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CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Evidence Development & Coverage

Advisory Committee

October 21, 2009

Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

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Panelists

Chairperson
Clifford Goodman, Ph.D.

Vice-Chair
Saty Satya-Murti, M.D., F.A.A.N.

Voting Members
Virginia C. Calega, M.D., M.B.A.
Mark D. Carlson, M.D., M.A.
Gregory J. Dehmer, M.D.
Mercedes K.C. Dullum, M.D.
William H. Maisel, M.D., M.P.H.
Mauro Moscucci, M.D.
Craig Umscheid, M.D., M.S.C.E.

Patient Advocate
Phyllis Atkinson, R.N., M.S., GNP-BC

Industry Representative
Neal Thomas, Ph.D.

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Guest Panel Members
Stephen C. Hammill, M.D., F.A.C.C., F.H.R.S.
Douglas L. Packer, M.D.

CMS Liaison
Marcel Salive, M.D.

Executive Secretary
Maria A. Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, October 21, 2009.)

MS. ELLIS: Good morning and welcome, committee chairperson, vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MEDCAC.

The committee is here today to discuss the evidence, hear presentations and public comment, and make recommendations concerning the use of catheter ablation for the treatment of atrial fibrillation.

The following announcement addresses conflicts of interest issues associated with today's meeting and will be made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflicts of interest during their introductions.

We ask in the interest of fairness

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that all persons making statements or presentations also disclose any current or previous financial involvement in any companies that manufacture equipment or drugs used to treat atrial fibrillation or that develop guidance for the treatment of atrial fibrillation for public policy-making. This includes direct financial investment, consulting fees and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside this room.

We ask that all presenters please adhere to their time limit. We have numerous presenters to hear from today and a very tight agenda and therefore, cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mic and state your name.

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For the record, voting members present for today's meeting are: Dr. Saty Satya-Murti, Dr. Virginia Calega, Dr. Mark Carlson, Dr. Gregory Dehmer, Dr. Mercedes Dullum, Dr. William Maisel, Dr. Mauro Moscucci, Dr. Craig Umscheid, and RN Phyllis Atkinson. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including nonvoting members, will participate in the voting. The voting scores will be available on our web site following the meeting. Two averages will be calculated, one for voting members and one for the entire panel.

I ask that all panel members please speak directly into the mics, and you may have to share. If you require a taxicab, there is a signup sheet at the desk outside the auditorium; please submit your request during the lunch break. Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MedCAC committee are only permitted in the following areas of CMS: The main lobby,

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the auditorium, the lower level lobby and the cafeteria. Any persons found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now I would like to turn the meeting over to Dr. Marcel Salive.

DR. SALIVE: Thank you, Maria. I am Marcel Salive and I am the division director for the Division of Medical and Surgical Services within the Coverage and Analysis Group here at CMS. Our role today is as the CMS liaison to the panel.

I want to start by thanking the panel, each and every one of you for coming today and serving in this important role. The role of the MedCAC, as stated earlier, is to give the Agency recommendations, and today we will be discussing catheter ablation for atrial fibrillation. We will discuss the evidence and hear some presentations, and we have a number of questions we want you to weigh in on based on that evidence. So with that, I will turn it over to Dr. Goodman.

DR. C. GOODMAN: Thank you, Marcel.

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Maria, when would you like us to go down the list and make disclosures, is it now or after the remarks from me?
MS. ELLIS: You can do it afterwards.
DR. C. GOODMAN: Thank you. Welcome all to what is a fascinating and important subject affecting millions of Americans, and much can be learned about atrial fibrillation and how to manage it. A couple of management notes.
First, we do have a tight agenda as always. There are quite a few people who are designated to speak for certain periods of time. We are going to do our very best to do that, and we need to be strict about that to cover all our territory, to hear from all in our allocated time.
Special requests that I make all the time, and will make again in further meetings, is that if you have something to say, we think it's probably quite important and we don't want to miss it. In order for us to capture that, and for our dear court reporter to capture it, please don't speak until recognized, please do come to the microphone, please do be concise.

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That way the panel will hear the important things you do have to say and that way our court reporter will be able to capture what you say with your name accurately, and if that doesn't happen, we're going to miss this very important input today.

Again, I will stress that we'll need to be strict. We do have the lights that will kind of flash in various colors, I may flash you how many minutes you've got left, I may give you a one or two-minute sign, and we ask that you stick to that. I think that's it for my introductory remarks as far as logistics and management.

Do you want us to walk through the disclosures at this time?

MS. ELLIS: Yes.

DR. C. GOODMAN: As we introduce ourselves, will you just say anything of importance that you want to disclose.

I'm Cliff Goodman, I'm with the Lewin Group healthcare policy consulting firm. I know that the Lewin Group is a subsidiary, one of several subsidiaries of Ingenix, which is a data analysis and healthcare information firm.

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Ingenix in turn is one of multiple subsidiaries of something called United Health Group, and among its multiple subsidiaries is United Health Care, a major payer. So far as I know, I have no personal financial interests. My company, the Lewin Group, has over the last 13 years that I've been there on occasion had contracts with some of the companies, pharmaceutical firms and medical device firms, some of which are involved in management of atrial fibrillation. To the best of my knowledge we have, and I have not done any work under those contracts pertaining to the subject matter today.

DR. SATYA-MURTI: Saty Satya-Murti. I am a neurologist and have consulted, three years ago I consulted on the general topic of treatment of atrial fibrillation, medical and nonmedical. The compensation was less than $500 and I have not since consulted for, on this topic, and it was not product-specific.

DR. CALEGA: I'm Virginia Calega. I'm at Highmark, which is one of the 39 Blue Cross Blue Shield companies, I am responsible for medical policy on our commercial side of our

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business, and I also serve on the medical policy panel for the Blue Cross Blue Shield Association.

DR. CARLSON: Mark Carlson. I'm an employee of St. Jude Medical, I'm medical officer for the cardiac rhythm management division. St. Jude Medical's atrial division manufactures equipment that's used for managing atrial fibrillation. Until three years ago I was a practicing cardiac electrophysiologist and participated in ablation procedures. Though I never did an ablation for atrial fibrillation, I did refer patients for that procedure, and for heart failure.

DR. DEHMER: I'm Gregory Dehmer, I'm an interventional cardiologist, a professor of medicine at Texas A&M Health Science Center College of Medicine, and director of the cardiology division of the Scott & White Clinic in Temple, Texas. I have no financial disclosures.

DR. DULLUM: I am Mercedes Dullum, cardiac surgeon at the Cleveland Clinic in Florida. I have no financial disclosures.

DR. MAISEL: William Maisel, a cardiac

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electrophysiologist at Beth Israel Deaconess Medical Center in Boston. I do perform atrial fibrillation ablation and I have no conflicts to disclose.

DR. MOSCUCCI: Mauro Moscucci, an interventional cardiologist and the chief of cardiology at the University of Miami, and no financial disclosures pertaining to this topic.

DR. UMSCHEID: I'm Craig Umscheid, an assistant professor of medicine at the University of Pennsylvania. I'm also co-director of the University of Pennsylvania Center For Evidence-Based Practice. I'm a hospitalist by clinical training.

MS. ATKINSON: I'm Phyllis Atkinson, gerontological nurse practitioner. I have my own geriatric medical house call practice, so many of those that I treat are very frail elderly adults. I have nothing to disclose.

DR. THOMAS: Hi, I'm Neal Thomas, I work with Pfizer Corporation, I'm a statistician, and Pfizer does have medications currently as well as under development for atrial fibrillation.

DR. HAMMILL: Steve Hammill, professor

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of medicine at Mayo Clinic, a former president of the Heart Rhythm Society. In the past I have been on the health policy advisory board for Pfizer and subsequently I have stepped down from that board.

DR. PACKER: I'm Doug Packer, a practicing cardiac electrophysiologist from the Mayo Clinic, and I'm also involved in some research there. I am the PI of the CABANA trial, which may be mentioned. That was funded by NHLBI and it's also funded by several industry groups. Some of my transactional work in clinical studies are also funded by industry groups. I've been on a series of advisory boards, not currently taking remuneration, in past relationships I have. I do have a couple of royalty bearing relationships that have to do with intellectual properties licensed through Mayo to an industry group. So those are the conflicts that should be kept in mind during the portion of this hearing.

DR. C. GOODMAN: Thank you all. And just as a reminder to our panel, make sure to file your disclosure statement before you leave today's hearing. Thank you very much.

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I think we will now proceed to the CMS presentation of the voting questions from JoAnna Baldwin, and I do hope that this background noise will fade soon.

DR. SALIVE: Before JoAnna speaks, I would like to mention that CMS has no national coverage policy on AFib ablation at this time and we have no open coverage decision at this time, so we are really just discussing the evidence at this meeting and getting a buzz. Thank you.

DR. C. GOODMAN: Thank you, Marcel, and Ms. Baldwin, you've got 15 minutes.

MS. BALDWIN: I am JoAnna Baldwin, and today I will be reading for the record today's MedCAC panel questions. For the questions we have today, we have a discussion section for the panel, and these questions will not be voted on.

Our first discussion question group regards clinical comparators. What is the appropriate clinical comparison for catheter ablation? Does the evidence use appropriate comparison groups?

Regarding population, what

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subpopulations of patients with atrial fibrillation should be considered for treatment of catheter ablation (paroxysmal, persistent, first-line, second-line treatment, et cetera)? Does the evidence address the appropriate patient populations? Regarding outcome, what are the outcomes of interest, for example survival, termination of arrhythmia, hospitalization, medications for heart rate, rhythm and anticoagulants, recurrence of atrial fibrillation, adverse events, scarring? Does the available evidence assess these outcomes? Have the adverse events been both qualitatively and quantitatively characterized? What is the appropriate duration of follow-up? Does the available evidence follow patients for the appropriate period of time? Regarding device characteristics and physician training, what is the importance of the varying devices and techniques used for ablation? Should the procedure be limited to physicians with specialized training such as electrophysiologists or surgeons? This is the presentation of the voting

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scale that will be used today. On a scale of confidence, one is not confident while five is highly confident.

The first voting question. How confident are you that the evidence is adequate to draw conclusions about health outcomes of interest to patients treated with catheter ablation for atrial fibrillation?

Voting question number two. How confident are you that catheterization for the treatment of atrial fibrillation improves health outcomes compared to other therapies or treatments in the following populations:

A, as first-line therapy;

B, as second-line therapy;

C, for first detected atrial fibrillation;

D, for longstanding, greater than one year, atrial fibrillation;

E, for paroxysmal atrial fibrillation;

and

F, for persistent atrial fibrillation?

Voting question number three. How confident are you that ablation improves long-term, greater than one year, health

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outcomes?
Voting question number four. How confident are you that the outcomes can be extrapolated to:
A, patients outside of controlled clinical studies, and
B, the Medicare beneficiary population aged 65 years and older, and 56 percent female?
Voting question number five. How confident are you that additional evidence is needed?
We've included another section of discussion questions regarding additional evidence. What type of additional evidence is needed to determine health outcomes? What study designs are most appropriate to obtain this additional evidence?
Thank you.
DR. C. GOODMAN: Thank you, Ms. Baldwin. Are we ready to proceed to Dr. Rosenberg now? I believe so.
Dr. Rosenberg, we have you scheduled for 30 minutes.
DR. ROSENBERG: Good morning. Thank you very much for the invitation. When

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Dr. Salive invited me to this meeting, he asked me to set the stage for a discussion by covering the background for atrial fibrillation, and I entitled my talk from Framingham to CABANA, which means I am going to cover very briefly some of the etiology evidence and its importance with atrial fibrillation. I will also weigh the various treatment options, including the CABANA studies that the NHLBI is presently conducting. What I will not do is cover any of the reasonableness regarding clinical use in the different populations, as this would be covered during the next presentation.

So this is where I have been working for the past 16 years. Some of you might wonder about my accent, that's where I come from, which is the town called Lyon, France, it's the largest city in France. Here's my disclosure side and I can assure you that my government salary will not go up, whatever the outcomes of these studies are.

So to start this presentation, here is a slide, and you see a physician and his patient having a toast with a glass of French

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wine. And the physician says mind you, only one doctor out of ten recommends it. So it's just outlining how important this meeting is to advise the physicians and patients who don't have this type of discussion, that it's based on some better evidence than that.

So, I am going to very briefly in the next 30 minutes outline the burden of atrial fib in the United States today, outline the mortality and morbidity associated with AF, some of the risk factors, and go over the pharmacological treatments for AF, very briefly of course, and conclude by outlining why maintenance of sinus rhythm might be important in the treatment of AF, by outlining some of the data from some of the studies that led us to decide to support CABANA as well.

So, the burden of AF, I think of course, as most of you know, AF affects mostly elderly people. That's why this is such an important problem and decision for CMS, and this slide outlines that with the three main immunologically caused studies that show a clear association between age and incidence of AF. AF is really a nonexistent problem before

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people reach the age of 60, showing only an incidence of one percent, which approximately doubles after each decade.

This shows you given the actual incidence and prevention of AF, and the data that we've seen in the last 20 years that AF may increase in a significant fashion in the next 50 years, affecting 12 to 15 million people in the United States at this time.

I will not comment in any detail what is, what are the risk factors for AF and how they need to be viewed as to AF and its complications, just, the slide just states how complex these relationships are. I will just for the record state that the most preventable condition associated with AF is hypertension, and we want to know what the relationship with age hypertension has. It is really a much stronger predictor of AF than any other of the risk factors. We know even other cardiovascular disease like prior MI and heart failure are, the associations with AF is much less prominent.

So why is AF such an important problem? As most of you know, there is a very

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strong association between AF and mortality, as has been shown by the Framingham study and others. This slide shows you with the younger ages on the left and the older age groups on the right, the doubling of the risk of mortality over time in both men and women. Not only AF increases mortality but it increases morbidity, and most of you, again, know that the main morbidity associated with AF is a stroke. This slide shows you how the risk of stroke increased with age in both men and women, but of course one of the corollaries of the morbidity associated with this whole area, the cost of treatment, and the right-hand side shows you that in most major age groups with both men and women, there is an increase of 20 to 30 percent within age groups of the cost of health care for people after atrial fibrillation or AF.

The relationship between stroke and AF is especially important in the Medicare age group because of the increased prevalence of atrial fibrillation with age, as I just showed you. So this is also going to, you see that the relative risk on the other slide is similar

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among older age groups, so the population as you go through the risk increases greatly with age.

The relationship between heart failure and AF is a much more complex one and there's still the controversy of which is what, does AF cause heart failure, or vice versa, but the data that we have shows that there is a strong association between the two conditions and when looking at the data before it's adjusted, like here on the left, and adjusted here when you pool data from most prospective clinical trials of heart failure, they have a strong association with AF.

So what is the treatment strategy for AF? We decided to just summarize the treatment options we have nowadays to treat AF. As I mentioned, the sinus rhythm with both pharmacologic and nonpharmacologic functions, including ablation, rate control functions with pharmacologics and nonpharmacologics, and stroke prevention, mostly from pharmacology.

I will start by outlining the treatment options for, the rate control treatment options for AF, just focusing on the

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main pharmacologic options. The nonpharmacologic options are used in a known small percentage of AF patients. So here's the main treatment options that we're looking at. First, you see the different treatment options that are used nowadays to control rate in the Medicare age population and you see that there's a wide variation of rate control and you need very often to consider a combination of these various treatment options. But if you do so, rate control can be achieved in a very high percentage of AF patients.

As this slide from the AFFIRM study shows you in yellow, that this very controlled treatment strategy could not be achieved and had to be abandoned only in about 10 percent of the AFFIRM patients that were five years apart. On the other hand, the gray or blue line in the bottom shows you that rhythm control was achieved also, it was achieved in more than 70 percent of the AFFIRM population, which was aged above 60.

So going to the reasonable control options, as I just showed you, it is possible to achieve reasonable control in a majority of

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patients if you use the various options that are available, and you see here that only using one treatment option can lead you to use different ones to see which is the most effective one and you can achieve rhythm control in a significant amount of patients. If you fail, you can combine these treatment options and achieve reasonable control in about 80 percent of patients.

So here's a meta-analysis summarizing the efficacy of antiarrhythmic drugs in terms of clinical outcomes. I just would remind you that when you look at clinical outcomes, the data as a group for many antiarrhythmic drugs, and whether they're type IA or type IC drugs, there seems to be an increase in events, whereas for class III drugs and metoprolol that we have, the meta-analysis is not able to show any difference. When you compare -- a note on this -- the other drugs as shown here at the bottom, the other one seems to be more effective in preventing clinical outcomes. But again, it seems to have an adverse effect.

If you look at the safety side of the antiarrhythmic drugs, and this is from the same

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meta-analysis, then you can see why maybe these drugs have some adverse clinical outcomes, as on the right-hand side here, while little effect observed with most of these drugs. And again, the only one that did not show an adverse effect is metoprolol compared to class I drugs, and sotalol does seem to have an adverse effect.

So, here's a slide that summarizes the difference and the reason that can be used to control rhythm in AF patients, and this is taken from the 2006 guidelines from the AHA/ACC and European societies, which are the guidelines that most cardiologists and other people will follow to treat patients with AF.

And so depending on the underlying heart condition, you can see how this difference, or these options can be used.

And just outlining that here, you can see the cardiac ablation is used only as a second or third-line treatment option as recommended for use by these guidelines.

Going down now to the question of rate versus rhythm, most of you are probably familiar with this data. The AFFIRM study, as

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we know, was the first large scale study directly comparing these two treatment options, and clearly demonstrated in this population of elderly patients with risk factors for stroke, that there were no advantage of rhythm control, and on the left-hand side you can see that there was a trend, there was an increase of mortality for the rhythm control option on the right-hand side, and with a combined endpoint there was really absolutely no difference between the two treatment options.

In this data from AFFIRM, it was conducted directly comparing those two treatment options and you can see there that it says virtually no difference, not including the PIAF and STAF studies, that was a sizable study population, and the result of these studies and the others that have been conducted mirror the studies in that there is no difference shown.

So, the third treatment option that is used in most patients is antithrombotic treatments to prevent most events, especially stroke. And for most patients as shown on this slide, warfarin is the most effective treatment whether you compare it to aspirin or to all

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other antiplatelet agents. This is based on a benefit of warfarin with a 70 percent risk reduction in stroke, and I also attempted to show you the safety of the use difference, antithrombotics accounting for the increase, and you can see that the increased reduction is still in favor of warfarin.

So what we know about these treatment options, and the latest one that's, that is available is the thrombin inhibitor Dabigatran. These have been studied and proven effective, but none of them have made it to the market because of various reasons like they're mostly, Dabigatran, at least from the results of the study shown here, it doesn't seem to have any adverse effect, at least in this study, and seems to be at least for the higher dose comparable to warfarin in the prevention of significant clinical events.

However, I want to outline, this is the results from the (inaudible) was presented, was most encouraging, and the results of the other studies, and we hope that Dabigatran won't have the same fate, but we will have to wait for the analysis.

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I want to briefly outline that we are trying to evaluate treatment with warfarin by using information regarding genetic science as shown in the prospective studies, to influence the effective dose of warfarin, and at least we are currently conducting the COAG trial, which is a trial conveying the strategy of initiating warfarin treatment while trying to achieve both clinical and genetic information to reshape warfarin treatment. And this trial will, the objective of this trial is to show whether or not the use of genetic information improves anticoagulation control after one month of therapy. The first stage has shown that the genetics may have a benefit, although it will need to be confirmed if this is positive by a larger effectiveness study.

This is the design of the COAG study, which is a standard double-blinded study, in which participants for the first five days, we initiated those, and then it's conducted, blinded both as to dose, and the dose of warfarin is unknown to the clinician, so at the end we will know if the influence was truly genetic information that we had at NCL.

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So going down now to the question of really, if we can safely and effectively maintain sinus rhythm, how or what are the benefits? The ATHENA trial is showing that there seems to be clinical benefits in terms of a combined clinical outcome and also in terms of (inaudible) cardiovascular event when you compare it to placebo or other treatments of AF. So as a first study, the first graph is to show clinical benefit of a well maintained sinus rhythm. However, I want to point out that this is done in the context of treatment for atrial fibrillation and that the main benefit of it was shown to (inaudible) knowing that (inaudible) effective, yet preventing AF, like shown in AFFIRM and shown in other studies, it was not too surprising that (inaudible) showed benefits in prevention of first occasion for AF, and that was a major benefit that's alleged to show a benefit using the combined endpoints.

So, I always reach this slide with a lot of trepidation because this on-treatment analysis has been cited by many as a basis for why if we do safely and effectively maintain

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sinus rhythm, this would be the preferred option in most patients. However, after many hours of discussion with statisticians and others with regard to the analyses, I'm going there very very carefully.

So we conducted at first, after the completion of AFFIRM, what we called an on-treatment analysis, where we looked at not only baseline predictors of maintenance of sinus rhythm, but also possibly at, during-treatment factors that could be predictors of maintenance of sinus rhythm and positive clinical outcomes, and we showed that when you use a (inaudible) type analysis, that sinus rhythm was highly predictive of a favorable outcome, as was warfarin use, when digoxin was shown to have adverse effects, but also rhythm control was shown to have a significant adverse effect on clinical outcomes.

So what is it that we can get based on these analyses? First, when sinus rhythm was included in the survival analysis as a separate factor, the sinus rhythm variable expressed the beneficial effect of antiarrhythmic drugs, and

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the antiarrhythmic variable drug expressed only the detrimental effects. Therefore, a possible conclusion may be that antiarrythmic drugs are associated with increased mortality. However, when sinus rhythm as a separate factor was removed from the analyses, the beneficial antiarrhythmic effect of antiarrythmic drugs in maintenance of sinus rhythm offset their detrimental effects such as toxicity, morbidity and mortality. Therefore, one possible conclusion is that antiarrhythmic drugs are not associated with increased mortality.

So one possible conclusion of these on-treatment analyses is that the association of sinus rhythm, but not antiarrythmic drugs, with improved survival may reflect that currently available antiarrhythmic drugs are neither highly efficacious nor completely safe. Therefore, a treatment that's highly effective in maintaining sinus rhythm with minimal adverse effects might be expected to improve survival.

However, as I stated in starting this presentation on the on-treatment analysis,

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these analyses cannot distinguish whether sinus rhythm is an important determinant of survival, or just a marker for other factors associated with survival.

So, what do the guidelines tell us now regarding the management of atrial fibrillation? So whether it's newly discovered AF, on the left-hand side, or if it's recurrent or paroxysmal AF, they show you that AF ablation right now shouldn't be a primary treatment option, it's not even a recommended option for newly discovered AF. The same thing when it's recurrent or persistent, the recurrent guidelines tell you not to even think of this option in the most recent protocol.

So, I'm now going to spend the last few minutes of this presentation presenting the CABANA study we're now currently conducting, in which we decided to fund based on the data shown you from other studies, to show that it may be a strategy that was safe and effective, it would (inaudible) option weighing all of those.

So as a hypothesis, the CABANA trial is designed to test that the treatment strategy

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of left atrial catheter ablation for the purpose of eliminating atrial fibrillation or AF will be superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing total mortality in patients with untreated or incompletely treated AF.

The primary outcome of the CABANA trial is to reduce mortality. We have a number of important secondary outcomes, the first one which combines some clinical outcomes, and you can see also down the list if you look at the other outcomes, you see the outcomes that were used in early ablation studies, and other endpoints associated with AF. Very importantly in CABANA, we're also going to look at quality of life and costs of the different treatment strategies.

The inclusion criteria for CABANA somewhat mirrors those of the AFFIRM study, therefore including the larger population that is concerned with AF, which is the Medicare aged population, which has a significant burden of AF and its risk factor for stroke. However, in CABANA, the patients have to be in the

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Medicare population and be eligible for catheter ablation and at least sequential rhythm control and/or rate control drugs. The CABANA patients cannot have failed more than one of the other treatment options, otherwise they will be a failure based on cause.

I am not going to go into detail on the CABANA exclusion criteria, just, I do emphasize that we do want patients who are at significant risks of complications from AF and as stated, we excluded patients who have failed.

So this outlines the very simple, in some ways, the design of the CABANA trial, outlining the randomization between the two treatment options, either pharmacology treatment or ablation.

The treatment arms used in CABANA are outlined here. The ablation will be primary vein isolation using a circumferential ablative approach in the left atrium, using circular mapping, antral isolation using a circular guided approach, or a wide area circumferential ablation.

As far as the patients randomized into

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the other arm, they will receive a current state-of-the-art drug therapy for atrial fibrillation for rate control or rhythm control. Following guidelines are encouraged, but the specific choice of rate control versus rhythm control and especially the drugs to be used are left to the discretion of the treating physician.

Here are the statistical considerations for the CABANA trial. Here are 3,000 patients, the trial was to be conducted in 140 sites. We hope to be able to recruit patients within three years and follow them for a minimum of two years. The study will have at least 80 percent power to detect a 25-to-30 percent mortality reduction, but also will have greater than 90 percent power to detect a 25 percent reduction in the key secondary endpoint.

Those statistical calculations are very conservative. The statistical data entered can be related to sample size and they assume loss to follow-up or cross-over, but we believe there is still plenty of power in CABANA to detect the assumed difference between

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the treatment options.
In conclusion, I tried in 30 minutes to set up the stage as Dr. Salive asked me for future discussions and outline why atrial fibrillation is such an important problem, especially in the Medicare-aged population, what are the various treatment options.
And just as a summary, we conducted a workshop on prevention of atrial fibrillation in April 2008, and although most of the work showed positive gains in intervention and prevention, it also showed gaps in knowledge regarding pathology and other factors leading to atrial fibrillation. There were also several recommendations regarding secondary intervention and institution of therapy for the prevention of AF, and that included a study of patients with presumed early AF to prevent frequent AF, which is really a question that CABANA will hopefully address. Such studies should include morbidity and mortality, and we have to use results of these studies to inform any future primary AF prevention studies.
And I want also to outline that in the Institute of Medicine report that was published

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also last June, which outlined the first quartile, it listed AF as its first priority, and they said that it was a very important priority to compare the effectiveness of treatment strategies for atrial fibrillation, including surgery, catheter ablation, and pharmacologic treatment, and we're very happy that we had decided to conduct the CABANA study way before the Institute of Medicine.

So in conclusion, I hope now that you know maybe a little more what the question is, and that you will be able to find the right answer. Thank you.

DR. C. GOODMAN: Thank you very much, Dr. Rosenberg, very helpful. We have a few minutes, and only a few, if any of our panel members have a question for Dr. Rosenberg, was there anything that you saw that didn't look right, anything that he did not mention that you would like to know at this point? We will have time later. Anything at this point? Dr. Umscheid, yes?

DR. UMSCHEID: There is one slide that you put up that was a meta-analysis of rate versus rhythm, and it looked like the

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meta-estimate was in favor of rate control and there was a significant reduction in mortality. I don't know if I saw that incorrectly or mischaracterized it.

DR. ROSENBERG: There was a trend that based on the risk analysis was insignificant.

DR. UMSCHEID: I think the confidence interval was low.

DR. ROSENBERG: It was, I don't remember the details, but there were several that were conducted in fact that both showed that there was no significant trend.

DR. C. GOODMAN: Okay. Dr. Satya-Murti.

DR. SATYA-MURTI: When you're going on with the CABANA study, these patients would obviously be coming for more medical encounters than if left alone, so would they also be getting attention to the comorbidities which may then help in the outcome, like they would see more physicians and hypertension would be more aggressively treated?

DR. ROSENBERG: We hope they will receive optimal treatment for comorbidities, so that this would not affect the outcome of the study, this would be another reason. We have

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in the sample population assumed that there will be optimal treatment and that's how we chose the event rates, assuming the optimal treatment for comorbidities.

DR. C. GOODMAN: Thank you. Then I have a question or two, Dr. Rosenberg. First of all, some of our background material I believe suggested that the prevalence was about two million people, but in one of your early slides I think I saw in year 2010, 6.1 million people. Is there a difference there that we're missing?

DR. ROSENBERG: I think that is a highly variable estimate that has to be looked at. I think the latter number may be more correct today. Most of the studies are presented using the suppression that was completely happening in the 1990s and then there was increasing incidence. So I don't want to be caught in any (inaudible) but the prevalence seems to be increasing as of today.

DR. C. GOODMAN: So the incidence is increasing, but your slide indicates roughly six million people, Americans have atrial fibrillation; is that what the slide suggested?

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DR. ROSENBERG: I think that's a fair assumption. Others may have other data, but I think that's correct.
DR. C. GOODMAN: And what percentage of those do you consider are age 65 and older or disabled, i.e., Medicare beneficiaries?
DR. ROSENBERG: Even the data I showed you on the by age group, there is, a huge majority of patients are 65, that's to both populations. As the population's age increases, the incidence and prevalence is increasing, and that's why this graph is showing such an increase over the next 15 years.
DR. C. GOODMAN: So in terms of relative magnitude of the problem, it sounds as though perhaps in excess of five million Americans, if not quite six, with atrial fibrillation are Medicare beneficiaries, and I'm reminded that the total number of Medicare beneficiaries is about 42 million, so that would appear to be a rather significant portion of our Medicare beneficiaries.
DR. ROSENBERG: It certainly is.
DR. C. GOODMAN: Dr. Moscucci.

