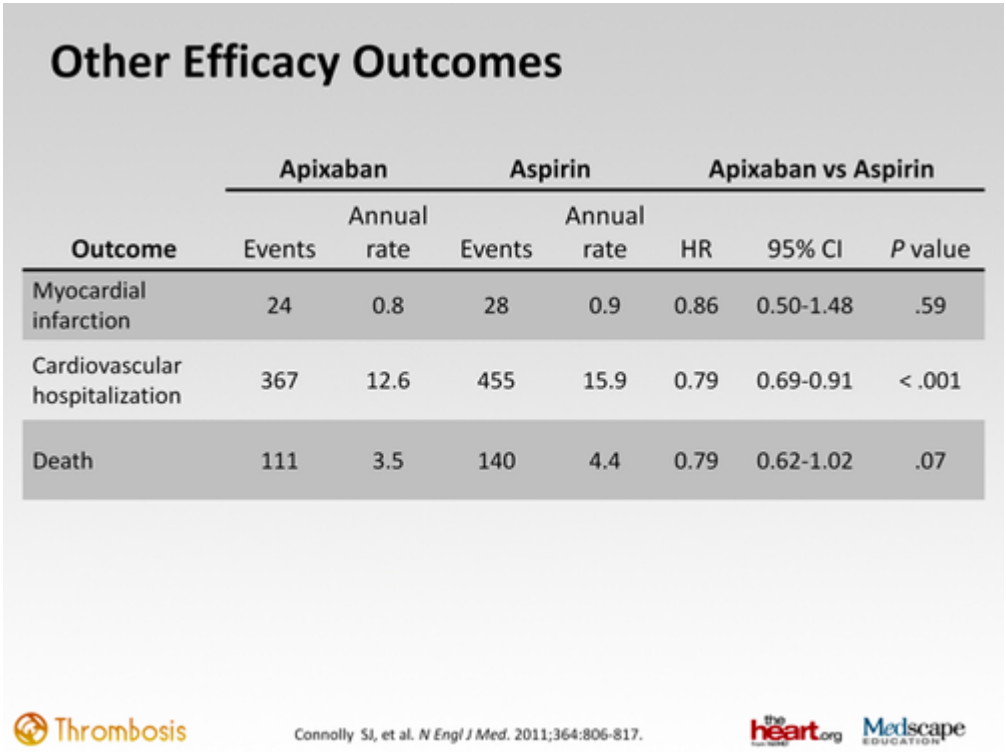
Slide 7.

Dr. Alexander: These are the primary results of the AVERROES trial. You can see that with aspirin at 1 year about 4% of this population had a stroke or systemic embolism. Apixaban reduces that by more than half, with a hazard ratio (HR) of 0.45. That is highly statistically significant.



Slide 8.

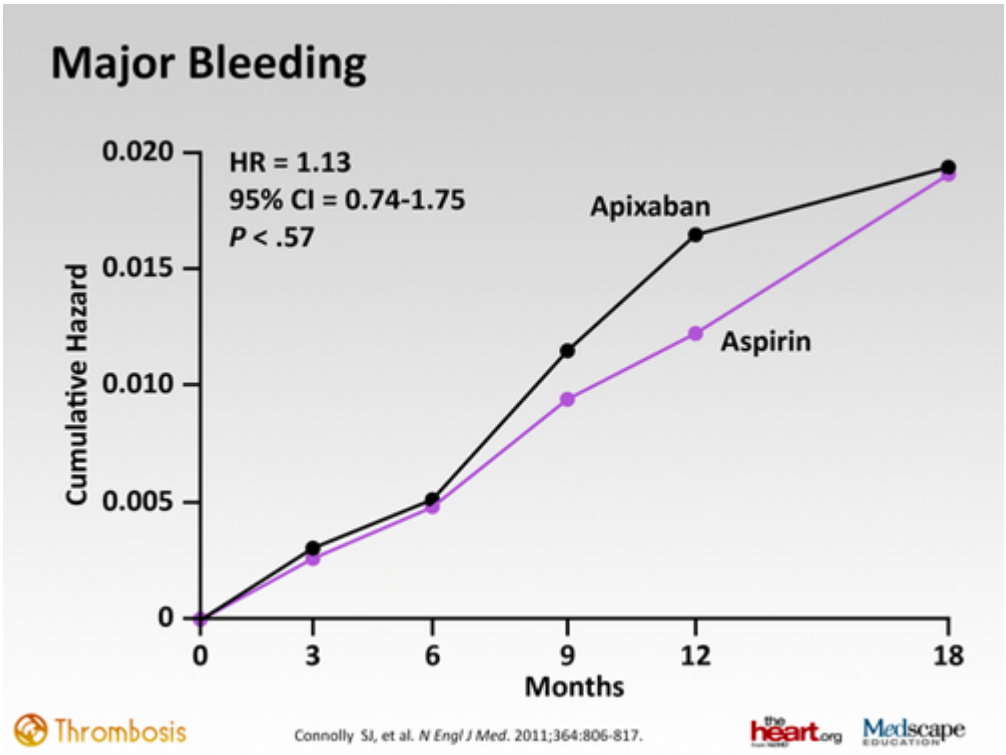
Dr. Alexander: This reduction in the primary outcome is made up of a reduction in ischemic stroke with an HR of 0.37, but also a reduction in hemorrhagic stroke with a one-third reduction HR of 0.67. There is also a consistent reduction in fatal or disabling strokes.



Slide 9.

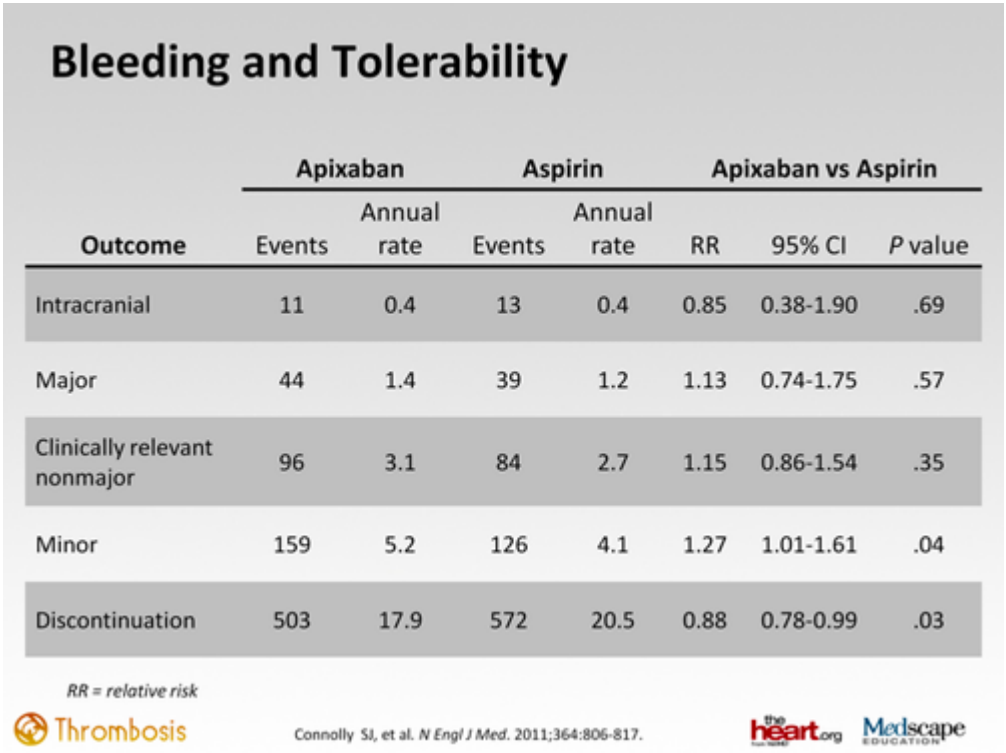
Dr. Alexander: We know that many of the strokes in patients with AF are quite severe and lead to significant disability. There was a numeric although not statistically significant reduction in myocardial infarction.

Importantly there was a reduction in cardiovascular hospitalization, I think reflecting the excellent tolerability of apixaban in this population. There was a trend, although not statistically significant, toward a reduction in all-cause mortality with an HR of 0.79.



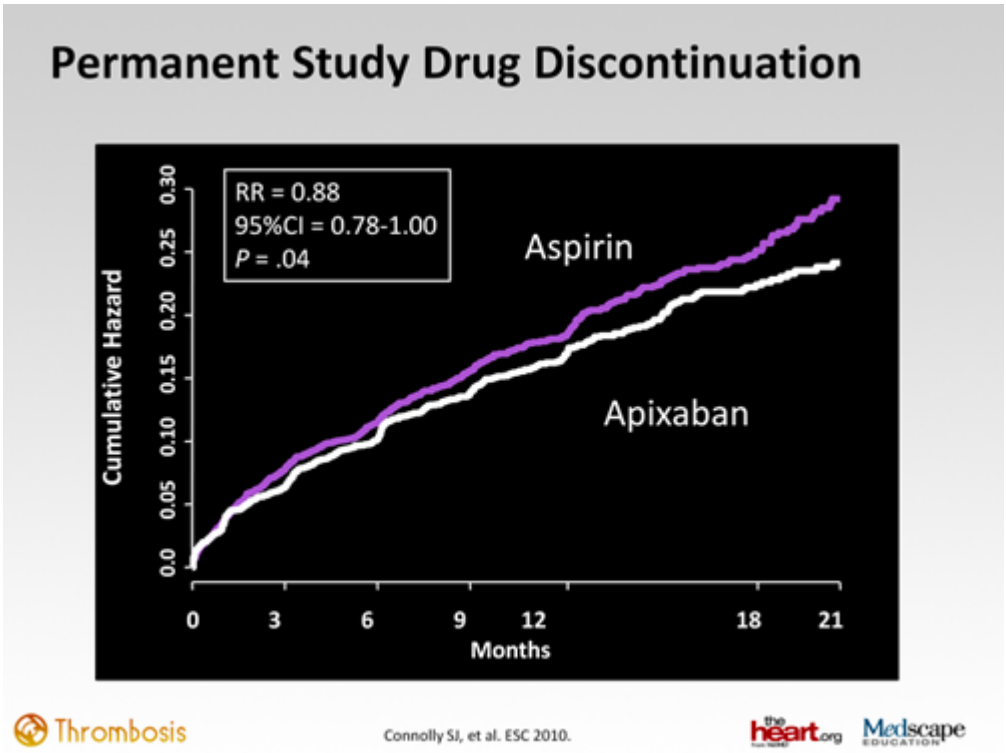
Slide 10.

Dr. Alexander: We know that apixaban causes bleeding. I think one of the key lessons from AVERROES is about aspirin. We have already seen from the efficacy data that aspirin is not particularly effective at preventing stroke and systemic embolism in our patients with AF. It does have a recommendation in the guidelines for patients who have a CHADS score of 1, but here you can see this is ISTH (International Society on Thrombosis and Haemostasis) major bleeding and during over a year of follow-up, the event rates here are about a quarter of what they are for the primary outcome. There is no statistically significant increase in bleeding with apixaban over aspirin. So, aspirin is a drug we all use in all of our patients with coronary disease. We use it and put it in the water basically, but we forget the bleeding risks with aspirin, which I think are highlighted here.



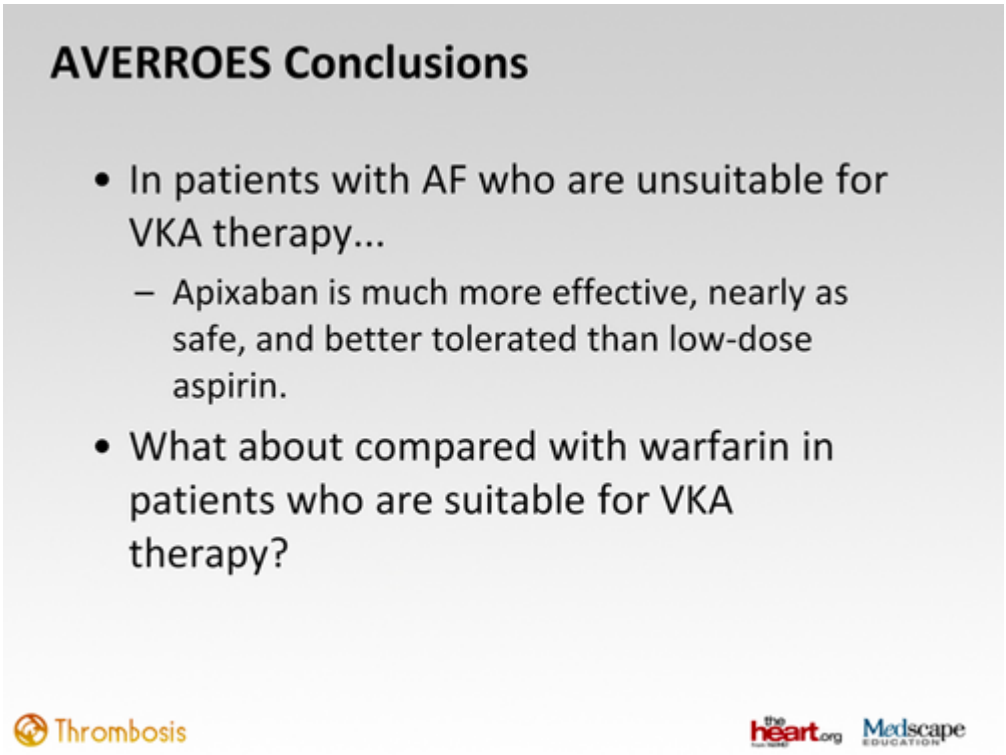
Slide 11.

Dr. Alexander: This has some more details about the bleeding. There was a lower rate, although not statistically significant, of intracranial bleeding. There is a numerically higher rate of major bleeding and clinically relevant nonmajor bleeding. If you look at minor bleeding or total bleeding, there is an increase in bleeding with apixaban with an HR of 1.27. Importantly and critically important for our patients who take these drugs long term, there is a lower discontinuation rate with apixaban than with aspirin, a drug we consider to be very well tolerated. This is in a double-blind trial with an HR of 0.88. I think it is critical in this trial as in all these trials as in our practice to remember that our patients who we start on these therapies don't stay on them long term. Over a year about 20% of patients stop aspirin and a slightly lower number in this trial stopped apixaban.



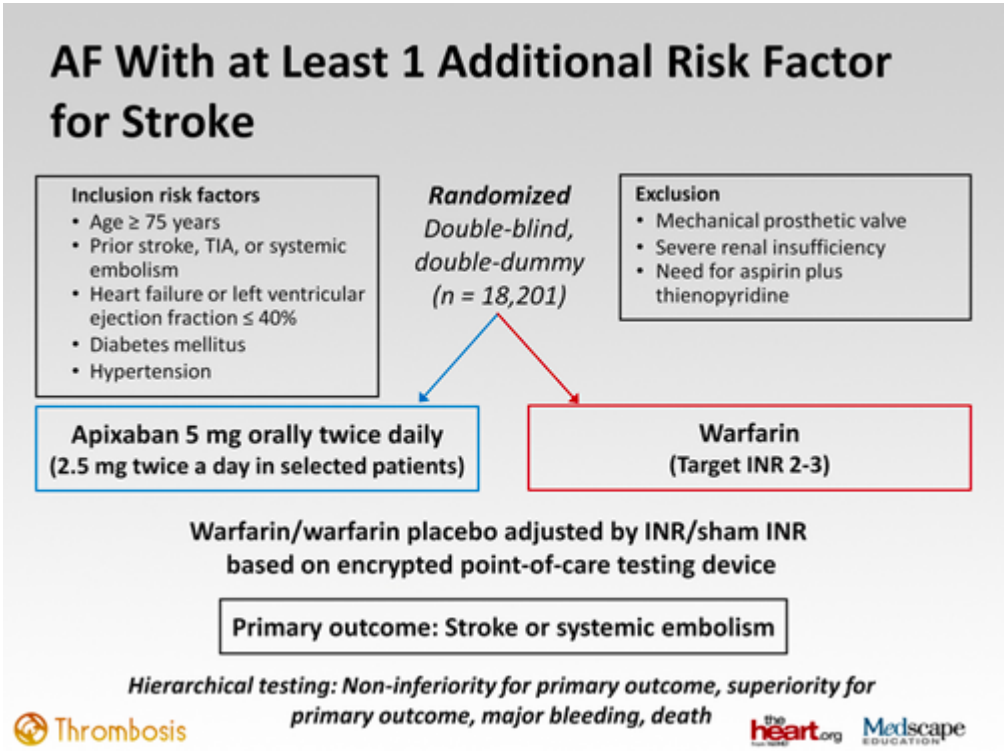
Slide 12.

