more data -- a little bit more of a consensus relative to the type of procedures, but if you look at the registry data published in 2005 a dramatic increment, with probably at least an order of magnitude more ablations being done than was reported in this registry data.

And this is paralleled, also, by the number of publications, with over 425 in 2006 related to afib ablation. However, the quality of these publications is low relative to the considerations today.

There are many limitations to them that Dr. Packer has gone through -- end points, treatment modalities, definitions of success, blanking periods, lack of detection of asymptomatic afib, which is really a very critical issue, as Dr. Calkins alluded to, and under reporting of adverse events, which we've heard about.

If we look at the randomized trials that were prospective randomized trials of paroxysmal afib, you'll notice success

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rates that are reported in the range of 55 up to 85 percent with a single procedure. These are selected individuals and selected institutions, and notice complication rates are low, about one to four percent, probably representing an under reporting of low probability but high impact events.

There have been, in fact, publications beyond the one abstract that include the Oral paper with chronic atrial fibrillation looking at 74 percent success rate at one year with an analysis that was based on recurrence rates per month.

So in terms of randomized controlled trial, very little high-quality data. That needs to be kept in mind.

The definition of success has been alluded to, and we don't need to go through each one of these, but I do think that we should adhere to the principles that have been outlined in the consensus statement by the Heart Rhythm Society and also relative to

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monitoring.

And Dr. Calkins, I think, summarized the group's sense on these important issues, including detection of asymptomatic episodes of afib. Now, this assumes importance, although the patient might feel better, because of anticoagulation issues.

There's a tendency when we do trials to do them in a very selective group of patients and then generalize well beyond that patient population. And I just would urge that we be mindful of this as we look at the generalize-ability of our data relative to the ages of patients in trials and the true demographics of patients with atrial fibrillation.

Whether we want to expand these to the older age groups in whom the prevalence and incidence is much higher or not is something we need to carefully consider in controlled trials.

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1 We also need to factor in very,
2 very carefully the issue of anticoagulation.
3 Question number six in particular was focused
4 on whether we need to do trials in which
5 anticoagulation may be continued or
6 discontinued in selected patients.
7 And I think the American Heart
8 Association's position on this is really quite
9 clear that there's good evidence-based
10 medicine that the CHAD score should be used
11 for the basis for continuation or
12 discontinuation of it, and that it really
13 would not be appropriate, because there's not
14 equipoise, to discontinue anticoagulation.
15 Those issues, I think, are wide of
16 the mark relative to what needs to be looked
17 at with afib. And that's summarized here.
18 Discontinuation of warfarin post-ablation is
19 not recommended in patients who had a CHAD
20 store less than -- greater than two because of
21 the risk reduction with anticoagulation.
22 I think it's very important that

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1 we keep in mind that it remains uncertain,
2 despite over 425 publications last year,
3 whether apparent cures represent elimination
4 of afib or transformation into an asymptomatic
5 form of paroxysmal afib.
6 This is an issue that was brought
7 up in the guidance document in 2006 and
8 remains an issue today which is unresolved.
9 The distinction is important, obviously, for
10 not only definition of success but also for
11 anticoagulation.
12 We have very little -- almost no -
13 - information about late success in patients
14 with heart failure. And this is a group that
15 will probably have more complications and
16 lower efficacy rates and, in my judgment,
17 remains wide of the mark relative to the
18 patients that are most likely to benefit.
19 Double blind studies are almost
20 impossible to perform. However, with the
21 hybrid approach one could certainly double
22 blind outcomes in follow-up. The consensus

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1 document that came out in May does give
2 sufficient room to individuals and
3 investigators to use afib ablation as first-
4 line therapy, but the position of the American
5 Heart Association has been much more
6 conservative.
7 Certainly, using this first-line
8 therapy, as Dr. Neaton alluded to, would make
9 the traditional trial design very attractive.
10 And I think that Dr. Schoenfeld made that
11 point as well.
12 I will add that much as expressed
13 by Dr. Calkins and others, the issue of
14 looking at a performance outcome, performance
15 criteria, is going to be a very vexing one in
16 either the traditional trial or in the hybrid
17 trial, because the results are all over the
18 place relative to efficacy and safety.
19 And establishing any kind of
20 reasonable goals can be very, very challenging
21 and vexing, and I think would perhaps be a
22 weak point of either trial design.

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1 So we obviously need to have a
2 comprehensive evaluation of both favorable and
3 adverse effects of the techniques. We need to
4 factor in quality of life and cost in the --
5 in both limbs.
6 And generation of these
7 comparative data over relatively long periods
8 of time, keeping in mind that most of these
9 trials are short-term, one year, is going to
10 be important. Certainly, getting out to the
11 point of 18 months or two years would give us
12 much more meaningful data relative to these
13 issues.
14 So I appreciate the opportunity to
15 present on behalf of the American Heart
16 Association and look forward to comments and
17 questions.
18 DR. YANCY: Thank you very much,
19 Mark.
20 We'll proceed forward with Dr. Pat
21 McCarthy.
22 DR. MCCARTHY: I'm Patrick

98938861-1d74-4600-8272-d58807a75e6d

1 McCarthy from Northwestern University, and I'm
2 here on behalf of the Society of Thoracic
3 Surgeons, where I am on the writing group for
4 atrial fibrillation with the Heart Rhythm
5 Society and also the chair of the New
6 Technology Committee, which is why I'm here.
7 I'm a consultant to Medtronic
8 regarding a device for a left atrial appendage
9 occlusion and on an advisory board for two
10 companies that have devices for atrial fib.
11 Today I'll talk briefly about the
12 history of surgery for atrial fib, prior
13 randomized trials, standalone afib trials.
14 First of all, the Cox Maze
15 procedure, almost 20 years old now -- the
16 important thing about this is that the lesion
17 set is very similar to catheter ablation,
18 fortuitously, with pulmonary vein box lesions,
19 a mitral annulus lesion, and right atrial
20 lesions, and the left atrial appendage is
21 excised -- very effective for asymptomatic
22 atrial fibrillation.

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This is showing 10-year follow-up in this group of patients from Washington University. On the right, you see the return of atrial systole as seen by MRI. This patient, the same day, had an echo showing no atrial systole, so it does point out the importance of the way that this is monitored.

On the left, you see a slide that came from a paper that Dr. Niv Ad will be speaking about. In yellow is the risk of stroke as seen in patients after the Cox Maze procedure after 12 years, less than one percent. That's from many different centers.

In comparison, our other groups of patients with atrial fibrillation, such as mitral stenosis and in patients -- hit the wrong button -- or mitral stenosis without anticoagulation, lone atrial fib with and without anticoagulation. So it appears to be very effective for stroke reduction in late follow-up.

So in summary, symptomatic atrial

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fib was very rare, about five percent, in that group of patients, but this was the early days. This is almost 20 years ago that it began, so there was no routine monitoring afterwards.

The risk of late stroke was very low, from many different centers, Mayo, Cleveland Clinic, and others that did quite a few of these operations.

Atrial transport was difficult to quantify, varied from 60 to 90 percent, depending upon the different type of technique, and I know that was one of the different -- one of the questions from the FDA panel.

It was effective with large left atrium, low ejection fraction, tachycardia mediated cardiomyopathy and patients with structural heart disease -- also, questions from the FDA panel about the high-risk patient population.

But in itself, the operation was

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too complex. In the U.S. there were only about 100 patients per year that were actually treated with this operation.

So that led to a variety of new energy sources and then technologies to treat the patients and to do the ablation, including cryoablation, unipolar and bipolar radio freqency, microwave, high-intensity focused ultrasound, and now laser that's recently been released.

There is, to my knowledge, two FDA trials that are just starting for radio frequency ablation devices in patients undergoing concomitant mitral valve surgery -- patients. To the best of my knowledge, those are single arm studies that have a set goal that they need to reach in terms of effectiveness.

There have been now five published prospective randomized trials of permanent atrial fib patients that were ablated at the same time as mitral valve surgery, and this is

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important for a few reasons.

Number one is that there were prospective trials set up here in the United States that were abandoned about five years ago because the surgeons had too much bias that they didn't want to treat the patients.

And in these prospective trials that were done outside of the U.S., the non-treated group had a low return to sinus rhythm. In all of them -- and with small numbers of patients, the return of sinus rhythm was significantly higher in the group of patients that were treated.

There also is some publication bias, and that had come up before, because I know, for instance, as a reviewer for a high-impact journal, we've looked at six randomized trials using a different energy source coming up with the same results but said since there's already five published, it didn't make that journal. Hopefully it's going to be published in a different journal.

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1 So there is quite a bit of recent
2 data looking at this with prospective trials
3 outside of the United States.
4 All of those were in favor of
5 sinus rhythm if the afib was treated.
6 Importantly, there were no peri-operative
7 atrial fib treatment complications in any of
8 those five different papers. None of those
9 were powered or followed long term to look for
10 late survival or other major adverse cardiac
11 events.
12 Just because of the 10-minute time
13 frame, I did not bring along data from large
14 registries and databases showing patients with
15 atrial fib who go through surgery have a very
16 high risk for major adverse cardiac events and
17 increase mortality. And those are from
18 propensity-matched studies done by Dr.
19 Blackstone, one of the panel members.
20 The return of sinus rhythm was
21 generally about 80 percent but was
22 heterogeneous depending on the patient

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population and the technology.

The Society of Thoracic Surgeons, with the HRS document that you've heard about a couple of times before, have a portion on surgery for atrial fib and, after reviewing all of the data, said that it is advisable that all patients with documented afib referred for other cardiac surgeries undergo a left or bi-atrial procedure for A.F. at an experienced center, unless it will add significant risk.