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DR. MOSCUCCI: I just was wondering if you could comment in relation to the inclusion and exclusion in CABANA and particularly in relation to a patient with atrial fibrillation failure, or perhaps Dr. Packer --

DR. ROSENBERG: One or two comments about that. We need to include patients that are reasonable for both treatment options, that's basically how we, and that's -- in which either treatment option may be effective. That's why we decided to exclude patients that had failed already several of those treatment options.

DR. C. GOODMAN: Dr. Packer, you have been summonsed.

DR. PACKER: Then I shall respond. In putting CABANA together we wanted to cast a broad net among populations for atrial fibrillation. Technically it's patients who have new onset or other treatment for atrial fibrillation, and these are patients who have not already, they are therapy naive to some degree in the sense that it's not fair to make a comparison of ablation and drug therapy if the patients have already received three or

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four drugs and failed. The thing that CABANA doesn't do is exclude patients based on age. It has to give us a lot of information about patients who are over 65 and not over 75, and it cannot exclude patients that have a cutoff of atrial size. If you look at a lot of the different trials you will see patients that if they have a 45-millimeter left atrial size, they don't get into the trial, and certainly if they're over 60 they don't get into those trials. And so CABANA is designed to look at a tougher group of patients and to come up with mortality conclusions.

DR. C. GOODMAN: Thank you very much, Dr. Packer. Dr. Rosenberg, we very much appreciate your presentation and hope you will remain for the remainder of the day so we can ask you further questions. We're going to move now to the technical assessment presentation, and Dr. Rosenberg, I would add this as a footnote to your wonderful presentation. Yes, AFib is one of the 100 top burdens to medicine, it is indeed one of the top 25 and top tier. It happens to be listed first by virtue only of

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the alphabet, as you certainly know, but it is certainly in the top 25. Thank you, sir. We will now proceed to the technology assessment presentation by Dr. Garlitski and Dr. Ip.

DR. GARLITSKI: Thank you. My name is Ann Garlitski, I am an assistant professor of medicine at Tufts Medical Center, and I'm also the codirector of the cardiac arrhythmia center. Dr. Ip and myself will alternate, we will both participate in the talk. I will start and finish and Dr. Ip will give the middle substance of the talk.

This review, the Comparative Effectiveness of Radiofrequency Catheterization For Atrial Fibrillation, was funded by the Agency for Healthcare Research and Quality. Potential conflicts of interest are that Dr. Alsheikh-Ali and myself do perform the procedure.

The topics we will review are as follows: Classification of atrial fibrillation; management options, I will be brief, because Dr. Rosenberg has already covered those; the analytic framework of the

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key questions; comparative effectiveness of radiofrequency ablation versus medical treatment; patient and intervention level characteristics; and the different approaches, techniques of RFA; and we will end with adverse events.

One note in regard to the classification of atrial fibrillation, the terms that are used are as follows: Paroxysmal atrial fibrillation is defined as recurrent AF greater than or equal to two episodes that terminate spontaneously within seven days. Persistent atrial fibrillation is sustained beyond seven days, or lasting less than seven days but requiring pharmacologic or electric cardioversion. Longstanding persistent is a continuous AF greater than one year in duration. And permanent is AF that is accepted as the final rhythm.

One note also about the term chronic. Prior to 2006 in the ACC/AHA/ESC and HRS guidelines, the term chronic was used for AF, which is now termed either longstanding persistent or permanent. To be most accurate, we will use the terms which were used in the

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studies. We have already discussed in detail the management options for atrial fibrillation, they are either one or a combination of what is below. Rate control, such as a blocking agent, AV node ablation and pacemaker implant. Rhythm control, most commonly one will see a class III agent. Surgery, which is most often used in conjunction with another cardiac procedure. And radio frequency catheter ablation. This is a schematic of our analytic framework. The patient population on the bottom left are the adults that are patients with paroxysmal, persistent or chronic atrial fibrillation. The intervention is antiarrhythmia agents or radiofrequency ablation, with the goal of sinus rhythm. Sinus rhythm may in turn prevent or improve clinical outcomes which are noted on the right-hand side. From that framework, we posed four key questions. Key question number one, what is the effect of RFA compared to surgical or a medical treatment on shorter, six to 12 months, or longer, which is greater than 12 months,

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long-term rhythm control, rates of congestive heart failure, volume changes, rates of stroke, quality of life, avoidance of anticoagulation, readmissions and reinterventions for atrial fibrillation.

Key question number two. What are the patient and intervention level characteristics associated with RFA on rhythm control?

Key question three. How does the effect of RFA on rhythm control differ among the techniques?

And finally, key question four. What are the harms and complications associated with RFA?

I will turn over the microphone to my colleague, Dr. Ip.

DR. IP: Good morning. I am Stanley Ip, I'm the assistant director of the evidence-based practice center at Tufts Medical Center. I'm essentially a methodologist, I don't have any conflicts of interest, I actually trained as a pediatrician.

What we're going to tell you about is how we went about doing this review and I'm going to review for you our inclusion criteria.

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The population that we're interested in basically are adults only, we did not look at any children. Many of the studies included patients who have had more than one radiofrequency ablation, so we made a rule that 80 percent or more of them have to be treated for the very first time for the study to be eligible. We did not consider patients with congenital heart disease, hypertrophic cardiomyopathy, or with Wolff-Parkinson-White syndrome.

The interventions of interest are specifically radiofrequency catheter ablation directed to the left atrium. They have to be explicitly targeting pulmonary veins. They may or may not use concurrent antiarrhythmic drugs. We only included ones who used eight-millimeter or irrigated tip catheters. And these could be either first-line treatment, i.e., patients that have not had any kind of treatment before, including antiarrhythmic drugs, or it could be second-line treatment, which in fact had failed previously.

We did not look at studies that combined open cardiac surgery with

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radiofrequency ablation or AV node ablation or ablation for standalone atrial flutter. We specifically excluded cryoablation and microwave ablation.
The comparator would be any medical or surgical comparator.
The outcomes of interest are, they have to have at least six months of follow-up.
We will look at rhythm control, i.e., freedom from any atrial arrhythmia, including other kinds of atrial flutter, congestive heart failure, volume size changes, stroke, avoidance of anticoagulants, readmissions and reinterventions, and quality of life.
The adverse events that we are specifically interested in are symptomatic or severe pulmonary vein stenosis, any cardiac tamponade, any periprocedural stroke or transischemic attacks, any reported atrioesophageal fistula, peripheral vascular complication, 30-day mortality, and any length of follow-up.
Here are the study selections. In our systematic review utilizing MEDLINE and Cochrane databases, we essentially identified

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roughly about 3,000 abstracts. From about 3,000 we retrieved possibly 400 full text reviews, and out of them 120 of them qualified for inclusion in our technology assessment. One of the primary things we do when doing a study is judge the quality of individual studies, and we used the Comparative Effectiveness Review Methods Guide as published in the AHRQ manual and we assigned one of three grades to each individual study, they're basically good, fair or poor. Basically the good study, we feel they have a low risk of bias, and a poor study could be a high risk of bias.

In addition, we rated the strength of the body of evidence for each key question, and they are dependent on the number and the quality of primary studies, the duration of follow-up, and how consistent are the results reported across different studies. The ratings are as follows. If we rate a body of evidence as high, it means that we have high confidence that the evidence presented in fact reflects the true effect. If it's rated moderate, we have moderate confidence that the evidence

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reflects the true effect; however, if the evidence is rated moderate, it may change, the effect may change and the estimate may change. If we rate it as low, we have low confidence that the evidence reflects the true effect, and there's a high likelihood in the future that these estimates will change. We also put in a qualifier as insufficient, either the evidence is unavailable or does not permit an estimation of the true effect. In terms of radiofrequency ablation versus open surgery, we did not find any study. For radiofrequency ablation versus medical treatment, these are the outcomes which I have mentioned previously, which I will go through one by one. In terms of rhythm control, rhythm control I had mentioned previously, they basically have controlled sinus rhythm or they don't have any kind of atrial arrhythmia. There are actually a total of six randomized controlled trials randomizing RFA versus medical treatment, they all found significant benefits from RFA in terms of rhythm control. However, three of those RCTs

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included many many reablations, so we discarded them in our analysis.
So our analysis of three randomized controlled trials are all second-line treatment, they only provided data for one ablation only, and they also provided 12-month follow-up data, and that analysis showed a relative benefit of radiofrequency ablation in maintaining sinus rhythm about three times lower than the patient who had medical treatment at 12 months.
There was one single randomized trial that enrolled patients who had never had any kind of treatment, i.e., first-time treatment. That one showed at 12 months, 88 percent of patients who had the RFA had maintained sinus rhythm, versus 37 percent, and you can see that. So we rated the strength of evidence moderate for second-line therapy and insufficient for first-line treatment because there's only one study with a small sample size.
For congestive heart failure, there was one retrospective observational study with a 30-month follow-up that found in the patients

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who had an RFA a decrease risk of congestive heart failure compared to those who were treated medically.

For volume changes, there is one randomized controlled trial that essentially showed that there was no difference at 12 months between left atrial diameter and ejection fraction between those two arms.

For stroke rate, we did a meta-analysis of six randomized controlled trials. In this instance we used risk difference because the event rate is low and some of the studies reported a zero event rate, and it showed that there is a nonsignificant increase in risk with RFA, 0.6 percent. We rated the strength of evidence as low because the stroke event rate was not systematically assessed in these studies.

For quality of life, there were three recognized clinical trials and one retrospective study that has looked at different components of the SF-36, and they found some significant increase in subcomponents of the SF-36. And we rated the body of evidence as low because there are quite

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a few methodological deficiencies in the primary studies.

For avoidance of anticoagulants, there is one randomized controlled trial at 12 months and it showed that patients who receive RFA, 60 percent of them avoided anticoagulants, versus 34 percent, and we rated the strength of evidence low.

For readmission, there were two randomized controlled trials. The first essentially found a significant difference. The second study, however, found that there were nine readmissions in the RFA arm versus 54 percent in the medical arm. We rated it low because of incomplete study details.

For question two, essentially we were examining patient and intervention characteristics to predict outcomes of RFA. We looked at the types of atrial fibrillation, paroxysmal versus non-paroxysmal. We looked at the left atrial diameter, the ejection fraction, the sex of the participants, age, and the operator experience and setting.

For paroxysmal versus non-paroxysmal AF, there are a total of 17 studies that did

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have multivariable analysis. 11 of them found no statistically significant association between types of AF and recurrence, and six of them found that non-paroxysmal AF predicted higher recurrence. We actually -- this is incorrect at the bottom. We actually rated the strength of evidence, it's actually mostly multivariable analyses, so the strength of evidence we actually rated as moderate. The left atrial diameter ejection fraction, what we found was, some of this Dr. Rosenberg referred to and Dr. Packer mentioned earlier, most of these patients have essentially normal left atrial diameter or ejection fraction, they have a left atrial diameter less than 55 millimeters and an ejection fraction greater than 40 percent. So a minority of the studies found a significant association between increased left atrial diameter and increased atrial fibrillation recurrence. And also, five of the 17 studies found a significant association between decreased ejection fraction and increase in atrial fibrillation recurrence. And the strength of evidence is rated moderate, that

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the LAD or the ejection fraction are not independent predictors of atrial fibrillation recurrence.

In terms of male versus female, there were 23 studies and none of them found an association with sex and AF recurrence, and the strength of evidence is rated high.

In terms of age, the studies that we looked at mostly looked at younger patients, most of them varied between age 40 to 70, and in those studies they did not find an association between the age and AF recurrence.

There is one lone study that found an association between older age and a decrease in AF recurrence.

There is no study that directly addressed operator experience or setting on how it would affect the outcomes.

Now I will turn it over to Dr. Garlitski to talk about the technical aspects.

DR. GARLITSKI: Question three addressed different techniques, pulmonary vein isolation versus wide area circumferential ablation, otherwise termed WACA; RFA plus or

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minus an additional left or right-sided lesion sets, in particular left-sided lesion sets; the eight-millimeter versus the irrigated tip catheter; and different imaging techniques.

First, WACA versus PVI, there were five randomized controlled trials of approximately 500 patients in general favoring WACA over PVI. However, we were unable to compare across the studies due to different follow-up periods, the permission of reablation, and the differences with antiarrhythmia drug use. The evidence is moderate.

This forest plot is a depiction of those trials. On one side you will see that three trials clearly favor WACA, one trial favors pulmonary vein isolation. However, if one goes back and reviews the methods used in those three trials which favor WACA, there's further evidence that ablation was performed mapping specifically electrograms in the pulmonary veins.

RFA with the addition of left-sided lines. The available evidence is six randomized controlled trials. There was no

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significant difference in two of the studies, decreased AF recurrence in four of them. There's insufficient data to state whether there is a difference with including left-sided lesion lines. There was marked heterogeneity in different types of left-sided lines, and reablation.

In regard to the different tips used to deliver the radiofrequency energy, there were four randomized controlled trials. There was no significant difference in rhythm control in a six to 12-month follow-up period between these two catheter tips, and the strength of evidence is moderate.

With regard to different imaging techniques, there were four unique comparisons in five studies. I will read them as follows: There's no difference in three fair quality RCTs or randomized controlled trials. What they looked at was 3-D mapping versus conventional fluoroscopy. They looked at CT integration versus CT registration, and CT integration versus 3-D mapping without CT integration.

Differences were noted in two poor

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quality RCTs. Three-dimensional mapping was shown to be superior to conventional fluoroscopy, although no statistical comparisons were noted. CT registration was shown to be superior to conventional fluoroscopy although, again, no statistical comparisons were made. The strength of the evidence is insufficient.

In regard to harms and complications, there were 83 studies which reported one or greater events. There is no systematic reporting of the data on time of occurrence of these complications, with the exception of pulmonary vein stenosis, which was reported at three months. Strength of evidence is low and that is due to nonuniform definitions and nonsystematic reporting.

Major adverse events are as follows: Pulmonary vein stenosis was noted from zero to 19 percent of the time. Cardiac tamponade from zero to five percent. Stroke or TIA at zero to seven percent. Atrioesophageal fistula, .07 to 1.2 percent. Of the 63 studies reviewed for adverse events, five deaths were noted. Of note in respect to those five deaths, it is

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possible that there may be duplicate data. In summary, there is a moderate level of evidence that RFA is effective as a second-line therapy with a follow-up of 12 months. There's insufficient data on first-line therapy. Major clinical complications are less than five percent of the time, but the reporting was not systematic. We need more data on the elderly, patients with multiple comorbidities, long-term, in other words years of follow-up, effect of radiation, quality of life and mortality. Thank you.

DR. C. GOODMAN: Thank you very much, Dr. Garlitski and Dr. Ip, an impressive compilation of evidence, thank you very much. Do we have questions from the panel now? We have leading up to pretty close to ten o'clock to take a look at the technology assessment, any questions or concerns that you have at this point. Questions by any of the panel for this? Yes, Dr. Carlson.

DR. CARLSON: Were you able to, when you looked at complications, morbidity and mortality, were you able to say anything about whether the incidence of those events remained

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persistent over time, or was there enough evidence to be able to say that? In other words, is the rate today the same as it was ten years ago?

DR. IP: We were not able to do this analysis because we didn't do a time analysis. And the trouble with it, many of the studies, they are like published from the same centers but have a different number of denominators, so we have no idea how they go about reporting each study.

DR. CARLSON: One other question is regarding left atrial dimensions, ejection fractions, and some of the evidence from these studies, counter to what we commonly teach and understand, is that there is a relationship between left atrial size and occurrence and recurrence of atrial fibrillation, and the same for heart failure. Is that because of the population in these studies and you're not seeing the complete spectrum perhaps of atrial fibrillation?

DR. IP: That's what our clinical cardiologist is telling us. But when we look at the studies, in fact the patients enrolled

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are not very sick and quite younger, and they don't have much to offer.

DR. GARLITSKI: Just to add a comment, if you recall the slide where the mean atrial diameter and ejection fraction was, you will see that they're not far from normal, so there isn't that variance that has been studied as of yet.

DR. CARLSON: Thanks.

DR. C. GOODMAN: Yes, Dr. Dullum?

DR. DULLUM: Thank you for your review. Actually, the written review is excellent. Discussing the rhythm control therapy, there's a moderate level of evidence for the second line. I wasn't clear in my mind from reading the information that this is the ablation solely and not ablation plus the medical therapy. Are you making that remark, like saying that all you have is ablation, and there are no more medical therapies?

DR. IP: That's not entirely true because most of the studies, the way they did the studies, they said we will give you the radiofrequency ablation, but then we'll put you on the antiarrhythmia drugs for like three

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months afterwards, and so some studies did that, some studies did not do that. So, you know, we cannot say.

DR. DULLUM: I mean, I'm concerned that there was no evaluation based on surgical therapy, but let's put that aside. It was very confusing to me what exactly they were talking about because everything was sort of mixed, and that's what I finally came away with from all of this, that there's no clear one line of treatment to say yes, this is the thing to do.

DR. IP: Which, I agree, because when I reviewed these studies, if you look at the details, some of them, especially the second line, you would have some other treatment at some point. But then the ones that we included, at least at 12 months when they did the evaluation at 12 months, they were off antiarrhythmic therapy at that point.

DR. DULLUM: And anticoagulation, or no?

DR. IP: I don't know that off the top of my head.

DR. C. GOODMAN: Further questions? Yes, Dr. Packer?

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DR. PACKER: One of the issues in a number of the trials that you talked about, they looked at the time to first recurrence. Is that the right way to be looking at this, because does time to first recurrence really give us a notice as to the value of the therapy, whether that's on the drug side or whether that's on the ablation side?

DR. C. GOODMAN: Did you investigate that, Dr. Garlitski or Dr. Ip?

DR. IP: No. We just took the studies as they were; we didn't say that was the right way or not the right way to look at it.

DR. C. GOODMAN: Dr. Garlitski?

DR. GARLITSKI: Yes. When the results were looked at, it was generally, or not generally, it was reported as freedom of AF at a certain time point. So again, the longer-term follow-up was what was taken, not necessarily the first recurrence. It was freedom from atrial fibrillation as defined by that trial and that author of that study.

DR. C. GOODMAN: Thank you. I think Dr. Umscheid was next.

DR. UMSCHEID: I also appreciate the

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very concise review of the trials that you covered. I had two quick questions, and they're both about your grading of the evidence.

For the issue around age, you said that you had essentially a high certainty that there was no impact of age on recurrence, but the window was very narrow.

DR. IP: That's correct, with a qualifying statement that most of the patients that we looked at, off the top of my head, their mean age was only 50 to 55.

DR. UMSCHEID: So if you had to take one more step and say age in general and not that narrow a window, it sounds like your level of certainty would be much lower about the impact of age.

DR. GARLITSKI: The data that we have from this review is a mean age of 55, so we can't comment on a mean age that would be higher.

DR. UMSCHEID: And I have a similar comment about EF. You said you had a moderate certainty that EF did in fact recur, and I assume that was within the narrow range of EF.

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DR. IP: Right, you are totally correct. We should modify that to say it's with moderate to high certainty, but it's within this narrow range.
DR. UMSCHEID: So it might be a low certainty or insufficient certainty if you were looking at all ranges of EF.
DR. IP: If that's the question, yes.
DR. UMSCHEID: Because that would probably be the most important question for this panel, whether EF impacts recurrence, you know, what a clinician would care about, you know, does the low EF impact recurrence of AF, or if not, what is the range of normal, you know, or does some variant have more impact.
DR. C. GOODMAN: Dr. Umscheid, I want to make sure we don't miss this point. What should we infer and conclude from the questions you asked and the answers you just received?
DR. UMSCHEID: The reason I bring those points up is because I feel like the levels achieved were too high given the evidence, so if there is no evidence about the impact of a wide range of EFs on recurrence of AFib, then I think we should be able to say

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it's insufficient evidence or low, but not necessarily a moderate. And the same with age, if all the studies are looking at a narrow age range, then they're not looking at a broad age range, and I don't think we can have a high level of certainty about the impact of age in general on recurrence.

DR. C. GOODMAN: So the difference between the level of certainty regarding the evidence as presented with regard to age versus perhaps a broader scope of age with which we might be concerned, correct?

DR. UMSCHEID: Yeah. My interpretation is that when people talk about the impact of EF and age, these different variables on recurrence, they're envisioning a broad range from low to normal EF, or from young to old, not a narrow range of these variables.

DR. C. GOODMAN: Okay, thank you, a point well made. Dr. Satya-Murti is next.

DR. SATYA-MURTI: Your written treatise explains this much better, I think, and I append it to Dr. Packer's question. So the moderate level of confidence in the first

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bullet point, the effectiveness is detection of the recurrence of atrial fib. So undetected, either asleep or at other times, they might have had a spontaneously converting event; isn't that correct?

DR. GARLITSKI: Certainly, they may have undetected, absolutely. The issue is that the studies reported detection of it in variable ways. There were different methods used in the studies to detect either symptomatic or asymptomatic atrial fibrillation.

DR. SATYA-MURTI: And in any of your reviews, were you able to find out the contribution of the rhythm abnormality to the overall morbidity of the patient? Because many of them have had other morbidities too, so what contribution did the rhythm abnormality alone make towards the patient getting ill or well? It's not known, isn't that correct?

DR. GARLITSKI: That would have to be presumptive. What we have is what the data told us, that at a certain time the investigators looked for the atrial fibrillation. Some stated that it was

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asymptomatic, some stated that it was symptomatic, and they didn't comment on what the other comorbidities may have been contributing. We don't know that.

DR. C. GOODMAN: Thank you.

Dr. Hammill is next.

DR. HAMMILL: Not necessarily a question, just a comment, because when you put up the adverse effects or adverse outcomes, you had broad ranges, and we've seen that throughout the literature. But I think it's important to focus in on the median, because it's much lower and closer. For example in pulmonary vein stenosis, the median of .3 and the stroke is I think .9 or .7, and I think that's a better way of representing that data.

DR. IP: It's difficult to state all of these variables. Some have very few subjects, some have more subjects.

DR. C. GOODMAN: Thank you.

Dr. Moscucci's next.

DR. MOSCUCCI: I first want to make a comment concerning age and ejection fractions, and also about atrial size. Most of the studies look at a very narrow range of size,

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particularly with a size of 38 or 39 millimeters, we cannot necessarily extrapolate that to a larger patient population. The question that I have is whether in your systematic review you run across any relationship between volume and outcome, a learning curve with respect to number of adverse events and how those relate to outcomes.

DR. IP: No, we did not come across those things.

DR. GARLITSKI: In regard to the studies, whether in the literature or not, those studies clearly did not meet the inclusion criteria, which we used when we screened the abstracts.

DR. C. GOODMAN: Dr. Maisel is next.

DR. MAISEL: I just wanted to make one observation regarding the issue of age, which is obviously a very important one with respect to the Medicare populations. I think we need to be careful about focusing too much on the mean age, because the standard deviations of age in most of those studies was in the eight to ten-year range, so there certainly were a

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lot of older patients that were included in some of those studies, and perhaps if you could comment on that.

DR. IP: Yeah. We didn't really specify them into subgroups but as you have noticed, I said most of the patients were between 40 and 70, so we don't really know how many were over 65, there could be quite a few.

DR. MAISEL: Well, I was just looking through the studies, and for example while the mean age in most of them is in the 50s, the standard deviation is in the nine to ten-year range, so that could imply that there are a substantial number of patients that are in their 60s or older, based on what I know about bell curves.

DR. GARLITSKI: I think because the study, not every study noted how many of those patients were at what age, we're not able to extrapolate and say how many were in the Medicare age range. But yes, they were studied, we just can't state definitely how many.

DR. C. GOODMAN: Thank you.

Dr. Garlitski, could you return to your summary

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slide? Your first bullet with regard to moderate level of evidence that RFA is effective as a second-line therapy, I just want to make sure I understand. When you say effective there, the only place you found something effective was not on outcomes, but it was rhythm and control. So when you say effective, you mean effective for rhythm control; is that correct?

DR. GARLITSKI: Yes. It is for recurrence of atrial fibrillation with rhythm control as an outcome, not other outcomes.

DR. C. GOODMAN: And one might state that rhythm control might be considered, if I might say an intermediate outcome, maybe a surrogate?

DR. GARLITSKI: Correct. If you look at the analytic framework from the beginning, our patient population are those with AFib. Our goal here was to determine whether effective or not, sinus rhythm, and we can't comment on the clinical outcomes.

DR. C. GOODMAN: Thank you. So that must be why in your fourth and final bullet of your summary slide, you talk about the need for

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more data on the elderly patients and so forth, long-term rates of not just AF recurrence, but effects from radiation exposure, quality of life and mortality. So that must be in part the evidence gap that you perceive, correct?

DR. GARLITSKI: Correct, yes.

DR. C. GOODMAN: So if we care, and we know that Medicare cares, and people need clinical evidence directed toward really healthcare outcomes, we didn't really, you haven't gleaned a lot about real primary endpoints from the available body of evidence. Is that correct?

DR. GARLITSKI: That's correct, it would have to be extrapolated. The effectiveness is not an AFib recurrence.

DR. C. GOODMAN: And then another question, and I'm not sure you addressed this directly, and in addition I hope that our panel can enlighten me and us. Can you summarize, what is the known relationship between sinus rhythm and the primary endpoint about which we care the most?

DR. GARLITSKI: I think I may try to summarize that for you, but I think in fact

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Dr. Rosenberg in some ways addressed those points. AFFIRM certainly made an attempt to address or link, and I certainly think some of my colleagues here may be able to speak more articulately, but AFFIRM is much of the data that we have that made an attempt at least to link sinus rhythm.

DR. GOODMAN: To detect an association that exists, and in your review you found what?

DR. GARLITSKI: This is, what we have is what I presented with regard to outcomes. Anything else that I would say would be an extrapolation or not reflective of this data here.

DR. C. GOODMAN: Thank you.

Dr. Moscucci, could you enlighten us, or at least me?

DR. MOSCUCCI: I think in relation to the issue of recurrence, there have been other comments here. Most of the studies look at recurrence after one year, and I think we would like to obtain additional data beyond just one year.

DR. IP: Yeah, the longest we have is 12 months, and there are some studies that have

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like 15 or 16 months, but it's generally only 12-month data.

Dr. GARLITSKI: Again, that is not to say that there is nothing in the literature with respect to that. We used very strict criteria to try to get the highest quality of evidence here in this review, so there may be other trials or cohort studies that address longer term, but none that met our criteria for inclusion.

DR. C. GOODMAN: Thank you.

Dr. Packer, were you going to venture an answer to my earlier question?

DR. PACKER: Yes. So this is a critical question, whether or not sinus rhythm is good for you. Part of that would depend on what you choose as your definition of good. If you look at ablation studies, they haven't been of sufficient size or conducted over long enough periods of time to say anything about mortality or some of those kinds of key endpoints, which is the reason for doing the data.

But if you go back to AFFIRM, and if you look at AFFIRM data, albeit looking back at

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it in kind of a post hoc analysis, and Yves showed this, one of the most important predictors was sinus rhythm. If you look at the (inaudible) whether you're looking in the treatment group or not, the patients who were in the sinus rhythm did better. So why is it so difficult, then, for a study like AFFIRM in its primary analysis, for instance AF/CHF in its primary analysis, to demonstrate a difference between those? And part of it is those studies were really looking at a treatment rather than a state, like sinus rhythm, so I think that's an important consideration.

The other thing is at the end of the day, whether you're talking about ablation or drug therapy or anything else, at the end of the day AFib may not be a risk factor for very very morbid events, or for them, or it just might be that it's a risk marker, or it may be that there really is benefit to sinus rhythm created by antiarrhythmic drugs but it's masked by the presence of therapies that are inherently toxic. It also may be that in the way these individuals in different trials look

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at endpoints, there may be a lot of sinus rhythm in the patients who appear to have ongoing atrial fibrillation, so they get categorized as being AFib failures. Or conversely, in the efficacy group it may flip the other way, so you may not have, in your determination of atrial fibrillation presence or not, you may not have a sufficient gradient to detect. So that bears on the issue of how hard do you look and how hard do the trials look to identify who really has fib and who really doesn't.

So I think that it's tricky, and there's some issues here that have to do with the consequences of therapy, the side effects of therapy that might mask a lot of the fundamental good, so hopefully that can be looked at closer in order to answer your question.

DR. GOODMAN: Thank you. If I may pick on a couple of our panelists, Ms. Atkinson as our designated patient advocate here today, do you have any views so far on how this intervention might affect outcomes that matter to patients?

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MS. ATKINSON: Well, the biggest concern I have in reading all of this literature and listening is the fact that the median age is about 55 plus or minus ten years, so you're still not looking at the very frail who often do have multiple comorbidities, and that's where the studies have failed to prove that this is good therapy.

DR. C. GOODMAN: Thank you. Other comments or questions? Dr. Umscheid, please.

DR. UMSCHEID: One other thing that struck me as somebody who practices hospital medicine for a small amount of my time, we usually focus on rate control and stroke prevention on patients who come in. And obviously most of the literature here is about rhythm control and I was surprised that there were very few, if any, actually I don't remember any trials that look at catheter ablation versus rate control and some of the important outcomes we care about, like stroke, mortality, heart failure, readmission. Can you comment on that?