Dr. Alexander: In conclusion, from AVERROES, in patients with AF who are unsuitable for VKA therapy, apixaban is much more effective, nearly as safe, and better tolerated than low-dose aspirin. I highlighted low-dose aspirin here because I think one of the key lessons from AVERROES is just how ineffective and how unsafe aspirin is, a drug that we are all very comfortable using all the time.



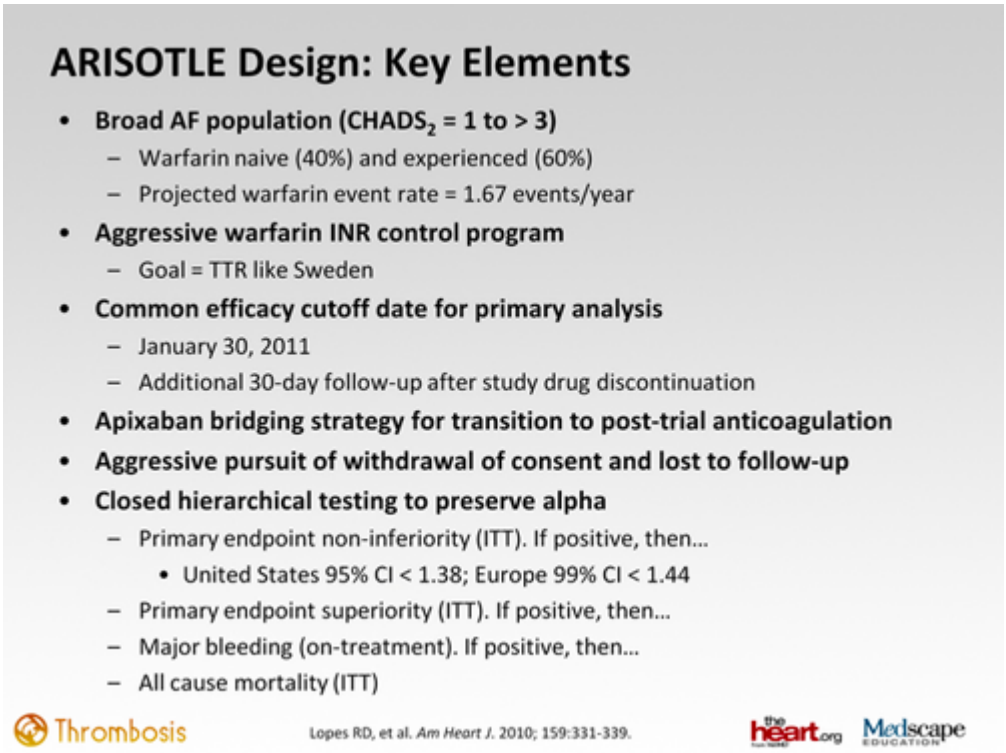
Slide 13.

Dr. Alexander: The next question is obviously what about compared with warfarin in patients who are suitable candidates for VKA therapy?



Slide 14.

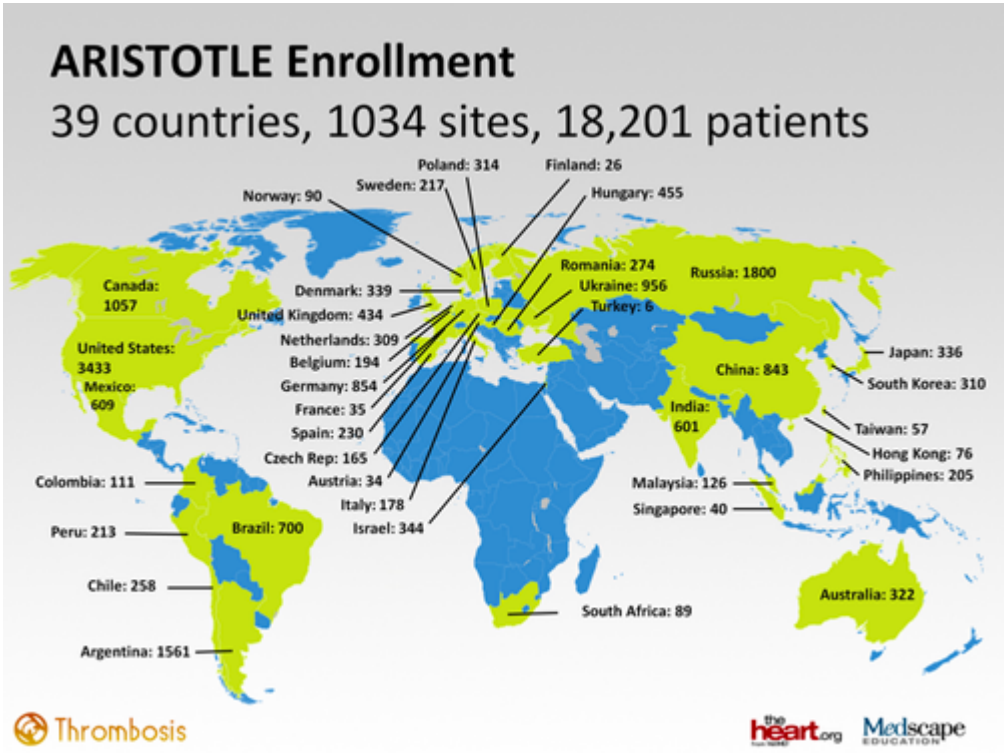
Dr. Alexander: This is a slide showing the design of the ARISTOTLE trial. ARISTOTLE [randomly assigned] 18,201 patients with at least 1 additional risk factor for stroke -- similar to RE-LY -- and [randomly assigned] people in a double-blind, double-dummy fashion to apixaban 5 mg twice daily. A lower dose was used in a small subset of patients who were projected to have higher exposure to apixaban or warfarin with a target INR (international normalized ratio) between 2 and 3. As in ROCKET, warfarin was monitored by encrypted a blinded point-of-care device. The primary outcome is stroke or systemic embolism. There is a hierarchical testing; the first test is the primary outcome for non-inferiority, then for superiority, then major bleeding, and then all-cause mortality.



Slide 15.

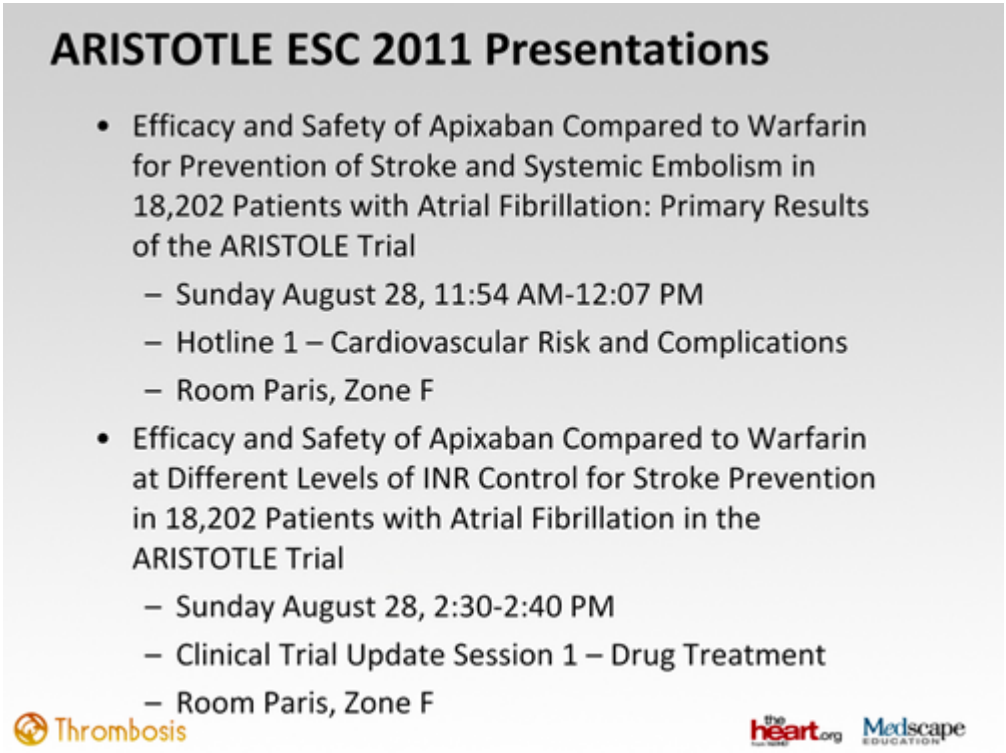
Dr. Alexander: Here are some key elements of the design that I want to highlight. ARISTOTLE is enrolling a broad AF population, approximately 40% of which is warfarin naive and 60% of which is warfarin experienced. We projected a baseline event rate of 1.6 per year on warfarin. We have an aggressive warfarin INR control program in the trial where we fed back to countries and sites after they had enough data, their INR control, and our goal was to get all countries in the trial to be like Sweden. We had a common efficacy cutoff date for the primary analysis where we counted all events up to January 30, 2011. We followed all patients for an additional 30 days after study drug discontinuation.

We had an apixaban bridging strategy for transition to post-trial anticoagulation. We had aggressive pursuit of withdrawal of consent and lost to follow-up, a growing problem I think in our large outcome trials. Then as I already mentioned, we had closed hierarchical testing, first with a primary outcome on non-inferiority, then on superiority, then on major bleeding, and then for all-cause mortality.



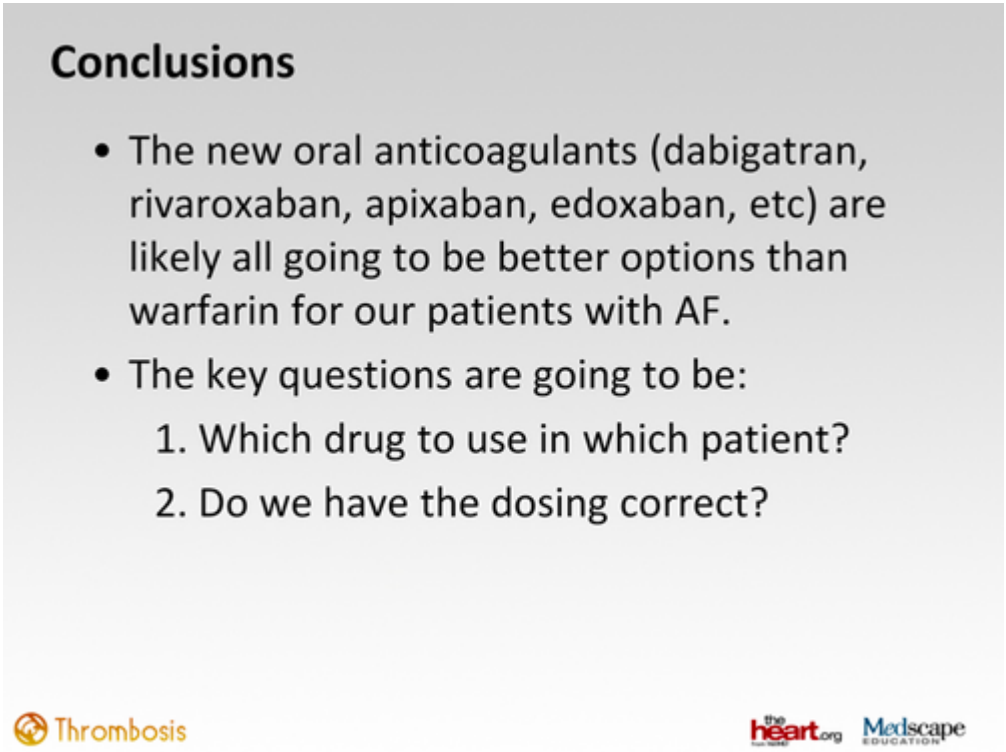
Slide 16.

Dr. Alexander: ARISTOTLE enrollment was global with 18, 201 patients enrolled in 39 countries at just over 1000 sites.



Slide 17.

Dr. Alexander: As I already mentioned, the main results of ARISTOTLE will be presented tomorrow late morning by my colleague Christopher Granger, and then tomorrow afternoon Dr. Wallentin will be presenting our analysis by center, time, and therapeutic range.



Slide 18.

Dr. Alexander: These new anticoagulants, dabigatran and rivaroxaban, apixaban, and as we will hear from Dr. Giugliano, edoxaban are likely all going to be better options for patients than warfarin. The key questions are

going to be which drugs to use in which patients and do we have the dosing correct. I look forward to the panel discussion, where hopefully w will get into some of these issues. Thank you very much.

Supported by independent educational grants from Bayer Healthcare, Daiichi Sankyo, and Boehringer Ingelheim.

This article is part of a CME certified activity. The complete activity is available at: http://www.medscape.org/viewprogram/32165

Contents of *A New Era in the Management of Atrial Fibrillation: An Update on Oral Anticoagulation* [http://www.medscape.org/viewprogram/32165]

All sections of this activity are required for credit.

1. Introduction and Overview of AF-Related Strokes [http://www.medscape.org/viewarticle/750177]
2. Development of Oral Direct Thrombin Inhibitors: Lessons From RE-LY [http://www.medscape.org/viewarticle/750178]
3. Development of Oral Factor Xa Inhibitors - Part I: Lessons From ROCKET AF [http://www.medscape.org/viewarticle/750180]
4. Development of Oral Factor Xa Inhibitors - Part II: Lessons From AVERROES and the Design for ARISTOTLE [http://www.medscape.org/viewarticle/750181]
5. Development of Oral Factor Xa Inhibitors - Part III: Design and Rationale for ENGAGE AF-TIMI 48 [http://www.medscape.org/viewarticle/750183]
6. Development of Oral Factor Xa Inhibitors - Part IV: Assessing the Next Wave of Agents [http://www.medscape.org/viewarticle/750184]
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Development of Oral Factor Xa Inhibitors - Part III: Design and Rationale for ENGAGE AF-TIMI 48 CME

Robert P. Giugliano, MD

Posted: 09/27/2011

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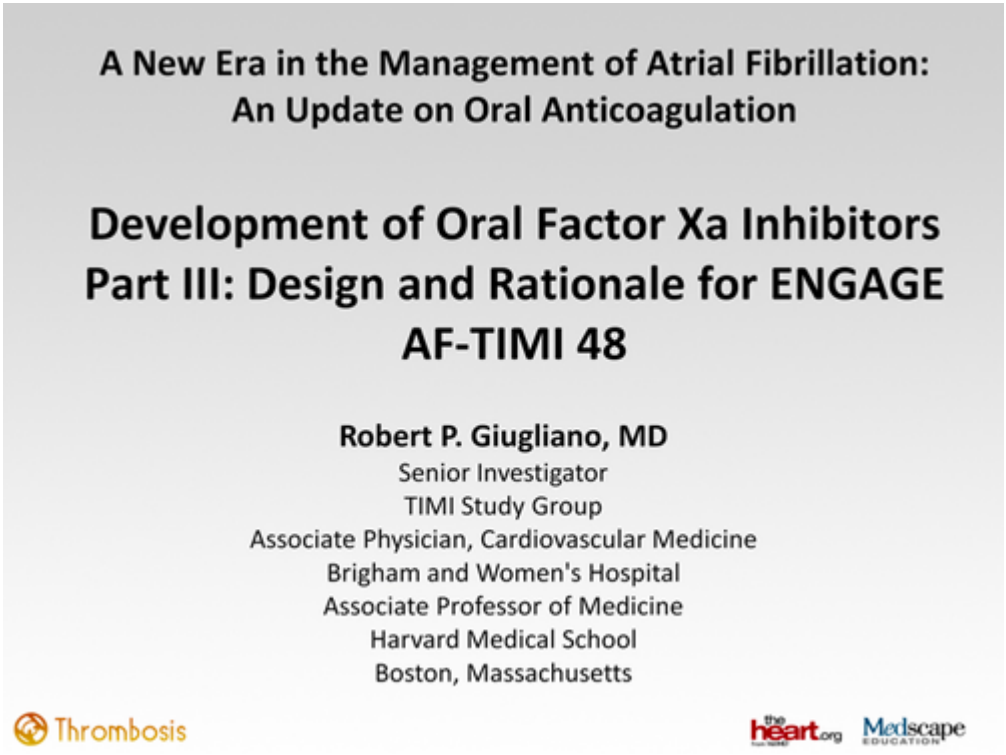


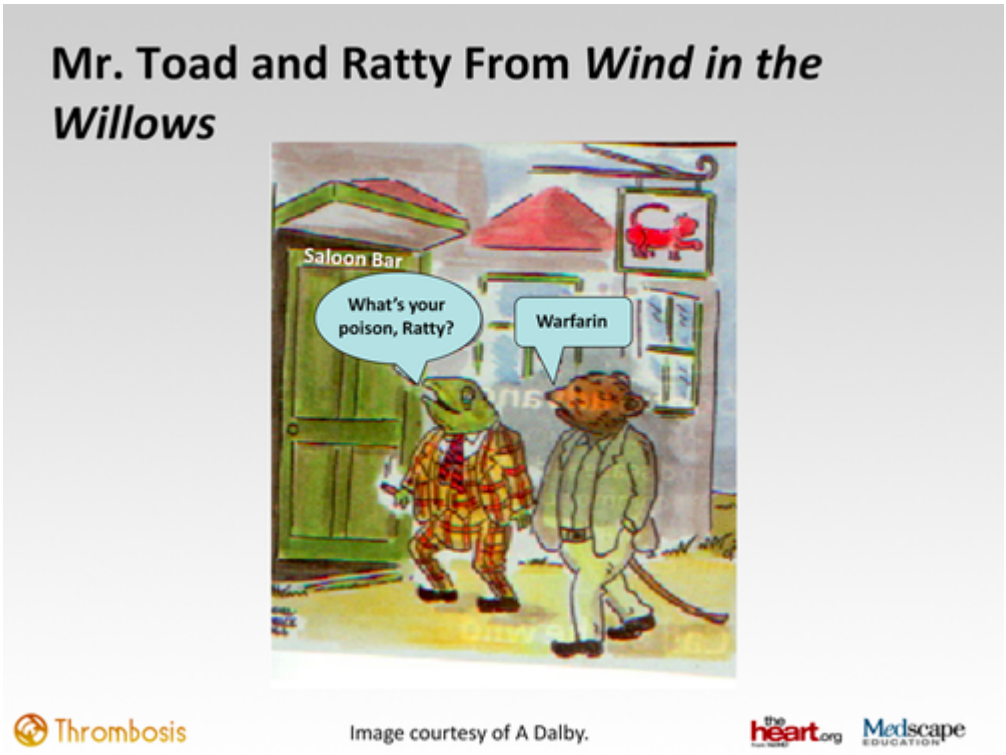
Slide 1.

