FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING

+ + + + +

TUESDAY,
DECEMBER 11, 2007

+ + + + +

The Committee convened at 8:00 a.m. in the Chesapeake Ballroom of the Sheraton College Park, 4095 Powder Mill Road, Beltsville, Maryland, William R. Hiatt, M.D., Chair, presiding.

COMMITTEE MEMBERS PRESENT:

WILLIAM R. HIATT, M.D., Chair
STEVEN D. FINDLAY, M.P.H.
ROBERT A. HARRINGTON, M.D.
FREDERICK J. KASKEL, M.D., Ph.D.
ABRAHAM MICHAEL LINCOFF, M.D., F.A.C.C.

TEMPORARY MEMBERS PRESENT:

BARRY M. MASSIE, M.D.
RICHARD CANNON, M.D.
THOMAS SIMON

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

DESIGNATED FEDERAL OFFICIAL PRESENT:

LCDR CATHY A. MILLER, M.P.H., R.N.

GUEST SPEAKER PRESENT:

CHRISTOPHER B. GRANGER, M.D.

FDA PARTICIPANTS PRESENT:

NORMAN STOCKBRIDGE, M.D.

ROBERT TEMPLE, M.D.

ELLIS F. UNGER, M.D.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

C-O-N-T-E-N-T-S

P R O C E E D I N G S

(8:04 a.m.)

CHAIR HIATT: We're waiting for one of the speakers to arrive, but I think we can begin, assuming he will be here in just a moment.

CALL TO ORDER AND INTRODUCTIONS

CHAIR HIATT: I want to welcome all of you to this meeting of the Cardiovascular and Renal Drugs Advisory Committee. My name is William Hiatt, and I'm from the University of Colorado.

And I guess I'd like to start with introductions around the table.

Dr. Stockbridge.

DR. STOCKBRIDGE: I'm Norman Stockbridge. I'm the director of the Division of Cardiovascular and Renal Products at FDA.

DR. KASKEL: Rick Kaskel, pediatric nephrologist at Albert Einstein in the Bronx.

DR. CANNON: I'm Richard Cannon. I'm the clinical director of the Division of

Intramural Research at the National Heart, Lung and Blood Institute, and I'm a general cardiologist.

MR. SIMON: Tom Simon. I have atrial fibrillation, and I'm the patient advocate for the committee.

LCDR MILLER: Cathy Miller with the FDA.

DR. LINCOFF: Michael Lincoff, I'm an interventional cardiologist and director of cardiovascular research at the Cleveland Clinic.

DR. MASSIE: I'm Barry Massie. I'm a professor of medicine at the University of California at San Francisco, and chief of cardiology at the San Francisco VA, and general cardiologist with a special interest in heart failure.

DR. HARRINGTON: I'm Bob Harrington, interventional cardiologist at Duke, and I'm the director of the Duke Clinical Research Institute.

CHAIR HIATT: Thanks very much.

You'll notice at these meetings there are some required statements that I have to read. So I will begin with this statement.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are held quite strongly. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder individuals be allowed to speak into the record only if recognized by the chair.

In the spirit of the Federal Advisory Committee Act, and the government and the Sunshine Act, we ask that the advisory committee members take care that any conversation about today's topic take place in the open forum of the meeting, and not during breaks or lunch.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

We are also aware that members of the media are anxious to speak with the FDA about these proceedings. However, like the advisory committee members, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

And finally, I'd like to remind everyone present to please silence your cell phones and pagers if you have not already done so.

We look forward to an interesting and productive meeting. Thanks for your participation and your cooperation.

CONFLICT OF INTEREST STATEMENT

LCDR MILLER: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drug Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and consultants are special government employees or regular

federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC 208 and 712 of the Federal Food, Drug & Cosmetic Act is being provided to participants in today's meeting, and to the public.

FDA has determined that members and consultants of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC 208, Congress has authorized FDA to grant waivers to government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to government employees with potential financial conflicts if necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this committee who are special government employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and for the purposes of 18 USC 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking/writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application vernakalant hydrochloride injection, 20 milligrams per

milliliter, for the proposed indication of use for conversion of atrial fibrillation to normal sinus rhythm.

Based on the agenda for today's meeting and all financial interests reported by the committee members and consultants, conflicts of interest waivers have been issued in accordance with 18 USC 208(b)(3) and 712 of the FD&C Act for Dr. Barry Massie.

Dr. Massie has been granted these waivers for being a member of the steering committee on an unrelated issue for an affected firm. Dr. Massie receives less than $10,001 per year.

The waivers allow this individual to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on the FDA website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the agency's

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

Freedom of Information Office, Room 630 of the Parklawn Building.

A copy of this statement will be available for review at the registration table during the meeting, and will be included as part of the official transcript.

Dr. Granger, an FDA-invited guest speaker, would like to acknowledge that Boehringer Ingelheim and Novartis supported research grant or contract project of his.

In addition, Dr. Granger serves as a consultant to Novartis.

We would like to remind members and consultants that if the discussions involve any other product or firms not already on the agenda for which an FDA participant has a personal or an imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any

financial relationship that they may have with any firm at issue.

Thank you.

CHAIR HIATT: Thanks very much. All right.

Norman, why don't we go to you?

INTRODUCTION AND BACKGROUND

DR. STOCKBRIDGE: I'd like to begin by thanking all four regular members of the Cardio-Renal Advisory Committee for their participation in today's meeting, along with two temporary voting members, Drs. Cannon and Massie.

And thanks also to our guest speaker, Dr. Granger.

Today's topic, I believe, is the most difficult regulatory issue we have brought to an advisory committee probably since carvedilol was taken here in `96-`97. So I think this is a very challenging area.

We all acknowledge that vernakalant is, in a very restricted sense,

effective in conversion of atrial fibrillation to normal sinus rhythm.

But it is, I think, very difficult to define a set of conditions where its use can be expected to produce clinical benefits that unequivocally exceed its risks.

In considering this issue, I would ask the committee to concern itself with the science behind this decision, and make a recommendation that it feels is supported by the data.

There are probably other issues that will impinge upon Dr. Temple's regulatory decision, including precedence and communications between the division or the office and the sponsor. But what I am seeking out of this meeting is a clear, science-based regulatory decision that is supported by the scientific data.

Thank you.

CHAIR HIATT: All right. Should we move to Dr. Granger's presentation, then?

CARDIOVERSION FOR ATRIAL FIBRILLATION

DR. GRANGER: Good morning.

It's a pleasure to be here, and I do think, as Norman has laid out, that there are a variety of interesting issues. And what I'd like to do is, in response to Norm's request, is to provide a little bit of background, really from the perspective of a general cardiologist, on issues of cardioversion in atrial fibrillation.

And I - so my perspective is, I'm director of our cardiac care unit. We actually run a cardioversion unit on our cardiac care unit.

I've not done any specific research, nor do I consider myself to be a particular expert in specific pharmacologic cardioversion issues. But nevertheless, I will provide you with this background, which I hope is helpful.

And I will address issues of when and why we cardiovert patients with atrial

fibrillation, and the subtotal being why not wait for spontaneous cardioversion, and when should we wait for spontaneous cardioversion, when and why do we acutely cardiovert, and how can we approach acute cardioversion?

And I'll address a few of the clinical trials. The field is really marked by a large number of relatively small trials, and then a few larger trials that were able to look more reliably at clinical outcomes.

And one of the most important ones was the AFFIRM trial looking at the longer term issue of rate versus rhythm control in a population of patients with atrial fibrillation, and who had risk factors for stroke and death. And the rationale was that there should be benefits for maintaining normal sinus rhythm, which are listed on this slide, including fewer symptoms and better functional capacity, perhaps less risk of stroke, avoidance of long-term anticoagulation, better quality of life, and

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

better survival.

The initial therapy, then, in the two arms, the rate control versus the rhythm control, are shown here with the number one antiarrhythmic being amiodarone, followed by sotalol, propafenone, and the others listed here, and a higher use of beta blockers in the rate control arm than the rhythm control arm.