DR. IP: Well, all I can say is rate control wasn't really in the analytic framework

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so we did not really examine that particular factor.
DR. GARLITSKI: Because the goal of catheter ablation is clearly rhythm control. Whether it's achieved or not is a good question, but the goal of catheter ablation is to maintain sinus rhythm, so the most appropriate comparators would then be another technique or medication which also serves to maintain rhythm control, in that case medications for those kinds of patients.
DR. UMSCHEID: Okay. Because what I might argue from a patient perspective is that if you have AFib, what you care about is not being symptomatic from it, so not having a rapid heart rate, not having heart failure and not being readmitted, not having a stroke. And so my guess would be that most patients don't care for the label of sinus rhythm or AFib as long as they feel well and they're out of the hospital.
DR. GARLITSKI: Certainly a reasonable comment. Our data simply does not address catheter ablation versus rate control.
DR. GOODMAN: Thank you. Dr. Dullum

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is next.
DR. DULLUM: Just a follow-up on the age issue in Dr. Rosenberg's presentation where it talked about as you get older you have a higher risk of stroke, et cetera, et cetera, but we know that that's going to happen with what, as Dr. Moscucci said, you have more multiple comorbidities as you get older, your incidence of stroke is higher. Do we really know that the AFib was causing it and the ablation is going to fix that? And Coumadin, we kind of talked about Coumadin, but when you're looking at the stroke events, are they responsible for preventing your stroke or hemorrhages. So to me, again, I'm not sure, is it just the rhythm, or they have the comorbidities, so we're doing this instrumentation and not really improving their outcomes?
DR. GARLITSKI: I mean, it's a very true statement, a very important point, the fact that many patients in the Medicare population do have comorbidities. Given the data that we have with what we were able to go through, it's extremely difficult to sift out

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unless the data explicitly states that they're symptomatic or their clinical data is directly related to AFib.

DR. C. GOODMAN: Thank you.

Dr. Satya-Murti is next, then Dr. Hammill, and we're going to have to see if we can just fit these two questions in before ten.

Dr. Satya-Murti.

DR. SATYA-MURTI: Those who did not do well with rhythm control, it makes me think if rhythm control is actually protective in a subpopulation of patients. It may be a protective measure in some patients that are trying to compensate for yet undetermined reasons, and is rhythm control necessarily determinative of improvement in those cases where they didn't do so well?

DR. GARLITSKI: Again, a very important point, I think we would all like to know the answer to that. What we have here is that, again, outcomes were the effectiveness of maintaining sinus rhythm by catheter ablation, so I can't speak to that based on this data.

DR. C. GOODMAN: Dr. Hammill.

DR. HAMMILL: Just a brief comment on

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what was brought up earlier about looking at the rate control and comparing that to catheter ablation. When you looked at the multiple studies that have been done to assess rate control versus rhythm control, AFFIRM, RACE, PIAF, those studies only entered patients who tolerated a rate control strategy, and we've all experienced many patients who even though their rate control is good, for one reason or another they don't tolerate atrial fibrillation, and it's those patients who move on to catheter ablation. So the ablation strategy has primarily been done as a symptom relief, not necessarily looking at the other endpoints as an issue.

DR. C. GOODMAN: Thank you. Ms. Atkinson, we do have time if you have another comment.

MS. ATKINSON: I just wanted to comment, I didn't see in a lot of the data as far as medication compliance with a lot of the antiarrhythmics. I think I saw one study that actually looked at the reason older adults failed was simply because they couldn't tolerate the side effects so they stopped the

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medications. Can you comment on that?
DR. IP: I mean, that's correct. We did not look for medication compliance data per se.
DR. C. GOODMAN: Thank you. Yes, Dr. Calega?
DR. CALEGA: Can you comment on the rates of complications, or reported complications and the fact that these were done at academic centers? Is there some commentary that there might be underreported complications for these procedures?
DR. GARLITSKI: So, to give an actual rate is very difficult based on this data, and the problem with that is it's not clear if some of the studies have the same subset of population, so you have, if you have two different studies, you can't just total all the patients and say one in 500, just making up a number. So it is not, unfortunately, possible to give you a rate, which is why we stated the range rather than to give you a rate, because it is difficult to assess the denominator.
DR. C. GOODMAN: A closing question. In your technology assessment you had a Table

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A, which was the summary of reviewed studies. Could you turn to that? And so, Dr. Garlitski and Dr. Ip, you're at the Tufts Evidence-Based Practice Center, which has been an EPC for quite some time now, a lot of studies, a lot of evidence appraisals. Take us to 30,000 feet, let's look at Table A. Does Table A look like --

(Discussion concerning audiovisual.)

DR. GARLITSKI: Please go ahead.

DR. C. GOODMAN: It has a summary of the studies by study type, number of studies, quality of studies, number of patients. I don't know that it's in your slide presentation.

DR. GARLITSKI: It is not in our slide presentation.

DR. C. GOODMAN: So then, it's being handed to you now. And in looking at the number of studies by quality, good, fair and poor, does this look like an overall strong body of evidence to you, vis-a-vis the evidence appraisals that you've done in the past?

DR. GARLITSKI: I will let Dr. Ip answer that question.

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DR. IP: We don't make comments on overall quality of evidence.

DR. C. GOODMAN: That's a judicious response.

I think with that, it is now exactly ten o'clock. We're going to take a 15-minute break. I want to thank, again, the team from the Tufts EPC, Drs. Garlitski and Ip, and Dr. Rosenberg before that. We will see you at 10:15. Thank you.

(Recess.)

DR. C. GOODMAN: We're now going to hear from our scheduled public comments, and I'm told that our speakers will have seven minutes per. We will do our best to stick to that, and I will give you approximately a two-minute warning.

First up is Dr. David Wilber from Loyola. Welcome, Dr. Wilber.

DR. WILBER: Thank you. I would like to thank the panel for being invited to talk to you today. I represent the atrial fib Thermocool investigators, and I would like to present to you in the next few minutes at least a summary of a clinical trial that hasn't been

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in the previous data. It has been presented at the Heart Rhythm Society. The study was completed in January of 2009 and is being submitted and evaluated for publication, but they have not made their final decision as of yet. We think this study does make an addition to some of the questions that have been raised this morning and so hopefully this will provide you some additional data.

The study was sponsored by Biosense Webster, and I have been a consultant and investigator for Biosense Webster, and these are the remaining other disclosures that I have.

So, this was a prospective multicenter trial that was comparing catheter ablation to antiarrhythmic drug therapy for treatment of symptomatic paroxysmal atrial fibrillation that was refractory to at least one antiarrhythmic drug. It was conducted in 19 centers. The study had a Bayesian adaptive sample size with a preplanned incremental analysis, and was sufficiently powered to detect at least a 25 percent absolute difference between the treatment for symptomatic AF recurrence by

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either catheter ablation or antiarrhythmic drug therapy. And there was a series of planned stopping rules depending on the outcomes of the interim analysis.

These are the enrolling sites and investigators.

The enrollment criteria was symptomatic atrial fibrillation, at least three episodes, one being documents in the six months prior to randomization, and prior failure of at least one antiarrhythmic drug, which was true in about 85 percent of the patients, or one AVN blocker, such as a beta blocker or calcium channel blocker, which was the other 15 percent.

There were a variety of exclusion criteria that you can see here.

Patients were randomized in a two-to-one fashion to catheter ablation or drug therapy, and then there was a nine-month efficacy evaluation period following a three-month blanking period in the ablation group and following a 14-day dose titration period in the drug group. There was intense transtelephonic monitoring throughout the study

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managed and adjudicated by an independent core laboratory. There were scheduled transmissions weekly for the initial eight weeks and then monthly thereafter, with added transmissions during all symptomatic episodes.

A quality of life assessment was an important part of the study. It was done at baseline, and three, six and nine months of the efficacy evaluation period, and this included the SF-36, which is a standard quality of life questionnaire, as well as an atrial fibrillation symptom checklist. There was also a CT/MRI at baseline, three months and 12 months in the ablation group, which addressed the issue of pulmonary vein stenosis.

There were a variety of endpoints.

The primary endpoint was the protocol defined success, which was freedom from documented symptomatic atrial fibrillation during completion of the nine-month efficacy evaluation period, and then in addition to that and irrespective of atrial arrhythmia recurrence, there needed to be acute procedural success, i.e., entrance blocking for pulmonary veins in the ablation group. No additional

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ablation beyond 80 days, and then no new drug therapy that impacted AFib during follow-up, which included both class I and III drugs, and also ACE/ARB, calcium channel blockers and beta blockers.

Then secondary outcomes included freedom from any documented symptomatic atrial arrhythmia, including AT flutter, freedom from documented recurrent atrial arrhythmia, either symptomatic or asymptomatic, and the quality of life data.

Patients that are selected for ablation have the Thermocool catheter and Carto electroanatomical mapping. All patients receive circumferential pulmonary vein isolation and then also receive optional lesions at the investigator's discretion, which is cardioelectrogram fractionation, left atrium linear lesions, and ablation of other non-pulmonary vein foci that initiate atrial fibrillation. And repeat ablation is permitted if performed within the first 80 days of blanking period.

There were more than 5,000 patients screened and of that, 4,500 or more did not

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meet inclusion/exclusion criteria, another 671 refused participation, so the study included 167 patients which was three percent of screened patients, and they were randomized with 106 ablation and 61 antiarrhythmic drugs. The trial started in October 2004, and subsequently seven patients were excluded and one patient was discontinued. These were predominantly to withdrawal of the patient after initial randomization. Efficacy was based on 159 patients and at the first planned interim analysis, the study already met the stopping rules for success of ablation therapy, and the present analysis was based on the final data set as of January 2009.

DR. C. GOODMAN: Two minutes, Doctor.

DR. WILBER: Okay. I'm going to briefly go over the outcomes. Of the protocol defined success at the end of the follow-up period, there were 66 percent who were being treated for atrial fibrillation in the ablation group compared to 16 percent in the drug group. If you look at symptomatic atrial arrhythmias it was 70 percent versus 19 percent ablation versus drugs. And if you look at total atrial

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arrhythmias, both symptomatic and asymptomatic, 63 percent of the ablation and 17 percent of the drugs at the one-year follow-up remained free of any atrial fibrillation recurrence. If one looked at the predictors of total atrial arrhythmia recurrence, the only thing that was a significant predictor was the treatment by catheter ablation and having included both clinical variables and randomization group, and at the specific centers the hazard ratio was 0.29 in favor of catheter ablation.

Quality of life studies with the SF-36, as you can see, substantial improvements in quality of life, both mental and physical components, with little change in patients with drug therapy. Similarly, symptom frequency was substantially reduced in the ablation group but little reduced in the drug treated group.

And major adverse events was similar in terms of numbers between the ablation group, five percent, and the antiarrhythmic drug group, nine percent.

So overall, we concluded that in patients with symptomatic atrial fibrillation

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nonresponsive to prior therapy, that ablation was associated with greater freedom from symptomatic atrial arrhythmia recurrence, greater freedom from any atrial arrhythmia recurrence, better quality of life, a very low risk of major adverse events associated with ablation. And the strengths of the study, it was a multicenter trial, unlike some of the other ones, that included more than 19 centers, all experienced in catheter ablation. It was rigorously adjudicated, with extensive external monitoring and audits of clinical data and outcomes. Thank you for the opportunity to speak.

DR. C. GOODMAN: Thank you very much, Dr. Wilber, for an efficient information transmission. I do wish we had more time but we will have some time later on for questions, so we're glad that you're here. Thank you very much.

Next is Dr. Stanton, from Medtronic. Welcome.

DR. STANTON: Thank you, and I appreciate the opportunity to speak today. I'm Marshall Stanton, vice president of clinical

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research and reimbursement at Medtronic. Medtronic has a couple of different technologies that are under development for the treatment of atrial fibrillation, and my obvious conflict is that I'm an employee of Medtronic. Prior to joining Medtronic I was a cardioelectrophysiologist practicing at Mayo Clinic, and my previous boss is on the panel. I don't know if that's full disclosure or too much information.

My purpose is, in looking at the evidence that you're looking at today, I wanted to make sure that you're aware of two trials that are ongoing, the results are not out yet, but they will be relatively shortly.

As you continue your deliberations today, I think one of the things that's important to keep in mind is that with any therapy, there is always a growing body of evidence, whether it's a therapy that has just begun, whether it's one that is in its early, mid, more mature evolution, but at no point in time can I recall ever seeing a therapy that all the questions were answered and we no longer had a need to do any further clinical

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studies, so I just ask you to keep that in mind.
The two different clinical trials we're going to talk about used two different approaches for the ablation of atrial fibrillation. One uses cryoablation, cryo is a freezing or temperature lowering technology, and the other uses radiofrequency ablation.
So the first, you can see here on the right, is a balloon that is based inside the pulmonary vein just at the antrum of the pulmonary vein. It occludes the vein and cryo, the freezing is applied, which causes the ablation of the pulmonary vein area. This technology is approved outside of the United States. As I mentioned, it is undergoing an IDE study right now that is aimed at looking at patients who have paroxysmal atrial fibrillation.
So, this trial is known as STOP AF.
It is currently underway in the United States.
There's 23 U.S. centers, three Canadian centers. It's a prospective randomized trial, 245 patients, looking at cryoablation using this technology compared with rhythm control

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using antiarrhythmic drugs. As I mentioned, it isolates the pulmonary veins as its approach to the therapy.

And this is a trial that will be submitted to FDA, so there's two key endpoints, one is a safety endpoint and the other is an efficacy endpoint. This is a 12-month follow-up study on new patients with paroxysmal atrial fibrillation looking for both the acute procedural success, but also chronic success in keeping people out of atrial fibrillation.

The second technology is shown on the right here, it is just two of a portfolio of catheters that are used for the delivery of radiofrequency ablation energy. This trial is also ongoing in the U.S. at 23 centers and one European center. It again is also prospective and randomized, with 210 patients in this trial. The important difference compared to the last trial is that this is aimed at the patients with atrial fibrillation that is persistent or longstanding persistent, what some people might call permanent atrial fibrillation, so a different patient population.

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Again, looking at both the safety and efficacy. Because of the difference in the patient population with these people in permanent or persistent atrial fibrillation, the study has been designed for a six-month follow-up to see if we can keep people out of atrial fibrillation with this ablation technique compared with antiarrhythmic drugs. I may have neglected to mention the fact that the previous trial, the STOP AF trial has completed its follow-up, the results have not been presented yet, and this trial, the TTOP trial is close to completing its follow-up. Again, its results have not yet been presented, but I wanted you to be aware that these will be coming out in the very near future. Thank you very much.

DR. C. GOODMAN: Thank you very much, Dr. Stanton. We will move to our next speaker if that's okay, and Dr. Stanton, I hope you stay with us for further questions, soon I hope. Next is Dr. Reynolds, from the Beth Israel Deaconess. Dr. Reynolds.

DR. REYNOLDS: I thank you for the opportunity to address the panel. Good

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morning. I'm Matt Reynolds, I'm a clinical electrophysiologist for the VA Boston Healthcare System, and also the director of Economics in Quality of Life Assessment Group at the Harvard Clinical Research Institute, and I don't think I have a disclosure slide. I do have, I serve as a consultant for Biosense Webster and also, my research organization has received grant funding from Biosense Webster. I'm here on my own today, however, and my views are my own and I paid my own freight today. I'm going to focus my comments on two outcomes that I personally believe are of particular importance for testing the value of a proposed technique, particularly from a payer perspective, and those two outcomes are hospitalization and quality of life. To start with hospitalization, numerous studies have shown that hospital care accounts for over 50 percent of the direct medical costs of treating atrial fibrillation. Using data from the FRACTAL registry, we recently showed that hospital care not only is the largest single component of medical costs in AF, but also the most variable. And as you

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might expect, hospital costs increase in an almost linear fashion with the number of documented recurrences that an atrial fibrillation patient has over time. The implication of this finding is that better rhythm control therapies might be expected to reduce hospital costs over time.

What we know so far about AF ablation is that it actually does appear to do a better job of keeping people out of the hospital than contemporary antiarrhythmia drugs.

This recently released meta-analysis from independent investigators at Duke pooled the results of three randomized trials with an endpoint of hospital admission, and this was recently published online. The Duke investigators reported a pooled rate ratio of 0.1 and an 85 percent reduction in favor of ablation. Now this finding also differs substantially from that reported in the AHRQ document, mainly because the Tufts team omitted the randomized trial from Pappone and colleagues in their analysis. Hospital admission data, however, has not been consistently reported in AF ablation studies

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and in my opinion going forward, it ought to be.
I'm going to spend the rest of my time talking about quality of life. To start out with, it is well established that quality of life is reduced in a great majority of atrial fibrillation. These are results from four different studies. At baseline, the AFFIRM study provides a registry for cumulative data in an AF ablation series, and in all cases you see the baseline at 12, and SF-36 summary scores for both mental and physical health were well below age-adjusted population norms as shown by the vertical lines.
I would argue that in 2009, quality of life is the most important endpoint of AF ablation studies after safety and rhythm control. This is the main reason we do these procedures in clinical practice, we do them to alleviate symptoms and to make patients feel better, and hopefully return their scores up closer to the normal level.
Now I am aware that neither the MedCAC nor CMS in general are charged with evaluating cost effectiveness data. However, I'm going to

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show you a little bit in order to highlight how crucial quality of life results are in judging the current economic value of AF ablation. Shown here is a cost effectiveness acceptability curve from a model done last year as part of the health technology assessment of AF ablation in the U.K. The model compared AF ablation and amiodarone over a five-year period. It assumed a slight benefit before ablation in reduction of stroke. The base case result in the model was a cost effectiveness ratio of approximately 25,000 pounds per quality of life year, and that's a little bit higher if the reduction in stroke prevention is removed.

But what I want to draw your attention to are comments made following a sensitivity analysis done by the investigators, and what they concluded is that the cost effectiveness of the procedure is highly dependent on a few things including, number one, prognostic benefits associated with normal sinus rhythm; and number two, the magnitude of any quality of life difference between catheterization and drugs.

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I recently published my own cost effectiveness model for AF ablation, and my results were actually highly concordant with those of the Nice investigators. This so-called tornado plot shows results from the study's sensitivity analyses, and again, I want to draw your attention to the fact that the widest bar at the top of the tornado here is the endpoint of quality of life or utility following successful ablation treatment, so the model is more sensitive to this parameter than any other single parameter. Again, the overall base case results in my model show just over $50,000 per quality adjusted life year.

What do we know about quality of life following catheter ablation for AF today? Actually, I would argue that we know quite a bit, and again, I think the Tufts technology assessment did not review any of this data. This is seven different observational series of AF ablation and the size of these studies range from 30 patients to over 500, and the results were remarkably strong and remarkably consistent, and that's why we're doing AF ablation in our patients. In every one of

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these studies, at least six of the eight test scales of the SF-36 were improved. The only scale that did not significantly improve across these studies was bodily pain, which is not a major manifestation of AF.

If you look at this effect size column, these effect sizes are very very large. They ranged from 20 up to 70 points on a 100-point scale, or expressed differently, between 0.5 and one standard deviation units. In the quality of life literature, a change from 0.2 to 0.3 standard deviation units is considered clinically meaningful. These changes are two to three times that threshold, and you cannot show me any data from any antiarrhythmic drug study or any rate control study that even approaches this magnitude in improvement. Again, these are some data from our center in Boston that show the same thing.

The one thing that I want to highlight here, the SF-36 scores six months and 12 months after ablation are in the neighborhood of 50. That's normal for the population. The increases were similar in magnitude whether it was paroxysmal or persistent atrial

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fibrillation. There have been four randomized studies comparing catheter ablation to alternative therapies. You can add a fifth, which is the study that Dr. Wilber told you about this morning. There are mutations of this data, but in every case the quality of life was superior with catheter ablation than with the alternative treatments.

DR. C. GOODMAN: Any closing comments?

DR. REYNOLDS: Closing comments. It is clear that quality of life is impaired, strong evidence indicated that quality of life is impaired in the majority of patients with AF, and therefore I think this is a critically important endpoint for any AF study. Catheterization clearly improves patients' quality of life with very large effect sizes in observational studies, returning scores to reference population norms. Multiple randomized trials have consistently shown greater improvement in quality of life following ablation than alternative therapy. These trials do have an important place in the topics you are discussing this afternoon.

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Thank you.
DR. C. GOODMAN: Thank you very much, Dr. Reynolds. Next is Dr. Bradley Knight, from the American College of Cardiology.
DR. KNIGHT: I would like to thank the panel for the opportunity to present on behalf of the American College of Cardiology. My name is Brad Knight, I am a practicing electrophysiologist at the University of Chicago. I have some relationships with industry in that I receive grants for research, fellowship support, and speaking honoraria from several different companies that make devices to treat atrial fibrillation.
I am presenting today for the American College of Cardiology, which represents a large number of talented cardiologists. I wanted to make a point related to the referral path that patients take before undergoing cath ablation. Many patients who undergo ablation for atrial fibrillation have been referred from their internist to their cardiologist to their electrophysiologist.
This referral path is important because it, for at least two reasons. One, I

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think it represents a real world support for the therapy. Many of these patients are referred from cardiologists outside their groups with electrophysiologists, and I think it's an indicator of the support in the real world for safety and efficacy of the procedure. And second, it provides an additional screening tool for the identification of appropriate patients for this procedure.

I'm going to present about 12 slides to try to reinforce three points. One is that atrial fibrillation can be debilitating for many patients based on the symptoms that they have. Number two, that there are important limitations of currently available medical therapies for treating atrial fibrillation and controlling its symptoms. And number three, that the evidence supports the safety and efficacy of catheter ablation for atrial fibrillation, and that the alternatives would be for these patients, antiarrhythmic medication or cardiac surgery.

As has been shown already this morning, atrial fibrillation affects more than two million Americans. Atrial fibrillation

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patients are at increased long-term risk of stroke, heart failure, all-cause mortality, and as pointed out this morning, there are major limitations to the current drugs that are used to maintain sinus rhythm. Many of the people in this room appreciate the low efficacy, the high incidence of side effects, risk of organ toxicity, risk of proarrhythmia, and the necessary need to hospitalize patients to initiate another drug therapy.

Dronedarone is the first antiarrhythmic drug to be approved by the FDA for the management of atrial fibrillation in ten years. This is not an indicator that the therapies have been inadequate, but more an indication that there are limitations to giving cardiac antiarrhythmic drugs for the treatment of atrial fibrillation. Importantly, this new drug that has finally come to commercial availability comes with a black box warning against use in patients with advanced heart failure, and is probably only half as effective as amiodarone.

There is no dispute that ablation can eliminate atrial fibrillation in some patients

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with frequent, debilitating, drug refractory atrial fibrillation. When we talk about efficacy, and these questions were raised previously, if you're looking at symptom control, there is no dispute that patients who present with paroxysmal atrial fibrillation as shown in this electrocardiogram show frequent bursts of very symptomatic atrial fibrillation, and a catheter ablation procedure can eliminate the atrial fibrillation through many years of follow-up in these patients.

The real issue from our perspective is what percentage of patients does this help and what are the risks involved in the procedure, not whether it can be effective in an individual patient. These are the risks, and this has been discussed previously. Vascular access complications, cardiac tamponade or perforation, thromboembolism or stroke, pulmonary vein stenosis, hemidiaphragmatic paralysis, left atrial esophageal fistula, and rarely, death.

There is important guidance in this society, professional societies, that are related to proficiency by physicians performing

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the procedures. At least two of these guidelines, including invasive EP studies, cath ablation, and cardioversion, are included in the statement that is sponsored by the American College of Cardiology and American Heart Association. It also makes a point, as does the American College of Cardiology, I think there's a general consensus and agreement between these professional organizations with relation to this therapy. In other words, the American College of Cardiology and the Heart Rhythm Society frequently cosponsor guidelines and documents with relation to this topic, and there is general consensus agreed on with its effectiveness.

And Dr. Calkins will be speaking later on a report by a task force on catheter and surgical ablation for treatment of atrial fibrillation, and it addresses the proficiency by the operating physician.

DR. C. GOODMAN: Two minutes, Doctor.

DR. KNIGHT: Catheter ablation is a reasonable second line treatment option to prevent recurrent atrial fibrillation in symptomatic patients with and without

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structural heart disease, and this is based on the ACC/AHA/ESC guidelines. This table has been shown previously and it emphasizes the fact that cath ablation is considered second line therapy in patients with and without structural heart disease. But importantly, many studies have been completed since these guidelines were published in 2006, there will be some additional presentations presented this morning that will discuss data that has been accumulated over the last three years, and I would like to also make the point that the guidelines from the ACC and AHA will have focused guidelines to be published in 2010.

Catheter ablation is performed for atrial fibrillation internationally. The ACC feels that patients who have atrial fibrillation should continue to have access to cath ablation. Without the availability of cath ablation for atrial fibrillation, many patients with drug refractory symptomatic atrial fibrillation will likely be referred for AV junction ablation as was performed previously for atrial fibrillation over ten

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years ago, which is associated with pacemaker implantation and perhaps cardiac surgery. AV junction ablation does not eliminate atrial fibrillation and often results in pacemaker dependence. Thank you.

DR. C. GOODMAN: Thank you very much, Dr. Knight, we hope you will stay for further questions and discussion. Next is Dr. Marcia Yaross from Biosense Webster.

DR. YAROSS: Good morning, and thank you for the opportunity to present to the panel this morning. My name is Marcia Yaross. I am employed at Biosense Webster, the company that manufactures the Thermocool ablation catheter, which was the first catheter approved by the FDA for atrial fibrillation indications.

This morning I will present evidence on the benefits and risks of catheter ablation for the treatment of AFib, with a focus on information that supplements the AHRQ assessment presented by Drs. Garlitski and Ip, as it relates to Medicare-aged patients.

Biosense Webster provides support for AF clinical research. The Thermocool study that led to our recent FDA approval was just

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discussed by Dr. Wilber, so I will skip this in the interest of time.

In the primary analysis on the left, catheter ablation subjects were more than four times more likely to be free from symptomatic AF recurrence. And in addition on the right, freedom from atrial tachycardia beyond a standardized norm was analyzed as recommended by the HRS consensus document in the catheter ablation group.

Comparative safety results were excellent. The incidence of recurrent events was lower in the ablation group than in the drug treatment group for all analyzed adverse events in this carefully monitored data set.

Quality of life was improved and ablation patients improved over the baseline SF-36 scores from significantly below to at or above the population norms. These results were well preserved throughout follow-up. No comparable improvement was seen in the drug treated group. Equally dramatic differences were reported between the two groups for AF symptom frequency and severity.

I would now like to look at the

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meta-analyses as published in the literature. This slide was a recent meta-analysis in a tech assessment that independently reached common conclusions. They all reported higher efficacy with lower complications with catheter ablation versus drugs, though with some differences across subcategories of AF patients. Details of this are part of your packets. Please note that there is overlap in the studies included in this meta-analysis.

The literature also provides substantial evidence of improved quality of life as assessed by the SF-36 for patients after catheter ablation, and Dr. Reynolds just spoke about this. Details are available in the packet as well.

One of the reasons, of course, that we're here today is because of the prevalence of AF in Medicare beneficiaries. While the mean age in some of these studies was 55, as just discussed already, there's accumulating evidence that the results seen in somewhat younger populations also apply to those aged 65 and older. Details of those studies and presentations are provided in our packet.

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While most are observational, they represent a large sample size and report outcomes in the Medicare aged population that are highly consistent with those from the randomized trials, and provide substantial evidence supporting the reasonableness of catheter ablation in appropriately selected Medicare patients.

Consistency of outcomes across age groups was also observed in our own study. Nearly one in four of the study subjects was 65 or older, and age was not a significant indicator for either safety or effectiveness of outcomes.

For presentation at this meeting we have stratified the results by age groups. Patients undergoing ablation who were 65 and older actually experienced slightly fewer primary adverse events compared to younger patients, although the study was not adequately powered to draw statistical conclusions for this subgroup analysis. Efficacy results were also consistent between the older and younger patients. The Kaplan-Meier curves on the left show suspected endpoints in the RF and therapy

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groups in only subjects age 65 or older. You can see the robust treatment effect favoring catheter ablation versus antiarrhythmic drugs in preventing symptomatic AF recurrence. The upper right curve compares freedom from atrial tachyarrhythmia between drug and ablation groups, and again, there is a comparable treatment effect which, again, favors the ablation group. Finally, the lower right-hand graph directly compares recurrent atrial tachyarrhythmias between ablation and drug for those less than, or aged 65 and over, and again, no difference was seen.

DR. C. GOODMAN: About two minutes.

DR. YAROSS: We similarly reanalyzed the quality of life results by age. The manifest improvement in SF-36 scores were comparable between older and all ablation patients, and the improvement was maintained throughout follow-up. Reductions in AF symptoms were also looked at in the older ablation subject alone compared to the whole ablation cohort.

I believe these supplemental results

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form an evidence base for catheter ablation for AFib. The evidence is growing rapidly. These graphs summarize recent searches on catheter ablation for atrial fibrillation on PubMed and clinicaltrials.gov, listing open and developing studies with nearly 13,000 patients from under 18 to 90 years of age, so this evidence base can be expected to expand over the next few years. The NIH, as discussed by Dr. Rosenberg, as well as some commercial entities, are investing substantially to build on the established studies. This slide lists a sample of studies currently funded either wholly or in part by Biosense Webster, some of which will include follow-up for two to five years.