Standalone afib therapy and trials are much earlier in surgery than they are in catheter ablation. This is data from a manuscript that's been submitted from the Society of Thoracic Surgeons database. This is a three-year period. Seventy-five percent of patients in the United States are entered into the STS database, so it's quite robust.

A total of 700,000 patients were entered during that time. Of them, 67,000, or 11 and a half percent, had had atrial fib pre-

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1 operatively. At the time of surgery of that
2 group of patients that had pre-op atrial fib,
3 there was 28 percent that had concomitant
4 ablation in '04. It was up to 40 percent in
5 '06.
6 Of the patients that underwent
7 mitral surgery, it's easier to do the
8 concomitant ablation with the left atrium
9 open, and so it was -- over 50 percent were
10 treated. It's not as easy when the left
11 atrium is not open, so with coronary bypass
12 and valve surgery -- aorta valve surgery, it
13 was less.
14 Standalone is still not very
15 common. During that three year time, at least
16 reported to the STS, were just over 1,100
17 patients. It was somewhat higher in '06 than
18 in '04. It was 660 patients in '06.
19 Importantly, regarding the safety
20 issue, again, this is a registry, but looking
21 at a large number of patients, they concluded
22 that after adjusting for differences in pre-op

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1 characteristics, mitral surgery patients with
2 surgical afib correction did not have a
3 significantly higher risk of mortality or
4 major morbidity, similar to what the
5 randomized clinical trials had found.
6 The goals of standalone surgical
7 therapy -- to do this off-pump, minimally
8 invasive, from the epicardium, try to achieve
9 the same high effectiveness and safety that
10 we've had with the classic Maze operation,
11 reduce stroke.
12 As part of this, we may also be
13 ablating the ganglionic plexi and closing the
14 left atrial appendage, and some of us are
15 working with the E.P. for a hybrid approach.
16 There's two procedures. One is
17 bilateral thoracotomies to isolate
18 predominantly the two pulmonary veins. The
19 second is this right thoracotomy port access,
20 which is about a 23-hour hospital stay in some
21 of the centers that have been using this, with
22 a variety of different energy sources that can

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1 be used to do the box lesion or even other
2 lesions on the right atrium.
3 What should the FDA expect from
4 these standalone A.F. surgical trials? The
5 first issue is going to be technology or
6 labeling. If a device is already approved for
7 A.F. in concomitant ablation, will it
8 automatically be approved for standalone
9 surgery? If you approve a heart valve for a
10 sternotomy, will you need a different approval
11 to do it through a minimally invasive surgery?
12 So you'll hear some of those
13 arguments from industry. I would say that on
14 a case-by-case basis you would have to
15 consider those.
16 Much of what we're going to do
17 will be very similar to catheter ablation
18 trials. We were on the HRS document. We'll
19 be looking at multi-center outcome trials,
20 industry-sponsored device approval.
21 STS and other registries will be
22 available to give additional data as I just

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1 showed. End points -- of course, very
2 important -- primary, secondary, quality of
3 life, because these are symptomatic patients,
4 very robust monitoring for atrial
5 fibrillation, and standardized reporting,
6 procedure-specific surgical adverse events and
7 serious adverse events. And those will need
8 to be defined.
9 The differences for surgery --
10 most of these procedures close the left atrial
11 appendage. Some also will ablate the
12 ganglionic plexus. These are going to be
13 epicardial ablation. Transmurality will be a
14 challenge for the technology. Hybrid will be
15 part of this, and there will be procedure
16 risks.
17 Inclusion criteria, symptomatic
18 patients -- many patients now who have failed
19 catheter ablation are referred for surgery or
20 not candidates.
21 So in summary, atrial fib surgery
22 has a very long history. The new technologies

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have expanded this. And experience in the standalone operations is very early at this point. The trials will leverage some of the preexisting technology that we already use.

And like HRS and others, the data will have to be standardized. Thank you.

DR. YANCY: Thank you very much, Dr. McCarthy.

The final speaker in this open public forum is Niv Ad.

DR. AD: Good morning. I represent our program and not any company. However, I have a disclosure to share with you. I am on advisory board for Boston Scientific, and I'm on a speaker bureau for Medtronic, and I am a consultant and P.I. on the ablate study for Ethacure.

Before I start discussing the surgery objective, I want to share some concerns I had a few days ago when I learned that I'm going to present in front of this forum.

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1 And I was relieved to learn that
2 there are some cardiac surgeon both in the
3 forum and in the audience, since I was
4 introduced the new definition for double blind
5 study by a colleague of mine from cardiology,
6 saying that a double blind study is two
7 cardiac surgeons trying to analyze an EKG.
8 (Laughter.)
9 DR. AD: Having say that, I think
10 that I can represent the case of cardiac
11 surgery for atrial fibrillation pretty well I
12 was trained by Dr. Jim Cox himself. I
13 acquired knowledge in electrophysiology. I
14 personally performed over 500 Maze procedures,
15 and we are currently running one of the
16 biggest program in the U.S. for atrial
17 fibrillation ablation surgically at the Inova
18 Fairfax Hospital.
19 Therefore, I think that I want to
20 include a few comments in this 10 minutes in
21 order to be able to influence and maybe
22 participate as a cardiac surgeon in the

98938861-1d74-4600-8272-d58807a75e6d

1 process of setting those clinical benefit bars
2 that we are all talking about and also
3 consider some benchmark approvals for the
4 cardiac surgery other than the binary freedom
5 from A.F., such as stroke reduction, A.F.
6 burden, as we all spoke about, and of course,
7 freedom from medication.
8 A word of caution regarding
9 quality of life. As far as I know, we are one
10 of the only programs in the U.S. and in the
11 world running a prospective quality of life
12 assessment on patients before cardiac surgery
13 ablation, and we have over 150 patients with
14 longer than six months hold-up now, and I can
15 tell you that the issue is much more complex
16 than yes or no.
17 The quality of life assessment and
18 outcome with a mental component, physical
19 component and general health component are
20 very, very hard to dissect and to, one on one,
21 relate it to the outcome of the surgery.
22 Next week on the 27 of September -

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- it's actually the exact date 20 years ago that the Maze procedure was first performed on a non-American citizen at Washington University.

As we all know, it's a two Maze with one entrance and one exist and many dead ends, and it had a few modifications within the Maze from Maze one to Maze four that was presented by Jim Cox himself the late '90s.

What happened with the procedure is very interesting, and Dr. McCarthy shared with you some information from the SDS database, but I consider what happened with A.F. surgery as a perfect storm.

At the end of the '90s, there were only few case data centers in the U.S. and in the world that were performing any procedure for A.F. However, what happened then is that cardiac surgery in general realize that revisualization for reason that it's beyond the scope of this discussion is going another direction.

98938861-1d74-4600-8272-d58807a75e6d

1 So talking CABGs, A.F. was
2 considered to be a major risk factor for
3 complication and premature death, maybe, and
4 some of the companies that develop some very
5 effective devices to ablate atrial
6 fibrillation surgically.
7 So it's a perfect storm and there
8 was a huge growth in the number of procedure
9 performed in the U.S. and throughout the
10 world. And this slide -- it was given to me
11 by the industry -- represent exactly what I
12 just said.
13 Having say that, most of the
14 procedure are done for concomitant procedures
15 such as valve surgery and CABG and hardly none
16 of the procedure is done for standalone
17 procedure.
18 Like the catheter ablation arena,
19 we face a huge challenge as surgeons in
20 standardizing the field, and this is an
21 editorial I wrote on a very good paper
22 published in the Journal of Thoracic from the

98938861-1d74-4600-8272-d58807a75e6d

Netherlands, stating exactly what I feel, that we don't spell Maze the same way when you speak about the Maze, and we don't have really rigorous definitions and goals with regard to the procedure.

And this leads to a few problems when we start to analyze our data and want to go ahead and design some clinical studies, because as surgeons we are not trained as electrophysiologist, and most of the surgeon are performing A.F. surgery based on some training, but it is a very much open field for self-interpretation of the procedure, based on the tool you have and the amount of understanding you have in the disease itself and your dedication to treat it.

This leads to another problem, which is the accountability of the results, to the point that I feel embarrassed to speak in front of forums and say yes, I have 90 percent success rate, because I know that simply nobody believes me.

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1 And I am saying 90 percent success
2 rate based on the latest HRS guidelines, which
3 is a very high standard of success rate.
4 So as a -- as surgeons, we have
5 very, very much work in order to standardize
6 the field in order to have definitions and
7 goals for, A, the definition of the procedure
8 and, of course, what's going on with the
9 follow-up.
10 And as for follow-up, I can tell
11 you that we are ready to share with a couple
12 of publication of ours that follow-up is not
13 just asking the question whether the patient
14 has A.F. or not.
15 Follow-up is also whether the
16 patient is being followed to a specific
17 clinical algorithm which states exactly when
18 should we intervene in case recurrence occurs,
19 which means what we can show now after -- in
20 24 months follow-up of patients that if
21 patients were on follow-up or on protocol
22 doing follow-up, their success rate is much

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higher than those who weren't followed any clinical protocol.

So I urge you to discuss and think about designing studies with definite algorithm to treat problems following the procedure.

And the variables of the surgical ablation are very clear. This is -- unlike other procedure done, started from animal experiment through primates procedure to the Maze procedure and some modification, we have a advantages in direct vision, mixed anatomy minimally invasive, and we are very effective in creating linear albation, unlike catheter ablation, transmural lesions, we can confirm conduction block and of course we can get rid of the appendage.

