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The Role of and Selection Process for the New Anticoagulants in Nonvalvular Atrial Fibrillation



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DR. REIFFEL: I'm Jim Reiffel, MD, cardiologist and electrophysiologist from Columbia University in New York City. With me are Drs Halperin, Kowey, and Naccarelli.

DR. HALPERIN: I'm Jonathan Halperin a cardiologist at the Mount Sinai Medical Center in New York.

DR. KOWEY: I'm Peter Kowey, cardiologist at Lankenau, Main Line Health, and Jefferson Medical College in Philadelphia.

DR. NACCARELLI: I am Jerry Naccarelli from the Penn State University College of Medicine at Hershey.

DR. REIFFEL: Today we're going to be talking about the role of and selection process for the new anticoagulants in nonvalvular atrial fibrillation. To start us off, Jon, maybe you could comment on what do we mean by nonvalvular atrial fibrillation as it pertains to three studies: Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY),¹ Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF),² and Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE).³

The following Expert Roundtable Discussion was held on August 3, 2012.

The discussion focused primarily on: (1) The definition of nonvalvular atrial fibrillation; (2) the advantages and disadvantages of warfarin; (3) the pharmacology of the new anticoagulants; (4) the major clinical trials that led to the approval of the new anticoagulants; and (5) determining what anticoagulant to use in patients already on warfarin—"starters" versus "switchers." (*Med Roundtable Cardiovasc Ed.* 2012;3(3):143–151) ©2012 FoxP2 Media, LLC

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DR. HALPERIN: These studies were all based on noninferiority designs, which means that they are basically comparing an active treatment—warfarin, the standard of care—to a new agent without a placebo control. Since that requires the extrapolation to efficacy against a putative placebo, such trials require parallelism or a constancy assumption with respect to the trials conducted years ago that compared warfarin to an inactive control, typically a placebo.

The inclusion criteria for the studies, excluded patients with rheumatic mitral stenosis of undefined severity, and any prosthetic heart valve, whether biological or mechanical. It was not stipulated in those days whether, for example, valve repair will have qualified the patient as "valvular atrial fibrillation" and excluded the patients from the trial, because so few of those operations were performed.

Also excluded were patients with thyrotoxicosis at the time of atrial fi-

brillation. So, essentially, patients with rheumatic mitral stenosis, any valve surgery, or thyrotoxicosis, would not fall under the umbrella of nonvalvular atrial fibrillation.

DR. REIFFEL: It is important to emphasize that nonvalvular atrial fibrillation for purposes of selecting a new oral anticoagulant is not the same as not having valve abnormalities. Therefore, if you've got a patient with mild or moderate aortic disease or mitral regurgitation—for these purposes, that would not be considered significant valvular heart disease. Patients with valve disease that did not need an operation within the next year were allowed into these trials. Nonvalvular atrial fibrillation does not mean that you can't have any form of valve disease.

Jerry, Jon mentioned the prior trials with warfarin as the background, so maybe you should talk briefly about the pros and cons of warfarin and why even bother thinking about the new agents?

DR. NACCARELLI: Prior to the release of the newer anticoagulants, the mainstay of therapy for preventing stroke with atrial fibrillation was the use of warfarin: this was based on a series of trials, the largest being Stroke Prevention in Atrial Fibrillation 1 (SPAF1)⁶ showing that if properly used, warfarin would reduce the risk of stroke by about two-thirds. This requires keeping warfarin in the therapeutic range, which has been found over the years to be 2.0 and 3.0 of an international normalized ratio (INR). Those patients with subtherapeutic INRs obviously have a higher risk of stroke, and patients with supratherapeutic INRs have a higher risk of bleeding.

Now these data have been known for more than 20 years and the issues relate to the following: First, in spite of these pretty impressive data, only about half of the patients in the United States who should be on warfarin by anyone's guidelines are on warfarin.

That of those patients taking warfarin, only about half of the patients in a community-based INR center keep within the therapeutic range. We do a lot better with our anticoagulation clinics where two-thirds of the patients are in the anticoagulation range.