In conclusion, there is substantial evidence that supports the health benefits of catheter ablation as compared to drug therapy as a reasonable choice for atrial fibrillation in appropriately selected patients, and included in those aged 65 or older. This evidence was reflected in the ACC treatment guidelines and the HRS consensus statement, both indicating catheter ablation as

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second-line therapy for treatment of atrial fibrillation.

We expect current research to further strengthen the evidence base, thereby helping clinicians and their patients make the best choice. I thank you for your attention and I will be happy to take questions when appropriate.

DR. C. GOODMAN: We will have a few questions in the next session.

Next is Dr. Hugh Calkins, from Johns Hopkins Medical Institutions, for the Heart Rhythm Society.

DR. CALKINS: Good morning. First, I would like to introduce myself as Hugh Calkins, and I'm a professor of medicine and electrophysiology at Johns Hopkins, so I didn't travel very far this morning. I'm here today representing the Heart Rhythm Society. As far as disclosures are concerned, I've been a consultant with Ablation Frontiers, Biosense Webster, and have participated in many multicenter clinical trials on cath ablation sponsored by Ablation Frontiers, Biosense Webster, ProRhythm and Bowers Medical.

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Now I just want to, before I begin my remarks I will state that I was hoping that we would have 30 minutes to present the Heart Rhythm Society's perspective on atrial fibrillation, but fair is fair and we ended up with six minutes. And I have about 40 slides, and I'm going to skip through virtually all of them and try to highlight what's important to the Heart Rhythm Society when we consider cath ablation.

Just to remind you, the Heart Rhythm Society is a large organization that represents electrophysiologists and other members of the health care community that treat patients with cardiac arrhythmias such as atrial fibrillation, which I think is one of our most important focuses at this time.

I'm going to cover a few things, and again, I will move very rapidly. First, we have our consensus document on atrial fibrillation ablation which was published in 2007, and this was a state-of-the-art review of the field, and we were charged with looking at indications, procedures and techniques, and the outcomes, and we also took the opportunity to

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try to assess standards for clinical trials in the future. As was brought out in earlier talks today, the clinical trials in the past have been somewhat variable as far as duration of follow-up, definition of success, reporting of outcomes, and we worked to try to standardize those aspects of the trials.

Let me just, a few points worth mentioning. First is when the panel convened to review catheter ablation for atrial fibrillation, we concluded that the appropriate indication for catheter ablation for AFib was a second-line therapy in most patients with symptomatic AFib who failed one or more drugs.

We did also state that in some patients, but rarely, it is appropriate as first-line therapy. And also in patients with heart failure, there are selected patients with heart failure where a catheter ablation procedure would be appropriate.

In terms of the techniques of AF ablation, we identified the pulmonary vein ablation as the cornerstone of the procedure, the most important thing that we want to accomplish. There's an objective technique for

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lines and cafes that are removed in variable studies but the essence is the electrical isolation of the pulmonary veins.

Now I'm going to skip over all the clinical trial aspects. Of course Doug Packer was very important in writing all of these and played an important role in his design of the CABANA study, which I think will be one of the most important studies going forward in looking at the issue about AFib and AFib ablation, and the heart outcomes that we found out today such as stroke risk and so forth. I think the CABANA trial is very promising on that.

Just a few more comments on the data. This is a meta-analysis that was done a number of years ago looking at four prospective randomized clinical trials on cath ablation and atrial fibrillation. And the point I think, that you've seen again and again today, is cath ablations are about threefold more effective than antiarrhythmic drugs in preventing recurrent symptomatic atrial fibrillation.

Since this meta-analysis was done, there is a more recent study done by Jais and colleagues, the A4 Study, and again they had patients with

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AFib randomized to cath ablation or drugs. They allowed two ablation procedures in the period, but at the end of the day, 89 percent successful ablation, 23 percent with drugs, and there was a very low complication rate. And then finally, I recently had the chance to work with a group to put together two meta-analyses of the world's literature on cath ablation and antiarrhythmia drug therapy to sort of look at the body of data and figure out what it tells us. Each of the panel members should have had a copy of this provided to them, but I just want to highlight the overall results which are shown in this slide. It basically raises the same points, the antiarrhythmic drug therapy is successful in about 52 percent of the patients. If you look at catheter ablation, the single procedure off drugs is 57 percent. Multiple procedures with cath off drugs, 71 percent. Multiple procedure success on or off drugs, 77 percent. And then I just want to make a few comments, you know, in closing, that what I think is important to consider is not only the huge body of literature, not all of which is

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perfect, but all this literature that we have to date shows that cath ablation works. All of the randomized studies have shown in favor of cath ablation. But one of the important things are the long lines of patients waiting at every one of our centers to have the procedure, I had to cancel a case today, to have this procedure done. And it's now, I think, the most common ablation procedure worldwide, patients benefit from it tremendously, the waiting lines are long, and I think the Heart Rhythm Society feels strongly that we want continued access to this procedure.

I also want to remind the panel that the body of literature is substantial, but it's growing fast and the questions that were brought up about long-term follow-up, the elderly, persistent AFib, there are multiple studies ongoing or recently published addressing these topics, so I think the field is evolving.

I thank you very much for the chance to be here.

DR. C. GOODMAN: Thank you very much, Dr. Calkins.

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I believe those were our six scheduled presenters, correct? If I could ask the six presenters to please come to the front of the room, we might have some questions.
(Discussion concerning audiovisual.)
So, we've had our presentations from our six splendid experts, and they were only seven minutes long and we were, there were no signups for the open speaker section, so we have more of that time to talk with our seven scheduled speakers, and I know that a lot of us have some questions.
I just wonder if the panel would consider the following. As you know, prior to our voting questions, we have several discussion questions and you will find that on your voting sheet, and it may be useful for us while we have questions for our six presenters if we might try to consider those.
I see four main areas of discussion questions and those were, if you recall, with regard to clinical comparators, population, outcomes, and device characteristics and physician training was that last category. So while we don't have to limit our discussion

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with our presenters to those four main categories, it would probably help us in our subsequent deliberations. Okay. Dr. Packer is first up, and if you can direct your questions to one of our six presenters, that would be good. If not, you can just state them generally. And I also ask, sorry for all the logistics, but if you're going to respond to one of the questions, if you could come to the microphone before speaking, that way we will make sure that our court reporter knows who you are and that we can hear what you've got to say. Dr. Packer. Well, Dr. Yaross, why don't you come back to the front row, because we will get to that. Thank you very much. Dr. Packer.

DR. PACKER: So, I have some outcomes questions for Dave Wilber. One of the problems with this is that all of this has been inherently rushed. Could you go back and tell us a little bit more about the downside of the study? It looked like there was a five percent risk of complications. Could you please state what were they, and what was the outcome, were these universally lethal or what was the issue,

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and then I have a follow-up question about the efficacy side.
DR. C. GOODMAN: Please speak directly into the microphone every time. Thank you.
DR. WILBER: Dave Wilber from Loyola. There were five complications that were from a list, a prespecified list, and you've all heard about what that list is, it includes stroke, death, tamponade. And actually the study had none of those serious complications. The complications were one patient who had a pericardial effusion that was asymptomatic and not treated. There was one patient with heart failure, one patient had vascular access complication that was treated conservatively, did not require a transfusion. So most of the complications were, although potentially serious, resolved without sequelae. And so that in fact, the danger of complications, perhaps the highest morbidity outcomes, is a small patient group. I think this is also remarkably reflected in the quality of life analysis that was shown.
DR. C. GOODMAN: Thank you.
DR. PACKER: Following up on the

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efficacy side, and that is, is there a discordance in the data between the quality of life and actual recurrence rates? Because your recurrence rate was down on the order of 64 percent, which seems low compared to most other studies, and yet the quality of life issues were different. Can you address that specifically?

DR. WILBER: I think for one, the major reason is what was pointed out previously, that lack of recurrence doesn't necessarily impact quality of life, and while it's the easiest one to measure, it's certainly not the most important one, and we're all struggling to measure improvements. Quality of life perfectly reflects that, and so in a patient that even had a single occurrence may have had little if any effect on quality of life.

DR. C. GOODMAN: Good, thank you. Dr. Yaross, was there a response to that question?

DR. YAROSS: Yeah, to Dr. Packer's question. Actually in that trial, that reflected a lot of protocol compliance issues

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as well as recurrence, so of that 23 percent of the subjects in the trial, it's not necessarily true that they actually failed due to recurrence.

DR. C. GOODMAN: Thank you. I believe Dr. Carlson is next.

DR. CARLSON: This is a question for David as well. You had a very large number of patients screened versus those that were actually entered into the trial. How reflective is that of other trials and what are the implications of that for the Medicare population?

DR. WILBER: That's an excellent question. I think for many of the trials, we actually didn't see that process from initial solicitation. And to be straightforward, a substantial number of patients screened simply didn't meet the inclusion and exclusion criteria because of the fact that the patient had to have a certain frequency of AF or have persistent atrial fibrillation, so the vast majority of the 5,000 screened, roughly 4,500 were really because they didn't meet exclusion and inclusion criteria.

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But the important thing is that once you get to the patients who were eligible, 80 percent of the eligible patients refused, and so only 20 percent of those eligible actually received the randomization, and that obviously would have some significant implications, and it reflects in some cases as a second line therapy.

One of the comments made by one of the other speakers was that patients are often strong advocates, as are other physicians, for catheter ablation. So once something's failed one or more antiarrhythmic drugs, they become much more reluctant to have further drug therapy as one of the options. And so I think perhaps the really good adjustment that was done by CABANA was to emphasize that we want to enter patients who are relatively early in therapy.

DR. C. GOODMAN: Thank you.

Dr. Maisel was next.

DR. MAISEL: I had a question for Dr. Reynolds. You characterized the quality of life issue (inaudible) with relation to quality of life issues, and I think it's going to be

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very interesting to show (inaudible) hospitalizations. You put up a slide that showed, that primarily relied on the SF-36 for assessing quality of life in these patients. Can you comment on how validated that is in the population? You also showed some data regarding the reduction of quality of life, or improvement rather, based on a point scale. Could you maybe tell us how that point scale correlates with how the patients actually feel?

DR. REYNOLDS: The SF-36 is not widely validated specifically for atrial fibrillation. It is the most widely validated quality of life measure for a wide variety of medical conditions, so it's a generic quality of life tool. It is relevant in that there is normally data for the population, and again, SF-36 has been used to measure treatment effects upon its particular scales. So that, to that extent it's a useful measure. It's not an ideal measure for the AF population. In fact there is no, in my opinion, ideal quality of life measure specifically stratified for AF. A lot of studies also use a symptom checklist which

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is helpful, it can give you useful measures, symptom frequency and symptom severity in a lot of trials that used it. There is at least one I know of, a disease-specific quality of life questionnaire that's in development for AF but it's not available for use in trials yet.

In terms of your second question, so what are the scales we use, historically, yes, the SF-36 had eight individual scales that range from zero to a hundred, so the higher the score the better. Again, I think the easiest way to sort of pull it out is to use a standard deviation, so the standard deviations on most of those hundred-point scales are in the range of 20, some a little more, some a little less. So again, in the observational studies and actually the randomized trials, the magnitude of the treatment effects most of the time was more than 20 points, 50 points, 70 points. Those sort of changes on the hundred-point SF-36 are two and three standard deviations, so those are really very very large treatment effects.

The SF-36 also has physical component and mental component summary scores, and these

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are normalized for the population. So those scores have a mean of 50 for the population as a whole and the standard deviation of ten for the population as a whole, so again, using that same metric of about 0.2 to 0.3 standard deviation, these changes are really very significant. And again, the SF-36 investigators have shown that changes in that range correlate with hospitalization in the Medicare population and they correlate with mortality. And again, across all the observational studies and across multiple randomized trials, the changes on the mental and physical component scores have been five points, six points, eight points, which is again, 0.5 to 0.8.

DR. C. GOODMAN: Dr. Maisel, are you satisfied that -- Dr. Reynolds made during his presentation a strong case that quality of life is an important outcome, perhaps the most important outcome. Are you satisfied that he has explained to you whether or not there is a very significant valid measure for that most important outcome?

DR. MAISEL: I agree with Dr. Reynolds

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that quality of life is an important outcome, and if we had nothing else, we would still have that as a very valid reason for providing the patient with the treatment. I think the SF-36 is the best available tool that we have. Could I imagine a better tool? I could imagine a better tool, but I'm satisfied that it accurately reflects quality of life in this publication.

DR. C. GOODMAN: Thank you. Dr. Calega.

DR. CALEGA: Just a question about the patient selection, for the first speaker. You said that patients over the age of 18 were included in the study, but what was the median age, what was the age range, and did it go beyond 70 for elderly patients?

DR. WILBER: The mean range was, I think was in the slides and was in the upper 50s. There were patients in the over-65 age group. And actually, the second study that you saw from Dr. Yaross is the same database, so they were divided between the two, so you basically see that the outcomes were no different for the Medicare population. So to

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answer your question, yes, the mean was low, but Medicare aged patients were about 20 to 30 percent.

DR. C. GOODMAN: Dr. Satya-Murti.

DR. SATYA-MURTI: As a non-cardiologist, I was making notes comparing speakers here, their conclusions and that of the TA. The TA refers to absence of concurrence of the abnormal group, but the speakers have emphasized not only that, but also the symptomatic relief, a key component that was not prominent in the TA's conclusions. And then the quality of life in all these papers not being included, and the age difference. So was the TA, then, making those conclusions based on the strength of evidence, or are you all relying on a more, a weaker basis of strength of evidence? Why is there this discrepancy?

As a non-cardiologist but as a neurologist who is used to refractory seizures and convulsion failures, so I'm trying to see, where is the difference coming from? And after you, perhaps the TA, maybe they can respond to this too.

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DR. CALKINS: It's interesting that the endpoint of clinical trials, the most common endpoint of most clinical trials in AF is freedom from recurrence of symptomatic atrial fibrillation, so the other issue that was raised earlier about what about asymptomatic atrial fibrillation, because you can have someone who is free of any symptoms from AFib can still have clinical evidence of an episode of AFib.

So the main endpoint of really the entire area is symptomatic recurrences of atrial fibrillation. I think the only set looking at total recurrences of atrial fibrillation, symptomatic or not, is the data from the Thermocool study where they analyzed the data and they were actually monitoring, you know, and looking at that. But I think the reason the procedures were performed is to prevent symptomatic atrial fibrillation and the indication for the procedure is, you know, symptomatic AFib after failing one or more drugs, so really symptoms and the occurrence of symptomatic AFib is the main thing we're concerned about.

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DR. C. GOODMAN: Thank you. Do Dr. Ip or Garlitski want to make a comment in regard to that?
DR. IP: We have mentioned it very basically. We just looked at the rate of recurrence without breaking out symptomatic or asymptomatic, we put them all together in the same house. So when we make a conclusion, we just say rate of recurrence, we don't qualify it as symptomatic or asymptomatic.
DR. SATYA-MURTI: But if symptoms were a prerequisite to come to a conclusion, then would a second look of the symptoms, taking symptoms also as a factor, would come a similar conclusion, or would that be different?
DR. IP: I wouldn't know that without looking at it in that fashion.
DR. C. GOODMAN: Thank you.
Dr. Dullum is next.
DR. DULLUM: I wrote myself a note when Dr. Rosenberg was up there about comparators, and being I guess the lone surgeon of the group, I was wondering why that was never included in any of those studies, maybe because of whichever company was doing their

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device study, this might be better for NIH, but I still have a concern that the data is not all that crystal clear to me of the benefit of ablation, because there are different techniques that are used, and I apologize, I forgot which presenter mentioned about different ablation lines, so there doesn't seem to be a clear lesion set yet in catheter ablation that everybody is following and I haven't seen one that says yes, you must do this line only, so it seems like comparing apples to oranges.

And also for the drug treatment, when they're free of drug therapy at the end of 12 months, is that all the cardiac drug therapy or are people still on beta blockers? What we define as antiarrhythmic is still, at least to me is still fairly muddy based on this evidence.

DR. C. GOODMAN: Dr. Calkins, I guess my first question is, do you have a concise response to that?

DR. CALKINS: Yes. Concerning the technique, you know, there is the consensus document, and the world of electrophysiologists

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and also cardiac surgeons recognize that electrical isolation of the pulmonary vein is the most important vein certainly in the case of surgery, so what the surgeons mainly are doing are isolating those veins. Now there are additional lines or what's called CAFE ablation and there's more data about how much incremental effectiveness that has, but if you were to ask every electrophysiologist, and I bet every cardiac surgeon who is doing these procedures, are you trying to ablate the pulmonary vein, the answer is absolutely yes, because that's the cornerstone of the procedure, and our consensus document was also written in conjunction with the Society For Thoracic Surgery, and several area surgeons were members of that committee, so I think there's more unanimity, I think there really is a consensus as to the procedure. There are some variances, but we all agree with what the guts and sort of the core is.

As far as the drugs during follow-up, all these refer to antiarrhythmic drugs class I or III, and not beta blockers or calcium blockers, or other type patients.

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DR. C. GOODMAN: Thank you, Dr. Calkins. Dr. Yaross, this is the question about your slide. This is the slide referring to patients aged 65 and older, so what I hope you can clarify is this. In your conclusions you say that the evidence supports consistent treatment effect in patients of 65 years of age, and I think I know what the word consistent means. When I look at the slide where the data have been sort of clustered under the age 65 and older population, when I look at the efficacy results on the right-hand side, that is highly populated with the statement no significant difference, and there's only like an instance or two where there's something other than no significant difference. Since we're so very concerned about this population of course, and trying to kind of extract that from the broader population, what actually are you concluding about that group, if most of the findings are no significant difference, what can we conclude?

DR. YAROSS: What I should point out

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here is, this is no significant difference across the age groups, so between the age strata in each study. There certainly were differences between, and remember, these were observational studies, these were not against comparator therapy but across the age strata. So in most of these studies, they are either a prospective or retrospective assessment of the effectiveness of the therapy of catheter ablation between younger and older subjects.

DR. C. GOODMAN: So when it comes to the question of the external validity of the data to the Medicare population in particular, one might infer or conclude from your slide that if it works in the broader population it works in the Medicare population, if it doesn't work in the broader population it doesn't work in the Medicare population? What's the proper thing to conclude about that?

DR. YAROSS: What we conclude is that the body of evidence showing reasonable effectiveness and reasonable safety in the general population with a mean of about 55 is equally applicable to the older population, because in these studies where they compared

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results between younger patients and the older patients, there was no difference between those age strata in the effectiveness of the safety or outcomes, with some small differences seen in one or two, but the consensus are, the takeaway that we got from our analysis, and these I believe were provided to you as a Table 5 in what we gave you, was that across those age strata, the effectiveness was consistent.

DR. C. GOODMAN: So the consistency has to do with age strata?

DR. YAROSS: Yes.

DR. C. GOODMAN: And what was consistent across those were largely the outcomes of sinus rhythm management, correct?

DR. YAROSS: Yes, sinus rhythm when looking at basically reduction in occurrence -- well, it was not comparative, but maintenance of sinus rhythm and safety.

DR. C. GOODMAN: Thank you very much. Dr. Calega.

DR. CALEGA: Just as a follow-up, the next two slides that you presented commented about the small sample size over 65, and that the study was not powered to draw statistical

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conclusions. Could you comment on that?
DR. YAROSS: Sure. These next slides were a post hoc stratification of the Thermocool study that Dr. Wilber presented, and in this study 22 percent of the subjects were 65 years or older, so we stratified that to see if we could shed some light on this question, and when we did that we saw that, again, freedom from any atrial tachyarrhythmia, as shown in the lower right-hand corner, was equivalent. And if you look at the top graph, it shows the difference in just the 65 and older population between drug-treated and ablation-treated patients.
DR. C. GOODMAN: Follow-up, Dr. Calega?
DR. CALEGA: I understand what you're presenting, but I'm still stuck on the fact that you've got a very small sample size, and can you really say statistically?
DR. YAROSS: We're not trying to make a statistical conclusion, simply to shed some light on this question where we stratified the data.
DR. C. GOODMAN: Thank you for that

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clarification, I know I find that helpful, and our audiovisual person can take down the slide projector. Thank you for that. Ms. Atkinson?

MS. ATKINSON: The only question I have, and it can be anyone on the panel or the speakers, but just for clarification, can I have a clearer definition of what we mean when we say failed drug therapy?

DR. C. GOODMAN: Dr. Calkins has risen to the challenge.

DR. CALKINS: Failed drug therapy means that the patient is placed on an antiarrhythmic drug class I or III agent and it either is ineffective, meaning symptomatic AFib occurs, or it's poorly tolerated and the patient has bad side effects and wants to stop the drug, so that's what we mean by refractory. Or if you look at -- you say what are the indications for catheter ablation for atrial fibrillation according to the American Heart Association or Heart Rhythm Society, and it's symptomatic atrial fibrillation which is refractory to one class I or III antiarrhythmic drug, and refractory means you try the drug, it's not tolerated, or ineffective.

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MS. ATKINSON: But for further clarification, are you saying failed one drug or are we saying failed two drugs?
DR. CALKINS: It's now one or more antiarrhythmic drugs. So if we say in clinical practice, what do patients do, the way I present it to them is here's the list of procedures, here's the efficacy of the procedure, you know, you can either have the procedure or we can try the drug first. If that fails, you know, the options are, you know, you can either try another drug or you get the cath ablation procedure. And patients fall into two groups in my experience. Some patients hate drugs, the procedure doesn't bother them at all, they say let's do the procedure tomorrow, and other patients are just the opposite, and I think it really comes down to patient preference where the threshold is whether they decide to have the cath ablation procedure done.
DR. C. GOODMAN: Thank you.
Dr. Hammill.
DR. HAMMILL: This is probably for Dr. Wilber and Dr. Calkins. We're attempting,

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putting together with the FDA a national AFib ablation registry, and one of the issues we're struggling with is defining freedom from atrial fibrillation 12 months out or longer, and what kind of monitoring is done. I would appreciate it if Dr. Wilber would give me more detail on the type of monitoring that was done in his study, and then if Dr. Calkins could give me an idea of what Heart Rhythm Society guidelines are with regard to the type of monitoring that should be done and how it affects the interpretation of these different studies.

DR. WILBER: The monitoring was really a compromise between what was practicable, and I think that's always the case unfortunately. I think Hugh might mention a study they did some time ago where they tried to get the patients to call in on a daily basis, very frequently, or wear a monitor frankly for months at a time, which is the only way truly to record AFib burden. So at some point you have to have a practical compromise between what people are willing to do for an extended period of time. So they basically got an event monitor for a year; anytime they were

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symptomatic they were to use it and transmit, and then there were scheduled transmissions. The schedule was weekly for the first two months and then monthly thereafter, one could have more or less in some studies, and this was the compromise for detecting asymptomatic AFib in that population. But also, I think it's very important to have a monitor available for any symptoms and interestingly, a significant amount of the symptoms people have aren't attributed to fibrillation, and so it works both ways in terms of documentation, and obviously that's important to the trial.

DR. HAMMILL: And for the periodic monitoring, was it with a Holter type monitor?

DR. WILBER: It helps with periodic monitoring, again, for a very short period of time, which prevents a patient visit, and in this study it was really just at the end of the study, one could possibly use a 24-hour Holter monitor to give just a short snapshot of a time period, but it's hard to know how that represents, so we tended to do less of that in this study. And that has varied from study to

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study, again, for detecting asymptomatic atrial fibrillation.

DR. C. GOODMAN: Thank you. Dr. Calkins, did you have something to add?

DR. CALKINS: Yes. In the Heart Rhythm Society consensus document we made several fairly stringent recommendations. One was that all clinical trials should provide follow-up data for 12 months minimum, and that's the mean follow-up we see in these studies, but every patient should follow up at least 12 months. We also set a very high bar for success where we said that success should be the freedom of symptomatic or asymptomatic atrial fibrillation or atrial flutter lasting 30 seconds or more, and that we want this data presented in all patients.

Now the question that you bring up is if you say asymptomatic AFib, then how long are you going to look and how are you going to look, and then it comes down to the realities of what is a patient willing to do. The more you look, the more you will see. In the document, we basically said there are a number of different strategies that could be used, you

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could use Holters intermittently, every two months 24-hour Holters. You could do it continuously with event monitors, you could go every three weeks, you could do standard event monitors. So that is sort of a gray area and obviously one of the challenges of these studies is to decide what they're going to do. And I think Doug Packer in the CABANA study has set a new high level for the intensity of monitoring with monthly Holters, every three-month table reviews, and daily event monitors, so that CABANA is going to be the most highly monitored study ever, probably the most expensive study ever, and how their compliance will be we're going to find out, but all great questions.

DR. C. GOODMAN: Thank you. Let's make this the last question for this session. Dr. Moscucci.

DR. MOSCUCCI: At most in the clinical trials, there were 5,000 patients screened and only a few hundred enrolled. I was wondering, did the study include also a registry, do we know what happened to those 5,000 patients that were excluded?

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Another thing I am wondering, for those patients while they are waiting to be ablated and are continuing to have atrial fibrillation, is there any clinical trial data as to what happens in the real world?

DR. WILBER: I think it's a great question, and unfortunately we did not have the resources to do a registry so we did not do that for the patients that were excluded, or those who were eligible but declined to be enrolled.

DR. C. GOODMAN: Thank you. Dr. Yaross, on this?

DR. YAROSS: What I would like to add is that we are now moving into a post-approval registry that is looking at all those patients, so that we will have some answers to those questions.

DR. C. GOODMAN: Good. We're going to break -- one more question. Dr. Carlson.

DR. CARLSON: Sorry. This is a question for Dr. Reynolds. What does all this monitoring do to quality of life scores, how do you adjust for that?

DR. REYNOLDS: They don't correlate

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very well. That's the short answer.
DR. CARLSON: So do these frequent monitors affect patients' quality of life, does it lower the overall score, or you just don't know?
DR. REYNOLDS: I have no idea. I don't think anyone has asked that question in a scientific way, if the monitoring affects the QoL scores, so I have no idea.
DR. C. GOODMAN: Thank you.
And before we break, Dr. Calkins, I just wanted to mention one thing, because in your talk you referred to the long lines of patients, and you would agree that while a long line of patients does tell us something about demand and certainly patient interest and so forth, it is not any type of evidence about safety or efficacy?
DR. CALKINS: It's clear there's no substitute for prospective randomized clinical trials, and I merely liken it to clinical trials where there is a sham, you know, replacement procedure, whatever, and that would be the ultimate. I know everyone chuckled a little bit in looking at the consensus

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document, and I concluded that this was completely impossible.

The thing that I think is striking, as someone who has been doing these procedures for ten or 15 years, is when you start seeing your colleagues lining up to have you do the procedure on them, and you see the patients in follow-up, yes, you know, it's possible this is all placebo effect, I think extraordinarily unlikely because of the data showing that after catheter ablation, the quality of life is dramatically improved, and I have actually never seen a procedure like this, even when you look worldwide, whether China or Europe or the United States, a procedure this really consistent.

You know, there's demand for this procedure, and ultimately it's patients who are informed about these procedures. It may also be doctors, but nowadays patients are very informed, very critical of things, and it's striking that these patients are, you know, the procedures are making these patients feel better, and they're demanding the procedure.

So it's not something that I think you can

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ignore, but again, scientific data is the best.
DR. C. GOODMAN: I think we agree that scientific data are the best.
DR. CALKINS: Yes.
DR. C. GOODMAN: Well, thank you all very much, a fascinating session. If the panel doesn't mind, and our presenters don't mind, when we reconvene following lunch at 12:35, if our six presenters could return to these seats to make sure that we have sufficient time to have our further discussion on the discussion issues, we will proceed from there.
I understand that even though CMS is kind of in a closed down mode, the cafeteria is still open, and we will return to reconvene at 12:35. Thank you all very very much.
(Recess.)
DR. C. GOODMAN: We've asked our six guest presenters, our two TA presenters and our presenter from NIH also to come to the front, and what we would like to do for this next hour or so is to focus specifically on those four discussion areas that we mentioned right before the lunch break, and if you don't mind, if we could just actually try to go through those

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four other areas in order, and certainly some of those will overlap. I just remind you of the four discussion questions which precede the voting questions, again, clinical comparators, population, outcomes, device characteristics and physician training. Let's have that discussion to the extent possible for the next hour, then we'll shift into the voting questions themselves. These are background discussions on those all to kind of prepare for the voting.

We will plan on, or anticipate that this meeting will go to the time, originally scheduled time of adjournment, which I understand to be 4:30. And since we're going to make that assumption, we will plan a ten-minute break halfway through the afternoon, which I know comes to a great relief to our court reporter among others, but if it looks like we're on an accelerated path, we might do without the break, but let's anticipate this is going to go pretty close to 4:30. Okay.

With that, we will turn to the discussion questions, clinical comparators, and I know that before the break Dr. Dullum made a

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statement about the role of surgeons and so forth. Do our panel members have any questions for our presenters with regard to the incorporated clinical comparators? And just to remind you, we're looking at the Medicare program here, what is important for Medicare beneficiaries with regard to clinical comparators, we care about that population, we care about what works in practice, comparison to actual alternatives. Dr. Umscheid, you can start.

DR. UMSCHEID: This question indirectly gets at that issue, and it's a follow-up to the question Ms. Atkinson asked earlier, and it's really me trying to understand who would get this therapy. So if a patient has AFib and they're treated with beta blocker and anticoagulation and they tolerate that, from what I'm hearing, I'm just wondering, would they be a candidate for that? Or is it only people who didn't tolerate rate control and then went to antiarrhythmias that weren't beta blockers or calcium blockers that would go to this catheterization? Maybe, if I could get a few

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individuals to come up and tell me if that's a correct interpretation or if that interpretation is wrong.

