# Navigating the Current Landscape for Stroke Prevention in Atrial Fibrillation: The Role of Oral Anticoagulants

*Interviews are based on data presented at the European Society of Cardiology Congress 2012, August 25-29, 2012, Munich, Germany**

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***Note**: This is a downloadable version of a web-based presentation. Programme interactivity only applies when viewing the activity online.*

Featured Presentations

Current Standard of Care in Stroke Prevention for Atrial Fibrillation: Updated Efficacy and Guidelines for Oral Anticoagulation

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Recent Insights on Stroke Prevention in Atrial Fibrillation: Exploring the Safety of Oral Anticoagulants

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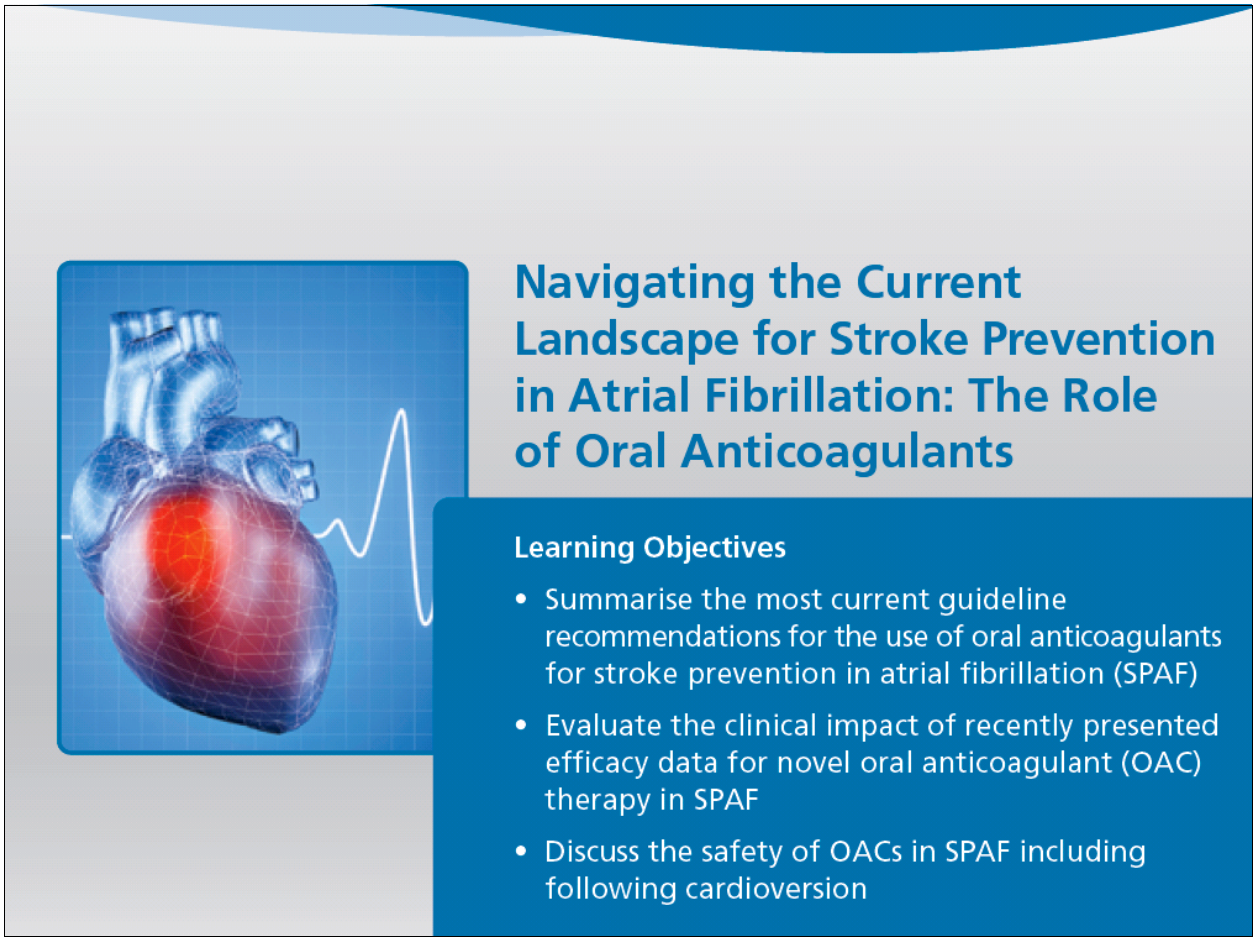
**Slide 1**



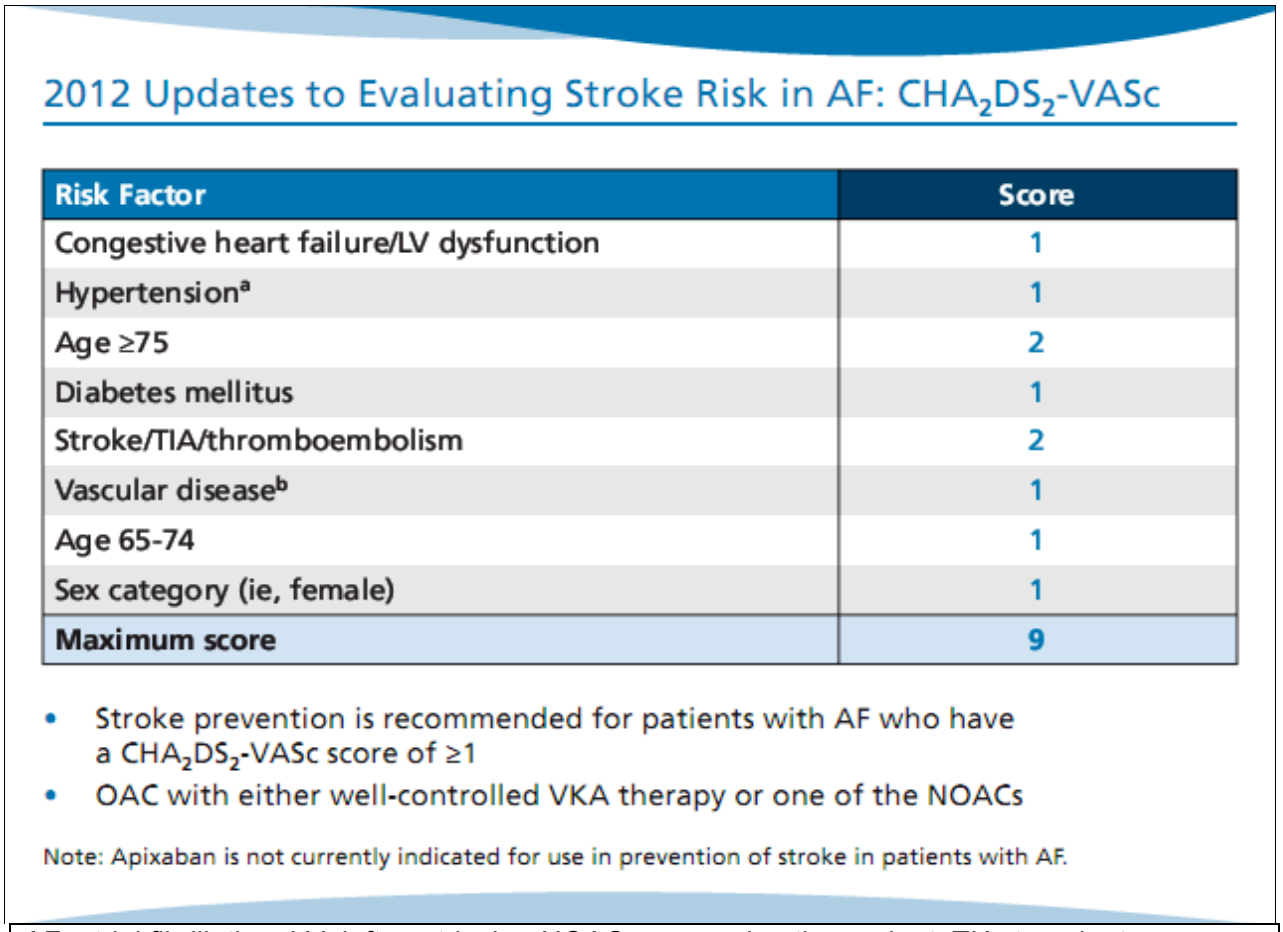

**Dr. Hohnloser:**
Hello, this is Dr. Stefan Hohnloser from the J.W. Goethe University in Frankfurt, Germany. Welcome to this PeerVoice educational activity on stroke prevention in atrial fibrillation. Throughout this activity, you will be asked to answer several PeerVoice questions. Your answer selection will be compared with your peers' responses, and, when appropriate, the best answer will be discussed in the subsequent slides and commentary.

**Narrator:**
This activity comprises 2 separate presentations.

**Slide 2**


**Dr. Hohnloser:**
In this program, we are focusing on recent findings, presented at the European Society of Cardiology Congress in Munich. Importantly, at this meeting, we published the updated guidelines for management of atrial fibrillation, based on recent scientific findings, particularly in the area of stroke prevention in atrial fibrillation.

**Slide 3**




AF: atrial fibrillation; LV; left ventricular; NOAC: new oral anticoagulant; TIA: transient ischaemic event; VKA: vitamin K antagonist.

Camm JA et al (published online ahead of print August 24, 2012). *Eur Heart J.* doi:10.1093/eurheartj/ehs253.
Lip GYH et al. *Chest*. 2010;137:263-272.
Camm JA et al. *Eur Heart J*. 2010;31:2369-2429.

**Dr. Hohnloser:**
We have a recommendation to use a new risk stratification score, $CHA_2DS_2$-VASc, rather than the previously used $CHADS_2$ score. With the $CHA_2DS_2$-VASc score, we can much better identify those AF patients who are truly at low stroke risk: those who are younger than 65 years of age and have idiopathic or lone atrial fibrillation. And this applies for men and women the same way.