And the baseline characteristics are shown here. I think this is important that this is a population of elderly patients who have atrial fibrillation, and I think that was reasonably well represented in this trial; 39 percent women. Most had atrial fibrillation of greater than two days in duration, and the median was about 13 days.

Some had heart failure, and most had symptomatic atrial fibrillation.

And then the primary outcome of all-cause mortality was the very important finding that actually patients do better with

rate control than with rhythm control with respect to mortality, at least a strong trend for better outcome in the rate control randomized group. And that when one includes other important outcomes, one still sees no benefit from a rhythm control strategy in this population.

And then another trial that was published at the same time, a European counterpart, the smaller rates trial, likewise showed no benefit from a rhythm control to a rate control. In fact, on the point estimate for better outcomes in the rate control group.

And when this is put into the context of other, smaller trials, one sees a consistent finding of really no benefit in these populations enrolled in these trials for a rhythm versus rate control.

And at least one hope was that functional status would be better. But even functional status and quality of life

measures, in the AFFIRM and other trials, have generally failed to show any benefit from a strategy of rhythm control versus rate control.

So the guideline committee, and we have a nice set of relatively recent guidelines that includes the American College of Cardiology, American Heart Association, and the European Society of Cardiology, summarizes these findings here, suggesting that, theoretically, rhythm control should have advantages, but that the trials don't show that.

This might suggest that attempts to restore sinus rhythm with presently available antiarrhythmic drugs are obsolete, but the RACE and AFFIRM trials did not address atrial fibrillation in younger symptomatic patients with underlying -- with little underlying heart disease, and in whom restoration of sinus rhythm by cardioversion, antiarrhythmic drugs, or non-pharmacologic

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

intervention still must be considered a useful therapeutic option.

One may conclude from these studies that rate control is a reasonable strategy in elderly patients with minimal symptoms, and an effective method for maintaining sinus rhythm with fewer side effects would address this unmet need.

One of the hopes was that, at least in patients who have heart failure, that there might be a population where these approaches for maintenance of sinus rhythm might provide more clear, or some evidence of clinical benefit, and the recently presented but not yet published AF-CHF trial then addressed this looking at a population of patients with symptomatic heart failure, injection fraction of less than or equal to 35 percent, or asymptomatic heart failure with lower injection fraction, or prior hospitalization for heart failure, randomizing to rhythm control, which was an

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

approach based on amiodarone, followed by electrical cardioversion if cardioversion did not occur versus rate control.

And here, once again, no benefit from the rhythm control strategy with anything, the point estimate being for lower mortality in the rate control group. And in fact, higher hospitalization rates, statistically significantly higher hospitalization rates and cost with the rhythm control strategy, which also had higher rates of bradyarrhythmias.

So I think the -- well, the summary probably won't change much from what I read from that guideline statement, that this is an area where the trials don't support rhythm control.

But nevertheless, we do it fairly commonly in practice mainly to deal with the symptomatic patients who tended to be under-represented in those trials.

How about the issue of acute

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

cardioversion? Why should we acutely cardiovert someone who comes in with atrial fibrillation?

And this is another area where I think clinical practices somewhat diverges from the evidence from trials, that we fundamentally believe, as cardiologists, that generally we should be converting patients who come in with atrial fibrillation.

Part of this comes from some of the experimental data suggesting that atrial fibrillation, if left unconverted, tends to propagate itself. And this is from this afib begets afib comes from a study in goats which shows that, in fact, atrial fibrillation will be more sustained if left unchecked.

The guidelines, then, and this is from a recent review from Greg Lip, published in Lancet, that is based on the UK NICE guidelines, but it's very similar to the other guidelines, suggests that, for patients with new onset atrial fibrillation, that they

may have early spontaneous cardioversion, but if hemodynamically unstable, they require urgent cardioversion. If hemodynamically stable, then generally rate control, anticoagulation, and then, if remaining in atrial fibrillation, they should have an attempt at cardioversion, including antiarrhythmic treatment or electrical-cardioversion without need for transesophogeal echo to assess risk of acute thromboembolic stroke if less than 48 hours, and if greater than or equal to 48 hours, then either a TEE-guided approach with three weeks of oral -- or three weeks of oral anticoagulation, followed by either electrical or chemical cardioversion.

Then this slide simply describes the varying issues according to presence of underlying structural heart disease, including which types of antiarrhythmic drugs have been shown to be effective.

Let me switch gears then to an

issue of what's the time course of patients who present with atrial fibrillation with respect to spontaneous cardioversion. These are two small trials; each had 100 patients randomized to either a pharmacologic cardioversion, or a placebo approach.

And in both of these cases, the placebo treated patients had a conversion rate of about 60 to 64 percent. In one trial with atrial fibrillation preexisting for less than a week, and the other for less than 48 hours.

And I think this is pretty typical of what we consider to be the case in practice, that half to two-thirds of patients will convert who present, say, to the emergency department with recent onset atrial fibrillation spontaneously, and this seems to be very closely related in a number of observational studies to the preexisting duration of the atrial fibrillation such that, if it's very recent onset, less than 24

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

hours, then in this study, 73 percent converted spontaneously. If it was 24 to 72 hours, then 45 percent.

And the duration of symptoms of atrial fibrillation was the only independent predictor of spontaneous conversion in this study.

How about over a longer period of time? And here we have an important study that established the use of transesophageal echocardiographic guidance of whether one can go ahead and do immediate electrical cardioversion based on presence or absence of thrombus in the left atrium, run out of the Cleveland Clinic, which also helps to establish, in this population of patients, who had atrial fibrillation for more than two days as an entry criterion, what happened to these patients, including the group that had conventional treatment with the three weeks of therapeutic anticoagulation prior to cardioversion.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

And in that group, about 21 percent had spontaneous conversion to sinus rhythm over an eight-week period.

The immediate cardioversion approach with transesophageal echo was associated with a somewhat less likelihood of bleeding related to less use of anticoagulant therapy, but a non-statistically higher rate of death.

One of the interesting findings in this study is that, with respect to the success of electrical cardioversion with one of the rationales for going ahead and immediately cardioverting being that one may be more successful if one has a shorter duration of atrial fibrillation. In fact, that was not held up in this study. There were identical rates of success of electrical cardioversion, whether it was done immediately with the TEE guided approach, or with the conventional therapy approach.

And then, when one looks at the

distribution of patients who had spontaneous cardioversion, one sees that it was much more common in patients who had shorter duration of preexisting atrial fibrillation.

Remember in this study, it was about 13 days of atrial fibrillation prior to entry in this study.

But also, when spontaneous cardioversion occurred, it tended to occur early, most commonly on the first day after enrollment in the study.

And then the predictors for spontaneous cardioversion are shown here. They are pretty consistent with other studies, the number one being shorter duration of atrial fibrillation, also less symptomatic heart failure, smaller left atrial size, absence of spontaneous echo contrast.

With respect, then, to some of the studies that have looked at pharmacologic conversion in the early hours of patients

presenting with atrial fibrillation here, hospitalized patients, AF onset less than seven days, one sees, first of all in the placebo group in this study, about 35 to 40 percent of patients had spontaneous cardioversion by eight hours. And one sees with intravenous treatment here, with propafenone in this study, one had a greater likelihood of conversion to sinus rhythm by one hour, but not by eight hours, which brings up this interesting issue of, is one shifting the timing of conversion, or the actual number or proportion of patients who were successfully converted.

Also for example, with ibutilide is an issue of which type of atrial arrhythmia, which has an impact on likelihood of conversion. So with ibutilide, there seems to be a more -- a higher likelihood of successful cardioversion with atrial flutter than with atrial fibrillation.

But of course with ibutilide

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

there's the challenge of torsades that occurs in somewhere around 3 percent of patients, and seems to be more likely with electrolyte abnormalities and/or heart failure.

Then these were the predictors of cardioversion with ibutilide, where patients again with recent arrhythmia were more likely to convert, atrial flutter, as I've already said, lack of heart failure, and lack of use of digoxin.

