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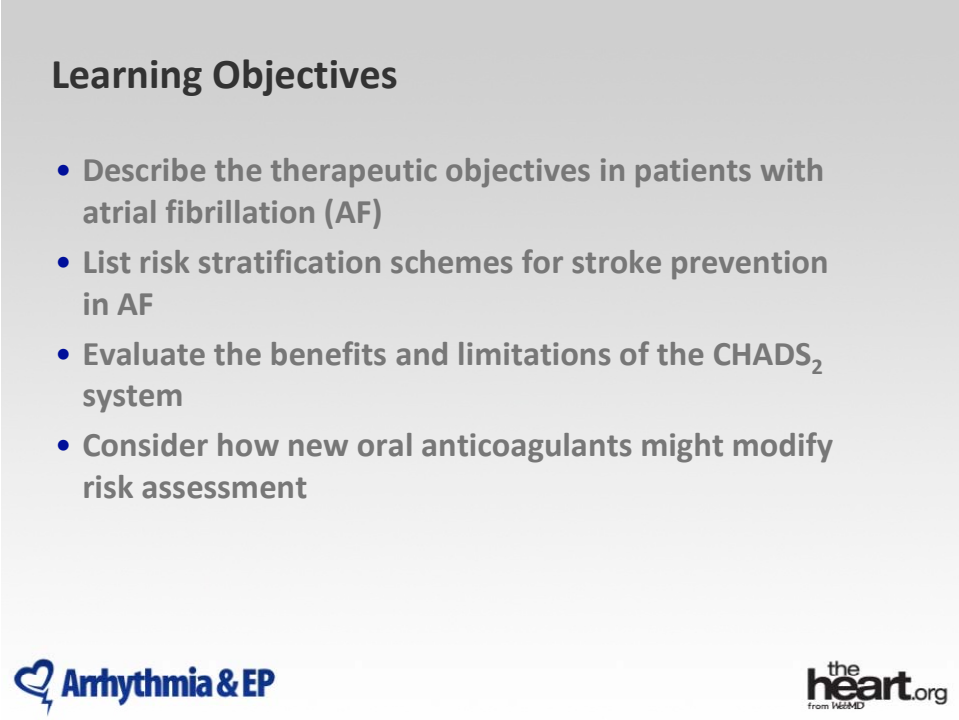
Gregory Lip, MD: Hello. Welcome to theheart.org. I'm Gregory Lip from the University of Birmingham in the United Kingdom, and I'm here in Venice, Italy, for the Venice Arrhythmia Meeting with Al Waldo from Cleveland. Welcome, Al.

Albert Waldo, MD: Hi, Greg.

Dr. Lip: In this program, we will be discussing the topic, "Will New Anticoagulant Strategies Change Risk Stratification in Atrial Fibrillation?"



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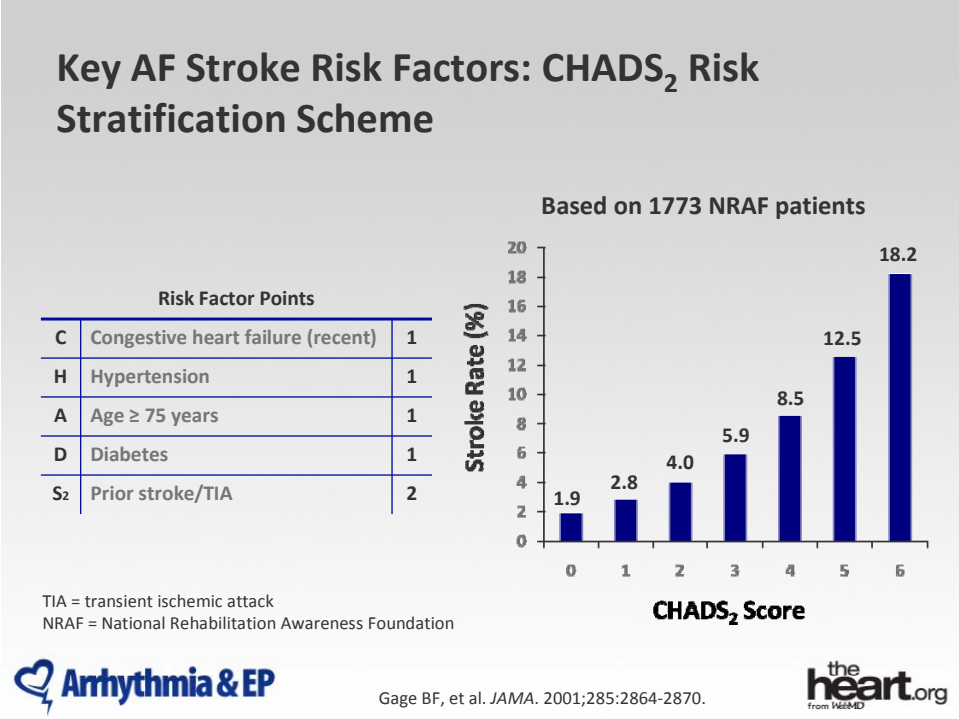
The objectives for today are: describing the therapeutic objectives for stroke prevention in patients with atrial fibrillation [AF]; we will be listing the risk stratification schema which are published to date for stroke prevention in AF; we will be debating the benefits and limitations of these published schema particularly the $CHADS_2$ system, and whether this is applicable with the new data we have on stroke prevention from the recent trials; and finally, we will consider how the new oral anticoagulants might modify risk assessment and whether we should be concentrating on identifying high-risk patients, and whether we should be getting better at identifying the low-risk patients with AF. So Al, if I can start off, could you summarize where we are now in terms of the evidence we have for warfarin in AF and aspirin in AF, at least until earlier this year.