**Slide 4**

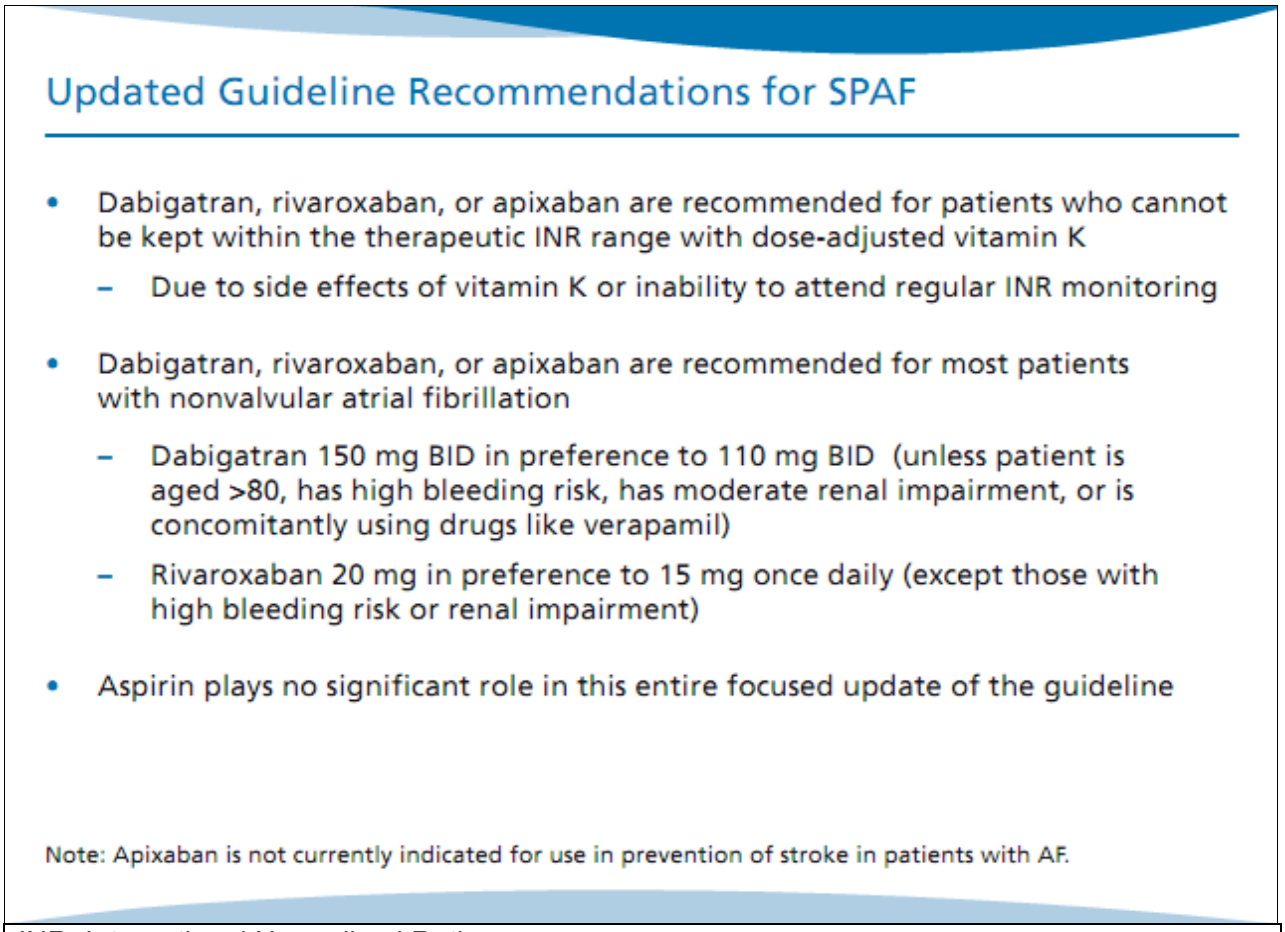
## Challenge Question

**According to updated ESC guidelines for SPAF, which of the following options is recommended for an 82-year-old man with nonvalvular AF and moderate renal disease? He has not been able to maintain therapeutic INR on warfarin.**

- ○ He should remain on warfarin
- ○ He should remain on warfarin plus aspirin 81-324 mg
- ○ He should be switched to dabigatran 150 mg or rivaroxaban 20 mg
- ○ He should be switched to dabigatran 110 mg or rivaroxaban 15 mg

*Go online to compare your answer with your peers' responses.*

**Slide 5**




INR: International Normalised Ratio.

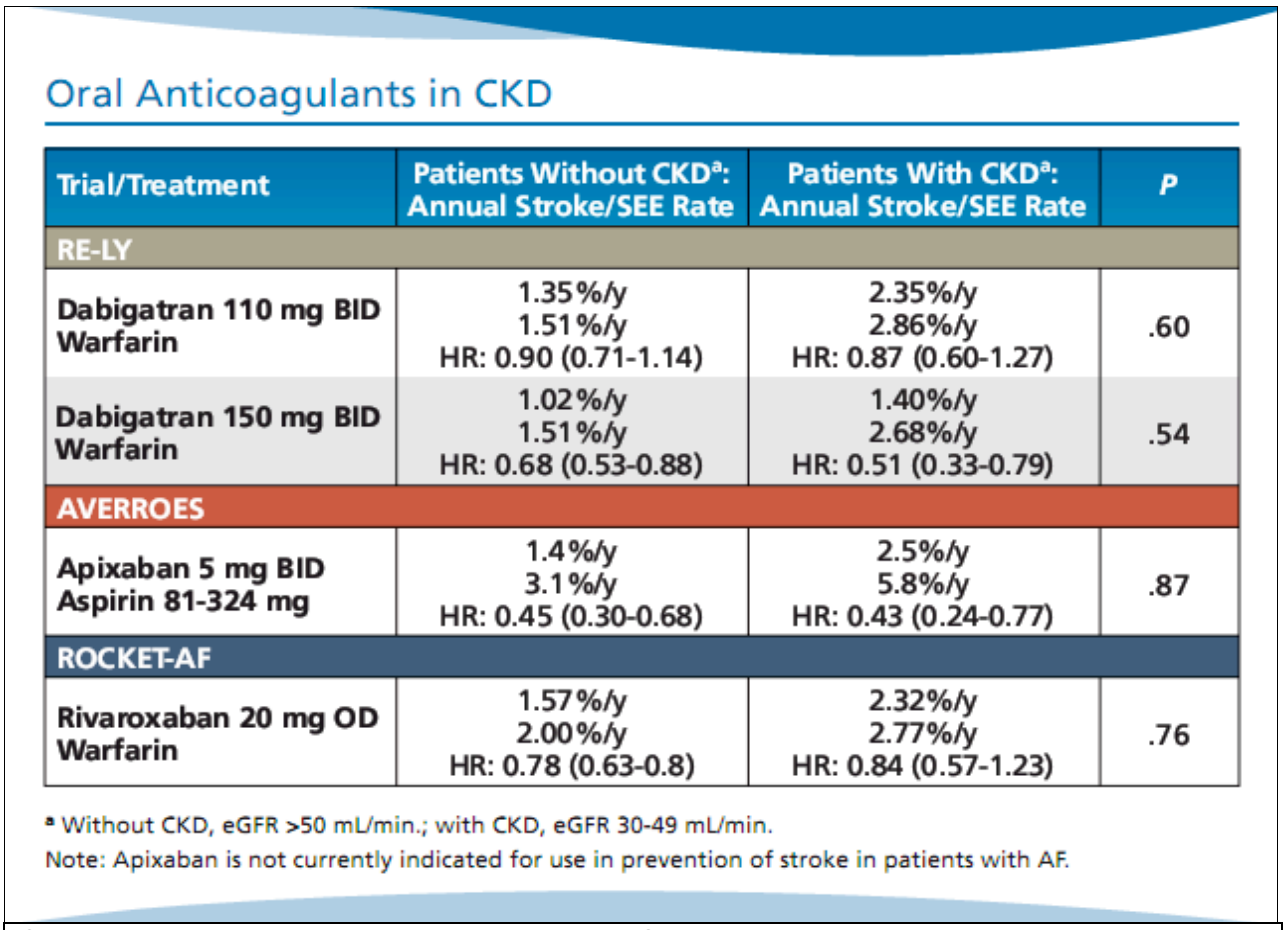
Camm JA et al (published online ahead of print August 24, 2012). *Eur Heart J.* doi:10.1093/eurheartj/ehs253.

**Dr. Hohnloser:**
If we further look on the new recommendations, these are dominated by the new oral anticoagulants. For instance, for those patients who cannot be kept with dose-adjusted vitamin K in the therapeutic level, we recommend either dabigatran as a direct thrombin inhibitor or rivaroxaban or apixaban as a factor Xa inhibitor. Either dabigatran, rivaroxaban, or apixaban should be considered rather than dose-adjusted VKA for most patients with nonvalvular atrial fibrillation, based on their net clinical benefit.

We also have specific recommendations regarding each of the new oral anticoagulants—for instance, in those who have a high bleeding risk and for those who have moderate renal impairment.

Aspirin no longer plays any significant role in the guideline.

**Slide 6**



## Oral Anticoagulants in CKD

| Trial/Treatment | Patients Without CKD[a]: Annual Stroke/SEE Rate | Patients With CKD[a]: Annual Stroke/SEE Rate | *P* |
|---|---|---|---|
| **RE-LY** | | | |
| Dabigatran 110 mg BID<br>Warfarin | 1.35%/y<br>1.51%/y<br>HR: 0.90 (0.71-1.14) | 2.35%/y<br>2.86%/y<br>HR: 0.87 (0.60-1.27) | .60 |
| Dabigatran 150 mg BID<br>Warfarin | 1.02%/y<br>1.51%/y<br>HR: 0.68 (0.53-0.88) | 1.40%/y<br>2.68%/y<br>HR: 0.51 (0.33-0.79) | .54 |
| **AVERROES** | | | |
| Apixaban 5 mg BID<br>Aspirin 81-324 mg | 1.4%/y<br>3.1%/y<br>HR: 0.45 (0.30-0.68) | 2.5%/y<br>5.8%/y<br>HR: 0.43 (0.24-0.77) | .87 |
| **ROCKET-AF** | | | |
| Rivaroxaban 20 mg OD<br>Warfarin | 1.57%/y<br>2.00%/y<br>HR: 0.78 (0.63-0.8) | 2.32%/y<br>2.77%/y<br>HR: 0.84 (0.57-1.23) | .76 |

[a] Without CKD, eGFR >50 mL/min.; with CKD, eGFR 30-49 mL/min.

Note: Apixaban is not currently indicated for use in prevention of stroke in patients with AF.

CKD: chronic kidney disease; HR: hazard ratio; SEE; systemic embolic events.

Hohnloser SH, Connolly SJ (published online ahead of print August 28, 2012). *Eur Heart J.* doi:10.1093/eurheartj/ehr344.