Warfarin is a drug that works. It's very effective, but the limitations of the use of this drug, have made us eager to have some options. The drug has a slow onset of action. There's a lot of genetic variation in metabolism. Since warfarin affects the vitamin K dependent pathways of the coagulation cascade, there are significant food and

"There is a role for each of these agents and the clinician is going to have to become familiar with the pros and cons of each of these, the drug interactions with each of these, the dosing issues with each of these."

-James Reiffel, MD

drug interactions. Anything you eat or take will talk to warfarin and have an impact on whether you're therapeutic or not. The therapeutic windows may narrow and we have to measure something—an INR—in order to try to keep people within a therapeutic range. This requires frequent coagulation monitoring. The dose requirements change depending on how much vitamin K is in the patient's diet and what medicines they are taking.

Frankly, there are a lot of drug-related patient medical characteristics and genetic issues that we understand, but really aren't totally incorporated into the use of this drug. It just has become complex. So there's been a real need of having an alternative anticoagulant that would be easier to use without

having to go to an INR clinic or have dietary interactions.

DR. REIFFEL: That's a good background. Let's move into the discussion about the new anticoagulants. Peter, can you tell us a little bit about the pharmacology of dabigatran and rivaroxaban and apixaban, the newer anticoagulants—pharmacokinetic/pharmacodynamic interactions and the like?

DR. KOWEY: I think one of the things that is important for physicians to understand is that, as Jerry said, we've had a long history of using a very complicated drug, which was warfarin. The new drugs are a significant advance, but they're not necessarily going to be a cakewalk. They're all complicated drugs that have their own individual pharmacology including drug interactions and particular pharmacokinetic/pharmacodynamic profiles that physicians are going to have to learn.⁷

One of the things I think we've seen now with the dabigatran experience is that bleeding is much more likely to occur when the drug is used incorrectly. Doctors are going to have to pay careful attention to dosing instructions. This will inevitably be true for the other newer agents as well.

But, these drugs are different, as you said, not only in terms of the mechanism of action—dabigatran being a direct thrombin inhibitor and the other two drugs being factor Xa inhibitors—but, also in terms of their pharmacology. For example, each has a different half-life. The half-life of dabigatran is somewhere between 12 to 17 hours. Rivaroxaban is in the 6 to 10 hour range and apixaban is about 8 to 15 hours. Rivaroxaban is the only one of the three drugs that's dosed once a day. The other two drugs are twice daily in the clinical trials that we'll talk about.

The other thing that's different about the drugs is their elimination. The highest amount of kidney elimi-

nation is for dabigatran. It's about 80%, whereas with rivaroxaban, it's somewhere in the range of about 60% to 65%—70%, and apixaban about 25%. The remainder of the elimination for rivaroxaban and apixaban is through hepatic metabolism. They are both acted upon by the CYP3A4 metabolic pathway. So this obviously leads to issues with regard to drug interactions. For example, concomitant use of ketoconazole, which is a potent 3A4 inhibitor, is problematic.

For dabigatran, we worry more about drugs that have an effect on the P-glycoprotein transport system that can either cause lower levels of dabigatran if those drugs are inducers like rifampin, or may lead to much higher levels in the case of drugs like amiodarone and dronedarone when there is the potential for inhibition of the P-glycoprotein transport system.

Without getting into much more detail, Jim, I think the most important thing for physicians to understand is that there is some burden to digest the pharmacology of these drugs (excuse the pun, by the way) before they're used in clinical practice. Because if they are not used properly, you get either more clotting or more bleeding.

DR. REIFFEL: I think, Peter, those are all important points. One of the things to comment on, at least as related to the potential complexity of this, using dabigatran as an example, is where you said, the P-glycoprotein inhibitors and inducers, but not the CYP3A4 agents can produce interactions. If you have good renal function, say a clearance of 100 cc a minute, and you drop down to 50 cc a minute, the serum concentrations of dabigatran will go up somewhere between two- and three-fold. In the clinical trials there were no issues in that range in the patients who were enrolled. But if you take the lower end of that range, and then add an agent that can double the serum concentrations, the bleeding risks become sub-

stantial. That is why the package insert for dabigatran cautions, for example, against using it concomitantly in the 150 BID dose with an agent such as dronedarone.