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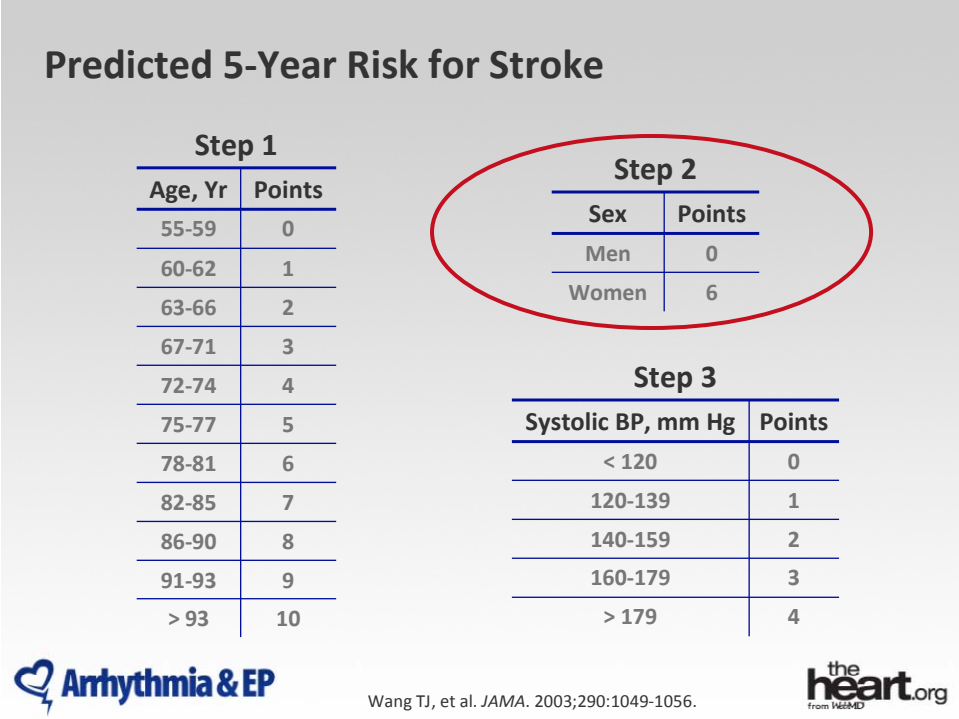
Dr. Waldo: Well, thanks, Greg. This is a very long subject because it really begins in the middle 90s when we began to risk stratify stroke risk for AF. Those data were from an era when we treated patients differently than we treat them now, but still, they were very, very useful. We found that previous stroke and TIA [transient ischemic attack] were the worst kind of risk and that hypertension, recent congestive heart failure, and increasing age were also risk factors. People forget that in the AFFIRM [Atrial Fibrillation Follow-up Investigation of Rhythm Management] trial, we used age as one of the risk factors for stroke because the relative risk for stroke increases by 1.4 per decade beginning at age 65. This is particularly still pertinent in this era. So heart failure, age, diabetes, and of course, hypertension, and previous stroke are factors, but there are other factors, too, that have waxed and waned.



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Gender, female sex was in the original guidelines with the stroke risks. Being a female was considered a big risk, but now, it's considered a weak risk in the guidelines, which I don't really understand. Valvular heart disease, mitral stenosis and the like are very high risk, but we don't see very much of that now, so these things are changing. We continue to look at these risk factors, and you've done that very recently with your new risk stratification which is very important because it adds some risk stratifications that were not part of $CHADS_2$.

Dr. Lip: We'll come back to that point, but we should consider that risk factor assessment is often based on clinical trial cohorts, and female patients are underrepresented in many of the clinical trials.

Dr. Waldo: Exactly.