With respect to electrical cardioversion, we do now have this very effective, especially with biphasic energy application, approach to cardioversion that even in -- with patients who are refractory to standard cardioversion with the biphasic approach, this is a highly effective means of cardioversion.

I think conventional wisdom would suggest that, of patients who do elect, that about 25 percent of patients are unable to be electrically cardioverted, either because

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

they are refractory, or they almost immediately go back into atrial fibrillation, and of those who are successfully cardioverted, within two weeks, as much as another 25 percent will revert back to atrial fibrillation.

There also is the possibility to combine pharmocologic, even acute pharmacologic and electrical cardioversion, including this study by Ferd Morady looking at the use of ibutilide in conjunction with cardioversion as being a way to deal with improving the effectiveness of electrical cardioversion.

How about in the longer term for conversion to sinus rhythm with atrial fibrillation? This, the PIAF study, looking at patients who have, on average, 110 days of atrial fibrillation, with some of the high risk patients excluded. You see the age here, about 60 years of age. And here the use of amiodorone versus diltiazem, which

shouldn't have much of an effect at all if any on cardioversion.

One sees that, with diltiazem, there was this low rate of cardioversion -- of spontaneous conversion to sinus rhythm in this more chronic population, of whom over 50 percent were converted with either amiodarone, or the combination of amiodarone followed by electrical cardioversion.

Interestingly, no effect on improving symptoms with that approach.

And then another study of about 700 patients looked at placebo amiodarone or sotalol for patients, again, with longer duration atrial fibrillation, showing that, with placebo, there was a very low likelihood of conversion. At 28 days, about a quarter of patients on amiodarone or sotalol converted.

So in summary, then, some of the advantages and disadvantages of electrical or pharmacologic cardioversion. Electrical,

highly effective, fast, can be combined in one procedure with transesophogeal echo for those patients who have had more than 48 hours of atrial fibrillation. And the cardioversion itself appears to be very safe. Pharmacologic works well, especially for recent onset, and with some drugs, for atrial flutter. One may avoid the sedation and some of the related costs of anaesthesia with electrical cardioversion, and the drugs may be needed anyway to enhance the maintenance of sinus rhythm.

I'll just briefly flip through what the guidelines say then about some of these issues, which include a description of agents with proven efficacy for pharmacologic cardioversion, not differentiating acute versus sub-acute cardioversion, but included here are IV, flecainide, ibutilide, propafenone and amiodarone as having class 1A recommendations.

And then for, before cardioversion

for patients with persistent atrial fibrillation, a number of drugs being effective to enhance cardioversion by electrical approach, and to suppress recurrence of atrial fibrillation as 1B recommendations.

Then with respect to the issue of pharmacologic cardioversion, a 1A recommendation being administration of flecainide, dofetilide, propafenone or ibutilide. And at 2A, including this pill in the pocket approach. So for patients who have paroxysmal atrial fibrillation, who have recurrence of atrial fibrillation, and who, in a monitored setting, have had proven effectiveness and safety of either propafenone or flecainide, then this is an approach which is recommended by the guidelines, and supported by small studies that a patient can, even at home, go ahead and take a dose of these drugs to enhance conversion more quickly back to sinus rhythm.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

And then for electrical cardioversion, recommended when symptoms of atrial fibrillation are unacceptable to the patient -- a lot of subjectivity there, but certainly many of these patients do have substantial symptoms that warrant this.

Then in case of relapse, repeated following administration of antiarrhythmic medication, and also this, as a two-way recommendation, a more long term strategy using intermittent electrical cardioversion.

And then also the postoperative setting is another time where, especially after bypass surgery, where atrial fibrillation is common, and the guidelines do is a two-way recommendation, level B, suggest that pharmcologic cardioversion is reasonable, or direct current cardioversion in that particular setting.

So then my final slide, cardioversion is common in practice, albeit not well supported in terms of proof of

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

improving clinical outcomes in most of the trials that have been done.

Most new onset and many paroxysmal atrial fibrillation episodes are treated with cardioversion if they do not -- especially if they do not spontaneously convert in 24 to 48 hours.

And while electrical cardioversion is generally preferred, acute pharmacologic cardioversion has a role that perhaps is not as well defined as it might be.

Thanks for your attention.

QUESTIONS TO THE COMMITTEE - PART 1

CHAIR HIATT: Thanks, Chris. I think we have a few minutes to ask you some questions and discuss this. Because I don't think you are going to be with us all day, is that right?

All right, one question I have is, you mentioned that electrical cardioversion is safe. Can you quantify that a bit further in terms of risk of thromboembolic events,

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

ischemic events, things we might care about?

I realize the context may vary according to the risk factors those patients may have.

DR. GRANGER: Yes. So the first, again, this is largely based on conventional wisdom, rather than a whole lot of data.

But we believe that with three weeks of therapeutic anticoagulation beforehand, then one can get results that are similar, for example, to what was seen in the acute trial, this trial from -- led out of Cleveland Clinic that showed that there was a few percent incidents of thromboembolic events.

The actual cardioversion, itself, can also be -- electrical cardioversion can be complicated by Brady arrhythmias, and by the anaesthesia that is administered during the procedure, which has a quantifiable risk and expense.

But I think generally we think of

electrical cardioversion in a patient who doesn't have other comorbidities that would put them at risk for any type of procedure like that is a very safe procedure.

DR. HARRINGTON: Chris, just a couple of questions.

In your early slides on AFFIRM, you point out the demographics of the AFFIRM population as being largely an older population, large number of women, et cetera.

Some of the things we're going to talk about a lot today is the representative nature of the population. Do we have any data from registries, large observational reports as to what is the typical population of afib patients who are being converted? Do they look like the AFFIRM population, or are they those younger patients without structural heart disease that the guidelines refer to?

DR. GRANGER: No, it's a great question , Bob, and I don't know of any good

registry data that address that, actually. I think most of our experience is that we have a -- there is a broad spectrum of patients. We do have a substantial number of the elderly population with comorbidity who have a high prevalence of atrial fibrillation, as well as the younger patients who more and more now are going towards ablation and other approaches as the strategy for the younger patient without structural heart disease.

But it's -- the guidelines talk about it. I think we know that it's likely to be the case that these different populations of atrial fibrillation have substantially different issues.

DR. HARRINGTON: And one more question if I might, Bill. What is the magnitude of the problem? How many elective cardioversions are we doing, for example? I guess I could have checked this before I left, but I didn't. How many are we doing?

DR. GRANGER: So we do, on average,

I think about 10 a week, probably, just in the -- in our CCU cardioversion unit, and then more get done in the EP lab.

DR. HARRINGTON: So it's sizable?

DR. GRANGER: Yes, it's sizable.

MR. SIMON: Can you please comment on the spontaneous conversion from afib to normal sinus rhythm? Do we know how, why, what, et cetera?

DR. GRANGER: There may be others here who can actually better comment on that. I don't know, other than we know that the natural history of atrial fibrillation tends to be especially early on for the typical patient, that there tend to be probably frequent episodes even of asymptomatic atrial fibrillation when Holter monitors are done, for example, for patients with paroxysmal atrial fibrillation.

DR. CANNON: Two questions. The first is, can you comment on the management of torsades de pointes. So we're going to be

talking about that a lot today and tomorrow. And with ibutilide, you mentioned there is about a 3 percent incidence of torsades. So can you comment on how big a safety issue is that? Is it fairly easy to deal with, either pharmacologically or electrically, what the fatality risk of torsades that occurs in response to a type three agent is, do you have any either personal experience or data on that?

DR. GRANGER: Certainly personal anecdotal experience. Again, I can't talk about this with a lot of confidence about kind of knowing all the available evidence.

But I think the anecdotal experience certainly is that if, in a monitored setting, with people used to dealing with the arrhythmia, that in the setting of, for example, ibutilide, that it's a relatively easily manageable problem. Of course the risk is the patient who might go home, and not be in the monitored setting.

Then we know that it may be fatal in a certain proportion of patients.

But I think generally in the monitored setting with the ability to give magnesium to cardiovert if necessary, to support, that it's generally a manageable problem.