The value of the surgical ablation recognize what the latest surgical consensus that was discussed earlier with -- by Dr. McCarthy, and we truly think that there are some patient that should be considered to be

98938861-1d74-4600-8272-d58807a75e6d

operated upon earlier, those patients with documented left atrial thrombus despite anticoagulation, those patients with very low yield of treatment.

And I just operated a week ago -- a patient that have had four consecutive left atrial ablation in another institute, and he came over to us only after being offered AV nodal ablation and a pacemaker, not surgery for God=s sake -- and of course, issue with anticoagulation, patient that have bled and have contraindication and -- to anticoagulation and very high CHAD score.

The results -- as I said, some reports are excellent results. Some are not. But there is no consistency. And we have significantly more effective treatment for patients than any other from a modality of failed treatment for persistent and longstanding A.F. and for enlarged left atrium.

Our complication rate, despite

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1 what everybody is thinking, is extremely low.
2 We are not -- I can tell you that in the last
3 300 or more cases I've performed a Maze, I
4 didn't perform a cut-and-sew Maze procedure.
5 So we are not doing the cut and sewing
6 anymore.
7 And we refer to a Maze procedure
8 as a Maze procedure. It's ablation guided
9 procedure and relatively short hospital stay.
10 And we have to keep in mind that catheter
11 ablation is not risk-free.
12 And of course, a few questions for
13 that data were already mentioned, so I don't
14 want to be repetitive, but I think that there
15 is a clear need to define the real role for
16 surgery in atrial fibrillation. Are we going
17 to comply with the new HRS guidelines so we
18 get specification?
19 And what type of clinical trials
20 and methodologies should be done for
21 indication devices in the field of surgical
22 ablation? Thank you.

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DR. YANCY: Thank you very much.

We now have approximately 15 to 20 minutes before breaking for lunch and an opportunity to question the speakers we just heard, particularly the representatives from the governing organizations for this entity, Heart Rhythm Society and the American Heart Association, as well as the Society of Thoracic Surgeons, and we've also had other important commentary.

Once again, if the panel will indulge, I just want to be clear with a response directed to Drs. Prystowsky and Estes regarding the importance of demonstrating complete resolution of atrial fibrillation following ablation, including asymptomatic episodes.

You seem to intimate that that was your preference in your statements, Eric and Mark, but I'd like for clarity that asymptomatic afib should be recognized and the direction of these trials should be to resolve

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that as well.

And I don't want to put words in your mouth.

DR. PRYSTOWSKY: I think Mark may be -- we may differ a little bit. The only indication for treating afib -- actually, in the treatment guidelines, the only Class I indication is to relieve symptoms.

DR. YANCY: No, I fully concur, but with regard to these catheter technologies.

DR. PRYSTOWSKY: Right, but that's for treating afib. We didn't specify with a drug or with a catheter.

I think we realized on the committee, as time went on and we did the second go round, that with all the data that had become available showing how frequent, if you look hard enough for it, runs of asymptomatic afib are, that we couldn't really, as a committee, as much as we tried to, come down to a formula.

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1 And so that's why we took the
2 pretty aggressive stand, I think, that at
3 least a lot of our colleagues thought, that
4 any coagulation would not be a part of that.
5 If you met CHADS2 scoring system, we would
6 still recommend warfarin therapy, and if you
7 know the CHADS, if you meet the other
8 criteria, you can follow that through.
9 So we separated those two on
10 purpose, Clyde, because we simply didn't want
11 those two to become a reason for doing the
12 procedure. So while I understand what you're
13 saying, and from a trial standpoint I would
14 totally be fine looking for asymptomatic, the
15 bottom line from the guidelines -- the ACC/AHA
16 guidelines, not HRS -- was relief of
17 symptomatic afib.
18 And I think you have to make it a
19 cut between what you would do in a prospective
20 trial when you're trying to get approval
21 versus general clinical care of a patient, and
22 that's what -- so we weren't talking about a

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trial. That fits more to the HRS document that Doug referred to.

DR. YANCY: Thank you.

Dr. Estes, you made a specific point to focus on asymptomatic afib.

DR. ESTES: Right. Just for the purpose of clarity, the ACC/AHA document in August of 2006, as Dr. Prystowsky said, focused on symptomatic afib. There was an evolution of thinking. Considerable thought went into this document, which was an HRS document but endorsed by the American Heart Association, which made it very clear that both symptomatic and asymptomatic atrial fibrillation should be the appropriate end points for assessing efficacy of afib catheter ablation.

DR. YANCY: Thank you.

Panel, do we have questions for -- Dr. Neaton?

DR. NEATON: I appreciate the -- kind of the clarification. I think it's

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1 helpful to get a -- between how guidelines are
2 written and how we design trials. But the --
3 both, I think, Dr. Packer and Dr. Estes
4 referred to a primary end point for a trial,
5 I think, which I need a little bit more help
6 understanding.
7 As I understood it, it was atrial
8 fibrillation, flutter tachycardia, in the
9 absence of drug therapy. And it's that last
10 piece that I don't think I fully understand
11 kind of the rationale for.
12 DR. PACKER: The intent with that,
13 with the consensus statement, was to have
14 available information providing us with a
15 sense as to how often a variety of end points
16 are being met, so that one can then use those
17 end points to determine their impact on long-
18 term outcome if the trials were sufficiently
19 powered long enough to do that.
20 From the standpoint of the
21 consensus statement, then we are saying that -
22 - that kind of a ground-level look requires

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1 elimination of A.F. of whatever type. You
2 have to look for asymptomatic atrial
3 fibrillation.
4 And when we say off drug therapy,
5 we mean off membrane-active anti-arrhythmic
6 drug therapy that is specifically designed to
7 either eliminate or prevent recurrent atrial
8 fibrillation. It's a very different statement
9 than making any comment about off of ACE
10 inhibitors or off of beta blockers.
11 The intent here is to also deal
12 with issues of coming off anticoagulants. And
13 if we're looking to come off an anticoagulant,
14 then the consensus statement requires that --
15 or recommends that patients who are at risk
16 and have CHAD scores of two or above -- they
17 remain on that drug regardless of the outcome
18 of the ablation.
19 If it is a CHADS one, then there
20 was consensus that would have them come off
21 that drug. The place that's gray is between
22 the one to twos and how you want to slice and

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1 dice that.

2 So when we say coming off drug, we

3 mean membrane-active drug, realizing that

4 there are other issues that are rather

5 difficult, particularly in the area of

6 anticoagulation.

7 Now, one of the problems with that

8 is the event rates are so small that even with

9 CABANA with 3,000 patients to come to a sense

10 as to whether or not you can randomize to have

11 someone come off a drug, that would take

12 12,000 patients.

13 So it's not intended that coming

14 off drug means anticoagulation.

15 DR. NEATON: I understood it

16 wasn't anticoagulant. I guess I didn't

17 understand why you would not count an outcome

18 for a patient that had been -- had gone

19 through the ablation procedure that had

20 flutter or atrial fibrillation develop later

21 while they were taking, say, amiodarone. Why

22 wouldn't that be an end point in a randomized

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trial?

DR. PACKER: Well, it is an end point. And one of the things that we classically talk about is the pyramid -- you know, the end point pyramid. What we're saying with the consensus document is the best end point is no A.F. or other related arrhythmias.

One of the problems we have is if somebody comes back with flutter or atrial tachycardia, that's not necessarily better, you know? In fact, it can be worse. And so we're trying to come up with the best, most stringent, realizing that there will be a kind of hierarchy of other end points that we will consider.

We just think that that's the best one to nail down other subsequent issues, and then if anyone wants to report these other lessers, that's perfectly reasonable. It's informative. It gives us great information. It isn't, though, what we're shooting for.

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1 I have to make one other comment,
2 and then I'll stop. It kind of begs the
3 issue, though -- you have to be careful with
4 this, because whatever end point you choose,
5 it still begs the issue of what percentage of
6 the patients you're going to require to
7 achieve the end point, and much of this is
8 going to be dependent upon the intensity of
9 monitoring.
10 So that's another part of this
11 puzzle as well.
12 DR. YANCY: It would help the
13 panel, Dr. Packer, if you would tell us
14 briefly about the CABANA trial so we can know
15 that that's an ongoing investigation.
16 DR. PACKER: CABANA is intended to
17 be a 125-center, 3,000-patient mortality trial
18 that tests the hypothesis that primary
19 ablation for atrial fibrillation is superior
20 to state-of-the-art drug therapy for patients
21 with atrial fibrillation that is either newly
22 diagnosed or undertreated, with the intent

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being that that would demonstrate 25 percent reduction in total mortality.

With a trial like that -- I think it absolutely has to be done, but with a trial like that, you do have to hold it to a very high standard. I think that that's different from what we're talking about here with device investigation studies.

DR. YANCY: Thank you.

Dr. Page?

DR. PAGE: I want to thank the speakers very much.

For clarity to the panel, I think we need to define a little bit your perspective on asymptomatic recurrence. I think it was mentioned that we should look for and measure that, and it might even be an end point.

But as Dr. Calkins gave the example of someone who has -- comes in six months later, feels great, thinks they've had a wonderful procedure, and they're in afib,

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1 the converse I think we need to consider, if
2 we're looking for 30-second recurrences -- if
3 I've got a patient who has weekly paroxysms of
4 atrial fibrillation that last an hour,
5 terminate spontaneously, that patient
6 undergoes an ablation, and six months later,
7 through intensive monitoring, we find a 30-
8 second episode of asymptomatic afib,
9 anticoagulation issues aside, I consider that
10 a success, because as Dr. Prystowski said,
11 we're looking for relief of symptoms.
12 So just so we're clear, you're not
13 advocating such a stringent end point that an
14 asymptomatic afib in the patient I outlined
15 would be a failure of therapy, or am I
16 misunderstanding? You.
17 DR. CALKINS: Yes, I think there's
18 two issues. There's this issue about the
19 highest standard that Doug referred to in
20 terms of, you know, we're trying to decide is
21 catheter ablation better than drug therapy,
22 you know, and if so, by how much.