Lars Wallentin, MD, PhD: We will continue to hear about the next exciting ongoing trial in this area, presented by Dr. Robert Giugliano from the TIMI group. This is the design and rationale for the ENGAGE AF-TIMI 48 trial.

Slide 2.

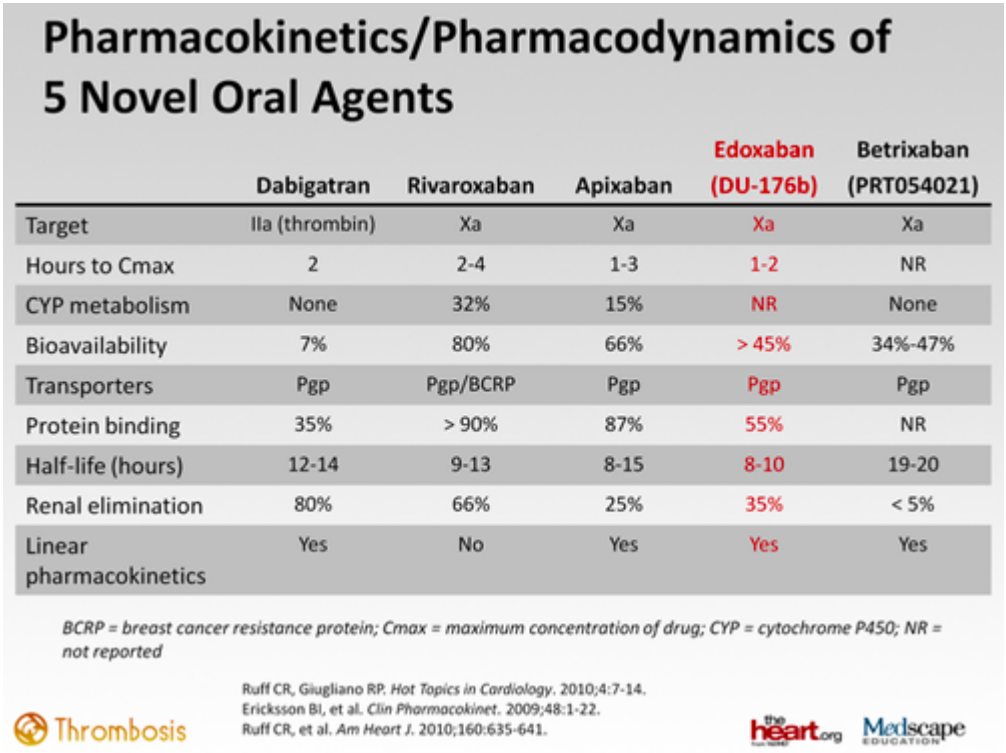
Robert P. Guigliano, MD: Thank you, Dr. Wallentin and Dr. Braunwald. I am going to tell you about a

Boston-based trial and drug, edoxaban, which is the third of the factor Xa inhibitors to be studied in a large trial of atrial fibrillation (AF) and the fourth anticoagulant. Here are my relevant disclosures and notably I am a co-principle investigator in the ENGAGE AF-TIMI 48 trial with edoxaban.



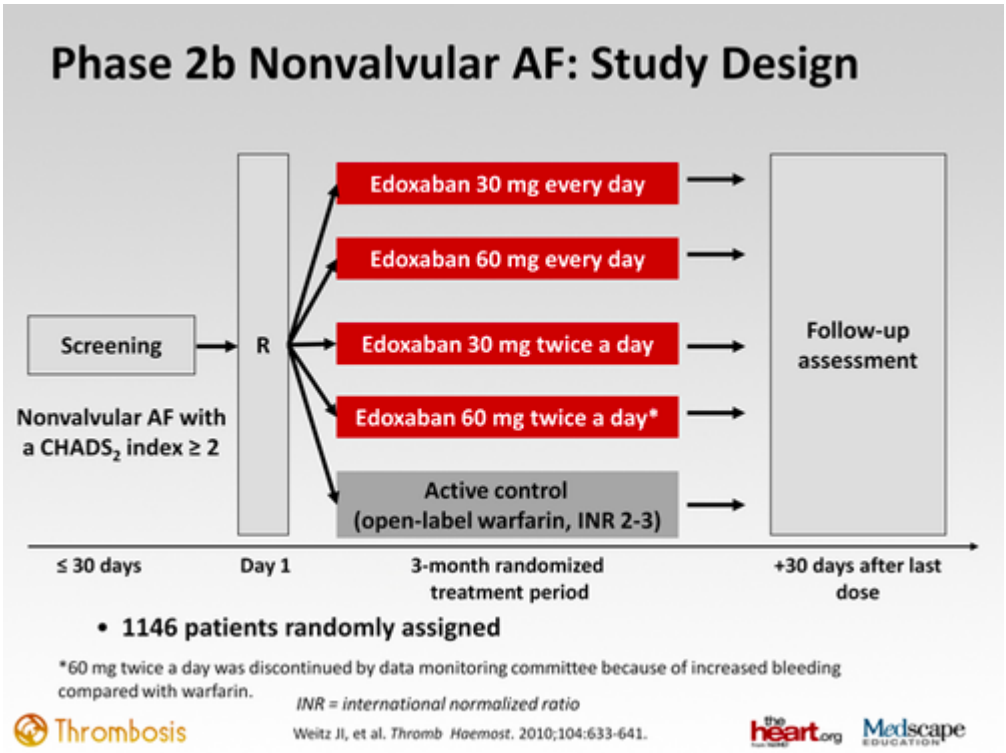
Slide 3.

Dr. Guigliano: I guess when you are third or fourth you want to make it interesting. You heard from Dr. Braunwald about some of the limitations of warfarin, and I am going to explain them with a cartoon from Mr. Toad and Ratty from *Wind in the Willows*, a publication 100 years or so ago from England. Mr. Toad and Mr. Rat are walking down the alleyway and they see a saloon. Mr. Toad says, "What's your poison, Ratty?" Mr. Rat says, "Well, warfarin of course." We all know that warfarin has many challenges, although it is quite effective and we are eager to find better alternatives.



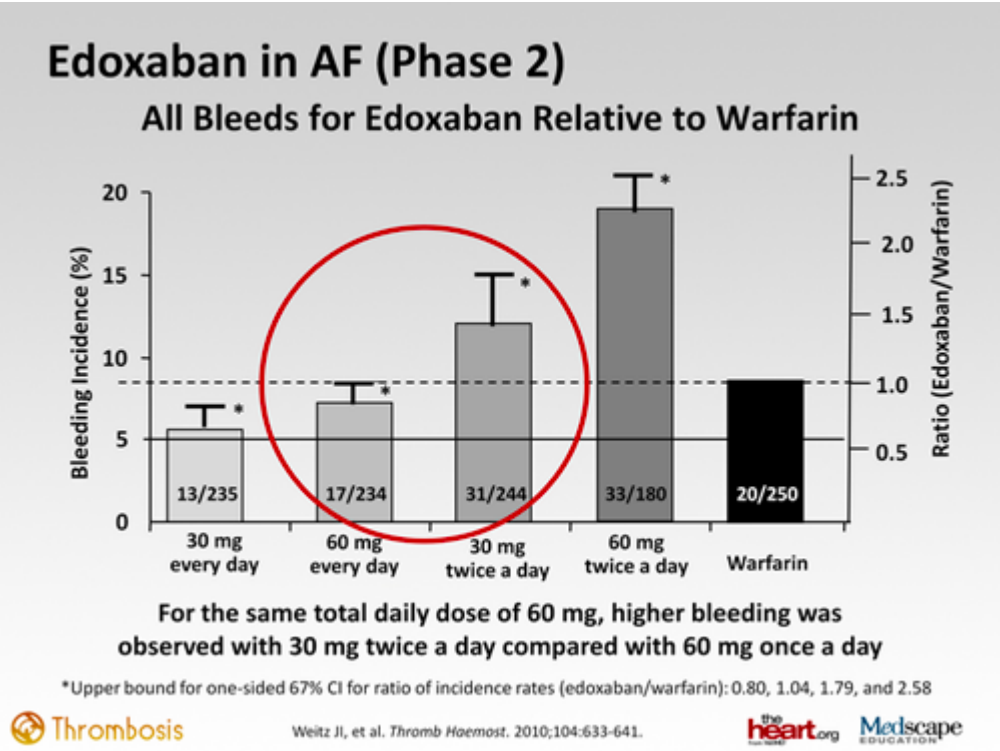
Slide 4.

Dr. Guigliano: Here are 5 of the novel oral anticoagulants lined up. I want you to focus on the column in yellow there, edoxaban. You can see it is a [factor] Xa inhibitor. It has a very short onset of action, 1-2 hours to reach its maximum concentration. It has minimal metabolism via the cytochrome P450 system -- < 4% in the latest data. Bioavailability is estimated at > 45%. So, [bioavailability] is intermediate between that of dabigatran and the other 2 [factor] Xa inhibitors you heard about earlier. The major transport system is via the Pgp(P-glycoprotein)pathway. It is about 55% protein bound with a half-life that is on the shorter end of these 5 drugs, 8-10 hours. It is cleared renally. Approximately one third of the drug is cleared renally and two thirds [are cleared] extrarenally. It has linear pharmacokinetics.



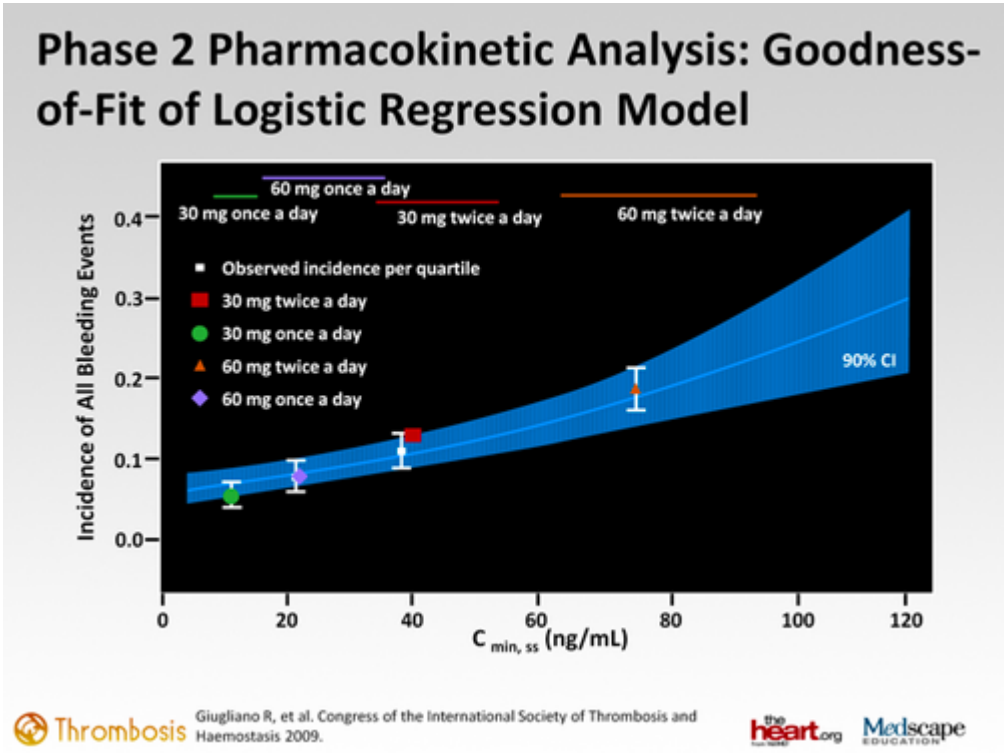
Slide 5.

Dr. Guigliano: Edoxaban was studied in a large phase 2b trial of patients with nonvalvular AF that enrolled 1146 patients. This was published by Jeff Weitz last year in *Thrombosis and Haemostasis*. Four different doses of edoxaban were studied at 4 different dosing strategies: 30 mg once daily, 60 mg once daily, 30 mg twice daily, and 60 mg twice daily. You will notice that that highest dose was discontinued early by the data monitoring committee [because of] increased bleeding compared with warfarin. This study was an active controlled study, although open label between edoxaban and warfarin. The dose of edoxaban was blinded, however. Patients were treated for 3 months and there was a follow-up period of 30 days afterward.



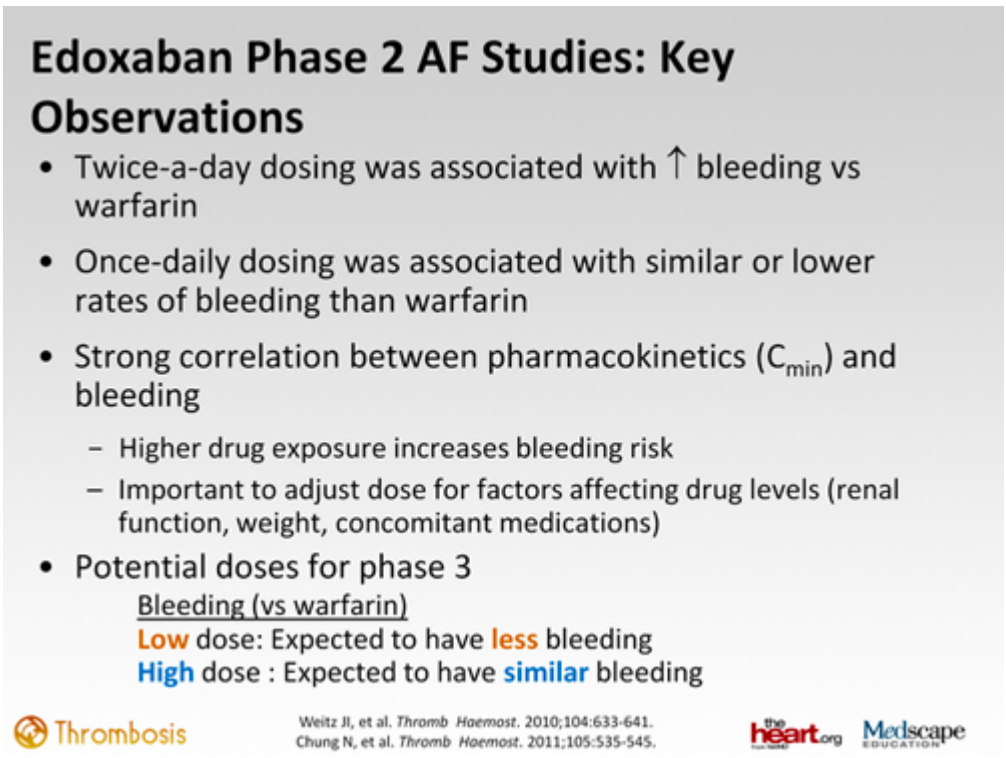
Slide 6.