**Dr. Hohnloser:**
We know from several large databases published over the last 10 years or so that people with chronic kidney disease are much more likely to develop atrial fibrillation. If they have atrial fibrillation, they are at much greater risk to suffer from a stroke and major bleedings. Chronic kidney disease is one of the reasons why many people with atrial fibrillation are not receiving appropriate stroke preventive therapy at all.

Now, with the new anticoagulants, I believe it will change. We looked at the crude rates of events, both for stroke and systemic embolism in patients with and without chronic kidney disease, and for all of these studies, there was no significant interaction *P* value for the treatment effects observed in the studies, whether or not a patient suffered from chronic kidney disease, which emphasizes that these people are probably better treated with one of the new oral anticoagulants than with vitamin K antagonists.

**Slide 7**

## Dabigatran and Rivaroxaban in Patients With CKD

**Use of the other new oral anticoagulants in patients with CKD should be discussed with some caution**

- **Dabigatran** is excreted 80% via the kidneys vs 25% for apixaban
- There is no significant treatment effect noted, but the manufacturer notes that patients with impaired renal function should use the lower dose of dabigatran 110 mg BID[1]
- **Rivaroxaban** should be used in the lower dose of 50 mg once daily in patients with CKD
- This dose achieves similar efficacy and safety[2]

1. European Medicines Agency (EMA) website. Dabigatran (Pradaxa) EPAR – Product Information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf. Accessed September 20, 2012.
2. EMA website. Rivaroxaban (Xarelta) EPAR – Production Information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf. Accessed September 20, 2012.

**Dr. Hohnloser:**
The question of whether this effect which we observed with apixaban can also be observed with the other new oral anticoagulants has to be discussed with some caution. First of all, dabigatran is excreted by the kidneys by 80% compared to only 25% for apixaban. So *a priori* there's a much greater likelihood of an overdosing effect (so to speak) in people with renal insufficiency on dabigatran. The data, however, which have been published so far, indicate that there is no significant treatment effect again. But there is a precaution, from the manufacturer and from the guideline writers, that in people with impaired renal function, it is recommended that the lower dose of dabigatran 110 mg BID is being used.

Now, for rivaroxaban we have a similar analysis. And here it is clearly shown that if you use the lower dose of 50 mg once daily, you can achieve a similar efficacy and safety of the drug, as that compared in the overall ROCKET AF study.

**Slide 8**

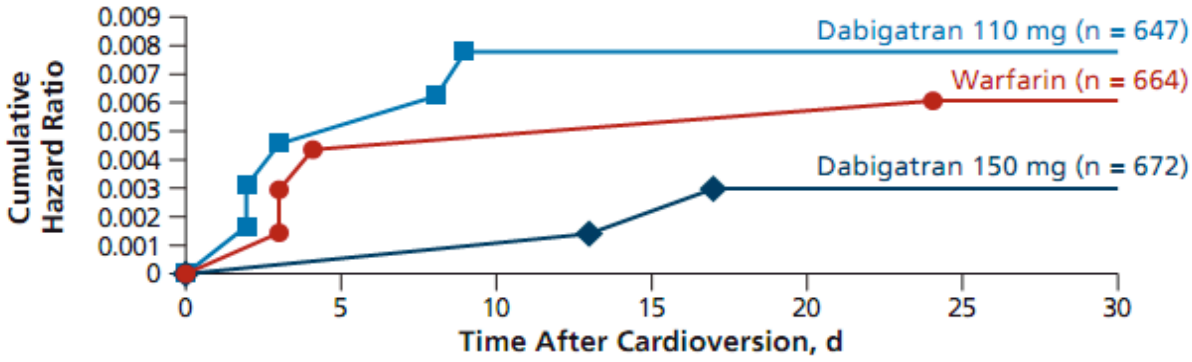
## Dabigatran vs Warfarin in Patients with AF Undergoing Cardioversion

**RE-LY: patients who underwent cardioversion during the study**

- 1,983 cardioversions were performed in 1,270 patients

**For dabigatran 110 mg, dabigatran 150 mg, and warfarin:**

- Rates of stroke and systemic embolism at 30 days were 0.8%, 0.3%, and 0.6%
  - D110 vs warfarin, $P = .71$; D150 vs warfarin, $P = .40$
  - Similar in patients with and without transesophageal echocardiography
- Major bleeding rates: 1.7%, 0.6%, and 0.6%
  - D110 vs warfarin, $P < .06$; D150 vs warfarin, $P = .99$




D: dabigatran.

Nagarakanti R et al. *Circulation.* 2011;123:131-136.

**Narrator:**
An analysis of data from the RE-LY study on patients undergoing cardioversion while receiving dabigatran showed a low rate of stroke within 30 days of cardioversion at either dose.

**Dr. Hohnloser:**
Dabigatran has the largest experience on cardioversion [which has] ever been published.

**Slide 9**

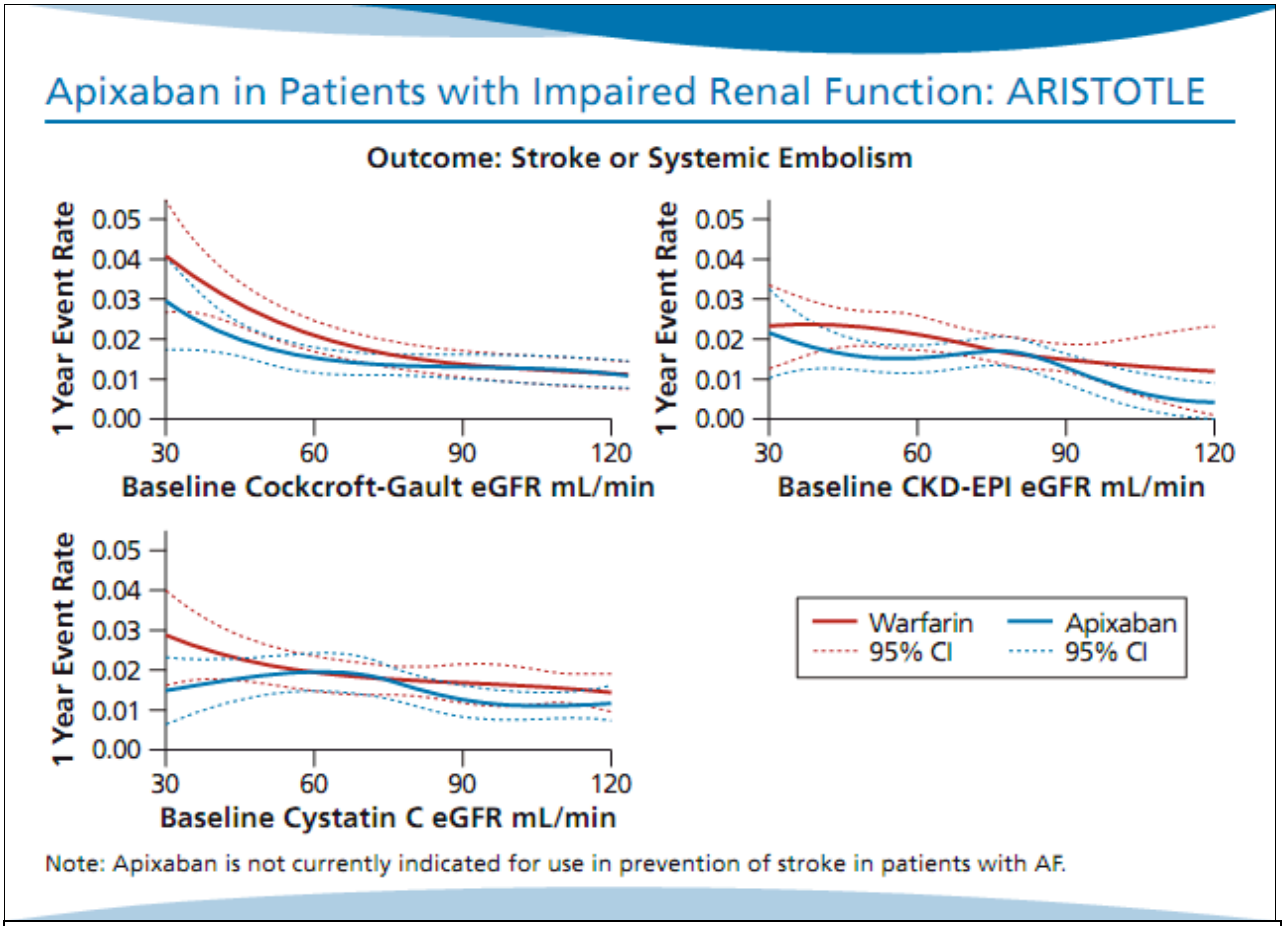
## Challenge Question

**Which of the following statements best describes the results of the renal substudy from ARISTOTLE?**

- ○ Patients with renal impairment receiving apixaban for SPAF had more strokes/SEE vs warfarin
- ○ Patients with renal impairment receiving warfarin for SPAF had more strokes/SEE vs apixaban
- ○ There was no significant difference in strokes/SEE between apixaban and warfarin