DR. CANNON: Okay. Then I have a second question. For atrial fibrillation of relatively short duration, less than 48 hours, do you know of any data indicating whether electrical cardioversion versus pharmacologic cardioversion has differential effects on atrial functions?

I know with prolonged atrial fibrillation, we all know that atrial function, even after cardioversion, is going to be out for a couple of weeks. But for short duration, is there evidence that electrical cardioversion stuns the left atrium, and is likely to knock it out for a couple of days, as opposed to ibutilide or

some other pharmacologic cardioversion?

DR. GRANGER: Yes, that's a great question, and I would suggest that the convention wisdom is that that may be the case.

I think there is more of a clinical concern over continued anticoagulation following an electrical cardioversion than a pharmacologic cardioversion. But in fact, I know of no data that support that.

I think the data all would suggest that the likelihood of thromboembolic events following either pharmacologic or electric cardioversion is similar, that really we should be considering them as similar issues.

CHAIR HIATT: Go ahead.

DR. MASSIE: Sorry. In terms of, obviously the group that seems to respond best to cardioversion is the group that's been there short term, often does revert spontaneously, as well.

Do you have any feeling for what percentage of those have identifiable precipitating factors, such as commonly being post-bypass surgery, but also with pneumonia, some types of drugs, alcohol intoxication, things like that, versus those that are early, but we don't know why they got it, it may actually reflect these people who have been building up toward it with spontaneous burst?

Do we have any idea which group is which, and whether, in fact, this spontaneous cardioversion would be equal in those?

My experience is that the ones you know why they got it often go away as you treat the underlying condition, or the time -- the alcohol and things like that. But I don't even know if there is any data to support that, either.

DR. GRANGER: I think there is relatively little data to support that. I think the other issue for that particular

population is that's a population where I think we are more comfortable either chronically treating with antiarrhythmic drugs, or chronically anticoagulating, if we find a reversible cause in a single episode.

But I think most of these trials, either those patients were excluded, or that was a relatively small population, that most of what we are talking about here are patients who don't have a readily identifiable reversible cause of their atrial fibrillation.

DR. MASSIE: Would you say that might explain why the control groups have very little spontaneous --

DR. GRANGER: Well, as I showed, the spontaneous cardioversion is actually pretty high, as long as you have short duration of atrial fibrillation.

DR. MASSIE: I mean, actually I'm getting to the trials of the drugs that --

DR. GRANGER: That may be, yes.

Although I -- in general practice, sometimes we think we may have a reversible cause, in fact, sometimes it's hard to prove that that, in fact, was a substantial contributor.

CHAIR HIATT: So Chris, we are going to be debating the merits of two drugs over the next two days that are given, as patients present, and the outcomes are assessed over the next couple of hours. And there you can see a clear distinction between drug and placebo.

Could you just help us, or clarify one more time, if we were to wait more than two hours, wait an additional 24 hours, you would say that half to two-thirds of the patients that will be deliberating in these trials might spontaneously convert on their own?

DR. GRANGER: Well, I think some of the -- I think there is some data from the trials to address that. But at least in general practice, yes, that that's the case.

I'm not suggesting that there might not be benefit, as long as it's done safely, in more rapid conversion in terms of both health care resource use and patient satisfaction, but yes.

CHAIR HIATT: What I'm getting at is I think we know pretty clearly what happens when you treat according to the protocols. And I think you can also assume that, when you give either of these drugs that, if you do convert, it's a fairly durable conversion out to 24 hours, and even out to seven days.

The question that is not really addressed is, if you were to use a different strategy, and wait longer, would the spontaneous conversion rates sort of pick up, and actually look a lot better? In other words, if you had sort of looked at a longer window of time, or delayed that decision, and what would be the risks of waiting?

DR. GRANGER: Yes, and I think the

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

-- so the risks of waiting include patient factors, you know, patient discomfort and anxiety about being in this abnormal rhythm, some of that warranted, some probably not warranted, the need for anticoagulation, and, you know, a delay in definitive treatment that also I think in medicine if we can fix something right away, I think there is a lot of almost infatuation with the trans-esophogeal echo-guided approach, for example, just in terms of a clinical correlate of going ahead and doing something quickly for those patients who are -- who have had atrial fibrillation for longer than 48 hours.

We like to take care of things right away if we can, not saying that the outcome data necessarily support that. But that's another factor, I think, that comes into play.

DR. LINCOFF: One of the other issues that we may be discussing relate to hypotension and bradycardia, which I know

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

occurs to some extent after electrical cardioversion, as well. Are there any data, or even suggestion of ballpark figures of the immediate rates of bradycardia or hypotension following electrical cardioversion?

DR. GRANGER: Yes, another good question, Michael. And I don't have any kind of firm data on that, although I think, and my anecdotal my answer would be, very common to have some bradycardia, especially some transient bradycardia, uncommon to have that something that can't be managed with atropine or simple observation and/or fluids for an hour or two.

DR. HARRINGTON: Chris, another issue that we are going to be discussing is the merits of drug therapy over electrical cardioversion, and some of the things about electrical cardioversion that you have already alluded to, particularly the sedation issue.

Has there been any published

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

information on how patients perceive the electrical cardioversion procedure? It's talked about and said that it may be uncomfortable, it may leave burns on the chest, people go to sleep, but is there actually data where people have been interviewed in a systematic way and published?

DR. GRANGER: Not that I know of.

DR. HARRINGTON: And do you know -- you made reference to the sedation complications, aspiration, et cetera. Again, what is the published rate of complication of the anaesthesia part of the procedure? It's got to be exceedingly low.

DR. GRANGER: I think it's very low. There is also a wide heterogeneity of how different centers deal with this, you know, whether you have an anaesthesiologist there administering anaesthesia under a very controlled setting, or whether you are giving high dose benzodiazepines in a kind of

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

conscious sedation approach is highly variable.

And I could find nothing about any systematic review of complications related to that at the time of cardioversion.

MR. SIMON: You mentioned rate and rhythm control. Could you please define both, the differences, and why should there be an advantage of rhythm over rate?

DR. GRANGER: So as you know, the data don't support that there really is for, at least for the trials that have been done, that, granted, have been selective on who even gets into those trials, to a certain extent that it's a patient who is entirely not tolerating their atrial fibrillation wouldn't even be enrolled in one of those trials, because there would be a feeling of an urgent need for some attempt at rhythm control.

But I think, you know, in terms of the trials probably are the best place to

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

look at how one defines the two different approaches. So for rhythm control, the definition would be a primary approach of using either antiarrhythmic therapy or recurrent electrical cardioversion, or the combination in attempts to maintaining sinus rhythm, whereas rate control, the primary focus being on simply using drugs that control the rate to improve the tolerability, understanding that some of those patients will either spontaneously convert, or will crossover, because they are simply not tolerating their symptoms, and vice versa, some of the rhythm control end up turning into simply chronic atrial fibrillation in spite of whatever else we do.

CHAIR HIATT: So given that, if a patient presents with mildly symptomatic, or asymptomatic atrial fibrillation, there is nothing wrong with leaving them in atrial fibrillation, giving them anticoagulation and controlling their rate.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

And so you would say that the main indication for immediate fix it, like you've just described, is driven by symptoms?

DR. GRANGER: Two things, I think. One is -- and I think all the guidelines support this, and these patients tended not to be included in the trials like AFFIRM, for example, is for patients with new onset atrial fibrillation, or for I think almost all of those patients, maybe with the exception of a very important population, that being the elderly relatively asymptomatic. I think many of those patients is perfectly reasonable and in fact probably may be best to simply rate control and anticoagulate.

But with the exception of that group, I think most -- the conventional wisdom approach is to go ahead and cardiovert the new onset atrial fibrillation in either the nonelderly or the symptomatic, and for the paroxysmal patients who are more highly

symptomatic, to go ahead and periodically convert them.

CHAIR HIATT: Other questions?

Well, thanks very much, Chris.

Norman, can we turn to your general questions now to the committee?