Dr. Guigliano: It being a phase 2b trial, the focus was on safety, and you can see here the rate of all bleeding for the 4 different dosing regimens of edoxaban compared with warfarin. Starting at the left, the 30-mg once-daily [dose] achieved a lower rate of bleeding compared with warfarin. The 2 doses in the middle are rather interesting. Both represent total doses of 60 mg throughout a single day, but the second column is 60 mg once daily and the third is 30 mg twice daily. You will see that the 30 mg twice daily dose actually [resulted in] a higher bleeding rate. The fourth column there in the red is the 60-mg twice-daily [dose], with a much higher rate of bleeding compared with warfarin. That was discontinued early by the data safety monitoring committee. Just to highlight that, it appeared safer to administer a dose of 60 mg once a day rather than breaking that out into 30 mg twice daily.



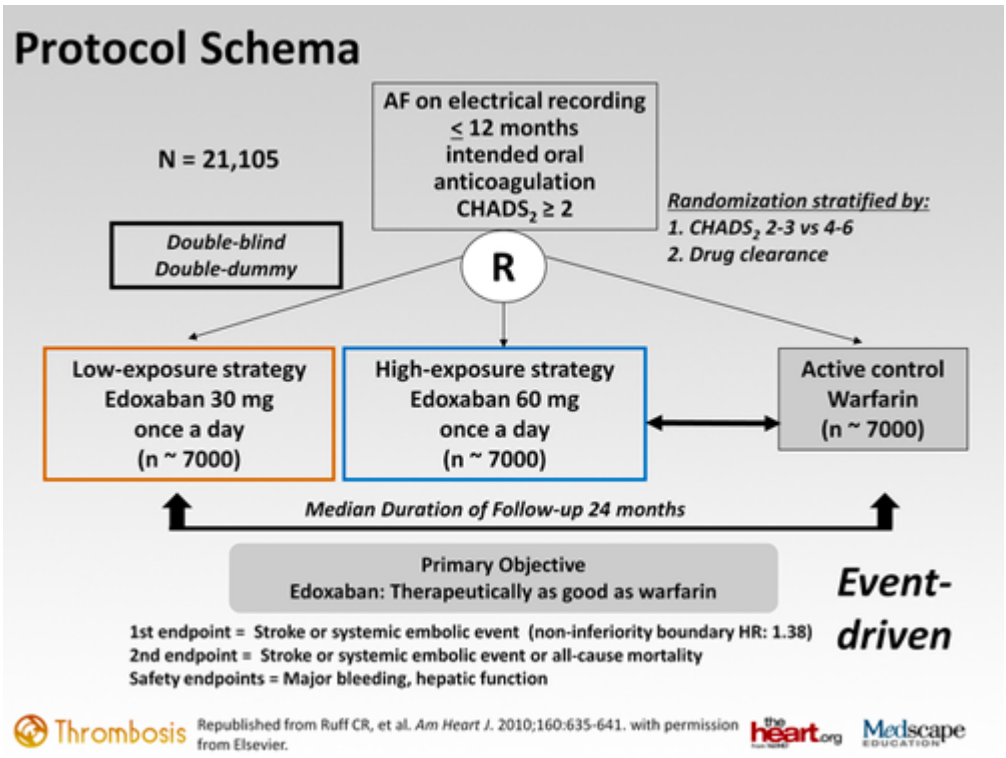
Slide 7.

Dr. Guigliano: Extensive pharmacokinetic analyses were performed with the data from phase 2. On this slide you see plotted the relationship for the data with edoxaban. The y axis is the probability of bleeding events and on the x axis is the minimum concentration at steady state ($C_{min,ss}$). In the white are the observed bleeding rates for the 4 dosing regimens studied in the trial. The colored symbols are the actual observed rates. You can see that the minimum concentration of the drug closely predicted the observed incidence per quartile.



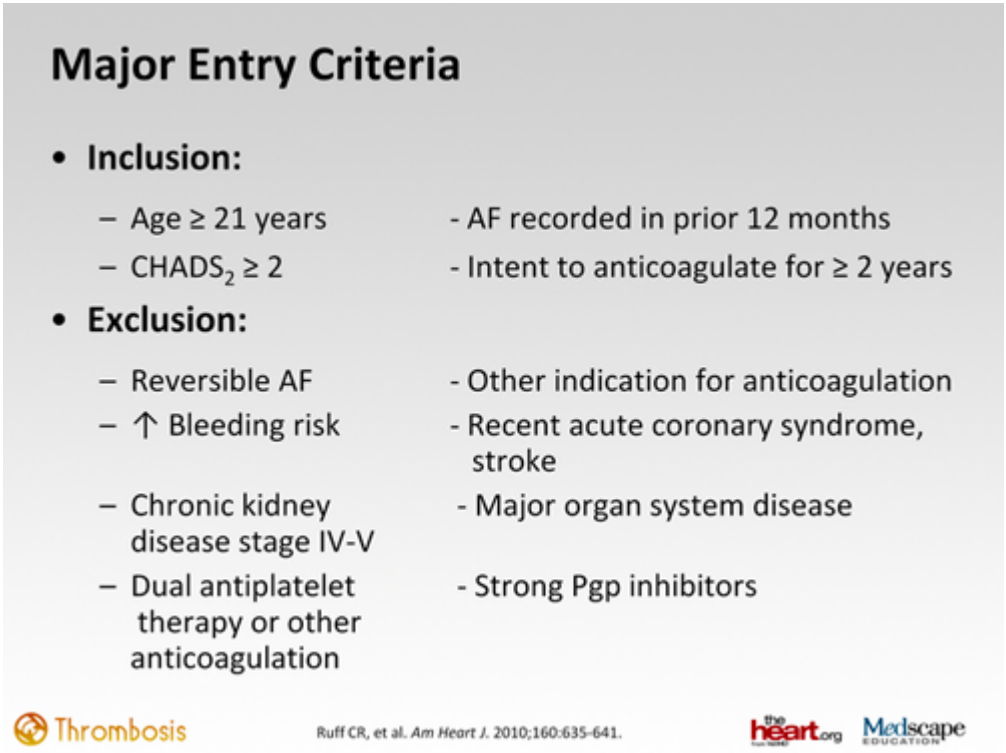
Slide 8.

Dr. Guigliano: The key observations then from phase 2 with edoxaban are as follows. The twice-daily dosing was associated with increased bleeding compared with warfarin and once-daily dosing was associated with a similar or lower bleeding rate compared with warfarin. I draw your attention back to that the [incidence of bleeding was less with the] 60-mg once-daily [dose] than [with] the 30-mg twice-daily [dose]. There was a strong correlation between the minimum concentration of edoxaban and the bleeding rate that was observed. Higher drug exposure of course increases the bleeding risk and it was found through the pharmacokinetic analyses that it would be important to adjust for factors that affect the concentration of the drug, such as renal function, weight, and interaction with certain concomitant medications that affect the Pgp pathway. Therefore, 2 doses were carried forward or 2 dosing strategies were carried forward for phase 3 testing: a low-dose strategy where it was hoped that we would observe a lower rate of bleeding compared with warfarin and then a high-dose strategy, which was expected to have a similar bleeding rate to warfarin.



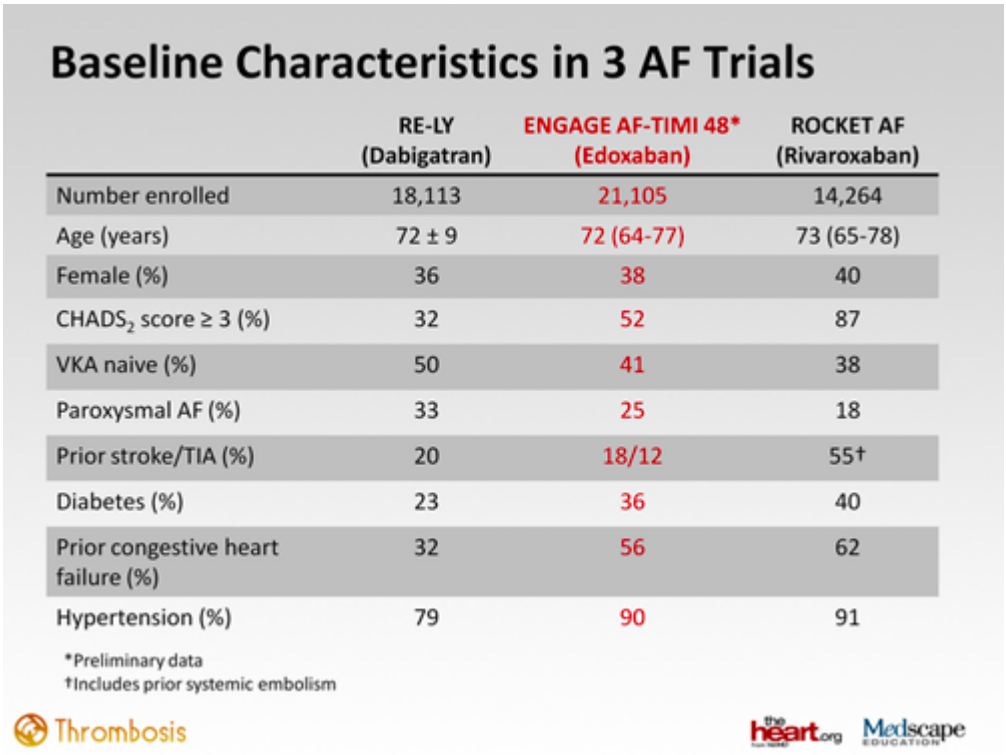
Slide 9.

Dr. Guigliano: This slide summarizes the schema for the phase 3 ENGAGE AF-TIMI 48 trial. That methods paper was published last year in the *American Heart Journal*. This trial [randomly assigned] 21,105 subjects and ended randomization in November of 2010. All the subjects had AF within the past 12 months recorded electrically. Patients had to be candidates with the intention to use anticoagulation during the trial and [had to be] moderate to high risk based on a $CHADS_2$ score of 2 or higher. This is a double-blind, double-dummy study. There were 3 treatment arms, a low-dose exposure strategy of edoxaban, a high-exposure strategy, and an inactive control with warfarin. Each of the 3 arms [randomly assigned] approximately 7000 patients. The median duration of follow-up is anticipated to be approximately 24 months. Again, like the other trials you saw, the primary objective is to show that edoxaban is as good as warfarin. In other words, a non-inferiority analysis is the primary analysis. The primary endpoint is a combination of stroke or systemic embolic events. This is an event-driven trial and the non-inferiority boundary is set at a hazard ratio (HR) of 1.38. Important secondary endpoints include the composite of stroke, systemic embolic event, or all-cause mortality and major safety endpoints such as major bleeding and hepatic function.



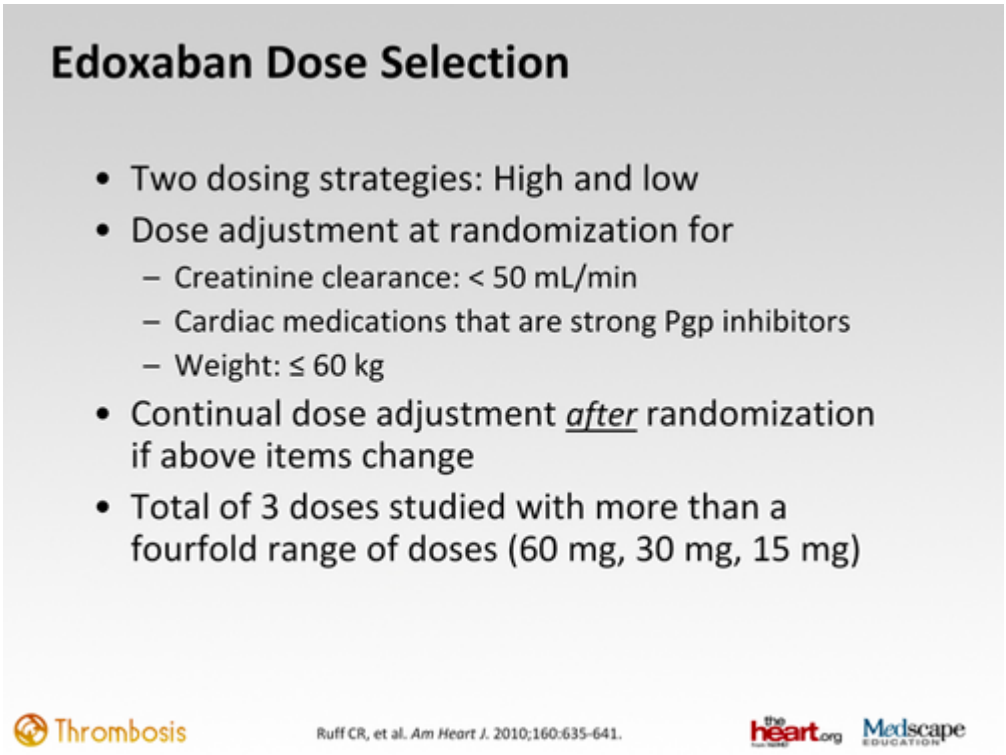
Slide 10.

Dr. Guigliano: The entry criteria are fairly standard, including age over 21, CHADS risk score of 2 or higher, AF recorded in the prior 12 months, and the intent to use anticoagulation for the duration of the trial. The major exclusion criteria shown here include reversible causes of AF, increased risk for bleeding, advanced kidney disease, the need for dual antiplatelet therapy or the need for other anticoagulants, indications for anticoagulation other than AF, recent acute coronary syndrome or stroke, major organ system disease, and a use of strong Pgp inhibitors were also excluded.



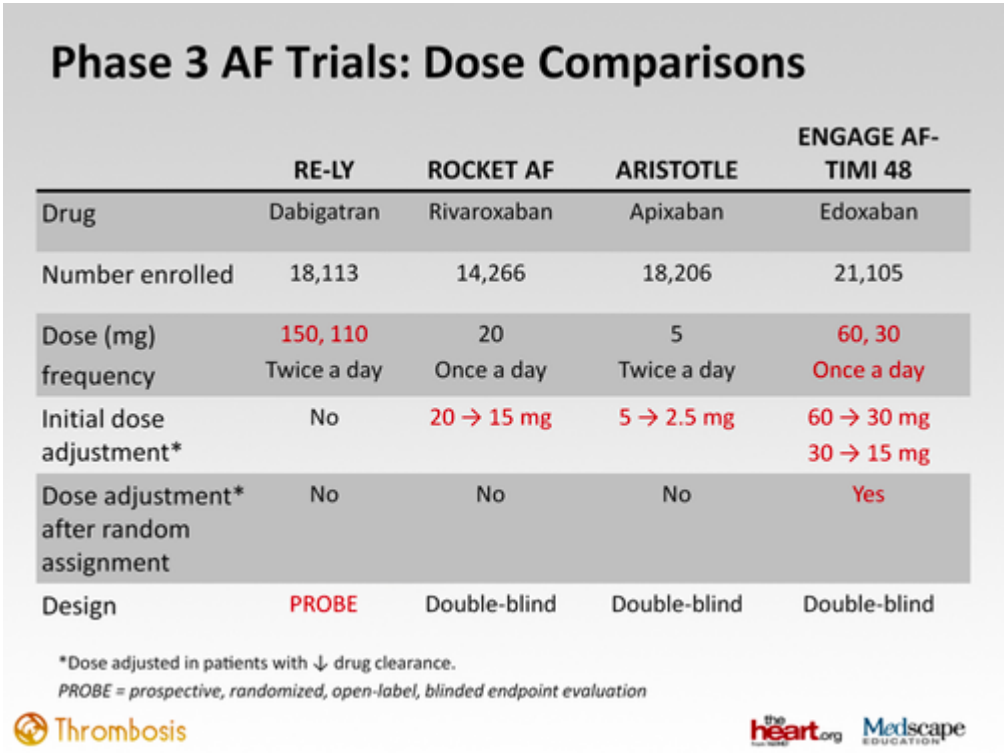
Slide 11.

Dr. Guigliano: Here are the baseline characteristics for 3 of the AF trials. These data are updated from the manuscript that was published, the methods manuscript that was published last year. You will see I put edoxaban in the middle between RE-LY and ROCKET because on most of these baseline characteristics, it stands in the middle. The age on average was 72; 38% were women. Just over half of the patients had a CHADS risk score of 3 or above, placing it right in between RE-LY, which was generally a lower-risk population and ROCKET AF, which had a higher-risk population. Forty-one percent of patients in ENGAGE AF-TIMI 48 were naive to VKAs. A quarter had paroxysmal AF. Just under a third had either stroke or transient ischemic attack (TIA), and 36% had diabetes. A little more than half had heart failure, and 90% had hypertension. Again, almost all of these baseline characteristics place ENGAGE squarely between RE-LY and ROCKET.