DR. C. GOODMAN: Dr. Wilber.

DR. WILBER: I think I will certainly speak for myself, and I think what the clinical practice is that most of us primarily deal with symptomatic atrial fibrillation, so as all procedures evolved in terms of technique, the efficacy evolved as well. We started with the highly symptomatic patients that had failed multiple drugs. As the procedures become more widespread, more standardized, more effective, and the number of drugs who failed declined. As you can see from the randomized trials, you can see that the vast majority of them had the requirement of failure of at least one antiarrhythmic drug and oftentimes not multiple ones. There are a few trials where in fact the results that you saw represented failure from a traditional class I or class III antiarrhythmic drug, and we think symptoms and drug failure or intolerance are probably the primary indications. And then again, there are patient requests, desires, and I'm a runner, I

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don't want to take drug therapy because I can't perform. So those are all failures, but I think, to summarize, I think this is appropriate. I'm sure others will have their own successes.

DR. C. GOODMAN: Yes, Dr. Reynolds, and again, I would ask that we try to concentrate on comparators as our first area.

DR. REYNOLDS: I think your formulation is reasonable and I think going back to the technology assessment, which you all reviewed beforehand, first-line therapy is a question area, so there is less evidence for first-line therapy than for second-line therapy with respect to control. So there is one trial, randomized trial for first-line therapy, and actually the results are generally in favor of ablation. But in terms of guidelines, it's not there yet because it was a single small trial, and its summary sort of reflects for the most part where we're at today.

DR. GOODMAN: Yes, Dr. Knight.

DR. KNIGHT: So, I think the point you made is very appropriate, that most patients are begun on rate control but as was mentioned

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by Dr. Hammill earlier this morning, the number of 10 percent of patients in the AFFIRM trial who could not tolerate or had to be switched over to rhythm control, that represented a group of patients who were enrolled in that trial who are clearly candidates for both arms. So I think there's many patients who after attempts at rate control, much higher than 10 percent had to move on to a rhythm control strategy.

DR. HAMMILL: And the only reason I brought that question up in this discussion is that one of the questions I was concerned with when I began my review, the tech assessment didn't look at studies that compared ablation to rate control. And we saw the AFFIRM trial, which obviously everybody knows about, and suggested that it was equal, and then the meta-analysis talked about a mortality benefit with rate controls as compared to rhythm control.

DR. C. GOODMAN: How close do you think we are, Dr. Umscheid, to answering the question whether it would be an appropriate clinical comparison to catheter ablation, do we

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have an answer for that yet?
DR. UMSCHEID: It sounds like it's basically a second-line therapy for people who have failed drug therapies, beta blockers, it could be beta blocker, calcium blocker, antiarrhythmic, but people who have failed drug therapy, and if that's the population we're talking about, I think we've defined the population.
DR. C. GOODMAN: Well, defined the population, but the comparator would be those drugs, right?
DR. HAMMILL: It would be, but unless all of the patients in the studies who were on antiarrhythmics on them because they originally failed just a rate control strategy.
DR. C. GOODMAN: Dr. Packer, on that point?
DR. PACKER: If it's appropriate for me to make a comment about comparators without asking a question of the group, I think that, you know, the rate control issue is important, but I think that that's what AFFIRM was about, that's what RACE was about, that's what STAFF was about, that's what AF/CHF was about. And I

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think it's unfortunate that they didn't show any particular mortality benefit when they had arrhythmic drug therapy for sinus rhythm, but the alternative is they didn't really show a deficit. So I think the comparison's there and the meta-analyses that have been done just show that it's not an excess benefit sort of thing. And that's where I was going before about masking potential effect because of the side effects of the drug, and so I think that the question at hand here presupposes that these patients have been through a rate control approach.

If you look at the CABANA pilot and I was going to ask Dave, on your trial, how many patients going into that trial had already done the rate control thing? You know, you have to fail one drug and as things, you know, lightened up, then it turned out to be mostly a rhythm control drug, but I suspect that most, as with the CABANA pilot, had already been on a rate control drug as the initial foray into the treatment for atrial fibrillation.

The other comment I wanted to make is one that addresses the surgical question. As

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far as the comparator goes, you know, should we really be thinking here about a trial between ablating intervention and surgery, so cath ablation versus surgical, and I think that the really simplistic answer to that is we're just not there yet. You know, since we've looked at the consensus document, and we struggled with this in designing CABANA, you can, not only if you're a surgeon but if you're a catheter ablation person, you can say that one or the other is not far enough along to get into a grudge match, you know, with defined endpoints. And so I think at this particular point, you know, the surgical comparator would be one that will undoubtedly emerge, but I see that in kind of a three-to-five-year NIH trial time frame.

DR. C. GOODMAN: So surgical, we're not ready for it for another five years?

DR. PACKER: I don't think that that trial is ready for prime time.

DR. GOODMAN: Okay. And then with regard to rate and rhythm, an appropriate comparator could be rate and/or rhythm, depending upon something? Frame it up for us.

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DR. PACKER: I think what I'm hearing from everyone, and this gives you a little bit of my bias anyway, there's something to be said from a standpoint of quality of life and the recurrence about sinus rhythm. Now, will we demonstrate that there's a mortality benefit, that's for CABANA to decide. In the meantime we've got all of the issues of how patients feel when they present and they've already been tried typically on a rate control drug. So I think the comparator here is to be an appropriate attempt at rhythm control with either method, so what you're doing is really talking about a treatment strategy, should be rhythm control either way. But as part and parcel of that, just reality, the patients are also going to be on rate control, so that's going to be a component.

In CABANA, what we're doing is we're leaving that decision to the investigators, we're letting them choose rate or rhythm. It just turns out that about 90 percent of those in CABANA are on rate, and so that the choice for perceived benefit will improve that, and it goes in the direction of rhythm control drug

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versus ablation. So I think that these clinical trials, the six-plus that have been described, I think are reasonable trials and they got the comparator right.

DR. C. GOODMAN: Okay, thank you. Dr. Dullum, a point on comparators?

DR. DULLUM: Well, you know, the explanation on the surgical is fine for me. The rate control which we're discussing, you know, from the presentations I heard today from the speakers was not looking at that 10 percent who failed advanced drug therapy, which is the population I think I'm really concerned about making a CMS decision, because those are people who are going to have other comorbidities. Are they the ones, then, who are going to be treated already with the drug trials? And what I saw was in one of the trials, 106 patients had atrial fibrillation and 53 had the drug trial, and that doesn't represent 10 percent of the population with AFib.

So if we're looking at your trial, whether it's effective or not, then I guess that's fine, but if we're looking at the

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age-related problems in the CMS population, are we going to be bringing this in and everybody's going to get ablation, or is it just the 10 percent who actually need it? Again, I apologize for my confusion in this, but I'm just trying to make it clear what we are talking about here.

DR. C. GOODMAN: Any response from our speakers? It looks like Dr. Calkins.

DR. CALKINS: Yeah. I think when someone develops atrial fibrillation, particularly someone in the Medicare age, 75, 72, whatever, shows up for a routine physical and it shows atrial fibrillation, and is complete asymptomatic, maybe that patient would be treated with anticoagulation and rate control. But if the patient shows up, you know, complaining of exertional dyspnea, fatigue, whatever, that's the patient where you know, you want to do a rate control strategy and that is drugs or cath ablation. I think Brad's point is well taken. If you take, you know, you have a patient in the Medicare age group with atrial fibrillation, how many will become asymptomatic

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with rate control alone and how many will remain symptomatic and benefit from drug therapy or cath ablation, I'm not aware of the breakdown, but I'm sure it is a lot more than 10 percent, because the AFFIRM study began with candidates with rate control coming in. So I don't know if it's 30 percent or 50 percent, you know, it's a percentage, it's not all, but I think rate control is the initial step, and then if the patients remain symptomatic despite rate control, then there's a response. But at least in my experience, a lot of patients fall into that group, they have fatigue, they have exertional dyspnea, and maybe they should have both.

DR. DULLUM: Do we know that's just from AFib, because these people have other comorbidities too.

DR. CALKINS: Well, you know, typically AFib shows up with quality control, exertional dyspnea, fatigue, you know, and we put them on an antiarrhythmic drug and then they come back saying, man, I feel fantastic. Well, the only thing that has changed is that they got on a drug and had a cardiac inversion.

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So, I think AFib itself results in a lot of symptoms over and above the comorbid conditions.
DR. C. GOODMAN: Thank you.
Dr. Moscucci is next, and then Dr. Satya-Murti.
DR. MOSCUCCI: Perhaps we should rephrase the question and say, instead of rhythm control or rate control, because when I look at these interventions I am just thinking about medical therapy, the intervention is just medical therapy. We saw what happened with the international angioplasty trial, and stop thinking about rate or rhythm control, but just make it medical therapy.
DR. C. GOODMAN: Medical therapy being all encompassing, and the publication would let us understand what they might have failed previously, okay.
DR. MOSCUCCI: Thank you.
DR. GOODMAN: Dr. Satya-Murti, still on comparators.
DR. SATYA-MURTI: The question that is really important from my point of view also, the types of patients I would be seeing in an older general neurology clinic would be those

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in whom to attribute a symptom to an abnormal rhythm is very difficult unless they have clear time defined palpitations. Many of them have other causes, diabetic control might be it, they might have been having an incidental TIA, or a focused incident from another infarct, so the identity of symptoms directly attributable to a rhythm anomaly is very loose in these patients.

DR. WILBER: A couple of issues. It works both ways. We spend a lot of our time with elderly patients trying to decide if their symptoms are due to AFib or not, we try to make our best guess, and sometimes we decide to go ahead and they don't respond or get better. On the other hand, there are patients that we miss that might have felt substantially better had we done something and didn't. So unfortunately, it is a matter of clinical judgment, as you indicate, so what better way to find out than to do a trial where we compare those things. So I would agree, there are some unknowns in the elderly.

The other point I think that's really, it sounds like people are coming around to, is

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that the whole distinction between rate and rhythm control is completely artificial. And one of the issues when you look at the effect is that a substantial number of the rhythm control patients were in atrial fib, and a substantial number of the rate control patients were in fact in sinus rhythm, because we use the same drugs for both.

And speaking to a prior question, in the clinical trial the majority of patients had had prior exposure to a calcium channel blocker, a beta blocker as part of the medical treatment. So it's typically a combination and we actually use rate and rhythm controls together when we treat these patients, so the idea that we can actually separate rate and rhythm control effect, you can't, and all the clinical trials that have been done to this point have really shown that you can't really separate these two.

DR. C. GOODMAN: Thank you for that insight. Dr. Umscheid, I will get back to you in a second, and I ask the Tufts people to think about this as well. Given what we just discussed with regard to how rate and rhythm

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come under medical therapy, what we were talking about with regards to surgery and so forth, how would you now say that the body of available evidence as compiled by Tufts stacks up or matches up against what we've been discussing with regard to appropriate clinical comparators? Is there a good match between the evidence and what we think are the clinical comparators or is there not a good match?

DR. UMSCHEID: Well, I was originally concerned about the issue of rate control, beta blockers, calcium channel blockers, because when I reviewed the description of the studies included in the TA report, and when you look at the control arm and you look at the antiarrhythmic being used, I thought maybe it was a beta blocker or calcium channel blocker, but it looks like for the most part it was antiarrhythmic drugs.

So if, you know, it's the case that patients in these trials have only been exposed to antiarrhythmics like amiodarone, then I am concerned that we are missing the nadir comparator, which is them being exposed to the rate control drugs. But if what the panel

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alluded to is correct, which is that amiodarone may have been the last drug they were exposed to but most of these patients were exposed to beta blockers and calcium channel blockers before the amiodarone, then I am comfortable with the evidence we have. So it all depends, and I don't know who could address that.

DR. C. GOODMAN: Dr. Garlitski.

DR. GARLITSKI: So, the data that we have include patients who used antiarrhythmic agents. We were not able to separate out because the studies simply didn't always report how many of those were in addition on a beta blocker, calcium channel blocker, or any medication for rate control in addition to the antiarrhythmic drug.

Clearly according to ACC guidelines, the patient must have failed, in order to be called second-line therapy, must have failed a medical therapy, most commonly an antiarrhythmic drug. If you look at the ACC guidelines, rate control is also part of that, and it's above catheter ablation. So clinically, one presumes that patients are tried on rate control, rhythm control, and

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catheter ablation as a second-line therapy consistent with what those guidelines are, so that's clinically. What we could simply assess is what data stated, what was reported, and it did not separate out how many of those patients were on blocking agents.

DR. C. GOODMAN: Thank you, Dr. Garlitski. Dr. Carlson is next.

DR. CARLSON: I wanted to go briefly on what David Wilber mentioned, and it was the futility of the distinction between rate control and rhythm control. Rate control, if it's successful, and it depends on whether you're looking at the treatment or the outcome. If you have an outcome of rate control, you control the rate, yes, but you're not in fact sure. If you achieve rhythm, the patient's in sinus rhythm, you achieve both, you have a normal rhythm and your rate by definition is controlled, so it really becomes very murky.

DR. C. GOODMAN: Thank you.

Dr. Maisel.

DR. MAISEL: I think we have to be a little bit careful about lumping all atrial fibrillation into one pile, and I think that's

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why we're struggling a little with the comparator treatments. I think it's analogous to asking is a stent good for coronary disease? Well, if you are able to manage (inaudible) it's not that good, but in a lot of people it's a treatment that it helps a lot. And so I think the question, the comparator would be different for different populations, and I think it's well established as a second-line therapy in patients who have tried rate control and have not been successful with that, who have tried rhythm control and not been successful at that, in who sinus rhythm is desirable, then I think the data is reasonably good. In a group of patients who presented with atrial fibrillation for the first time, then I don't think it is, and those two comparators are completely different. I might compare that latter group to rate control. I might say since you're in atrial fibrillation we might try rate control or primary ablation, or antiarrhythmia drug therapy.

So I think we just need to be careful about, you know, trying to make this equation fit all of the atrial fibrillation patients,

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and we need to explicitly talk about which patients we're referring to.

DR. C. GOODMAN: And we're about to try to do that, so I think we've kind of capsulized that very well, Dr. Maisel, in that discussion. Thank you. Since we've been talking -- Dr. Umscheid, did you have one more comment on how we stand on comparators?

DR. UMSCHEID: One thing I wanted to come back to because it was mentioned before, and it's the issue of sham therapy, so is the antiarrhythmic the appropriate comparator, and instead, is a sham therapy the best comparator? And the only reason I bring that up is because so much time was spent on quality of life, and there was also a comment that a lot of patients would feel symptomatic while they're on a monitor or actually being monitored, so you know, there may be a placebo effect here that could be worth exploring. I'm just curious if anyone has any other comments.

DR. C. GOODMAN: Sure. We've seen sham therapy as very important in other areas.

DR. KNIGHT: I think sham therapy has a role here in questioning whether the therapy

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has any efficacy at all, and I don't think there's any doubt that there are patients who have atrial fibrillation many times a day in whom it can be completely wiped out, so I think the biggest issue is what percentage of the patients benefit overall.

DR. C. GOODMAN: Okay, thank you. Population --

DR. REYNOLDS: Just one thought.

DR. C. GOODMAN: Sure.

DR. REYNOLDS: From a very practical perspective, a sham therapy randomized trial is never going to get done. There is now an FDA-approved catheter for this procedure, they had us screen 5,000 patients to enroll 180 or 190, and that from a capital perspective is just not feasible going forward.

And then it was mentioned about quality of life and placebo effects. It's not universal that a list of cardiac procedures are associated with placebo effect on quality of life, and the best counter example I can give you is the COURAGE trial. In the COURAGE trial quality of life was not superior with PCI versus medical therapy over about three to six

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months, and this was bandied about in the New England Journal of Medicine, about the quality of life effects in that study. So if there is a ubiquitous universal placebo effect in basic cardiac procedures, then you can't always explain those kinds of results.

DR. C. GOODMAN: Dr. Umscheid, are you okay with us now?

DR. UMSCHEID: Yes.

DR. GOODMAN: With regard to population, our next discussion question asks what subpopulations of patients with atrial fibrillation should be considered for treatment, it says of, but with catheterization, and there we have about six general types of patients mentioned here. Let me say that they should comply to what the evidence might indicate to date, which might be separate from what should be examined in clinical trials. So, I'm going to ask the Tufts people to be thinking about this as well. Among those subpopulations of paroxysmal, persistent, permanent, first line, second line, what can we say, or do we have any questions for our presenters with regard to

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clarifying which among those would be appropriate for atrial fibrillation, or which among those is there evidence in support of for the catheter ablation? Questions, comments? Dr. Satya-Murti.

DR. SATYA-MURTI: As I have been listening to it after having done the reading, it almost seems like there is a double pump in this population, one who are pre-Medicare, symptomatic, and the symptom being directly attributable to atrial fibrillation, and then the types of Medicare patients who we tend to see more often with hypertension or sleep apnea, and diabetes, and congestive failure and so on, and it makes it so hard to relate one symptom to occurrence of an event, if we catch one or two or three fortuitously.

So we might be looking at two diverse populations. Maybe CABANA will address this, but that seems to be the case. You're all advocating for one type, and then the evidence doesn't quite exist for the second type of patient we're seeing. Is that a fair summary?

DR. C. GOODMAN: Dr. Calkins?

DR. CALKINS: I mean, I think it's

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clear that the body of literature, and I guess the Tufts people can clarify this further, but clinically most patients with paroxysmal AFib that are less than 70 years of age, that's probably where the biggest body of literature is, or at least I think it is, as far as being crystal clear that cath ablation is a very good procedure.

Then when you say let's take patients over 65, there has been, I think we saw some data earlier, about five or six or seven studies comparing the outcomes with cath ablation for AFib in the elderly, whether it's over 65 or over 70, versus the young, and all the studies have shown similar efficacy and safety in both groups of patients. So I think, you know, even though yes, we need more studies in patients who are over the age of 65 and 70, you know, right now we have a fair amount of data regarding quite confidently that cath ablation can be applied effectively and safely in elderly patients.

The other point you brought up is the issue about, are patients' symptoms related to atrial fibrillation or not, and obviously that

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was mentioned when Brad said before a patient gets to an electrophysiologist, they started with their internist who tried to sort that out, or a cardiologist, and then they were finally referred for antiarrhythmic therapy or cath ablation, are the ones where there is a reasonable likelihood that it's related to AFib.

And when you see this in clinical practice, you see a patient like you're describing in front of you, they feel dramatically improved, before they were feeling lousy and you treated them for AFib, you've sort of completed the hypothesis, AFib in fact does cause symptoms in many patients, not just the young but also the elderly.

DR. SATYA-MURTI: But what you mentioned, if in fact the escalating process for preselection as to who would benefit is correct now, but if you then extrapolate that to stating that rhythm control through catheter ablation is just as good in Medicare versus the others, then that either incentivizes or energizes the patients who haven't gone through the serial escalation, the family practice,

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internist, cardiologist before getting to the electrophysiologist, so if we just assume if it's that good at the end, then it ought to be very good in the Medicare population in whom you happen to detect atrial fibrillation.

DR. CALKINS: Well, I think if we look at the data, cath ablation is a second-line therapy. You start with a class I, and if you look at the consensus document, symptomatic patients who failed class I or III antiarrhythmic medication, would now be considered for cath ablation. Now very few internists that I know of start their patients on antiarrhythmic drugs, and only a small number of cardiologists feel comfortable doing that, so these patients have all gone through, at least to my mind, a reasonable stepped approach. And like our consensus document specifically says, although in exceptional cases you may consider this as first-line therapy, that is the exception rather than the rule, and this is particularly true in the elderly where first-line therapy of the elderly would be I think a pretty big leap forward, something that at least I wouldn't encourage at

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this point.
DR. C. GOODMAN: Dr. Calega, I know your hand isn't up, but this general line of population, we first talked about that, you pointed that out very well this morning. Do you want to comment on your confidence with regard to any of these particular subpopulations or more broadly as the available evidence might apply to the Medicare beneficiaries?
DR. CALEGA: I think that the evidence, as somebody has pointed out, has really been in the average age range of 55, and very small populations, subpopulations in the studies that have been presented looked at our geriatric population over 65. And I don't think, and the expert panel may disagree, but I don't think anybody looked at patients over age 70, so it's very difficult to try to extrapolate beyond what has been studied.
DR. C. GOODMAN: Thanks. Dr. Knight.
DR. KNIGHT: So, we've gotten a lot of flack about the Medicare population not being represented in clinical trials, and I think that a different way to look at that is that

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reflects, I think, the clinical judgment that's already in place for the last ten years, that all patients who may meet indications by this criteria for cath ablation for atrial fibrillation aren't necessarily being referred and undergoing the procedure. So although it's underrepresented, that may actually be a good sign that there's a good system in place where clinical judgment is applied to which patients get the procedure based on other comorbidities and such.

DR. GOODMAN: That's a partially satisfying answer.

DR. CALEGA: I thought one of the speakers just said that there is a stratification process going on whereby people are seeing cardiologists, who are being referred to EPS, so if you're telling me that the geriatric population, the elderly population is underreported in these studies or they're not being studied, I would challenge that, because if you're telling me that there is a stratification process in place, then they should be going on and being referred for these studies if it's appropriate, and they should be

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represented in the studies if they are being properly referred.

DR. C. GOODMAN: Dr. Calkins, on that point?

DR. CALKINS: Yes. The question really, is there an age over which one would include a cath ablation as not going to work through a risk-benefit ratio difference. And if you look at both clinical experience and clinical trials, most clinical experience, if you look at most of us doing this around the United States, have no age cutoff, I have no age cutoff, I think it's appropriate in patients that are 85. I don't have a hundred patients over 85, but there's no age cutoff at Hopkins, I bet there's not at the University of Chicago or anywhere else.

When you look at the data, it's not that the data ends at the age of 70 or 75. The data continues, and there's now been two or three published series with patients 70 years of age or older, versus, you know, stratifying them. So I, at least as I'm doing these procedures, I can see no absolute age cutoff where you say that's it, you know, you're now

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77, this isn't going to be offered to you, but what I see is a continued benefit. But obviously with any procedure, your threshold for doing a procedure on an 80-year-old is going to be different than in a 50-year-old because the 80-year-old is frailer than the 50-year-old, and you want that patient to be more symptomatic and probably more likely to be paroxysmal AFib.

DR. C. GOODMAN: Well, there may be no clinical cutoff in practices yet, but that doesn't tell us if we have enough people in those age groups from which we might make some conclusions?

DR. CALKINS: Yeah, and I think it was mentioned earlier that with any therapy, the data sort of evolves over time, so yes, the procedure started being performed in a 55-year-old with paroxysmal AFib, but now with increasing experience with the procedure, with FDA-approved catheters for the procedure, you know, we're sort of expanding the patients who are getting the procedure, with that we're getting the data, there's a huge number of clinical series being published, people are

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looking at that, and if you go to all the national meetings they're discussing elderly versus young, and I think we're fighting that issue. But right now there's nothing to say that this is a procedure that's inappropriate in the Medicare population.

DR. C. GOODMAN: Dr. Yaross, on the point of these groups, thank you.

DR. YAROSS: Just to state one thing that is obvious, with a mean of 55, half are over, half are under, and if you refer back to page five in the materials we presented, those studies encompass over 1,700 patients. So while the subset presented was in fact a small number, there is literature out there, albeit observational, but the results of those observational trials corroborate very well to the results seen in the more broadly aged population.

DR. C. GOODMAN: So the observational data amounted to the 1,700. Tufts, does the evidence address these populations? Could you, if it's possible, could you run down that list of half a dozen subpopulations, starting with paroxysmal, and if it's possible, I know it's a

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tall order right now, could you kind of summarize the extent to which you think the available evidence as you found it matches up with those half dozen subpopulations? It could be we have a whole lot, we've got nothing, or something in between.

DR. GARLITSKI: So, the statement I can make most clearly is the one that I presented in the summary slide, that there is moderate evidence available as a second-line therapy for patients, again, as second-line therapy, i.e., who have failed medical therapy for a follow-up period of 12 months. So the answer to that, for second-line treatment, yes, moderate evidence.

For first-line therapy, there was one randomized controlled trial which did indeed favor radiofrequency ablation, but we considered that as insufficient data to make any statement about first-line therapy.

DR. GOODMAN: Thank you. Now, do you care to comment on any of the other subgroups here, or you're not in a position to do so?

DR. GARLITSKI: As far as paroxysmal versus nonparoxysmal, which is how we divided

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up the types of atrial fibrillation, sometimes it was difficult to state whether it was persistent, longstanding, or to use the old term, chronic. In summary, it was difficult to separate out the number of patients. The majority were paroxysmal that were studied, but in our summary statement we do not separate it out, paroxysmal versus nonparoxysmal.

DR. C. GOODMAN: You did not. Thank you. Do any of our representatives have anything specific to say with regard to whether or not, aside from paroxysmal or non, there is a strong body of evidence saying, for example, persistent or permanent? Yes, Dr. Calkins?

DR. CALKINS: Yeah. If you look at the literature, most of the studies looked at patients comparing paroxysmal and persistent, meaning shorter duration for symptomatic atrial fibrillation. So certainly my interpretation of the literature and the meta-analysis that we performed is that the results are similar between paroxysmal and persistent patients. I think the group that starts to differ are the longstanding, more than 12 months continuously, but particularly those with continuous AFib for

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three years or more, that's the group where I think there's quite minimal data suggesting the efficacy at three years, that's where we have very very little data.

DR. C. GOODMAN: Great. Thank you.

All right. We need to move now to outcomes, and I know that we've addressed this somewhat this morning, but I don't know that we came to any resolution about it. For the Medicare program, Medicare beneficiaries, what are the outcomes of interest?

We talked this morning about, just to sum up quickly, the importance of sinus rhythm and how far that goes and how far it may not go. That's certainly an intermediate outcome, some might say it's a surrogate or something else. We heard a good discussion about the importance of quality of life and how that's important to patients, and at least one of our presenters contended strongly that quality of life is the most important outcome, although our ability to measure it in a valid way is not necessarily great, but yes, it seemed to be doing well enough for some of our panelists, that's fine. And I think we heard that there

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is little evidence with regard to stroke and mortality.

So in the interest of the Medicare beneficiary population, we want to explore now, what are the outcomes of most interest? And by the way, just as a footnote to an earlier discussion, if you want to talk about costs, it's okay. The question was raised in the cost effective data presented by Dr. Reynolds, and yes, it's okay for us to hear and discuss that. What the Medicare program does in any coverage decision is another matter. So, do our panelists on this area have any interest? Dr. Moscucci?

DR. MOSCUCCI: I have a question for our consultant. We learned today that most of the patients had been enrolled in a clinical for catheter ablation for atrial fibrillation, a long-term outcome was that there was not a stroke. Do you think that eventually we will be able to say that for our Medicare population patient group?

DR. C. GOODMAN: Dr. Calkins is up again.

DR. CALKINS: I mean, right now

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there's no data that catheter ablation lowers the risk of stroke. That hypothesis certainly in the AFFIRM study didn't hold true, that there was any indication of reduced stroke risk. So in the consensus document we specifically state that a desire to stop your anticoagulation strategy should not be affected by the outcomes of the procedure, that we just don't have enough data now.

That said, if you take a patient with a CHADS score of zero, the guy doesn't even need to be on Coumadin, you stop Coumadin two months after the procedure, you can ask to stop Coumadin two months after for CHADS 2 patients, but right now I think there's questionable data suggesting you should stop Coumadin, I would certainly never recommend it. Actually one of the studies was from Michigan looking at this, so I think we really don't have enough data on stroke risks to cancel the procedure, and as far as I'm concerned, that's a completely independent topic, we need more data and the data is forthcoming.

DR. C. GOODMAN: We don't have data and that's forthcoming. Dr. Packer, is it an

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important outcome for our population?
DR. PACKER: Stroke?
DR. C. GOODMAN: Yes.
DR. PACKER: Absolutely. You know, we have spent most of our time, I think, talking about freedom from symptoms all of your life, but I think if you have somebody who's already had a stroke, they will tell you that their quality of life, depending on how severe the stroke is, is not good. So I think it's a critically important issue and it's one of the reasons why it's in CABANA and why it's being considered in other trials.
This may be someplace where there's a little bit of a difference in comparators, though, because we don't have a lot of data, and Hugh was referring to it, in talking about anticoagulation. And you know, if it really does something, then that will be interesting and there may even be a sea change here, but that's yet to be determined.
But I think in a Medicare population, we have to keep that in mind, but it will take a larger trial to tease out whether or not ablation or any other intervention is going to

have an impact on relatively uncommon events. So I think, should we be paying attention to stroke, absolutely. Does that mean to only do it in small trials, no, it's not, and are we more comfortable with things at the end of the day in the CHADS 2 and above, obviously.

DR. C. GOODMAN: Thank you.

Dr. Hammill.