QUESTIONS TO THE COMMITTEE PART 1

CHAIR HIATT: Dr. Stockbridge has posed some questions to us, so let's turn to those for a bit of a general discussion. We actually have until 9:30 before we turn to the sponsors' presentation.

So we've been asked to opine on the appropriate role of two proposed new drugs to effect conversion of atrial fibrillation to normal sinus rhythm.

The time dependency that make this determination challenging is illustrated by the diagram - there we go.

So this is time in atrial fibrillation over time, and it shows essentially the possible benefits of

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

treatment, the bottom line, versus no treatment, the top line.

Any effective therapy reduces the risk of being in atrial fibrillation corresponding to region A. There may or may not be a region B representing risk reduction for patients who never have converted spontaneously.

Using an effective therapy too early, period A, is of no utility, because the spontaneous conversion rate is high, as we've just heard. So the opportunity for benefit is small compared with the risks of treatment.

If region B exists, delaying treatment too long, period B, loses any opportunity to benefit patients who are at risk because their atrial fibrillation for moderate periods of time.

That we're not complicated enough, one may have to consider that some of the risks associated with being in atrial

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

fibrillation, for example having an embolic stroke, are also likely dependent upon time in atrial fibrillation.

Before considering drugs to effect conversion atrial fibrillation and flutter to normal sinus rhythm, the advisory committee is asked to consider how well characterized is the time course for spontaneous conversion, how well characterized are the harms of being in atrial fibrillation, how well characterized is the time course for successful electrical conversion?

So I guess I'd like to entertain a discussion amongst the committee on question #1.

DR. HARRINGTON: Well, I think that Chris showed us the state of the state, which is most of the evidence, Bill, that is available. And as Chris points out, this acute care issue is perhaps less well studied than the chronic issue of things that were studied in things like AFFIRM.

In the acute care issue, most of the studies that have been reported are pretty small, and so the best estimate we seem to have from the small studies is that short periods of atrial fibrillation are highly likely -- or short durations of atrial fibrillation appear highly likely to convert spontaneously over the next, let's say, day or two.

And I think the best evidence that Chris showed were the studies that looked at it at the end of 24 hours, and suggested upwards of half to two-thirds of the patients are spontaneously converting.

That certainly mirrors, I think, the -- what the clinical anecdote would be.

But to me, one of the troubling issues here, or the challenging issues, is that the data, in fact, are pretty limited, the actual published data.

So shorter durations in afib seem to have a high likelihood of being converted.

Barry brings up some of the other issues of, if you have a reversible cause, that as you treat the reversible cause, people perhaps are more likely to be converted, and people who have normal structural hearts are likely to more readily be converted spontaneously.

CHAIR HIATT: So the question around this curve I think is that, as I asked earlier, if that's true, then we have a clear drug effect at two hours, and this is speculation about what a study would look like had the duration, or had you waited for the spontaneous conversion to reach its 50 percent or 75 percent asymptote, and then randomized patients, what that would look like.

We've got clear primary endpoint evidence of drug efficacy over the next two days. What does that mean in terms of very short term benefit, as Norm has shown in the figure?

DR. HARRINGTON: The phrase that

always sticks in my brain is, live longer, feel better, avoid unpleasant things.

And it's sort of one of our central charges here. And I know a lot of the discussion we'll have over the next couple of days is that you can measure something at 90 minutes or two hours, but does that really matter?

And I'll reserve my statement on that until I hear all the discussions over the next, you know, at least over the next day.

DR. MASSIE: I think probably the most relevant, and seems like somewhat characterized thing is what that time course -- partly I'm depending a little bit on the data from these applications where you couldn't be entered if you were known to be in afib for less than 72 hours.

And that sort of fits with my own experience, which is, those people, they are not the ones that have been drinking, they

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

are not the ones that, you know, may come in with a URI, and lots of bronchodilators. They sometimes overlap with the cardiac surgery patients, but then we're not dealing with that exactly today.

If it really is 72 hours, and I would guess that 72 hours is a pretty good threshold, I think it would make sense, unless the patient is for some reason hemodynamically unstable in a way that you couldn't deal with it, or perhaps having bad angina, together with -- although most of the time we can control the rate pretty well if they are in the hospital, the real question becomes, we got past that point where the high rate of spontaneous conversion, and I think there is that point, and I guess that will be the crux of things.

And I think it's pretty well characterized, at least in the population for these, and I don't know how much the external data that Chris reviewed adds to that in

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

terms of a 72-hour time point. It certainly fits with my own experience. Often, if people aren't too symptomatic or too fast, we'll just send them home, and have them come back 24 hours later and see if they are still in it, as a way.

So I guess that's the crucial part of the first question from my -- you know, we talked about the arm. At some point, there are two arms. One is, you worry about emboli, and the other is you begin to worry about bleeding, because the highest risk time for anticoagulation is early, partly because you uncover bleeding, unknown bleeding risks at that time.

And I guess it does appear that, with time, it gets harder to convert. I don't know exactly when that occurs. And I think that was less clear, but obviously well organized cardioversions, even quite a bit later, electrical, do seem to have success.

CHAIR HIATT: And the third arm

would be the quality of life that you take, and the exercise --

DR. MASSIE: Yes, for those that are really miserable, and I certainly have seen that happen, although usually with rate control in the older population I deal with, not many people are miserable.

CHAIR HIATT: So you'd say that, the committee would say that the time course for spontaneous conversion is reasonably well known?

Okay, Michael.

DR. LINCOFF: You know, it's interesting that, as we'll discuss, it looks like most of the benefit from the pharmacologic cardioversion seems to be up to the seven-day period, although patients were enrolled as early as three hours after their onset of symptoms.

So clearly within the first couple of days, I think, as you suggested, maybe the first two or maybe three days, there is going

to be a very high rate of spontaneous cardioversion.

But it looks like there continues to be benefit even in patients who persisted longer, and beyond two or three days, I think the likelihood of spontaneous cardioversion is low enough that this becomes an incremental benefit.

CHAIR HIATT: Thoughts on this side?

DR. CANNON: I think there are special populations where the time line for spontaneous cardioversion is less clear, where a drug or a pharmacologic intervention has appeal, and that is a postoperative population.

So as a consulting cardiologist, I see a lot of them. And that is a real problem. Some of these patients have tenuous blood pressures, and they go onto atrial fibrillation, and we really feel like we need to do something, not because they are

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

symptomatic, they may still be intubated, but because the surgeon is concerned, and we are concerned about their hemodynamic status.

And I think they are waiting 24 hours, 48 hours, to see if they spontaneously cardiovert, which would make a lot of sense in the ambulatory setting, I think is less tenable in the post-operative population.

So I would be interested, when we get the presentation, the industry presentation, about getting more data on that conversion rate.

MR. SIMON: Just a comment. I guess from the patient's standpoint, frustration plays a big part in atrial fib. When I woke up this morning, I was fine, sinus rhythm. During Dr. Granger's talk, I was fine, about halfway through, I went out.

And I don't know if anybody saw me, I took a pill, and within five seconds, I was back in rhythm. The pill did not work within five seconds, but I don't know if it's

mind over matter or whatever, but I'm back in sinus rhythm.

So the frustration with atrial fib, just to let you all know, there is a point where it just is, intolerable is not the right word, but there is a frustration.

And I understand from listening to everybody else there is a frustration from your standpoint, also.

CHAIR HIATT: Any more comments on that?

Michael.

DR. MASSIE: I just would like to chime in on the post-bypass or the post-cardiotomy at least group of patients. It's a pain in the neck, but they go in and out no matter how I treat them, you know. So that I'm not sure, and I think there are some data from some of the drugs that we are dealing with, but it wasn't really presented to us, and great information whether a drug that usually is effective still 24 and maybe 72

hours later would, in that population, be still effective, or whether they would be back in afib within an hour. Because we see that, which is sort of why a lot of people move to amio if we are going to do anything, because there is something that sticks around.

The problem isn't going to go away for five days. You begin to get the worry of anticoagulation on top of a post-bypass patient, and it's a nightmare.