DR. KOWEY: Jim, I think it's very important to get the dose right. We're a little bit handicapped that we don't have the 110 dabigatran dose in the United States, but we do have a 75 mg dose. I completely agree with you. I think as you get down into these borderline creatinine clearances, if you do

"I think the strongest argument in favor of making the change, is that results in clinical trials of all of the new drugs that have thus far been reported offer substantial reductions in the risk of intracerebral hemorrhage."

-Jonathan Halperin, MD

add drugs that potentially may have an effect on elimination, it's probably a good idea to step down the dose. For rivaroxaban, we have the 15 mg dose. For dabigatran we have a 75 twice daily dose, which is probably a little bit lower than we'd like it to be, but it is usable in certain clinical circumstances.

DR. REIFFEL: Why don't we talk a little bit about where those doses came from. They are from the three pivotal trials, RE-LY, ROCKET-AF, and ARISTOTLE. So, Jon, would you tell us a little bit about RE-LY, and then Jerry, ROCKET, and Peter, ARISTOTLE?

DR. HALPERIN: RE-LY was an open-label comparison of dabigatran, the direct thrombin inhibitor compared to warfarin in 18,113 patients who had nonvalvular atrial fibrillation and at least one additional stroke risk factor from the CHADS₂ risk scoring sys-

tem.¹ Patients were randomly assigned to either open-label warfarin at an INR of 2 to 3, or to one of two blinded doses of dabigatran, 110 mg twice daily—a dose not subsequently approved by the Food and Drug Administration (FDA) for use in the United States—and a higher dose of 150 mg twice daily, which has been approved. There were approximately 6000 patients in each group. The primary objective was noninferiority compared to warfarin for the primary outcome of all stroke—including both ischemic and hemorrhagic stroke—and systemic embolism. The minimum exposure of the patients was one year, the maximum about three years, and the mean exposure about two years. The key safety measure was bleeding during treatment with these drugs.

The primary outcomes were a "home run" for the sponsor of the trial. The higher dose of dabigatran was statistically superior to warfarin for prevention of the primary events—event rates of 1.7% per year with warfarin and 1.1% per year with dabigatran, 150 mg twice daily. And the lower dose, 110 mg twice daily, proved noninferior, but not superior to warfarin with an event rate of 1.5% per year.

The criteria for major bleeding events were defined differently across the trials. In the RE-LY trial, this was defined as clinically overt bleeding associated with a hemoglobin drop of 2 grams per deciliter or more, transfusion of 2 or more units of blood, or bleeding at a critical anatomical site.

Here, the lower the dose of dabigatran proved safer and the higher dose of dabigatran noninferior to well-adjusted warfarin.

In regard to the worst complication of anticoagulant therapy in patients with atrial fibrillation, which is a hemorrhagic stroke, rates of intracerebral hemorrhage were amongst the lowest ever reported in clinical trials. Warfarin

actually performed very well compared to historical rates at 0.4% per year in the RE-LY trial. The rates on the two doses of dabigatran were approximately the same at 0.1% per year, lower than on warfarin with respect to this terrible complication of anticoagulation.

When you look at overall bleeding, which as I said, with the higher dose of dabigatran was statistically comparable to that with warfarin, the excess of bleeding on dabigatran was predominantly in the gastrointestinal (GI) tract. There was more GI bleeding with dabigatran 150 mg twice daily than warfarin, substantially less intracerebral hemorrhage, and was comparable between the two treatments for most other types of bleeding.

There was a so called “signal,” that did not reach statistical significance for higher rates of myocardial infarction (MI) in patients given dabigatran compared to warfarin. When all MI events, including clinically silent events diagnosed based on new Q waves on the electrocardiogram, were included in the analysis, the differences were not statistically significant. It remains controversial whether or not there is an incremental risk of MI in patients with atrial fibrillation treated with dabigatran compared to warfarin. It’s worth emphasizing that regardless of how you interpret the statistical differences, the overall rates of MI in patients with atrial fibrillation are relatively low compared to the rates of stroke.