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1 And our thinking is if that's --
2 if that's why you're doing the procedure, you
3 want to get rid of afib, and certainly since
4 we have evidence that the procedure can render
5 symptomatic afib into asymptomatic afib we
6 could still have the same amount of afib, we
7 need to have some monitoring for that.
8 So I -- where HRS came down on it
9 was, you know, it's freedom from, you know,
10 all afib, flutter, tachycardia, off drugs, 30-
11 second episode, with the understanding that
12 the same standards apply both to the drug arm
13 and to the catheter ablation arm.
14 So that, you know, should get rid
15 of the fact that we're using a stringent end
16 point for both sides of the table. And then
17 the question's going to be okay, so we show
18 that catheter ablation's 20 percent, 30
19 percent better than -- than, you know, anti-
20 arrhythmic drug therapy, and then the -- let's
21 say that number is 40 percent, or 35 percent,
22 or 45 percent. Is that enough?

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1 And that's why I think all these
2 other measures will be helpful to the panel in
3 deciding whether to approve this catheter in
4 terms of yes, it statistically is better, but
5 also clinically.
6 You have all these other
7 parameters of quality of life and so on and so
8 forth, and other measures we've had of
9 symptomatic episodes that also speak to the
10 value of this, and yes, this is worthwhile
11 technology that should be approved.
12 So I think that was our thinking.
13 But let me see what Doug's comments were,
14 because Doug was the chair of the clinical
15 trial section, so he deserves a lot of the
16 credit for what we -- what we -- the success.
17 DR. PACKER: Again, that's what
18 I'm referring to when I say it kind of begs
19 the question. If we conventionally say there
20 ought to be a 70 percent success rate for A.F.
21 ablation, if we adopt a more stringent
22 standard, then that's going to go down. It

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1 could be 50 percent for persistents, or for
2 chronics it could be as low as 20 percent.
3 That doesn't necessarily mean that
4 we would advise that this panel adopt a
5 standard where a device could not be approved
6 unless it were 70 percent effective at this
7 higher standard.
8 We're simply saying that you have
9 to know. You know, these single-center trials
10 have not been held to any standard, and so I
11 think that it's appropriate to say that we're
12 trying to at least give a bar, and we're
13 saying at least tell us this information.
14 So then groups like the FDA can
15 say okay, so now we at least understand what
16 the ground rules are, we at least understand
17 what's going on, and we at least understand
18 what the outcomes are.
19 And your patient, Rick -- we have
20 patients all the time who come in for horribly
21 symptomatic atrial fibrillation. And with
22 whatever procedure we do, someplace around 70,

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75 percent of the time, we'll eliminate the atrial fibrillation.

Now, if we looked harder, I'm sure that some of ours where we don't have that degree of screening for asymptomatic events, I suspect that our results would be less than that.

And the patients don't come back for repeat studies. Repeat ablation or recurrence or our re-do rate is 14 percent. But we're unsuccessful in more like 25 to 30 percent depending on what the underlying disease is. But why don't they come back? Because like your patient, they're just fine.

And so I do think that that's acceptable from the standpoint of taking care of that one patient. It may not be acceptable from the standpoint of at least give us the information so that we can make intelligent decisions about device approval -- or more relevant to you and me is stopping anticoagulation.

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1 That's the biggest issue, I think,
2 for a clinical trial.
3 DR. YANCY: Dr. Tracy, then Dr.
4 Schoenfeld, and then Dr. Slotwiner.
5 DR. TRACY: Just a brief comment
6 about the observation or monitoring for atrial
7 fibrillation, and maybe you could comment on
8 a little bit, either Doug or Hugh. It would
9 be extremely uncommon for a patient pre-
10 ablation to have gone through as rigorous
11 monitoring as many set points as they are
12 monitored post-ablation.
13 So I agree that having a very
14 clear on or off switch as a -- you know, this
15 worked, or -- this is successful, this isn't
16 successful is an appropriate level. But there
17 still has to be something in terms of the
18 burden, the afib burden.
19 How do you reconcile those two
20 sort of distinct things? We don't really know
21 what happens to these people pre-procedure
22 versus with close monitoring post-procedure,

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and how do you look at that?

DR. CALKINS: Yes, we've had some prior experience with this problem of afib burden, and, you know -- you know, if you tell a patient to get into the study, here's this monitor, record every episode, and then we'll decide if you can get in, they're very motivated to have a heck of a high A.F. burden.

But then six months later, when they're still having afib, they say this didn't work, the heck with it, stop sending in tracings. And you say fantastic, this is a great success, no more afib's been transmitted. They just haven't transmitted, they're so fed up with it.

So that's where -- you know, it's very tricky, this afib burden concept. The only -- you know, you have these implanted, obviously, devices -- pacemakers or veel devices being modified for this is one level, and then you have these -- there's the event

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1 monitors, you know, that pick up symptomatic
2 and asymptomatic afib whether it's cardio or
3 standard event monitors.
4 And then you have these trials
5 that have been done using seven Holter
6 monitors. But then, as you know, it becomes
7 a heck of a burden for the patient to wear
8 this Holter around for seven days. You know,
9 I mean, you know, it's an extraordinary
10 burden.
11 That's why I think how many of
12 these studies have landed -- which is weekly
13 transmissions, even if they're asymptomatic,
14 with good compliance, plus transmissions when
15 they have any symptoms, perhaps with a Holter
16 monitor and some EKGs thrown in, and have the
17 same monitoring of both the drug arm and the
18 ablation arm may be the best we can do without
19 overtaxing our patient until -- you know, we
20 can't put in, you know, implanatable monitors
21 in these patients, and even telling them to
22 wear a 30-day continuous event monitor -- very

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few patients will put up with that.

So that's the challenge, but that also speaks to why we need a randomized study, and I think anything short of that won't give us, you know, any sense of what we're looking at.

But let's see what Doug's thoughts are.

DR. YANCY: Let's go to Dr. Schoenfeld.

DR. SCHOENFELD: I think that these presentations have been fantastic, and I think it helped, at least for me, clarify the whole aspect of asymptomatic A.F.

I think this whole concept of burden is burdensome to me, quite frankly, just because the same issues have come up with cardiac resynchronization therapy and the burden of ventricular arrhythmias and what does a burden mean, essentially. What are we, again, looking for in terms of what we wish to accomplish?

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1 So I think that the way that the
2 consensus statement worked for the ablation
3 was nicely finessed in terms of primary versus
4 a secondary end point, and I don't think that
5 that -- I think that that might be a
6 reasonable answer for the FDA. It can't be an
7 all or none necessary end point to
8 characterize success.
9 The issue that actually I'm more
10 interested in, and it goes back to one of the
11 issues that the FDA wanted addressed, has to
12 do with one of the slides that Dr. Estes
13 showed, that nice slide from circulation in
14 terms of the patient population.
15 And I'd like to get an idea from
16 the presenters in terms of who we are actually
17 treating in the various trials to date,
18 because one of the various issues is are we
19 more concerned about atrial fibrillation in
20 patients with heart failure, left ventricular
21 dysfunction?
22 Are these single-center studies

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that have been published to date addressing patients that are the paroxysmal fibrillators with perhaps less structural heart disease? What are the implications for treatment of atrial fibrillation in patients with structural heart disease?

Because I think that that -- I mean, are we just touching the tip of the iceberg or are we really dealing with a more global issue that we really are not -- that we have not addressed to date?

So I just want to get a feeling from the presenters in terms of what to do with the patients with structural heart disease. How does the data -- or how do the recommendations reflect structural heart disease?

DR. ESTES: Well, as I showed with my slides of the randomized controlled trials -- there have been five with paroxysmal afib -- only one of them had patients with a small amount of more persistent afib, so it's

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1 largely paroxysmal afib and the absence of
2 structural heart disease who have failed anti-
3 arrhythmic drugs.
4 There have been two trials that
5 I'm aware of which looked specifically at
6 patients with more persistent atrial
7 fibrillation or in the setting of heart
8 failure. Efficacy rates were low; in
9 aggregate, probably fewer than 150 patients
10 with structural heart disease or persistent
11 afib in the medical literature who have been
12 randomized into trials.
13 I think everyone senses that the
14 efficacy rates will be lower and complication
15 rates probably higher.
16 DR. YANCY: Please, Mark, did you
17 need to follow up with Dr. Estes?
18 DR. SCHOENFELD: Well, I guess the
19 other follow up and the most important
20 question I would guess is in terms of the
21 prevalence of atrial fibrillation in terms of
22 the patients that we see -- I mean, this is a

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public health phenomenon.

And the question is are we -- are the paroxysmal fibrillators, for example, that we're dealing with -- is that a relatively small subset of the entity that we're treating, or -- and are we totally missing the mark, no pun intended?

DR. ESTES: That's just fine, Mark.

(Laughter.)

DR. SCHOENFELD: From one Mark to another, right?

DR. ESTES: Yes. We know that in the randomized trials that have been published to date -- and I think they're the relevant ones for this discussion -- the average age is 55- to 60-year-old group. I think that in looking at enrollment, at criteria, inclusion-exclusion criteria, we need to be mindful that the burden of afib really begins at about age 60 and is incremented.