*Go online to compare your answer with your peers' responses.*

**Slide 10**



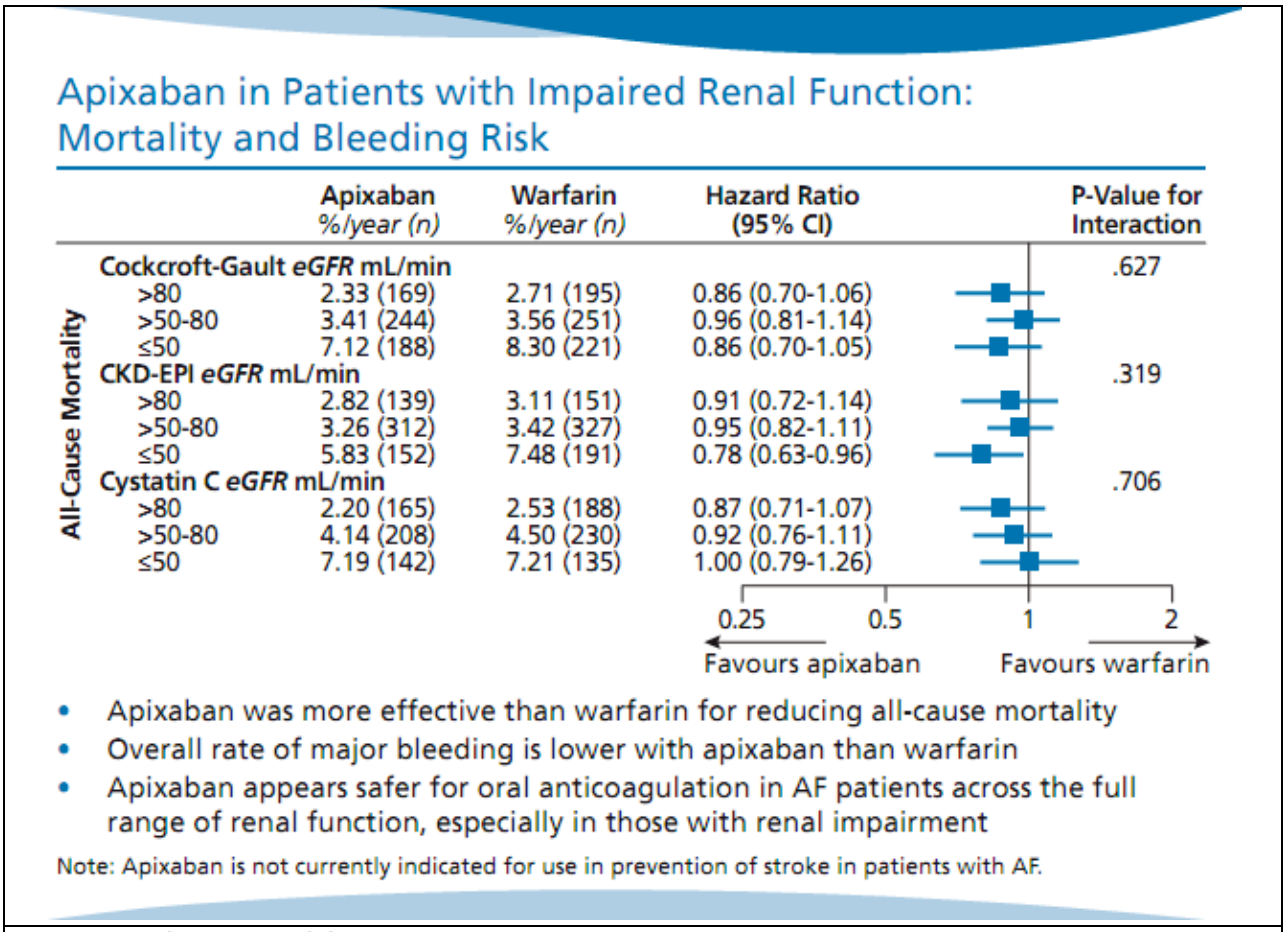

eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Hohnloser SH et al. European Society of Cardiology 2012 Congress (ESC 2012). Presentation 5172.
Hohnloser SH et al (published online ahead of print August 29, 2012). *Eur Heart J.* doi:10.1093/eurheartj/ehs274.

**Dr. Hohnloser:**
At this recent ESC Congress, there were several abstracts presented with subanalyses from the 3 large randomised trials on the new oral anticoagulants. What these subanalyses confirm is that the new oral anticoagulants in the various subgroups of patients are at least as effective as vitamin K antagonists and, in general, tend to be safer than these compounds.

Now, at this meeting, we presented what we believe is an important subanalysis from the ARISTOTLE trial according to renal function. For the primary endpoint of stroke and systemic embolism, there is no interaction between the treatment effect and the presence or absence of any of these categories of renal dysfunction.

**Slide 11**




Hohnloser SH et al. ESC 2012. Presentation 5172.
Hohnloser SH et al (published online ahead of print August 29, 2012). *Eur Heart J.* doi:10.1093/eurheartj/ehs274.

**Dr. Hohnloser:**
This holds also true for the endpoint of all-cause mortality. Apixaban did reduce the primary endpoint—stroke and systemic embolism—as well as all-cause mortality to a similar extent regardless of the degree of renal dysfunction.

Now, we looked at the incidence of major bleed, and what we found to our surprise was that the effect of reducing major bleed was particularly evident in those patients who had the most advanced kidney dysfunction—that is, a Cockcroft-Gault estimated GFR of <50 mL/minute. And if we looked at major bleed as a function of continued GFR values, this effect opposite to warfarin becomes even more obvious: the lower the eGFR, the greater is the reduction in bleeds with the use of apixaban. This is for the first time shown for any of the new oral anticoagulants, and we believe therefore that apixaban is actually meeting an unmet need, so to speak, which is safer and more effective treatment of atrial fibrillation patients with impaired renal function. As I already pointed out, these people are often not receiving any form of

antithrombotic therapy, and apixaban will make a difference in this particular high-risk population of patients.

**Slide 12**

## ARISTOTLE: Cardioversions and Clinical Outcomes

| Cardioversions, n | Warfarin | Apixaban | All Patients |
|---|---|---|---|
| 1 | 281 | 272 | 553[a] |
| 2 | 76 | 51 | 127 |
| ≥3 | 62 | 15 | 77 |
| Total | 419 | 338 | 757[b] |

| Outcomes, n (%) | Warfarin (n = 419) | Apixaban (n = 338) | Total (n = 757) |
|---|---|---|---|
| Stroke or systemic embolism | 0 | 0 | 0 |
| MI | 1 (0.2) | 2 (0.6) | 3 (0.4) |
| Major bleeding | 2 (0.5) | 2 (0.6) | 3 (0.4) |
| Death | 8 (1.9) | 9 (2.7) | 17 (2.2) |

[a] Number for description of baseline characteristics.
[b] Number for major clinical events.
Note: Apixaban is not currently indicated for use in prevention of stroke in patients with AF.

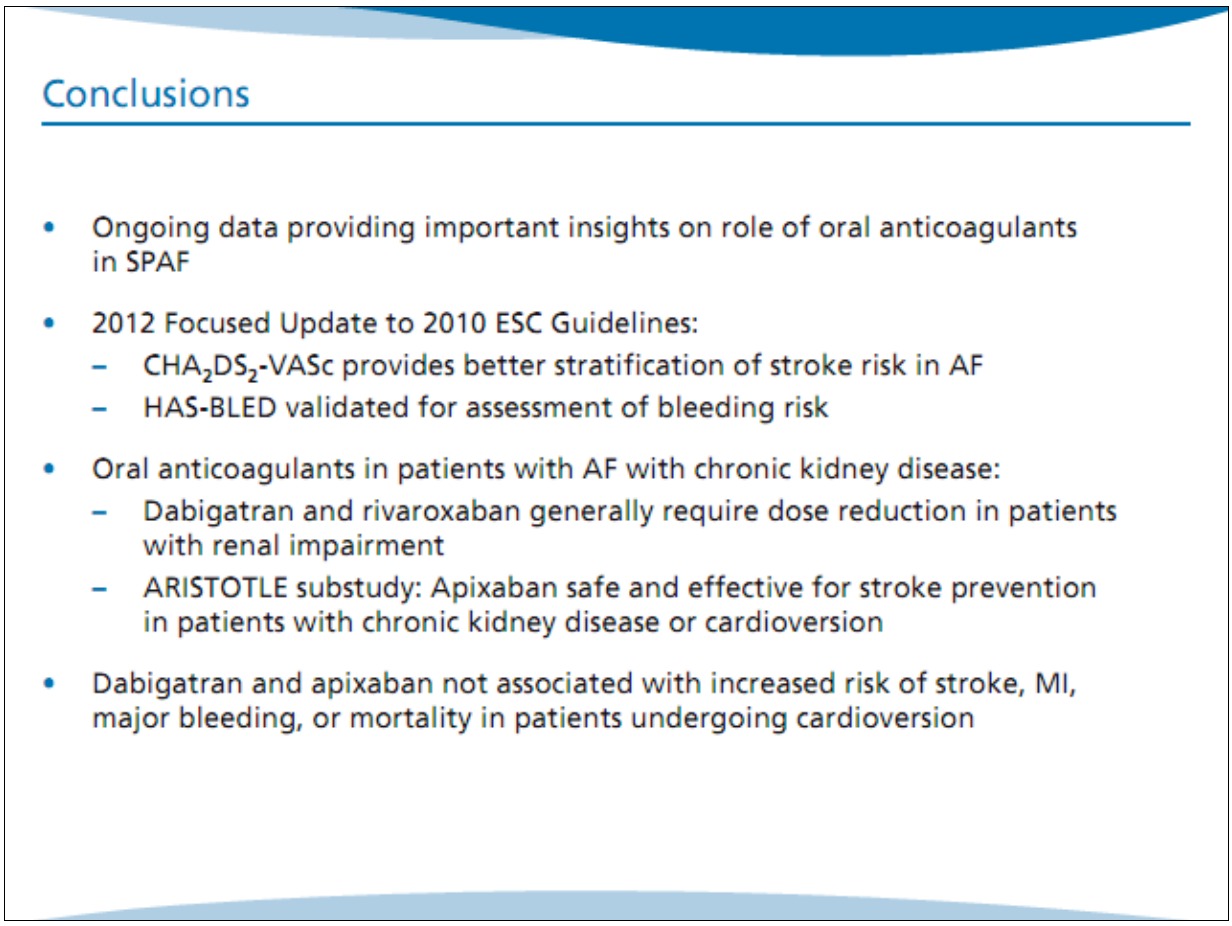
MI: myocardial infarction.

Flaker G et al. ESC 2012. Presentation 4048.

**Dr. Hohnloser:**
Another substudy presented from the ARISTOTLE trial dealt with the issue of cardioversions. We have, in retrospect, about 550 participants undergoing cardioversion attempts during the study period, about half and half assigned to apixaban and warfarin. Now, overall in terms of safety of cardioversion, there was not a single stroke or systemic embolism following cardioversion. This is due to the relatively small number of patients undergoing this procedure, but it also emphasizes that the drugs are probably safe to be used.

Now, is that enough evidence for apixaban to say you can safely cardiovert a patient with this form of antithrombotic regimen? My personal opinion is we that we need more data for apixaban, in a prospective study with at least several hundred if not a few thousand patients.