But I don't see how we can extrapolate data from any other type of patient population to that population, and knowing what the success rates are going to be, the persistence rates are going to be, and the risks are going to be.

But it is -- keeps all of us who are on call up at night all the time.

DR. LINCOFF: Despite all the talk of spontaneous reversion to normal sinus rhythm, the bottom line is that the data is

relatively limited, but in the studies that have been done with the two agents that are already approved, and the drugs we are seeing now, we are looking at placebo rates, which are relatively low, and these are the early periods.

So discussions of other reversible causes, including cardiac surgery or, notwithstanding, what little data that does exist is in these more recent studies, and it does suggest that there is a relatively low rate of spontaneous reversion in those patients that present, depending upon what the time period, the window is for how long they've been in atrial fibrillation.

So I think it would suggest that it's not particularly high for these patients.

DR. HARRINGTON: But Mike, isn't that one of the key questions? It depends upon how well characterized the patient population is, and in the studies we're going

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

to talk about today and tomorrow, patient population is actually very narrowly specified, as opposed to the challenges that Dr. Ken and Barry bring up, for example with the postoperative patients.

DR. LINCOFF: I think that's absolutely true and, in fact, it characterizes a relatively healthy population which, if anything, would be probably more likely to have spontaneous reversion to normal sinus.

So in the less healthy population, which may be the population we are more interested in, and the efficacy is something we'd discuss, you might even expect rates of spontaneous reversion to be lower.

CHAIR HIATT: You know I would say, Michael, that I was surprised a bit at the conversion rates being fairly low on placebo in both these programs early.

But what we really don't know is, had you waited, and I think for both

programs, one of the fundamental issues I have with the data is that we know an awful lot about drug and placebo comparisons across a variety of endpoints, including some symptomatic endpoints, over a two-hour window, but then other things happen after that. You know, your option for electrical conversion comes in. Placebo patients are going to be treated differently. What I don't know is the symptomatic difference at 24 hours, or at seven days. And so I think the treatment window we are going to wrestle with here today, as Norman put out in his figure, you know, shows clear efficacy very early on. But I think what is a little muddled in my mind is this sort of temporal thing in terms of what happens if we were to wait out to 24 hours. And we really don't know if there are symptomatic differences.

So in other words, if you are randomized to placebo, you get converted, are you now asymptomatic? We don't have the

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

symptomatic data at 24 hours. I'd like the sponsor actually to come up with that before the end of the day. That's the hard part.

Then the last thing here is, is it well characterized, the time course for successful conversion?

It looks like, from Chris' data that, and we all know that there are a certain number of patients that are refractory, or who go back into atrial fibrillation over time. But there still appears to be a treatment effect of electrical conversion in that "D" area of the curve.

Is that correct? Do you all agree with that?

Okay, we have a few more minutes on this. What are the disadvantages of waiting for spontaneous conversion? Staying symptomatic, risks of being in anticoagulation, reduced rate of success, poor hemodynamic outcome, shorter duration of

normal sinus rhythm, or other issues.

DR. HARRINGTON: Before we go to that one, could we do the middle question: how well characterized are the harms of being in afib? Because I'd like some help in understanding that.

I mean, Mr. Simon I think talked nicely about one of the issues is the frustration issue. But -- and that's an important quality of life issue.

But what about other things? What do we know? I mean we know with anticoagulation for example, the teaching and what the guidelines say is that atrial fibrillation more than 48 hours warrants consideration for anticoagulation or a TEE-guided approach if you are going to consider cardioverting that.

But in our practice we -- if someone is beyond 48 hours, we'd anticoagulate them, and either if they feel pretty fine about it, wait four to six weeks.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

So what are the harm issues of afib? Thromboembolic one is certainly there. Chris talked about the AF begetting some abnormality in the atria, but as Chris said, that's data from goats. I don't know how relevant that is to people.

What do we know? I don't have an answer for you. I'm asking you.

DR. MASSIE: Well, let me -- I mean, I've always been surprised a little bit about the anticoagulation issue. But it seems like it's a major quality of life issue for patients. To be anticoagulated, or even the thought of it. I know people who just refuse it because they assume it's going to be miserable, and they are likely to bleed.

So now we are getting away from this really early acute setting, which is, I think, the thing we know the most about from these trials, although those people I believe were anticoagulated because it was already 72 hours for entry in most of them.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

But so I think chronic anticoagulation, either the perceived quality of life issues, the real ones, and the bleeding issues, are there. And it doesn't show up in the rate control versus rhythm control because, in fact, starting and stopping seems to be worse than continuing. But not that they love anticoagulation, it's just that having fairly long periods of time off anticoagulation doesn't prevent you from the bleeding and the quality of life issues when you have to go back on, I guess. And I think it's pretty well characterized that, when you start anticoagulation, you are likely to get two-thirds of your year's bleeds in the next four weeks.

So I think that is one of it. I think, depending on your population, symptoms would be important. I have some young friends my age who really are miserable in atrial fibrillation. So I think that is another, although those don't tend to be the

people we enroll in any of these trials. So I think that is certainly -- the symptoms, and being on anticoagulation, I think are really major harm, somewhat harm. The symptoms don't seem to be as bad in some populations as in others.

CHAIR HIATT: Okay, let's assume that's true. And this committee has debated a couple of years ago the merits of newer anticoagulation agents to treat atrial fibrillation, in particular. So there is clearly a need for better therapy for sort of chronic background therapy for atrial fibrillation.

I think it's clear that there are thromboembolic risks of not being treated, and there are certainly bleeding risks of being treated with anticoagulation.

I mean the problem I think with, with sort of thinking about that issue is, what's your alternative? And Chris showed us that, if it was rhythm control, it's not

necessarily better, by trying to avoid anticoagulation in terms of major clinically relevant irreversible harm endpoints.

There is a symptomatic issue, which I think there are a number of patients who have commented on it, who are completely asymptomatic, don't know they are in it. And there are a lot of people, I imagine anybody at this table who was in atrial fibrillation, would certainly not like that.

Other comments?

DR. HARRINGTON: But isn't one of the things we learned from AFFIRM is that part of the difference between the rate and rhythm arm might have been the differential use of anticoagulation, that there is this -- there had been this fallacy that, if you were in a rhythm strategy, that you could avoid the burden of anticoagulation, but in fact, both RACE and AFFIRM suggest that that is not true, that one of the reasons that those arms may differ in favor of rate -- I think Mr.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

Simon had asked the question why might one be better than another. One of the reasons that rate might have been better than rhythm in these trials is that there was better use of anticoagulation.

CHAIR HIATT: I totally agree with that interpretation, which means I think, for today's deliberation, we may not be able to avoid that particular background therapy.

DR. CANNON: Along the lines of the risks of not doing something about the rhythm, just rate control with anticoagulation, another special population that I seem to deal more and more with is the very elderly population.

So the elderly population, most of them tolerate rate control very well, and I can manage their anticoagulation very well. But I worry about very elderly, about compliance with coumadin and the 10 other pills that they are taking, and stumbling and

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

falling and so forth.

And that's become more and more of a headache maybe the older I get. But I think that is an emerging special population where the rate control with anticoagulation is going to be problematic.

DR. HARRINGTON: And along with that, I'd be interested to hear what Barry says, the elderly that we all see that have, you know, systolic preserved heart failure. So that they've got these stiff ventricles, and being in sinus rhythm seems to make them perhaps feel a little bit better, because they have better diastolic feeling.

Barry, is that a real entity?

DR. MASSIE: I think it is. And the flip side is, when they go into atrial fib, they tolerate it least well.

MR. SIMON: Being in the, since I'm 61, I guess I'm in the elderly, not the super-elderly, but I think there's pros and cons with regard to being on a drug and being

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

on an anticoagulant.

I have problems sometimes with the anticoagulant that I'm on, but I get that fixed fairly easily.

The drug I'm on has a number of side effects. And I can take those -- actually, I can take those better than the side effects if I'm not -- for example, if I'm playing tennis, and I go into atrial fib, and it can go to 300, 350 beats a minute, it just wears me out.