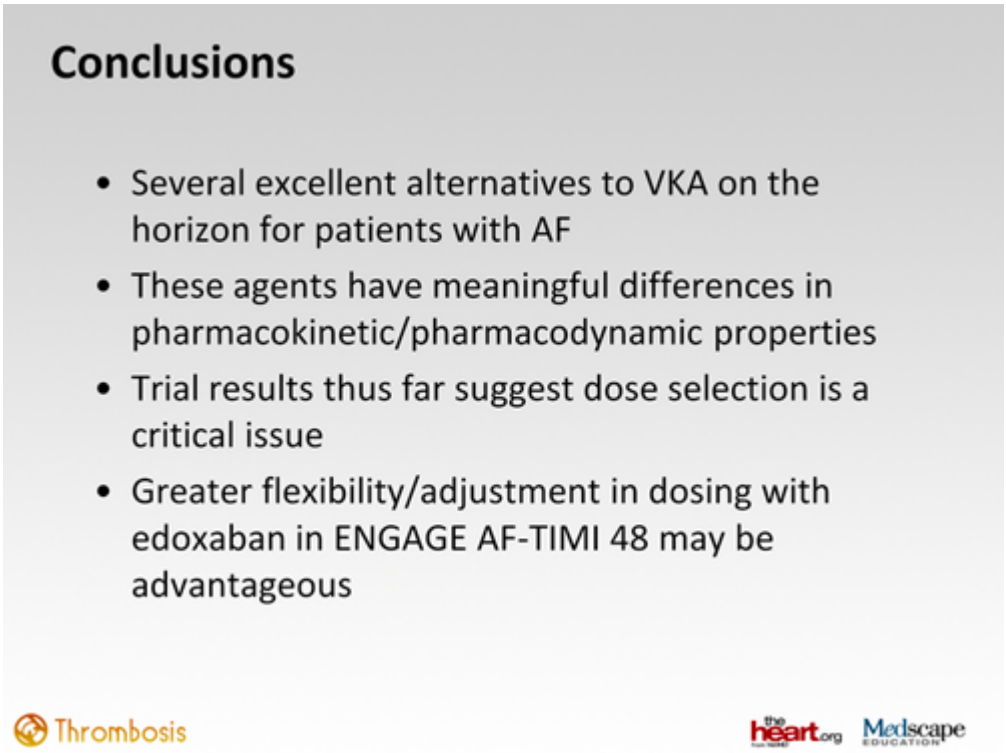
Slide 12.

Dr. Guigliano: Importantly, when you are third or fourth depending on how you count these drugs, you have an opportunity to focus on what lessons [have been] learned from the prior studies. We felt that it was important to have 2 dosing strategies, a high and a low, because in studies of anticoagulation, dosing is a critical feature. We also had dose adjustment, both at randomization and after randomization. At the time of randomization there was the ability to reduce the dose by 50% for those patients who had impaired creatinine clearance of < 50 mL/minute, who were on cardiac medications like verapamil and quinidine that are known strong Pgp inhibitors and are known to reduce the clearance of edoxaban, and for those of low body weight of ≤ 60 kg. Different and unique from any of the other studies, I believe we had continual dose adjustment even after randomization should any of the above characteristics change.



Slide 13.

Dr. Guigliano: We actually are studying 3 different doses in this trial. Although the randomization is between 60 mg and 30 mg, either dose could be reduced in half if one of these dose adjustment features were satisfied. So, there is a fourfold range of doses being evaluated in ENGAGE AF-TIMI 48: 60, 30, and 15 mg. If we compare our approach in ENGAGE AF to the prior study, you can see ENGAGE AF is the largest study, with [more than] 21,000 patients. It is evaluating 2 dosing strategies, a 60-mg and a 30-mg strategy with the ability to reduce the dose by 50%, yielding now 3 different doses over a fourfold range. This is unique for our trial, ENGAGE AF-TIMI 48, and it is the only study that permits dose adjustment after randomization. Like the other 2 [factor] Xa inhibitor trials, it is a double-blind, double-dummy study.



Slide 14.

Dr. Giugliano: In conclusion, I believe -- and as the other panelists have stated -- that there are now several excellent alternatives to VKAs on the horizon and one has already arrived in dabigatran. There are important and meaningful differences in pharmacokinetic and pharmacodynamic properties among the various new agents. The trial results thus far suggest that dose selection is a critical issue in establishing the risk/benefit of these agents. We believe that the greater flexibility and the ability to dose adjust with edoxaban in ENGAGE AF-TIMI 48 may be an advantage over some of these other agents in comparison.

Supported by independent educational grants from Bayer Healthcare, Daiichi Sankyo, and Boehringer Ingelheim.

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6. Development of Oral Factor Xa Inhibitors - Part IV: Assessing the Next Wave of Agents [http://www.medscape.org/viewarticle/750184]
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Development of Oral Factor Xa Inhibitors - Part IV: Assessing the Next Wave of Agents CME

Alexander G. G. Turpie, MD

Posted: 09/27/2011

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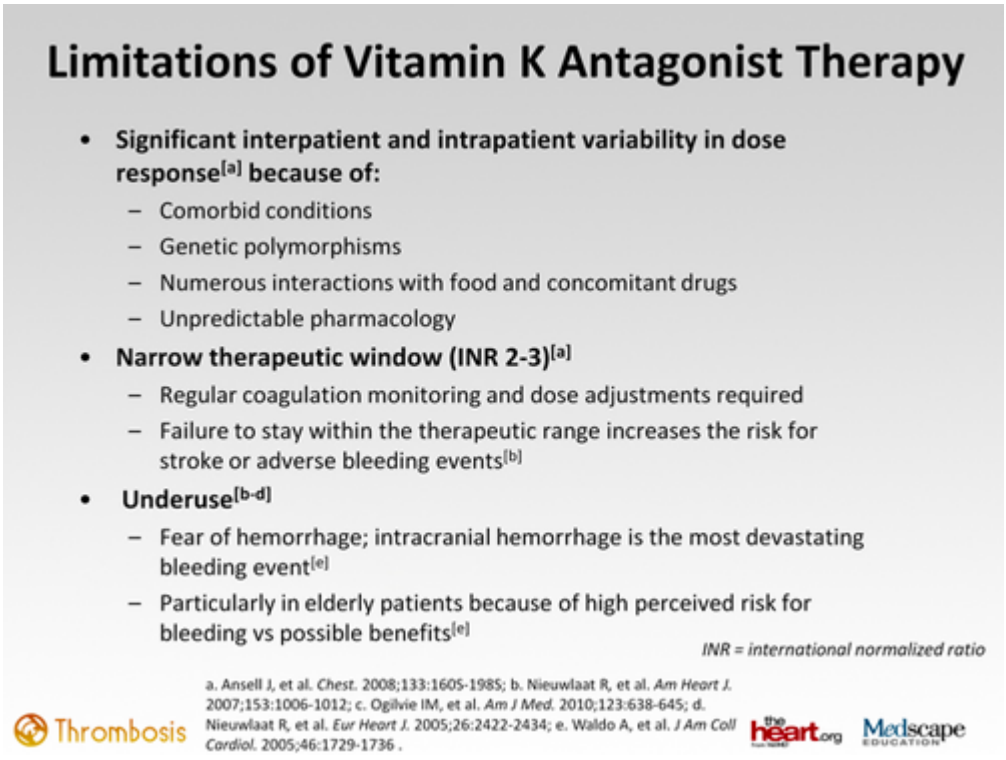
Slide 1.

Eugene Braunwald, MD: Our last speaker is Professor Alexander Graham Turpie, who is going to talk about the large next wave of agents in the development of oral factor Xa inhibitors.

Slide 2.

Alexander G. G. Turpie, MD: Thank you very much indeed, Professor Braunwald. Ladies and gentlemen, let

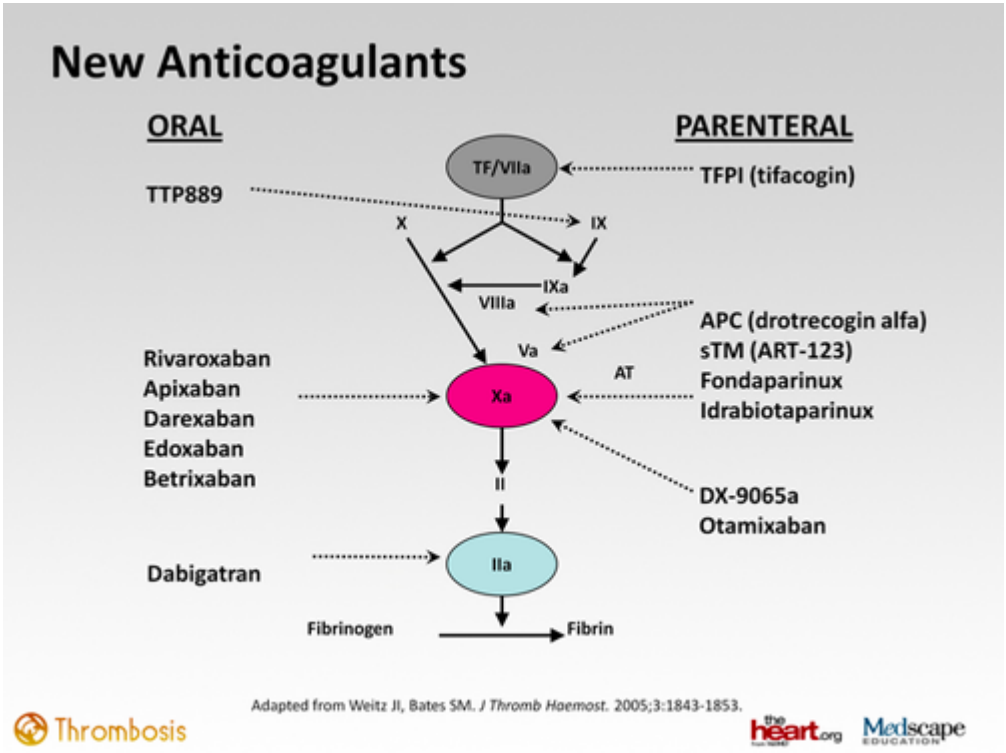
me give you my disclosures. I have watched the evolution of antithrombotic therapy from the old standbys of heparin and warfarin over the last 30 years through low-molecular-weight heparin with the introduction of targeted inhibition of single coagulation factors and now with the introduction of new orally active drugs that target single coagulation factors. We have seen very encouraging data from the already published trials and the potential of the new drugs under development to change clinical practice.



Slide 3.

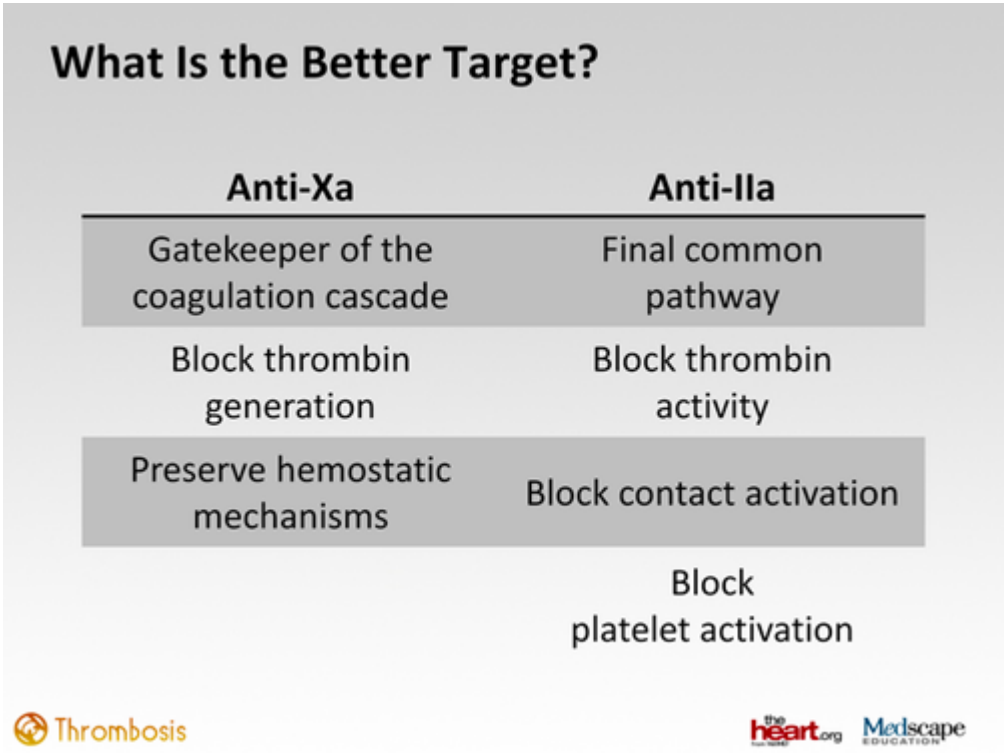
Dr. Turpie: What I would like to do is go over these data with you and find out some of the limitations and where we as clinicians will have to pay attention when using these new drugs.

As you heard from Professor Braunwald, the new orally active drugs are really being targeted at replacing warfarin for all of its major indications. As you have heard, there are limitations with warfarin shown here that the new drugs will potentially overcome.



Slide 4.

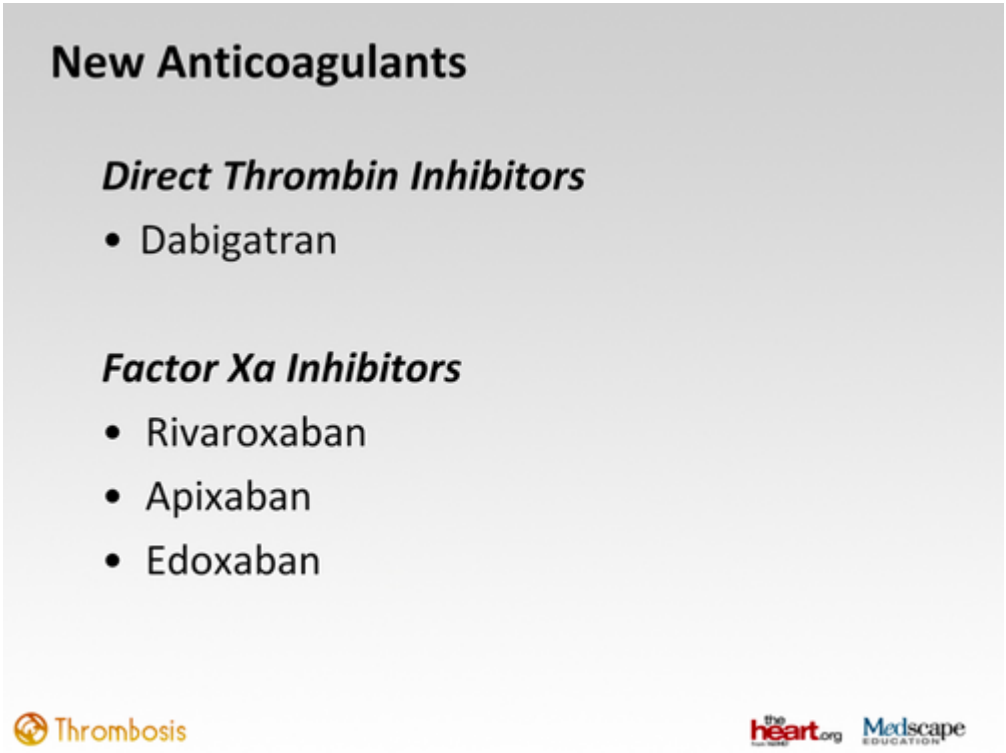
Dr. Turpie: The new anticoagulant drugs are developed largely based on our much better understanding of coagulation. It is complex but if you look at coagulation as having 3 components, you can see how these new drugs fit in. The first component is initiation, which is tissue factor, factor VII. There are drugs targeting these particular agents but largely in the setting of acute coronary syndromes, which makes sense because of course tissue factors present at high concentrations at sites of atherosclerotic plaque rupture, which is the primary cause of acute coronary syndromes. The second component of coagulation is propagation. Activated factor X is the key coagulation factor. Coagulation cannot occur through the coagulation cascade until factor X is activated. It is really not a surprise that much of the interest in developing new anticoagulant drugs is targeting activated factor X. The third component is thrombin action itself. Intuitively of course this would be the most important way of inhibiting coagulation and it is certainly very important.



Slide 5.