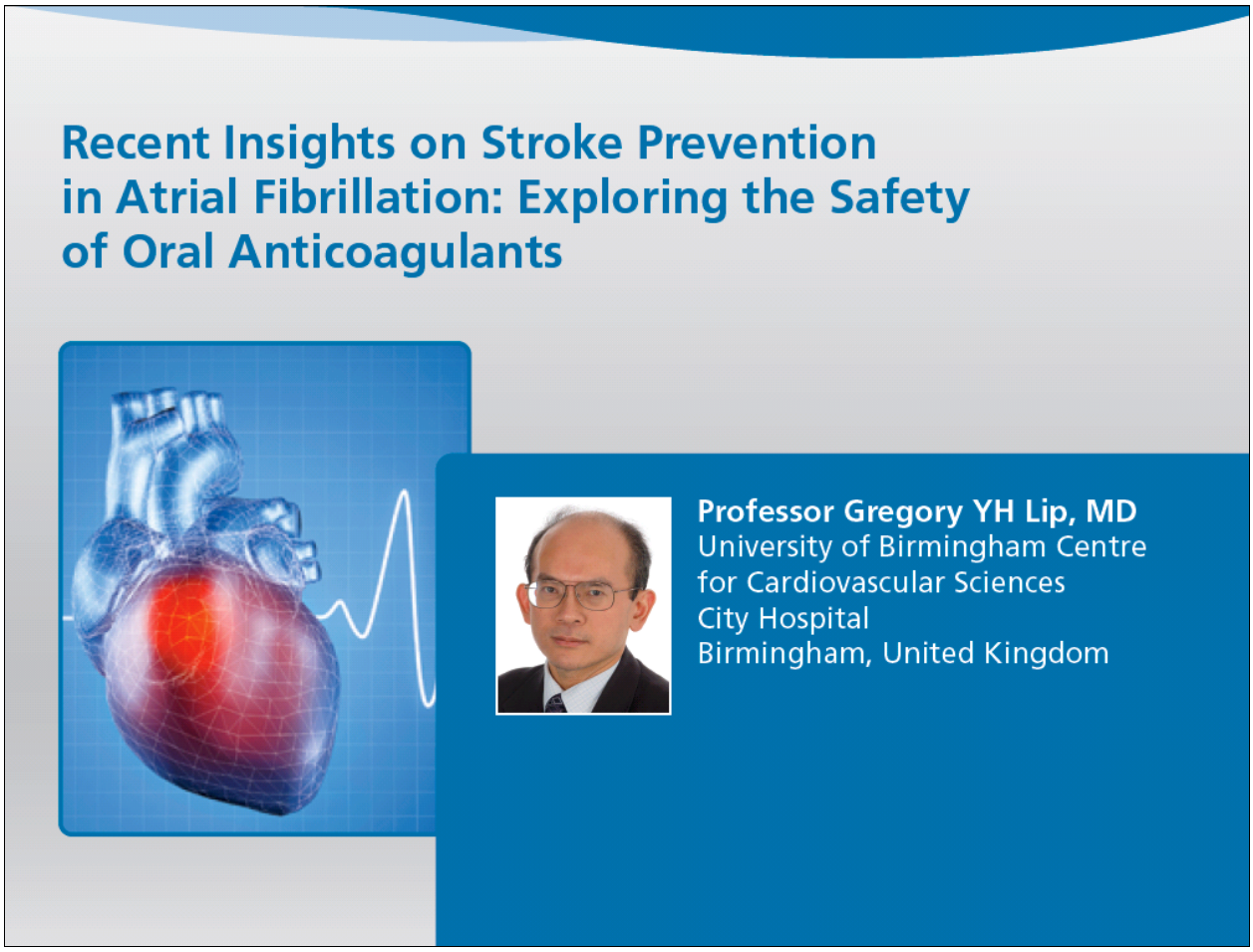
**Slide 13**




**Dr. Hohnloser:**
In conclusion, this recent ESC Congress has provided a plethora of new data on stroke prevention in atrial fibrillation. First of all, we have a focused update on our 2010 guidelines. We have new risk stratification scores recommended—the $CHA_2DS_2$-VASc score and the HAS-BLED score—to estimate the bleeding risk of people with atrial fibrillation. And we have a whole set of very specific recommendations, with respect to the use of new oral anticoagulants in this regard. We also have a series of presentations of important substudies of the major anticoagulation trials with the new oral anticoagulants, and I believe each and every one of these subanalyses is important for the future, because it emphasizes the role of the new oral anticoagulants in subpopulation of atrial fibrillation patients.

What is the future to bring? Number 1, there is a fourth trial of one of the new oral anticoagulants using edoxaban in comparison to VKAs. I'm sure we will see a continued growth of publications of substudies of all of these new trials, and again I believe that this is very important information for the future.

**Slide 1**




**Dr. Lip:**
I'm Gregory Lip. It gives me great pleasure to be able to discuss some recent insights into stroke prevention in atrial fibrillation, with particular focus into some of the recent information presented at the European Society of Cardiology meeting in Munich in August 2012.

The first priority is identification of truly low-risk patients who do not need any antithrombotic therapy. After that, patients with AF and 1 or more stroke risk factors can be considered for oral anticoagulation. This leads on to one of the aspects of assessment, which is bleeding risk assessment.

**Slide 2**

## Challenge Question

**Which of the following clinical characteristics does the HAS-BLED bleeding risk assessment score take into account?**

- ○ Age, hypertension, and drug or alcohol use
- ○ Age, previous MI, and weight
- ○ Hypertension, previous anticoagulant therapy, and type 2 diabetes
- ○ Stroke, drug or alcohol use, and previous MI

*Go online to compare your answer with your peers' responses.*

**Slide 3**

## ESC 2012 Updated Guidelines for Management of Atrial Fibrillation: Assessing Bleeding Risk

- Clinical benefit in AF depends on the balance between stroke prevention and prevention of major bleeding events
- ESC 2012 Focused Update recommends HAS-BLED for evaluating bleeding risk in patients with AF
- Patients with HAS-BLED score >3 should receive regular follow-up

| | Clinical Characteristic | Points Awarded |
|---|---|---|
| H | Hypertension | 1 |
| A | Abnormal renal and liver function | 1 point each |
| S | Stroke | 1 |
| B | Bleeding tendency or predisposition | 1 |
| L | Labile INRs | 1 |
| E | Elderly (eg, age >65 y, frail condition) | 1 |
| D | Drugs or Alcohol | 1 point each |
| | **Total** | **Maximum 9 points** |

AF: atrial fibrillation; INR: International Normalised Ratio.

Camm JA et al. *Eur Heart J*. 2010;31:2369-2429.
Lip GYH et al. *J Am Coll Cardiol*. 2011;57:173-180.

**Dr. Lip:**
In the 2012 focus update, the HAS-BLED score is the recommended score to assess bleeding risk. Bleeding risk is multifactorial, and it's not a static risk and does change over time. That's why the HAS-BLED score is practical, because calculating a HAS-BLED score allows the clinician to make an informed decision about potential risk of bleeding, and they can therefore flag them for careful review and follow-up.

**Slide 4**

## Validation of HAS-BLED

- HAS-BLED score performs well in relation to predicting bleeding events compared to older bleeding scores and the ATRIA score[1-4]

**Outcomes of Bleeding Scores: Cox Regression Analysis[3]**

| Score | Any Clinically Relevant Bleeding | | Major Bleeding | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| HEMORR$_2$HAGES >1 | 1.2 (0.9-1.5) | .30 | 1.8 (0.9-3.5) | .06 |
| HAS-BLED >2 | 1.9 (1.4-2.4) | < .001 | 2.4 (1.3-4.6) | .006 |
| ATRIA >3 | 1.2 (0.8-1.7) | .50 | 2.3 (1.1-5.1) | .03 |

- HAS-BLED was the only tested score with significant predictive value for intracranial bleeding[3]

HR: hazard ratio.

1. Bannerjee A et al. European Society of Cardiology 2012 Congress (ESC 2012). Poster P555.
2. Lip GYH et al (published online ahead of print August 24, 2012). *Circ Arrhythm Electrophysiol.* doi: 10.1161/CIRCEP.112.972869.
3. Apostolakis S et al. *J Am Coll Cardiol*. 2012;60:861-867.
4. Roldán V et al (published online ahead of print June 21, 2012). *Chest.* doi:10.1378/chest.12-0608.

**Narrator:**
Recent data presented at ESC 2012 by Bannerjee and colleagues corroborate published studies that validate HAS-BLED.

**Dr. Lip:**
A number of validations show that the HAS-BLED score consistently outperforms other bleeding risk-scoring systems, including the older HEMORR$_2$HAGES score and the ATRIA score, in predicting the risk of clinically relevant bleeding events. In the paper by Apostolakis et al, the HAS-BLED score was the only tested score which had a significant predictive value for intracranial bleeding. And that's quite relevant, because intracranial bleeding, of course, is the most severe form of anticoagulant-related bleeding.

**Slide 5**

## Predicting Bleeding Risk in RE-LY

- Subanalysis of the RE-LY trial of dabigatran for SPAF
- The *CES1* gene single-nucleotide polymorphism (SNP) rs2244613 variant was associated with "a consistent and significant association" with any bleeding and, separately, with minor bleeds, independent of randomised treatment in the trial

| Endpoint | OR (95% CI) | *P* |
|---|---|---|
| Ischemic stroke or systemic embolism | 0.70 (0.33-1.47) | .34 |
| Any bleeding | 0.67 (0.55-0.82) | .00007 |
| Major bleeding | 0.66 (0.43-1.01) | .06 |
| Minor bleeding | 0.70 (0.57-0.85) | .0004 |

Odds ratios are per minor allele for clinical outcomes associated with rs2244613, adjusted for dabigatran dose, age, sex, $CHADS_2$ score, aspirin use, and creatinine clearance.

OR: odds ratio.

Pare G et al. ESC 2012. Presentation P5170.

**Dr. Lip:**
One interesting presentation at this year's ESC meeting was the prediction of bleeding risk in the RE-LY trial related to gene polymorphisms. This was a subanalysis of the RE-LY trial where they identified, at the CES1 gene single-nucleotide polymorphism (SNP), the rs2244613 variant was associated with a consistent and significant association with bleeding, independent of the randomised treatment in the trial.

So this raises the exciting possibility of even personalised medicine, where bleeding risk can be related to a particular patient's gene polymorphisms.

**Slide 6**

## Bleeding Risk and Renal Impairment in AF: Results from Danish National Registry

| Characteristic | No Renal Disease (n = 127,884) | Non-End-Stage CKD (n = 3,487) | Disease Requiring Renal Replacement Therapy (n = 901) | *P* |
|---|---|---|---|---|
| Age, y | 73.2 ± 12.9 | 76.5 ± 11.0 | 66.8 ± 11.7 | < .001 |
| **Risk factors for bleeding, %** | | | | |
| Hypertension | 42.2 | 54.5 | 53.9 | < .001 |
| Abnormal liver function | 1.6 | 3.0 | 4.0 | < .001 |
| History of stroke or systemic thromboembolism | 14.0 | 18.0 | 14.8 | < .001 |
| History of bleeding | 7.0 | 16.3 | 15.2 | < .001 |
| Age ≥65 y | 74.6 | 84.6 | 59.2 | < .001 |
| Use of NSAIDs | 20.8 | 23.5 | 11.0 | < .001 |
| Alcohol abuse | 3.6 | 4.0 | 4.8 | .05 |

CKD: chronic kidney disease; NSAID: nonsteroidal anti-inflammatory drug.