If I'm playing on a golf course, I can barely -- I can make it up the hill, but it really wears you out terribly.

So I take the drug for the obvious reason: I want to get rid of those symptoms. But at a point, I'm at a maximum dosage right now on the drug I'm on, so I'm considering at this point in time the surgery, the radio-frequency ablation.

In any case, there are pros and cons with both, the anticoagulant and the

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

drug itself, but it's a lot better being in sinus rhythm than not.

CHAIR HIATT: Yes, so let's just acknowledge that, in addition to the special populations that Dr. Cannon mentioned, the symptomatic versus the asymptomatic patient bears particular attention.

DR. MASSIE: And of course we didn't, I guess it sort of doesn't need to be said, but it should be said, that the flip side of the anticoagulation is there is the real risk of stroke, whether or not you're anticoagulated, but obviously different.

So we -- I think the patient, my patients seem to be often more concerned about the anticoagulation than the stroke. But really, this is the leading preventable cause of stroke.

CHAIR HIATT: Indeed it is. Hypertension, too.

Any more comments on question #1?

So what are the disadvantages of

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

waiting for spontaneous conversion? Comments on that? We've hit some of this.

DR. LINCOFF: Since we are talking about acute drug, I think the issue is less whether or not we ultimately want to cardiovert or not, which is a different issue, but again, what is the delay in waiting -- or what is the consequences of waiting.

From my understanding, the data is not clear that you can avoid the need for anticoagulation after cardioversion, even if you've cardioverted relatively early.

So I don't know that we can hang our hat on the idea that, if you convert them before a certain period of time, you can avoid anticoagulation that you wouldn't otherwise, because I think that's unclear.

To some extent, it depends upon how long they've waited before they've come to attention. But certainly, I think for most of the people in these studies, beyond

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

24 to 48 hours, the issue of anticoagulation is moot, because you pretty much want to or need to do it anyway.

So it really comes down to issues of flow of patients through the hospital system, and that is going to be dealt with in the emergency room, potentially sent home rather than monitored. But then there is periods of time to monitor for the drugs themselves.

There's the issue, the very real issues, of patient anxiety or frustration in dealing with being in atrial fibrillation longer, and waiting around to see it converted.

But I think it's very hard to show, aside from the hemodynamically unstable patient, which I don't think any of us -- I think that is very clear, that it's class 1A indications to convert them fairly rapidly.

For patients who are not hemodynamically unstable, not having the

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

angina from the rapid response -- and again, we are not talking symptoms, because this is not at home or playing tennis, but this is sitting in the hospital.

I think it's very hard to show a disadvantage of waiting. I think they are mostly theoretical, as Bob and Chris pointed out in goats, that you may make it more difficult later on to convert.

DR. HARRINGTON: I think you have said it, Bill. I think one of the conversations we'll have over and over today is about symptomatic versus asymptomatic patients. Because as Mike said, that's very, very different in terms of the urgency with which you want to do something.

And the anticoagulation issue is something that is going to be there. That if you have a structurally normal heart, and you are out of afib in the first two days, I think you can make a case based on the evidence to not provide longer term

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

anticoagulant therapy.

Everyone else, I think you have a tougher case. If you do not have a structurally normal heart, or if you are in afib for greater than 48 hours, most of the evidence would suggest anticoagulation, as Barry said.

I mean, few things are better in medicine than oral vitamin K antagonism for the reduction of stroke. I mean, there's almost a 70 percent risk reduction in stroke with oral vitamin K antagonists relative to placebo.

CHAIR HIATT: Yes, and thanks for characterizing that, because I think we sort of -- we hit on this just a little bit earlier, but just to kind of maybe restate it, it sounds like that there may be a subgroup of patients who, for example, have alcohol withdrawal, and will have a spontaneous conversion to sinus rhythm, structurally normal heart, and they

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

potentially could stay in sinus rhythm the rest of their life, and that patient would not get anticoagulated.

But most patients that would be considered in these kinds of trials are at risk for recurrent or chronic, and therefore, the concept of background anticoagulation therapy for all patients is one I think the committee seems to be supporting as most likely for most of these patients.

Am I right in saying that?

DR. HARRINGTON: I think another way to say it is that we should probably take off the table, for most patients you are not avoiding the risk of anticoagulant therapy, for most patients that we will be talking about, though there will be special situations where perhaps you can.

CHAIR HIATT: Okay, so then if that's true, then once again we are dealing with symptomatic issues in many respects.

DR. MASSIE: Although it does seem

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

like recent guidelines are beginning to push the envelope of the non-anticoagulated patients. It makes me scared, but I guess they have been compending the data. You know, the low risk patient, now it's gone up to 65, and some people are saying the area between 65 and 75 with those of less evidence of heart disease are low risk.

I guess it's going to take awhile for me to practice that way for the reasons Bob just talked about.

But again, the types of patients that we are talking about here tend to be the chronic hypertensive person. The median age is 65, and it looks like the AFFIRM population, at least in that demographic, background of hypertension, so I think most of these will end up being anticoagulated. And I guess the other thing is, I see a lot of them end up on chronic antiarrhythmic therapy because somebody thinks they are at risk.

It seems to me that if you are willing to use chronic antiarrhythmic therapy, all those people should be on anticoagulation, unless there is a direct contraindication.

CHAIR HIATT: Excellent.

Any more comments on question number two?

DR. STOCKBRIDGE: Did anybody want to comment on the potential difference in terms of hemodynamic outcomes? Anybody think that is a pertinent consideration?

DR. MASSIE: There certainly are people who are harder to rate control, particularly the post-op patients sometimes who tend to have fairly normal hearts, and are on a real catecholamine high, and all the rest, and if you can't control the rate, it can be an issue. And some of the drugs we give to control the rate begin to take their toll, multiple hypotensive agents, then we get into the second part of the hemodynamic

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

problem.

So I think it can be pretty miserable. Now the types of people that were in the study, I see the mean heart rates were 100. I don't think there probably was a big issue with hemodynamics making them need to have urgent cardioversion if you could get the heart rate down to 100 pretty easily. Although there must have been a couple of 140s in there, I think the upper range reached that level.

So I think the hemodynamics, the angina patient, the poly-pharmacy that hemodynamic control requires isn't benign, but I don't think it's a huge problem.

DR. STOCKBRIDGE: Okay, but this wasn't about whether the strategy ought to be rate control, it was about waiting some period of time for spontaneous conversion.

DR. MASSIE: That was what I was actually referring to. It's this period, they are in the hospital, you know, do you

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

want to watch another couple of days. I mean, I guess I took the data from these studies to say, at least this particular population, waiting isn't going to be very productive beyond the 72 hours that they were supposed to have already been observed to be in atrial fibrillation.

Whether a week later it would happen or not, I guess we just don't have enough data to know. But the fall off between that early, pretty high percentage of spontaneous conversion to what we saw from 72 hours to the next few days, was pretty dramatic. It didn't seem to me like that would be likely.

So I was talking about the hemodynamic problems there. This population is pretty well controlled in their rate. I don't think it was really probably hard to deal with their hemodynamics, but I think there are problems with hypotension, with multiple rate control drugs that are real.

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

And sometimes you get periods of bradycardia together with your tachycardia, and it really depends on the population.

I think that is an issue, but usually manageable.

DR. STOCKBRIDGE: Let me ask the question a little bit differently. If you were to convert, either spontaneously or with some product, some other strategy, if you were to convert, do you think there is a difference in your hemodynamic state at that point, depending on how you got converted?

DR. MASSIE: I wouldn't want to say that I can imagine a really big difference. They both can cause hypotension for various reasons, you know, being the medicines that we give with the cardioversion, and other things, and they both get bradycardia some of the time.

But I think those are manageable with appropriate observation in either case. So no, I don't think there's a big

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

difference.

DR. LINCOFF: I think spontaneous cardioversion probably spares you -- I think it's much less likely to be bradycardiac or hypotensive in the case of spontaneous cardioversion, so I think from that standpoint - but again, these are relatively manageable, and I think that, if you do wait and decide to default to electrical cardioversion, you are probably not buying yourselves much.