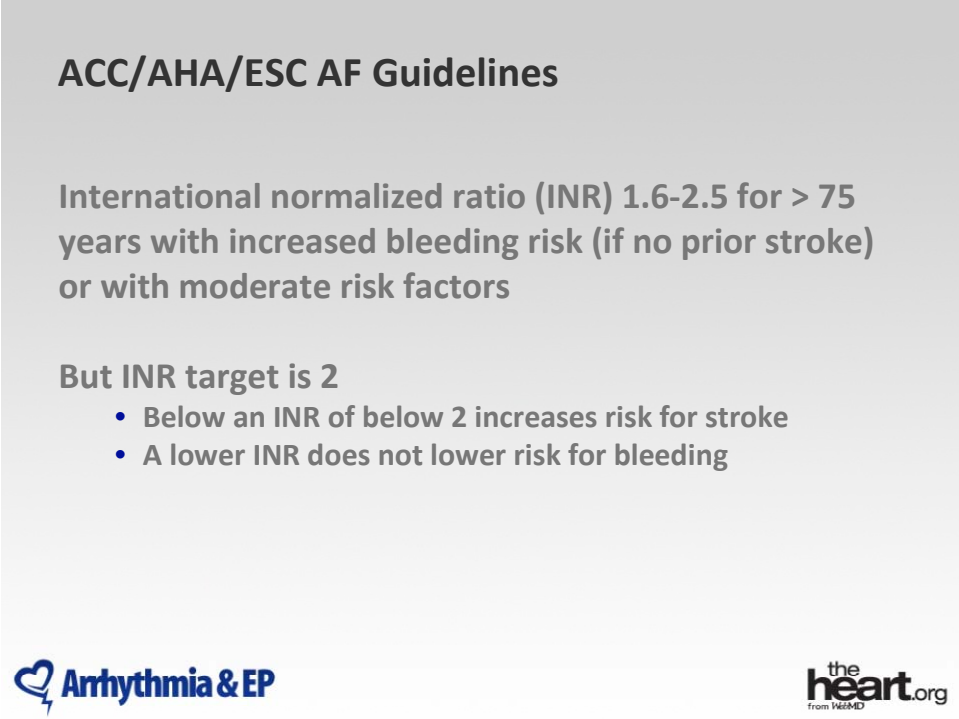
Dr. Lip: The evidence for anticoagulation in high-risk patients is warfarin. From the clinical trials and various meta-analyses, warfarin compared with placebo reduces stroke by about two thirds. There is a view that that could even be much higher.

Dr. Waldo: The original thought was 68% risk reduction, so yes, two thirds.

Dr. Lip: It could well be much higher if we were controlling warfarin much better.

Dr. Waldo: Yes, indeed. We're still learning about that because it turns out time in therapeutic range (TTR) is very important, and the identification of an INR [international normalized ratio]

of 2-3 with a target of 2.5 is really critical because we know that when the INR falls below 2, there is a very sharp rise in the odds ratio for stroke. An INR or 1.7 doubles the risk for stroke, an INR of 1.5 more than triples the risk for stroke. So this is very important.



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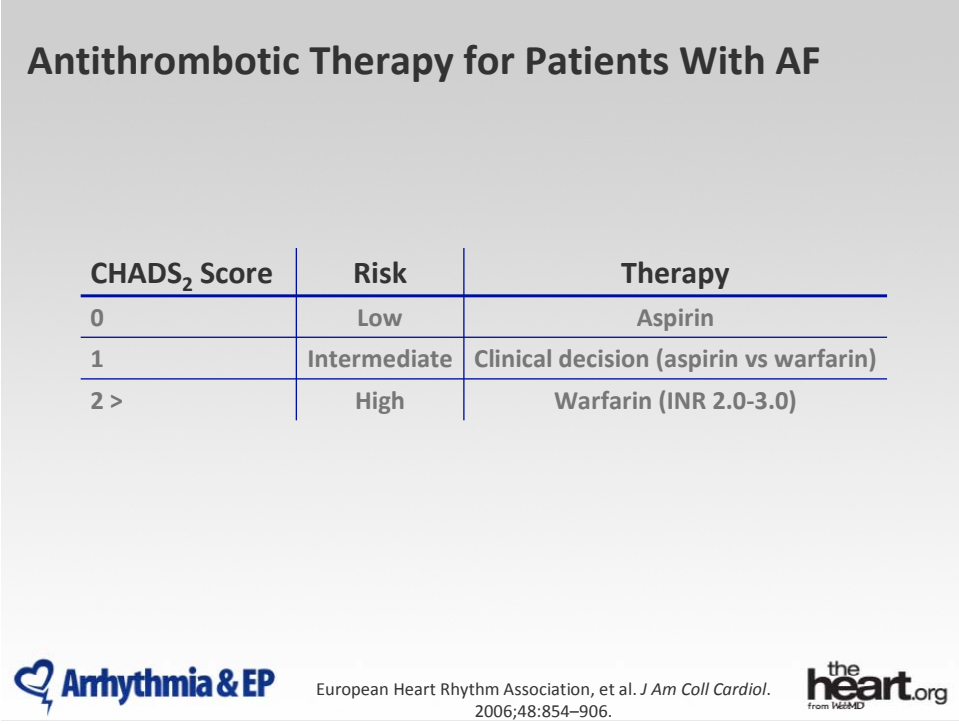
Dr. Lip: In the 2006 AHA/ACC [American Heart Association/American College of Cardiology] Guidelines state that for elderly patients with AF, we should aim for a target INR range of 1.6-2.5 to try and minimize the risk of anticoagulation. What is your view on that?

Dr. Waldo: This is very problematic for several reasons. First, when they say 1.6-2.5, the target is 2, and we know how difficult it is to keep patients in the therapeutic range, and as soon as you get below 2, you rapidly lose efficacy. The data show that there is a very steep rise in the odds ratio for stroke so that with an INR of 1.7, you double the risk for stroke; an INR of 1.5, you more than triple the risk for stroke. The second thing is data from Dan Singer's and Elaine Hylek at Boston University, which they showed some time ago, that when you lower the INR, you don't get any benefit and less bleeding, so all you suffer then is the increased morbidity of stroke.