Olesen JB et al. *N Engl J Med*. 2012;367:625-635.
Olesen JB et al. ESC 2012. Poster 1046.

**Dr. Lip:**
Bleeding risk also features in another presentation at the ESC meeting, looking at bleeding risk and renal impairment with a dataset of over 127,000 individuals in a Danish National Registry. The overall message is that patients with chronic kidney disease who are not on renal replacement therapy are at extremely high risk of stroke, which is significantly reduced by anticoagulation with warfarin. But equally, such patients are also at risk of bleeding on anticoagulation therapy. And very clearly, more work needs to be done to identify net clinical benefit in these patients. Nonetheless, it does highlight that this is a high-risk category of patients that, whilst being treated on warfarin, carry a significant risk of bleeding, but that has to be balanced against significant reduction in the risk of ischaemic stroke.

**Slide 7**

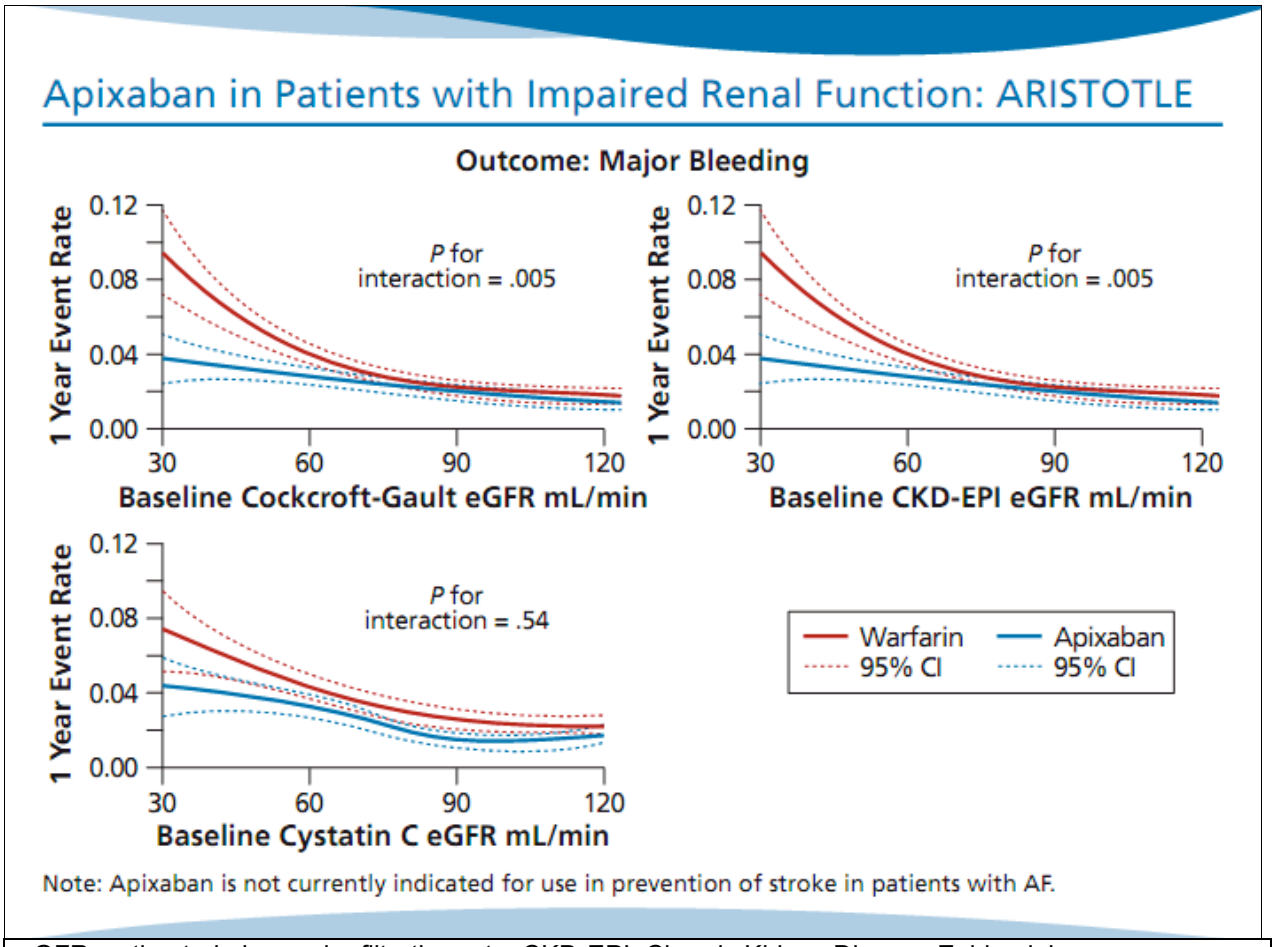
## Challenge Question

**Which of the following statements best describes the bleeding risk associated with apixaban therapy in patients with renal impairment, according to the ARISTOTLE renal substudy?**

- ○ Patients with renal impairment had a significantly higher risk of major bleeding with apixaban
- ○ There was no difference between bleeding risk in patients with renal impairment and those with normal renal function
- ○ Patients with moderate renal impairment had a reduced risk of major bleeding with apixaban
- ○ Patients with mild renal impairment only had a reduced risk of major bleeding with apixaban

*Go online to compare your answer with your peers' responses.*

**Slide 8**

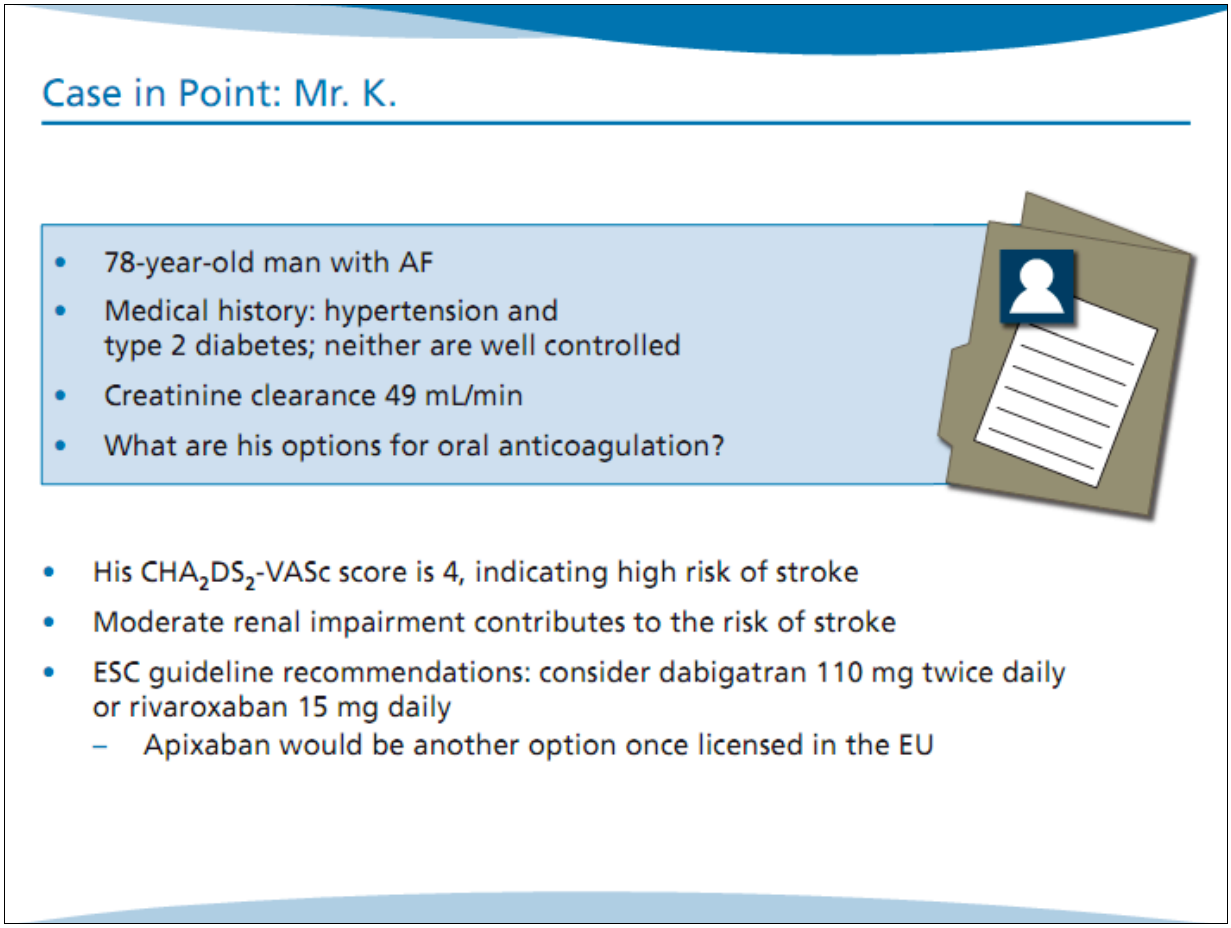



eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Hohnloser SH et al. ESC 2012. Presentation 5172.
Hohnloser SH et al (published online ahead of print August 29, 2012). *Eur Heart J.* doi:10.1093/eurheartj/ehs274.

**Dr. Lip:**
What options do we have? Well, another interesting presentation was the substudy from the ARISTOTLE trial looking at apixaban, an oral factor Xa inhibitor in patients with impaired renal function. There were benefits in terms of stroke reduction; but if you look at bleeding outcomes, the profile seems in favour of apixaban in those patients with moderate renal impairment. So certainly this does suggest apixaban may be a good option, offering a good balance between stroke reduction and the potential for major bleeding.

**Slide 9**




**Dr. Lip:**
Turning now to a case, which tries to illustrate the complexities that clinicians have to deal with. This is a case of Mr. K. He's a 78-year-old man with atrial fibrillation, history of hypertension, type 2 diabetes. Neither are well controlled. His creatinine clearance is 49 mL/min. And what are his options for oral anticoagulant therapy?