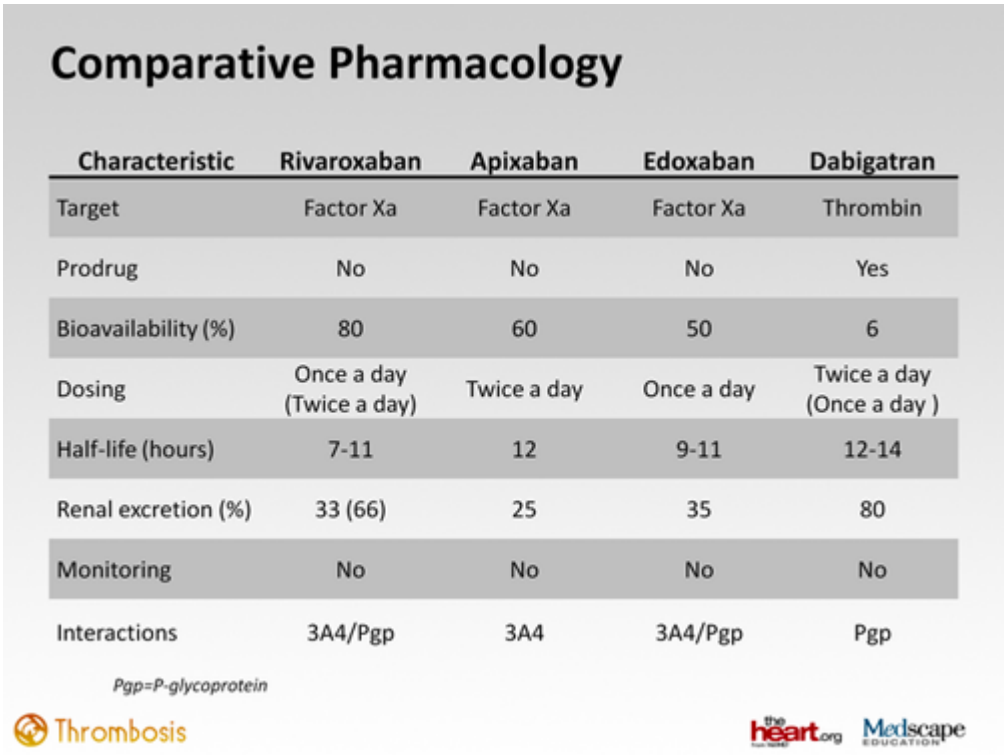
Dr. Turpie: There has been a lot of discussion. We really don't have an answer because we have not had any direct comparisons in the clinical setting, but if you look at the features of [factor] Xa inhibition for example, as I have pointed out, it is the gatekeeper of the coagulation cascade. When factor X is activated, it amplifies the generation of thrombin a thousandfold. If we inhibit factor X, we have a profound effect in inhibiting the generation of thrombin. It does this but to some extent will preserve some of the hemostatic mechanisms. So, we have this very potent anticoagulant, antithrombotic effect with the potential to preserve some hemostatic actions.

When you look at factor IIA as in thrombin inhibition, this is the final common pathway of activation of coagulation. Thrombin inhibition will completely block thrombin's action. It will block contact activation and it will have an effect in inhibiting platelet activation. There is a very potent antithrombotic effect of inhibiting thrombin. [However,] as indicated we have no direct comparison so it is not possible from a clinical point of view to say which is better.



Slide 6.

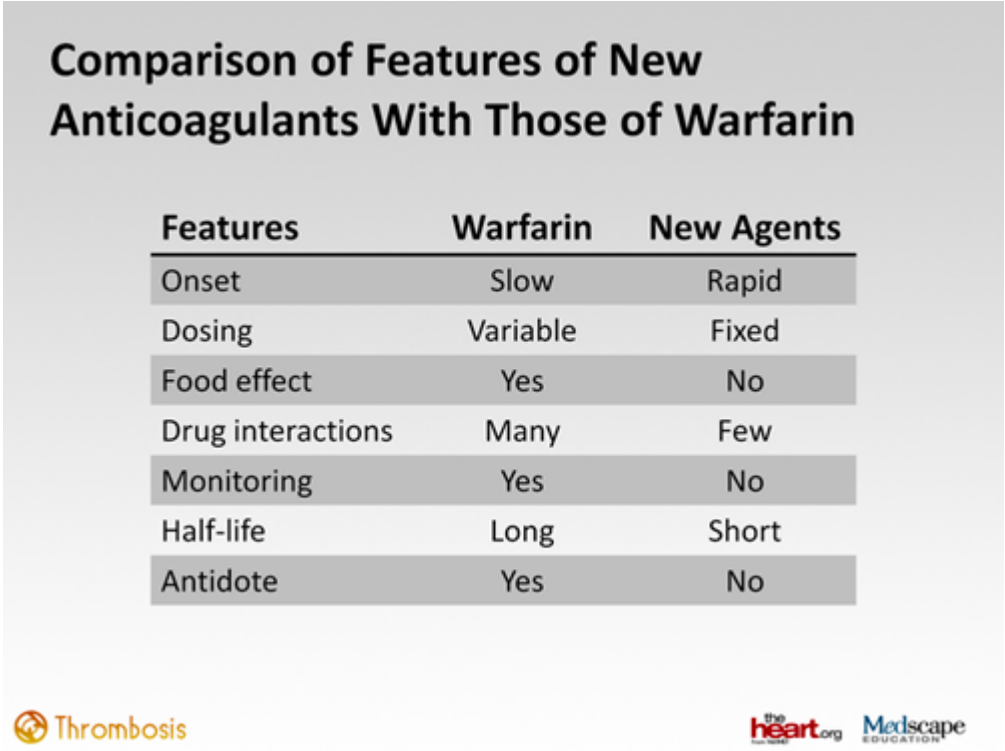
Dr. Turpie: The most advanced of these new anticoagulant drugs in development are the direct thrombin inhibitor dabigatran and the factor X inhibitors rivaroxaban, apixaban, and edoxaban. I would like to point out a number of features of these that are important clinically. As you have already heard, the bioavailability is quite different and ranges from 80% with rivaroxaban down to 6% with thrombin. As pointed out by Professor Wallentin, they were concerned about that low bioavailability, but in the clinical setting it turned out to be effective.



Slide 7.

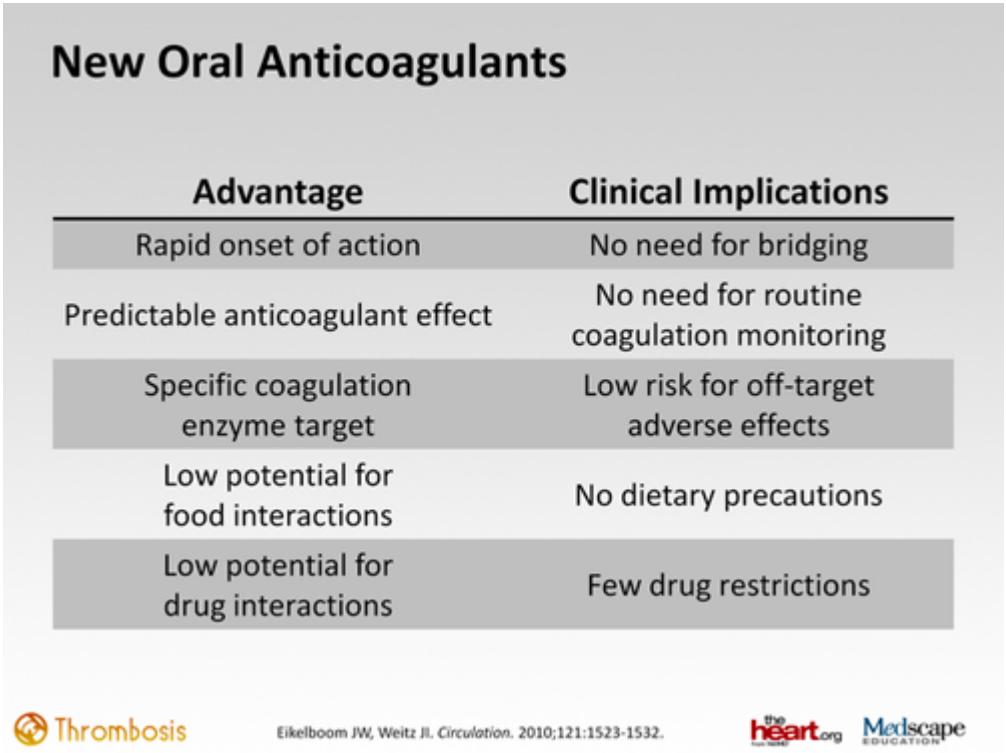
Dr. Turpie: You can see that there are different dosing regimens in terms of once or twice a day. For different indications, there are twice-daily regimens and once-daily regimens of rivaroxaban. In the setting of AF it is a once-a-day regimen. Apixaban is twice a day, edoxaban once a day, and dabigatran for AF is twice a day. As you know, when you survey clinicians and patients alike, all of them prefer the once-a-day regimen for long-term treatment.

The half-lives are very similar but it is very important to point out that of course it is much less than warfarin, which results in rapid onset and rapid offset of action. I think from the clinician's point of view the most important thing to appreciate is that they are all to some extent excreted by the kidney. We really must pay attention to renal function when using these new drugs. There is no question that there will be accumulation in patients who have renal insufficiency and that accumulation will result in the potential for increased bleeding complications. Please pay attention to the renal function of any patient to whom you administer these drugs.



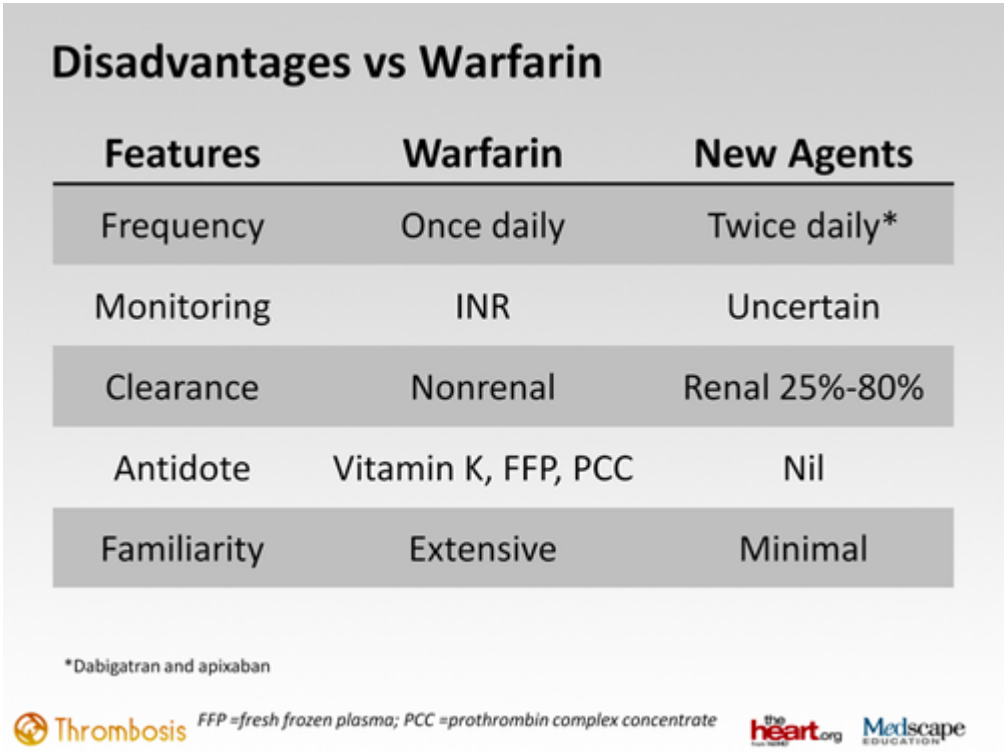
Slide 8.

Dr. Turpie: Because it really is in comparison with warfarin that we would like to use these drugs in the clinical setting, let's look at the features which are different and what the potential benefits are. The onset of warfarin is slow and often bridging therapy is necessary. It is not necessary with the new drugs because they have therapeutic levels within 2-3 hours. The dosing with warfarin is variable, requiring coagulation tests to monitor the response and adjust the dose. For the most part, the new drugs are given in a fixed dose without coagulation monitoring. A third effect with warfarin often cited as a problem, which in my view it's not too much of a problem, but with the new drugs there is no concern regarding food effects. There are many drugs interactions with warfarin. There are very few, as already pointed out, with the new drugs. From the point of view of practicality, there is no requirement for monitoring with a coagulation test because of the fixed dosing of the new drugs, and as already pointed out, rapid onset and offset of action is an advantage. One thing of concern for many clinicians is the absence of a specific antidote. We can discuss that in the panel session shortly.



Slide 9.

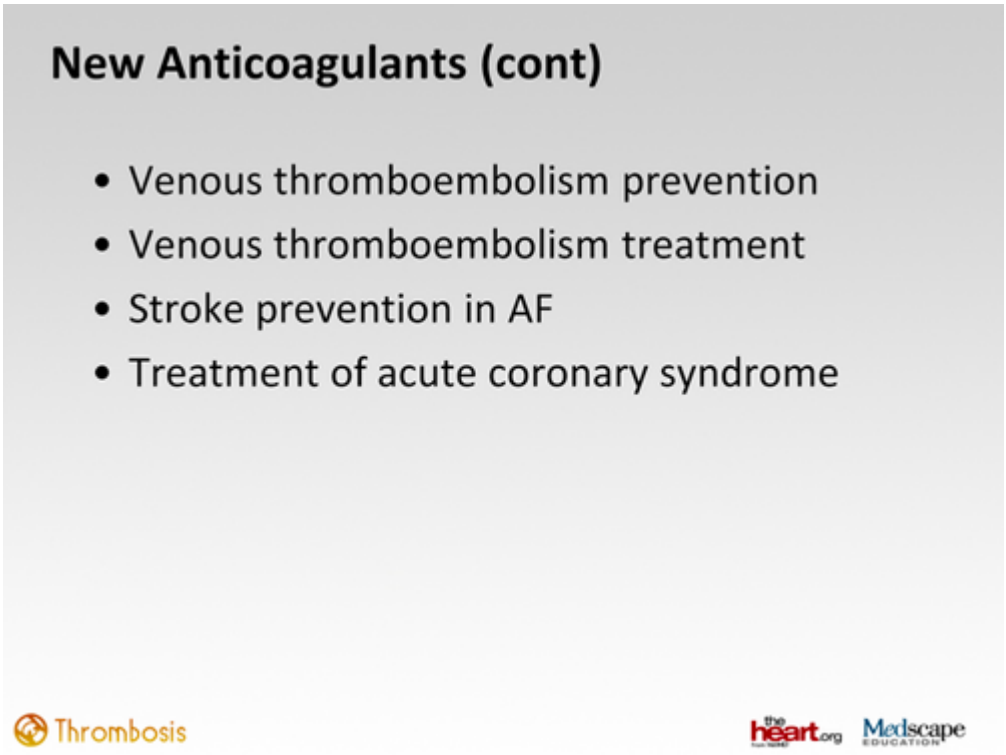
Dr. Turpie: Let's have a look at these advantages. There is no need for bridging and no need for routine coagulation monitoring. There is a low risk for off-target adverse effects because they are specifically targeting single coagulation factors. There are no dietary precautions and few drug interactions.



Slide 10.

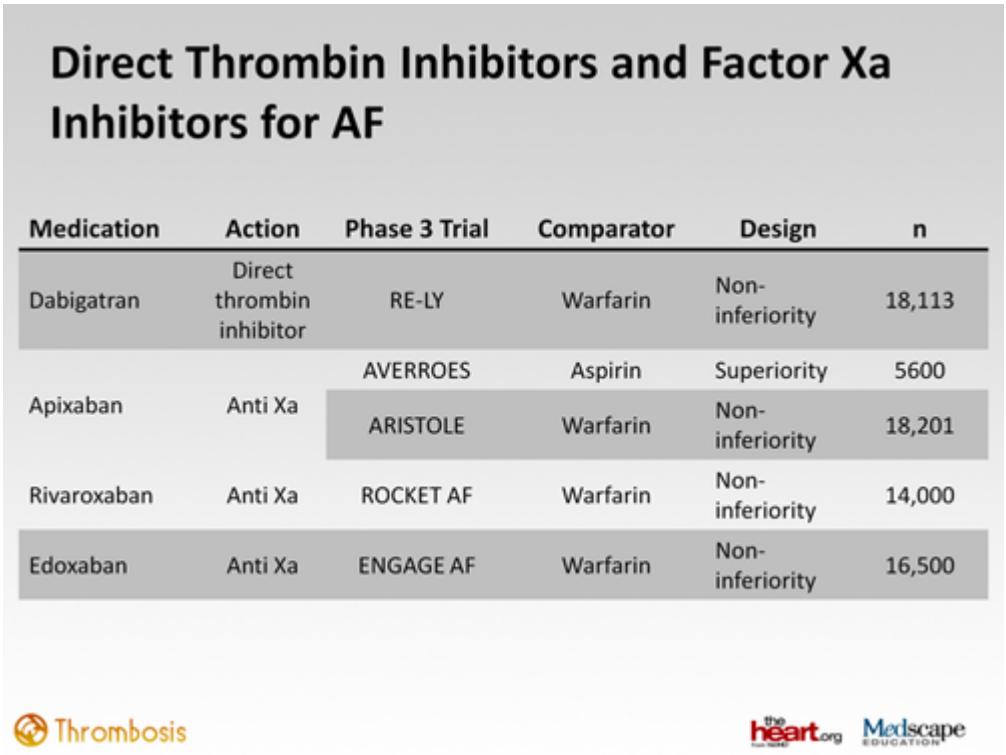
Dr. Turpie: There are potential disadvantages. For example, the monitoring, the uncertainty about the lack of monitoring will be of concern for some clinicians. I have pointed out very forcibly the concern regarding renal

function and the lack of an antidote is a concern for many patients.