And I think as much as clinical

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1 cardiac electrophysiology has been data-
2 driven, we want to be evidence-based that the
3 risks and the benefits are the same in the
4 patients in whom the clinical trial results
5 are applied.
6 So we just need to be mindful of
7 this, that it is a selected group of generally
8 younger, healthier patients that have gone
9 into these trials, in whom the results may be
10 as good as they're going to get relative to
11 the older patients as the afib progresses its
12 usual natural history.
13 DR. YANCY: Dr. Prystowski, a
14 brief comment?
15 DR. PRYSTOWSKY: Yes, very brief.
16 Two points, really, Mark, that speak to your
17 point. One of the things that we had
18 suggested in the task force we're working on
19 this with the HRS and even the FDA was that I
20 think if you're going to go through trial
21 design, you have to be as pure as you can be.
22 We all feel that pulmonary vein

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1 isolation is the cornerstone of ablation, at
2 least at this point. And when you start to
3 get into persistent afib, you can look at 10
4 labs and each one has their own particular way
5 of approaching persistent.
6 But if you stick to paroxysmal
7 afib, pretty much everybody in the field says
8 at least isolate the pulmonary vein. So from
9 a regulatory standpoint, our suggestion has
10 been that if you were going to go ahead with
11 a trial, we thought that you ought to keep it
12 at least monolithic in that regard.
13 As far as what kind of patients,
14 in early trials, frankly, I think if you're
15 looking for regulatory approval, you should
16 take patients that are not your heart failure
17 patients.
18 But to put life in perspective, I
19 actually have switched around after writing
20 the document about this heart failure issue.
21 The reason we moved it up to second therapy
22 was those patients, if you look at the paper

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from Bordeaux and subsequently supported by the paper from University of Pennsylvania, actually did fabulously.

And we missed the fact that irregularity of rate, even controlled, can really affect myocardial performance. So I actually, in my own group, am moving in a little different direction. I think we have undertreated patients with heart failure. And I'm not talking about Class IV failure, but Class II heart failure.

I think we're going to see a wave in the future, if you're good at ablation, frankly, of helping these people. But I wouldn't put them in my initial trials. I would try to keep the trials monolithic, paroxysmal afib with minimal, you know, heart disease.

I think that's the way to go with a trial, but that's -- may not be in the final analysis the kind of people we may be seeing to give our most improvement.

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DR. YANCY: Dr. Slotwiner, please?

DR. SLOTWINER: Thank you.

I had a question, actually, for Dr. Prystowski and Dr. Estes regarding the A.F. treatment guidelines. I'm curious. The guidelines are very clear that A.F. ablation is second-line to anti-arrhythmic drug therapy. I think that was primarily for safety.

And I'm just curious how we could -- I don't see how we can overstep that in considering appropriate trial design from the FDA perspective.

DR. PRYSTOWSKY: Oh, you mean for regulatory trial design.

DR. SLOTWINER: Yes.

DR. PRYSTOWSKY: Yes. I think that's a very good point you raise, but do remember -- this is really an important point, I think, from a person who sat on this guideline committee, because you could make a very good case, in my opinion, that in the

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1 patients with, for example, hypertension, if
2 you look in the algorithm, we put amiodarone
3 as your first choice, and if it doesn't work
4 we put ablation.
5 Now, we did that for substantial
6 hypertension because most of us in the field,
7 I think you might agree -- I hope you would --
8 that most of the other anti-arrhythmic drugs
9 are not that safe with substantial LVH.
10 But I would submit to you, from my
11 almost 25 years using amiodarone that if I had
12 a choice in a person where it was just a thick
13 ventricle of 10 to 15 years of amio versus a
14 shot at ablation that, quite frankly, those
15 lines would have been equal.
16 But we just didn't have enough
17 data on safety for ablation in that group to
18 say they would be equal. That's really what
19 it came down to. I will tell you it is
20 getting very close in the normal heart group,
21 very close. I mean, that's where most of the
22 discussion went.

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1 But in heart failure, CAD and the
2 other groups, the data were just too immature
3 to bring it up to a point where we could say
4 the safety of the published data in ablation
5 was robust enough to say it could be equal to
6 a drug therapy.
7 So I would have no problem in a
8 trial, absolutely none, to say in an informed
9 consent to a patient that here's your drug
10 choice and here's your ablation choice, and
11 you have risks and benefits of both, we know
12 they're out there. I really don't have a
13 problem with that.
14 But for a general guideline for
15 the world community, I -- we didn't think it
16 was at that level, and that's different, in my
17 opinion, to a trial.
18 DR. YANCY: Dr. Zuckerman?
19 DR. ZUCKERMAN: Yes. I think Dr.
20 Prystowski has very well illustrated the
21 difference between guidelines and an IDE
22 trial, and we would certainly have no problems

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at this -- in this day and age potentially with initiation of that important trial.

But the point that I wanted to get back to is that this morning AHA, HRS and STS have well documented the problems with the current literature due to poor reporting standards and a variety of other problems.

The documents that they've recently written are quite helpful, but what's really needed is better reporting standards so we can understand the literature. Moving -- or in more detail. Moving forward, how are the professional organizations going to engage on that critical topic?

(Laughter.)

DR. PRYSTOWSKY: Going forward? I don't -- do you want to know the truth from a -- from a now -- I can't speak for HRS. I'm not currently an officer in it anymore, but I would say that's not up to an organization to mandate anybody how to look for afib.

Remember -- trials aside, remember

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1 -- the guidelines have said elimination of
2 symptomatic afib is the reason for treating
3 somebody with a drug or ablation for afib. I
4 mean, that's what we've said. And we, as a
5 group, accepted failure of being able to
6 recognize every asymptomatic episode that
7 could ever happen. It's just not going to be
8 a possibility.
9 So I don't know where you put the
10 benchmark. From a regulator's standpoint,
11 Bram, that's a different issue. So HRS has
12 done the best they can to say the most
13 rigorous thing that Doug has said. But that's
14 for a trial. That is not a position HRS is
15 taking for the world out there to treat afib.
16 DR. ZUCKERMAN: Okay. I don't
17 mean to put you on the spot. But again, you
18 know, we get back to Dr. Tracy's key point and
19 that of others: Why is the system less than -
20 - less efficient than we would all like it to
21 be?
22 And part of the problem is our

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interpretation of the literature. I don't hear, you know, how many papers are published each year, if we can't ideally -- optimally interpret the literature, it's a problem.

Now, each professional organization does publish a well-respected journal, and certainly from the agency's perspective it would be ideal if just the professional societies could think about future steps. After all, this is an important public health problem that affects all of us, and what we really need here are good data.

DR. PACKER: I agree largely with what Eric said. I think from the standpoint of the society -- and Mark can also comment on this -- we viewed this as the initial step, so we viewed this as, you know, again, recommendations that were obtained through consensus that we could begin to -- we can't require them, but at least hold each other to that standard.

You're kind of getting into the

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1 issues of competencies and credentialing and
2 payment, and I do agree that those are kind of
3 outside the bailiwick of HRS.
4 Having said that, Cynthia wrote a
5 document that came out about eight or nine
6 months ago and within the document, the
7 consensus document, there are comments about
8 competencies. And so we believe that we have
9 moved beyond just saying gee, this is how you
10 should report it to making recommendations
11 about what the minimum standards should be for
12 someone performing A.F. ablation.
13 So I think it's moving in that
14 direction, but again, I think societies are
15 different than regulatory agencies are
16 different than CMS are different from hospital
17 boards in their requirements.
18 DR. CALKINS: One comment. So
19 what, you know, HRS did is we -- we defined
20 what we expect from manuscripts, you know, in
21 the future. We want to, you know, know if
22 you're monitored for -- you know, because

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1 papers in the past said we needed a Holter
2 monitor every day for three years and never
3 told you what the compliance was. They just
4 said they did it and never gave you the
5 results.
6 So what the document says is sort
7 of obvious. You know, if you're going to do
8 monitoring, tell us what it is, tell us what
9 you found, and define success this way.
10 And then the question is is this
11 document going to get any teeth or any
12 traction in the community of people that
13 publish these 350 papers a year. And that's
14 where, you know, as -- we should get Eric back
15 on the spot. It's his hat as the editor of
16 Journal of Cardiovascular E.P.
17 Because I know as a reviewer for
18 that and many journals, I insist when I review
19 an afib ablation article -- I say absolutely,
20 these are the new definitions, these are the
21 new standards, I reject it until they come
22 back with the real data.

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1 And my hope is that every reviewer
2 for every journal will hold our peers up to
3 these standards, because, you know -- you
4 know, it just doesn't happen.
5 And whether it's -- so anyhow,
6 that's our hope, and I think over time we hope
7 more and more reviewers for these journals
8 will hold these standards up and sort of
9 insist on this, because that's absolutely what
10 we need, because when you're sitting here
11 interpreting the results of a trial, you
12 really can rely on -- I mean, you can rely on
13 some of the things that are written, but
14 there's a lot of variability in how the data
15 was obtained and the definitions and
16 everything else.
17 DR. YANCY: Dr. McCarthy?
18 DR. MCCARTHY: Speaking for the
19 Society of Thoracic Surgeons, we published a
20 paper about how to report guidelines last
21 March and then also the HRS document was sent
22 out to all of the members of the Society of

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Thoracic Surgeons.

And finally, we're a smaller group, and so there's really two major journals that we deal with, and you would have a very hard time having a paper published in either of those journals with the type of data collection that used to be used five to 10 years ago.

And for instance, the five prospective randomized trials that I referred to earlier all were well documented with Holter monitors at end points and periodically along the way, so the bar is clearly a lot different than it used to be.