RE-LY was a game changer, because these trials were all designed with the idea of noninferiority, yet for the first time—and we thought this could not be done—we have an oral anticoagulant that achieved statistical superiority in the form of high-dose dabigatran, the major methodological limitation being the open-label nature of the trial. The FDA chose to approve only the higher dose and it remains debatable whether that dose is in fact too high a dose for some patients, particularly

elderly patients, with respect to major extracranial bleeding.

DR. REIFFEL: Thanks Jon. Jerry, how would you comment on ROCKET with that background from RE-LY?

DR. NACCARELLI: ROCKET-AF was a prospective randomized trial.² It had similar endpoints to the RE-LY trial using rivaroxaban. It was done a little bit differently in that where the RE-LY was in a prospective, randomized, open-label, blinded-endpoint (PROBE) design as Jon just discussed, ROCKET-AF was a randomized,

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-Peter Kowey, MD

double-blind, double-dummy study. So patients taking either rivaroxaban or warfarin were not aware of what they were taking. The entry criteria were similar except for on purpose, the CHADS risk factors were higher, so the mean CHADS score in ROCKET-AF was 3.5, which was different than the 2.1 from the RE-LY trial.

The other subtle difference, or not so subtle difference, was that patients were randomized to rivaroxaban 20 mg a day if their creatinine clearance was 50 or higher. But if their creatinine clearance was 30 to 49, they were prospectively randomized to a lower dose adjustment of 15 mg per day, and the medicine was given with the evening meal. Now, if we look at the efficacy results related to the primary endpoint

of stroke in non-central nervous system embolism, the intention to treat results were noninferior compared to warfarin, but they weren't superior. There was a hazard ratio of 0.88. Interestingly, the hazard ratio was 21%, which was statistically superior, if one just used the on-treatment data.

If you look at bleeding, the results were very similar to what Jon just discussed in the RE-LY trial. Overall, there was no major difference; with major bleeding between rivaroxaban and warfarin, they were very similar. However, GI bleeds were higher, and when you look at fatal bleeding, it was lower. Intracranial hemorrhage was statistically lower. So these are very similar to the results from rivaroxaban; that is, there is no difference in the overall bleeding rate and increased risk of GI bleeding counterbalanced by a reduction in intracranial bleeding, and thus, fatal bleeding.

The other subtle differences in this trial, compared to what Jonathan just told you, is that the mean time in the therapeutic range for the warfarin arm was lower. It was about 55%. Some of this would be expected because of the higher CHADS score. So people with the higher CHADS score, if you look at studies in the literature, have a lower chance of keeping in the therapeutic range. The other subtle difference is that although hemorrhagic stroke was statistically reduced and similar to dabigatran, ischemic stroke was not any different between the rivaroxaban and warfarin arms.

The other—probably—piece of information that I think is important is when the RE-LY trial was done with dabigatran, patients were continued on dabigatran for a period of time and some were enrolled into a longer trial called Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation Who Completed RE-LY Trial (RELY-ABLE).⁸ There was a little bit of a les-

son maybe in trial design here, that at the end of the ROCKET trial, the centers were notified and said, “The study is over; thanks for participating. Since rivaroxaban is not commercially available, you need to discontinue the rivaroxaban and switch patients to whatever the therapy you or the patient decide on.” So this actually left patients after the trial, whom had been on rivaroxaban, exposed for a period of actually close to two weeks with a subtherapeutic INR. Some of the warfarin patients also had a short period of subtherapeutic INRs, because they went from double-blind, double-dummy warfarin to open-label warfarin.

There were 22 strokes in the rivaroxaban arm after the discontinuation of the trial compared to only six in the warfarin arm and some people had raised the issue of a rebound phenomenon.² Although rebound phenomenon can't be completely ruled out, what this probably told us is that people with a higher CHADS score, like were in ROCKET-AF, who discontinue their therapeutic anticoagulation, do expose themselves to some embolic events. Some people have actually done the math and come up with almost the same exact numbers of events if you had patients for weeks on end without therapeutic anticoagulation.