DR. HAMMILL: I think when we look at the data that's been presented to this point, it's pretty clear to me that we don't have adequate outcomes looking at patients beyond a year, so we don't know the answer on stroke. The guidelines from the professional societies clearly state that AFib ablation is not a reason to stop anticoagulation therapy, that you need to look at the patient's other risk factors for asymptomatic atrial fibrillation. And I think the other issue with whether we look at longer-term data acquisition is the generalizability of the results that we're seeing from the controlled trials like CABANA, which are involving the best centers, or the most experienced centers in the United States, with other centers that are doing the

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procedure and not participating in trials, because there are different volume levels and experience, and that is something that also needs to be tracked.

DR. C. GOODMAN: So Dr. Hammill, just to be quite specific about it, the outcome that matters here is? What's important to you?

DR. HAMMILL: The three outcomes are symptom relief, stroke and survival.

DR. C. GOODMAN: Symptom relief, stroke and survival.

DR. HAMMILL: Symptom relief is frequent enough that I think it can be answered with a smaller trial. I think that stroke and survival is infrequent enough that it requires a much larger kind of trial or registry to gather that information.

DR. GOODMAN: And is symptom relief the one that will be picked up by whatever the measures are that have been presented today, for example?

DR. HAMMILL: Yes.

DR. C. GOODMAN: That's very helpful. Just a moment. Dr. Dullum, I think was next.

DR. DULLUM: I just wanted a further

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explanation, Dr. Reynolds, on your slide, just since we mentioned costs. You had that slide out that showed the increasing -- I was actually confused, because it looked like the drug cost was lower but the hospitalization was higher, because I know these procedures are expensive. So I wasn't sure if you were saying that over time if it's purely drug treated, then eventually the costs would reach what it would cost to do one of these procedures in the hospital. Do you mind clarifying that?

DR. REYNOLDS: I'm sorry, I will try to do it without even showing the slide. These were patients that were followed in a registry according to, first of all, whether -- this was, by the way, a registry of patients for first onset atrial fibrillation. There was a small group that developed permanent atrial fibrillation from the outset, so that was one category. The majority of the patients, that first episode may have terminated somehow or other, and then the patients were followed and symptomatic recurrences were reported. They were broken down into four groups, first whether they developed permanent AF, which was

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a very small group, and then those that had no recurrence, one or two recurrences, or multiple symptomatic recurrences over a period of about two years. And what was shown in the figure is that the hospital cost was a tremendous disparity between the patients who had no recurrences and the patients who had multiple recurrences. The other costs didn't vary very much. The drug costs actually did increase the more occurrences there were, but not nearly as much as hospital costs. And the point that this registry has shown is that at least 50 percent of the direct cost of treatment in atrial fibrillation comes from the hospitalization, so for the Medicare program, I would think that there's little question really that hospitalization ought to be an outcome of interest, because to a great extent it drives the costs.

DR. DULLUM: You mentioned that people had to be hospitalized frequently to start this medication, but I'm assuming that the AFib ablation is done also in a hospitalization admission; is that right?

DR. REYNOLDS: Yeah. Generally most

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centers require an overnight stay, so it's like 23 hours.

DR. DULLUM: But nowhere on the slide did you compare the procedure, the AFib procedure to --

DR. REYNOLDS: That was actually a registry that sort of finished collecting data just at the beginning of the AFib ablation era, so that actually none of the patients in that registry are shown with ablation.

DR. C. GOODMAN: So Dr. Dullum, what is our take-home point from that?

DR. DULLUM: Well, I was just trying to compare costs, you know, so if you show us the costs of the medical therapy, I didn't see that compared to the costs of the AFib ablation, so in my mind I was wondering what that last one was, and you clarified it.

DR. C. GOODMAN: So the offset was there or not there?

DR. DULLUM: Based on this, there was no comparison from a cost standpoint.

DR. C. GOODMAN: Dr. Carlson.

DR. CARLSON: A question for Steve. On your list there was nothing about recurrence

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or frequency of recurrence of the arrhythmia. Any thoughts about that?

DR. HAMMILL: You mean as far as an outcome?

DR. CARLSON: As far as the three most important outcomes, or of outcomes, you listed three, but recurrence of the arrhythmia was not on there.

DR. HAMMILL: I was lumping that in, because one of the reasons to do the procedure, one of the primary reasons we're doing it now is to improve symptoms, and so when I talk about quality of life at one year, it's that, rolled into it is the symptom reduction in atrial fibrillation and then the other perceived benefits and then the quality of life.

DR. C. GOODMAN: Thank you. Dr. Moscucci, I know you have to leave in just a few minutes. We want to give you your opportunity to shine one more time before the taxi whisks you away. On the matter of outcomes, Dr. Moscucci, is there any point that you need to have clarified or emphasized with regard to the outcomes? If not, that's fine.

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DR. MOSCUCCI: I think it has been answered, thanks.
DR. C. GOODMAN: Dr. Satya-Murti, we're still on outcomes.
DR. SATYA-MURTI: Dr. Hammill, I like your listing of what's important. And symptom relief, what symptoms do you specifically have, is that listed here or do you have specifically enumerated symptoms?
DR. HAMMILL: The symptoms to me are much more difficult to define because they are so patient-specific. We talked about this. At times you clearly recognize that the symptoms are related to do this because they're rapid palpitations associated with an irregular rhythm. There are other times when patients talk about having fatigue, lethargy, lack of energy, and that's the kind where, I think it was Dave and Hugh both commented, and it's also my practice, let's get them back to sinus rhythm and see if those symptoms clear, to see if they're related to atrial fibrillation.
So I think the distinction in trying to define symptom relief is difficult, it's just what I would do as a physician is symptoms

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attributable to atrial fibrillation, and to see if the treatment provides relief. And again, it seems that the better global way to measure those is with some kind of quality of life scale.

DR. SATYA-MURTI: And would the comparator be designed to take into account that subjective issue of definition of symptoms?

DR. HAMMILL: You know, I think it's always a problem. If we look at the studies where they tried to say we'll look at symptoms related to atrial fibrillation, we'll look at palpitation, exercise intolerance, fatigue, those sorts of things. But one of the comments to be made about the whole quality of life thing is I'm just not real sure that the SF-36 does a particularly good job of dealing with symptoms, and that's why these other symptoms for us have emerged. They're kind of hot in the midwest with what's going on right now with these symptom scores, and so I think the way to look at it, and this is the way we're looking at it in CABANA, is you have to have something like SF-36, but you have to have something

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more, and you have to drill down a little bit. And I agree with what's been said by a number of people about sometimes you don't know until you get them out of it, especially if they have underlying disease. If there's somebody who's got congenital valvular disease or heart disease, you don't know if it's a pump problem, there's pumping problems and electrical problems, and until you get rid of one or the other, for example by getting them back into sinus rhythm with an angiogram or stress test, you may not know. But I do think that all of these trials need to track it, and I think we need to do a better job of, you know, taking care of patients over the age of 65.

DR. SATYA-MURTI: I agree. Just very briefly. This is a pretty important issue in that once you register someone as going into ablation therapy or any kind of treatment, they would also hand in hand be getting better medical attention for their hypertension or sleep apnea, so we have a lot of better focused medical attention to other issues too. So to what extent do they contribute to nonspecific

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symptoms, and I don't mean palpitations? It's all so unclear, they come into the medical system and then they would be demanding or deserving of more attention; isn't that true?

DR. HAMMILL: Well, just to comment, I think that's true for the randomized trials, because they're followed very carefully and the study monitors and nurses make sure that their other comorbidities are taken care of. I don't think that's true for patients who fall outside the randomized trial, because they typically come into the electrophysiologist, the electrophysiologist does the procedure, you might see the patient one time in follow-up, you see the patients at three months to make sure they're doing well, just for any complications, but then their care falls back to their primary care physician or their primary cardiologist. So I don't think anything about the ablation specifically brings them in to closer attention in the medical system other than those few days around the procedure.

DR. C. GOODMAN: Thank you.

Dr. Dehmer, I just wanted to ask you, we have

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been discussing these three major categories of outcomes of interest, that being symptom relief broadly, including things like recurrence as measured by quality of life measures such as SF-36, we talked about stroke and we talked about survival. Is this discussion on point from your standpoint as a clinician or are we missing something?

DR. DEHMER: Absolutely on point.

DR. C. GOODMAN: It is on point, thank you. Ms. Atkinson, I was going to ask you if we're still on point, recalling your comments of late this morning.

MS. ATKINSON: I actually have two questions, but one question has to go back to population, if I may, in order to ask the outcome question.

DR. C. GOODMAN: Sure, if you've got a point.

MS. ATKINSON: Okay. When we think of that older population, we have two basically subgroups of people, we have the robust older adult and we have the very frail older adult. And I need clarification from the speakers, of the people that were included, just based on

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inclusion criteria for these studies, I am assuming that most of the people that were included in these studies were the robust older adult. Am I correct?

DR. WILBER: There's no quantification of that in the studies, but I think it is what many people mentioned, it's the filtering system, and safe to say that it's robust 80-year-olds that are having ablation.

MS. ATKINSON: And then my outcome question is, do we know how many of these robust older adults were able to discontinue their medications, especially their beta blockers and their calcium channel blockers? If they were robust, I'm assuming that many of them probably did not have significant enough CKDs that they were able to tolerate the ACE or a diuretic to control their hypertension, and henceforth were able to discontinue the beta blocker or the calcium channel blocker, but do we know that?

DR. WILBER: I think from the standpoint of most of the drugs, other than Coumadin, that adds to your CHADS score, so you wouldn't stop Coumadin in following the

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guidelines which, and over age 75 is one of the criteria. So eliminating that, I think the differences in stopping drug therapy between younger and older patients, we didn't see, certainly not in the Thermocool trial, although I can't answer quantitatively, but I can tell you in my own clinical practice, it's no different, the election to stopping drug therapy in the older patients is the same as in the younger patients, other than the Coumadin.

DR. C. GOODMAN: Tufts team, back to you. I know you addressed most of this before, but if you could summarize for us, in those three main categories that Dr. Hammill laid out, so symptom relief as you understand it, stroke, survival, the body of evidence as examined in your technology assessment addressed those three areas how well or to what extent, kind of the high level of the three main categories?

DR. GARLITSKI: So, quite clearly, we do not have the mortality data other than what was reported, which was five deaths among 63 trials. I can't make a comment on rate, because again, we didn't have the denominator.

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So that's the only comment that I can objectively make on mortality. And those were five deaths as far as complications go, I wanted to clear that out. The other deaths, we can't make a comment on mortality. The time frame was a 12-month follow-up so there was no data reported.

DR. C. GOODMAN: Okay, and stroke?

DR. GARLITSKI: I will just use these slides on quality of life data, I know Dr. Satya-Murti had been asking it. Our data revealed that there were three randomized controlled trials that looked at quality of life, and one retrospective study. Our strength of evidence for that, for quality of life was low, and that was because of methodologic deficiencies in the primary study. Dr. Reynolds presented other data that could have been included with these trials, in addition to other ones, so I don't comment on the results of his study as he presented on quality of life.

We may have presented different data because we used very different inclusion criteria as to what studies we reviewed. For

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example, they had to have outcome data greater than six months, including retrospective studies of no less than 100 patients. So again, the summary from our data on quality of life, that which I had to consider was three randomized controlled trials and one retrospective study, which did indeed show improvements, but in summary the level of evidence was low because of the kinds of trials that they were and the numbers of patients.

DR. C. GOODMAN: And the ones that you listed were the shorter than six months and retrospective.

DR. GARLITSKI: Correct, six-month outcomes, plus they had to have more than a hundred patients in a retrospective study.

DR. C. GOODMAN: And can you comment on stroke? Do you have any comment on stroke?

DR. GARLITSKI: Again, what we have is that there was one randomized controlled trial that was looking at avoiding anticoagulation, there was a 12-month follow-up, 60 percent versus 34 percent, with a P value of .02. Therefore, we rated the strength of evidence as low.

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DR. C. GOODMAN: The strength of the body of evidence?
DR. GARLITSKI: Correct.
DR. C. GOODMAN: Because there was only one?
DR. GARLITSKI: Correct. I apologize. That was indeed that one trial. In addition -- that was avoiding anticoagulation. Looking at stroke specifically, there was a meta-analysis of six randomized controlled trials, a total of 689 patients were evaluated, and again, the strength of evidence was determined to be low because the stroke event rate was not systematically assessed in those six randomized controlled trials.
DR. C. GOODMAN: Was it prospectively assessed or captured in some other way?
DR. IP: Basically what we're saying is the stroke event rate was not a primary outcome, so they sort of like, if it happened, they reported. They didn't tell us.
DR. C. GOODMAN: They were not prospectively identified.
DR. IP: Right.
DR. C. GOODMAN: Thank you very much.

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Dr. Satya-Murti.
DR. SATYA-MURTI: Is this a homogenized stroke, because there are strokes from other causes, and a stroke from AFib is quite different than a hemorrhagic stroke, or stroke that looks like stroke on the surface. So I'm not detracting from what any of you said, but from what you mentioned, I have a feeling that multiple etiologic processes affecting stroke are probably coming into play here.
DR. IP: Yeah. We are not saying that the stoke is attributed to AF, we're simply saying if it was reported or not.
DR. C. GOODMAN: Dr. Hammill, back to the three categories. Did you just hear that there are strong bodies of evidence for any or all three of those, symptom relief, stroke or survival?
DR. HAMMILL: I think from my personal perspective that there is a reasonably strong body of evidence for symptom relief, not for stroke, not for survival.
DR. C. GOODMAN: Dr. Maisel.
DR. MAISEL: Dr. Hammill's list is an

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excellent list, but I hope that's not the bar we're using to decide whether or not this therapy is appropriate. I think there are very few therapies that we have, taking into account risk of stroke at the time that the therapy decision is made, I think there's very few interventions that we demonstrate mortality, although certainly there are some. So I think, I enjoyed the conversation and the discussion and I think it's an important one, but I want to draw a line in the sand for myself, that I don't think this therapy needs to demonstrate a reduction in stroke.

DR. C. GOODMAN: What about symptom relief?

DR. MAISEL: I certainly agree that symptom relief is important. I prefer the term quality of life to symptom relief, I think symptom relief is fine, but I think it's very difficult to measure in a reliable reproducible way in these trials, and for me that's more a quality of life issue.

DR. GOODMAN: And did you find that the quality of life is measured in a valid way thus far?

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DR. MAISEL: I think it's a satisfactory measure, and we've seen some of that data.

DR. C. GOODMAN: Dr. Umscheid.

DR. UMSCHEID: I think stroke is important because most providers, I would say in the general community, are potentially treating AFib to prevent stroke. So if you're not showing an improvement in stroke with the procedure, and there are current procedural risks and adverse event data, I think it's very important to talk about.

The other issue that I want to bring up is the quality of life measurement. I think there are some very objective surveys that I think a lot of us could agree would represent quality of life, things like admission to a hospital, admission to an urgent care clinic, and if we're not seeing data that shows improvement in those types of measures, then I think it's difficult to say that quality of life is improving in patients because of a particular therapy.

DR. C. GOODMAN: That's an interesting point that has not been made thus far today.

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You're contending if those events are not reported, that you would perhaps question whether or not the quality of life has been affected.

DR. UMSCHEID: Exactly, and the same goes for symptomatic heart failure as well.

DR. C. GOODMAN: In other words, if you think about the events you mentioned in the different facilities and so forth, as I understood you, you can count those events, you could find codes, whether they be ICD codes, what have you, so those are countable.

Dr. Maisel.

DR. MAISEL: I wanted to respond to that. Hospitalization is an excellent endpoint and worth measuring, it's very concrete, I think there would be more confidence if we had this as a measurable benefit, but I disagree that quality of life is measurable by these major events. Many patients with atrial fibrillation have quality of life issues that don't get captured in a major event like heart failure, many patients that just feel better, and that's the whole point of having these subtle questionnaires that can pick up on those

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types of issues.
DR. C. GOODMAN: So your conclusion is that quality of life is important in some of the ways that we discussed, but the way it was assessed was inadequate, so the way that you would get at real evidence for impact on quality of life, if not those aforementioned approaches, would be what, the type of questionnaire that you just mentioned? How do we get that data?
DR. MAISEL: Concerning the SF-36 measurements, the SF-36 would be one that I'm fine with, but it doesn't have to be the only one. There are formal, there's a science to measuring quality of life, that's my point, like relying on hospitalization to be a measurement of quality of life, we don't need a major, you know, heart failure, hospitalizations or strokes or admission to a hospital in order for a patient to feel differently.
DR. C. GOODMAN: So just to integrate what we've heard here, those events which can be measured such as visits to facilities, it sounds as though the panel feels that while

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those may be important outcome measures, they may be in part indicative of quality of life, but probably not the best way to get to quality of life, and you just suggested ways that you think are better. Is that it?

DR. MAISEL: I can't speak for the whole, but you accurately reflected my advice.

DR. C. GOODMAN: That's good.

Dr. Dullum.

DR. DULLUM: Actually, just to follow up on that point, the studies that were reviewed at Tufts were ones that had good follow-up, what they considered a good study. As far as the follow-up performed with the patients, I mean, what was your loss rate on follow-up, was it 98 percent of patients that were followed up? I asked about a registry, you said that was too expensive to perform, and then as Dr. Packer just clarified, you had said that in a big center you do the procedure and then they go back to the cardiologist or primary care physician. And I'm worried about the follow-up too. If the patient goes to another hospital and unless the doctor calls and says hey, your patient is here, we don't

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know.
So following up sort of on Dr. Maisel, if we don't have that follow-up somewhere in a registry, we may not know what the actual complication rate or the improvement in quality of life is, or readmissions, so that's something that I think in the papers that you evaluated, you did have a requirement for at least some follow-up; is that right?
DR. IP: I don't have those actual numbers off the top of my head, but we have a grading criteria for dropout rate, and if it's greater than 20 percent dropout, it got downgraded.
DR. DULLUM: Right, because when we look at the data for these readmissions, we want to have an accurate number for them.
DR. C. GOODMAN: Thank you, good point. Dr. Hammill first.
DR. HAMMILL: Just to comment on what you just brought up, I think one thing we're looking at with the national AFib ablation registry is to assess quality of life with another way of doing it, which is the Canadian scoring system, which is analogous to a heart

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failure class I, II, III, IV, with regard to their symptoms, so that's another thing we would like to track.

And there is -- now, with what Dr. Packer is talking about is the extent of the registry, and that's best if you follow the patient to the nth degree in a randomized trial. In the ICD registry we're following 450,000 patients now, and if we enter the data at the time of the procedure and the implant, then matching their data with Medicare claims data gives us information on subsequent complications, adverse outcomes, rehospitalizations and those other issues. That is a much easier way and cheaper way to track patients.

DR. DULLUM: So they would be merged in that way?

DR. HAMMILL: They would be merged in with the registry as a way of getting a follow-up.

DR. C. GOODMAN: Dr. Calkins, on that point?

DR. CALKINS: If you're an internist treating a patient with AFib to prevent stroke,

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you don't -- but certainly a cardiologist doesn't treat a patient simply trying to change the risk of stroke because it's never been a proven symptom relief, and we anticoagulate and if you have a patient with AFib then there are guidelines that you follow, you know, the CHADS score, and then symptom relief. So the reason I treat patients for AFib, while following the guidelines for anticoagulation, but I'm treating them for quality of life issues. And I think one of the important things in terms of the Tufts data, why their data sort of said this quality of life data wasn't as robust as it was in, for example, the Thermocool study, which is a prospective, multicenter, 12-month follow-up, you know, study that showed the value of quality of life. It wasn't included in the analysis, it hasn't been published yet, but you saw it here today. The FDA panel saw it when they approved the Thermocool. So I think it's important to realize the Tufts analysis was done at a certain point in time, and there's been new data since then that you're having the benefit of, you know, considering.

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DR. C. GOODMAN: Thank you.
Dr. Carlson, I skipped over you before, I'm sorry.
DR. CARLSON: To what extent do we know about the correlation between recurrence of atrial fibrillation, particularly symptomatic recurrence, and quality of life? Is one necessarily asserted or recommended?
DR. REYNOLDS: We don't know enough. There have been a couple of series, the one that comes best to mind is the European, that tracks quality of life in a cohort of patients after atrial fibrillation, and it's the only one I know of that separated the patients according to whether they had recurrences or not recurrences.
Earlier today we heard about the inexact science and the measurements, and that's a problem in and of itself, but in that one European study there were in fact quite large and statistically significant improvement in quality of life with patients with no recurrences, and in patients with recurrences there were still improvements in quality of life, they were much smaller and not as

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significant as the one in the published data, but there is insufficient evidence overall on that question.

DR. C. GOODMAN: Dr. Reynolds, though, if all the evidence we had, if all the good evidence we had was on recurrence, that was everything you had, would you, should Medicare consider that as a sufficient body of evidence on that outcome and that outcome alone, to provide specific coverage for this procedure, if that was all the evidence we had?

DR. REYNOLDS: If you're asking my personal opinion, my personal opinion is, I think you need both.

DR. C. GOODMAN: Both?

DR. REYNOLDS: You need information to assess the value or the effectiveness of this intervention. The goal of treatment for atrial fibrillation is to maintain, the mechanistic goal, as far as we understand it, is to show that you improved quality of life without showing a change in the rhythm status. People aren't going to trust that, people want to see more, and we knew that, but to show an improvement in rhythm control without showing

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that transfer to some of those outcomes that are meaningful to patients, I think that's also insufficient. That's my opinion.

DR. C. GOODMAN: Okay. This is important for us to consider as a panel, so if all -- okay. Dr. Calega, and then Ms. Atkinson. If all we show, if all we had in the way of good evidence was that we knew how to manage sinus rhythm, period, without the quality of life data, would that suffice as an outcome of interest?

DR. CALEGA: I think that we have to have multiple endpoints, so quality of life is important. Rhythm versus rate, the rehospitalization, I think that's a very important measure that we should be measuring going forward, whether it's part of a registry, whether it's part of a clinical trial prospective, or if you look at what's available retrospectively. Hospitalization is very key when you talk about quality of life, when you start to talk about costs, but then it gets to the definition of what is a hospitalization. As we were just talking here, does hospitalization include observations, so we

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need to be clear on the status of the hospitalization, but rehospitalization is a very key measure that CMS is looking at and that private insurers are looking at as well.

DR. C. GOODMAN: So in our sort of basket of outcome measures that we've talked about so far, we have symptom relief, stroke, survival, hospitalization, which may include health care visits, and symptom relief may include something called quality of life, or overlapped with it, but recognizing the importance of quality of life in and of itself. It sounds as though management of sinus rhythm in and of itself in the absence of improvement in quality of life would be insufficient. I think that's where the discussion is roughly now.

What are we missing or what else do we need to know, Ms. Atkinson?

MS. ATKINSON: I don't know if we're missing anything. I think one of the things that we haven't talked about, though, is if we can't reduce medications after ablation, then we need to follow them because the side effect of these medications definitely impacts quality

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of life, and not only the side effects but the cost of the drugs. And when it comes to side effects, some of these patients with calcium channel blockers, that can make a pretty miserable quality of life in some of these older adults, just that medication alone. Depression and fatigue with beta blockers definitely impacts quality of life. So if we're not able to discontinue some of these medications, then quality of life is still impacted.

DR. C. GOODMAN: Thank you very much. Dr. Hammill and then Dr. Packer.

DR. HAMMILL: I just want to correct a misunderstanding. When we talked about not being able to stop medications after catheter ablation, it's just the Coumadin, warfarin, so the beta and channel blocking drugs, those are all discontinued.

MS. ATKINSON: But is there enough evidence to show that they need not be continued in that population?

DR. HAMMILL: Well, I don't know whether there is enough evidence to say that, but it's pretty standard practice once the

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ablation is done and patients are beyond that three-month window that the drugs are stopped, and I think when you look at the data that Hugh presented, they talked about 71 percent of the patients were free of atrial fibrillation and antiarrhythmic drugs at one year.

MS. ATKINSON: Are they having to stay on the calcium channel or beta blocker for hypertension?

DR. HAMMILL: Yes, they might, though it's not related to the atrial fibrillation. So they may need a medication for another issue such as treatment of their hypertension. But one of the advantages is that having had the ablation, they may be able to switch now to an ACE inhibitor because you no longer need to do the combined rate control plus the blood pressure, and now you can focus just on blood pressure.

DR. C. GOODMAN: So where does that leave us in regard to your issues?

MS. ATKINSON: The same. I mean, it's the same. We need to discontinue those medications, that's great.

DR. C. GOODMAN: Good, thank you.

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Dr. Packer.
DR. PACKER: I might have missed something here, but I was just going to add something to your comment about management of sinus rhythm, or getting there by itself in the absence of quality of life indicators. You still have this whole issue of the contribution of asymptomatic atrial fibrillation to stroke risk, and if you still have that contribution issue now, as Hugh said, if they're CHADS 0 or CHADS 1, we might be able to stop the anticoagulation. If they're CHADS 2 and above, we keep going with the guidelines.
But there's that interim group where as near as we can tell, they are free of atrial fibrillation from the standpoint of, you know, quality of life measures, but I still think knowing whether there's sinus rhythm or not, whether there's ongoing underlying atrial fibrillation plays a role in that, and so we need to know more about that from other trials and that sort of thing, for sure, but I wouldn't underestimate the importance of that.
And the one place, and this didn't come out, that does look at quality of life,

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and this is a publication that's coming out, that the whole Coumadin issue had a huge impact on the patient's quality of life independent of everything else, so I'm not sure you can just cut off that, I think there's more to the combination than that.

DR. C. GOODMAN: Dr. Packer, in and of itself, management of sinus rhythm would or would not suffice as being a useful outcome of interest for the Medicare population?

DR. PACKER: I think it's problematic because then you get into the whole cascade of how hard are you going to look, who's going to pay for it, what's the intensity of monitoring. So inherent in what I've just said is there's some complications in really trying to find, but I think from an academic standpoint, it's important.

DR. C. GOODMAN: Thank you. Dr. Reynolds.

DR. WILBER: I'm Dr. Wilber.

DR. C. GOODMAN: Pardon me, Dr. Wilber.

DR. WILBER: Just to answer the question about the drugs, there's pretty good

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evidence, six randomized trials, including the clinical trials, and in all but one, the use of antiarrhythmic drugs by patients for all causes was five percent or less, so that in fact is extremely unusual. So I think at least when you look at the database, you know, it's hard to say what people are doing, but at least when you look at the trial database evidence, that's pretty much success, with only one exception out of all of those.

DR. C. GOODMAN: Great, thanks, Dr. Wilber. Dr. Packer, I want to return, and we'll start with you as kind of our fall person to answer this question, and then if you don't, if you've got kind of a blank space, we'll go to someone else. I just want to run down our list of kind of our current basket of outcomes that matter in the Medicare population, and if you could comment on how long we have to wait to figure out whether we've got an outcome difference or not. For example symptom relief, for trials where you've had an intervention with symptom relief, are we talking days, weeks, months or years to see if symptom relief has been achieved and whether it's been

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sustained?
DR. PACKER: I think that that has most to do with underlying events, you know, what was the event rate in the first place. If you're having a symptomatic event that occurs once every six months, then the intervals you're going to have to look at to decide whether we have an impact on that may be double or triple that. So if you have someone with paroxysmal atrial fibrillation and they're having daily episodes, you may not need more than two days to kind of figure that out. So, I think that that's a classical events rate combination.
DR. C. GOODMAN: So it may be a matter of days or weeks, or in some cases months?
DR. PACKER: Yes.
DR. C. GOODMAN: Okay. Stroke, if we're trying to measure the impact of these things on stroke, it's years, is it not?
DR. PACKER: Yeah, stroke is tough. Stroke is tough because the event rates are small. Stroke is tough because we can quibble about whether atrial fibrillation has anything to do with it or whether it's underlying risk

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factors or vascular events or those kinds of things, so I mean, I think stroke is in the bailiwick of a longer trial.

DR. C. GOODMAN: Just in the Medicare population, two years, five years, ten years?

DR. PACKER: If you're trying to decide whether there is an event that is related to a therapy sort of thing, then I think you might be in the two or three-year time range. But if you're talking about the likelihood or prevalence of a stroke that's going to occur because of background factors in conjunction with whatever the therapy is, it may take five to ten years.

DR. C. GOODMAN: Okay, thank you. And again, this is one of our questions to discuss, survival, same thing, is a long-term issue?

DR. PACKER: Yeah, survival is a long-term issue, again because of event rates. So if you're looking at the firm type of event rates, you're thinking that the mortality rate is going to be someplace between, you know, four percent per year, you know, and you have a trial that lasts a median follow-up that is, say 36 months, that's a fair number of events,

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that's 12 percent in that, and then you try to look at that with some other therapy, and then you would expect that you could see something over a two or three, maybe four-year time frame. And if you think your event rates on mortality are down in the Athena range, then the event rates in your comparator, the catheter ablation in this case, would also have to be lower, and that likely would be from the standpoint of background therapy. So you're still looking at a three to five-year trial, and that's why it's going to take as long as it's going to take.

DR. C. GOODMAN: Okay. Dr. Calega, hospitalizations, other sorts of visits, how soon do we start picking this up in a way that reflects the impact of our therapy on the treatment, is this next week, the next day, months, years, what is it?