DR. YANCY: Dr. Estes, did you need to --

DR. ESTES: Just a brief comment from the perspective of the American Heart Association. It is a critical issue. It's a public health issue. And as you know, that's really at the center of what the American Heart Association does.

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1 This is a rapidly evolving field.
2 Back in April of 2006, working with a number
3 of people through the Heart Rhythm Society and
4 the American Heart Association, we decided it
5 would be best to try to tap the brakes a
6 little bit.
7 By May of 2007, we had this
8 consensus document formulated with the huge
9 effort of -- I think it was seven
10 organizations endorsing it ultimately and
11 about 33 authors. And I do think it will set
12 the standard as to what should be used for
13 publication that editors and reviewers will
14 consider.
15 It's a work in progress. This was
16 done in the course of 13 months, recognizing
17 that the field was in some respects getting
18 ahead of itself. So we're continuing to work
19 on it. From AHA's point of view, it's an
20 extremely important public health issue that
21 we are focusing on.
22 DR. YANCY: This really has been a

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great discussion, and we've deliberately let it run long so we can take advantage of the expertise that's in the audience.

Are there any panel members that have a final question for our guest speakers?

If not, then we will terminate this part of the program and reconvene after lunch. We'd like to get back on time, so let's try to get back for 12:15 -- 1:15.

(Whereupon, the meeting went off the record at 12:31 p.m. and resumed at 1:23 p.m.)

DR. YANCY: We do need to begin, please, so if you would come to your seats. While you're coming to your seats, let me advise you of a schedule change for this afternoon. We will lose the critical mass of our panel by approximately 5:00 p.m., so we are rearranging the afternoon so that we can entertain the additional public comments first.

We will then follow those public

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comments by deliberations between panel members, and directed towards the most recent speakers, and then immediately evolve into addressing the FDA questions so that we can have the majority of our expertise available for most of those questions.

So with that having been said, there will be four speakers, one that has signed on -- may not be any documents you have. We will hear from Julie Broderick, Ruey Dempsey, Alexei Shvilkin, and David Haines.

At the time of your presentation, please identify your affiliations.

I'm sorry, just a minute, please.

DR. KATO: I'm sorry, Mr. Chairman, are we going to have copies of the presentations that were given this morning from the various society and association members?

DR. YANCY: We have requested those copies as a requirement for presenting. They may not be available today, but they

98938861-1d74-4600-8272-d58807a75e6d

should be posted.

Please, Ms. Broderick? Thank you.

MS. BRODERICK: Thank you.

Ladies and gentlemen of the panel and representatives of FDA, thank you for the opportunity to speak at today's meeting.

My name is Julie Broderick, and I'm the vice president of regulatory and clinical affairs for Bard Electrophysiology, which is a division of C.R. Bard. I don't have any slides, but I did provide a handout with highlights of my comments, which you should have.

Like many other sponsors that you're hearing from today, Bard is developing a novel ablation catheter for percutaneous treatment of atrial fibrillation. We have not yet initiated our pivotal study, but we're in the advanced stages of preparation to do so.

And as you've heard, FDA's current requirement for studies of A.F. ablation devices to randomize patients between the

98938861-1d74-4600-8272-d58807a75e6d

1 device and anti-arrhythmic drugs has resulted
2 in studies that present significant challenges
3 to patients, investigators, and sponsors.
4 As you're hearing today, there are
5 a number of A.F. ablation studies under way,
6 with considerable competition among the
7 sponsors for patients and skilled
8 investigators. Over the last two years, we
9 have heard the stories of the other sponsors'
10 difficulties enrolling their A.F. ablation
11 studies, and we, at Bard, fear that our own
12 study will meet the same fate.
13 Bard believes that the public
14 health is not served by the unreasonably long
15 timelines for these A.F. ablation studies, and
16 the lack of commercially available ablation
17 devices that are specifically labeled for A.F.
18 Our first specific request for FDA
19 and panel consideration relates to the
20 complexities of assessing safety outcomes in
21 a device versus drug trial, including how best
22 to draw risk-benefit conclusions.

98938861-1d74-4600-8272-d58807a75e6d

1 In these trial designs, a
2 procedure is compared to a drug regimen, and
3 therefore, the safety events are significantly
4 different in terms of type, timing, and
5 severity. This comparison is difficult to
6 accommodate statistically, and will certainly
7 require the clinical judgment of FDA and the
8 panel as they balance the impact of the
9 ablation procedure with the anticipated
10 benefits of reduced or eliminated A.F.
11 episodes and the need for AADs.
12 Another aspect of the safety
13 analysis problem, which I don't think has been
14 brought up previously today, is the loss of
15 control subjects from the AAD arm when they
16 fail the effectiveness end point and cross
17 over to the ablation arm.
18 Such a crossover provision is
19 essential to successful enrollment, yet it
20 undermines the comparison between the two
21 groups. The timing and conditions under which
22 control group crossovers are permitted needs

98938861-1d74-4600-8272-d58807a75e6d

consensus definition, as does an understanding of how to analyze a progressively underpowered AAD arm for safety assessment.

The requirement that A.F. pivotal studies be powered both on safety and effectiveness can result in extremely large studies that chase non-inferiority proof for small differences in infrequent event rates. In practice, this may mean trial sizes over twice as large as those powered carefully on effectiveness alone.

Furthermore, there's a significant likelihood that, after enduring several years of enrollment, the study might still fail on the basis of an underpowered safety analysis.

The risk-benefit assessment in the comparison of an invasive procedure with long-term pharmacologic therapy is complex, and should involve much more than statistical consideration.

Bard believes it is appropriate to power studies such as this, where there is a

98938861-1d74-4600-8272-d58807a75e6d

complex but important risk to benefit trade-off, on effectiveness alone.

Safety can be satisfactorily addressed by providing to FDA a formal analysis of the study's power to detect a difference in safety. We believe this is a reasonable balance of conflicting scientific priorities, and would help to avoid an unnecessarily overpowered study.

Bard requests that FDA and the panel consider these issues, including mandatory powering of studies on the basis of safety, as well as effectiveness. We ask that this evaluation include careful consideration of the need to accommodate both early and late entrants into the pivotal trial phase.

A second issue we put forth for consideration by FDA and the panel is the regulatory status of active therapies as a control group. We appreciate FDA's initiatives to resolve the difficulties with A.F. ablation studies, first with Dr.

98938861-1d74-4600-8272-d58807a75e6d

1 Brockman's speech at the Boston A.F. meeting
2 in January, and now with today's panel
3 meeting.
4 Encouraged by Dr. Brockman's
5 proposal to use standard of care ablation as
6 a control group, Bard began discussions with
7 FDA about a study comparing our novel ablation
8 catheter to standard of care ablation.
9 Unfortunately, our further
10 discussions with FDA revealed the view that
11 A.F. ablation is off-label, and cannot be used
12 as the primary comparison for regulatory
13 reasons. One solution proposed to us is the
14 trial B design that you've seen today, which
15 is the design to make the primary outcome
16 comparisons for effectiveness and safety to a
17 historically derived performance goal.
18 But this study design also keeps
19 the standard of care ablation arm for the
20 important information that it would yield.
21 And while this may have its desirable aspects,
22 we feel that we would be paying for a complex

98938861-1d74-4600-8272-d58807a75e6d

1 randomized trial, yet getting a single-arm
2 study for regulatory and labeling purposes.
3 This leads us to be puzzled by
4 some recent advice that we received from FDA
5 that the AAD arm of our proposed ablation
6 versus AAD study should include amiodarone, a
7 drug that does not have FDA approval for
8 treatment of any form of A.F.
9 Bard requests that FDA and the
10 panel clarify for potential sponsors whether
11 or not off-label drug and device therapies
12 recommended by specialists and supported by
13 peer-reviewed publications may be used in
14 pivotal trials for pre-market approval of
15 cardiovascular devices.
16 And in particular, we request that
17 the panel discuss why the trial B design
18 requires a performance goal.
19 The third issue we propose for
20 further clarification relates to which drugs
21 must be failed before enrollment into a
22 secondary A.F. treatment study. FDA has taken

98938861-1d74-4600-8272-d58807a75e6d

1 the position that only patients who have
2 failed at least one Class I or Class III AAD
3 be enrolled in trials of A.F. ablation
4 devices.
5 It is our understanding that this
6 position is derived from the August 2006
7 guidance on the care of A.F. patients. In
8 practice, patients who have failed only beta
9 blockers are often ablated, and the A.F.
10 ablation devices we are discussing are
11 investigational, and are being studied with
12 approved study protocols, carefully defined
13 conditions, close monitoring, and skilled
14 investigators.
15 Thus, we do not understand the
16 reason for restricting the patient population
17 in a manner that does not accord with that of
18 the clinical practice into which these devices
19 will subsequently be used when they're
20 approved.
21 We request that FDA and the panel
22 consider whether it would be reasonable to

98938861-1d74-4600-8272-d58807a75e6d

1 include patients who have failed only beta
2 blockers and studies of A.F. ablation devices.
3 Finally, we raise the issue of
4 primary A.F. treatment designs. We request
5 that FDA and the panel consider whether
6 studies of novel ablation devices could
7 include patients who have not failed any AAD.
8 Is there any reason why a study should not
9 investigate ablation as a primary therapy?
10 We see no reason why a clinical
11 trial must necessarily comply with guidance
12 that is meant for routine care of patients in
13 normal clinical practice if patient safety is
14 properly protected in the trial.
15 This could simultaneously advance
16 clinical knowledge with an important study
17 design, and achieve marketing approval for a
18 new device treatment, all at industry expense.
19 Finally, we request that FDA and
20 panel provide regulatory predictability to
21 industry. If, after this panel meeting, FDA
22 evolves its position with regard to the