In summary, I think the differences were that this drug was not inferior. The bleeding rates were similar. This was done in a double-blind, double-dummy fashion. This raises the issue for all these drugs that you have to be careful that if they cause bleeding, not to stop them, because if you stop them, you expose the patients to embolic risk. So, I think that summarizes the bulk of the highlights from that trial.

DR. REIFFEL: Thanks, Jerry. Peter, would you give a similar brief review of ARISTOTLE?

DR. KOWEY: ARISTOTLE was probably somewhere in between these two

in terms of its design.³ That is, it was a double-blind study and it was, obviously, a warfarin comparator study, but the patients who were enrolled in this study were not as vascularly sick as the patients in ROCKET. They were a bit more similar to the patients in RE-LY. That is, it was in a broader spectrum of vascular risk.

Like the ROCKET study, however, there was an opportunity to dose adjust based on clinical characteristics including renal function. This variability in dosing limited the exposure of patients who, otherwise, may have

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~Gerald Naccarelli, MD

been overexposed to the drug. I think it really sets something of a new standard with regard to the results. What we saw in ARISTOTLE was not only superiority on the combined endpoint of ischemic and hemorrhagic stroke and systemic embolism, but what also looked to be an advantage with regard to bleeding.

One other interesting aspect of ARISTOTLE was that it had a companion study called A Phase III Study of Apixaban in Patients with Atrial Fibrillation (AVERROES),⁹ which was an aspirin-controlled study in patients who were deemed not to be suitable for warfarin. Most of us regard aspirin to be a fairly ineffective drug for this indication. So in some respects, it actually constitutes a placebo control. The reason why AVERROES is such an interesting study is because the bleeding was actually comparable to or

even less for apixaban than it was for aspirin. This is remarkable. That result also held up in ARISTOTLE where the risk of bleeding was lower for apixaban compared to warfarin.

The final part of the study that I think is of interest is that there was also a strong trend—actually, a nominal *P* value for significance—for total mortality. So ARISTOTLE was successful in many respects with regard to what it proved for some meaningful endpoints. It did not prove a benefit in terms of ischemic strokes as did the RE-LY experience that you heard about, but it was similar to rivaroxaban in showing a reduction in hemorrhagic strokes. That really was the driver for the endpoint reduction that was seen in this study.

The final comment about ARISTOTLE is that the data haven't yet been completely reviewed by regulatory agencies. We haven't seen a public display of the data at an advisory committee as we have for rivaroxaban and dabigatran. After having been involved in regulatory medicine for a long time, I always like to see these things aired in public and at an advisory committee before I will accept all of the results as being as good as they look in a manuscript. That having been said, if the data do hold up and this drug has done what it's been reputed to do in the manuscripts, it will be a big help for our patients, I believe.

DR. REIFFEL: Peter, in light of the last comments you made, it may be of interest—and very timely—that in this week's issue of *Stroke*,¹⁰ new guidelines were published. And those guidelines say that warfarin is a Class I, level of evidence A; dabigatran, Class I, level of evidence B; apixaban, Class I, level of evidence B; and rivaroxaban, Class II-A, level of evidence B. So it says they are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular atrial fibrillation. The selection of the antithrombotic

agent should be individualized from the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other important clinical variables, including the time in an INR therapeutic range if the patient has already been on warfarin. It seems rather unusual, however, and perhaps inappropriate, that these new guidelines already include apixaban, given the fact that it has not yet been approved by the FDA, which has requested additional information from the manufacturer.

We've covered the background behind these new recommendations and it's a very timely topic. Because the issues always come up when we talk about these three trials, let me now make a couple of comments as to whether one can compare one to the next. There are important similarities and the guidelines extrapolate from the trials and make them now all equivalent to warfarin, but there are also significant differences. And when we compare across trials, we have to be a little cautious to be sure that the comparisons are fair. So for example, if one has placebo control trials, which is not true in this case, and one wants to compare them, if the placebo rates are different you can be sure the populations are different. Then it becomes hazardous to compare the actual drug efficacy rates.