DR. CALEGA: It could take months to get that information based on whether rehospitalization occurs after some time frame with the ablation. So it could be days if a patient is readmitted, but giving a blanket period of 12 weeks, I think you would have to

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look at three months and later for when rehospitalization would occur.
DR. C. GOODMAN: Three months and later. Okay.
Ms. Atkinson, on the matter of medications, you were interested, as I understand it, on whether the use of one of these interventions might affect the need for other medications. How soon do we know that, if there's an impact?
MS. ATKINSON: If, as Dr. Hammill said, according to most of the research is three months, then three months.
DR. C. GOODMAN: Okay. Dr. Maisel and Dr. Umscheid, back to the quality of life, and we've had interesting comments about that. Dr. Maisel, quality of life, as you were explaining it to us, how soon after this kind of intervention would we start to see some of these particular effects? How long should we be watching?
DR. MAISEL: I think you can see an effect on quality of life very quickly, within days or weeks. Certainly there is evidence to suggest that it can take several months for

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effects to show from an ablation procedure, so I would think that something in the six to 12-month range would be appropriate.

DR. C. GOODMAN: So the six to 12-month period should encompass the impact about which you spoke earlier?

DR. MAISEL: Yes.

DR. C. GOODMAN: Dr. Umscheid, anything to add?

DR. UMSCHEID: No, I think I would agree with that, and I also agree with the three-month hospitalization.

DR. C. GOODMAN: Great. Our presenters or teams from Tufts, or Dr. Rosenberg, did you hear anything just now about durations to capture important impacts on these measures of outcome with which you quibble, or something you would like to add to that?

DR. REYNOLDS: Just very briefly regarding hospitalization, I think probably one to two years is a better time frame than three to six months, and the reason for that is that there is throughout this trial a reintervention rate, and that rate is probably in the

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neighborhood of 20 to 25 percent right now, and if you've got ablation on hospitalizations, you've got to go beyond that period. So a minimum of a year, but I think two would be better.

DR. C. GOODMAN: Good, that's very helpful. I just want to remind the panel, one of the important issues we're going to try to capture now is one of our questions later on, and that is what research needs to be done and we're going to want to know vis-a-vis the outcomes of interest. Okay. Did we miss anything very very important about our discussion for outcomes? Did we miss anything? Dr. Packer, yes?

DR. PACKER: Just one thing. We have been at this, we're talking here about the time that it takes to measure an outcome, but it also depends on what the sample size is for what you're doing, and so it may take less time if you've got a huge population to look at, or it may take a lot more time if your study group is small and the event rates are small.

DR. C. GOODMAN: Great. I should have clarified that. We're kind of looking at the

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natural history of how things might unfold in order to attach a significant number percent and gather up all the patients and so forth. Point well taken, thank you. We're going to cover one more thing on device characteristics and physician training, and what we'll plan to do is, I hope no later than 2:20, is take a 10-minute break just for comfort purposes. Let's move, then, to device characteristics and physician training. We heard some discussion about this issue this morning and our first discussion question here is, what is the importance of the varying devices and techniques used for ablation? I think we heard a little bit about that this morning from the Tufts preparation. Panel, any questions or concerns that you want to raise with regard to the importance of varying devices and techniques? Yes, Dr. Dullum.

DR. DULLUM: Well, I guess it's the same discussion about the lesion sets and making that homogenous, I think we discussed that enough, I just want to voice that as a concern. I just thought about the different

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energy sources because cryotherapy, I know there was a presentation, and that has been a longstanding, that we don't get better trans neutrality, but that's not really in this discussion, it's just one of the devices that I think we should look at.

And operator experience, I know there wasn't enough evidence based on what you guys evaluated, but that's certainly, I think that's true for most highly technical procedures, and this certainly is a highly technical procedure, so I think it's something we need to address.

So the bottom line is, two things we need to address. Energy source which, I don't know if that's out of the realm of this discussion today, but I did hear that there's one trial going on with that now, and also operator experience.

DR. C. GOODMAN: Thank you. Yes, Dr. Dehmer.

DR. DEHMER: I guess I'm having a little trouble with the experts here. This is a very rapidly changing technical field, and how the procedure is done today is much improved from the way it was five years ago,

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but is this technology going to plateau at some point where, you know, our ability to treat with catheterization, we'll say this is as good as it's going to get? Does anybody see it plateauing in the next five years?

DR. C. GOODMAN: Dr. Calkins.

DR. CALKINS: If you look at the field, you're absolutely right. Certainly over the last decade it has changed dramatically, the tools are a lot better, our understanding is a lot better. What I see now is a plateauing of the rate of sort of, you know, new breakthrough approaches is diminishing very dramatically and now you know you've got to isolate veins, and you've got to do it so it's affirmative. There's some remaining questions about blading other areas, CAFEs and other areas, but I sort of see that we're now at a plateau. I hope we're going to get better because we want our success rate to go up further and our complication rates to drop further, but I think we're now at sort of a plateau.

In terms of training, I think that's something that is really very important. In

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terms of our data, there is at least one published study comparing, or at least looking at the effect of operator experience and also institutional experience, and the assumption was that if your center has done a hundred of these, they get better outcomes than in centers that have done less, which I guess is sort of obvious. In the consensus document we recommended that some of the centers start doing these things, you know, they need to get training during fellowship and doing, I think it was at least 25 procedures during their training, and then maintain a certain frequency at least, you know, at least one every several months, sort of five per year or six per year. But I think that's really critical, operator experience and training and that sort of thing. And certainly speaking for the electrophysiologists that are trained to do that procedure, I think that's who is doing the procedure now, and I think that's very very important.

DR. C. GOODMAN: Dr. Calega first, then Dr. Carlson.

DR. CALEGA: Just a follow-up

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question. Given that training and experience are critically important in the success rate of this procedure, do you believe that the procedure should be done at centers of excellence, designated centers of excellence and not in your local community hospital?

DR. CALKINS: That's an interesting question. There's been analyses done looking at the number of patients who are candidates for this procedure and the number of experienced, at least highly experienced electrophysiologists that do this procedure, and there's a tremendous gap. So if one says that only centers of excellence should do the procedure, we will never increase the number of centers doing the procedure and we'll never address the unmet needs for cath ablation. In every major center of excellence that I'm aware of there's a three to 12-month waiting list to get the procedure done right now.

So what's happening now is we're training fellows in the larger centers that are being hired in the smaller centers, and I think provided they have an institutional commitment to this procedure and they have been trained

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well, the institution is committed to back them up, in the consensus document it's recommended that every center should track their outcomes so they know what their own safety and efficacy is.

So it clearly has to do with commitment and training, at least to have the availability for surgical backup, not necessarily having an angioplasty surgeon sitting there scrubbed, but I think it is a commitment to the procedure. But no, I don't think it needs to be restricted to the centers of excellence.

DR. C. GOODMAN: Thank you.

Dr. Carlson.

DR. CARLSON: I had a question about the implications of the question itself. So the question about lesion sets and the approach is the implication that if one didn't follow a particular procedure for doing the ablation or one added a lesion somewhere, that one would not be compensated for the procedure? That's a pretty significant implication. And if that's not the implication of the question, what's the importance of the question?

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DR. C. GOODMAN: I'm not reading that into the question. I think that we do want to hear anything about the difference in devices and techniques, and we've heard some of that from Tufts, but with regard to the procedure being limited, this panel is in no position to make a coverage decision at all, but we are interested in understanding the relationship between physician training and perhaps things like outcomes.

DR. CARLSON: Yes, I understand. In terms of lesion sets, it's my experience that different centers have different approaches and may have very similar outcomes, and even within some centers, and many of these guys can talk about it better than I, the approach taken with one patient may be a little different than another because they have some difference in their anatomy or their underlying symptoms, somebody may have atrial flutter as well as atrial fibrillation.

DR. C. GOODMAN: Dr. Wilber, on that point.

DR. WILBER: I would just add a nuance to perhaps what Hugh said. I'm not sure we're

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quite at a plateau, I think there's still all sorts of issues, but maybe we're at a plateau with the number of new energy sources we use, but in terms of technological applications, how we apply it, durability, that sort of thing, I think we have a lot to learn yet and I don't think we're at a plateau. So I wouldn't want people to leave today thinking that somehow we're at the final state concerning the technology that we're using, and it's just a matter of deciding which patients should be treated, because it's far more complicated.

DR. C. GOODMAN: The history of technologies would concur with your statement. On this point, Dr. Calkins?

DR. CALKINS: On this issue about, does everyone get the same procedure or a different procedure, and it was interesting. If you asked that question five years ago, there was a lot of uncertainty, and there was a tailored approach to AF fibrillation under the concept that everyone needed kind of a tailor-made suit to give to them. And I think now we've learned that the tailor-made approach doesn't work and basically everyone is getting

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their veins isolated. Your point is well taken that if we see triggers, you might isolate them as well, so we will do that, but I think the cornerstone of ablation as isolating those veins is very much established today. Whether it was not ten years ago or five years ago, and I would say that in 99 percent of worldwide centers today, when a patient leaves the lab, all four veins have been isolated, so I think we really have moved to the point of consensus. And then when you talk about the finer points, what are the lines, there's still some evolution, but the underpinning I think is quite well established. Thank you.

DR. C. GOODMAN: Dr. Maisel.

DR. MAISEL: I just have a response to Dr. Carlson's point, why is the question here, and I actually feel that it's a very important question, meaning that if we felt the evidence showed that one technique was not working effectively, then we should be steering people away from that. I don't think the evidence shows that, and I think the consensus probably is that there's no one technique that's better than another, as long as the pulmonary veins

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are basically isolated.
And also, I think on the issue of the varying devices, I think we should be looking at procedural endpoints, and so I think a device that provides the pulmonary vein isolation, from a reimbursement standpoint, should be considered satisfactory.
DR. C. GOODMAN: Two very good points. Dr. Hammill is next.
DR. HAMMILL: Two points regarding who should be doing the procedure. So, I've been doing for EP for 30 years and I've been in the Mayo lab for 20 years, and this is by far the most complex procedure we do in the lab, complex enough that I never took it up because I didn't think I had the skill set to do this procedure, so I think it's a very very challenging procedure.
I think it is something we can track in the ICD registry. We've published a paper in JAMA relating outcomes and device selection with training, and we showed that electrophysiologists had better outcomes than surgeons and cardiologists with regard to ICD implantation. So I think this is one,

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especially this procedure needs to be in the hands of the trained individuals.

DR. C. GOODMAN: Dr. Hammill, though, did you hear anything today that would provide any evidence?

DR. HAMMILL: I have not, so I think it's all our opinion, but I think it's something that is definitely trackable in the future and would be something that we would -- but I think it's something that needs to be promoted.

DR. C. GOODMAN: Other comments? Dr. Umscheid, yes.

DR. UMSCHEID: I didn't see any data on the number of procedures and efficacy in reducing symptoms or other outcomes, but there was some data from Bradley about number of procedures and adverse events, and it looked like there was more difference between individuals who performed fewer than 50 versus those who performed more than 50. I assume those adverse events were measured in a systematic way and I'm assuming all those people were specialty trained.

The other issue as part of the

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learning curve here is in terms of volume per center. It looks like centers that did procedures, after the first 100 cases have a lower adverse event rate than their first 100 cases, so just something to keep in mind.

DR. C. GOODMAN: Good, thank you.

Dr. Packer, on that issue.

DR. PACKER: I think I'm going to actually have a question to Hugh that weighs in on this issue of sort of the numbers on the outcomes side and then on the safety side. You have been part of both the first and second international registries and you've also done meta-analyses. I think that there are data in the registry on that particular issue, and I wonder if you could comment on it or give us your interpretation of it of what you think we know based on the fact that we've got the meta-analysis done on this registry, and how it contributes to this issue.

DR. CALKINS: Yes, two points. The registry has two different looks at the data that basically shows the relationship between, you know, operator experience and outcomes, and I think that's where the hundred data comes

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from, centers that have done a hundred or more have better outcomes than those that haven't done a hundred, with regard to the Sprague paper that was from our institution, so the thing that was standard was the same institution that does a lot of backup things like technical staff, equipment, status reports and so forth.

So in that setting, I think in a center with established AFib programs, you can bring in new operators without dramatic changes in the safety profile. It's really a question for the new centers, how do you get them up the learning curve, and that's the commitment and proper training before they start, at least that's my sense.

Now, Doug, you know as well as I do, about the specific numbers of the registry.

DR. PACKER: Well, if you look at the registry, you look at the centers and you can see them even going up above 300, but that's something that, you know, is available in that particular registry, and you get less of a sense of it in meta-analyses, I didn't sense, than what I've heard from the, in the TA

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analysis.
DR. C. GOODMAN: Dr. Yaross, and let's make this the final comment in this area.
DR. YAROSS: We are currently in our post-procedure registry comparing what, measuring the adverse event rate in both groups of physicians, the more experienced physicians with 50 or more procedures with those having less than 50 procedures, and those data are forthcoming.
DR. C. GOODMAN: Great. Panel, any final thing before we go to break here? Let's do this. We'll take a ten-minute break now and then when we reconvene, the panel will have discussions that address directly our voting questions, so we will do that.
(Recess.)
DR. C. GOODMAN: Why don't we convene now, and we're going to move into our voting questions, including some discussion of each before we vote. And as is often the case when we finally get to some of these voting questions, there is typically some ambiguity, and we may address some of that, but we may not achieve perfection of clarity and that's okay,

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because that's in the world. So, good.
In a few minutes we will be asking our panel to assign a number ranking from one to five with their little numbered cards where the lower number is going to indicate low confidence and the higher number is going to indicate the higher confidence. And the first question has to do with, well, I'll just read it. How confident are you that the evidence is adequate to draw conclusions about health outcomes of interest to patients treated with catheter ablation for atrial fibrillation? So this is with regards to what we think about the evidence itself, not what the findings were in particular.
And this question one on our voting sheet is not broken out into pieces that, given our most recent discussion about outcomes of interest, I'm just going to propose that we have three, or actually four categories of outcomes of interest. I think it's apparent to all of us that the bodies of evidence for each of those several are not aligned. And so what I would propose, and I understand that it won't be perfect, is that we have the following four

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categories, you might want to jot these down and we can discuss them briefly. The first one being recurrence, okay? Let me tell you what I think the four are, and we can discuss them further. Number one is recurrence, number two is symptom relief, which includes in a very large way quality of life, okay? So number one, recurrence, number two, symptom relief, including most of what we discussed regarding quality of life. Number three, stroke, and number four is survival. Now I know we talked about some other outcomes and they too are of some interest, but I think these may be the higher, what appeared to be the most important in those discussions. And so again, now, recurrence can also be related to part of symptom relief, I think I see some heads nodding to that effect, but I just think it's helpful to break out recurrence separately although we know it is not independent of symptom relief or quality of life. So recurrence, symptom relief including quality of life, stroke, survival. Panel, is that okay as a taxonomy? Dr. Maisel.

DR. MAISEL: Can I ask for a point of

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clarification on this regarding the patient part of this, meaning we discussed different patient groups, and there may be more evidence to a different patient group and there is a subgroup of patients that may benefit in each of these, or may not benefit in each of these four things. In other words, are we saying all patients?

DR. C. GOODMAN: I think that's a fair statement, because we could not say, in no instance can we say that there is swell evidence for any groups of patients, but we certainly heard about some major patient groups for all of these. Yes. Was it Dr. Dehmer?

DR. DEHMER: Can I get further clarification, that this occurs over what period of time?

DR. C. GOODMAN: Do we want to venture on that? I see a couple heads shaking no. Well, we'll get that --

(Discussion off the record between Dr. Goodman and Dr. Salive.)

DR. C. GOODMAN: Unless somebody has a real good reason to be more specific, it's going to be hard for us to be more specific.

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So, as was the issue raised by Dr. Maisel, if there is some sizable proportion of people that may stand to benefit, that would suffice.
Dr. Umscheid?
DR. UMSCHEID: It sound like when we talk about recurrence in terms of outcomes we're talking about recurrence of symptomatic events, so it seems like recurrence and symptom relief are the same thing. I don't think any patient really cares about recurrence if they have no symptoms, and I know that recurrence is an outcome that most studies have looked at, and I know the experts have commented that most of those recurrences were symptomatic, that's how they're actually being detected, but I think we could probably combine A and B into just recurrence of symptoms.
DR. MAISEL: And I don't mean to pick on my colleague to the right, but I would argue for keeping them separate, and maybe we can add the word arrhythmia in front of the word recurrence. To me that question means, is the procedure effective at eliminating atrial fibrillation symptoms?
DR. C. GOODMAN: Dr. Satya-Murti.

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DR. SATYA-MURTI: I would prefer to keep them apart. We could have a separate opinion on each of them or maybe they would be the same, but I would like to keep them separate, recurrence and relief of symptoms.

DR. C. GOODMAN: Dr. Packer, I know you mentioned some of this in your earlier comments. Do you have an opinion one way or another with regard to recurrence as a separate first category or encompassed under the symptom relief?

DR. PACKER: I agree that for purposes of conversation we should keep them separate, and I think they bear differently on some of the issues like anticoagulation, so I think it would be a useful exercise to keep them separate.

DR. C. GOODMAN: And we will note that although we're keeping them separate for purposes of this voting exercise, that certainly they are not independent.

DR. PACKER: No, they're not, but to what extent they're concordant or discordant would depend on what study you're looking at, if you looked at all.

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DR. C. GOODMAN: Any other discussion about our confidence about the evidence with regard to these now four categories before we vote? Yes, Ms. Atkinson?

MS. ATKINSON: Just for clarification, we are referring to all patient age populations when looking at that question.

DR. C. GOODMAN: I would guess that we care most about the Medicare population. Marcel?

MS. ATKINSON: Because when we --

DR. SALIVE: Well, I think I need to clarify this. Question number one really is about overall adequacy of the evidence, so it's more of the go or no go kind of question. So that if the answer is no, we don't have any evidence, we really stop at that point, versus if it's really something we have to get into to define the details of the evidence. And so we don't need to repeat the adequacy of the evidence for each subsequent question, we're really asking about the overall adequacy of the evidence before addressing the other more specific questions. So, I appreciate dividing it by certain outcomes, but I really don't want

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to go any further than that.
DR. C. GOODMAN: Important point, so answer this question. When we look at question one for each of those four main categories, do you mean that we should confine our consideration to the evidence pertaining to the Medicare population or the whole body of evidence?
DR. SALIVE: The whole body of evidence.
DR. C. GOODMAN: So if there's a study where the mean patient is age 55, that's in, right?
DR. SALIVE: Yeah.
DR. C. GOODMAN: I just wanted to clarify. Thank you very much. So we've got the answer to that, we're not confined, and I'm glad you asked that question.
And one good point is that under question 4.B, we actually do get to some consideration about the Medicare beneficiary population in particular, and when we talk about additional evidence, that may or may not be as well raised, so thank you for raising that.

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DR. SATYA-MURTI: So we're combining all four together?
DR. C. GOODMAN: No. We're going to address each of these four categories separately and I will insist on that because I think it would be impractical to put them all together, but we will not be breaking it out by other subgroups of patients. Dr. Umscheid?
DR. UMSCHEID: The one thing I wanted to note is, these are outcomes of interest to patients, not an electrophysiologist, so I'm still a little hesitant on recurrence, because symptoms that recur, I totally agree with that, but recurrence of arrhythmia, apart from any of those, I don't know if patients care about that.
DR. C. GOODMAN: Okay. Dr. Maisel.
DR. MAISEL: Do you want to know if this has implications for ongoing management, other treatment strategies? I agree, I mean, I made the point earlier that it's probably not enough to just know about arrhythmia, it's of interest.
DR. C. GOODMAN: Dr. Umscheid and Dr. Maisel, I think in kind of the context in which

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you two gentlemen have this commentary, we understand what we're doing, and I think it will be helpful later when CMS does examine what was behind this. Dr. Calega, did you want to add anything? Okay.

Well, why don't we pull out our handy dandy cards one through five, and do recall that one is low confidence and five is high confidence. We'll take these in the order that I mentioned them earlier.

And so, how confident are you that the evidence is adequate to draw conclusions about recurrence of arrhythmias treated with catheter ablation for atrial fibrillation, talking about recurrence of arrhythmia, the efficacy of the evidence, one is low, five is high. And just for point of record, the chair is not voting.

So let's put them up, folks.

(The panel voted and votes were recorded by staff.)

DR. C. GOODMAN: Thank you very much. That was the first one. Great.

Now we're going to talk about symptom relief, which includes the way we discussed quality of life. So how confident are you that

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the evidence is adequate to draw conclusions about symptom relief including quality of life with catheter ablation for atrial fibrillation? Please hold up your cards.

DR. DULLUM: Can I just clarify? We're voting now on whether there's evidence available, not that we believe that the therapy works, correct?

DR. C. GOODMAN: Correct, this is about the adequacy of evidence, not what the evidence is.

(The panel voted and votes were recorded by staff.)

DR. C. GOODMAN: Next is stroke. How confident are you that the evidence is adequate to draw conclusions about incidence of stroke in patients treated with catheter ablation for atrial fibrillation? One is low and five is -- one is low confidence and five is high confidence.

(The panel voted and votes were recorded by staff.)

DR. C. GOODMAN: Thank you. The next is survival. How confident are you that the evidence is adequate to draw conclusions about

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survival for patients treated with catheter ablation for atrial fibrillation, survival? (The panel voted and votes were recorded by staff.)

DR. C. GOODMAN: I want to remind everyone that one is low confidence in the evidence and five is high confidence. Thank you for that, and thank you for agreeing to have that question broken into four categories. I think the discussion that we had prior to this vote clarifies that we understand there is some overlap in some of these categories. Okay.

Now, we will have a brief discussion as necessary for question two, and this has to do with how confident we are that catheter ablation for the treatment of atrial fibrillation improves health outcomes compared to other therapies or treatments in the following populations. So this one is about, is it really good or better compared to something else, and there are I see six categories, and these terms should be fairly familiar to us at this point.

One is with regard to first-line

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therapy, you heard about that today. Second-line therapy. First detected atrial fibrillation. Longer-standing, and that is greater than a year atrial fibrillation. Paroxysmal atrial fibrillation. And persistent atrial fibrillation. Before we get into the voting for those six categories, is there any discussion?

DR. SATYA-MURTI: This is overall health outcomes?

DR. C. GOODMAN: Yes, improves health outcomes.

DR. UMSCHEID: I wanted to ask the experts to comment on the issue of first line therapy. It seems like the impact of catheter ablation compared to the antiarrhythmics in recurrence of arrhythmia is not statistically different in the first-line study compared to the few second-line RCTs. So what would be the argument against not using catheter ablation as first-line therapy, or considering to use it in the future for first line.

DR. C. GOODMAN: Dr. Calkins.

DR. CALKINS: So in the consensus document, our recommendation is that it's

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appropriate for second-line therapy, and that reflects the fact that some of the complications of cath ablation for atrial fibrillation were very serious, cardiac tamponade, atrioesophageal fistula, whatever. And so if you have a patient in front of you, yes, the chance of a drug working is relatively low, but it's something. And we have heard that the field is still maturing and so if a patient goes on a drug, they tolerate it, it works for four years, and then they get the procedure four years from now, there may very well be a better safety procedure than the one they get today. So certainly if it was me, I would want to try the drug first and I might be one of the lucky ones where the drug worked. The other point is, most of the clinical trials on AF ablation, one of the inclusion requirements was that you had failed the drug, and once you fail one drug, you're more likely to fail the next drug. So I think still, you know, if you look at the ACC guidelines, the HRS guidelines, it clearly is second-line therapy.

And I think there are exceptions. You

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know, if you're a superstar athlete or something, where the first line is appropriate after a detailed discussion about potential risks, but they aren't always predictable.

DR. C. GOODMAN: Good. Any other questions or points with regard to confidence for improving health outcomes for these six populations before we start voting? Seeing none, we'll start with first line therapy.

How confident are you that catheter ablation for the treatment of atrial fibrillation improves health outcomes compared to other therapies or treatments for first-line therapy?

(The panel voted and votes were recorded by staff.)

DR. C. GOODMAN: Thank you. Let's now move to second-line therapy. How confident are you that catheter ablation for the treatment of atrial fibrillation improves health outcomes compared to other therapies or treatments for second-line therapy?

(The panel voted and votes were recorded by staff.)

MS. ELLIS: Thank you.

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DR. C. GOODMAN: Thank you. Next, how confident are you that catheter ablation for the treatment of atrial fibrillation improves health outcomes compared to other therapies or treatments for first detected --

DR. CARLSON: I just realized that I do have a question.

DR. C. GOODMAN: Oh, before we vote, okay. Go ahead, Dr. Carlson.

DR. CARLSON: What's the difference between first-line therapy and first detected atrial fibrillation?

DR. C. GOODMAN: I'm going to point to Dr. Packer to try to address that distinction.

DR. PACKER: I think the first detected is just that, you see it on an ECG, or the first time it comes to the attention of purveyors of fine medicine everywhere.

DR. CARLSON: So it could be first-line therapy then, right, if I treated it?

DR. PACKER: See, that implies you've made a decision. A patient may have atrial fibrillation for ten years, and for whatever reason the clinician comes to the decision that

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it doesn't need to be treated. All atrial fibrillation doesn't need to be treated. First-line therapy can mean when the clinician says you know what, based on my experience and the body of evidence and guidelines and so on, this needs to be treated, and then first-line therapy, for example, would be ablation or not.

DR. C. GOODMAN: Just a moment. Is first detected before first line?

DR. CALKINS: I think this is based on the AHA guidelines. They make a big point that if everyone gets a pass, you can have one episode of AFib before you embark on any treatment, everyone's first AFib, fine. But once you have a second episode, then it's recurrent AFib and all their treatment algorithms fall into place. But I think this is talking about upstream therapy when you first detect AFib, we're going to do an AF ablation procedure without, you know, even having a second episode.

DR. C. GOODMAN: So this is the absolute first, that's how I understood it. Is that okay, Dr. Carlson?

DR. CARLSON: Yes.

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DR. C. GOODMAN: So, Dr. Hammill, did you have a comment on that?
DR. HAMMILL: No. I was just going to say about the same thing Hugh said, so I'm fine.
DR. C. GOODMAN: All right. So it's asking about first detected atrial fibrillation.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. C. GOODMAN: All right. We will move to longstanding, which here means greater than one year, for atrial fibrillation. How confident are you that catheter ablation for the treatment of atrial fibrillation improves health outcomes compared to other therapies or treatments for longstanding, greater than one year, atrial fibrillation? One through five, one is low, five is high.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. C. GOODMAN: Thank you. We will now move to paroxysmal atrial fibrillation.

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Any questions about paroxysmal? Seeing none, okay. How confident are you that catheter ablation for the treatment of atrial fibrillation improves health outcomes compared to other therapies or treatments for paroxysmal atrial fibrillation?
(The panel voted and votes were recorded by staff.)
DR. SATYA-MURTI: Again, this is all outcomes, not just the -- are we considering all of those that we identified.
DR. C. GOODMAN: We have talked about the health outcomes of interest and it is in that context.
MS. ELLIS: Thank you.
DR. C. GOODMAN: The next and last of the set of six is going to be persistent atrial fibrillation. Persistent, any discussion or questions about definitions, meaning, context? No. Okay. How confident are you that catheter ablation for the treatment of atrial fibrillation improves health outcomes compared to other therapies and treatments for persistent atrial fibrillation?
(The panel voted and votes were

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recorded by staff.)
DR. C. GOODMAN: Our next question, which looks a little similar to something above you is question three, how confident are you that ablation improves long-term, greater than one-year, health outcomes.
DR. CARLSON: If I may, it is a little different. One is looking at how long you had it before and the other is looking at follow-up, right?
DR. C. GOODMAN: I believe so, you're distinguishing between three and 2.D?
DR. CARLSON: Yes.
DR. C. GOODMAN: So Dr. Carlson, why don't you just state that distinction again.
DR. CARLSON: Okay. So, 2.D is looking at how long the patient had atrial fibrillation before the procedure, and three is looking at the outcomes beyond one year following the procedure.
DR. C. GOODMAN: Right, exactly. Any other questions or considerations for question three? Dr. Dullum.
DR. DULLUM: Again, is this everybody that we've seen the data presented on, or the

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Medicare population?
DR. C. GOODMAN: We're still talking about everyone; is that right, Marcel?
DR. SALIVE: Yes. We're not going into anything specific with regard to the Medicare population just yet.
DR. C. GOODMAN: Okay. So how confident are you that catheter ablation improves long-term, that is greater than one-year, health outcomes?
(The panel voted and votes were recorded by staff.)
DR. C. GOODMAN: Now we're going to move to what they call external validity or generalizability, how well things work in the real world, sometimes we talk about it as effectiveness versus efficacy. What we're trying to understand is how does the body of available evidence translate into real world practice, i.e., getting it out of the controlled world of the study, so this is a two-part question. Keep in mind the distinction. 4.A is going to ask about moving from controlled conditions to outside of those, presumably in a real world practice, and B is

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going to talk about the extent to which the evidence is generalizable to the Medicare beneficiary population in particular. Are people confident about looking at 4.A that the overall, and we're only asking it one time here, so this is not broken down into patient types or indications or so forth, that's okay with everyone? All right. Well then, how confident are you that the outcomes can be extrapolated to patients outside a controlled clinical study?

(The panel voted and votes were recorded by staff.)

DR. C. GOODMAN: We're going to move next to outcomes being extrapolated or generalized to the Medicare beneficiary population, which we recognize as being age 65 years and older, and also which is 56 percent female. Any need for discussion here about this? I know we've had quite a bit of discussion here today about what the data showed, some of the analyses, but I wanted to make sure that we understood the concept here and ensure that you got any questions that you may have about this maybe clarified. Does any

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panelist have a question or comment about this before we put it out for vote? Seeing none, we will proceed then.