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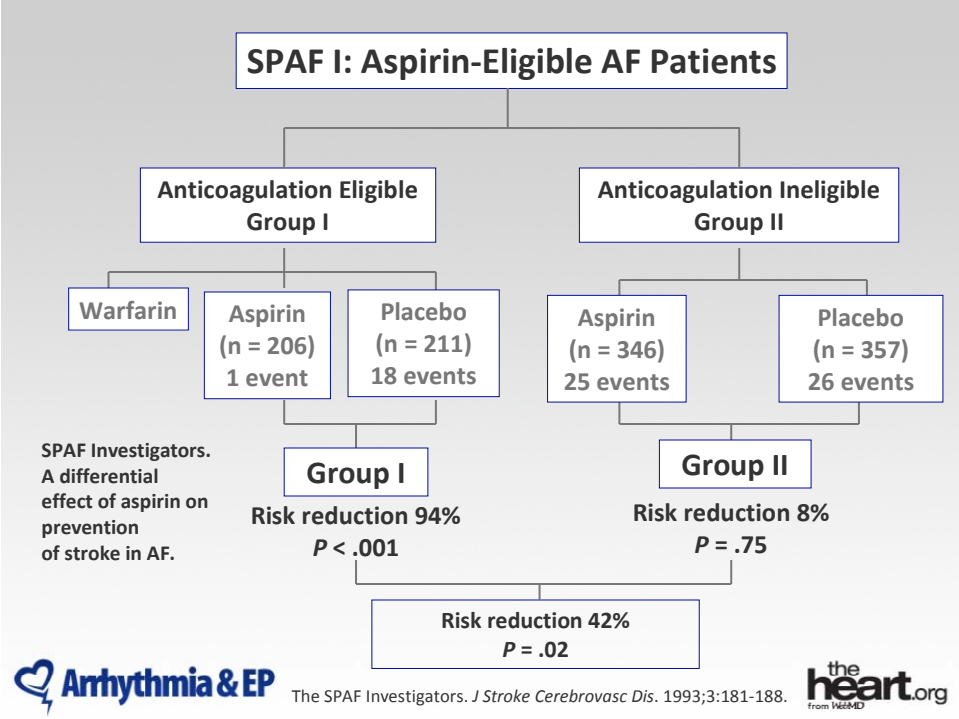
Dr. Lip: Okay. And what about aspirin? Currently, aspirin is recommended for low-risk patients with AF. Aspirin is also recommended as an alternative to warfarin in intermediate- or moderate-risk patients with AF. What are your views on the use of aspirin for stroke prevention in AF?

Dr. Waldo: This is another problematic thing as far as I'm concerned. Among all the studies, there has only been 1 study that has ever shown that aspirin was better than placebo, and that was SPAF I [Stroke Prevention in Atrial Fibrillation]. In SPAF I, there were 2 groups.



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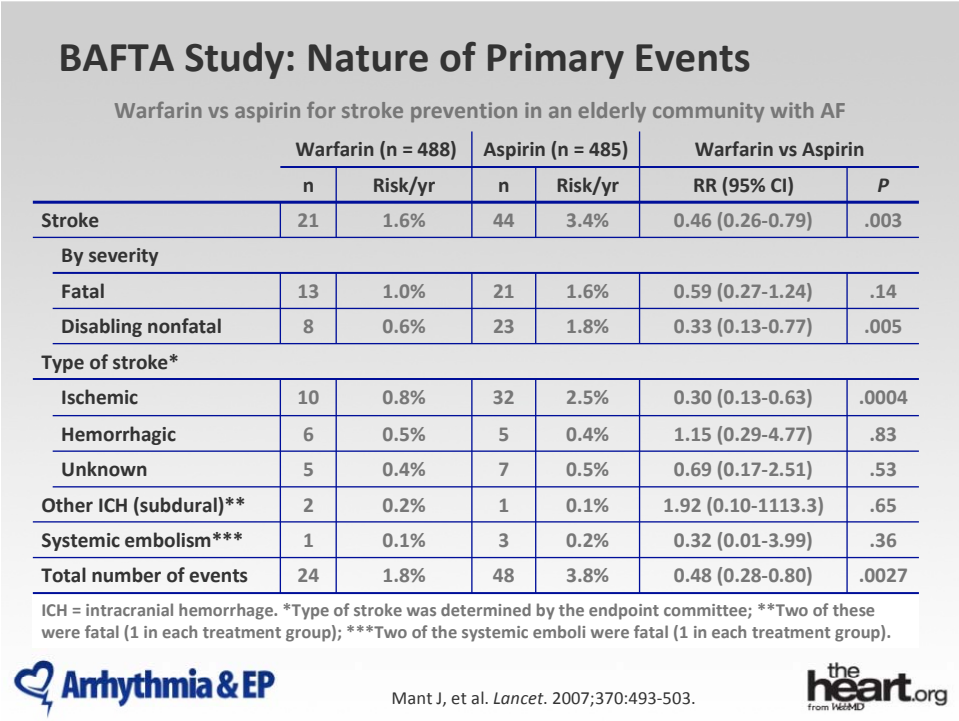
Group 1 was patients who were eligible for warfarin, aspirin, or placebo, and group 2 was patients who were not eligible for warfarin for any number of reasons. If you look at the patients in group 1, and look at aspirin vs placebo, there was only 1 stroke in the aspirin group and 18 in the placebo group. Then if you look at group 2 there were 25 strokes in the warfarin group and 26 in the placebo group, no difference, which is really what I think it should have been in group 1 as well. So there was a 94% risk reduction in group 1; that's never been duplicated before. It was much better than warfarin and if anything, in my judgment, it's clearly an outlier. I'm not sure why that happened, but that has driven much of the data that suggest aspirin is not as good as warfarin but is better than placebo.