Until very recently, his only option was warfarin therapy. He's got a $CHA_2DS_2$-VASc score of 4, which puts him at pretty high risk of stroke. He has moderate renal impairment, which probably has some degree of contributory aspect to the risk of stroke.

By the ESC guideline recommendations, he would be considered for dabigatran 110 mg twice a day, or for rivaroxaban 15 mg a day, the lower-dose option of those 2 novel anticoagulants which are licensed in the European Union at the moment. When apixaban gets its license in the European Union, that would be certainly another option for use in this patient.

**Slide 10**

## RE-LY: Events After Cardioversion

- Stroke/systemic embolism and major bleeding rates after cardioversion were low in the dabigatran- and warfarin-assigned groups

| Events | Warfarin | Dabigatran 110 mg | Dabigatran 150 mg | RR (95% CI) and *P* value | | |
|---|---|---|---|---|---|---|
| | | | | D110 vs Warfarin | D150 vs Warfarin | D150 vs D110 |
| Total randomised, n | 6,022 | 6,015 | 6,076 | — | — | — |
| Cardioversions, n | 664 | 647 | 672 | — | — | — |
| Electric, n | 553 | 554 | 550 | 1.03 (0.98-1.08); *P* =.2420 | 0.98 (0.94-1.03); *P* = .4886 | 0.96 (0.91-1.00); *P* = .0631 |
| Pharmacologic, n | 111 | 91 | 122 | 0.84 (0.65-1.09); *P* = .1836 | 1.09 (0.86-1.37); *P*= .4886 | 1.29 (1.01-1.66); *P* = .0436 |
| Major bleeding events <30 d after cardioversion, n (%) | 4 (0.60) | 11 (1.70) | 4 (0.60) | 2.82 (0.90-8.82); *P* = .0617 | 0.99 (0.25-3.93); *P* = .9865 | 0.35 (0.11-1.09); *P* = .0585 |

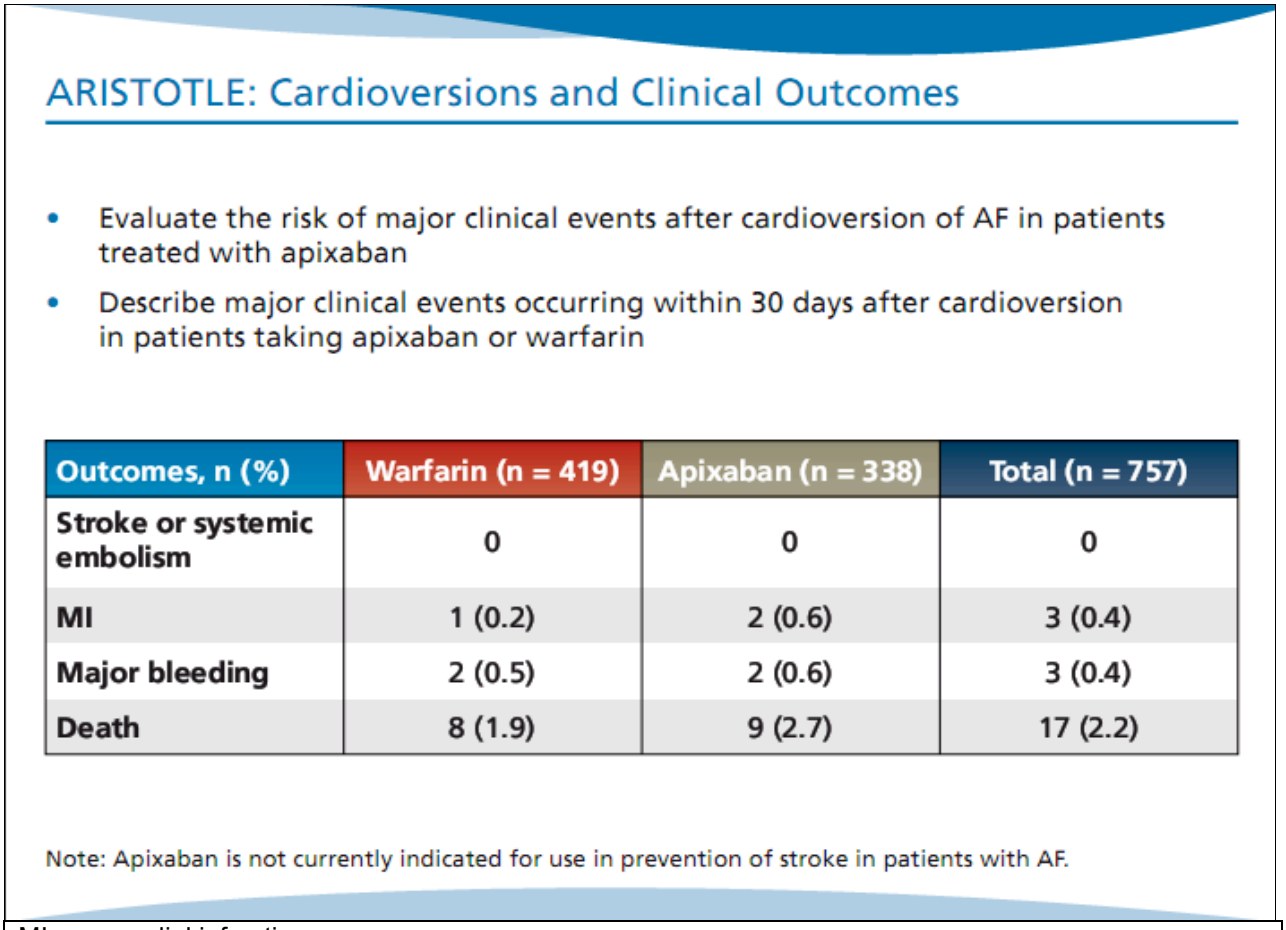
D: dabigatran; RR: relative risk.

Nagarakanti R et al. *Circulation.* 2011;123:131-136.

**Narrator:**
The safety and efficacy of oral anticoagulants in patients with atrial fibrillation undergoing cardioversion has also been explored. These data add to what has been previously published, such as this substudy from the RE-LY trial.

**Dr. Lip:**
From the RE-LY trial, there was a substudy of 1,800 cardioversions, and this did show, in that study, dabigatran to be associated with similar thromboembolism and bleeding events, compared to warfarin, although this is not a randomised trial cardioversion, but it's more a observational subgroup from the main RE-LY trial.

**Slide 11**



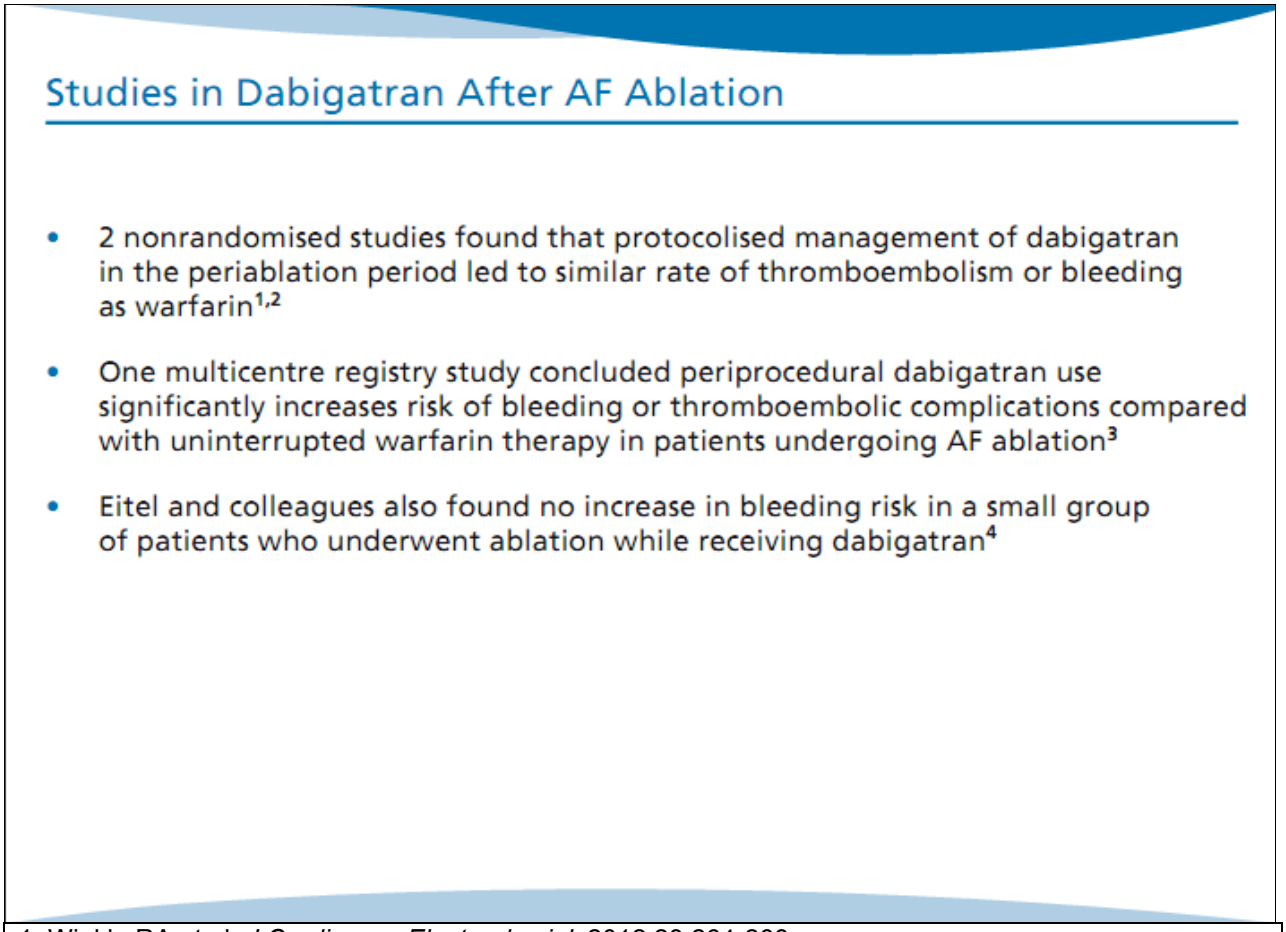

MI: myocardial infarction.

Flaker G et al. ESC 2012. Presentation 4048.

**Dr. Lip:**
We have not seen any cardioversion data for rivaroxaban from the ROCKET-AF trial, but what was quite reassuring to see was the cardioversion substudy from the ARISTOTLE trial. For major bleeding, this was 0.5% in the warfarin-treated patients, and 0.6% in the apixaban-treated patients.