98938861-1d74-4600-8272-d58807a75e6d

1 requirements for A.F. ablation studies after
2 sponsors have already started their trials,
3 then, in the interest of continuity and
4 fairness, sponsors of ongoing studies should
5 be allowed to either modify their
6 investigations without statistical penalty, or
7 to continue their trials as originally
8 designed.
9 I would like to thank the panel
10 and FDA for your time and attention. We look
11 forward to your discussion of these issues.
12 We hope that this panel will be able to
13 provide clear and concrete guidance to FDA and
14 industry today so that we can all find a
15 reasonable path forward to bringing safe,
16 effective, and properly labeled A.F. ablation
17 devices to American patients. Thank you.
18 DR. YANCY: Thank you very much.
19 We'd like to proceed with Ruey C.
20 Dempsey.
21 Please identify your affiliation.
22 MS. DEMPSEY: Yes. I'm Ruey

98938861-1d74-4600-8272-d58807a75e6d

1 Dempsey, director of technology and regulatory
2 affairs at AdvaMed. AdvaMed, the Advanced
3 Medical Technology Association, is the world's
4 largest association representing manufacturers
5 of medical devices, diagnostic products, and
6 medical information systems.
7 Our members produce nearly 90
8 percent of the health care technology
9 purchased annually in the United States.
10 AdvaMed commends the FDA for
11 providing an opportunity for stakeholders,
12 including recognized experts in the field of
13 atrial fibrillation, to provide input on
14 clinical trial designs.
15 Current clinical trial designs
16 have been influenced by the FDA guidance
17 document on clinical trial designs for atrial
18 fibrillation published in 2004. Although the
19 guidance, consistent with 21 CFR part 820.7,
20 recognizes a variety of potential trial
21 designs that provide valid scientific
22 evidence, medical device companies have been

98938861-1d74-4600-8272-d58807a75e6d

1 encouraged by FDA to conduct randomized
2 controlled trials comparing catheter ablation
3 to anti-arrhythmic drugs.
4 This has been unduly burdensome
5 for patients, clinical investigators, and
6 industry. Patients for whom drugs have been
7 unsuccessful may be randomized to drug
8 therapy. Investigator time is consumed with
9 fruitless screening activities, and sponsors
10 are burdened with high costs of conducting a
11 lengthy trial that may jeopardize the
12 viability of their company.
13 Since the issuance of the FDA
14 guidance in 2002 -- 2004, the AHA and ESCA
15 have issued guidelines for the management of
16 patients with atrial fibrillation, and the
17 Heart Rhythm Society has issued an expert
18 consensus statement on catheter and surgical
19 ablation of atrial fibrillation.
20 These publications reflect the
21 current standard of care for treating atrial
22 fibrillation patients, and describe advances

98938861-1d74-4600-8272-d58807a75e6d

in atrial fibrillation treatment strategies. These documents recognize catheter ablation as the second line of therapy following attempted medication therapy.

Since the issuance of the guidance in 2004, the routine performance of atrial fibrillation ablation procedures with catheters has expanded significantly in the clinical community. This expansion was acknowledged by FDA at the 2007 Boston Atrial Fibrillation Symposium with Dr. Randall Brockman's reference to standard of care ablation catheters.

However, no ablation catheters have been approved for treatment of atrial fibrillation. This fact is a reflection of the difficulty industry is experiencing in conducting clinical trials in a timely fashion. It is not a reflection of industry's lack of interest in developing treatment devices that ultimately receive FDA approval based on sound clinical data.

98938861-1d74-4600-8272-d58807a75e6d

1 Currently, there are two major
2 challenges when conducing atrial fibrillation
3 ablation trials. Patients are reluctant to
4 participate in current studies that require
5 randomization to medication. They have been
6 reticent to participate in randomized trial
7 when the control arm is anti-arrhythmic drugs,
8 because the majority of patients referred for
9 ablation have not been successfully treated by
10 medication, or the side effects of medication
11 have proven to be intolerable.
12 Patients do not want to delay
13 potentially effective treatment by
14 participating in a clinical trial that could
15 require them to continue drug treatment that
16 has been unsuccessful for them in the past,
17 when they can receive the standard of care
18 with off-label use of an ablation catheter
19 today.
20 This has resulted in very slow
21 enrollment rates, and therefore very long
22 clinical trials. The enrollment problem is

98938861-1d74-4600-8272-d58807a75e6d

exacerbated by the limited numbers of qualified ablation centers to serve as study sites, and who are willing to conduct studies with randomization to drugs.

As a result of the long enrollment times, the investigators at these expert centers may be conducting two or more trials simultaneously, and distributing patients among the trials. Enrollment statistics from three ongoing trials show that approximately 14,000 patients must be screened to yield 250 study subjects. In other words, less than two percent of screened patients are successfully enrolled.

Clinical study sites report that patient refusal is a key reason for screen failures in these studies. After enrollment is complete, a one-year follow-up is typically followed by at least another year, during which data is analyzed, and a regulatory submission is prepared and reviewed.

Based on current enrollment rates,

98938861-1d74-4600-8272-d58807a75e6d

more than six years can elapse between the time a company completes its feasibility clinical study, and the time the new device is available to American patients. This is a significant burden on industry, and unduly impedes the evaluation of an important therapeutic device.

The second challenge is the nature of atrial fibrillation itself. As a disease, and as an arrhythmia to be ablated, atrial fibrillation is highly variable compared to other supraventricular tachycardias. Therefore, the establishment of objective performance criteria, as an alternative clinical trial design, has historically been difficult.

It's important to note, however, that with the publication of the Heart Rhythm Society Expert Consensus Statement, we believe clinical studies can be conducted with sufficient consistency in design and evaluation criteria to allow for alternate

98938861-1d74-4600-8272-d58807a75e6d

1 study designs to be established for
2 demonstrating safety and effectiveness.
3 Furthermore, we believe that well
4 designed and executed approaches, such as
5 objective performance criteria or patient as
6 own control, would be more clinically
7 meaningful than a comparison of an ablation
8 procedure outcome to a medication therapy
9 outcome in a patient population that is
10 medication resistant.
11 AdvaMed recognizes that the field
12 of atrial fibrillation ablation is dynamic,
13 and treatment strategies will continue to
14 evolve. We also acknowledge that a revised
15 FDA guidance may have an effect on currently
16 approved pivotal IDE studies.
17 With this in mind, AdvaMed
18 proposes the following. One, for pivotal IDE
19 studies currently under way, allow the trials
20 to continue as approved, or allow sponsors to
21 amend their protocols to improve enrollment
22 conditions.

98938861-1d74-4600-8272-d58807a75e6d

1 FDA should be open to the use of
2 hybrid and/or Bayesian statistical analysis
3 that allow pooling of already enrolled subject
4 data with the new study design data, without
5 inflicting a sample size penalty, or weighting
6 one data set more than the other.
7 Two, for clinical designs proposed
8 prior to FDA approval of the first ablation
9 catheter for the treatment of atrial
10 fibrillation, allow sponsors to follow the
11 principles of the Heart Rhythm Society Expert
12 Consensus Statement.
13 These studies should include any
14 of the following options: randomization to
15 standard of care catheter ablation, single arm
16 utilizing safety and efficacy end points, and
17 objective performance criteria based on expert
18 clinical opinion as supported by the
19 literature, or patients used as their own
20 controls.
21 After revised guidance is issued,
22 we recommend allowing FDA-approved studies to

98938861-1d74-4600-8272-d58807a75e6d

1 continue as approved, or allow protocols to be
2 amended to be consistent with FDA-approved
3 guidance.
4 For the trial designs proposed
5 after one or more ablation catheters have been
6 FDA-approved for marketing for treatment of
7 atrial fibrillation, allow all of the options
8 previously mentioned, with the marketed
9 devices included as standard of care ablation
10 catheters.
11 In addition to its general support
12 for the Heart Rhythm Society expert consensus
13 statement, AdvaMed makes the following
14 additional recommendations for A.F. clinical
15 trial designs. One, if standard of care
16 medical management is used as a control arm,
17 expand the drugs that are allowed to include
18 those routinely used, but not specifically
19 indicated for, the treatment of atrial
20 fibrillation, for example, amiodarone.
21 Two, ensure consistency of
22 definitions and terminology by adopting the

98938861-1d74-4600-8272-d58807a75e6d

1 Heart Rhythm Society definition for
2 paroxysmal, persistent and longstanding
3 persistent atrial fibrillation.
4 Three, to facilitate enrollment,
5 allow patient consent at the referring site.
6 Four, allow six-month safety and
7 efficacy end points with post-approval follow-
8 up and reporting for 12-month efficacy.
9 AdvaMed thanks FDA for the
10 opportunity to provide comments on this
11 important health issue. AdvaMed appreciates
12 FDA's recognition of the potential public
13 health impact of untreated or sub-optimally
14 treated atrial fibrillation, and
15 acknowledgment that, today, there are no
16 ablation devices specifically approved for its
17 treatment.
18 While we understand that FDA
19 regulates medical devices, and not the
20 practice of medicine, or the off-label use of
21 medical devices by clinicians, we appreciate
22 FDA's willingness to innovate potential

98938861-1d74-4600-8272-d58807a75e6d

alternative study designs.

Industry recognizes the challenge in balancing the need to reflect advances in clinical treatment of atrial fibrillation since the issuance of the 2004 FDA guidance, the disciplined evaluation of innovation catheter technology, and sound clinical trial design.

DR. YANCY: Thank you very much.