It's fair to be skeptical and say that, "If it's better, it's not much better." This is easily borne out, as far as I'm concerned, if you look at the ACTIVE-W [Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events] trial. The ACTIVE-W trial was warfarin vs a combination of aspirin and clopidogrel. The trial was stopped early because the rate of the primary endpoint of aspirin plus clopidogrel was almost double that compared with warfarin. Even if you look at stroke alone, the result was the same. So 2 antiplatelet agents were not better than 1, and I think what this really means is that if you really need protection against stroke, you need a legitimate oral anticoagulant. What we did learn from ACTIVE-A is that clopidogrel plus aspirin is a little bit better than aspirin alone. And Greg, we also have to point out that one of the concerns about warfarin in the elderly is another reason people are given aspirin. Meta-analyses show that if aspirin does anything, it works less in the elderly. Secondly, in the BAFTA [Birmingham Atrial Fibrillation Treatment of the Aged] trial, your trial showed that warfarin was significantly better, and enormously better in my judgment, than aspirin; there

was no difference in bleeding between the 2, and there were far more strokes, and when you get a stroke on aspirin, it's much worse than if you're taking warfarin.



BAFTA Study: Nature of Primary Events

Warfarin vs aspirin for stroke prevention in an elderly community with AF

	Warfarin (n = 488)		Aspirin (n = 485)		Warfarin vs Aspirin	
	n	Risk/yr	n	Risk/yr	RR (95% CI)	*P*
Stroke	21	1.6%	44	3.4%	0.46 (0.26-0.79)	.003
By severity						
Fatal	13	1.0%	21	1.6%	0.59 (0.27-1.24)	.14
Disabling nonfatal	8	0.6%	23	1.8%	0.33 (0.13-0.77)	.005
Type of stroke*						
Ischemic	10	0.8%	32	2.5%	0.30 (0.13-0.63)	.0004
Hemorrhagic	6	0.5%	5	0.4%	1.15 (0.29-4.77)	.83
Unknown	5	0.4%	7	0.5%	0.69 (0.17-2.51)	.53
Other ICH (subdural)**	2	0.2%	1	0.1%	1.92 (0.10-1113.3)	.65
Systemic embolism***	1	0.1%	3	0.2%	0.32 (0.01-3.99)	.36
Total number of events	24	1.8%	48	3.8%	0.48 (0.28-0.80)	.0027

ICH = intracranial hemorrhage. *Type of stroke was determined by the endpoint committee; **Two of these were fatal (1 in each treatment group); ***Two of the systemic emboli were fatal (1 in each treatment group).

Arrhythmia & EP

Mant J, et al. *Lancet*. 2007;370:493-503.

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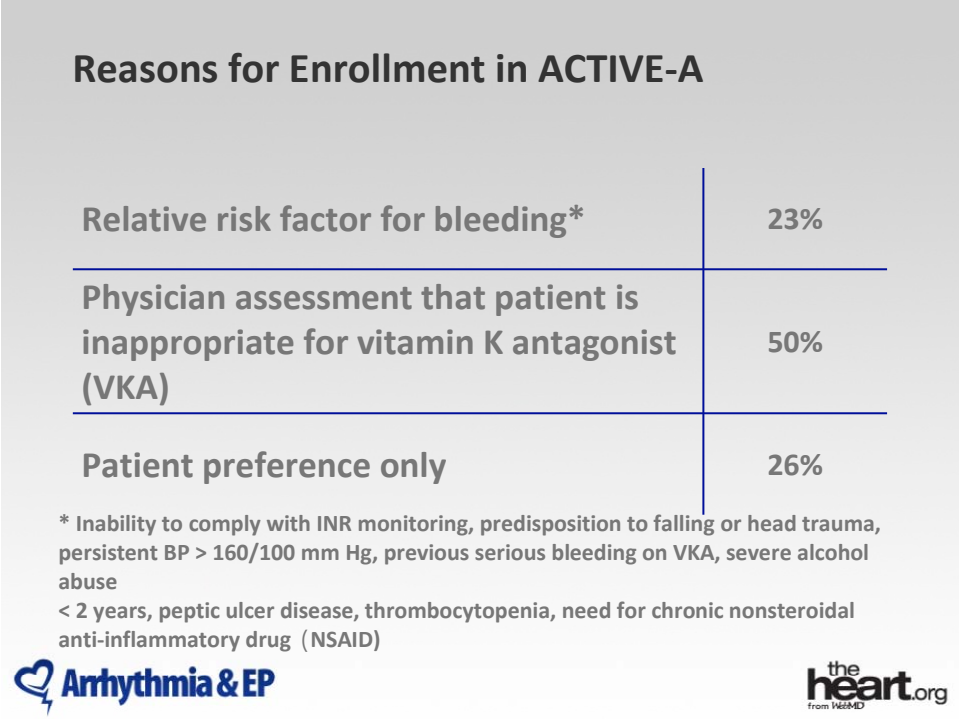
We know that. So in the elderly population, which is growing, right now, half the people with AF are 75 or older. Soon it'll be half the people over 80 and two thirds over 75. So we're really talking about an elderly population, and aspirin doesn't work in that group.