In these trials, the comparison was not placebo, but it was warfarin given essentially the same way. One would like to look at the warfarin event rates in the three trials if one wants to extrapolate the drug effect rates. You'll see if you do that, the data from ARISTOTLE and RE-LY are very similar. The warfarin rates were similar. However the warfarin rates were higher in ROCKET-AF, and that tells us the population is different. And, in fact, ROCKET-AF had a higher mean CHADS score of 3.5 compared to about 2.1 for RE-LY and for ARISTOTLE. Thus, it's a little hazardous to take the absolute event

rates in each of these trials and make direct comparisons.

That having been said, there are clearly other issues—and I think we've covered them—the issues of drug interaction, issues of renal function—and they all have to come into play when we go ahead and make recommendations for particular patients. Peter, you mentioned that the FDA did not approve of the 110 twice daily dose for dabigatran and that perhaps was a shortcoming for clinicians in this country. It certainly is available in other countries, including Canada. Can you speculate for us why the FDA did that?

DR. KOWEY: Well, Jerry and I wrote an editorial in the *American Journal of Medicine* asking the same question and I've had an opportunity to discuss this at length with the regulatory people.¹¹ The reason boils down to the fact that if you look at the hard numbers—if you just take a statistical approach—it's very difficult to identify a subpopulation of patients for whom the 110 mg dose represents a therapeutic advantage over risk. Every way you look at this—remembering that the 150 mg dose is superior for the indication—it is very hard to find that there is so much more bleeding at the 150 mg dose that it outstrips the benefit of stroke reduction. I think there is also a belief that it's much better to prevent a stroke than to prevent a bleed and, therefore, it's better to err on the side of the therapeutic advantage. That's not an arguable point. It's completely true.

What Jerry and I said—and I know you and Jonathan have said the same thing—is that this is probably a decision that's better left to the judgment of clinicians rather than to regulators. There clearly are some patients who are at such a high bleed risk, that we would probably want to spare them that bleeding risk, but still provide them with the drug that is at least noninferior to warfarin for the indi-

cation. That's what rivaroxaban is—it's noninferior for the indication. In most other countries where the drug has been approved, the 110 mg dose is available and I think American physicians need to have that kind of latitude. But again, as I said, if you take a very hardline mathematical approach to the question, the 110 mg dose really doesn't pass muster.

DR. NACCARELLI: Jim, if you look at the Canadian use of the 110 mg dose, it's as high as in one in four patients. Now if all those are appropriate, it shows that clinicians, based on the data that they know from these trials we just discussed, think it's the right dose.

Not having the 110 mg dose in the United States, works against dabigatran. What will happen is if you have a patient, say with borderline renal clearance, with a drug interaction like dronedarone, instead of going to the lowest dose of 75 mg twice a day, which was suggested in the package insert based on no data, no trials, patients will use a different drug. You could use rivaroxaban with a creatinine clearance of 38 saying, I know I've already dose adjusted in the trial and it's a safe thing and I know what my outcome is. So I think it's worked against dabigatran. I still think it was mistake. Peter and I have been pretty strong about that, but whether that will change in the United States, who knows in the future?

DR. REIFFEL: Right, I agree with those comments. I also wrote in response to that FDA decision. We know in Europe it's being used at the 110 mg dose, primarily as Peter identified in patients with modest renal insufficiency who are taking potentially drug interacting agents. And I must say, I've now seen probably about two dozen patients who have gotten the dose of 110 mg in another country and have come back with supplies. So there are some people using it. I've got physicians around me who referred in-patients taking 75 mg three times daily or alternating

75/150 mg trying to mimic the daily dose of the 110 mg. So I would agree with Peter. I think this decision would have been better left to the clinicians than having taken the choice out of our hands by the FDA.

DR. NACCARELLI: In addition, you have the 150 mg dose being used in people with creatinine clearances of 32 on amiodarone and they had a bleed. Then it comes back to haunt the drug—“Oh, well your drug causes bleeding”—and I think if we had the 110 mg dose, people would have used that. Theoretically or based on the trials there was less bleeding on that dose.