And in terms of the hemodynamics in the waiting period, I think you will know up front for most cases, although it's very true as Dr. Massie pointed out that some types of medications we use in the interim to control the rate do precipitate their own treatment emergent hemodynamic consequences that then push you to cardiovert.

DR. CANNON: I'm just wondering if maybe what you are driving at is the benefit of atrial systole. So obviously one

justification for restoring sinus rhythm is to restore atrial systole. And for some patients with stiff hearts, hypertrophic cardiomyopathy, which I used to see a lot of at the NIH, I don't see quite so much nowadays, but atrial systole can mean a lot.

And I think the earlier the cardioversion, whether it's spontaneous or electrical, or pharmacologic, the more likely you'll see a fairly rapid restoration of atrial systole.

So what's one disadvantage of waiting in that -- again, we are talking about a special population. Well, I think restoration of atrial systole will be more delayed. So if you wait a month or so, or six weeks, more than likely if you then decide to cardiovert, or they spontaneously cardiovert after six weeks or so in atrial fibrillation, I think there is going to be a longer time for atrial systole.

And that's one of the reasons why

we continue anticoagulation for three or four weeks beyond that point, because we know that, by echo, the atrium just doesn't move, or doesn't move very well for a time. And the longer that interval from the onset of atrial fibrillation to cardioversion, the longer I think it's going to take for the atrium to wake up and do some benefit that we hope will be achieved.

DR. LINCOFF: In that regard, with the atrial mechanical activity, it's sort of paradoxical that the period of time that we're probably likely to recover the most, that there is the most difference for every smaller increment of time in recovery of atrial activities probably early on.

So a patient who comes in seven days, 10 days after their onset of afib, you know, the extra couple of days are probably going to make very little difference.

But on the other hand, that's the time period where their likelihood of

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

spontaneous cardioversion is very low anyhow, so that the pharmacologic cardioversion is more of a margin.

On the other hand, very early on, even though there may be a fairly high rate of spontaneous cardioversion, you may be doubling the time -- if they are presented within a day, and you wait a day and a half or two days, you may make quite a substantial difference in terms of their recovery.

It's theoretical, but there is a lot of talk about how long it takes before -- in the first couple of hours to the first couple of days before you are left with a substantial period of atrial inactivity, even with restoration of electrical activity.

DR. MASSIE: Let me just make one more point about hemodynamics. Those that you don't rate control, it doesn't take more than 24 hours before ventricular function declines, too. I mean, I think this issue of tachycardia myopathy is something that we

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

overestimated -, underestimated for many years. I guess the dog model emergent, and the ablation of pediatrics with incessant supraventricular tachycardia, with EFS going from 20 to 50 in a couple of weeks has finally alerted us to it.

But if you don't rate control, and you have you people going 120 or faster, I think there is a real toll in ventricular -- it's not irreversible, but can make -- can really cause problems until it does reverse.

CHAIR HIATT: Why don't we go through these next two questions.

Can you describe the magnitude and durability of these disadvantages? I think we've hit on some of this. Does anybody want to add any more discussion to that?

And the last one: what is the right interval to integrate the success of spontaneous conversion?

If someone were likely to convert spontaneously within the next hour, would it

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

make sense to consider treatment options within the next day or the next week? This gets back to that timing issue.

DR. HARRINGTON: So as I read through both packets for the next few days, this is the analysis I want to see, is the time-dependent risk-benefit analysis, and that you could almost view it as a continuous function. Because at some point, I mean Norm has thrown out for us some broad categories within the next day, within the next hour. But you almost wonder, using sort of like landmark techniques, if you couldn't get at this in a more quantitative way of, you know, say in six-hour increments or something.

But there are analytical techniques that should allow us to consider the risk-benefits in each of those periods of time. So, you know, just to set up the straw man, Norm asked within the next hour - what about the next two hours after that? The next six hours after that?

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

I think we are going to need to think about this in a more quantitative way, and it would help if the sponsors could actually show us data looking at the risks and benefits at different time points.

CHAIR HIATT: Yes, I agree with that. And let me also, I think I mentioned this earlier to both sponsors, we know a lot about the defined treatment interval for the primary endpoint, and then things change.

And what I really want to know is what happened when conventional therapy was employed, more frequently on placebo patients than in drug-treated patients. Nevertheless, cardioversion did occur after two hours.

And what was their symptomatic state at 24 hours? I mean, those are the kinds of things. Now, we can't frame shift those trials, as you were asking, Bob, across a variety of intervals, because they all kind of have the same design.

But we do have data, or there must

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

be data, that can look at those questions that occur between groups after conventional therapy occurs.

DR. HARRINGTON: Well, remember, one of the advantages of the landmark technique is that you're parsing things into periods of time, for which you then reset the clock. So you can take into consideration, for example, if you are doing a landmark analysis with six hour intervals, that when you get to zero hours, you are looking at all the baseline characteristics. If you then reset it for six hours, you then look at everything that has happened from zero to six, and you can consider that in your analysis.

And then you can look overall at what the effect is. They start to do that when they are talking about the three-hour to seven day, and then the seven day to many more hours. That's a variant of it.

And one of the issues is is that,

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

you know, all of the effect appears in the early group, although when you look at the overall effect, it's still preserved.

It's only because the early effect is so impressive. But there are ways of quantitatively teasing that out in smaller portions of time.

CHAIR HIATT: Yes, I agree with you, and we do see that evidence, and the curve kind of looks like the one up there. So you can kind of go back and look prior to randomization, but the question is, can you go forward from that point?

DR. HARRINGTON: Analytically, you can. It's just a matter of, has it been done?

DR. LINCOFF: I think we need to be realistic about the limitations of the data that exists, though. This wasn't -- these strategies were not to test against never cardioverting in the groups that didn't convert. So this isn't natural history, and I don't think that there is much landmark we

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

can do beyond, because the strategy was, you try the drug, and if it doesn't work, then you default to cardioversion.

So what we are being asked is, if this drug is approved, and now enters as an armamentarium as a way of avoiding the cardioversion, then, you know, how does that change outcome, but not compared to people who would never get cardioverted.

I think the more interesting question is, if there were a way to stratify according to how long patients had been in atrial fibrillation ahead of time, but it sounds like that is somewhat limited. It's clearly going to be limited by the numbers. We don't have many patients in overall studies, anyhow, to try to do risk benefit at different time periods of preexistent afib before they presented, even if one knows exactly when the patients were in atrial fibrillation. And that gets very hard, as well, for many patients to know exactly how

long they have been in atrial fibrillation. Sometimes all you have is the last ECG that showed sinus, and that's how you know how long they've been in atrial fibrillation.

So I think for the trial data that exists, it's going to be very difficult to say much about what's long term benefit compared to something else. Because something else is fixing the rhythm in many patients anyhow, and it's going to be unfortunately hard to answer what I think is the more relevant question, when we are faced with a patient in the emergency room at time zero of what to do, that is, is there a benefit to using a drug or using electrical cardioversion, or should we just wait and see what happens to them spontaneously. Because there is not much data for natural history that we can rely on, and I don't think we can take the data from this study in terms of risk-benefit, because the risk side is going to be so small numbers, especially once you

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0

start to parse it into different intervals of how long they've been in afib.

CHAIR HIATT: One more comment I'd like to make before we transition to sponsor presentations is, an FDA reviewer commented that AF is an endpoint to surrogate. What does the committee think about that?

DR. HARRINGTON: It goes back to my earlier comment of, you know, live longer, feel better, avoid unpleasant things. And it depends how you view cessation of atrial fibrillation.

And this might get to your question, Bill, of symptomatic versus asymptomatic. If you are asymptomatic, conversion to sinus rhythm, one could argue from a patient-centric perspective, are you living longer, are you feeling better? You can't feel better if you didn't feel bad.

And did you avoid something unpleasant? Well, if the alternative was to do nothing anyways, you really didn't meet

0ab32ca8-5db0-4cbe-a2ce-fdd7f7782df0