Dr. Lip: Let's turn to some of the more recently published or presented trials.



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You mentioned the ACTIVE program, and you mentioned ACTIVE-W, but I'll turn now to ACTIVE-A because ACTIVE-A was a trial where patients who were either ineligible for warfarin but declined, or were deemed unsuitable who were then considered for the trial. Now, can I have your comments on the patient population suitable for aspirin/clopidogrel?

Dr. Waldo: You know, for aspirin/clopidogrel, the problem with the ACTIVE-A in my judgment was how it was decided patients were warfarin unsuitable. It turns out many of the patients were already on warfarin and then stopped it. Many of the patients went onto warfarin after the trial; that's number 1. Number 2, when you look at the categories, only about 25%-26% were thought to have a legitimate reason for not being on warfarin. Falling was one of them, and that's a legitimate reason not to be on warfarin and previous bleeding also, that sort of thing. But 50% were physician determined; another 25% were patients' desire not to be on warfarin. That's pretty amorphous stuff, not rigorous really at all. I don't think ACTIVE-A helps us at all.

Dr. Lip: Certainly, it's not a treatment regimen, using aspirin and clopidogrel on somebody who doesn't take warfarin because of a bleeding risk, because the bleeding risk with aspirin/clopidogrel was similar to what was seen with anticoagulation.

Dr. Waldo: Exactly.

Dr. Lip: So we are moving into the era of new oral anticoagulants, and of course, at the European Society of Cardiology meeting this year in Barcelona, we had the results of the RE-LY [Randomized Evaluation of Long-term anticoagulant therapY] trial.

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It's certainly a very interesting trial, very much a benchmark trial, and certainly a landmark trial even in terms of how we progress with the new oral anticoagulants. Can I ask how you think RE-LY and the results of the stroke prevention with dabigatran in that trial would influence our approach to treating patients with AF?

Dr. Waldo: It's made a dramatic impact in my judgment for 2 reasons. One is that the 150-mg twice a day dose of dabigatran beats warfarin, and then second, the 110-mg dose twice a day was not inferior to warfarin and in fact was safer than warfarin. Even the 150-mg twice a day dose was a trend toward being safer than warfarin. There are all sorts of advantages because one of the problems with warfarin is concern for bleeding. There is less bleeding with dabigatran and better efficacy, and that's hard to beat.

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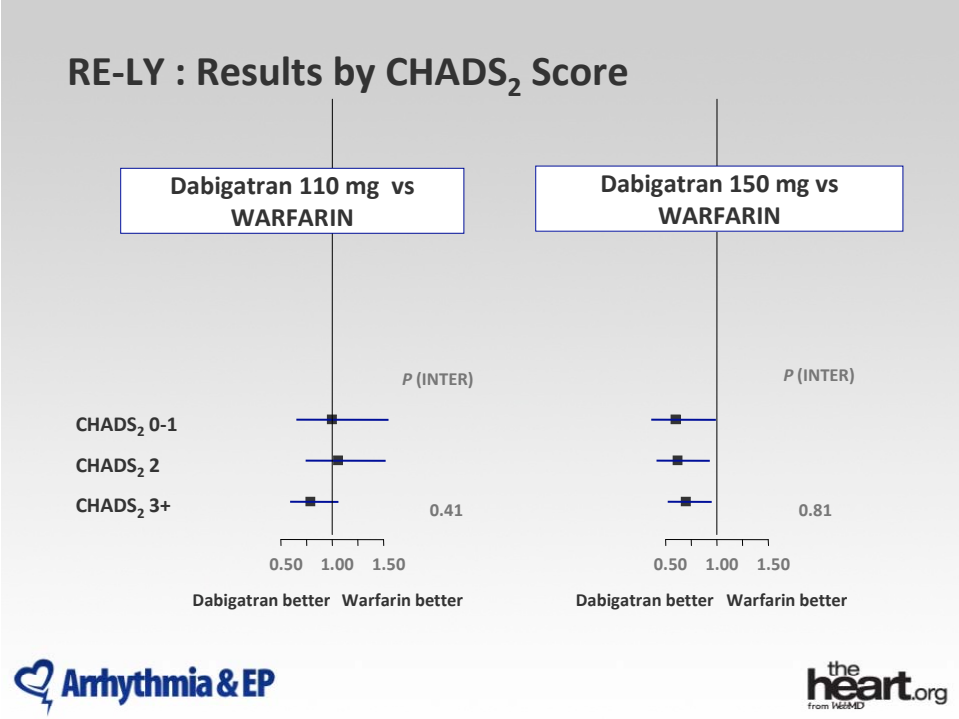
And there are a lot of other reasons; there is virtually no interaction with foods and drugs, and that's an enormous change. Then the other thing is all the things that I always call the "landmines" out there for patients because of all the interactions with warfarin, food and drugs, that are not present. Patients could be fairly well tolerant for a long time, and suddenly, something happens: they get an antibiotic and don't tell the doctor that they're on warfarin, and their INR goes too high; or they take licorice as one of my patients did sometime ago and their INR went to 1.4; if they go have some kiwi and don't realize it's very high in vitamin K, they're in trouble. There is just a huge list.