DR. HALPERIN: I think that was borne out by John Eikelboom’s paper based on a secondary analysis¹² looking at the patients over 75, in whom there was an excess of major extracranial bleeding with 150 mg of dabigatran twice daily that did not appear in those given the 110 mg twice daily dose.

DR. REIFFEL: Correct. So I think this is a deficit in what we have so far. Jerry, could you make a couple of brief comments about the information we have regarding cardioversion with these new agents?

Dr. Naccarelli As you know, one of the issues is that the embolic rate, if the patient has persistent atrial fibrillation and has been in atrial fibrillation more than two days, patients who have cardioversion, whether it’s a medical cardioversion or a direct current cardioversion have a real embolic rate, maybe as high as 1% to 2%. Now that sounds high, but it’s actually relatively low, so to do a prospective trial with a 1% to 2% endpoint, you would have to do tens of thousands of patients.

Now the data that’s been published, that’s the best, actually came from the RE-LY trial with dabigatran. It was published in *Circulation*¹² where they actually had 1200 patients and 1900 cardioversions. The stroke and systemic embolism rate with the 110 mg dose

twice a day was 0.8%. With the 150 mg twice a day dose of dabigatran was 0.3% and with the warfarin was 0.6%. So in spite of this not being a randomized prospective trial, this was at the investigator discretion, there is no signal here that dabigatran has a higher or lower embolic rate than warfarin. In fact, although the hazard ratios are large here and they are not statistically different; the dabigatran had half the stroke rate for warfarin within higher budgets.

Now I would point out that I’ve seen anecdotes and case reports of patients on dabigatran properly treated who have had an embolic event following a cardioversion. In spite of the limitations of this trial, or whether this trial is true or not, I think we’re still going to see some emboli, just like we saw in RE-LY, that there were actually twice the embolic rates in warfarin than on the higher dose of dabigatran.

For rivaroxaban and apixaban, there are some smaller data sets available. Some of this is in abstract form and has not been published, but there are no data in those trials, even though the numbers are much lower, to suggest that there are more embolic rates with these drugs than there are with warfarin. Those trials were a little more limited being double-blind, double-dummy that again, left to the investigator’s discretion less people went on to have, for example, open-label dabigatran cardioversions like we did in RE-LY.

So there’s just not as much data with the other two drugs. You might argue dabigatran has the best data out there, but the data that are least known, and a lot of this will be presented in future meetings, could be similar with the other drugs. No difference, but they are very small data sets.

DR. REIFFEL: Thanks Jerry. Let’s come to the final section and I’m going to ask Jon to lead this off. We’ve talked about the limitations of warfarin. We’ve talked about the pharmacol-

ogy of the new agents. We’ve talked about the major clinical trials that have led to their approval for two of them and in the approval process for the third. Now we’ve got a patient sitting across from us that we have not yet had on anticoagulant or we have a patient who’s been on warfarin. Jon, how do we decide which agent to use or whether or not to change somebody who is already on warfarin?

DR. HALPERIN: The question of whether or not to change gets to this issue of so-called, “starters” and “switchers.” We know from the broad literature that patients during the first year of anticoagulant therapy with warfarin who have not previously been anticoagulated face about three times the bleeding risk of those who have been managed reasonably well with warfarin for some period of time. So there’s a “run-in” phenomenon that occurs during anticoagulation where people with problems sustaining therapy tend to fall-off treatment because of bleeding or events of one kind or another and, after a while, this leaves a select population. When this occurs, in general the event rates tend to be lower.

What is less clear is whether we can utilize that to make clinical decisions for, say, the patient who is doing just fine on warfarin. Does it make sense for them to change to one of the newer oral anticoagulants? Well, certainly we have the matter of convenience and the lack of need for routine coagulation monitoring. I will distinguish that from lack of monitoring at all, because we do need to keep an eye on such things as renal function, and this “run-in” phenomenon makes it very difficult.