This is question 4.B. How confident are you that the outcomes can be extrapolated to the Medicare beneficiary population aged 65 years and older and which is 56 percent female?

(The panel voted and votes were recorded by staff.)

MS. ELLIS: Thank you.

DR. C. GOODMAN: Now question five is, you might say, rather broadly worded. It is, how confident are you that additional evidence is needed? Dr. Packer first and then Dr. Carlson.

DR. PACKER: Can we break that down in a similar fashion to what we did with number one?

DR. C. GOODMAN: We could do that. Does anyone else on the panel think that would be a good idea? Dr. Maisel.

DR. MAISEL: What about breaking it up by patient population?

DR. C. GOODMAN: So we've had two breakdowns before. The first breakdown was the

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four main categories of outcome interest. The second breakdown was by patient population, there were six of those. So where does this make the most sense? It could be one or both frankly. Dr. Dullum.

DR. DULLUM: I think if you're going to do that, you're going to have to break it down to energy source, different types, you know, breaking down more and expanding it. Or do you just want to keep this as more evidence, because we could go on and on about how much more evidence we need in different categories.

DR. C. GOODMAN: That's a good point. We may not have to do that. CMS asked us to look at the categories of patient population and we took the initiative to having considered about the ranges of evidence, to break it down into these broad categories of interest. So I would submit that if we're going to break out question five, we would break it out by one or both of those very same categories that we addressed in the earlier questions.

So just proposing to the panel, you know, we're moving on pretty well with time here, we could do a breakdown in outcomes, we

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could do a breakdown out in patient populations. To do both would be holding up a card ten times. Dr. Umscheid.

DR. UMSCHEID: When you say needed, what is meant by that? Is that needed by the treating physician, is it needed by CMS to make a decision.

DR. C. GOODMAN: Marcel, I don't think this is really on the table, but you tell me if I'm wrong? My response would be that we're here to support the Center for Medicare and Medicare Services in formulating an objective picture of the availability and quality of evidence that may be used at some time to, in coverage considerations, and I think that they are our primary, though not sole target audience for this. And so I would say, evidence needed to support CMS would be my take. Dr. Salive?

DR. SALIVE: I can hardly disagree with that. I think, your advice to us, you think we need more evidence. And you know, actually, and just in comment on breaking down further, I think we do want some discussion about where your feelings lie here, so no

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matter how this gets voted, we would like to have some discussion on the next area.

DR. SATYA-MURTI: We could air our feelings on that, but to vote for this en bloc.

DR. C. GOODMAN: The chair would offer that it would be good to at least do the four outcomes at the very least and then if there's a strong case to be made for the six patient populations, we can do that too, and we would be glad to do that if panelists feel we should. Dr. Maisel.

DR. MAISEL: Maybe I will say the phrase that no one seems to want to say, but is this about coverage with evidence, because if that's the case, then answering the outcomes issue isn't going to help with what patients might need additional evidence if they're covered.

DR. C. GOODMAN: That's a good question and that is fair game and can be put on the table if you so choose when we reach the additional evidence discussion after this. If you think that coverage is not going to be delayed without the additional evidence if needed, we can talk about it then. Yes, Dr.

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Stanton.
DR. STANTON: I think Dr. Salive made an important statement at the beginning, which is this is not a national coverage decision meeting. There is coverage by Medicare through the local carrier mechanism for AFib and ablation, so I'm not sure that it is appropriate to get into recommendations about national coverage or about coverage for evidence development.
DR. C. GOODMAN: I will have a comment on that too.
DR. SALIVE: You're right, that that is a question about how do we implement their advice, and I would rather not discuss that because we don't have to really get your advice first to decide that. I agree that we haven't got any policy and nothing is contemplated right now. I think we wanted to get the advice and try to sort through it and figure out how we might deal with that advice, so I think it can be broad advice.
We have done that, as you know, asked for it in other decisions, but it would take quite a bit of work. So you can give us advice

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on that, but our main focus is really what evidence is needed and what do you think we should be focused on.

DR. C. GOODMAN: Just to iterate, there is no coverage determination on the table here today, and so it appears that I will add that in our discussion about the additional evidence if needed, that we're not federal employees, we don't work for CMS, we're here to help inform them, however, and if you have an opinion about something that might be helpful to them, and it happens to be coverage evidence as a potential thing some day, nobody is going to stop you from suggesting that if that's what you would like to put on the table, but you don't have to do that either, but the focus will be on what evidence is needed.

Yes, Dr. Carlson.

DR. CARLSON: Is this question focused on the evidence that's available at this point today or is it focused on the evidence that will be available when current trials like CABANA are completed? That's a very important distinction, at least for my answer.

DR. C. GOODMAN: It certainly is.

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CABANA is not completed and published yet, is it, Dr. Packer?
DR. PACKER: Tragically, no.
DR. C. GOODMAN: So I would suggest that I would not presume that CABANA or anything else will produce the needed evidence. You may hope it does. What we're interested in most from you is understanding what evidence is needed beyond what's in the hopper today.
DR. CARLSON: Let me point out the box that puts me in, and I think a lot of us at the table. If I didn't think additional evidence were needed, why would I support doing the CABANA trial? So it really reduces the meaningfulness of the question, because obviously I support the CABANA trial, I think more evidence is needed.
DR. C. GOODMAN: I will restate it. The evidence that we have is the evidence much as was presented by Tufts today, that's in the peer reviewed literature, that's open for consideration. There is certainly some evidence pending in the pipeline that we haven't seen yet. We'd like to know what you think we don't have yet, including what might

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not be in the pipeline.
DR. CARLSON: Okay.
DR. C. GOODMAN: Dr. Dullum?
DR. DULLUM: Could we just make it simple, do you think you need more evidence, everybody vote yes or no, whatever we vote, and then during the discussion period you could outline what evidence you think you need. That would maybe simplify the process.
DR. C. GOODMAN: Well, we can certainly get into more detail with the discussion. I would just say when we talk about what's needed, it's what may be needed beyond what is already captured particularly as including what has been captured by the Tufts TA.
Now, I again want to propose that we do the four outcome categories at least. Does anyone feel strongly about doing the six populations as well? Dr. Packer.
DR. PACKER: I guess, I think that the Tufts study was great. I think that it took an incredible amount of data and put it together. The question I have, though, is if that's your evidence body, then I think we have an equal

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problem with our randomized clinical trials. They went from 2,952 cites or references down to 120 articles, based on legitimate criteria, but restraining or restricting their criteria nonetheless. It's almost like you need a registry of that process just as you would need a registry with a trial like CABANA to try to say well, we tried to enroll 25,000 patients and we got a few thousand out of it.

So I guess my point would be that I think that was a noble effort, I think it's a great body of literature, even though others would argue on behalf of meta-analysis, registries, that sort of thing. I'm not sure that that by itself, though, is the gold standard for evidence, nor would I think that this entire deliberation on whether we need more evidence is strictly a function of that.

DR. C. GOODMAN: Absolutely agreed, and I thank you for the clarification. I referred to that only as capturing much of it but certainly not all. We've certainly heard about other evidence that is available and that is part of the body that we're talking about available now. So we're talking about beyond

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available evidence, including certainly what Tufts captured, including some other studies we've heard about today. What evidence do we not have somewhere that we need? Thanks. Okay. Let's do at least those four outcome categories again. I didn't hear or see a strong push for the six subpopulations and unless someone's got one, we'll just stick with the outcomes, is that okay? I see heads nodding. All right. How confident are you that additional evidence is needed for, or with regard to recurrence of arrhythmias, how confident are you that additional evidence is needed pertaining to recurrence of arrhythmias, one is low need, five is high need? Excuse me. How confident are you that additional evidence is needed? So five means I'm very confident that additional evidence is needed. If you're confident that a lot of, if you're highly confident that additional evidence is needed, you might vote a five. If you're not very confident that additional evidence is needed, you might vote something that looks closer to a

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one.
MS. ATKINSON: Can I just clarify again? Is this for Medicare beneficiaries or for all populations? Are we focusing on Medicare beneficiaries when we talk about this?
DR. SALIVE: All.
DR. C. GOODMAN: Dr. Salive indicated that the Medicare beneficiary question was 4.B in particular.
DR. UMSCHEID: And all time periods too, not just the six months?
DR. C. GOODMAN: Yeah, we're not limiting, correct.
(The panel voted and votes were recorded by staff.)
DR. C. GOODMAN: Thank you. Next, how confident are you that additional evidence is needed regarding symptom relief, including quality of life? Five is you're very confident you need more evidence, and one is you're not confident at all.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. C. GOODMAN: Thank you. Next, how

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confident are you that additional evidence is needed pertaining to stroke?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them.
DR. C. GOODMAN: Okay, thank you.
Next, how confident are you that additional evidence is needed pertaining to survival?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. C. GOODMAN: Thank you. So we've gone through our voting questions one through five. As was made clear by some of your comments before and even during this voting process, there's some gaps in evidence and some considerations that you wanted to lay out here going from the scope of the questions. So based on your, the panel's vote on question five, it seems as though, and certainly in some cases additional evidence is needed, and our discussion now moves to well, additional evidence, if needed, at least two main questions.
So we're presented here with the first

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point of, if there is additional evidence needed, what type of additional evidence is needed to determine health outcomes, what type of additional evidence is needed to help determine health outcomes. In other words, we can talk about subcategories that we voted on just now under question five. So Dr. Hammill, were you ready to make a comment?

DR. HAMMILL: Yes. I would like to start this out. I agree with what was said earlier that consideration of coverage with evidence is ultimate. I think this area is a very appropriate approach for CMS to take. I think it's quite analogous to the ICD registry where we had questions that weren't being covered by the literature, by the randomized control trials. And the questions I think about, one is long-term survival or mortality, stroke, but also the generalizability of the data to hospitals of smaller volume and physicians of less experience.

So I think that's a huge gap that we have now and the only way we can get it is with some type of registry. I worry about a registry that's voluntary because I think

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patients will not be entered in sequentially so they will cherry-pick for a better outcome. I also worry that if it's voluntary, we will not get representation from the smaller hospitals because they won't want to participate, so I think CED provides that leverage.

A worry has been that the average age is younger and below the Medicare beneficiaries, but my argument to that again goes back to the ICD registry. With the ICD registry, the only requirement was that a patient, for participation, was to enter patients who were primary prevention Medicare beneficiaries. However, nearly 80 percent of the hospitals in the United States have elected to enter every patient, Medicare and non-Medicare, and there are a lot of things that drive them to do that, one of which is quality improvement and one of which is benchmarking and being compared to other hospitals, and it's always to a hospital's benefit to have these data looked at in a younger population versus just exclusively a Medicare population.

So, I think that the other issue that

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we've seen at Mayo is that as people are more comfortable with this technique, they move the technique further and further into the Medicare population. The procedure was initially done in the younger lone AF patients, normal hearts. That's only five percent of the population. The bulk of AF comes from the elderly population, so I think that that's a natural course of where this procedure is going to go, and I do worry about it being done in smaller centers with less experience. So I think tracking that in a registry under a CED is appropriate.

DR. C. GOODMAN: What you said, Dr. Hammill, you are interested in more data on survival, stroke, generalizable to community hospitals and the elderly, and you're saying that a good way to capture those data would be in a registry?

DR. HAMMILL: Correct.

DR. C. GOODMAN: Just, we will state, once again, there is no national coverage decision here on the table today, I just want to make sure, and we've said that several times. But we are interested in the kinds of

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additional evidence that you think are needed, in particular for health outcomes. Yes, Dr. Carlson.

DR. CARLSON: I'm concerned that it may be difficult in retrospect when people are looking at these scores to understand the reasons that people voted one way or another, so I'm going to take a moment to explain mine. I think there's very good evidence, and my vote reflects that, to suggest that ablation decreases recurrence and decreases symptoms in appropriate patients. So the patients that have been in the trials have been symptomatic and I think the results have shown that that's been effective. If we are to use ablation to decrease the risk of stroke, then that's a different and larger patient population that has not yet been studied, and that's a completely different question in my mind, and it's a different coverage decision if it ever comes to that as well.

DR. C. GOODMAN: And based on what you just said, is there a need for additional evidence with regard to, let's say outcomes?

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DR. CARLSON: Well, I think CABANA is going to give us that.
DR. C. GOODMAN: Dr. Maisel.
DR. MAISEL: I said at the top that we need additional evidence for stroke and mortality, and it's not so we can prove ablation for atrial fibrillation reduces stroke or reduces mortality, we just need to be confident that it doesn't make things worse as a treatment option. So I do feel we need additional evidence, but I don't think that evidence needs to show that it helps necessarily in the specific outcomes.
DR. C. GOODMAN: A very helpful clarification, thank you. Dr. Satya-Murti.
DR. SATYA-MURTI: I heard from the presenters that an average wait time of six to eight months is not unusual for waiting to get the procedure performed, so this is not an incident that some of the earlier studies found on temporal lobe epilepsy where waits were also fairly long, so patients waiting to get in have already been assigned an intention to treat. They were compared to those who actually underwent surgery, so there may already be

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data, let's say for a typical patient waiting to have the procedure done, and those who got in, and compare them, say within that eight or nine-month period, those who did not get in but were about to, their quality of life and symptoms might form a basis to compare with those who have already had the procedure. Is that kind of data, can it be culled out?

DR. C. GOODMAN: Do any of our presenters or team from Tufts have a response to Dr. Satya-Murti? Dr. Calkins.

DR. CALKINS: I don't think the data is available, or whether those data sets exist. Whether that question could be addressed in a prospective clinical trial is another question, and speaking as someone who's involved in clinical trials, certainly one of the main problems we have now is very little funding for clinical research to do the high quality studies that are needed. CABANA has been funded, so far as the registry that people have been talking about. But I think all of us would like more money to do research to answer important questions, and that would be one study design that could be contemplated.

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DR. YAROSS: To put my input on the question of what happens during a waiting period, I go back to conversations that Dr. Packer and I had recently, and I believe CABANA has the potential of getting that intention to treat period, events will be counted from randomization, and it may help.

DR. SATYA-MURTI: What kind of time period are we looking at?

DR. PACKER: What this is referring to is in the CABANA pilot study, the time to medical therapy is three days, the time to ablative therapy is 23 days, and so it would give you information in terms of event rates after they get randomized, but I think you're speaking to a longer waiting period.

DR. C. GOODMAN: Dr. Rosenberg.

DR. ROSENBERG: I think it would be an interesting concept if there was some way you could harmonize those groups. I don't know if it's possible, but I would like to warn you that there's a lot of baggage in this kind of comparison and I would be very cautious about that.

DR. C. GOODMAN: Thank you for the

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clarification, Dr. Rosenberg. Yes, Dr. Umscheid.

DR. UMSCHEID: I just want to bring up a point that although I felt the data was compelling about decreasing recurrence of arrhythmia, I do think there is a need for more data even for that outcome, because of some of the facts that were presented earlier. The majority of patients that I see in the hospital don't have arrhythmias, they have structural heart disease, they have EFs that are abnormal, usually less than 45 percent, and we don't have enough data on patients outside the normal EF range.

So I would like to see more trials not only in the elderly and people with comorbidities in general, but specifically in people with structural heart disease, because I think there is a theoretic rationale that this therapy may not be as effective in people with structural heart disease and it is in people without it.

DR. C. GOODMAN: Dr. Umscheid, just to be clear, do you think that the available data they have, subject to the registries and

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subject to analysis, they could draw any findings there, or do you think we're in need of new prospective data collection with regard to the structural abnormalities?

DR. UMSCHEID: Well, there was a question that led to us getting to this issue, which was does EF impact the efficacy of catheterization, and the answer was probably not. But the problem with that was there wasn't a wide range of EFs to be found, it was a very narrow range of relatively normal EFs. And the patient that we're seeing in our ordinary care academic hospital presents with structural heart disease and EFs that are likely lower than 45 percent.

DR. C. GOODMAN: Great, thank you. Other comments about the type of additional evidence or needs to determine health outcomes? We've talked about survival, stroke, talked about the elderly, structural heart conditions, generalizability to community hospitals. We talked a little bit about prospective data collection and the need for a registry for this. What other gaps do we need to consider filling with regard to determining

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health outcomes? Did anybody want to venture on hospitalization and those kinds of events? I know we discussed it earlier. Is it still something of importance to us? Dr. Calega.

DR. CALEGA: I was just going to say that the cost effectiveness which we looked at with hospitalization greater than 12 months, what happens with these patients, what happens from the perspective of what all medical costs are, doctor visits, hospitalization, medication, laboratories, are they on Coumadin, do they know they need Coumadin, looking at the cost impact and the cost effectiveness for greater than a 12-month time frame.

Dr. C. GOODMAN: So under the broad term resources, cost, and we may be venturing into cost effectiveness. Just as a reminder, I'm fairly confident that CMS does not take into account cost effectiveness when or if they get into making coverage determinations, but this has been raised.

DR. SALIVE: Generally we do not use that data in making coverage decisions but there are some exceptions to it in the preventive services area, in which we discuss

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that in relation to screening. And so there are some exceptions, but as a practice we don't.

DR. C. GOODMAN: I just wanted to raise that. That doesn't mean we can't make a suggestion, which would be very helpful. Ms. Atkinson.

MS. ATKINSON: I think again, going back to the two populations, robust versus frail, and looking at all the other comorbidities, the effect of ablation on those other comorbidities, even arthritis and pain. If they're now able to get up and ambulate, there may be decreased pain, so maybe looking at that as well.

DR. C. GOODMAN: Okay, arthritis and pain. Other comments on health outcomes? Dr. Umscheid.

DR. UMSCHEID: I would say that hospitalizations are important even beyond resources. I think they are a surrogate at some level for quality of life. I would also say that a systematic assessment of adverse effects and clear definitions of adverse events is very important for future trials. And for

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whatever it's worth, I wanted to just state that I strongly agree with Dr. Hammill's opening remarks about registry, applicability to community hospitals, et cetera.

DR. C. GOODMAN: Good, thank you. Dr. Packer is next. Yes, Dr. Knight.

DR. KNIGHT: We spent a lot of time talking about all the available evidence and how we determined its quality, and with all due respect I would say that a registry probably wouldn't offer those high quality data that we are seeing, a registry will not be as powerful as the randomized clinical trial would be in looking at some of these questions. So you've raised a lot of important questions, but I don't know that it answers the type of evidence that we're looking for from randomized clinical trials.

DR. GOODMAN: Yes, Dr. Satya-Murti.

DR. SATYA-MURTI: Could we not have a registry and a randomized clinical trial also? They are not mutually exclusive.

DR. C. GOODMAN: Dr. Yaross.

DR. YAROSS: In a perfect world, of course we would like to have all of that. What

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I would like to point out is that many of these questions that are being raised in terms of the subpopulation of the elderly, et cetera, are ones that there is great interest both from the industry, from the clinicians, institutions in answering, but we have to realize that we live in areas of limits, and as a result in considering recommendations such as Dr. Hammill has raised with a registry, we have to think about the opportunity costs, will it be possible to do all these higher quality clinical trials, which raises different questions. So I would just recommend that the panel continue doing what it's doing, identify what the questions are, but then also think about what's the most appropriate way, recognizing that it's not always possible to do everything.

DR. C. GOODMAN: Right. I would just add that registries are basically prospective observational studies, they are very useful for, among other things, identifying rare and/or delayed adverse events. They're very good for identifying hypothesis generation, they are very good for identifying associations

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that might be tested in RCTs. So yes, the point is well taken, that there are a lot of evidence questions that can't be answered here, we're not going to take one particular study design and try to do those, but we will hopefully kind of draw from our portfolio of study designs subject to time constraints, force constraints and so forth, but a point well taken. Dr. Hammill.

DR. HAMMILL: Just to elaborate on that a bit, with this national AFib ablation registry which we're working on in conjunction with the FDA, the data collection forms which will be coming out in about two weeks, we have looked, those forms have been developed with the CABANA forms, and we will be using similar definitions. So trying to see what's happening in an RCT like CABANA, and then how generalizable is that to the subpopulation.

DR. C. GOODMAN: Great. Dr. Packer.

DR. PACKER: An extension of that comment, you know, at the end of the day, there are a bunch of different trial types, and if we're looking at some kind of diagram with observational studies, multicenter studies, and

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then registries, and eventually mortality trials, we hope that we get to some ethereal point on all knowledge of treatment on somebody who's got atrial fibrillation. I'm not sure that we can get it all, I'm not sure that there is any one of these trials that we're talking about that is going to get us all the information about all those things that we would like to know.

I think that, you know, if you look at the slope of my theoretical curve, there's some threshold there, we seem to have a threshold where we're comfortable with moving on with some part of what we're doing, I think from the standpoint of symptoms to the standpoint of recurrence and so on. I think with the evidence we've got now, we've exceeded that threshold. Having said that, we always can learn more, and I think the more we can learn from whatever approach we happen to use, it's going to be of ultimate benefit.

I happen to be quite enamored with the concept of clinical trials, because I think one of the problems, and I don't mean to be too critical of the Tufts approach, but one of the

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reasons that we've heard over and over and over again, why they had to go through a large number of studies down to a smaller number of studies is because they weren't designed very well, perhaps the critical questions weren't being asked and they weren't being set up to get an answer for those particular questions. I do think that randomized control trials will give you the greatest control of all of those issues and at the end of day, when we have this conversation three or four or five or six years from now, nobody stands up and says we had to exclude this one because of, we had to exclude this one because of, we had to exclude these three because of, but we have something that has, you know, the standing of a well constructed clinical trial. And hopefully CABANA will be that, and you know, we hope the RAFT will be, and that, you know, COC/AF II will be that, and all the other trials that are now underway. I would hope that they would control for therapy. I would hope that what they do is kind of even out all the iterations so that at the end of the day, your question is this therapy or that,

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or this treatment strategy or that. I think that's important because of clinical decisions we make.

So if we approach a patient, then we have to say I'm going to treat him this way or I'm going to treat him that way, after we made the decision to treat him at all. So I think the randomized clinical trials are pointing in that direction and I think that there are probably way too many of them that are being planned or are now underway.

Having said that, I think there are different added questions that can be asked and answered using other approaches as well. I might bob and weave in the direction of randomized clinical trials but there are other questions that can be asked and answered with the others and I think it will be interesting to see where we go with that.

As long as we -- we have to capture on the registry things, I know what problems occurred in the international registry. The critical issues would be capturing so you have enough information, including the baseline study forms, so that you're not getting 45

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different approaches, such that when you look at events over a short period of time, which may be difficult to get a long-term follow-up with the registries, then you have enough data with enough reproducibility of the approach in what was used that you can ask and answer the questions.

So that bears more on the issues of construction of that registry and to that end, one of the things we tried to do is to create a situation such that at the end of the day CABANA, or the registry, or this trial, or RAFT, or the FTF database or whatever, can talk to each other at the end of the day.

DR. C. GOODMAN: Thank you, Dr. Packer. Dr. Umscheid.

DR. UMSCHEID: I think the trial design that you want to look at depends on the question you're asking. One of the major issues here is, can community EP docs replicate the results from controlled trials, and if we're saying that you have to be a highly trained EP doc to do it, Dr. Hammill was saying, you know, he was concerned about his own skill set so he decided not to do it, so

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there's obviously some very common threshold of a skill set volume that we're talking about, in order to do this effectively without causing adverse events.

So if we want to make sure that people out there in the community aren't causing adverse events, I think it's really important to follow the patients that are being treated out there, so that's where the registry comes in, and that's where a mandatory registry comes in. Because when we are talking about the efficacy of this procedure, we're talking about recurrence of, preventing recurrence of arrhythmia that we're not sure is symptomatic, we're talking about improving quality of life that, we're not sure if the SF-36 is the right measure, so the benefits are not necessarily clear. And when we get down to generalizing the procedure to community docs, I think it is really important to find out if adverse events are occurring in the community.

DR. C. GOODMAN: Thank you. It doesn't take into consideration these poorer study design, as you pointed out. Other comments with regard to either the evidence

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needed for determining health outcomes or study designs to obtain this evidence, any other comments from our panel regarding that?

DR. CARLSON: One more comment then. I think it would, we would all benefit from looking at the question that we're trying to answer and then look at the best mechanism for answering the question. For instance, in solving the questions or answering the questions that need to be solved or answered. I heard we need to be looking out for the possibility that patients are being harmed in community hospitals. Well, do we know that that is a problem, and are there better ways than spending a lot of money on a big registry to determine or answer that question? There may be very simple ways to line up national death registry information with Medicare databases and answer that question, to know if we need to dig deeper in another way that doesn't require the same amount of resources, so I urge us to keep those ideas in mind.

DR. C. GOODMAN: A point very well taken given the discussion we had about outcomes, population and study design. Very

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good. Any further comments? Dr. Hammill.
DR. HAMMILL: Well, I will just say to Mark there, I think that that, we could try to look at that, but the Medicare claims data and national death index doesn't define the patient well up front, doesn't define the type of procedure that was done on a patient, and ablation isn't a code that's followed, so right now we can't get to that data on even what procedure has been done or who is doing the procedure.
DR. C. GOODMAN: Okay, Dr. Satya-Murti, do you have a comment?
DR. SATYA-MURTI: If coding were the issue, and speaking as one who has been a Medicare medical director, for various purposes they would be willing, I think, to provide a code tracking service, I think. Marcel might know, but I think we have done this in the past.
DR. C. GOODMAN: Okay. Although the agenda asks for some closing remarks on my part, we'll do this. I have a final question for all of our panelists, and I'm going to ask you to answer it in 30 seconds or one sentence,

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whichever is less, okay? So basically you've got 30 seconds or a sentence, and here's the final question. This is kind of an overarching question and I hope you will take into account what we've heard and said today. And that is what is that essential kernel of advice or insight that you would offer to Medicare, CMS, that is CMS for Medicare, and/or those in the field whose responsibility it is to generate evidence henceforth to better address the question of the appropriateness of these interventions? So what's the insight, or last observation that you can make in 30 seconds or less that you would like to express as a final remark to people here at CMS, and/or the people who are responsible for generating this kind of evidence about which we have spoken all day, these people in the field for this kind of intervention? And if it's your turn and you want to say it, you can say ditto, but you have to add another twist or another element to it. So let's start, going with Dr. Packer at the far end of the room, and just go in order. Dr. Packer, in 30 seconds or less, what's that last gem of wisdom that you've got

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to offer here?
DR. PACKER: Get the evidence.
DR. C. GOODMAN: Dr. Hammill.
DR. HAMMILL: The need to obtain evidence to make sure the outcomes are generalizable to the full community.
DR. C. GOODMAN: Thank you.
Dr. Thomas.
DR. THOMAS: I think we need to define the healthy robust 80-year-old.
DR. C. GOODMAN: Ms. Atkinson.
MS. ATKINSON: I think to make the inclusion criteria not so strict that it excludes the older adult population.
DR. C. GOODMAN: Dr. Umscheid.
DR. UMSCHEID: To be relatively clear with the indications for either procedure, who should be getting them.
DR. C. GOODMAN: Thank you. Dr. Maisel.
DR. MAISEL: I think we've come a long way in ten years and I feel fortunate that we have a viable therapy that we can offer our patients that helps some patients greatly, and I think we need to do a better job of

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clarifying exactly who those patients are.
DR. GOODMAN: Thank you. Dr. Dehmer.
DR. DEHMER: Inasmuch as this technology is very similar to many other technologies, clearly we need to get the evidence, so ditto on that, but we need to better define which patients and which conditions will have the most benefit.
DR. CARLSON: I quote my former boss, Dr. Albert Waldo, perfect isn't the enemy of good.
DR. CALEGA: Ditto to a lot of what's been said, but let's provide the funding to get this evidence.
DR. C. GOODMAN: Evidence is not free. Dr. Satya-Murti.
DR. SATYA-MURTI: Select a patient very carefully, and set the inclusion criteria and stick to it.
DR. C. GOODMAN: Thank you. My feeling has to do with giving signals. These MedCAC meetings have certain purposes. One of the perhaps unstated purposes but perhaps most helpful is that this is an opportunity to get very strong and often helpful signals from

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diverse national experts on any given issue, and whether it has to do with outcomes of interest, patient populations, Medicare beneficiaries, real world settings, study designs or other, this panel has brought forth some very important and useful signals moving forward for the kind of evidence the decision-makers, patients, clinicians, payers and others are going to be seeking, and I think that those signals bear high regard.

Before I turn it back to Dr. Salive, I want to thank all of our panel very very much for your wonderful insights. It was worth it, every penny that you got paid to come here to Baltimore for your excellent insight. I wanted to thank the six expert presenters for the splendid job that they did and your patience with our questions. I want to thank the expert team from Tufts EPC for doing a fine job, Dr. Rosenberg, who is not here, gave a splendid presentation earlier. So, he is still here, okay, out of sight. Thank you for that great job kicking us off.

Dr. Salive.

DR. SALIVE: Well, I have to echo all

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those thanks. I think this was a very thorough discussion of the evidence and very helpful, and sets the bar high for all the next MedCACs in terms of discussing evidence. The panel did a great job, the presenters all did a great job, and I want to thank especially the public for their attendance and attention for a long time here today, so everyone, safe travels home.

(Whereupon, the meeting concluded at 3:53 p.m.)