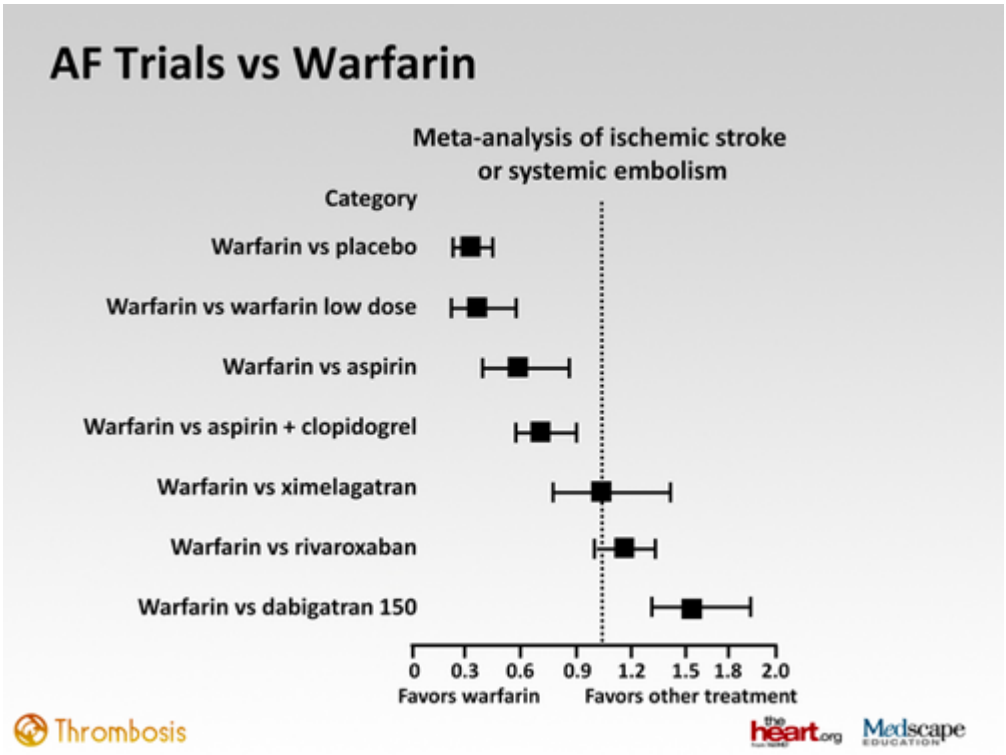
Slide 11.

Dr. Turpie: All of the new drugs are being tested across the whole spectrum of thrombosis and we have seen very important and excellent results in venous thrombosis prevention. We have seen good results in the treatment of venous thromboembolism, and as already pointed out at this symposium we have seen spectacular results in AF. There are very large numbers of patients being tested in clinical trials in AF, so we are very confident with the outcome of these trials, which can tell us from a clinical point of view what is appropriate.



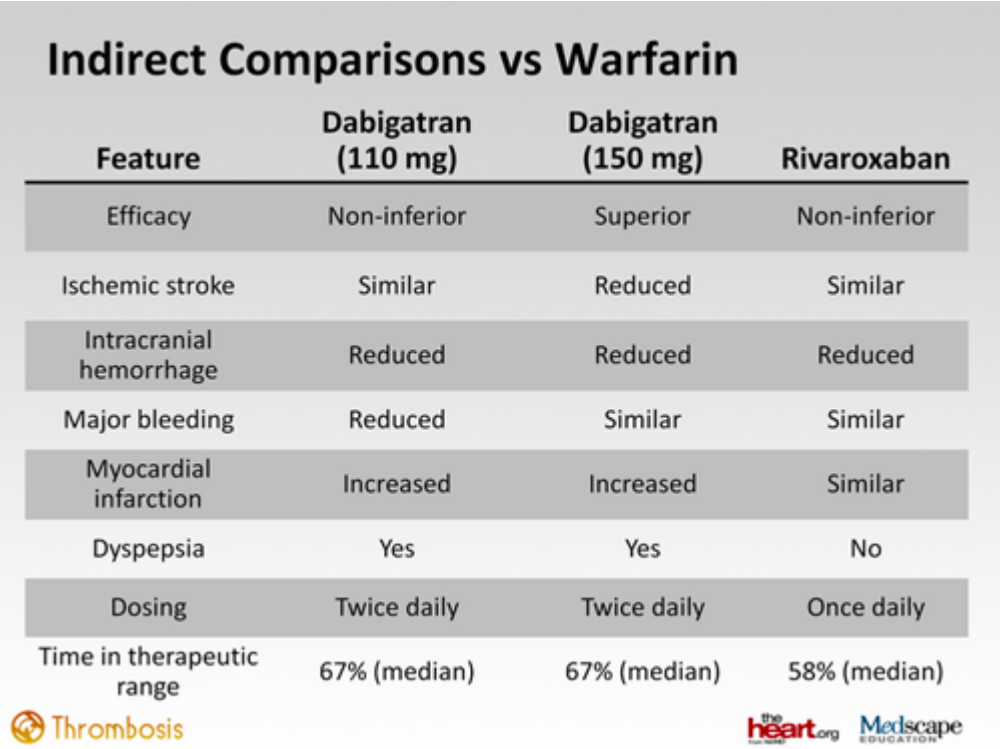
Slide 12.

Dr. Turpie: As you can see here, almost 60,000 or 70,000 people have been involved in clinical trials involving these new agents.



Slide 13.

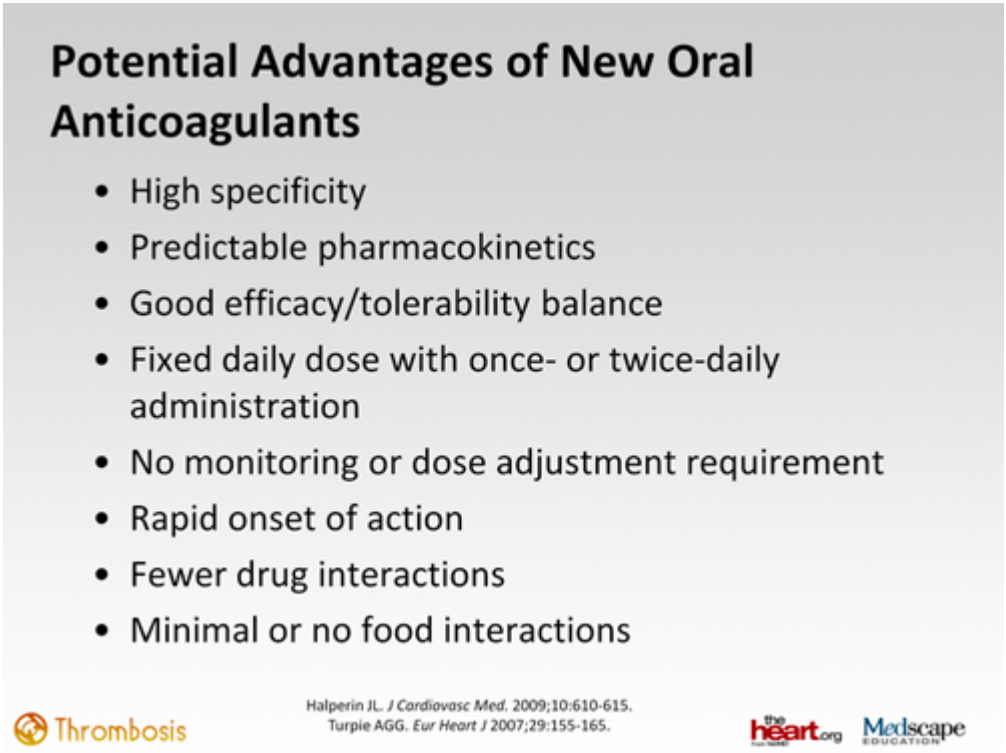
Dr. Turpie: If we look at the evolution of anticoagulant therapy in AF, you can see in comparison with warfarin we have seen this dramatic shift toward improvement in the outcome with the new anticoagulant drugs. First of all, you see warfarin is very effective. Warfarin has to be given at a therapeutic level of 2 to 3 to be effective. It is better than aspirin. It is better than aspirin and clopidogrel. The first of the new drugs regrettably discontinued because of hepatic insufficiency showed equivalence, and then we begin to see superiority with the new factor X inhibitors and the direct thrombin inhibitor dabigatran.



Slide 14.

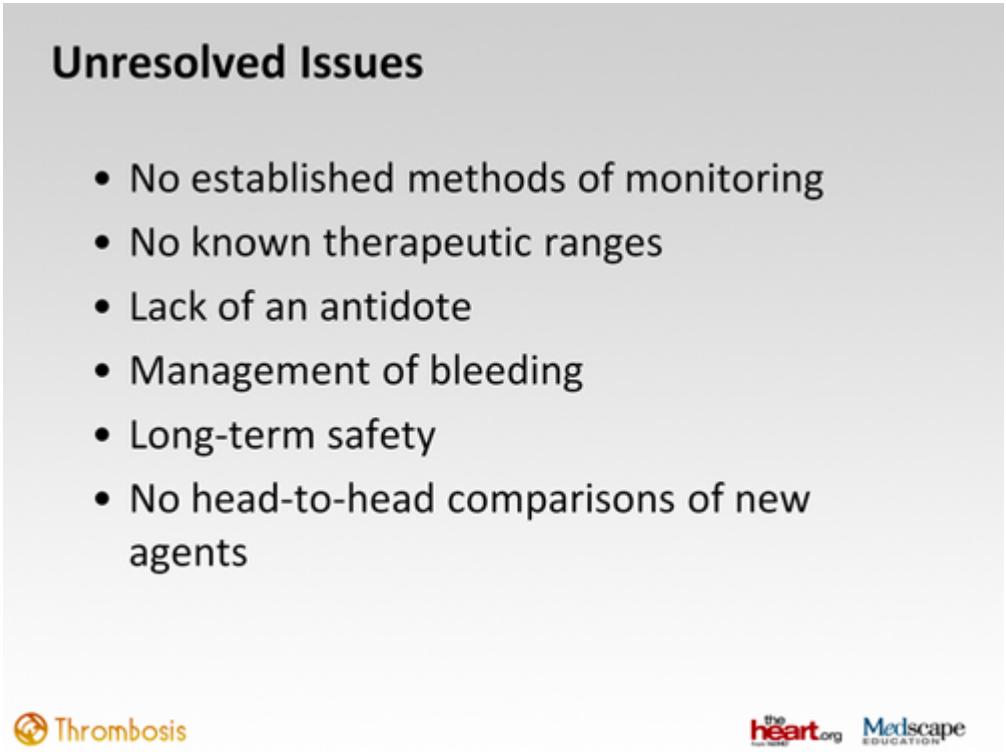
Dr. Turpie: There are no comparisons between one and the other, but we have indirect comparisons with warfarin and I think that these are important from the point of view of making a decision regarding clinical use. Dabigatran is clearly superior at a higher dose in comparison with warfarin. Rivaroxaban is non-inferior. The rates of ischemic stroke are similar with low-dose dabigatran and with rivaroxaban, but reduced with the higher dose of dabigatran. Intracranial hemorrhage is reduced by all of these new anticoagulant drugs. I know that when I sit with a patient in front of me who is going to be on long-term anticoagulant [therapy because of] AF or a heart valve replacement, I know that the risk for intracranial hemorrhage is about 1 in 300. Now I am confident that it is 1 in 500-600. What a big benefit in terms of a reduced risk for intracranial hemorrhage.

There is a concern with the thrombin inhibitors that there might be an increased rate of myocardial infarction. In the initial report in the dabigatran RE-LY trial, there was an increased risk. A subsequent report said it was not statistically significantly different, but in more recent studies in the treatment of venous thromboembolism, there is a concern regarding an increased risk for acute coronary syndromes. [Therefore] we have to be concerned about the potential for acute coronary syndrome in patients receiving a thrombin inhibitor. There is no such concern with the factor X inhibitors. There are practical issues regarding dyspepsia with dabigatran. There is no dyspepsia with the thrombin inhibitors.



Slide 15.

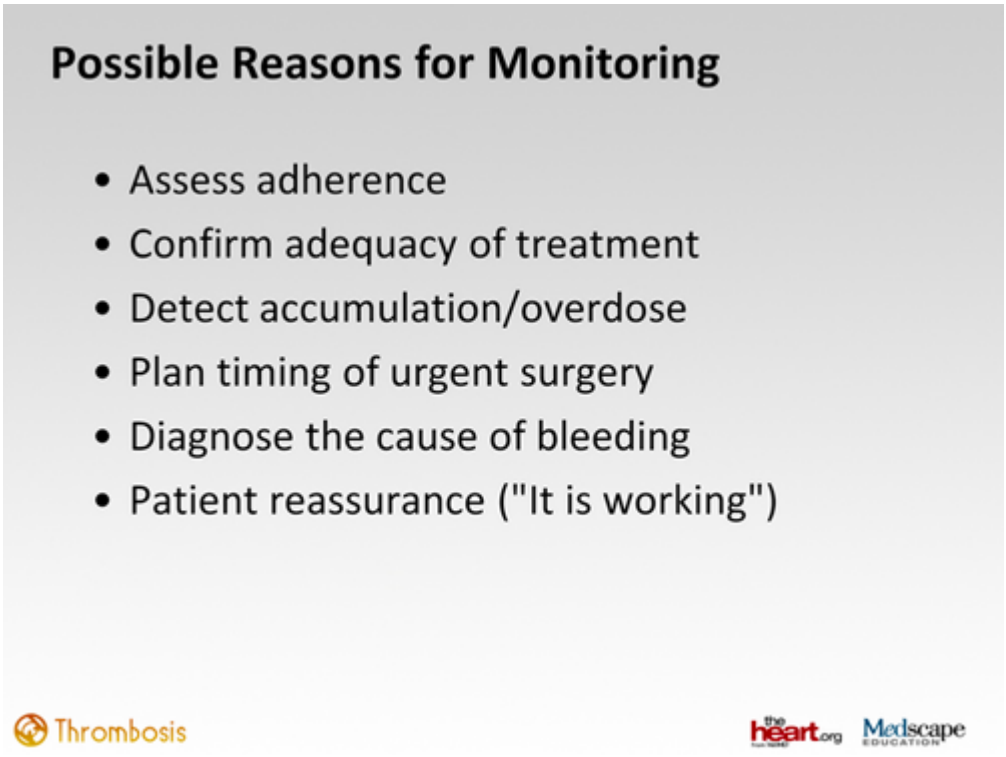
Dr. Turpie: What are the potential advantages of these new drugs in the setting of AF? We have heard about the pharmacokinetics and the pharmacodynamics, giving them advantages over warfarin. Does this translate to a better clinical outcome?



Slide 16.