I think the strongest argument in favor of making the change, though, is that results thus far reported show uniformly that each of the new oral anticoagulant drugs offers a substantial reduction in the risk of intracerebral hemorrhage compared to warfarin.

Even when anticoagulation intensity with warfarin is maintained within the appropriate therapeutic range, there appears to be an increased risk of intracerebral hemorrhage compared to these new agents. That's the strongest argument, clinically, that I can think of for making the change.

When it comes to choosing among the drugs, then we have to fall back on the limitations that you pointed out, Dr. Reiffel—the fact that these really cannot be subjected to cross-trial comparisons. We do know some things, though. We know that there are three key similarities. First, all of these new drugs proved noninferior to warfarin for preventing total stroke rates and systemic embolism. All reduced the risk of intracerebral hemorrhage. I believe that's the strongest finding, the most concordant finding across the three trials reported to date. The reductions in mortality are pretty comparable at about 10% per year.

There are some differences that I think we can be conclusive about. Dabigatran in the 150 mg twice daily dose reduced ischemic stroke more than warfarin, but caused more extracranial bleeding, as I mentioned, particularly in the elderly. Rivaroxaban, given once daily, 20 mg for most patients, reduced fatal bleeding, but caused more extracranial bleeding. Apixaban given twice daily in the main dose of 5 mg twice daily, reduced major bleeding and all-cause mortality, but not cardiovascular mortality or rates of ischemic stroke compared to warfarin. So, there are a lot of uncertainties in this field that we have to live with and we can talk about that next.

DR. REIFFEL: Thanks Jon. So for the reader—if you have a patient sitting with you and you're trying to decide what to use, how closely do they match the population in the clinical trials? What's the renal function?

What other agents are the patients taking? They're all affected by P-gly-

coprotein, transport inhibitors and inducers; and, by the way, it is not just prescription drugs that interfere. Some of the herbals—ginkgo, St. John's wort, and others—can also do so. Thus, one needs to go through the package insert when talking with patients. Also, what's the patient's GI history? The biggest limitation with dabigatran is the GI side effects, the gastroesophageal reflux disease-like symptoms. So, as the new guidelines in *Stroke* say, I think there is a role for each of these new agents and the decision has to be made considering the patient, the patient's concomitant drugs, and the patient's medical history all taken into consideration at the same time.

I think with that, we're just about out of time. So I think the best conclusion is the new guidelines.¹⁰ There is a role for each of these agents and the clinician is going to have to become familiar with the pros and cons of each of these, the drug interactions with each of these, and the dosing issues with each of these. And finally, none of these require anticoagulation monitoring, as Jon pointed out, but one can use blood tests to determine whether patients are compliant or whether the drug has been washed out adequately prior to a procedure. The factor Xa inhibitors do affect the INR to a significant degree. So if the INR is normal, the patient has not recently taken a dose of the drug. The direct thrombin inhibitors, in this case dabigatran, affect the activated partial thromboplastin time, the ecarin clotting time, and the thrombin time. If those are normal, the patient has not taken a recent dose of dabigatran or the drug is washed out.

So the pharmacology becomes important for all clinicians to become familiar with if they're going to prescribe these agents. But the fact that we have effective agents that have no significant dietary interactions, that have far fewer drug interactions, that are noninferior, and for two of them, superior

to warfarin, I think it's important to begin to use them in a more widespread fashion than we have. Warfarin still has the bulk of the marketplace in this arena, and I personally think that using it so often is not providing the best care to patients. These are new exciting agents and we should be moving toward them.

So unless there are final comments from the three of you—last chance to weigh in—I would like to say thank you to each of you for participating, and I hope that the readers find this roundtable useful in their care of patients.

DR. KOWEY: Jim, I think this practical approach should be very helpful to clinicians. I think, as I said in the very beginning, the big problem here is that we're all going to be deluged with information about these new drugs. A lot of trial data, a lot of pharmacology information—so it is very valuable for all of us to drill down to the hard facts that will help us make the right decision for each of our patients as we did today.

DR. REIFFEL: Thank you all for taking time to take part in this discussion.

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