What is reassuring is that the rate of cardiovascular events [and] bleeding were not really much different between the warfarin-treated patients and the apixaban-treated patients.

**Slide 12**

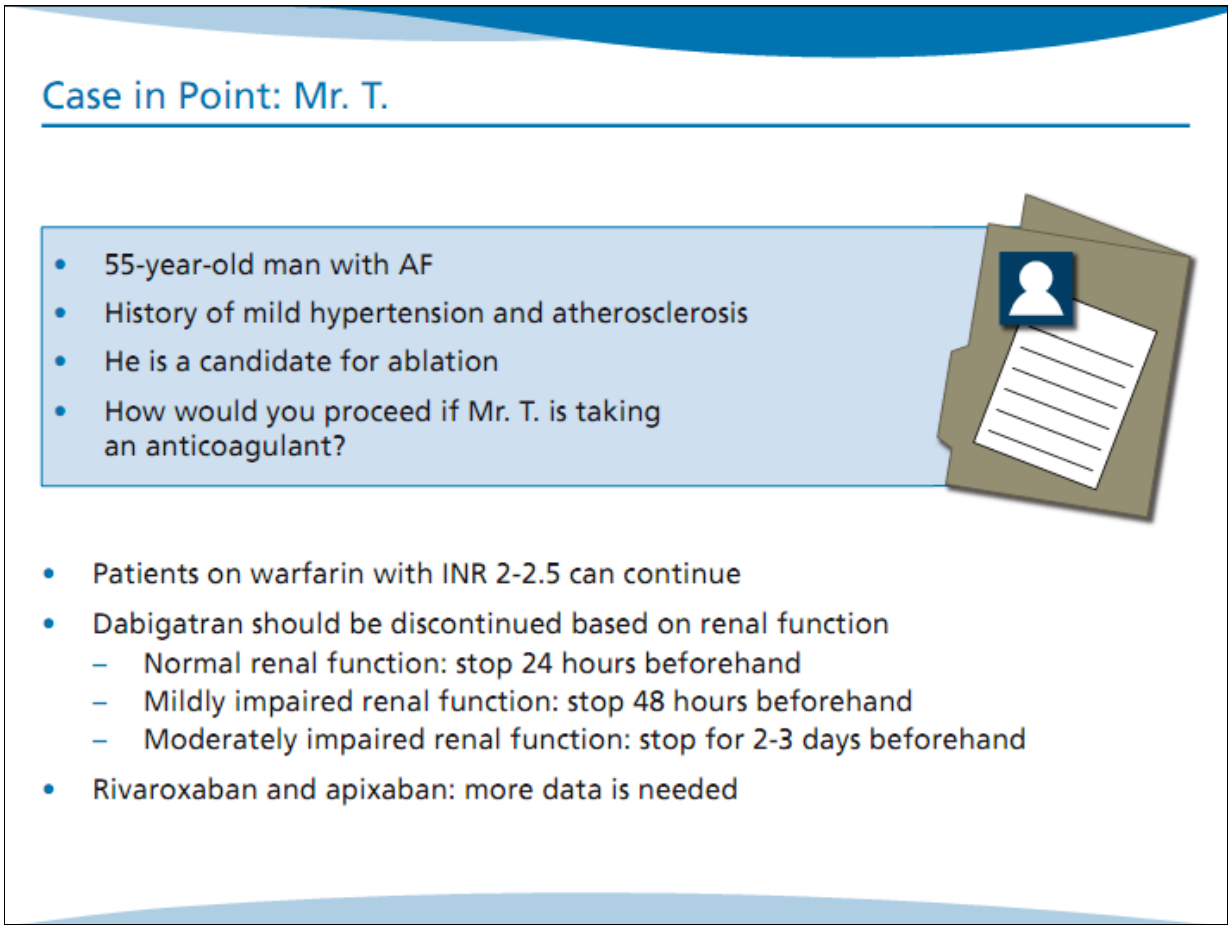



1. Winkle RA et al. *J Cardiovasc Electrophysiol.* 2012;23:264-268.
2. Kaseno K et al. *Circ J.* 2012;76:2337-2342.
3. Lakkireddy D et al. *J Am Coll Cardiol.* 2012;59:1168-1174.
4. Eitel C et al. ESC 2012. Presentation P5369.

**Dr. Lip:**
Turning now to another aspect of atrial fibrillation management that electrophysiologists have particular interest, which is ablation. How should patients on novel oral anticoagulants be managed? Well, the data are a little limited. Of the 3 recent papers on dabigatran and ablation, 2 concluded that the protocolised management of dabigatran in the periablation period was associated with similar rate of thromboembolism or bleeding, compared to warfarin.

However, one multicentre study where the perioperative cessation of dabigatran was a little varied did suggest more events in dabigatran-treated patients.

**Slide 13**

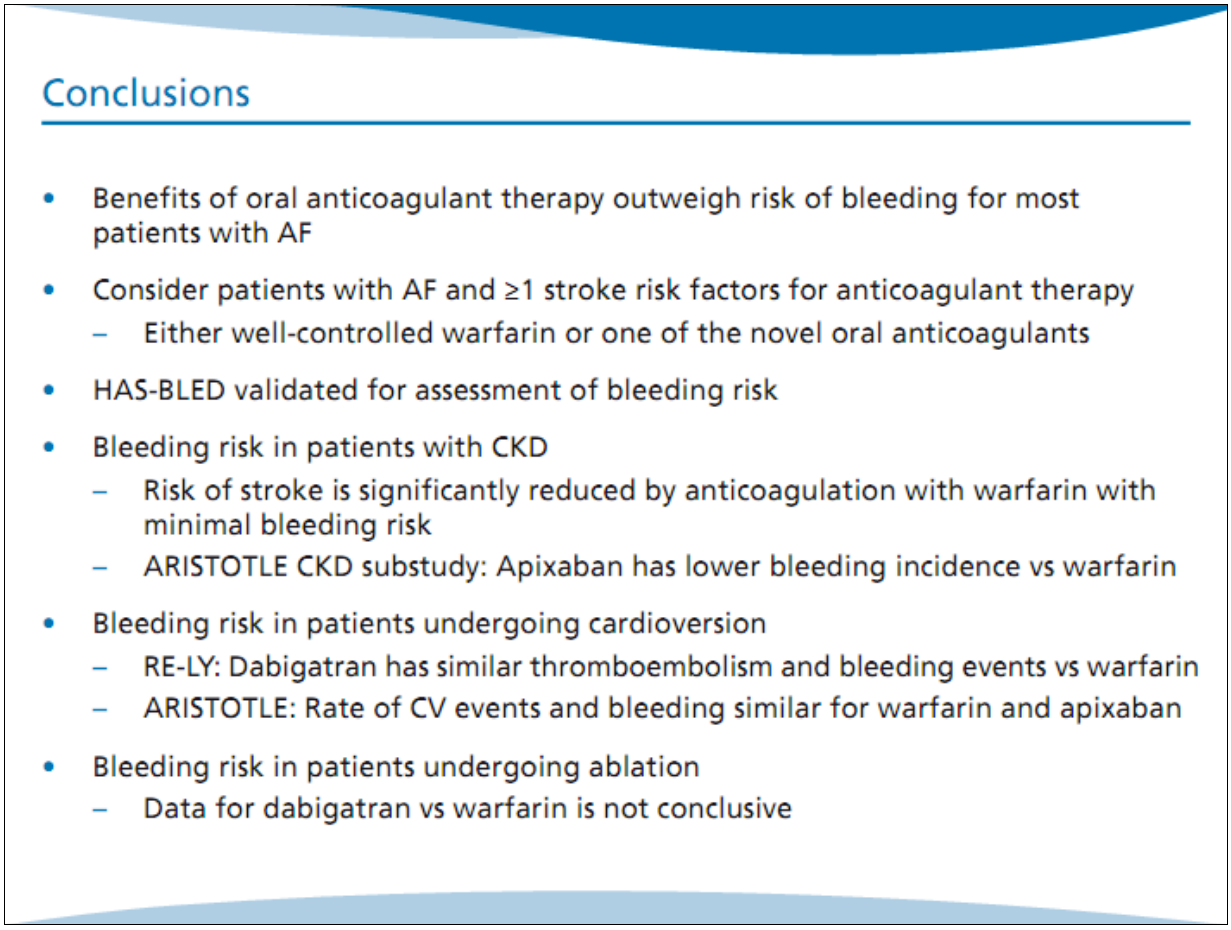



**Dr. Lip:**
So we turn now to another case, the case of Mr. T. He is a 55-year-old man with a history of mild hypertension and atherosclerotic vascular disease with peripheral artery disease. He is a candidate for ablation. How would you proceed if he is on a novel oral anticoagulant?

Well, if this patient were on warfarin, the electrophysiologist would undertake the procedure whilst the patient is on warfarin, within an INR of perhaps 2 to 2.5, without stopping the warfarin. Dabigatran should be stopped as if the patient were getting an interventional or operative procedure. And the time that the dabigatran should be stopped is a little dependent on the patient's renal function.

The actual ablation procedure itself is covered by heparin; and post-procedure, dabigatran can be restarted again once there is satisfactory haemostasis. Once we see more data for rivaroxaban and, eventually, apixaban, this would still be managed in a protocolised manner, especially since the novel oral anticoagulants do not have a specific antidote.

**Slide 14**




**Dr. Lip:**
There are very important clinical practice shifts, strongly recommended in the ESC guideline, much more focused on the identification of truly low-risk patients with atrial fibrillation at the initial step, as these patients do not need any antithrombotic therapy. The patients with AF with 1 or more stroke risk factors can, therefore, be considered for effective stroke prevention, and that is oral anticoagulant therapy, whether with very well-controlled warfarin or one of the novel oral anticoagulants. There is also the focus on the HAS-BLED score to make an informed assessment of bleeding risk, and importantly to make clinicians think about the correctable risk factors for bleeding, rather than guesswork. A high HAS-BLED score is not to actually be an excuse to stop anticoagulant. In fact, such patients actually derive an even greater net clinical benefit from anticoagulant therapy. The absolute gain from stroke-reduction by anticoagulant therapy will outweigh the small increase, in absolute terms, of a serious bleeding.

Lots of studies on atrial fibrillation were presented at the ESC, and I think this reflected the great interest into atrial fibrillation, particularly relating to stroke risk and to bleeding risk.

**Slide 15**

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**Narrator:**
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