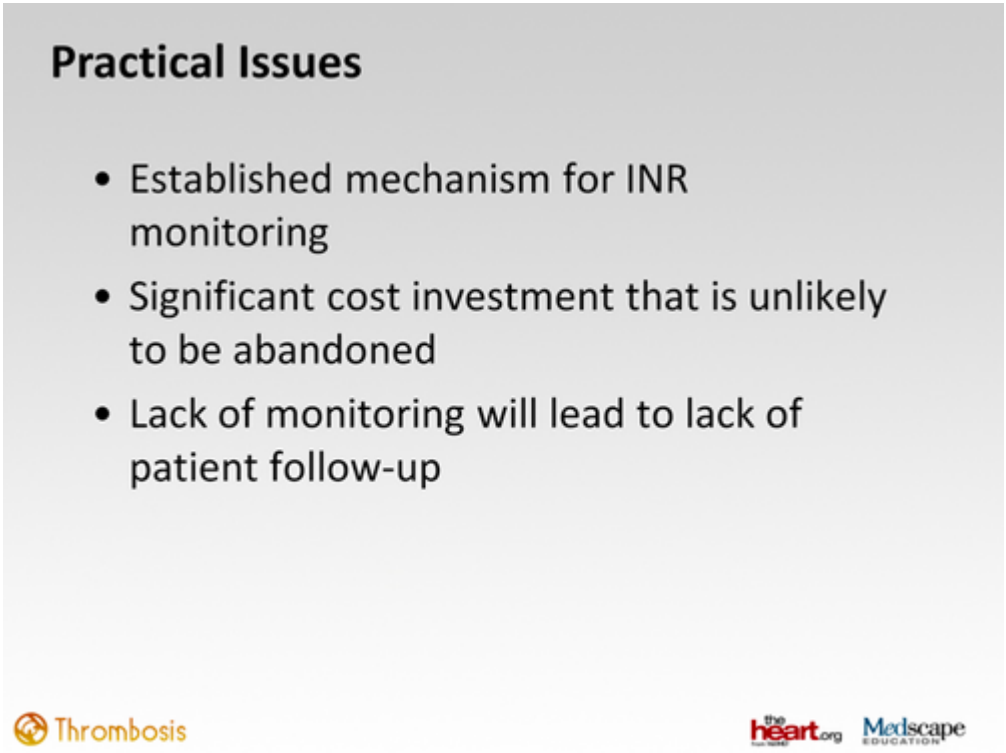
Dr. Turpie: There are some unresolved issues that I think we have to consider as clinicians. We all quote that the lack of anticoagulant monitoring is a big advantage, but we don't have a way or an established way of

monitoring these new drugs. Do we need it? There is no known therapeutic range. There is no antidote. We have to be concerned about how to monitor and treat bleeds with these new drugs because inevitably there will be bleeding with the anticoagulants. The long-term safety has been a concern at the beginning because of the experience with ximelagatran. With all of the experience of 60,000 people, some treated for more than 2 years, there is no concern regarding hepatic toxicity. Finally, we don't know which one of these is best.



Slide 17.

Dr. Turpie: Let me go back to this question about monitoring. We all think that patients find monitoring a bit of a chore, but there are some reasons why monitoring is beneficial. It does assess adherence to treatment. It confirms the adequacy of the treatment. It will detect accumulation and overdosing. It will help us plan how to intervene in these patients and it might also help tell us why a patient is bleeding. Finally, we can be certain when we tell a patient that his or her INR is 2.5, you are doing well. We can't do that with the new drugs when we give them a fixed dose. So, the patient reassurance factor is not present.

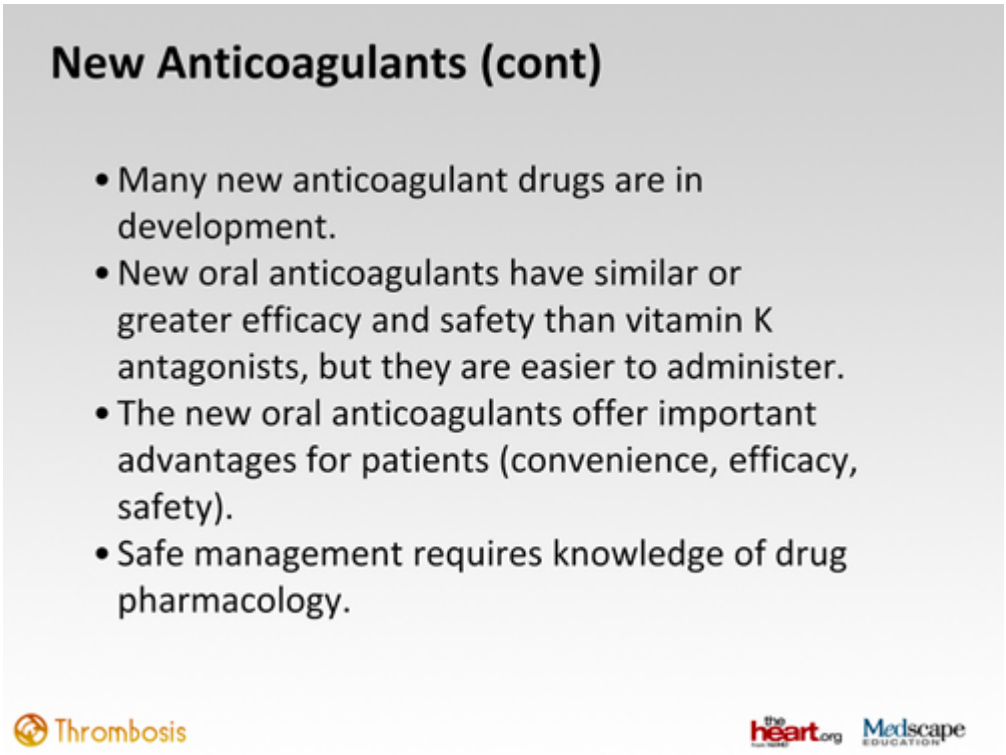


Slide 18.

Dr. Turpie: There is also the problem of, are we going to completely change our patterns of practice because we already have an established way of dealing with warfarin? It costs a lot of money to set up these clinics with computerized monitoring of anticoagulant dosing. Are we going to abandon that? I don't think we will, at least in the short term, and I think that there is that question of monitoring that we have to consider with the potential to lose patient follow up.

Slide 19.

Dr. Turpie: Finally, what will be the cost? It quite clearly will be much more expensive than the few cents that is required to keep a patient on warfarin. I think that given that we already have 3 or 4 of these new drugs under development, the good thing is that there will be competition and that the costs will come down.



Slide 20.

Dr. Turpie: To conclude, there are many new anticoagulants in development. They have similar or greater efficacy in comparison with vitamin K antagonists with respect to efficacy and safety. They are much easier to administer with the proviso that we have lost that monitoring and the potential advantages, but they do offer important advantages for patients -- the convenience, the efficacy and safety -- but the key thing for us as clinicians is to have knowledge of their pharmacology and in particular their renal excretion, which will allow us to administer these drugs for the long term.

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Panel Discussion and Implications for Patient Care CME

Eugene Braunwald, MD; Lars Wallentin, MD, PhD; Robert M. Califf, MD; John H. Alexander, MD, MHS; Robert P. Giugliano, MD; Alexander G. G. Turpie, MD

Posted: 09/27/2011

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Slide 1.

Lars Wallentin, MD, PhD: Thank you. Please come to the podium and we will start the panel debate. There are some microphones out there for people who would like to put questions, and maybe we could discuss something about the patients, the treatments, the results and side effects, and implementation. I could maybe ask you to focus on the patients. Between these trials there are some differences in patient populations. I think the largest difference is in relation to the ROCKET. So, in relation to the usual population, Rob, can you comment on the population in the ROCKET? Is that representative of the general AF population? What are the advantages and disadvantages of this high-risk group?

Slide 2.

Robert P. Giugliano, MD: Lars, from my perspective we have to be careful to distinguish high-risk and low-risk trials from decisions about patients. ROCKET was designed to be a different trial -- no question about that -- by including a much higher-risk population because we had a lot of concerns clinically that the trials were weighted toward the lower risk with fewer comorbidities and there was not much direct evidence about what to do with these high-risk patients. Whether that means that there is an advantage to one drug over another in these populations I think can only be determined by head-to-head trials, which I hope will happen fairly soon because just to put down my 2 cents worth here, I don't think there is any way by indirect comparisons you can actually figure out which drug is better than the other.

Dr. Wallentin: There is a warning that we really cannot draw any conclusions from indirect comparisons. I mean even in the ENGAGE AF trial, you selected higher-risk patients and not the CHADS score ones. Still I think in the RE-LY trial we had some important information because obviously there seems to be an advantage in the lower-risk population which adds to our armamentarium for this patient population.

Dr. Giugliano: Yes, but we were not saying that including low-risk patients was a bad thing. It was just that in the next trial we thought including high-risk patients would be good.

Robert M. Califf, MD: Lars, I think the one population of patients that isn't in any of these trials is the CHADS zero, and that is a group that we are not really going to know what to do with in terms or risk and benefit from these trials.

Dr. Wallentin: Let's continue. Dr. Giugliano, the dosing, this must be a key of course in relation to the success. It is always the dose that matters. Can you comment on the selection of this twice- or once-daily dosing? It is kind of surprising that when we look into the pharmacokinetics that the drug with the longest half-life, apixaban, is used twice daily while the drugs with shorter half-lives are used once daily.

Dr. Giugliano: The decision to go with a once-daily dosing of edoxaban was based purely on the phase 2 experience. Both the observed bleeding rates with a total of 60 mg was less if administered once daily than if 30 mg [was given] twice daily. Second, the more extensive pharmacokinetic analysis of all the doses studied indicated that the minimum concentration was more important. Now, why that is, and I agree it is somewhat

surprising, I think we could theorize a number of explanations about maybe the minimum concentration is the critical variable for bleeding because it allows some recovery or what have you. I don't know, but those were the observed outcomes and I think when you look at the phase 2 data with edoxaban it is difficult to support giving that drug twice daily with the bleeding risk. So, it is purely empirical.

Dr. Wallentin: The dosing seems to be relevant, especially at least the magnitude of the dose in relation to certain populations. I think John, you have experienced from let's say aspirin-created populations, and in these trials we have around 20% to 30%, maybe even more who get aspirin during the trial. Could you maybe from your APPRAISE experiences with apixaban comment on this issue?

John H. Alexander, MD, MHS: Yes. Lars is alluding to the APPRAISE trial which was just presented and published and I commented on it briefly in my presentation where we compared apixaban vs placebo, so not vs warfarin but vs placebo, on a background of antiplatelet therapy, both aspirin and aspirin plus clopidogrel. With the addition of the anticoagulant, you do see more bleeding than with placebo. In the population that we enrolled in APPRAISE, we did not see the efficacy in terms of a reduction in ischemic events. So, I would say the efficacy piece of that is very different in AF, where we know that anticoagulants, warfarin, and these new drugs are highly effective, but I would expect some increased risk for bleeding in patients who are concomitantly treated with antiplatelet therapy. In my view at least, we need to be carefully assessing the need for and the duration of antiplatelet therapy in our patients with AF and mostly related to coronary disease and procedures.

Dr. Califf: Can I get John to comment on one other item? John, could you comment on the people with coronary disease and AF? Based on emerging data, might it also make sense to drop the aspirin in those people?

Dr. Alexander: I don't think we know the answer to that, and that is a population that I think has been very understudied. All of these drugs as they are being used more aggressively in patients with AF, we need to understand how to use them on top of antiplatelet therapy. Rob, you raised the very important thing that we all consider aspirin the sort of default background of antiplatelet therapy and we are talking about, do you drop the thienopyridine or the P2Y12 antagonist? It may be that aspirin as we saw in AVERROES has a really worse safety profile than we think and we might be better off dropping the aspirin. There is a lot of work to do.

Eugene Braunwald, MD: I just wanted to add that we are just in the process of completing a trial called ATLAS 2 TIMI-51. In that trial we studied a population of a little over 15,000 patients with acute coronary syndrome who receive antiplatelet therapy. We have not yet locked the data so we don't know what the results are, but we do know that the data safety monitoring committee allowed us to complete the study and so at least there is a possibility. That population was not quite as sick as your population because we excluded patients who had a previous stroke, but that certainly is no guarantee of a positive outcome.

Dr. Wallentin: The AF population looks a little bit like the APPRAISE 2 population unfortunately. These are elderly patients. I think we have 2 questions from the audience.

Member of Audience: Dr. Wallentin, you put the emphasis on the dose. In the prescription I read the statement that when we choose the written control strategy, the dose of dabigatran should be reduced 75 mg per day. What is the source because I wrote a review about this topic? I did not find the source of this statement, which is included in the official prescription in our country.

Dr. Wallentin: No, it comes from the US Food and Drug Administration. I think it is based on pharmacokinetic modeling from the company. You will have the same exposure in patients with renal dysfunction, but the dose has never been tested. I think in most other countries' dosages, the 150-mg and 110-mg doses are available. Still I think it is an upside of this because in the trial we excluded patients with renal dysfunction. It is really an appropriate way I think to translate the result into another population, but there are no data from a clinical trial at the 75-mg dose. Thank you for this question. We have a question over there.

Member of Audience: Could you please summarize the data on older patients who are more than 80 years old? Also, please comment on an issue that is unresolved. It is related to patients with risk for coronary disease.

With dabigatran, it seems that in the trial it is increased, although there is some theoretical antiplatelet defect. Please comment

Dr. Wallentin: I think concerning the elderly patients, there have been presentations that of course the bleeding risk is increased and it seems appropriate to reduce the dose in the elderly. I think it is definitely a disadvantage that this dose of 110 mg is unavailable in the United States I think the company is going back to the FDA to try to have the lower dose approved because you have non-inferiority and less bleeding, but as you say we need to focus on the elderly because they have more comorbidities. Are there any comments from Rob, because you had a really high-risk elderly population?

Dr. Califf: We had a lot of patients over the age of 80. If you go to the hotline tomorrow, Professor Keith Fox, my co-chair, will be presenting the results of a 15-mg dose reduction, which was written into the protocol based on creatinine clearance. Of course if you are over the age of 80, there is a very high probability that you will have reduced creatinine clearance as a normal function of aging. Basically, the results with the reduced dose were the same as with the 20-mg dose in younger patients or patients with normal renal function. So, it does look like a dose reduction is going to be needed and for each drug there will need to be empiric data to really understand what the best dose would be.

You brought up black patients also, and here I think it is shameful in all of the trials there is an under-enrollment of black patients. I think we have learned now that particularly in the coagulation system there can be differences. So, this is an area that I think needs a lot more work. It is equally true of our trial ROCKET as the other trials.

Dr. Wallentin: We have one more comment behind you there, another question.

Member of Audience: Could the panel comment on planning for elective surgery and also as there is no antidote, what do you do when people bleed apart from cross fingers?

Dr. Wallentin: I think Graham, you have not been involved. You need to answer this difficult question.

Alexander G. G. Turpie, MD: I will start with the bleeding question. I think it is reasonable to treat patients the way you would currently treat a patient who is bleeding. We know that the half-life is relatively short and that at 24 hours the patient will be hemostatically competent if you discontinue administration of any of the new drugs. If you think about how you handle a patient who is bleeding on warfarin, you don't give them any more. You will give them vitamin K and the patient will become hemostatically competent within about 12 to 16 hours with vitamin K. It is about the same time. How you would handle patients who are bleeding? It would be stop the anticoagulant drug, apply pressure if the bleeding site is accessible, and administer fluids as necessary. We now have experimental evidence that PCC, prothrombin complex concentrates, will reverse inhibition of the anticoagulation by the factor X inhibitors and the recombinant factor VII will also reverse the inhibition. They have not been tested in the clinical setting; however, I think that many of us will use these if patients continue to bleed after conservative measures.

With respect to discontinuation prior to surgery, in the clinical trial protocols in orthopaedic surgery for example, surgery was permitted 24 hours after the last dose with no evidence that this increased the bleeding risk. So, I would discontinue the drug 24 hours prior to surgery, but there are some caveats, particularly with dabigatran and in patients who have diminished renal function. There are protocols derived from the pharmacokinetics which give guidance for the use of dabigatran in the preoperative setting based on creatinine clearance.

Dr. Wallentin: Can you just comment in relation to dabigatran? Within the trial we have looked into the results in relation to interruption for surgery. These results have not been presented but at least I can tell you it looks very comforting from the dabigatran point of view.

Dr. Califf: If I could comment on bad news on that perhaps. Within the rivaroxaban data, discontinuation for surgery looks quite comforting but discontinuation at the end of the trial, there was a definite spike in events on

which we have done a lot of analyses. I wish I could present all the data here. There is not time, but I am going to make a prediction that with all of these drugs there is going to need to be some concern about bridging and overlap of anticoagulation, and in the bleeding patient there is going to need to be careful study of how much reversal of anticoagulation you can do and do it safely These are event rates that are not in the range where an individual practitioner could ever see it, but there is a definite spike that you see in a population that I think should be of concern.

Dr. Wallentin: You might say this has in no way been concealed in the RE-LY trial, but the fact is that almost all patients in the RE-LY trial on dabigatran continued on the treatment and they were given the treatment for free until the drug was approved in the respective countries. Therefore, we had no chance in the RE-LY trial to get these observations.

Dr. Braunwald: On the [factor] Xa inhibitors, help is on the way. There is a company in San Francisco called Portola and scientists from that company are presenting an abstract at this meeting which shows an antidote, a specific antidote to all [factor] Xa inhibitors, but these are only animal studies. It looks quite promising. I would think that by next year at the time of this meeting we should have some clinical information on that.

Slide 3.

Dr. Wallentin: We are approaching the end of this symposium. Dr. Braunwald, can I ask you what do you think about the future for warfarin when you see all of this coming?

Dr. Braunwald: Well, I am not optimistic about warfarin. I think as Professor Turpie pointed out, I think there will be some people who will be reluctant particularly for reasons of cost to get rid of warfarin, but as I have seen other therapies come, I think these drugs do represent a new era. I was around when warfarin was introduced and I am pleased to be around at the time of the impending but not quite yet but the impeding funeral of warfarin.

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