There are so many other important things. In respect to dabigatran, you take the drug and just a few hours later, you're anticoagulated. And with warfarin, when you start the patient, the average is at least 5 weeks before you reach a stable INR, and it can take a lot longer. And then, if you have to stop for anything from a procedure like a colonoscopy or any kind of surgery, you have to stop warfarin far ahead, whereas with dabigatran, you could stop just before; you don't have to start bridging with low-molecular-weight heparins and the like. So there are many advantages.

Dr. Lip: Let's examine the impact of the RE-LY trial and dagibatran on stroke risk assessment because in the RE-LY trial, about one third of the patients have a CHADS score of 0-1, one third of the patients have a CHADS score of 2, and about 1 third of the patients have a CHADS score of 3 and above.



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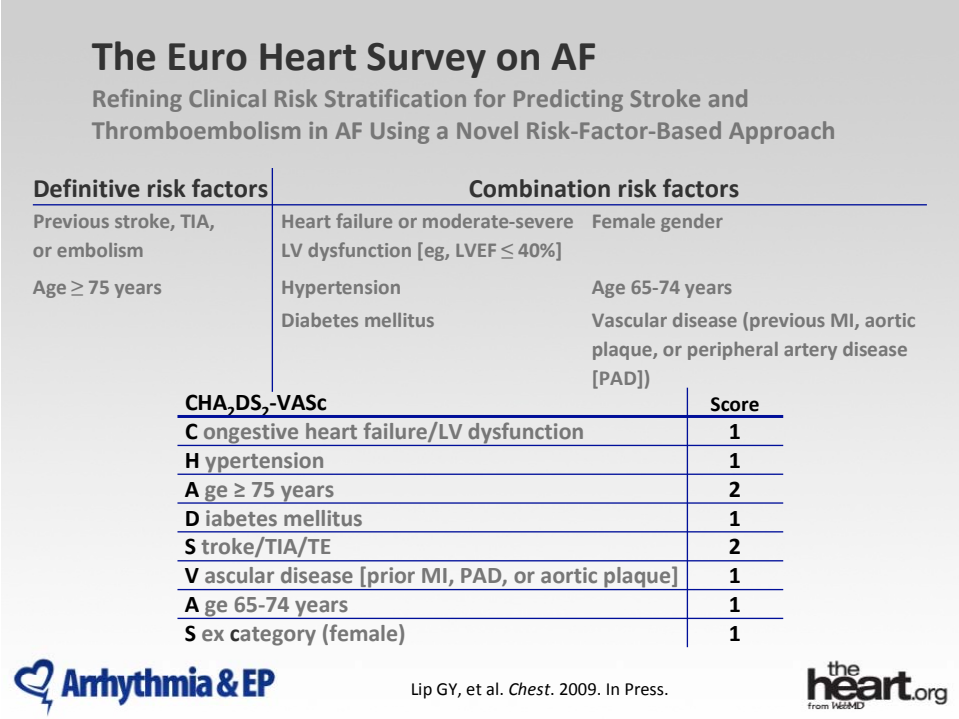
Now, conventionally, many clinicians would not think about trying to start an anticoagulant in somebody who has a CHADS score of 0-1, and this, therefore, raises the whole issue of should we change our approach to identifying high-, moderate-, and low-risk patients with AF? Should we still be obsessed with trying to identify the high-risk patients, or should we maybe concentrate on identifying the low-risk patients?



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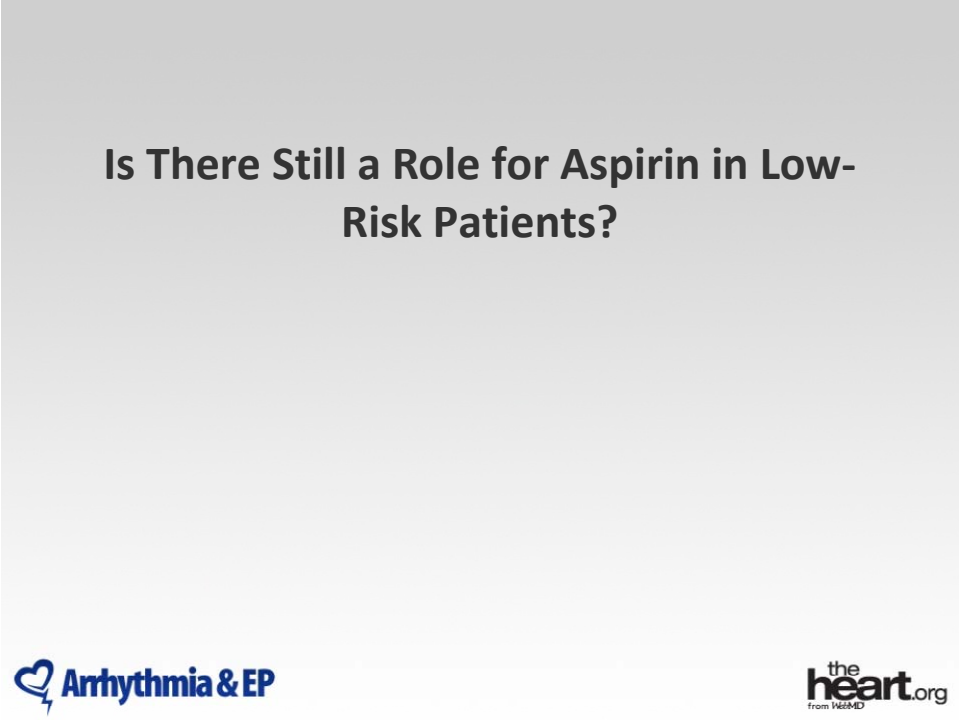
Dr. Waldo: That's very well put. That's one of the nice things about the new stroke risk stratification scheme that your group has developed. And the acronym is not easy to say but it's the CHA_2DS_2- $VASc$