Our next speaker is Alexei Shvilkin.

Please identify your affiliation, and any potential conflicts.h

DR. SHVILKIN: Good afternoon. My name is Alexei Shvilkin, and I'm an electrophysiologist at Beth Israel Deaconess Medical Center. I also work for Arrhythmia and EKG Core Lab at Harvard Clinical Research Institute, on behalf of which I make this presentation.

The HCRI have paid my trip here, and it's the institution that conducts and

98938861-1d74-4600-8272-d58807a75e6d

over-reads a number of multi and single-center atrial fibrillation ablation trials as the core lab.

I'm also -- have a consulting agreement with Medtronic and NewCardio.

So as has been alluded by multiple presenters earlier today, the HRS Expert Consensus Statement provides the groundwork for standardizing choice of end points, and follow-up for trials for atrial fibrillation ablation.

And the fact that a single recorded episode of atrial arrhythmias can make a difference between a positive and a negative outcome of the procedure, that puts a significant weight on the accuracy of our interpretation.

And basically we -- once that event recorder is coming through the phone line, we have to make sure that we make the correct diagnosis. And when we look at how well we are at identifying rhythms using

98938861-1d74-4600-8272-d58807a75e6d

1 various electrocardiographic techniques, we
2 can see that there is significant room for
3 improvement.
4 For example, a recent study that
5 analyzed over 35,000 consecutive EKGs from a
6 single hospital which was -- were over-read by
7 54 primary EKG readers, all of which were
8 certified in internal medicine, more than half
9 of them certified in cardiology, and that
10 included two board-certified
11 electrophysiologists, it demonstrated that,
12 out of 2,800 tracings with true atrial
13 fibrillation, there was about eight to nine
14 percent rate of misdiagnosis.
15 It was -- the authors noted that
16 misdiagnoses were more likely to happen when
17 the patient was placed in the ventricle.
18 However, even in native rhythm, there was a
19 significant amount of discrepancy.
20 Factors that favored
21 misinterpretation of electrocardiograms in
22 that study include four missed diagnoses of

98938861-1d74-4600-8272-d58807a75e6d

1 atrial fibrillation, irregular rate, and high
2 amplitude atrial activity, which made these
3 tracings misdiagnosed as atrial flutter.
4 Atrial fibrillation was
5 overdiagnosed when there was significant
6 baseline artifact, low amplitude atrial
7 activity, or rapid ventricular rate.
8 Another study looked at the
9 results of a voluntarily ECG interpretation by
10 a survey of responders. All the participants
11 were sent with -- sent three
12 electrocardiograms to interpret, and this is
13 one of them. When the results came back,
14 surprisingly, 34 percent of internal medicine
15 physicians identified this written correctly
16 as atrial fibrillation. Twenty-one percent of
17 board-certified cardiologists identified this
18 as atrial fibrillation, and overall
19 performance was 31 percent.
20 When it comes to interpreting
21 events recorded by Coulter monitors and other
22 transtelephonic methods of monitoring, there

98938861-1d74-4600-8272-d58807a75e6d

are several features that make the diagnosis more challenging compared to a 12-week EKG.

Usually, there is either single-lead recording, or few leads. The sampling rate and signal resolution is much lower than on a standard 12-week electrocardiogram. There is usually a lot of low- and high-frequency noise. And there are few electronic filtering options on the work stations that are designed to analyze these tracings.

So, for example, a tracing like this provides plenty of opportunity for a misdiagnosis. And as we all know now, the difference between over-reading the tracing correctly can make the difference between positive and negative outcome of the whole study.

So from our internal quality assurance and overall experience, we see that the most often misdiagnosed situations involve misreading atrial fibrillation versus atrial flutter. Next in frequency is ambiguous

98938861-1d74-4600-8272-d58807a75e6d

statements like atrial flutter/fibrillation, atrial flutter versus sinus tachycardia, and atrial fibrillation versus sinus rhythm with premature beats and noise. So these four situations encompass probably 85 percent of all mis-read tracings.

So, in order to try to find out why this is happening, if there's any way to improve the correct interpretation -- so what we tried to do is we tried to reinforce basic electrophysiological concepts regarding discrimination, atrial fibrillation and atrial flutter, providing in service training for inside and outside monitoring technicians. And we tried to keep a continuous feedback.

We also streamlined and standardized written nomenclature used by event monitor readers, with elimination of nonessential or misleading diagnosis, such as coarse afib, regularized afib.

And as far as differentiation between atrial fibrillation and flutter, we

98938861-1d74-4600-8272-d58807a75e6d

used two simple rules. The first one was stabilitive morphology and cycle length of atrial signal in atrial flutter when we have an adequate atrial signal on the event recorder.

When we don't have adequate signal from the atrium, we put attention on the recognition of R.R. patterns characteristic for multilevel atrioventricular block.

These are examples of monitor recordings that were originally misinterpreted. The upper one was interpreted as atrial flutter. The lower one was interpreted by -- as atrial fibrillation. As you can see, in red circles they show a difference in morphology of flutter waves, and cycling characteristic to atrial fibrillation.

The second concept that we tried to reinforce is the concept of multilevel atrioventricular block, and here the diagram shows a two level block in the A.V. node, with two to one block in the upper level, and four

98938861-1d74-4600-8272-d58807a75e6d

to three ventricular block in the lower level, which results in a characteristic two to one, two to one, four to one pattern of QRS response in the ventricle.

And here's the example of the tracing with this periodicity, and we emphasized the stable R.R. intervals within the same beats in a sequence.

So before we did all this, we had approximately 15 percent rate of disagreement regarding a diagnosis atrial flutter versus atrial fibrillation, and we had approximately three to five percent rate of reading -- ambiguous reading atrial flutter/fibrillation. These are percent -- percentages normalized to total number of atrial fibrillation tracings, not the whole tracings.

After we started this reinforcement program, we had significant improvement in consistency of our reading, with almost complete disappearance of ambiguous readings, and a decrease in the rate

98938861-1d74-4600-8272-d58807a75e6d

of misinterpretation of atrial flutter, and the atrial fibrillation less than five percent.

There are other potential sources of inter-observer reporting variabilities, such as mixed rhythm, as this intermittent atrial fibrillation that it is interspersed with periods of sinus rhythm, and also the reported duration of arrhythmia is -- can be a factor in reporter variability.

So we eventually came to the conclusion that, for event recordings for report a total duration that would be recorded atrial fibrillation to be exactly precise with our readings.

Same -- again, we see, in this tracing, when there is 50 seconds of noise, and the last 12 seconds come demonstrating atrial fibrillation. Depending on the trial design, this can be either a positive or negative outcome.

We looked -- also looked in some

98938861-1d74-4600-8272-d58807a75e6d

computer-assisted algorithms to improve our reading. And in finalizing this, we feel that a centralized arrhythmic core lab, which is electrophysiologist staffed, especially for multi-center trials, can result in improving assessment.

And training feedback with monitoring technician and primary reading sites also helps improve the accuracy, and standardization of written diagnosis and reporting is necessary to achieve consistent results across the trials. Thank you.

DR. YANCY: Great. Thank you very much.

We have one final speaker, unless there's been someone who signed up before we received the list, and that speaker is David Haines.

And again, sir, if you would identify your association, and express any conflicts. Thank you.

DR. HAINES: I appreciate having

98938861-1d74-4600-8272-d58807a75e6d

the opportunity to speak to Dr. Yancy and the panel this afternoon. My name's David Haines. I'm a clinical cardiac electrophysiologist at Beaumont Hospital in Royal Oak, Michigan.

I did not receive any support for my travel to this meeting, although I'll take a ride back to the airport if anyone's offering.

(Laughter.)

DR. HAINES: I am a paid consultant and investigator for Boston Scientific Corporation, ProRhythm, CardioFocus, Bard and Toray Medical, and I'm a co-founder of nContact Medical, which is a surgical A.F. ablation company.

I'd like to make two points to the panel today. The first point readdresses some of the issues brought up earlier, and covers both safety end point issues, as well as the challenges of patient enrollment.

As a clinician researcher, I view my job is to advance medical science through

98938861-1d74-4600-8272-d58807a75e6d

clinical trials, as well as take the very best care of my patients, and keep my patients' welfare at the highest level in my decision-making.

Now, the patients who tend to fit into the criteria for the current and planned pivotal trials are a very select group, as we've discussed. They tend to be younger, they tend to have a higher prevalence of normal hearts, and they have highly symptomatic, frequent episodes of paroxysmal atrial fibrillation.

In this regard, they look to the clinician a lot more like the typical SVT patient that we're used to taking care of, rather than the typical A.F. patient, who is older, may have less symptoms, and may have more persistent arrhythmia.

By the time they're referred to me, if they have failed a suppressive anti-arrhythmic drug trial, they come to me requesting catheter ablation. Rightly or

98938861-1d74-4600-8272-d58807a75e6d

1 wrongly, they view catheter ablation as
2 definitive therapy.
3 In order for me to induce the
4 patient to consider entry into a randomized
5 trial, I find that the only viable strategy is
6 that I essentially have to promise to the
7 patient early crossover should they fail
8 medical therapy, early crossover to the
9 ablation treatment arm.
10 Now, safety end point is one of
11 the major considerations in all of these
12 trials, and it's a bit of an apples/oranges
13 comparison. But we know, with medical
14 therapy, that the safety end point is a
15 cumulative end point.
16 Early crossover eviscerates the
17 safety end point analysis in the drug arm.
18 And yet, as the clinician, that is the deal
19 that I am frequently making with my patients
20 to allow them into the trial.
21 Now, if a patient comes to me
22 having not been on a suppressive anti-

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