Dr. Lip: They call it CHADSVASC.

Dr. Waldo: CHADSVASC is good, but the point you missed, we used to say $CHADS_2$, CHADSVASC is okay but there are two sub-2s in it. That's really important because by doing that, by adding peripheral vascular disease, by adding older age, giving age over 75 more value and age 65-75 less value, that sort of thing, what you've done in this is you have made the low-risk population clearer. Your data clearly show that there were no strokes in that group at all; this is very, very important because in CHADS, that's not the case at all, and in the other risk stratification schemes, even Framingham, that's not the case. So I think when you know who you don't have to treat, that's a very, very important new addition to the way we should approach patients with anticoagulation therapy.

Dr. Lip: Now, we discussed earlier about the value of aspirin in patients with AF, and of course, the current guidelines as they stand from 2006 or so suggest we give aspirin to low-risk AF patients.



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The data for aspirin in that category of patients, for example, in the Japanese AF trial, aspirin compared with control or placebo in patients with lone AF didn't have any benefits. So should we still be prescribing aspirin to low-risk AF patients if we can correctly identify truly low-risk patients?

Dr. Waldo: Well, I don't think so, but I have been a skeptic about aspirin for a long time. I rarely prescribe aspirin to low-risk patients in any event because like anything, if you prescribe something that has virtually no benefit, you just subject the patient to the risk, and I don't see that that is valuable. And aspirin certainly has well-described risks, so again, I think that's one of the real advantages of CHADSVASC.

Dr. Lip: Well, thank you very much, Al, but if you have CHADSVASC, and if you got a CHADSVASC score of 0, which means truly low risk, then one option may be even to consider new antithrombotic therapy.

Dr. Waldo: I would say that.

Dr. Lip: If you've got a CHADSVASC score of 1 and above, which suggests, I suppose, it's a moderate- to high-risk patient, then you give then an anticoagulant which does nothing if you give aspirin.

Dr. Waldo: Exactly. The mantra that I have always suggested is that if you're really worried about stroke, you take an anticoagulant. There are so many reasons for that. Data from the

Hylek-Singer group showed that if you get a stroke and if you're on warfarin in the therapeutic range, the mortality rate is far less by a factor of about 3. The intensity of the stroke is far less as well, whereas if you are on aspirin, there's very little difference from placebo with a higher death rate and both acutely and at 30 days. If you survive the stroke, it's still far more severe.

Dr. Lip: Well, let's turn a bit to the skeptics who would say that, "It's really a matter of benefit-to-harm," or the ratio between benefit and harm. Obviously, there is some analysis and the net clinical benefit in relation to stroke risk. But there is certainly a viewpoint that we may be dealing with stroke rates and bleeding rates which are perhaps declining because of better control of hypertension.

Dr. Waldo: Because we take so much better care of comorbidities this has made a difference. It has been particularly due to hypertension, but that's only 1. Just look at the so-called 2-fold increased risk in mortality in AF patients who have heart failure. We take such good care of patients in the year 2009 compared with how we did a decade ago or 2 decades ago. We have to take good care of the patient in all respects, and anticoagulation is one of them.

Dr. Lip: Well, that's certainly weird that aspirin sometimes is used to treat the physician, not necessarily the patient.

Dr. Waldo: I'm glad you said that. I really think that's true. Many people regard aspirin as benign. It isn't benign and we see that from the data.

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Will New Anticoagulation Strategies Change Risk Stratification in Atrial Fibrillation?

Dr. Lip: We're moving in exciting times because we have a lot of new oral anticoagulants. We've had a bit of a discussion on dagibatran in the RE-LY trial where clearly, we have a vision of what is changing with new drugs coming along.

Dr. Waldo: Trials with new factor Xas will be coming to conclusion fairly soon. These are large trials such as ROCKET-AF [Rivaroxaban – Once-daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation] with rivaroxaban and trials with apixaban and edoxaban

Dr. Lip: As these new therapeutic options come along, our approach to risk stratification will need to evolve accordingly. We've had a superb discussion on how we perhaps should change the paradigm, concentrating more perhaps on identifying the low-risk patient.

Dr. Waldo: I would like to emphasize that the historical risk stratification schemes have to be continually reexamined because it's a changing landscape.

Dr. Lip: Thank you very much, Al, for that superb discussion. We've covered quite a range from history to recent trials, having a look at the future, and then with new exciting developments in therapy. Clearly there will be the need to change our approach to risk assessment of outpatients with AF as well as the holistic management of associated comorbidities and risk factors.